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LIPID METABOLISM

SYNOPSIS

1. DIETARY LIPIDS

–INGESTION

–DIGESTION

–ABSORPTION

–TRANSPORTATION

–UPTAKE BY TISSUES

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2. LIPOLYSIS: LIPID CATABOLISM
   - ❑ FATTY ACID OXIDATION
   - ❑ KETONE BODY METABOLISM
3. LIPOGENESIS:
   - ❑ LIPID BIOSYNTHESIS
   - ❑ DE NOVO BIOSYNTHESIS OF FATTY ACIDS
4. LIPOPROTEIN METABOLIM/ TRANSPORTATION OF LIPIDS
5. DISORDERS ASSOCIATED TO LIPID METABOLISM

INGESTION OF DIETARY LIPIDS/ EATING OF DIETARY LIPIDS

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- **Lipid** is the **chief constituent** of human food.

Why To Eat Dietary Lipids?

OR

Importance Of Ingesting Dietary Lipids

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Importance Of Ingesting Dietary Lipids:

- To obtain **TAG** a **secondary source of energy for body tissues.**
- To get source of **Essential Fatty acids /PUFAs structural components of tissues.**
- To get source of **Fat Soluble Vitamins (Vitamin A,D,E and K)** associated with Fatty foods.
- To improve **taste of recipes.**
- To increase **palatability and satiety value.**
- **Thus daily consumption of dietary lipids** is essential
- For the **maintenance of normal , growth, health and reproduction** of human body.

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In What Amount & Form The Dietary Lipids to be Eaten?

- The **daily consumption** of dietary **Lipids by human beings varies** and depends upon:

  –**Dietary habits of an individual**

  –**Economic status of a family**

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RDA OF DIETARY LIPIDS

- **Per day quantity** of dietary Lipids **for an adult individual** is:
  - **60-80 grams** of **dietary Lipids** in his/her diet.

FORMS AND SOURCES OF DIETARY LIPIDS

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Dietary Forms Of Lipids

- **The dietary ingested Lipids contain following forms of Lipids:**
  - **Triacylglycerol** (TAG):Predominant form of dietary Lipid - **98%.**
  - **Phospholipids**
  - **Cholesterol Ester**
  - **Fat soluble Vitamins:** are soluble in Fat hence associated with fatty foods.

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- The **quality of ingested Lipids** should contain adequate amounts of **Essential Fatty Acids (PUFAs).**

- The **ideal ratio of dietary Fatty acids** in a **TAG** should be :

PUFA : MUFA : SFA

1 : 1 : 1

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Trans Fats are Detrimental To Health

- The sources of dietary Lipids **should be free from Trans Fatty acids/less than 1%.**
- Trans Fatty acids are **not readily metabolized by human body.**
- Trans Fats **increases the risk of Atherosclerosis.**

Dietary Rich Sources Of Lipids

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- The dietary **rich sources of Lipids**

- Obtained from foods **of Plant and Animal origin.**

Sources Of Plant Lipids

- **Plant Oils:** Peanut ,Safflower ,Sunflower, Olive, Mustard Oils, Margarine etc.

- **Nuts:** Peanuts , Walnuts , Cashew ,Almonds, Sesame ,Pine etc

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Sources Of Animal Lipids

–Milk
–Ghee, Butter , Cheese
–Egg Yolk
–Fish
–Animal-Fat ,Meat , Liver and Brain

Characteristics Of Food Fat Sources

Visible Fat

- Butter, Margarine, Salad oils and dressing, Shortening Fat Meat

Invisible Fat

- Cheese, Cream portion of homogenized milk, Egg yolk, Nuts, Seeds, Olives.

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Digestion Of Dietary Lipids In GIT

Digestion Of Dietary Lipids
Is
Cleavage Of Ester Bonds
Present In Various Lipid Forms
By
Lipases/Lipolytic Enzymes

In
Different Parts Of GIT

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Insignificant Digestion Of Dietary Lipids Occurs in Mouth and Stomach

- Though the **Salivary juice contains Lingual Lipase** and **Gastric juice contains Gastric Lipase** .
- The digestion of dietary Lipids in **mouth and stomach is negligible.**

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Insignificant Digestion Of Lipids In Mouth and Stomach Due to:

- **No optimal pH** in juices **for optimal activity** of **Enzyme Lipases** to act on dietary Lipids of Mouth and Stomach

- **No Emulsification Process in Mouth and GIT**

- As non polar **Lipid droplets** are **insoluble in the juices**.
- **Dietary Lipids do not have contact with polar and soluble Enzymes present in the aqueous phase of salivary and gastric juices**.

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- Since there is **no contact** of dietary insoluble forms of **Lipids** and soluble forms of **Enzymes.**
- **There is no cleaving of the Ester bonds** of Lipid structures in the **salivary and gastric juices** for digestion of Lipids in **mouth and stomach**.

Significant and Complete Digestion Of Dietary Lipids Occurs In Small Intestine After Emulsification

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What Is Emulsification?

Emulsification is an Essential Prerequisite Physicochemical Process in Small intestine

To Initiate and Complete Significant Digestion of Dietary Lipids

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- **Emulsification** is a Physicochemical process
- Which **forms Emulsions** from the dietary ingested Lipids.

- Emulsification takes place in the **lumen of small intestine**.

- This is **very essential** process to **occur before the digestion** of dietary Lipids.

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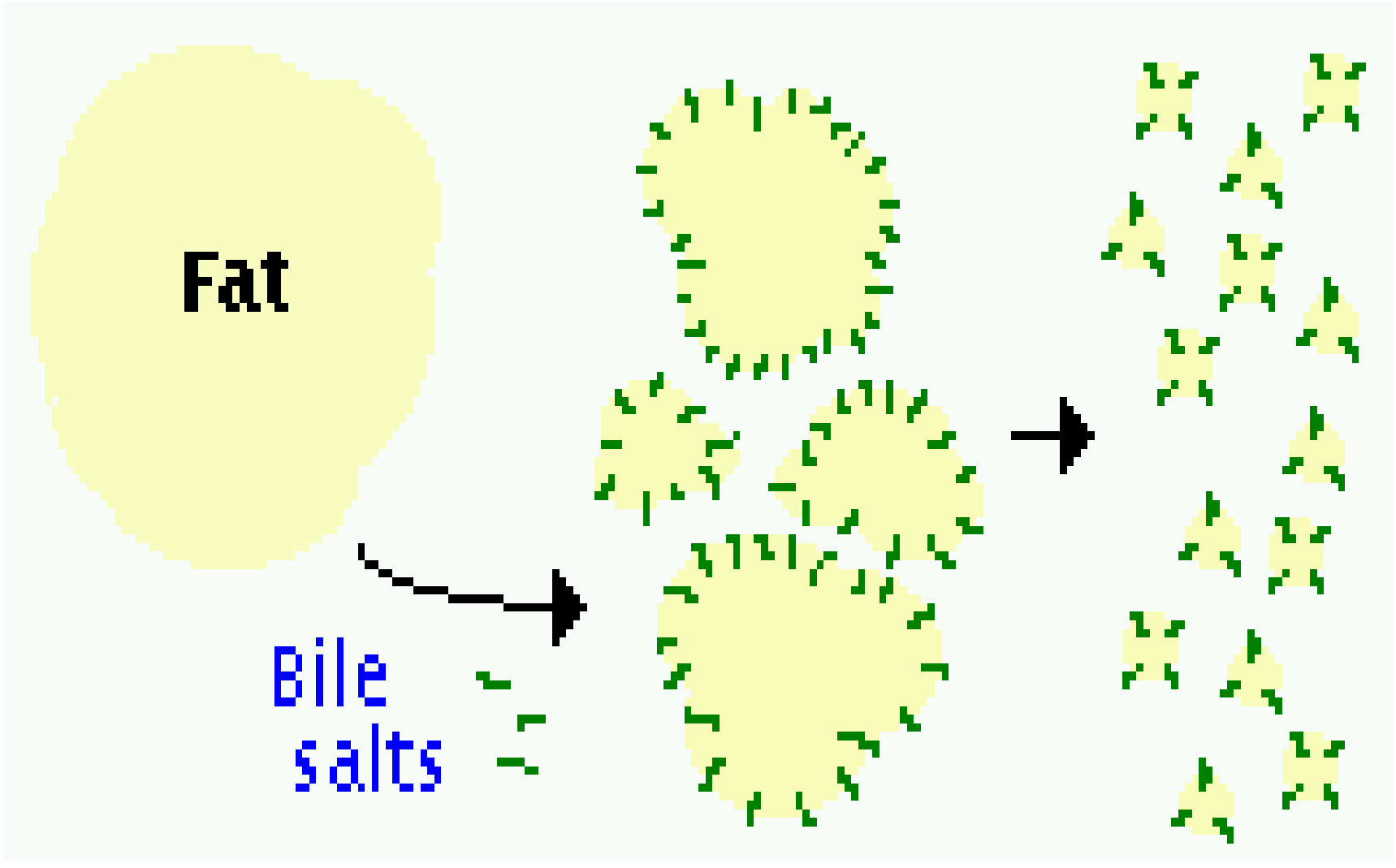
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Requirements Of Emulsification To Form Emulsions

- Emulsification takes place to form Emulsions with the help of **Emulsifying agents:**
  - **Emulsifying Agents/Surfactants:**
    - **Bile Salts** (Sodium Glycocholate, Sodium Taurocholate)
    - **Amphipathic Lipids** (present in diet)
  - **Mechanical force :**
    - Provided by **peristaltic movement of intestine.**

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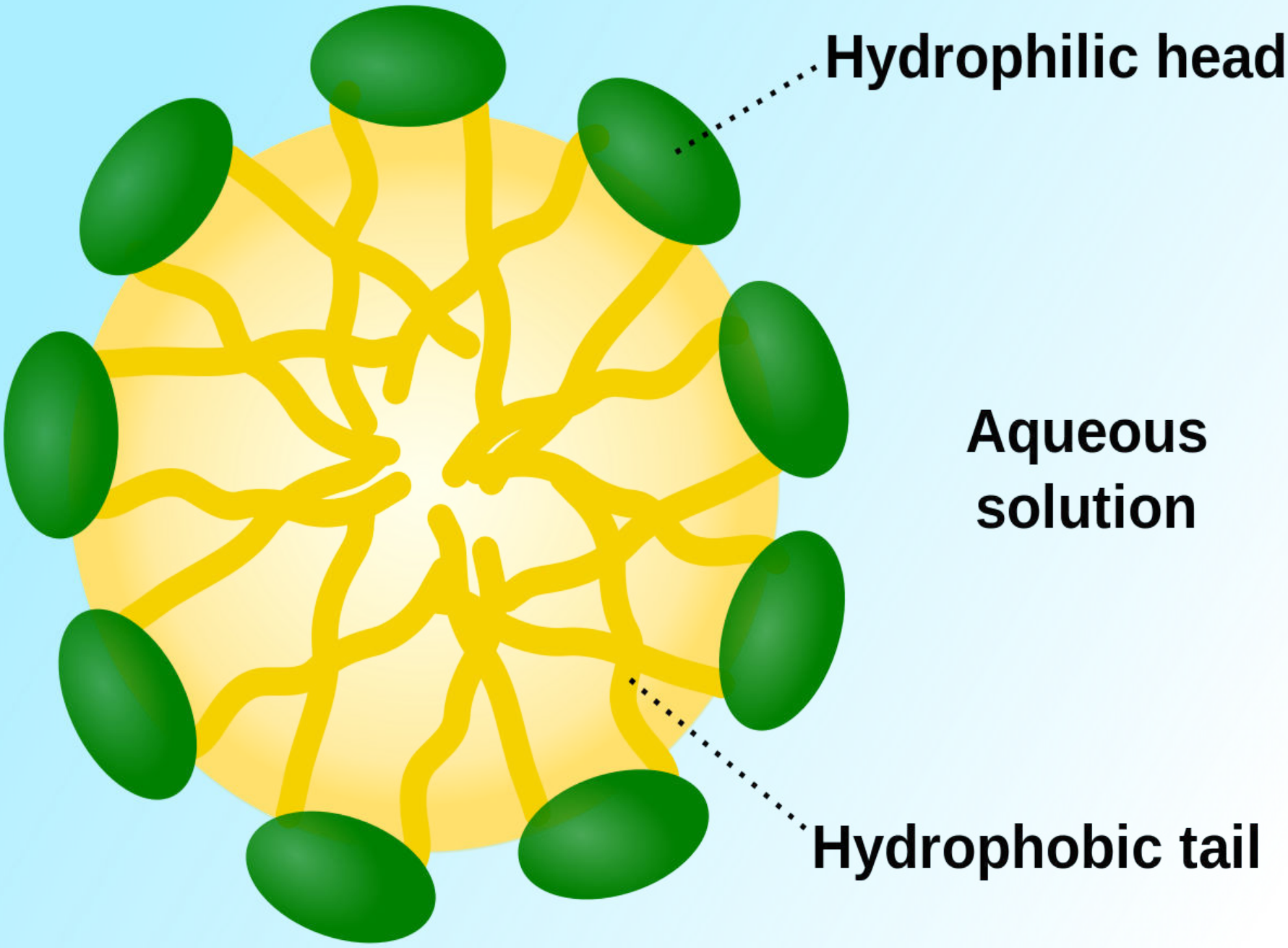
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- During the process of Emulsification there is **dispersion of large droplets** of **Fats/Oils**
- Into **small, miscible droplets** which are termed as **Emulsions.**

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- **Emulsions** have non polar lipids (TAG) in center
- Covered with a **peripheral layer of Bile salts** and **Amphipathic Lipids.**

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Requirement Of Bile In Small Intestine For Lipid Digestion and Absorption

- **Bile** is a **greenish fluid produced in Liver.**
- It is **concentrated and is stored in Gall bladder**.
- Carried through bile duct
- Later **secreted in Small intestine**

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- **Cholecystokinin** (CCK) and **Secretin**
- Stimulates the: Gallbladder to contract and release bile.

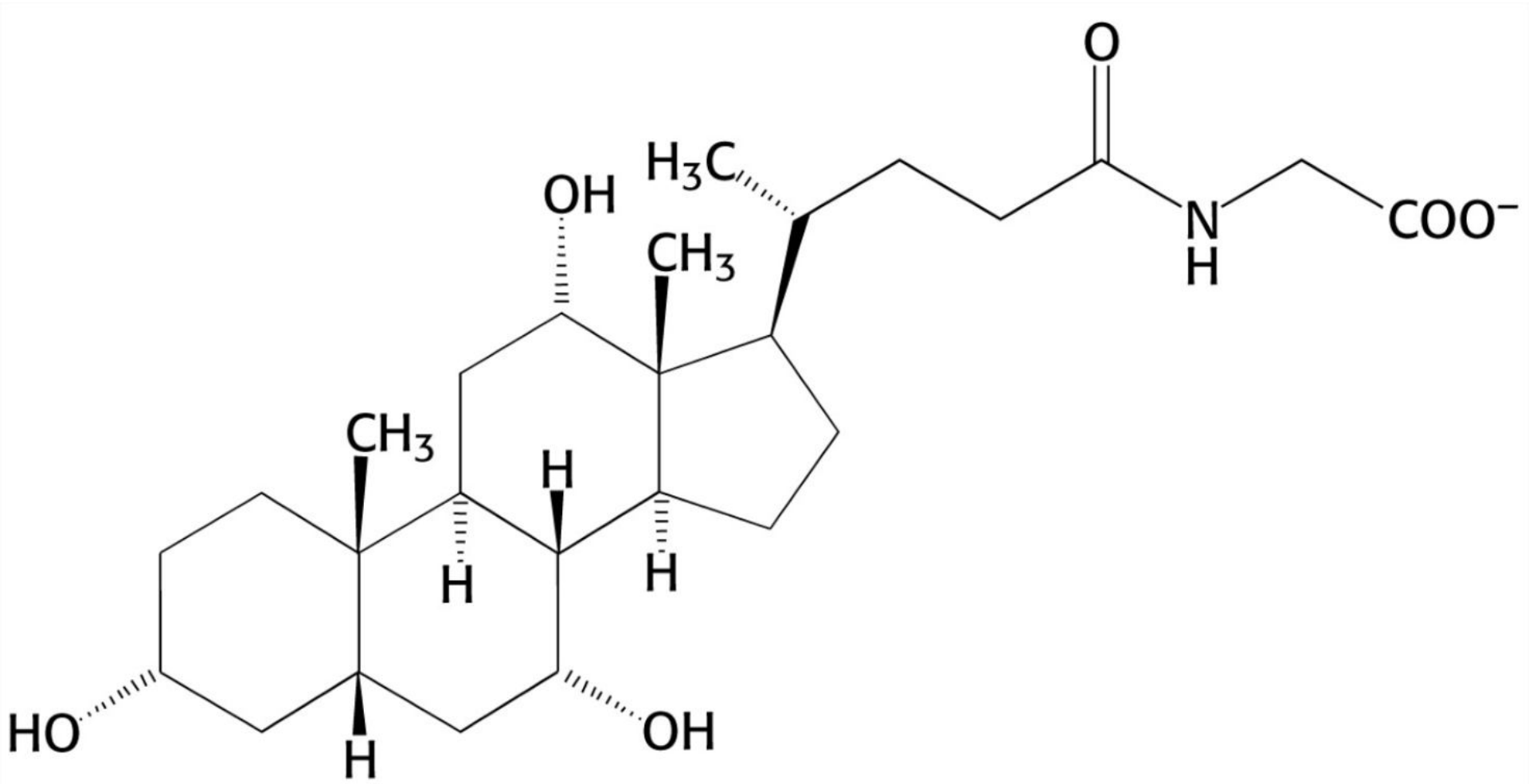
Composition Of Bile

- Bile is an **Alkaline solution** composed of:
  - **Bile Salts (Surfactant)**
  - Bilirubin (Bile Pigment)
  - Cholesterol
  - Lecithin
  - Bile acids

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Bile Acid



Glycocholate

Role Of Bile Salts In Emulsification

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- **Name Of Bile salts :**

–Sodium Glycocholate

–Sodium Taurocholate

– Bile salts present in the bile **have detergent like action**

– **Bile salts are emulsifying agents**

- They are **responsible for fat Emulsification**

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- **Bile salts** present in Bile and dietary Amphipathic Lipids by their **detergent like action:**
  - **Reduces surface tension**
  - **Increases surface area** of Fats/Oil and made them miscible with aqueous phase.

- **Emulsions bring non polar dietary Lipids in close contact with Lipid digesting Enzymes** present in aqueous phase of intestinal juices.

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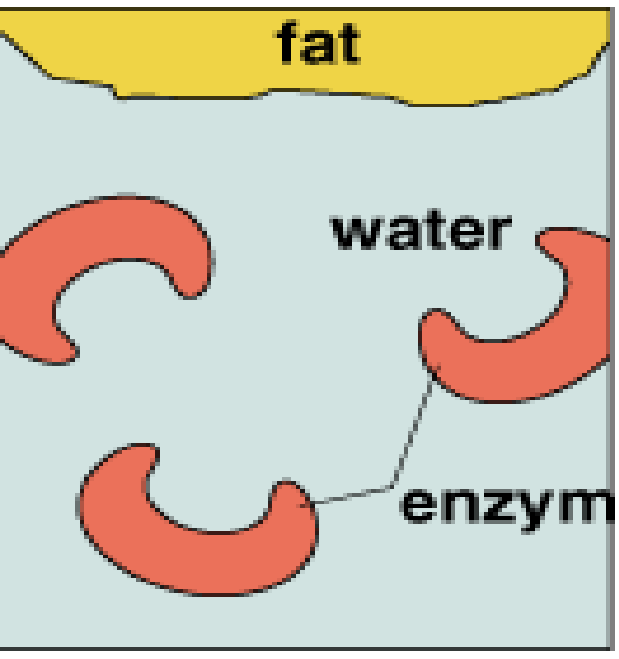
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Significance Of Emulsification

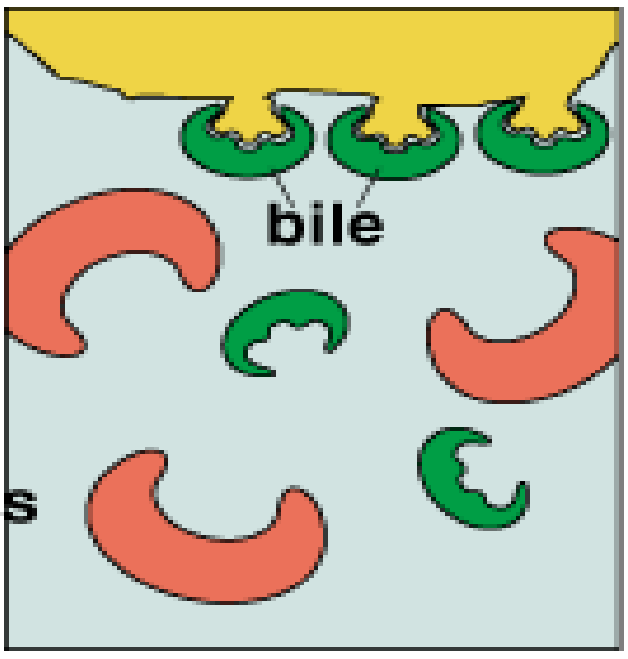
- Emulsification **facilitate in the digestion of dietary ingested Lipids** in small intestine by:
  - **Reduces surface tension, increasing surface area** of Lipids
  - Forms **Emulsions**
  - **Improves the miscibility** of non polar Lipids TAG in aqueous phase.
  - **Brings contact** of dietary Lipids with Lipid digesting enzymes.
  - **Facilitates cleavage** of **Ester bonds** of dietary Lipids.

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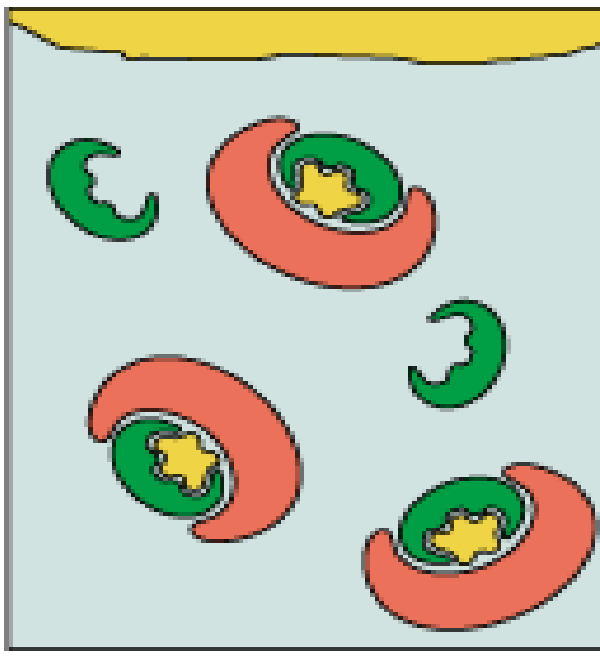
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Fat and water tend to separate. Enzymes are in the water and can't get at the fat.

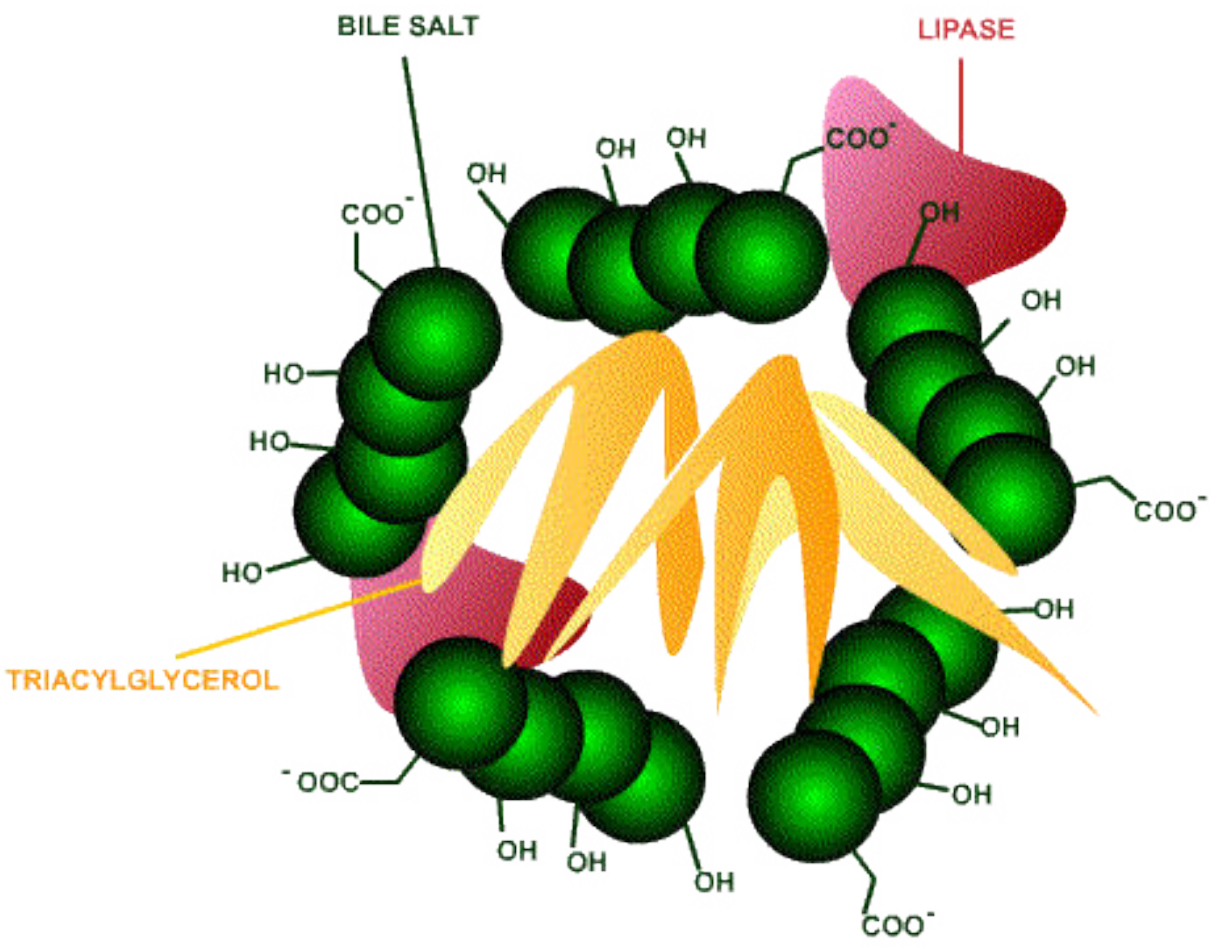


Bile (an emulsifier) arrives. Bile has an affinity for both fat and water and can therefore bring the fat into the water.



After emulsification, the fat is mixed in the water solution, so fat-digesting enzymes have access to it.

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Emulsions formed by Bile salts, Triacylglycerols and pancreatic lipase.

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Action Of Specific Lipid Digesting Enzymes (Lipases) in Small Intestine

- Dietary forms of Lipids are digested:
  - –By the action of **specific Lipid digesting enzymes**
  - –Present in **Pancreatic and intestinal juice**

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- Digestion of Lipids is **cleavage of Ester bonds** present in their structures.

Digestion Of Triacylglycerol (TAG) By Enzyme Pancreatic Lipase

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- **Dietary** Fat/Oil which is chemically **TAG** is the **predominant ingested Lipid form.**
- **TAG** is predominantly and **significantly digested in small intestine**
- After the process of Emulsification.

Action Of Pancreatic Lipase

- Digestion of Triacylglycerol is **cleaving** of **ester bonds** present in its structure.
- Triacylglycerol in small intestine is specifically acted upon by enzyme **Pancreatic Lipase.**

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Colipase Facilitates Pancreatic Lipase Activity

- **Pancreatic Colipase**

–Is activated by Trypsin

–Colipase interacts with Triacylglycerol and Pancreatic Lipase

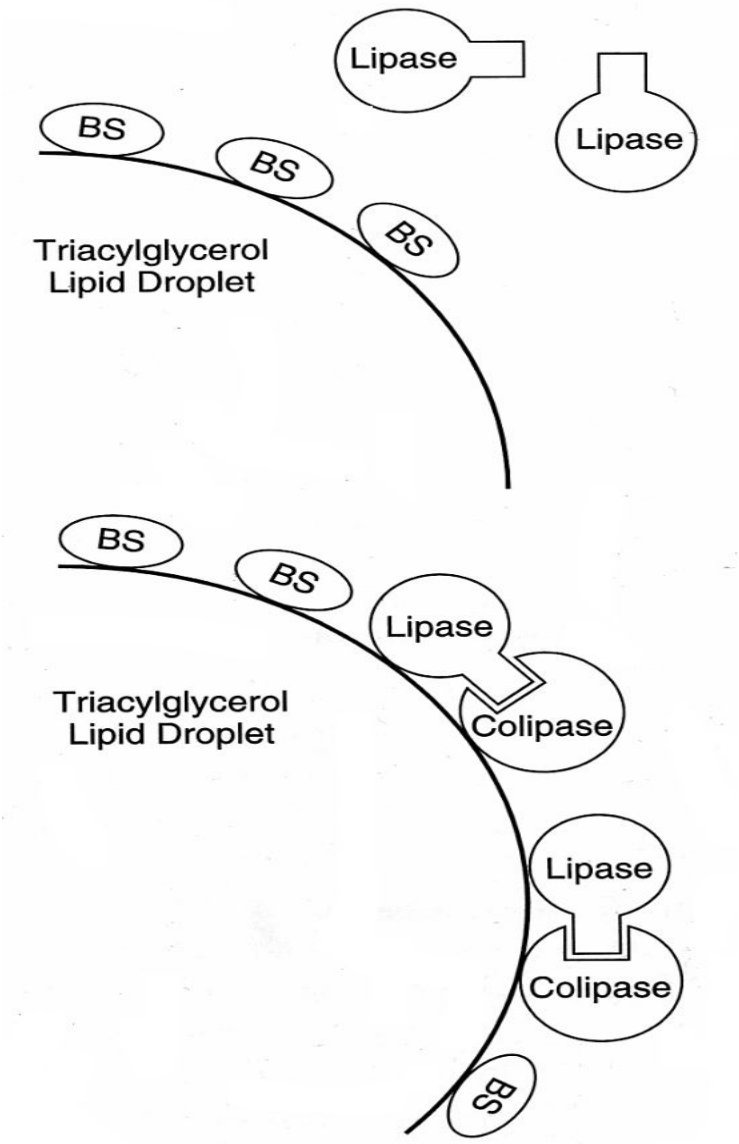
- Displaces Bile to allow recycling
- Improves activity of Pancreatic Lipase

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Role Of Pancreatic Colipase

- Secreted from Pancreas as **Procolipase**
  - Activated (cleaved) by Trypsin
- **Colipase anchors Lipase to the Emulsion.**
  - One Colipase to one Lipase (i.e., 1:1 ratio)

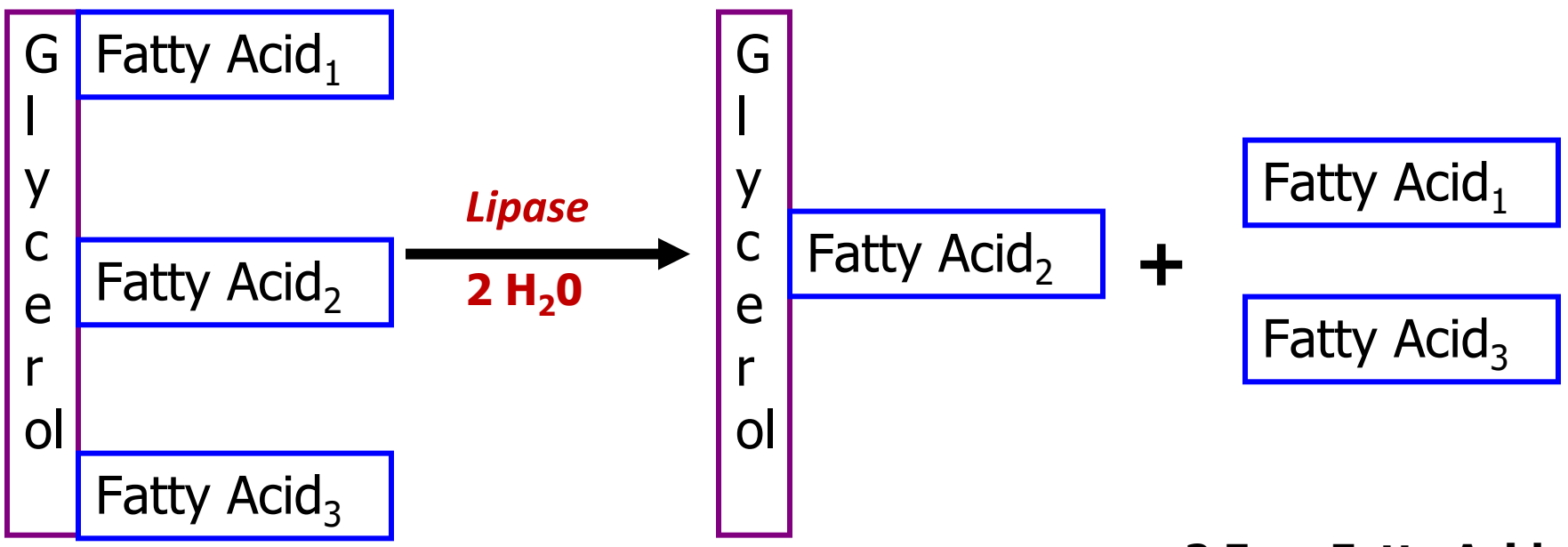


- **Pancreatic Lipase** digest TAG
- By specifically cleaving **first** and **third ester bonds** of **TAG** structure.

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- **Pancreatic Lipase attack TAG at 1 and 3 positions of Ester bonds.**

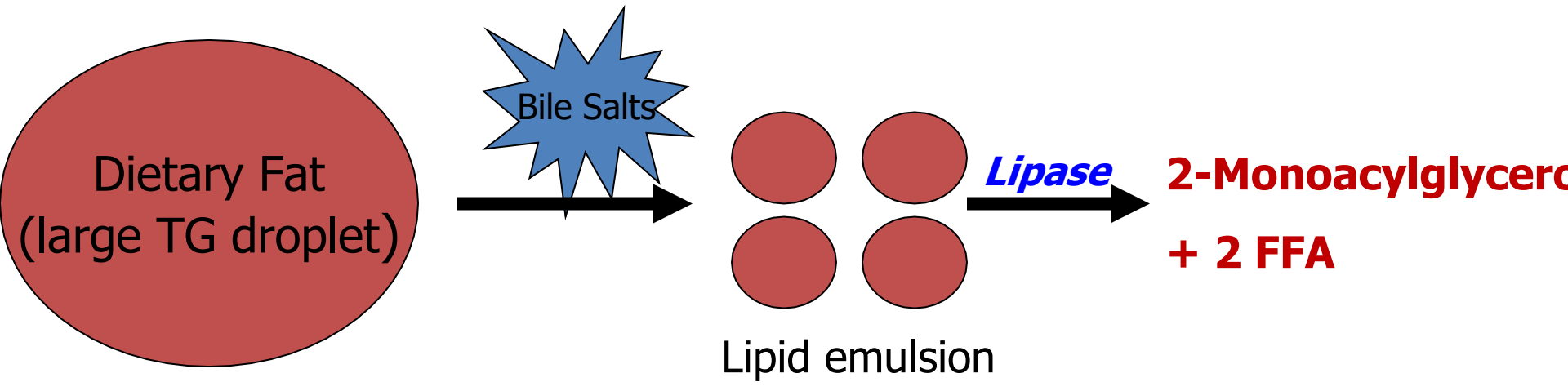


Triacylglycerol **2-Monoacylglycerol** **2 Free Fatty Acids**

- The **products of TAG digestion**
- By **Pancreatic Lipase** activity are:
  - **Free Fatty acids**
  - **Monoacylglycerol** (2MAG)

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Triacylglycerol

Colipase

Optimum PH 6

Pancreatic Lipase

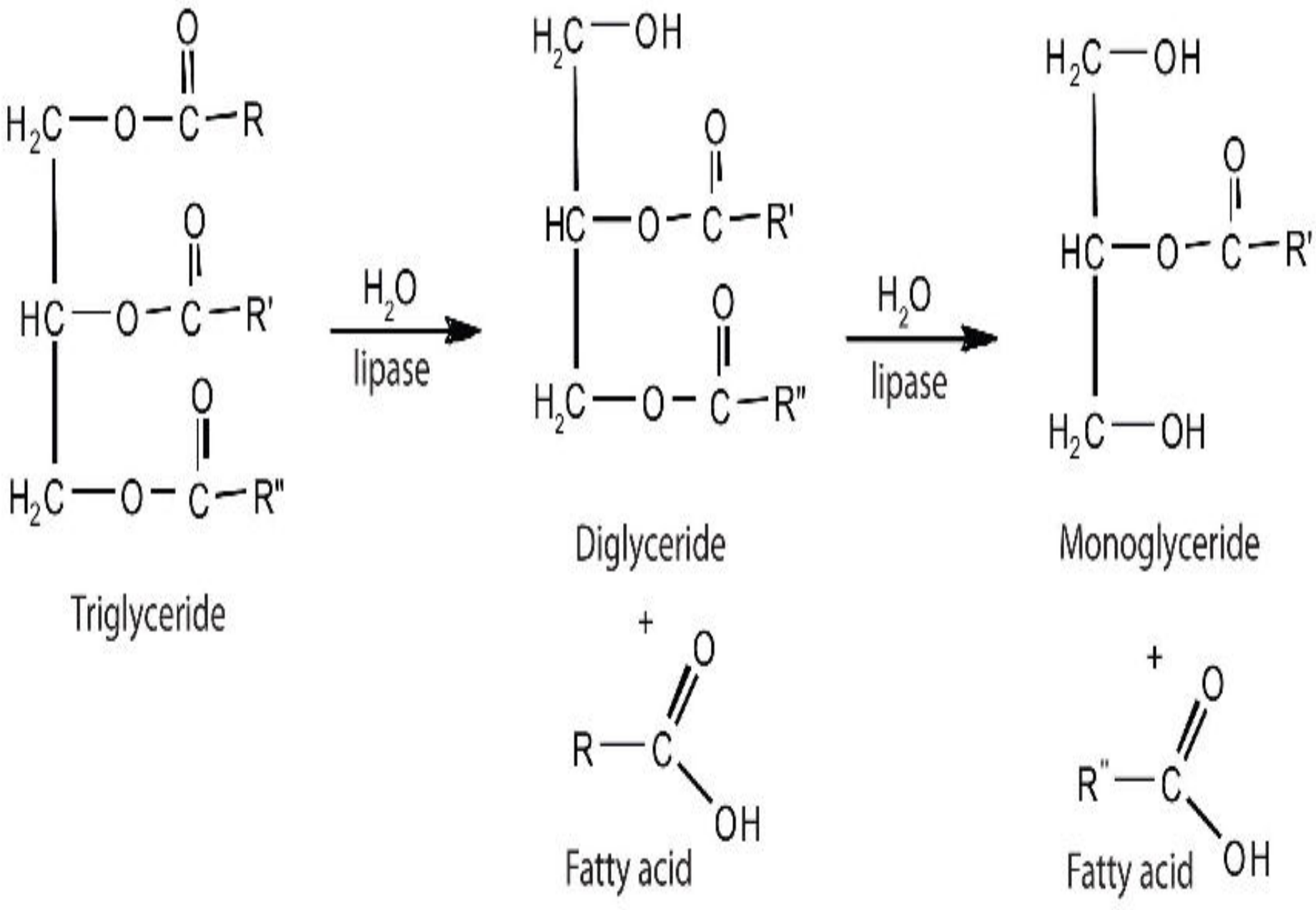
Cleaves 1st and 3 rd ester bond of TAG

Free Fatty acids + 2-Monoacylglycerol

(Fatty acid esterified at C2 of Glycerol)

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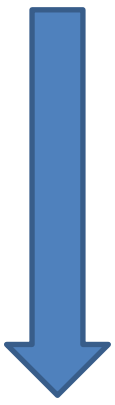
Action of Non Specific Lipid Esterases

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- **Non specific Lipid Esterases** act on **2-MAG /Retinol Ester**.
- It cleaves the ester bonds and releases **Free Fatty acid** and **Glycerol/Retinol** respectively.

2-Monoacylglycerol



Non Specific Esterase

Cleaves Ester bond at C2

Free Fatty acid + Glycerol

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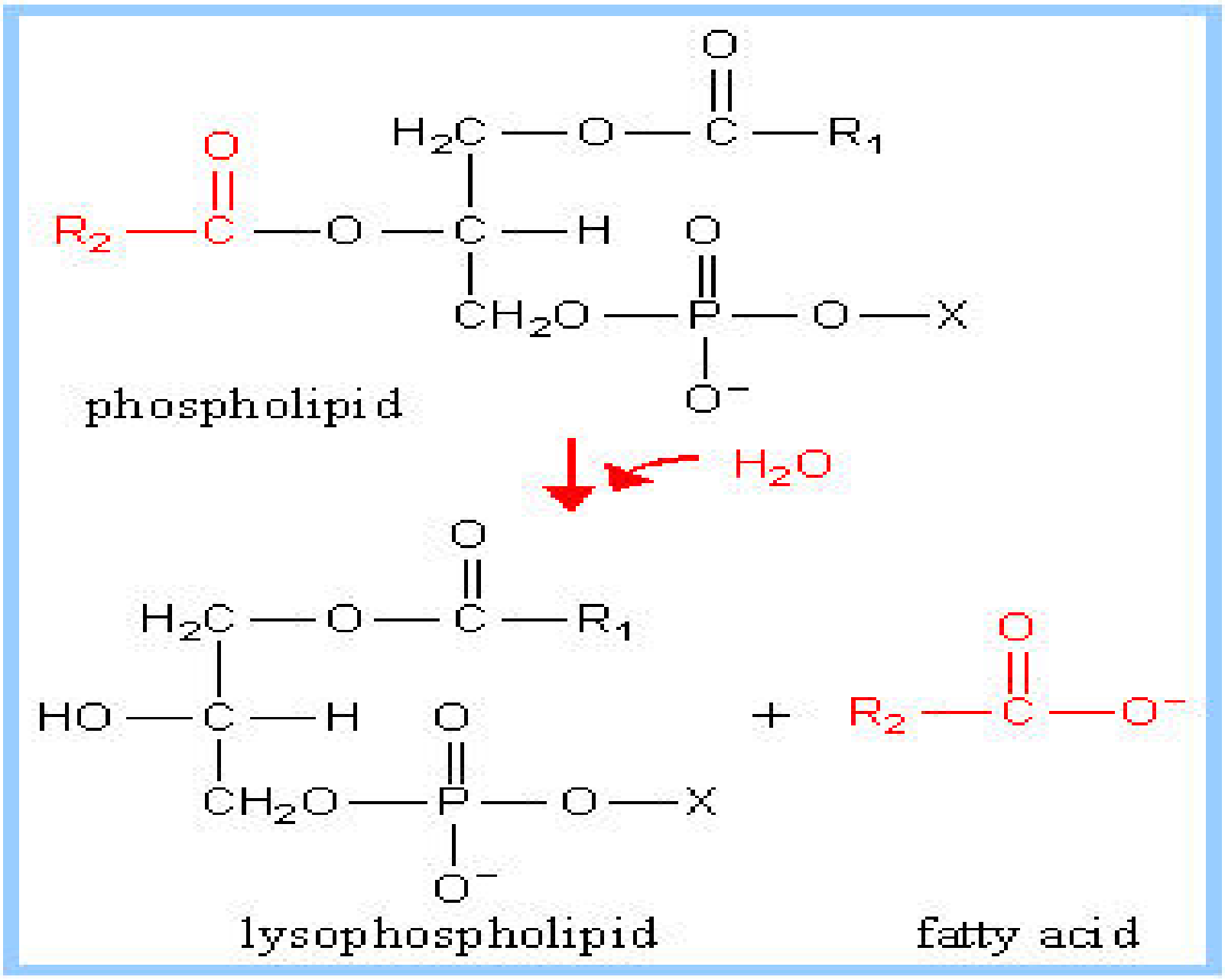
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Digestion Of Phospholipids by Action of Phospholipase A2 and Lysophospholipase

- The pancreatic juice enzymes **Phospholipase A2** and **Lysophospholipase** digests dietary Phospholipids.

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Phospholipid

↓

Phospholipase A2

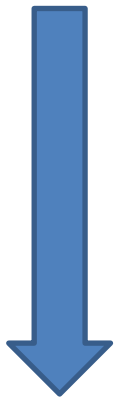
Cleaves Ester bond at C2 of PL

Lysophospholipid+ Free Fatty acid

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Lysophospholipid



Lysophospholipase

Cleaves Ester bond at C1

Glycerophosphorylcholine+ Free Fatty acid

- **Phospholipase A2** cleaves **second** position **ester bond** of Phospholipid and form **Lysophospholipid** and Free Fatty acid.
- Lysophospholipid is then acted by **Lysophospholipase** which **cleaves ester bond at C1** to generate: **Glycerophosphorylcholine and Free Fatty acids.**

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Digestion Of Cholesterol Ester By Cholesterol Esterase

Cholesterol Ester



Cholesterol Esterase

Cleaves Ester bond at C3

Free Cholesterol+ Free Fatty acid

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End Products Of Lipid Digestion

- **5 Simple Forms as End products of Lipid Digestion**

1. **Free Fatty acids**
2. **Glycerol**
3. **2-Monoacylglycerol (2-MAG)**
4. **Glycerophosphoryl-Choline**
5. **Free Cholesterol**

Absorption of Dietary End Products Of Lipid Digestion

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- **Absorption** of end products of Lipid digestion takes place in **small intestine.**

- The **rate of absorption** of different types of **Lipids differ**.
  - **Pork fat is almost absorbed completely.**
  - **Castor oil is not at all absorbed.**

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Theories Of Lipid Absorption

- Absorption of Lipids is a complex mechanism and various theories are proposed to explain its mechanism.
  - **Lipolytic Theory**
  - **Partition Theory**
  - **Bergstorm Theory (Most Recent and accepted one)**

- The simple forms of Lipids as digestive end products are ready for absorption.

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Mechanism Of Lipid Absorption

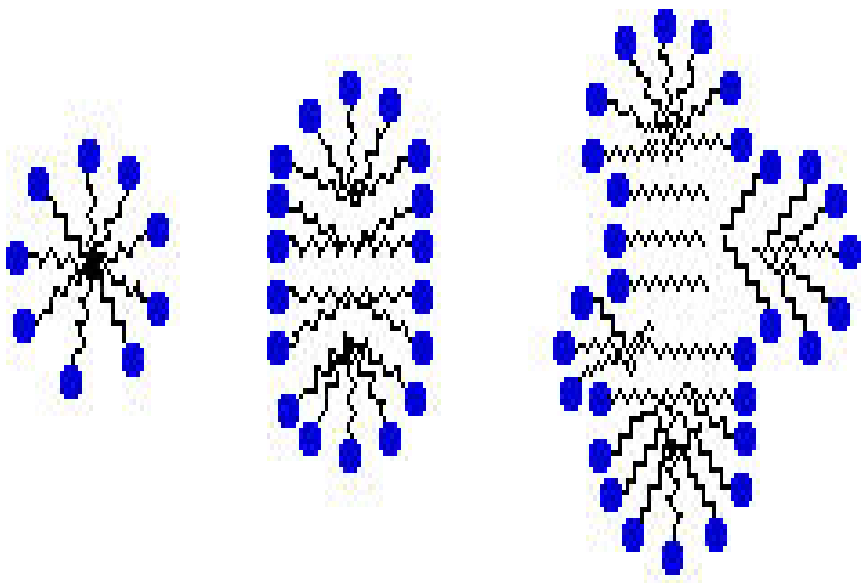
- **Bile Salts play an important role in absorption** of digestive end products of dietary Lipids.

- **Bile salts help in formation** of **Mixed micelles**.

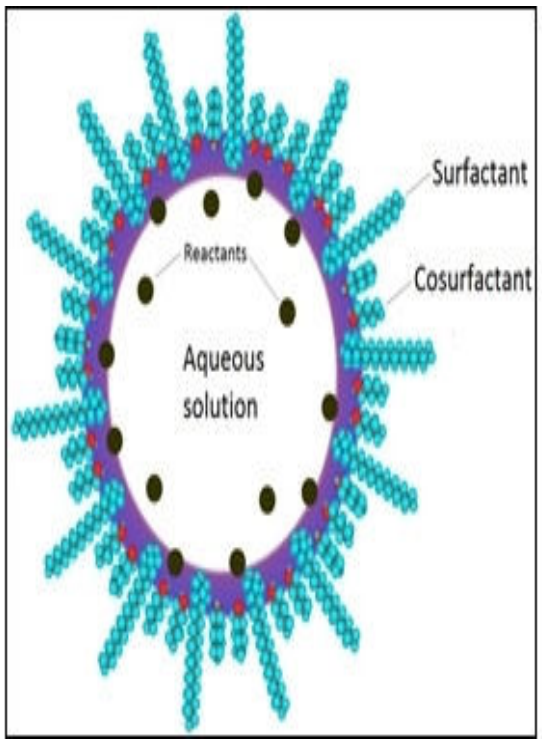
- **Mixed Micelle** is a aggregation of **digestive end products** of **dietary Lipids** with a **peripheral layer of Bile Salts**.

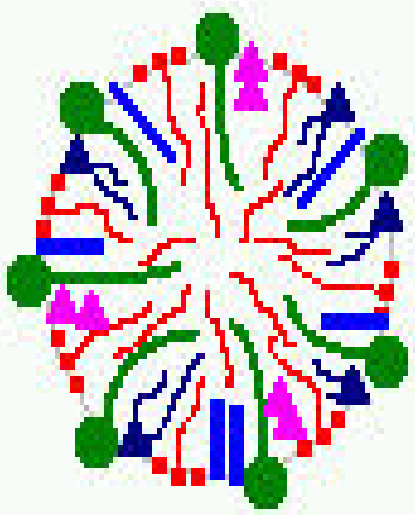
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micelle assemblies of amphiphiles





Bile salts
Monoglyceride
Fatty acids
Phospholipids
Cholesterol

- The **efficiency of Lipid absorption depends** upon:
  - –The **quantity of Bile salts**
  - –Which **solubilizes and form Mixed Micelles**.

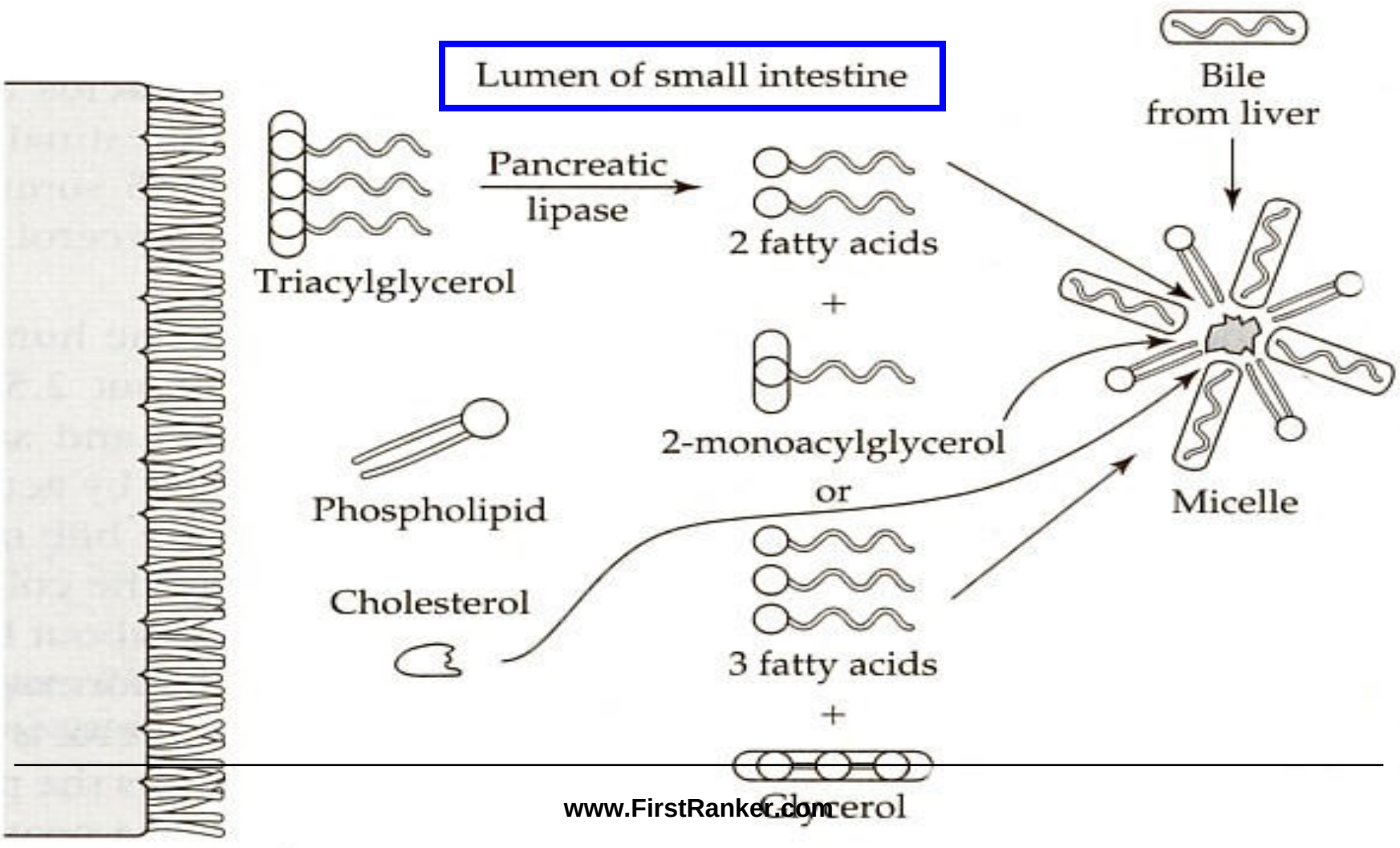
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Mixed Micelle Formation

- **Mixed Micelle** is a **complex of Lipid materials and Bile salts** soluble in water
  - It contains Bile salts, end products of Phospholipids & Cholesterol at **periphery** of a **Mixed Micelles.**
  - 2-Monoacylglycerol, Free fatty acids and fat-soluble Vitamins in **center** of **Mixed Micelles.**

Mixed Micelle Formation



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- In the Mixed Micelle the **non polar long chain fatty acids are at the center**
- At the **periphery** are **Amphipathic Lipid moieties and Bile salts.**

- **Bile salts and Amphipathic Lipids** of Mixed Micelle
- **Exert a solubilizing effect on non polar Lipid** moieties and **help in their absorption.**

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- **Mixed Micelles** then **get attached to the intestinal mucosal cell membrane.**

- This help the **Lipid end products to slowly cross the mucosal membrane.**

- **Bile salts** of Mixed Micelles **do not cross the intestinal mucosal cell membrane.**

- They get **retained in intestinal lumen** and **later get recycled.**

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- The Bile salts are **reabsorbed further down the Gastrointestinal** tract (in the ileum)

- Bile salts are **transported back to the Liver through enterohepatic circulation**
- Finally recycled and secreted back into the digestive tract

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Re-Esterification of Simple Lipids
OR
Resynthesis Of Complex Forms Of Lipids
In Intestinal Mucosal Cells

- Once the simpler forms of Lipids enter the intestinal mucosal cells
- They are resynthesized into complex forms of Lipids in the intestinal mucosal cells.

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- Free Fatty acid (FFA) + Glycerol → Monoacylglycerol
- MAG +FFA → Diacylglycerol
- Diacylglycerol + FFA → Triacylglycerol
- Glycerophosphorylcholine + FFAs → Phospholipid
- Cholesterol +FFA → Cholesterol Ester

- Note the **resynthesized complex Lipids** in intestinal mucosal cells
- Are **usually different from** those ingested through diet.

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- The **dietary absorbed Lipids** in intestinal mucosal cells are then **mobilized out as Lipoproteins**.

Formation Of Lipoprotein Chylomicrons

In Intestinal Mucosal Cells For The Transportation Of Dietary Lipids

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- The Lipids of dietary origin present in intestinal mucosal cells are mostly **non polar** (TAG) and **hydrophobic** in nature.

- The **transport** of these dietary Lipids through aqueous phase of lymph and blood is
- **Facilitated through** formation of a **Lipoprotein -Chylomicron** in intestinal mucosal cells.

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- **Lipoprotein Chylomicron** is formed in intestinal mucosal cells by
- Aggregation of **dietary ingested, digested and absorbed Lipids** and **Apoprotein (ApoB48).**

- **Chylomicron** structure has the **non polar Lipids aggregated at center**, the **Amphipathic Lipids and Apoproteins are at periphery.**

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- Chylomicron has 98% of TAG (dietary origin)
- 1% other Lipids and
- 1% Proteins.

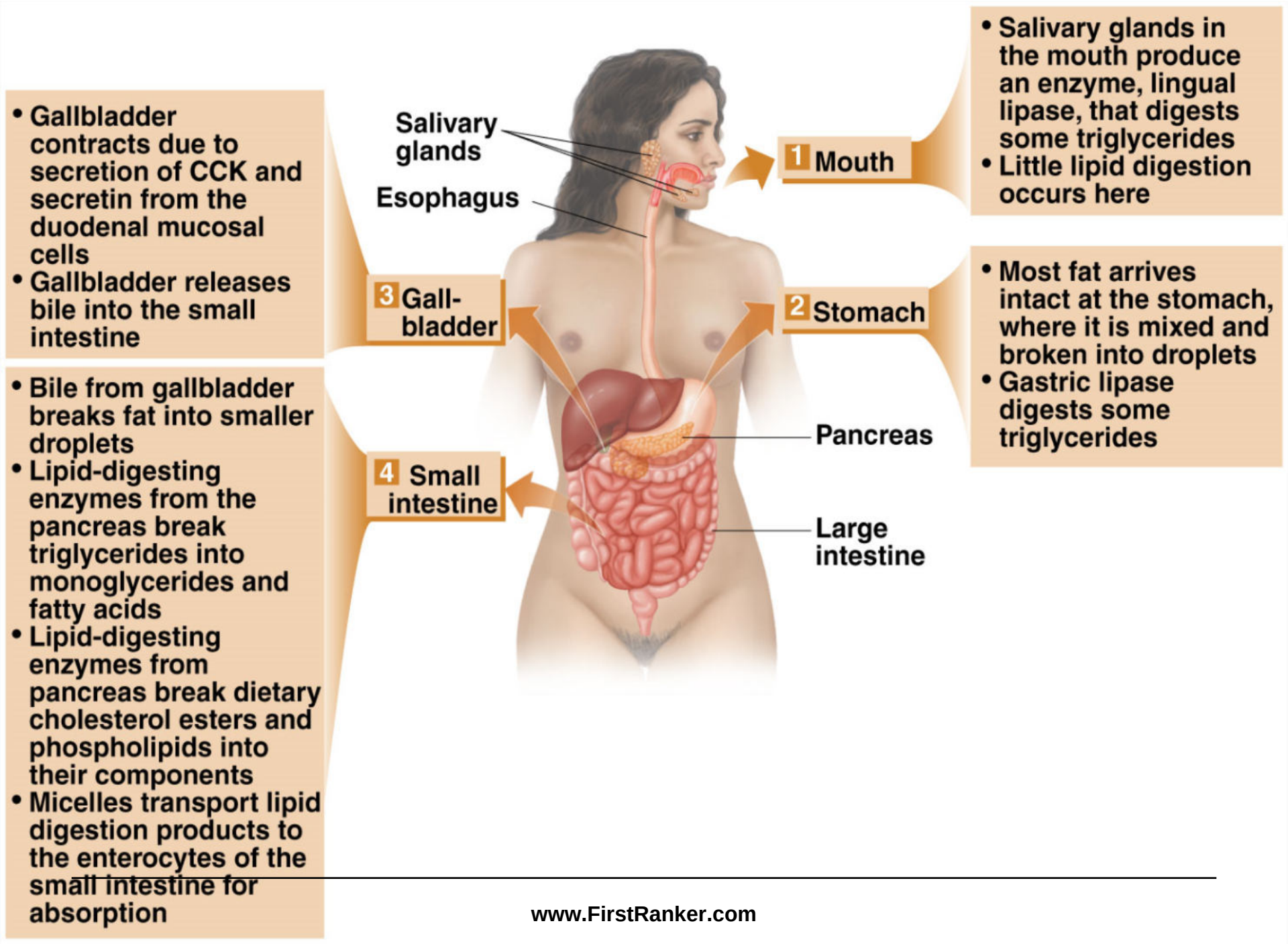
- Chylomicrons from intestinal mucosal cells are **first released in Lacteals (Lymph vessels) of Lymphatic system**
- Which then enters the **systemic blood circulation via Thoracic duct.**

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- Thus **Chylomicron serve as a vehicle for transporting** the exogenous forms of **dietary Lipids**

- **From Small intestine to Liver** via aqueous phase of **Lymph and Blood.**



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Lipid Digestion Absorption and Transport

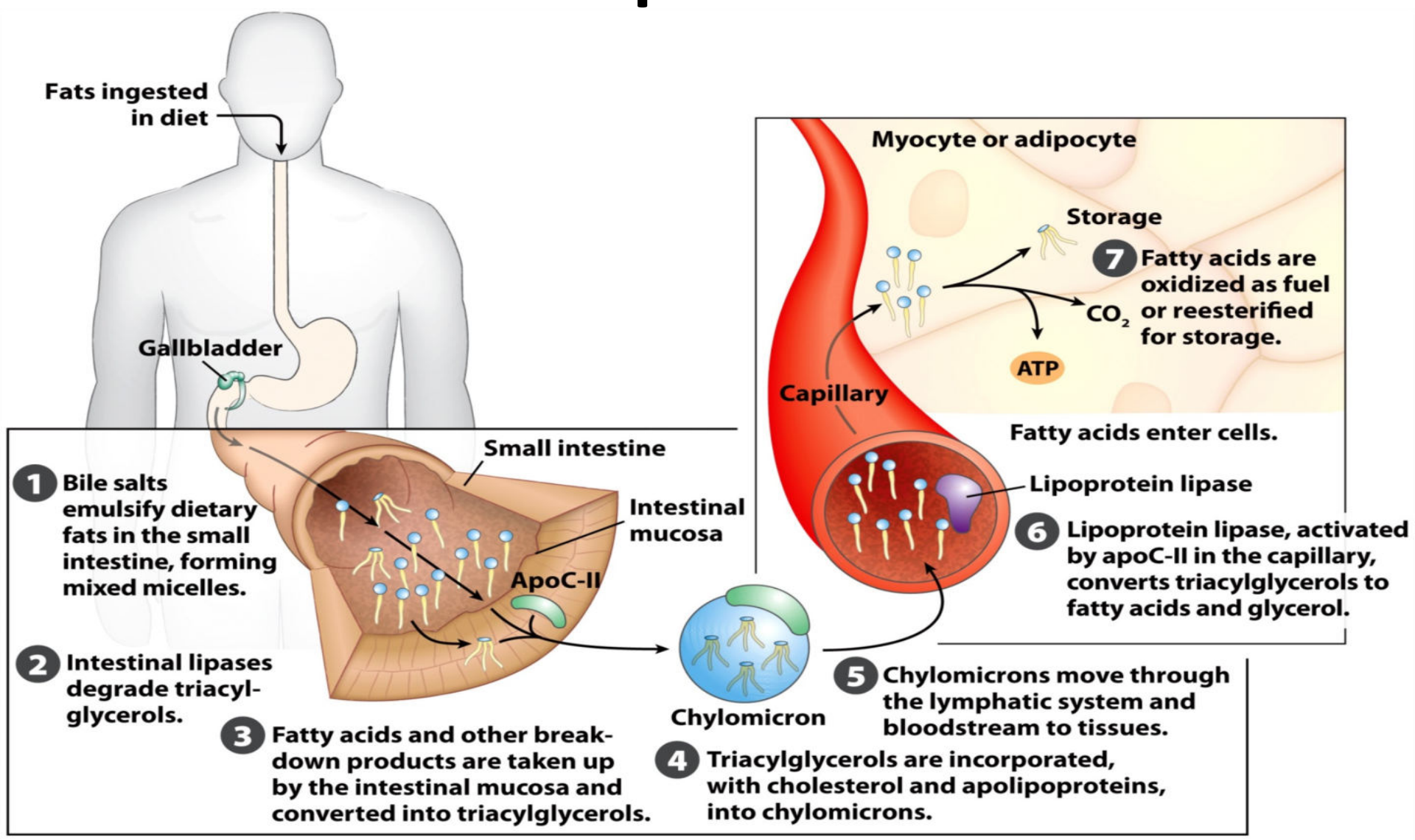
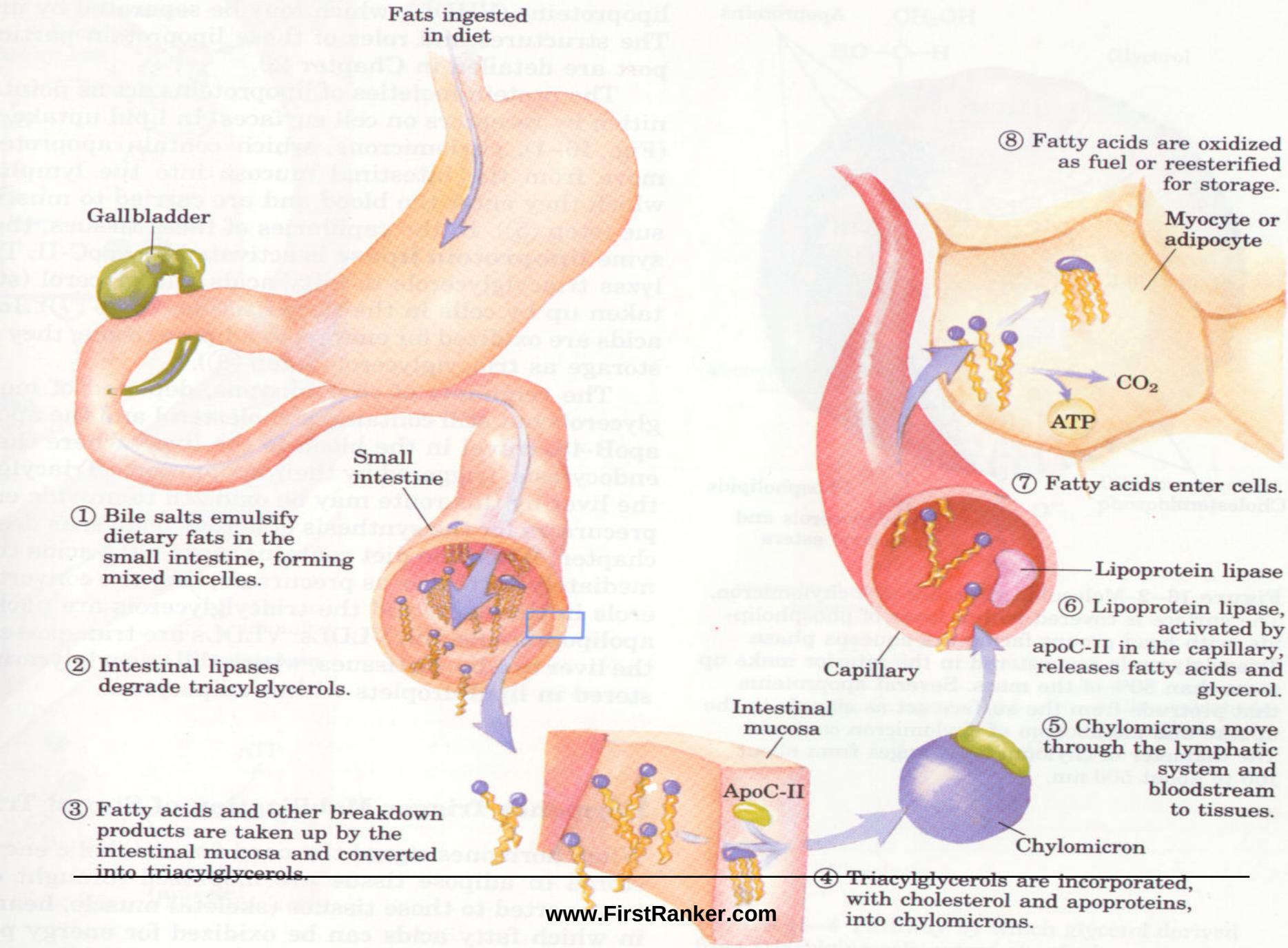


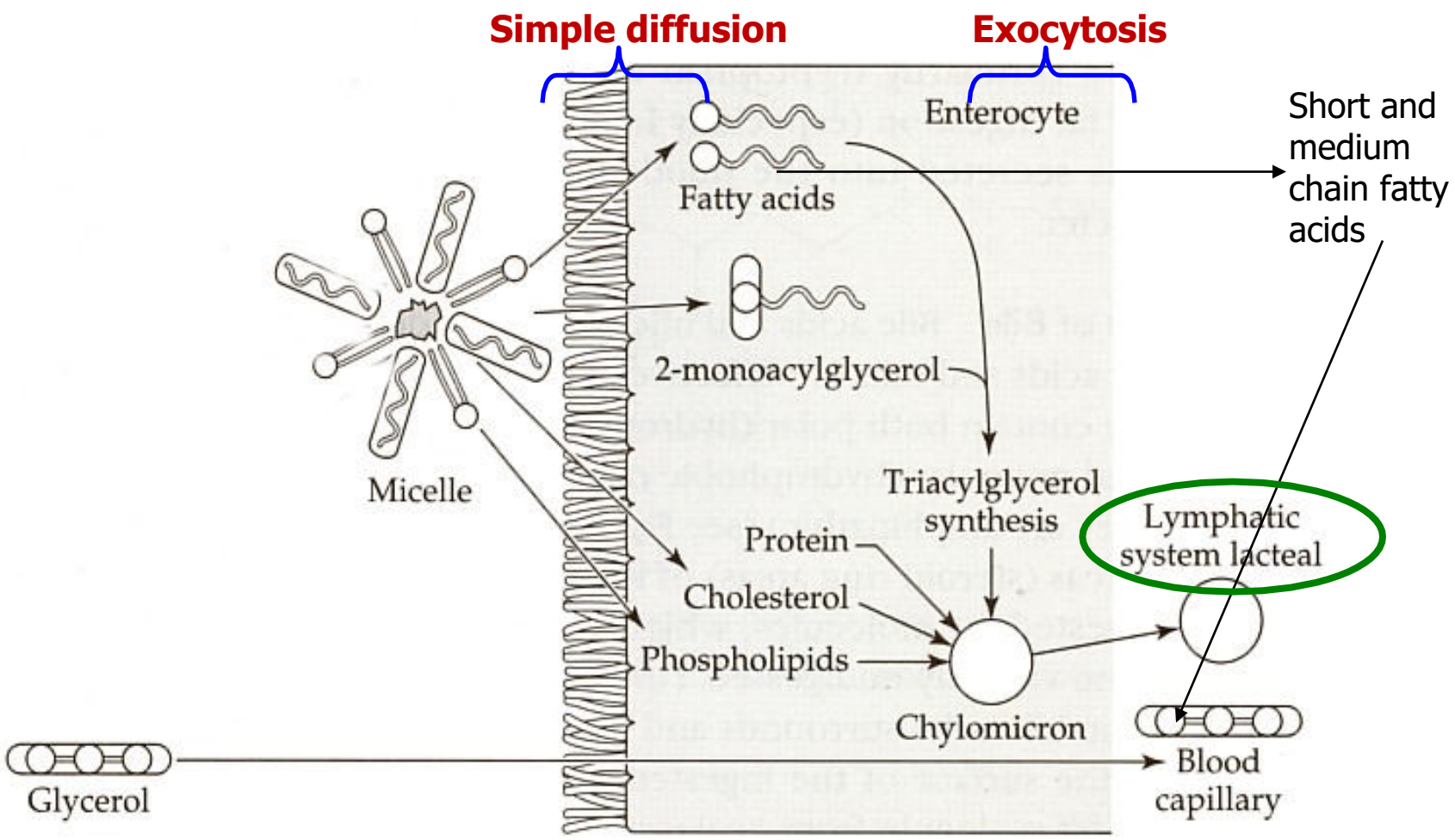
Figure 17-1

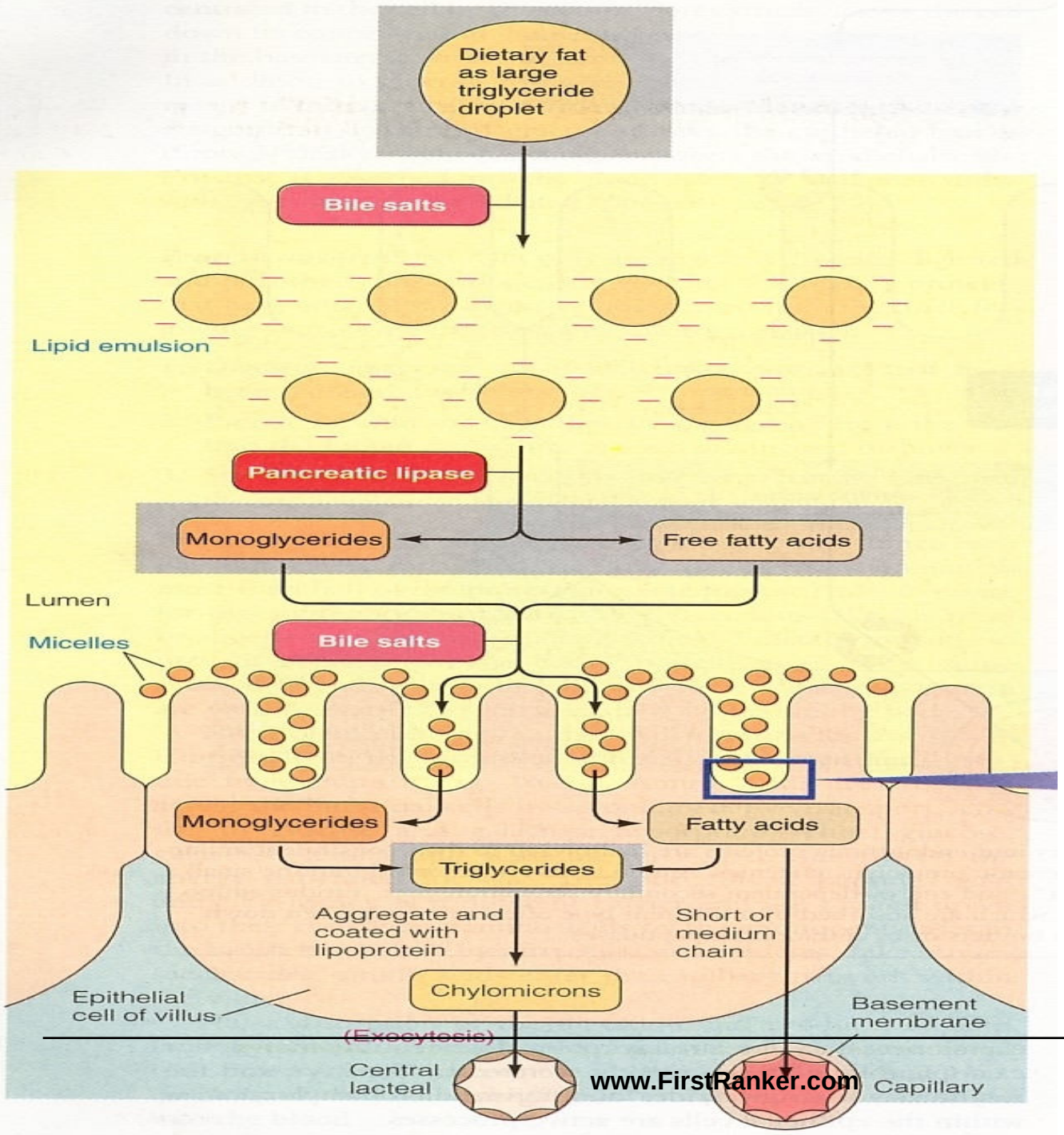


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Mechanism Of Lipid Absorption





Overview of Lipid Digestion and Absorption

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Absorption of Lipids

Absorption of fat.

Transportation Of Chylomicrons Through Blood Circulation

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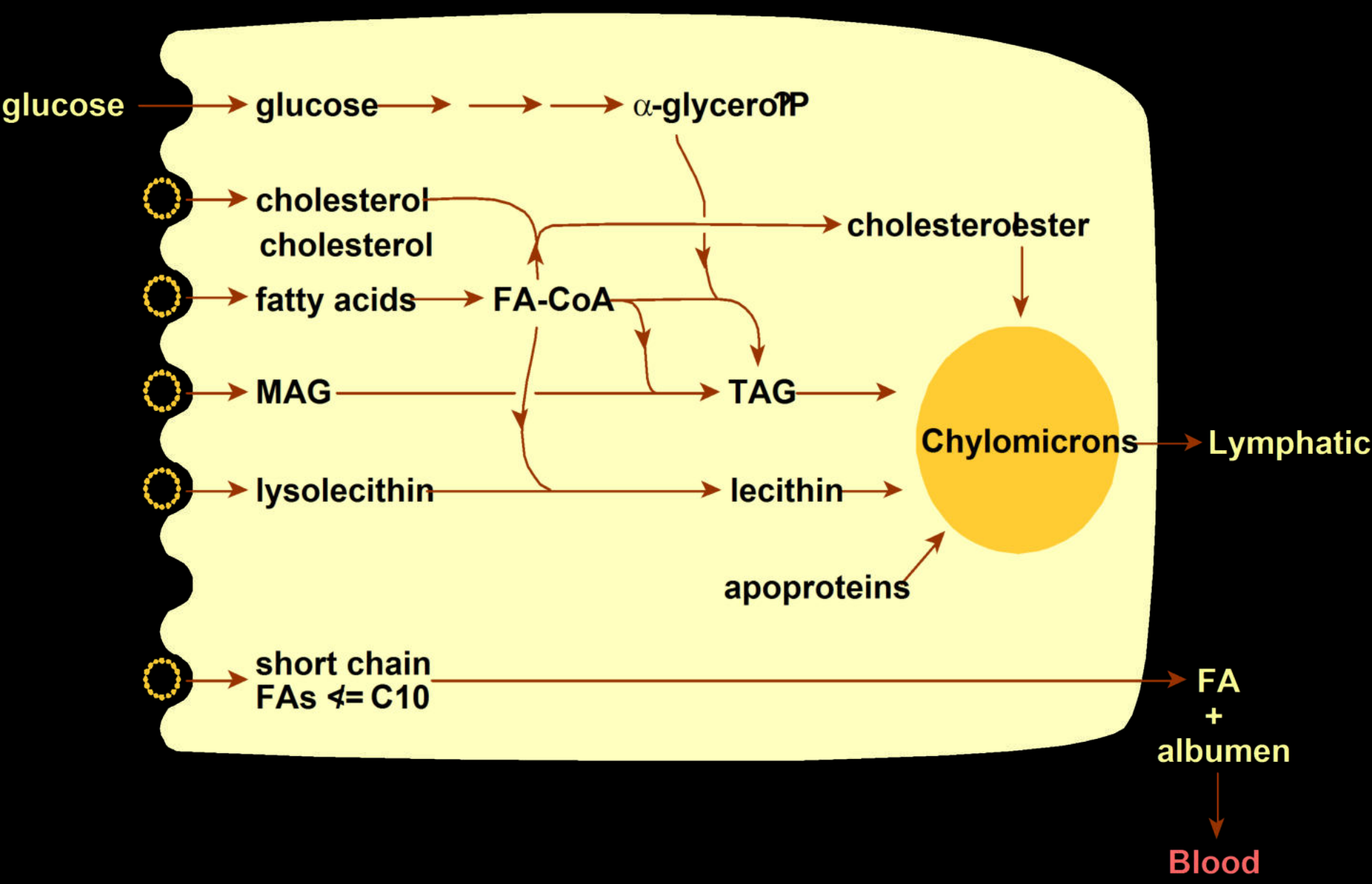
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Action OF Enzyme Lipoprotein Lipase On Lipoproteins (Chylomicrons and VLDL)

Plasma Lipid Clearance OR Role Of Clearing Factor

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- Unlike **Carbohydrates (Glucose) and Protein (Amino acids)** who **use enterohepatic circulation to reach first to Liver.**
- Most **Lipids do use systemic circulatory system.**
- This allows **Lipids to be cleared by the whole body** and **avoids overwhelming the Liver with Lipids**.

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- Most of the absorbed Lipids from GIT mucosal cells **do not** directly enter the blood stream.
- Instead, they are packaged into **Chylomicrons** and first released into the lymph.

- The lymph dumps **into the Aortic arch** (at the **Thoracic duct's** connection with the **left Sub Clavian vein**) .
- Where it then is transported through the blood stream to be **cleared and taken up by:**
  - **Adipocytes**
  - **Liver**
  - **Muscle**

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- Clearance of Lipoproteins from circulation
- Is mediated by an enzyme **Lipoprotein Lipase (LPL)** **acting upon TAG of Lipoproteins.**

- **Nascent (New) Chylomicrons** released from intestinal mucosal cells are circulated **first through lymph** and **then in systemic blood circulation**.

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- **Nascent Chylomicrons** in blood circulation **get matured**

- After the receipt of **Apo C II and ApoE from HDL.**

- **Apo C II** of Mature Chylomicron then **stimulates an enzyme Lipoprotein Lipase (LPL)**

- **LPL associated in endothelial lining of blood vessels,** of **Adipose, Heart,** and **Skeletal Muscle** tissue, as well as in **Lactating Mammary glands.**

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- Stimulated **Lipoprotein Lipase** then acts **upon the TAG** of Lipoproteins (Chylomicron and VLDL).
- Lipoprotein Lipase **hydrolyze the TAG** of Lipoproteins to **Free Fatty acids and Glycerol.**
- Released **Glycerol and Free Fatty acids enter the adjacent** Adiposecytes.

- Glycerol and FFAs entered in Adipocytes are **transformed into TAG.**
- **TAG is storage form of Fatty acids**
- **TAG** serve **as a reserve source of energy.**

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- The **LPL by its activity on Chylomicrons reduces its content of TAG.**

- The Chylomicrons after the action of LPL reaching to Liver are
- **Maximally reduced with TAG content** and now termed as **Chylomicron Remnant.**

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- The **Chylomicron remnant** in comparison to Nascent Chylomicron is
- **Smaller in size**, and has very **less percentage of dietary TAG**, associated to it.

- **Chylomicron remnants** get fixed to their **specific receptors** present on **Hepatocytes and get internalized.**
- The internalized Chylomicron remnants inside the Liver gets ~~further **metabolized.**~~

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- **Lipoprotein Lipase is also termed as Clearing Factor**

- Since Lipoprotein Lipase clears Lipaemic sera(Chylomicrons) in post absorptive phase.

LPL Activity On Chylomicrons

- In **Post absorptive phase** most of the **blood Chylomicrons** are transformed to **Chylomicron remnants**
- By the **Lipoprotein Lipase activity**,
- The released moieties from Chylomicrons are **internalized by Adiposecytes and Hepatocytes**
- This **clears the circulating Chylomicrons from blood.**

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❖ **Defect In Lipoprotein Lipase**
Do not clear blood Lipoproteins

Accumulates Chylomicrons and VLDL in blood circulation

Heparin Is a Coenzyme For Lipoprotein Lipase

- **MI patients** are administered with **Heparin injections**
- Which may **stimulate the Lipoprotein Lipase activity**
- And **clear blood with elevated Chylomicrons and VLDL**.

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Lipoprotein Lipase	Adipocytes Striated muscles Pancreatic islets Macrophages	Hydrolysis of TG present in chylomicrons and very-low density lipoproteins
Hepatic Lipase	Hepatocytes	-Hydrolysis of TG and phospholipids in very-low density lipoproteins, remnant particles and HDL -Facilitates CE uptake from HDL -Removal of remnants

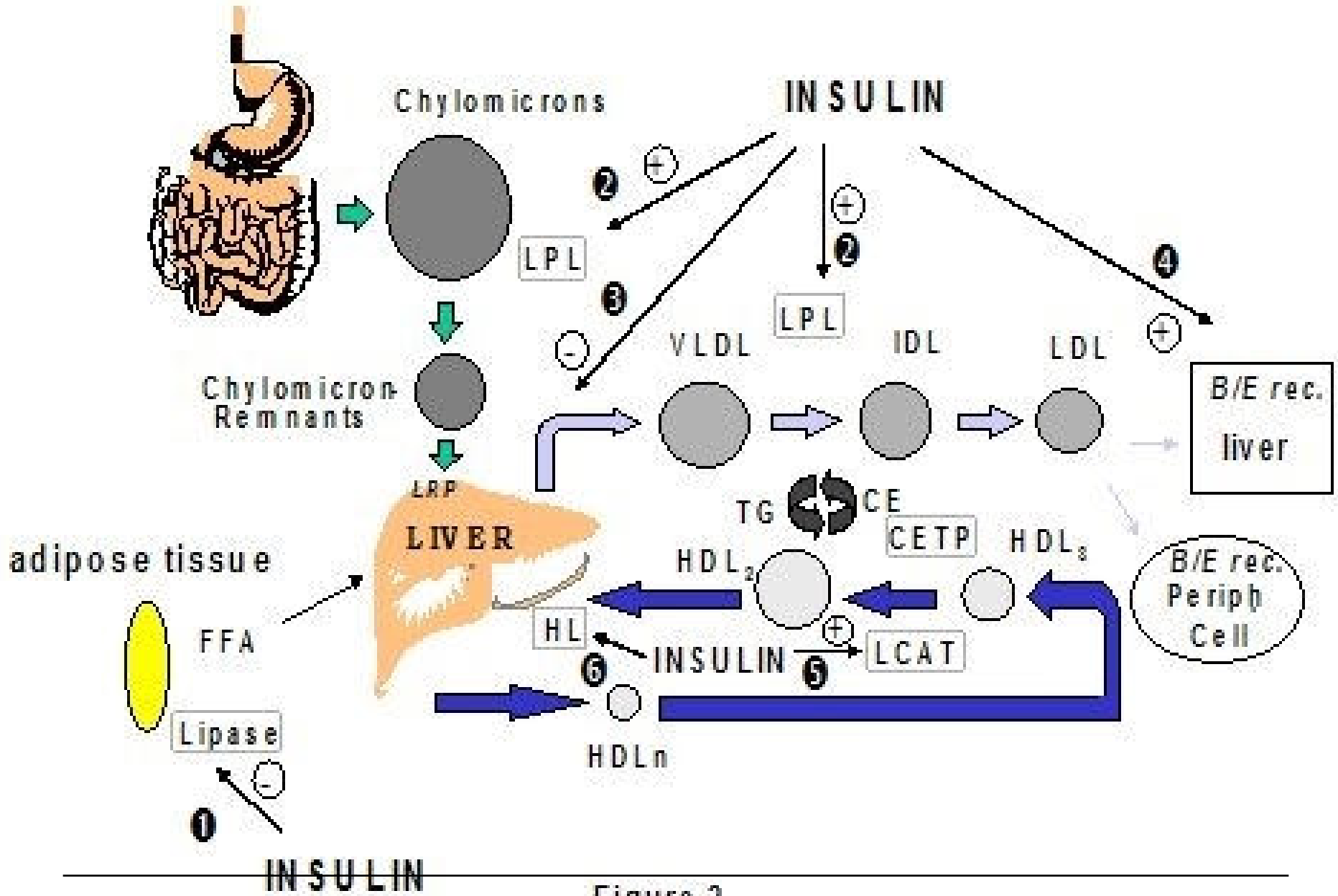
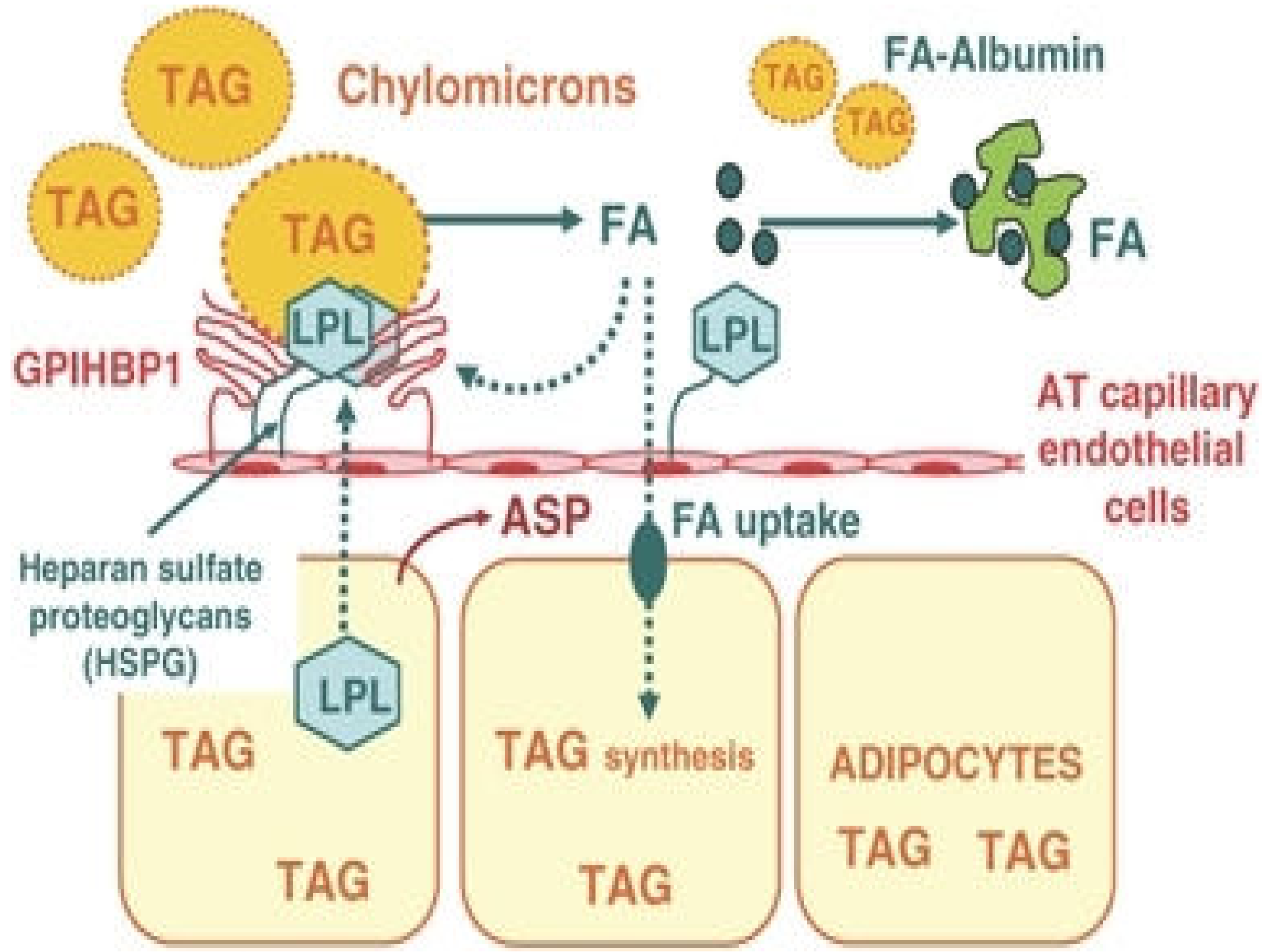
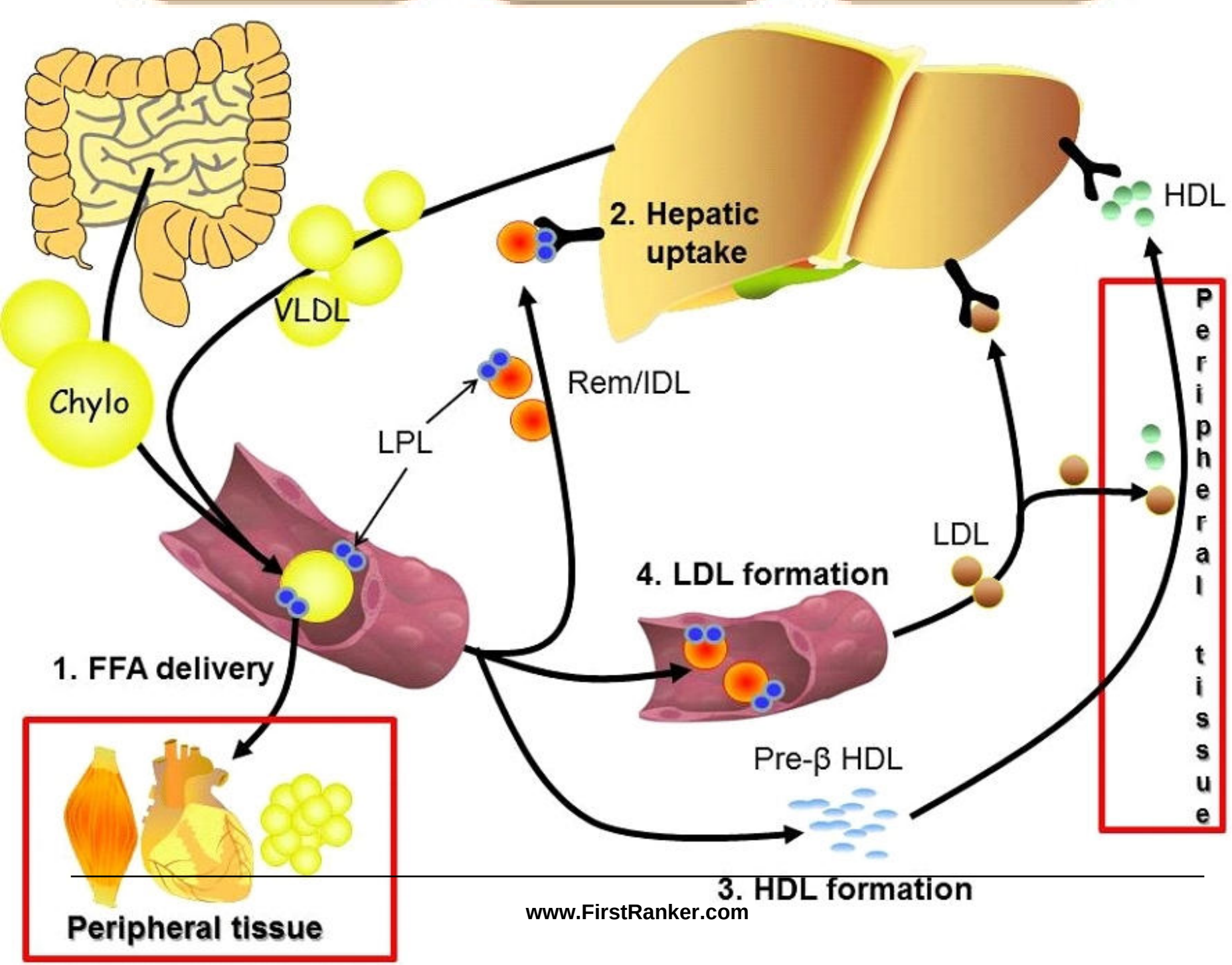


Figure 2

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Transport of Short Chain Fatty Acids And Medium Chain Fatty Acids Is Different From Long Chain Fatty Acids

- **Transport of Short and Medium chain Fatty acids**
  - –These enter portal blood directly from enterocytes
  - –Transported after bound to Albumin in blood
    - **Albumin–FFA complex**

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–**FFA which are internalized in Liver**

- Oxidized to liberate ATPs

OR

- Elongated and used for TAG formation

- **Long-chain Fatty acids**
  - –Transported in the form of **Chylomicrons**
  - –Drain into the Lymphatics via the Lacteal in Mammals
  - –Enter blood stream at the **Thoracic duct**

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Important Role Of Bile Salts In Lipid Digestion and Absorption

- Bile Salts are formed in Liver from Bile acids.
- Bile Salts are mixed and carried through Bile via Common Bile Duct(CBD) to small intestine.

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- Bile Salts in intestine helps in **Emulsification of dietary Lipids** to **form Emulsions** and **Facilitates Lipid Digestion.**
- Later Bile Salts **form Mixed Micelles** and **facilitates the absorption** of digestive end products **Lipids**.

Disorder Related To Lipid Digestion and Absorption/ Steatorrhoea

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Steatorrhoea

- **Steatorrhoea** is a **Malabsorption condition**
- Where there is **no digestion** and **no absorption** of **dietary Lipids in GIT**
- Dietary **ingested Lipids** are **excreted out** through **feces**
- Steatorrhoea leads to **Fatty stools**

Causes Of Steatorrhoea

- The basic cause to suffer from Steatorrhoea is:
  - **Absence of emulsifying agents- Bile salts** in the **small intestine.**
  - **Absence of specific Enzymes for Lipid digestion.**

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Thus Any Condition Affecting, Synthesis, Secretion and Transport of Bile to Intestine leads to Steatorrhoea

- Extensive Liver damage affects Bile Synthesis.
- Celiac Diseases: Sprue, Crohn’s Disease
- Surgical removal of intestine

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- Obstructive Jaundice
- Obstruction due to narrowing of bile duct after surgeries
- Obstruction of CBD due to Gall Stones

Biochemical Alterations in Steatorrhoea

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- No/Less Bile Salts in small intestine
- No/Less Emulsification of dietary Lipids
- No/Less Emulsions formed
- No/Less Contact of Lipids with Lipases

- No/Less digestion of dietary Lipids
- No/Less formation of Mixed Micelles
- No/Less absorption of dietary Lipids
- More excretion of dietary Lipids through feces.

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Consequences Of Steatorrhoea

- In Steatorrhoea person suffers from **deficiency of essential Fatty acids and Fat Soluble Vitamins.**
- Body **lacks exogenous TAG as secondary source of Energy.**
- **Body lacks** from Exogenous source of **Phospholipids and Cholesterol**.

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Diagnosis OF Steatorrhoea

- **Determination Of Fecal Fat**

- **Microscopically** (Fat Globules present)
- **Quantitatively** (Gravimetric Method)

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Chyluria

- **Chylomicrons in Urine** is termed as Chyluria.
- Abnormal condition where **lymphatic drainage system opens in urinary tract**.
- Urine appears milky
- **Chyluria occurs in Filariasis.**

Chylothorax

- **Chylomicrons in Pleural fluid** is termed as Chylothorax.
- Abnormally **Thoracic duct opens in pleural cavity**.

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Overview Of Lipid Metabolism

- Lipid metabolism involves:
  - **Lipolysis**
  - **Lipogenesis**

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- **Liver and Adipose tissue** play a central role in Lipid metabolism.

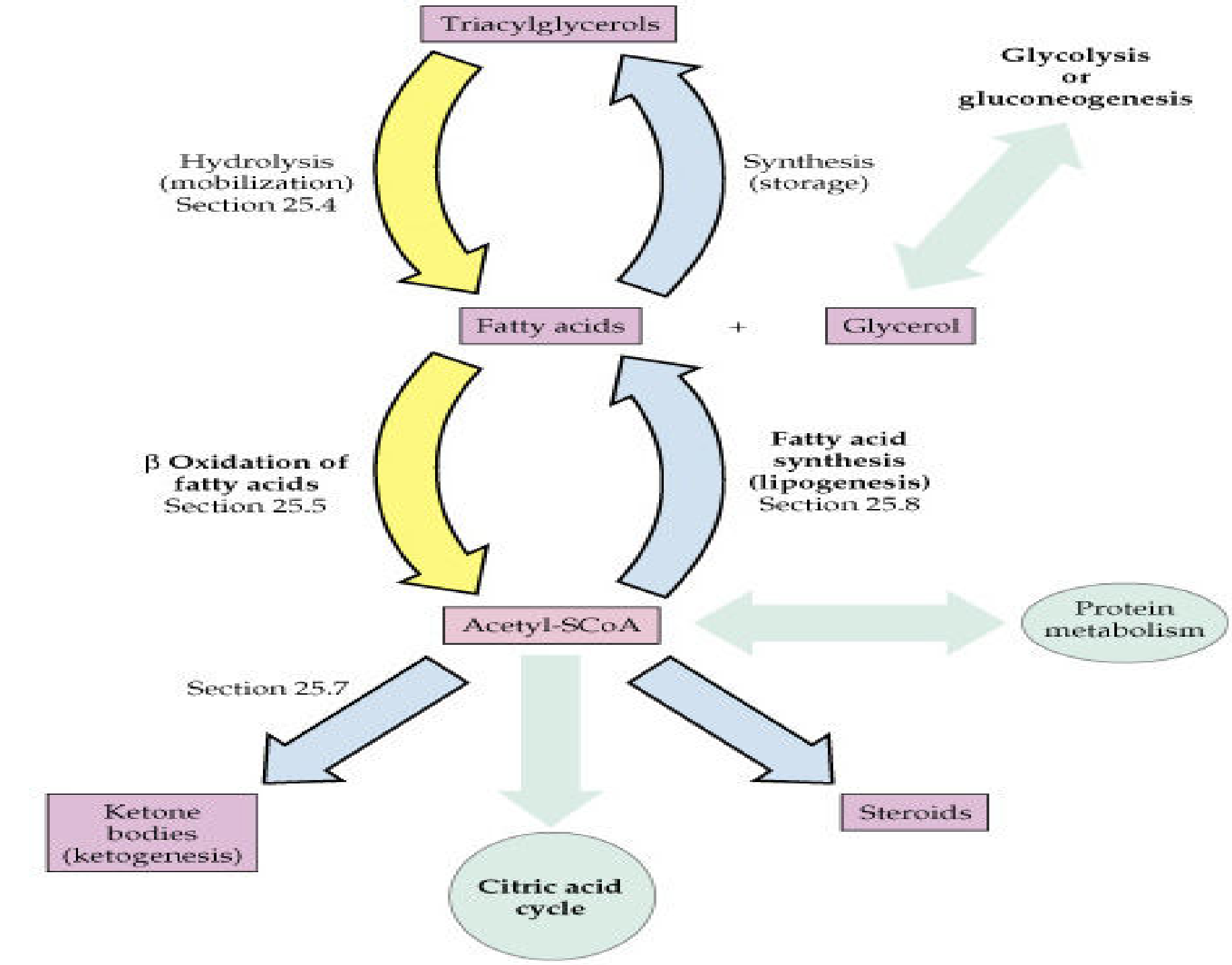
- **Adipose tissue** is the **main store house of Triacylglycerol** in the body.

- **Fatty acids** are reduced compound **oxidized/catabolized** to **Acetyl CoA**

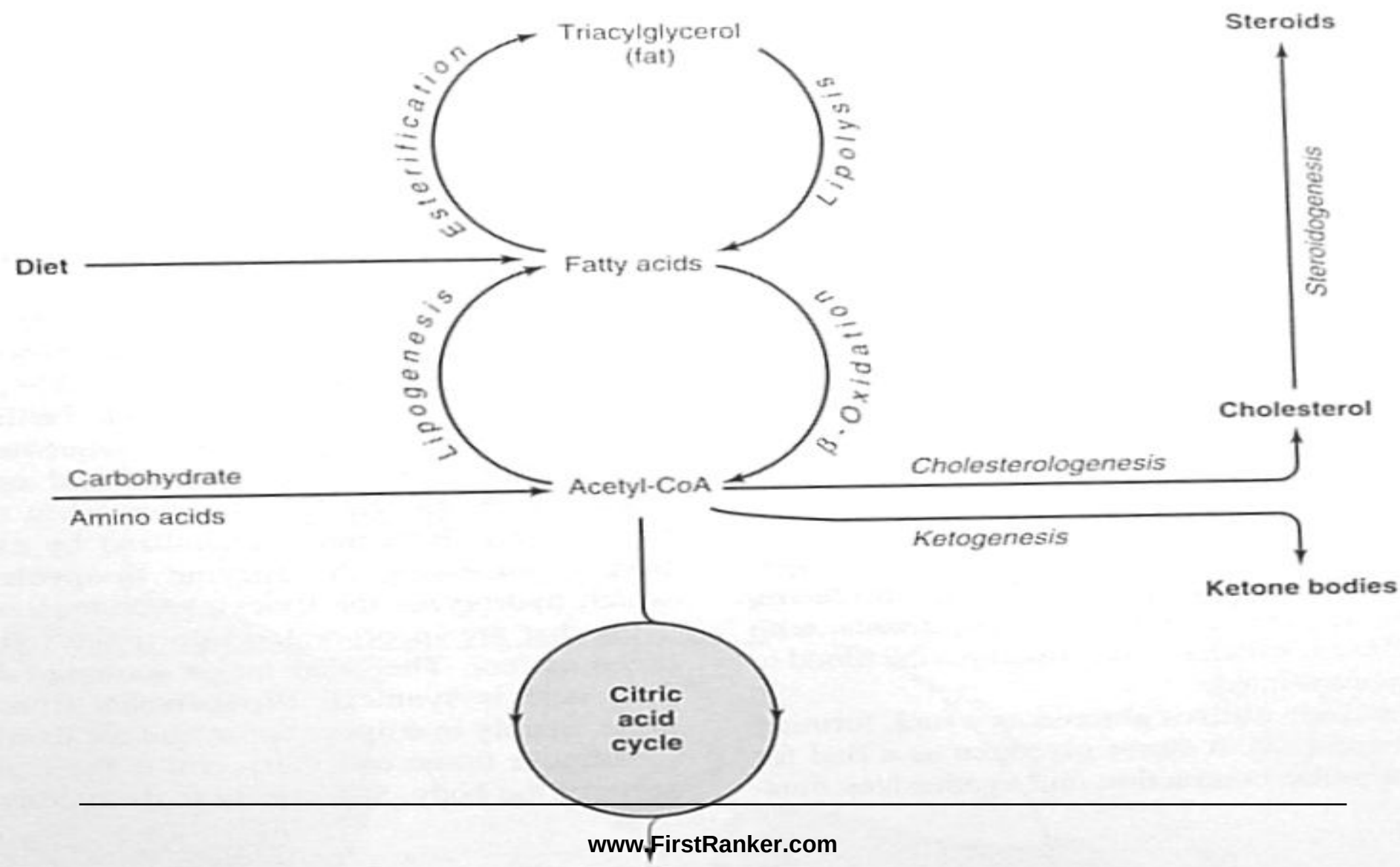
- **Fatty acids are biosynthesized** using **Acetyl CoA as a precursor**.

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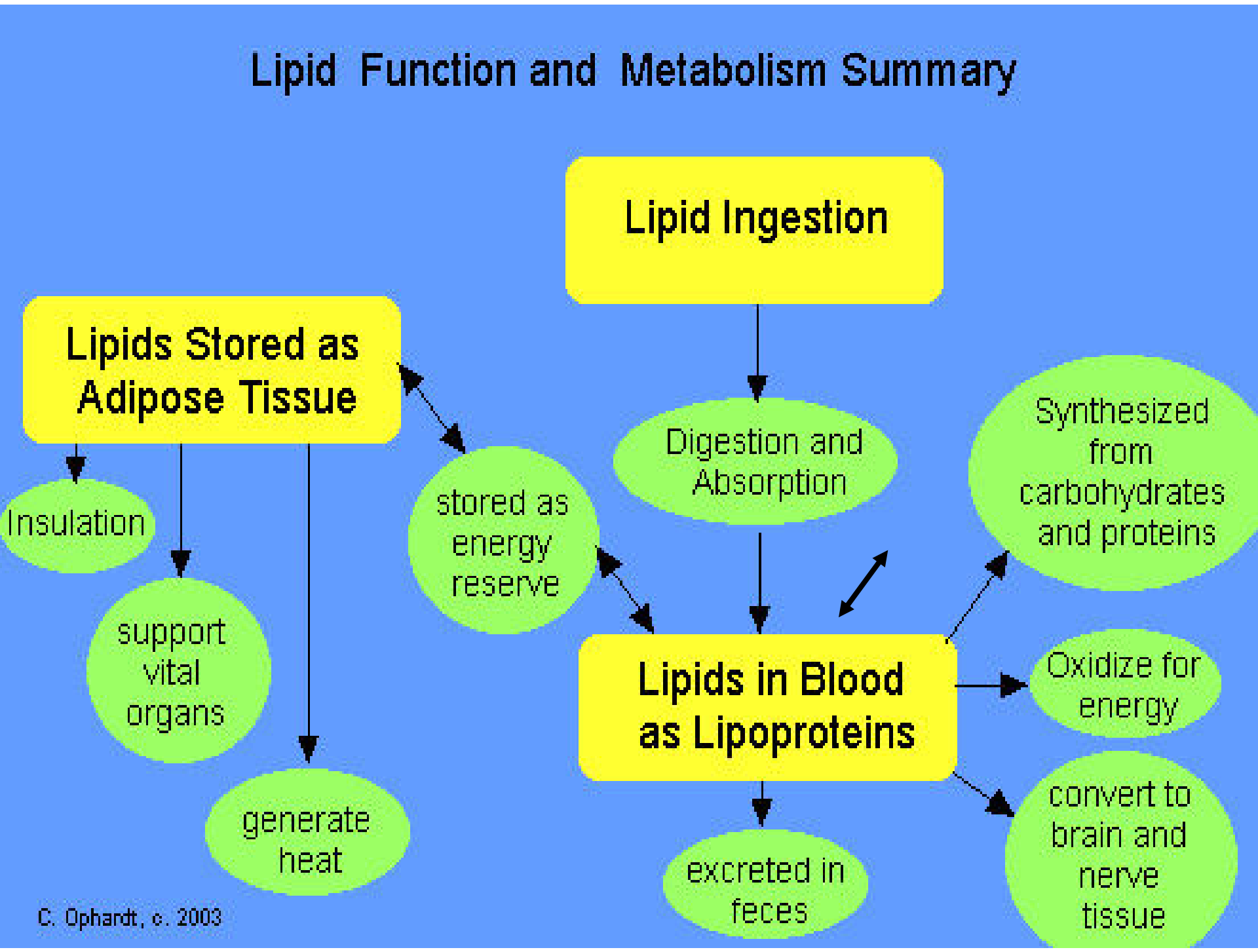


Lipid Metabolism



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What Is Lipolysis?

OR

Role Of Hormone Sensitive Lipase (HSL)

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- In a **well fed condition** **TAG** is stored as **reserve source** of energy in **Adiposecytes.**

Fat Storage in White Adipose Tissue

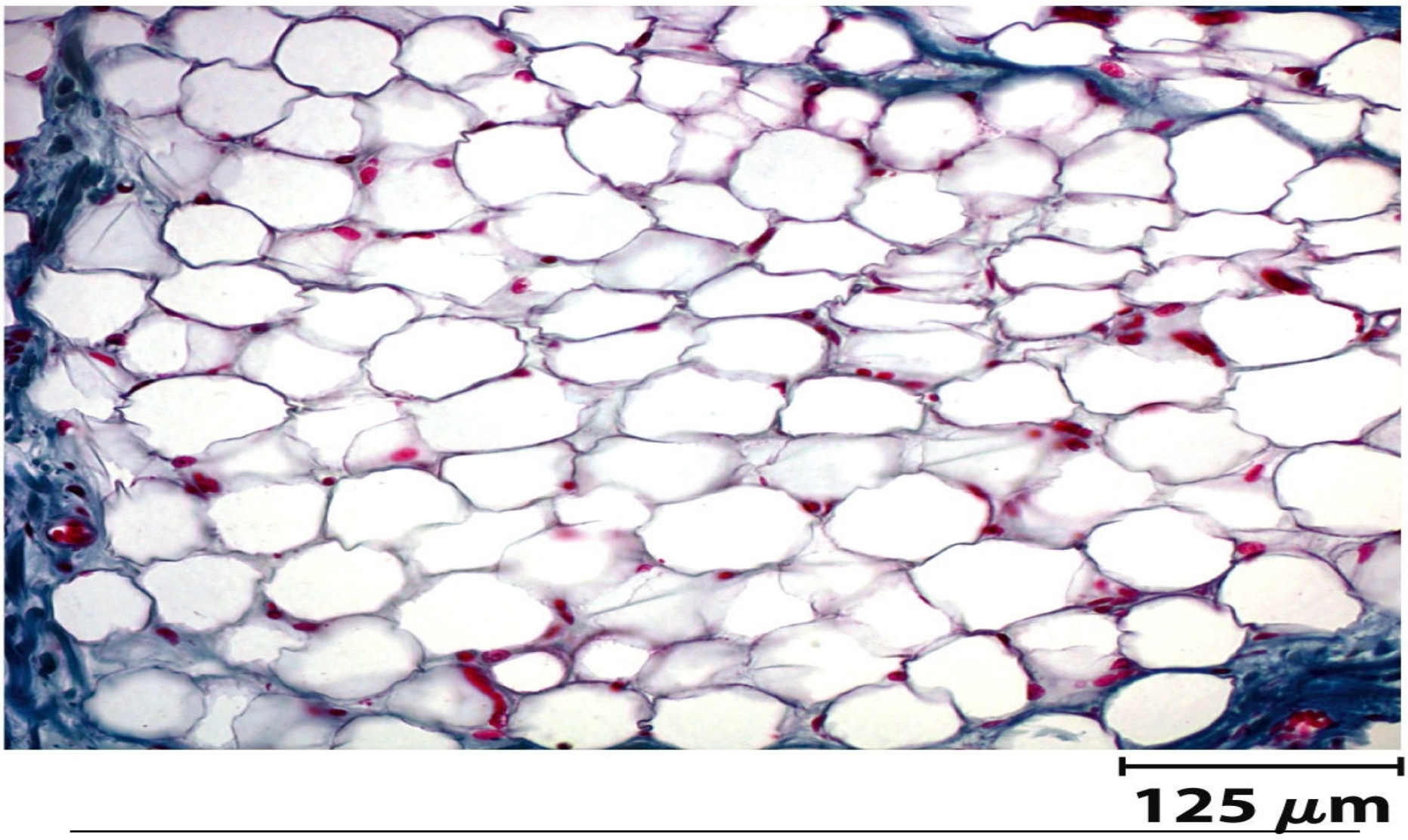


Figure 10-4a
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- **Lipolysis occurs in emergency conditions**
- **Lipolysis** is the **break down of Depot Fat-**Triacylglycerol(TAG)
- Into **Free Fatty acids and Glycerol**
- By enzyme activity of **Hormone sensitive Lipase**

Triacylglycerol

In Adipocytes ↓ **Hormone Sensitive Lipase**

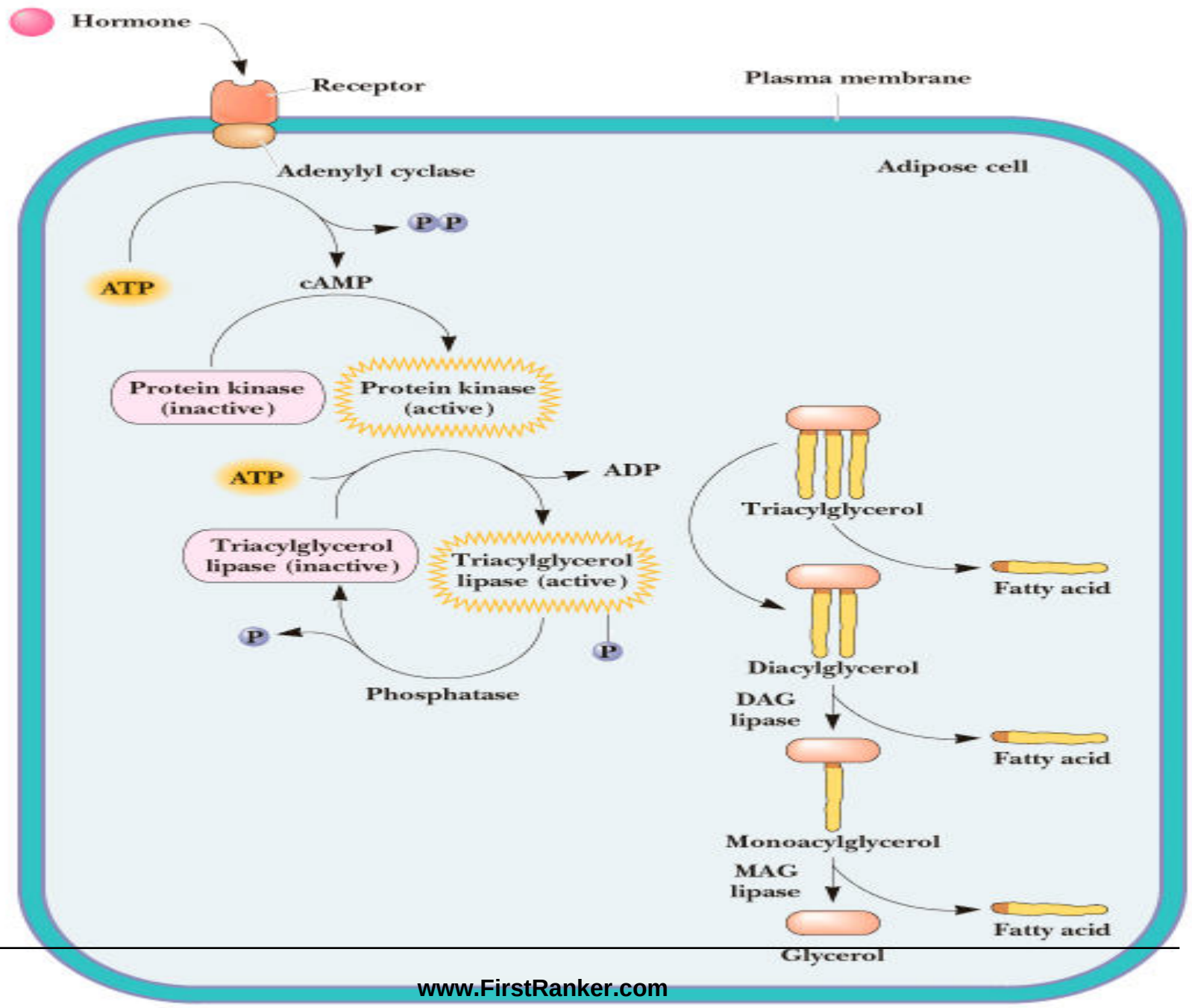
Cleaves Ester bonds

Glycerol+ Free Fatty acid

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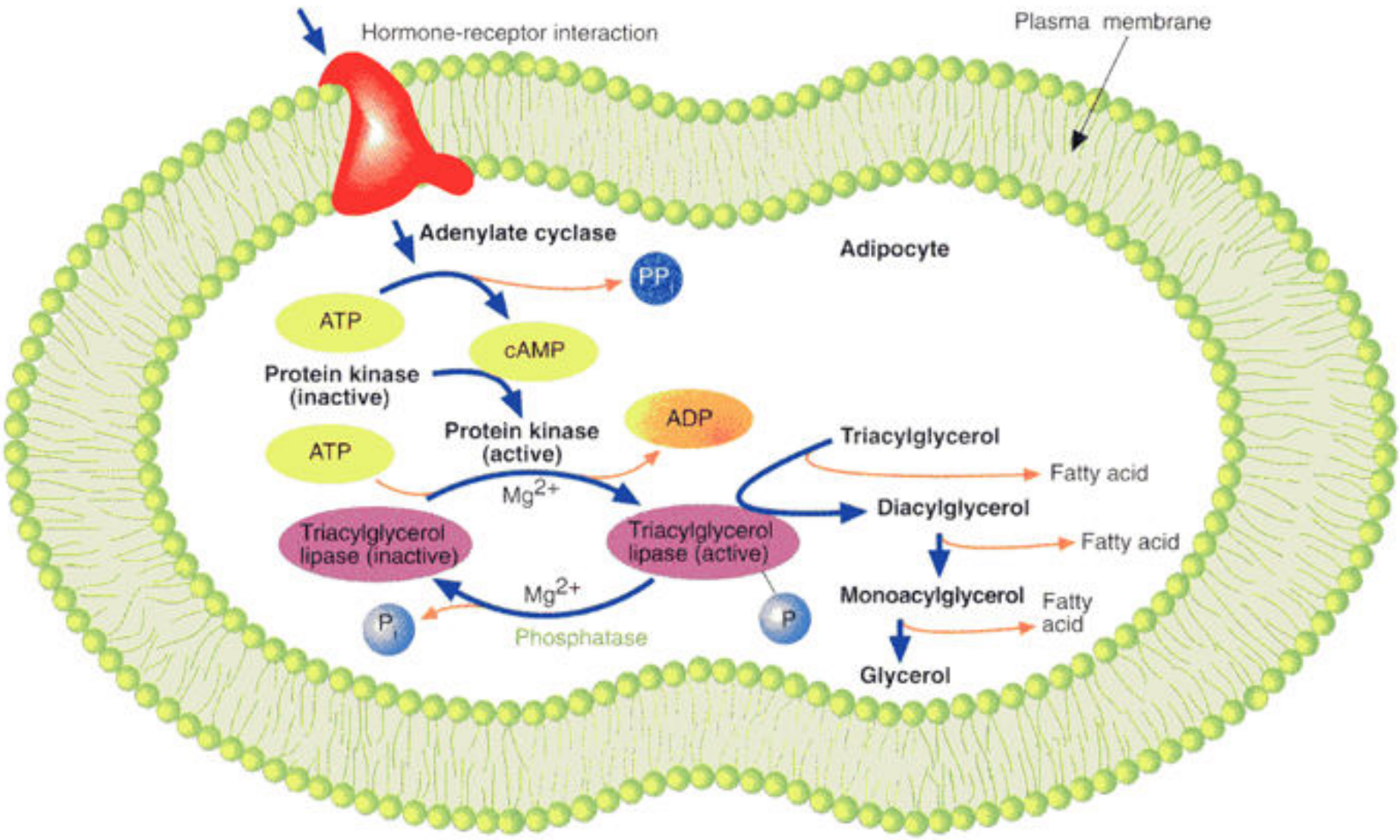
- During **Lipolysis** the secondary source of energy **TAG**
- **Stored** as depot Fat **gets utilized.**



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Diagrammatic View Of Lipolysis



Conditions Of Lipolysis

- **Lipolysis significantly and efficiently occurs :**
  - In emergency **fasting condition**
  - **In between long hours after meals**
  - When the primary source of energy **Glucose go below normal range** in blood
  - In presence of **Hormones Glucagon or Epinephrine**
  - ~~**By activity of Hormone Sensitive Lipase**~~

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- The Enzyme **Hormone Sensitive Lipase** of Adipocytes is stimulated By Hormones:
  - **Glucagon and Epinephrine mediated via cAMP**.

- On Lipolysis the Free **Fatty acids** and **Glycerol** are **mobilized out of adipocytes in blood circulation.**

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End Products Of Lipolysis

- Free Fatty Acids
- Glycerol

Fate Of Glycerol After Lipolysis

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- **Glycerol** (polar moiety)released in emergency condition during Lipolysis
- Is carried through blood and **enters in Liver and Muscles**.

Fate Of Glycerol In Muscles

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Glycerol Enter into Glycolytic Pathway (In Muscles)

Glycerol



Glycerol Kinase

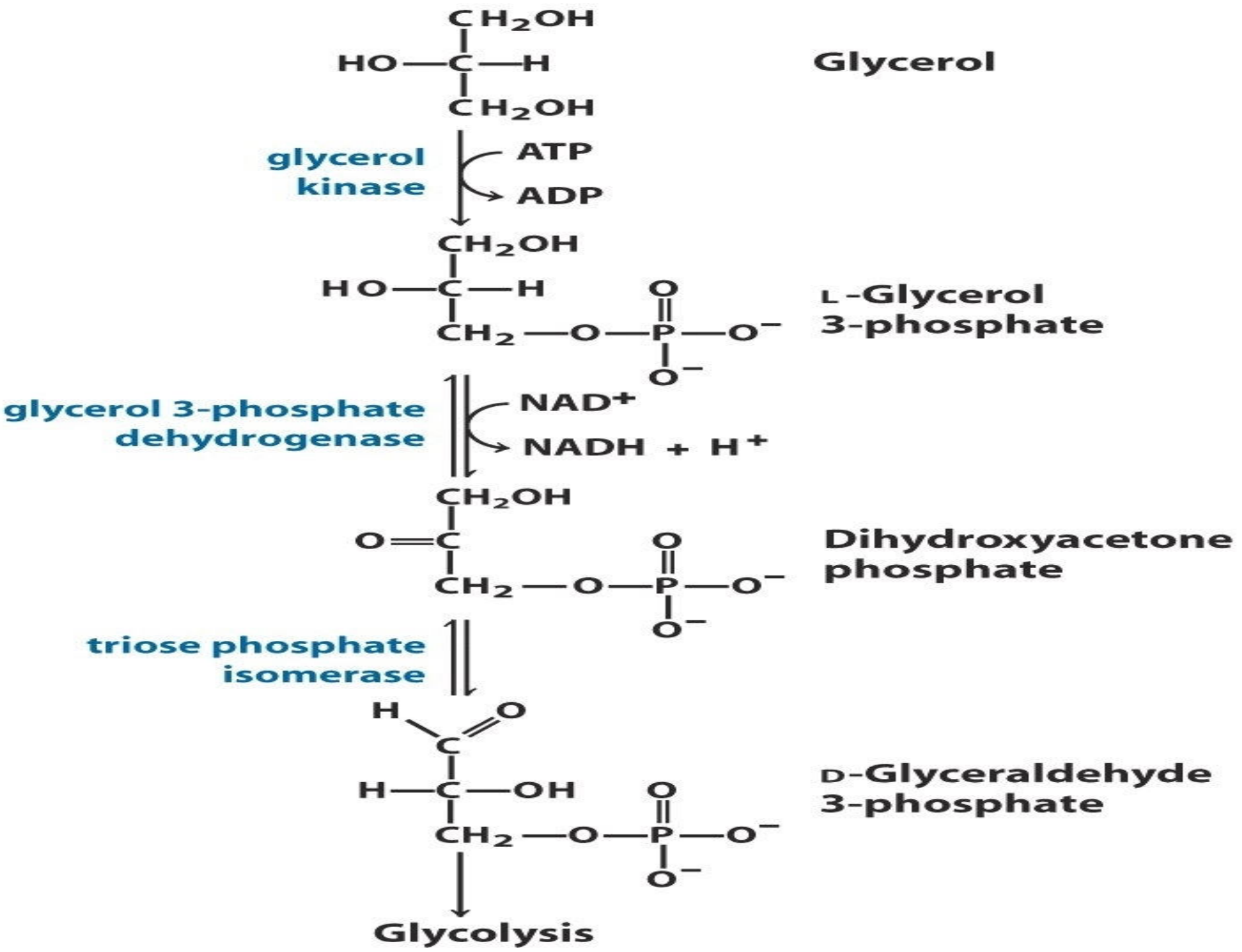
Glycerol-3-Phosphate



Glyceraldehyde-3-PO4

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- **Glycerol** of Lipolysis is metabolized **via Glycolysis in Muscles**

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- Glycerol in muscles is Phosphorylated to **Glycerol-3-PO4**

- Glycerol-3-PO4 is further oxidized to **Glyceraldehyde-3-PO4**

- Thus Glyceraldehyde-3-PO4 in **Muscles** make its **entry in Glycolysis**
- Further gets metabolized to **generate energy (ATP)** for muscle activity.

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Fate Of Glycerol In Liver

Glycerol Of Lipolysis Is a Precursor For Gluconeogenesis (In Liver)

Glycerol Is Used For Glucose Biosynthesis In Liver

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- Glycerol of Lipolysis is metabolized via **Gluconeogenesis in Liver**

- Glycerol in Liver is Phosphorylated to **Glycerol-3-PO4** by **Glycerol Kinase**

- Glycerol-3-PO4 is further oxidized to

- Glyceraldehyde-3-PO4 and isomerized to DHAP

- This then is converted to Glucose.

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- Thus Glyceraldehyde-3-PO4 in **Liver** make its entry in **Gluconeogenesis** and
- Further gets metabolized to **produce Glucose.**

- **Glucose formed in Liver** is mobilized out into blood and
- Supplied to Brain and Hepatocytes in **fasting condition.**

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Fate Of Free Fatty Acids After Lipolysis

- **Non polar Long Chain Free Fatty acids** released **in blood circulation** after Lipolysis are not transported on its own.
- Needs the help of a polar moiety.

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Polar Moiety Albumin Transports Long Chain Free Fatty Acids In Blood Released After Lipolysis

- Long chain Free Fatty acids are uncharged/nonpolar/hydrophobic
- They are linked with polar Protein moiety **Albumin**
- **FFA-Albumin complex** get transported through blood circulation.

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- Albumin remain in the blood circulation
- Free Fatty acids make its entry in Muscle cells.

Fatty Acids In Muscles Oxidized To Liberate Energy (ATP)

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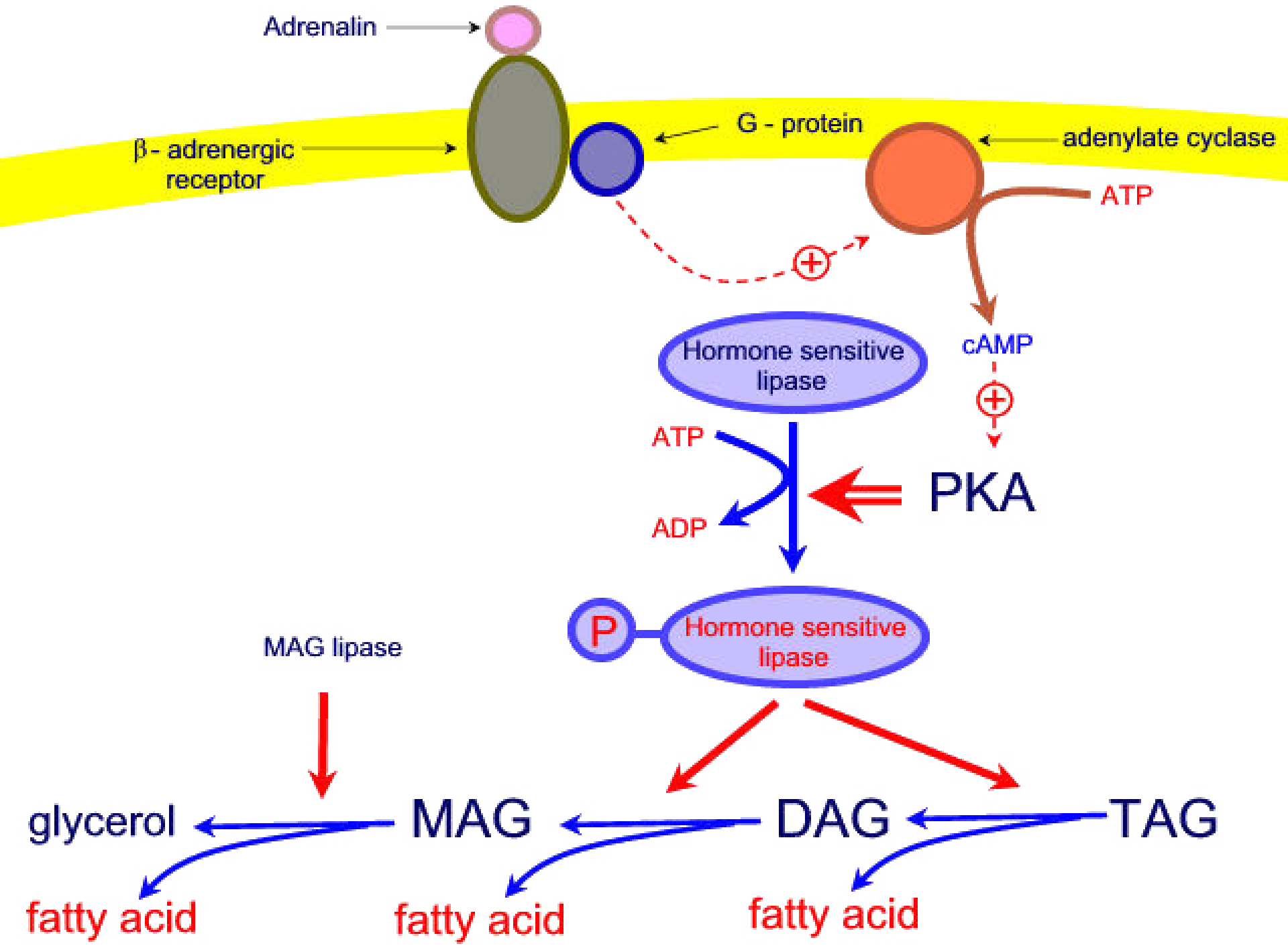
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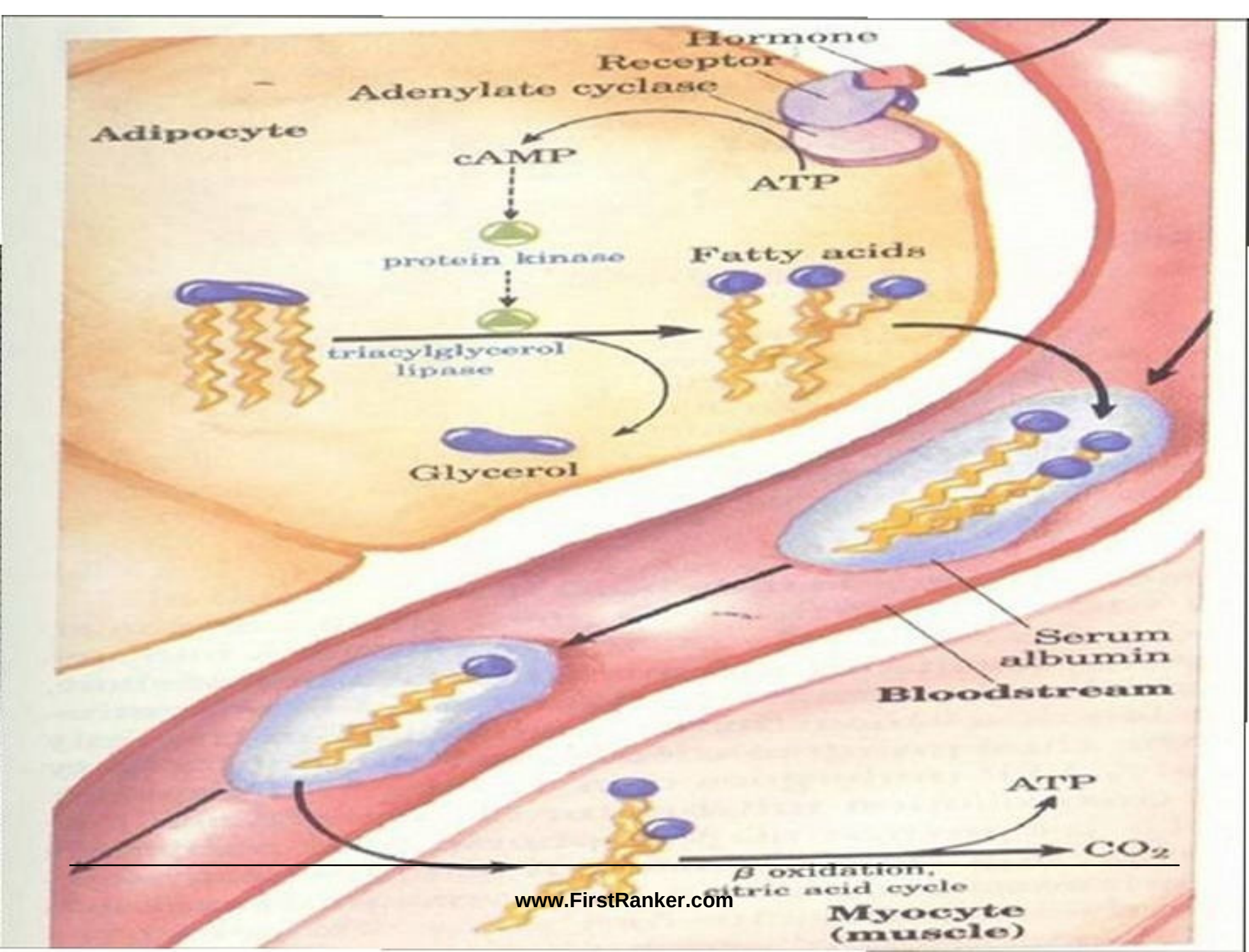
- Free Fatty acids are **highly reduced compounds.**
- **Free Fatty acids entered in Muscles** during emergency condition
- After Lipolysis, are **oxidized to liberate chemical form of energy ATP.**

- Thus after Glucose Free **Fatty acid** serve as **secondary source of energy** to body tissues.

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Oxidation Of Fatty Acids

OR

Catabolism/Degradation Of Fatty Acids

How Fatty Acid Oxidation Serve As Energy Source?

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- **Fatty acids** are an important secondary source of **energy** to body.
  - Since **Fatty acids** are **reduced compounds**
  - Possess **CH2-CH2** hydrocarbon **bonds with bond energy** in their structures

- **Oxidation of Fatty acid /Catabolism or breakdown of Fatty acid is by:**
  - **Removal** of **Hydrogen from hydrocarbon chain (CH2-CH2).**
  - Which are **temporarily accepted by Coenzymes**
  - With **formation of reduced Coenzymes**
  - **Reoxidation of these reduced Coenzymes by entry in ETC /Oxidative Phosphorylation generates ATP.**

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- **Oxidation of the Hydrocarbon bonds of fatty acid chain makes them weaker**
- **Easy Cleavage of hydrocarbon bonds** of Fatty acid
- Which helps **in shortening of the long Fatty acid chain.**

Types Of Fatty Acid Oxidation

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1. Oxidation Based On Type Of Carbon Atom

- **Alpha(α) Oxidation**(Phytanic acid –Branched Chain FA)
- **Beta (β) Oxidation** **(Most Predominant)**
- **Omega(ω) Oxidation** (When defect in β Oxidation)

2.Oxidation Based On Number Of Carbon Atom

- **Beta Oxidation** of **Even Carbon Chain** Fatty acid oxidation
- **Beta Oxidation** of **Odd Chain** Fatty Acid Oxidation
- **Very Log Chain Fatty Acid** (VLCFA) Oxidation

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3.Oxidation Based On Nature Of Bonds

- Oxidation of **Saturated** Fatty acids
- Oxidation of **Unsaturated** Fatty acids

4.Oxidation Based On Cellular Site

- **Mitochondrial** Fatty acid Oxidation
- **Endoplasmic Reticulum** Fatty acid Oxidation
- **Peroxisomal** Fatty acid Oxidation

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The General Pattern To Study Metabolic Pathways

- Synonyms/Different Names of Pathway.
- What is the Pathway ? (In brief)
- Where the pathway occurs/Location? (Organ/Cellular site)
- When pathway occurs/Condition? (well fed/emergency/aerobic/anaerobic)
- What type Of Pathway? (Catabolic/Anabolic)

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- Requirements for the Pathway
  (If Anabolic Pathway)
- How the pathway Occurs/Stages/Steps?
  (Type of Rxn , Enzymes ,Coenzymes)
- Why the Pathway occurred?
  (Significance of Pathway)

- Precursor, intermediates, byproducts and end products of metabolic Pathway.
- Energetics of the pathway/Net ATP Use and Generation
- Interrelation ships with other Pathways
- Regulation of Pathway :Modes of regulation.
- Regulatory Hormone/ Regulatory Enzyme/Modulators.
- Inborn Error of the Metabolic Pathway

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How Palmitic Acid is Completely Oxidized In Human Body? Calculate Its Energetics

Beta Oxidation Of Even Carbon Saturated Fatty Acid At Mitochondrial Matrix

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Historical Aspects Of Beta Oxidation of Fatty Acids

- **Albert Lehninger** showed that
- **β Oxidation of Fatty acids** occurred in the **Mitochondria.**

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- **Knoop** showed that Fatty acid is **oxidized and degraded by removal of 2-C units**

- **F. Lynen and E. Reichart** showed that the **2-C unit released** is **Acetyl-CoA**, but **not free Acetate.**

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Beta Oxidation Of Palmitate (C16)

What Is Beta Oxidation Of Fatty Acid ?

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Definition Of β Oxidation of Fatty acid

- Oxidation of a Fatty acid at the **Beta Carbon atom/C3** (-**CH2)**

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- **Beta Oxidation of Fatty Acid is the most predominant type of Fatty acid oxidation.**

- **Most of the Fatty acids in the cells get oxidized and catabolized via Beta Oxidation of Fatty Acid**

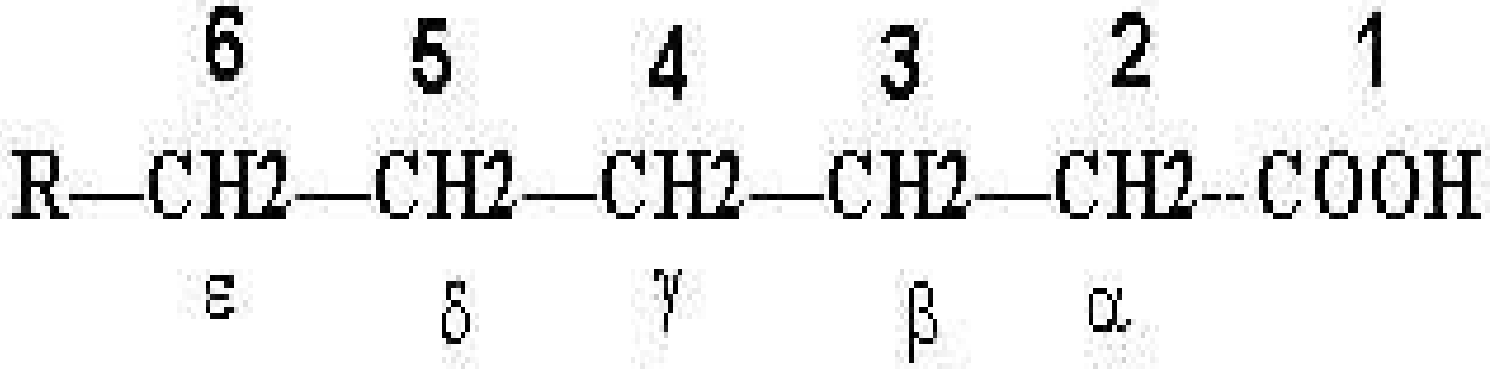
β-Oxidation OF Fatty Acid

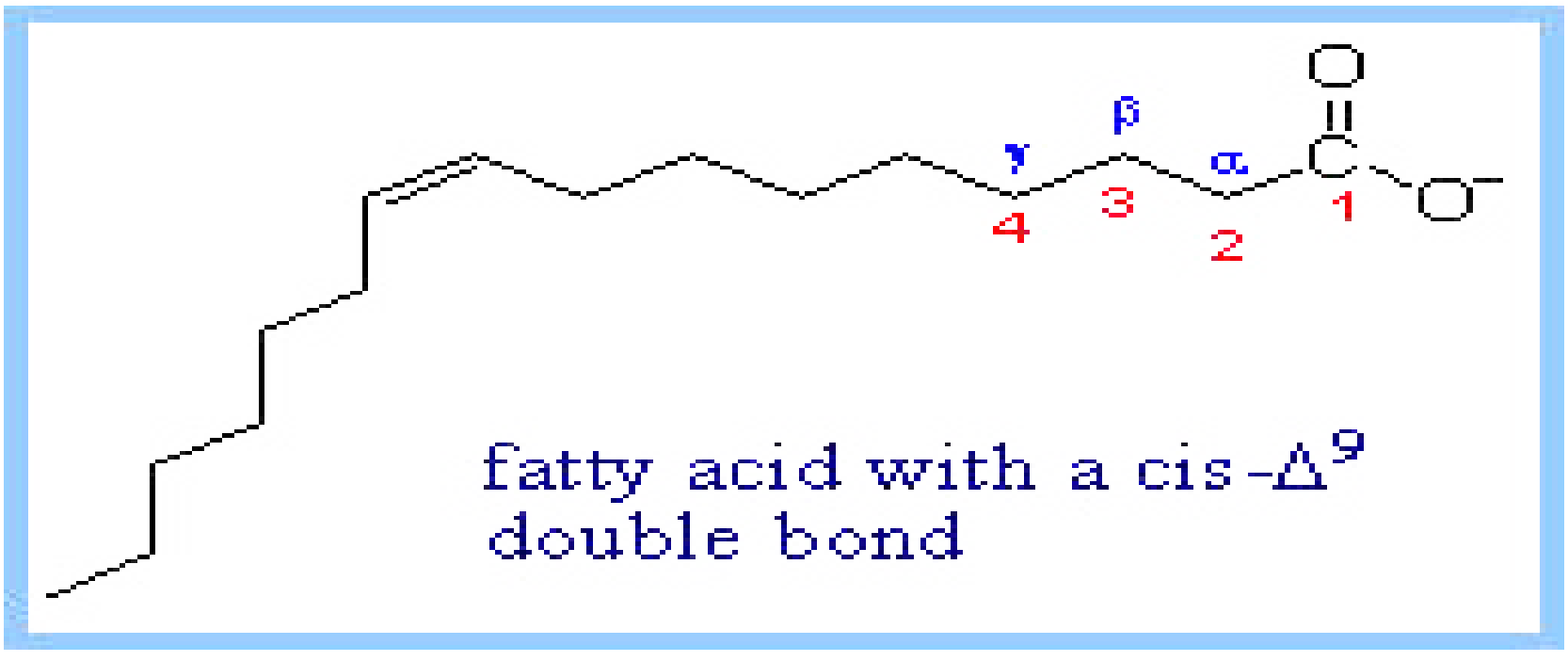
- **β-oxidation of Fatty acids is the catabolic/ degradative , energy generating metabolic pathway of Fatty acids**

- It is referred to as the **β-oxidation** pathway, because **oxidation occurs at the β-carbon (C3) of a Fatty acid**.

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- During Beta oxidation of Fatty acid **(-CH2) of Beta position is oxidized and**
- **Transformed to Carbonyl atom (-C=O)**

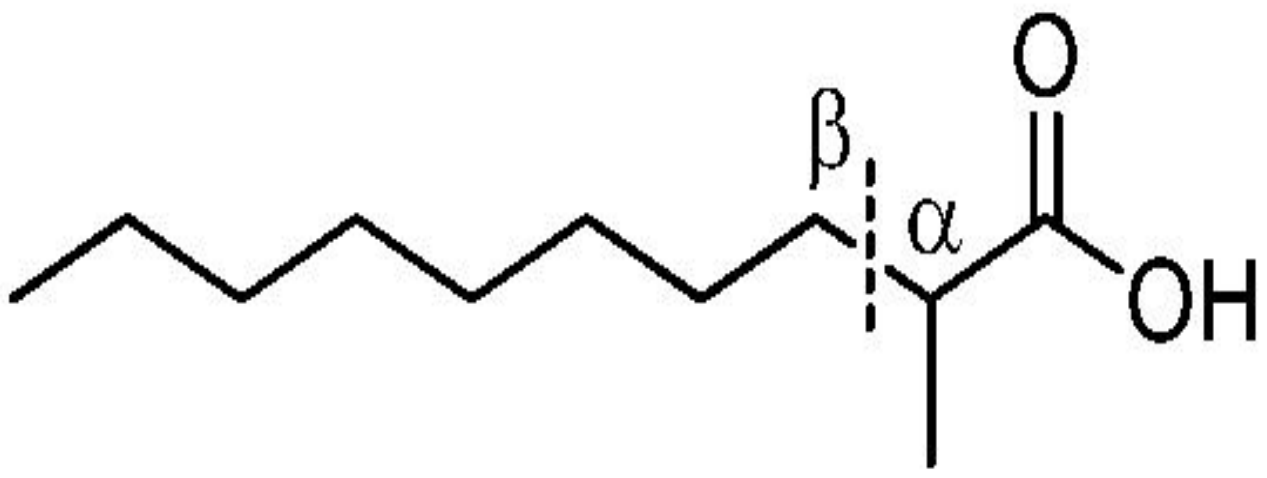
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- The oxidized and transformed Beta positioned -**C-H2** to **-C=O** during the steps of Beta Oxidation Proper.

- **Makes** the **bond between Alpha and Beta Carbon Atom weaker and cleavable to release 2Carbon unit Acetyl-CoA.**

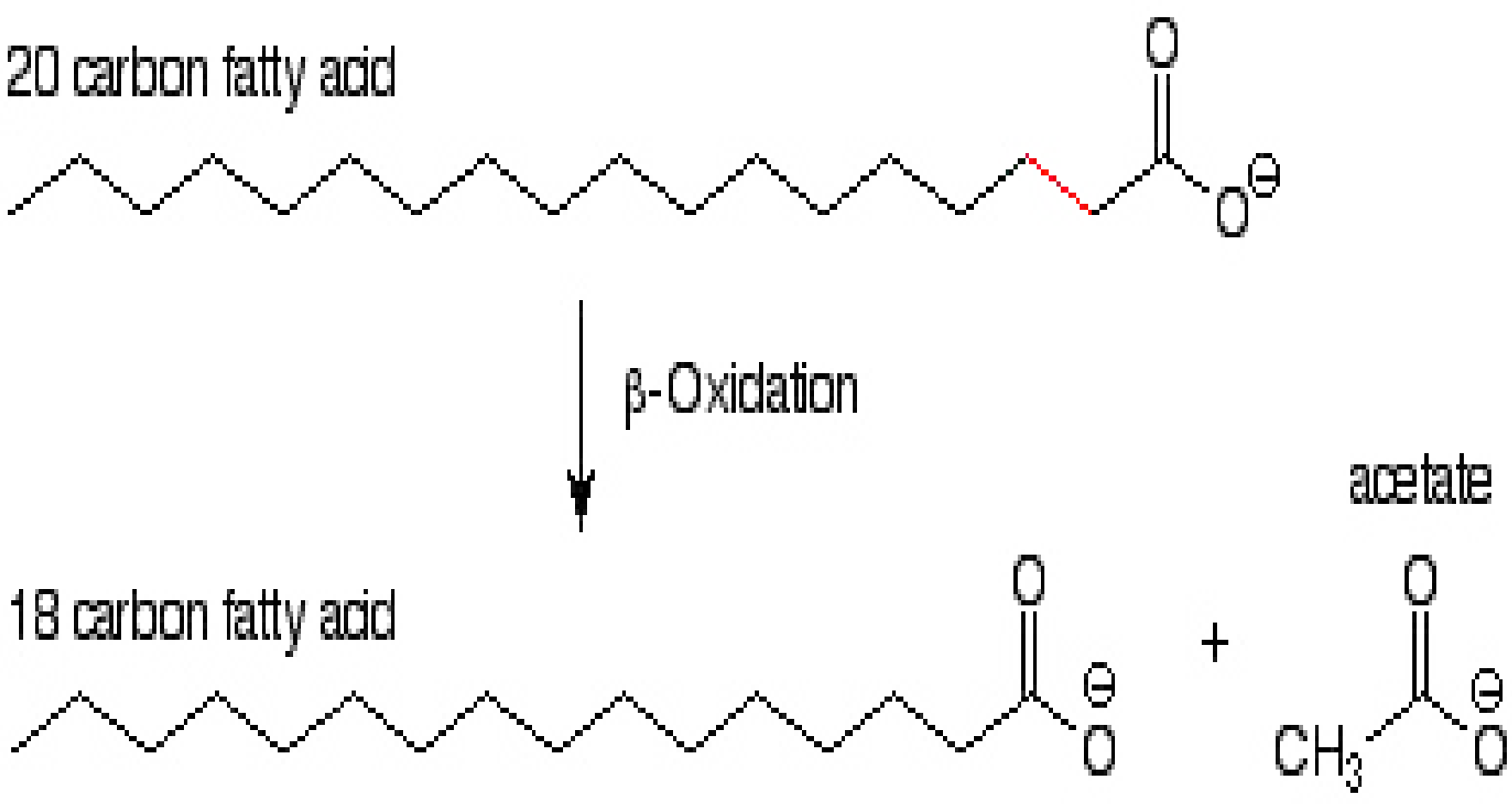
The Weak bond between Alpha and Beta Carbon Atom is Cleaved to release 2Carbon Unit Acetyl-CoA



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- **With a removal of 2-C units there is shortening the Fatty acid chain.**
- The **2-C units** released after the steps of Beta Oxidation is **Acetyl-CoA** (active Acetate) **which enters TCA for its complete oxidation.**



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β-Oxidation OF Fatty Acid Is a Catabolic Energy Producing Pathway

BETA OXIDATION

- The fatty acyl chain is shortened by two carbon atoms as a result of these reactions,
- FADH2, NADH, and acetyl Co A are generated.
- Because oxidation is on the β carbon and the chain is broken between the α (2)- and β (3)-carbon atoms—hence the name – β oxidation .

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Organs Involved with Beta Oxidation Of Fatty Acid

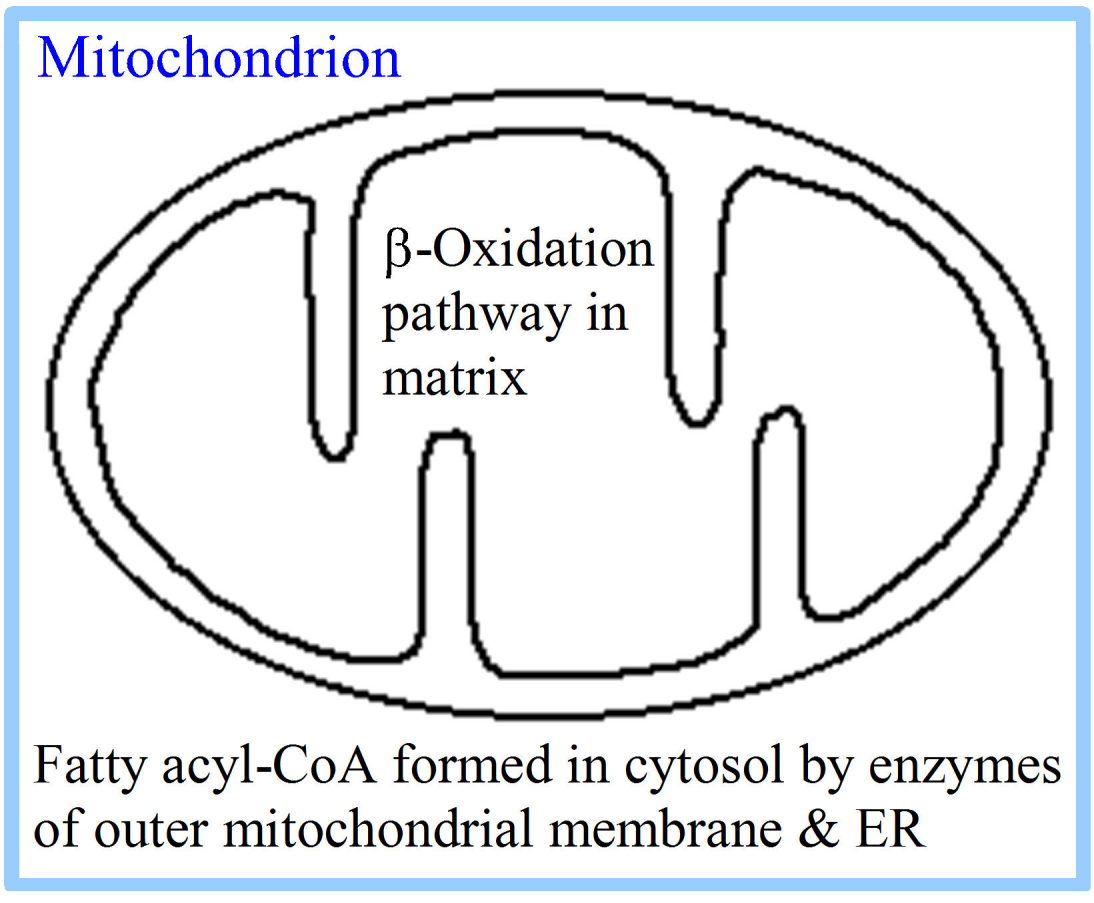
- Skeletal Muscles
- Heart
- Hepatocytes
- Kidney

Cellular Site For Beta Oxidation Of Fatty Acid

- **Cytosol**
  (Activation of Fatty acid)
- **Mitochondrial Matrix**
  (Beta Oxidation Proper)

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β-Oxidation pathway:

Fatty acids are degraded in the **Mitochondrial Matrix** via the β-Oxidation Pathway.

Organs Which Do Not Operate Beta Oxidation Of Fatty Acid

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Remember In Brain and Erythrocytes Fatty Acids Do Not Serve As A Source Of Energy

- Free Fatty acids cannot cross the blood brain barrier
- Hence Fatty acids do not enter Brain to get oxidized.

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- **Beta Oxidation proper** of Fatty acid **takes place in Mitochondrial matrix**
- Since mature **RBC's has no Mitochondria**
- Hence **no oxidation of Fatty acids occurs in Erythrocytes**.

- **In emergency conditions**

–**Since Brain and Erythrocytes cannot oxidize Fatty acids** and use as energy source.

–These organs **has to depend only on Glucose for getting energy for their vitality**.

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Type Of Metabolic Pathway

- **Beta Oxidation Of a Fatty acid is a:**
  - –**Catabolic** Pathway
  - –**Degradative** Pathway
  - –**Energy generating** metabolic pathway in emergency phase

Condition Of Its Occurrence

- Usually Beta Oxidation of Fatty acids efficiently occurs **after Lipolysis.**
- When there is low use of Glucose by body cells
  - –In **Fasting condition**
  - –In **between Meals**
  - –During **Severe Exercises** and Marathon Races
  - –In Patients of **Diabetes mellitus**

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Stages And Reaction Steps Of Beta Oxidation Of Fatty Acids

Three Stages Of Beta Oxidation For Fatty acid Palmitate

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Stage I

Activation of Fatty acid (Acyl Chain) to Acyl-CoA In Cytosol

– Palmitate to Palmitoyl-CoA

In Cytosol

Stage II

Translocation of Activated Fatty acid From Cytosol into Mitochondrial Matrix

Through The Role of Carnitine

(Carnitine Shuttle)

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Stage III
Steps of Beta Oxidation Proper
In Mitochondrial Matrix

- Oxidation Reaction
- Hydration Reaction
- Oxidation Reaction
- Cleavage Reaction

Stage I
Activation Of Fatty acid
In Cytosol
Is a Preparative Phase

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Site Of Fatty acid Activation

- Fatty acid(Acyl Chain) is activated in **Cytosol** to **Acyl-CoA** .

- A **long chain** Fatty acid is termed as **Acyl chain.**

- **Every Fatty acid** which undergoes β Oxidation of Fatty acid is **first activated** to **Acyl-CoA.**

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- **Activation of a Fatty acid means:**

- Linking of **Acyl Chain** to **Coenzyme A** to form **Acyl-CoA with a high energy bond.**

- **During Activation of Fatty acid (Acyl Chain)**

- '**H**' of **CoA-SH (Coenzyme A)** is substituted by **Acyl chain**

- To form **CoA-S Acyl**, i.e **Acyl-CoA** an activated Fatty acid.

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- Thus **CoA** is a **carrier of Acyl chain** in an activated fatty acid.

Requirements of FA Activation

- **Enzyme:**
  - **Thiokinase /Acyl CoA Synthetase**
- **Coenzymes/Cofactor:**
  - CoA-SH
  - ATP
  - Magnesium ions (Mg^{++})

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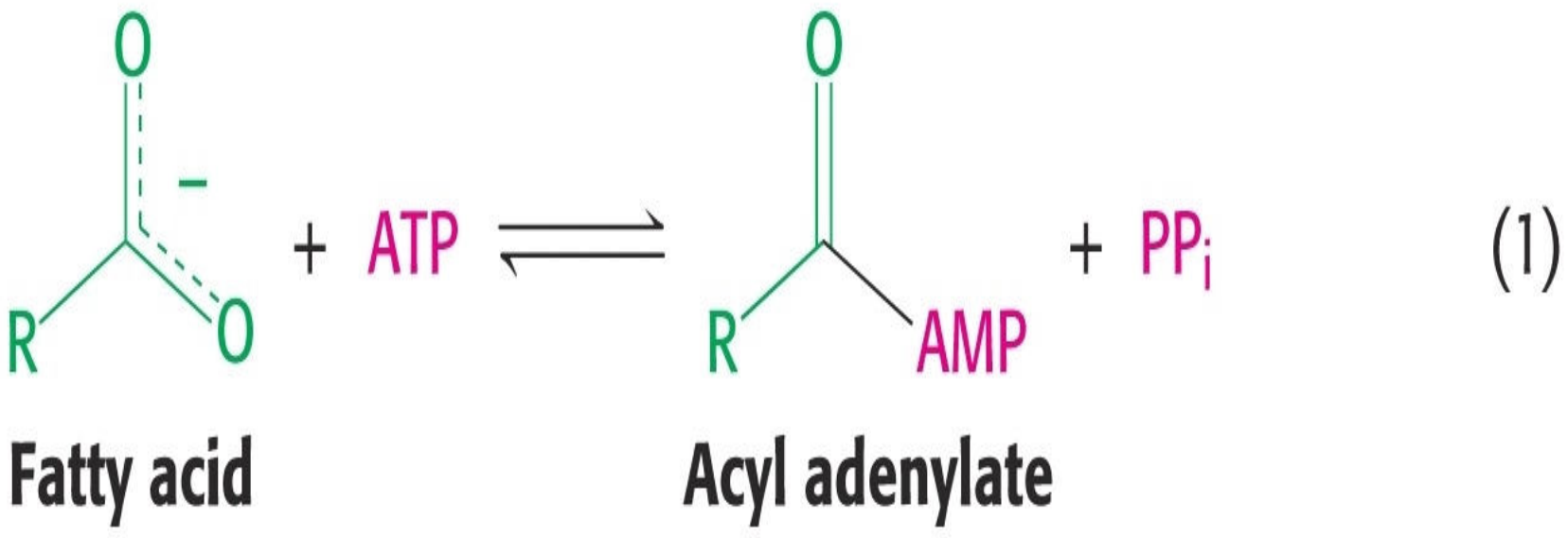
Steps Of Fatty Acid Activation

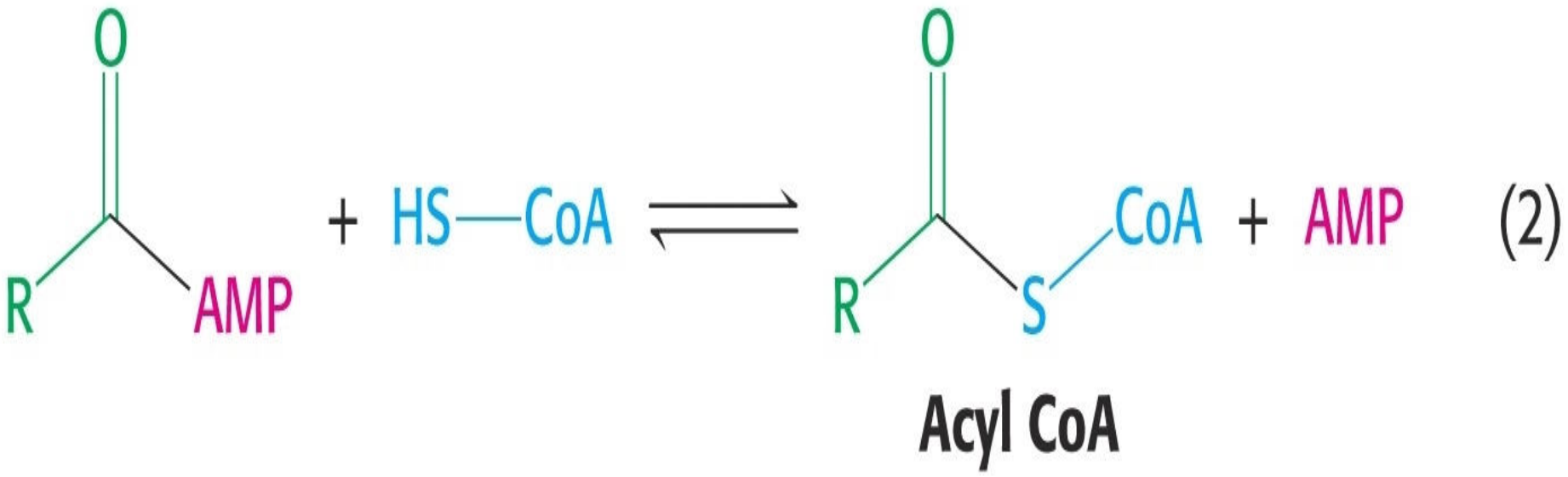
Activation of Fatty Acid



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- An **Acyl-CoA is an activated energetic compound having high energy bond.**

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Activation Of a Fatty Acid Is ATP Dependent

Converts ATP to AMP

Hence equivalent to 2 ATPs

- Thus formation of Acyl–CoA is an **expensive energetically**

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CoezymeA (CoA-SH) Activates Fatty Acids for Beta Oxidation

Acyl-CoA Synthetase/
Fatty Acid Thiokinase
condenses Fatty acids with CoA,
with simultaneous hydrolysis of ATP to AMP and PP_i

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Fatty acid Activation

- Activation of Fatty acids is **esterification of Fatty acid with Coenzyme A**
- In presence of **Acyl-CoA Synthetase** (**Thiokinase**) **forming an activated Fatty acid as Acyl-CoA.**
- This process is **ATP-dependent**, & occurs in **2 steps.**

- During the activation of Fatty acid **ATP is converted to AMP and ppi.**
- **Two high energy bonds** of **ATP** are **cleaved** and **utilized** in this activation which is **equivalent to 2 ATPs.**

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- Subsequent hydrolysis of PP_i from ATP drives the **reaction strongly forward.**
- Note the **Acyl- Adenylate** is an **intermediate** in the mechanism.

- There are **different Acyl-CoA Synthetase** for fatty acids of **different chain lengths**.

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Activated Fatty Acid (Acyl-CoA) is a High Energy Compound

Which Facilitates The Second Stage Of Beta Oxidation Of Fatty Acid

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Stage II
Translocation Of Acyl-CoA From Cytosol Into Mitochondrial Matrix
With The Help Of Carnitine

- β-oxidation proper occurs in the Mitochondrial matrix.

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- **CoA** part of Acyl-CoA is **impermeable to inner membrane of Mitochondria**

- Since **CoA is a complex structure.**

- **Long-chain Fatty acids cannot be directly translocated** into the Mitochondrial matrix.

- However **short chain Fatty acids are directly translocated** into the Mitochondrial matrix

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- **To translocate the activated long chain Fatty acid** (Acyl-CoA) from the **cytosol to the mitochondrial matrix**

- **Across the mitochondrial membrane** operates a specialized **Carnitine Carrier System.**

What Is Carnitine?

- **Carnitine** is a functional, **Non Protein Nitrogenous** (NPN) substance.
- Carnitine is **biosynthesized** in the body **by amino acids Lysine and Methionine.**

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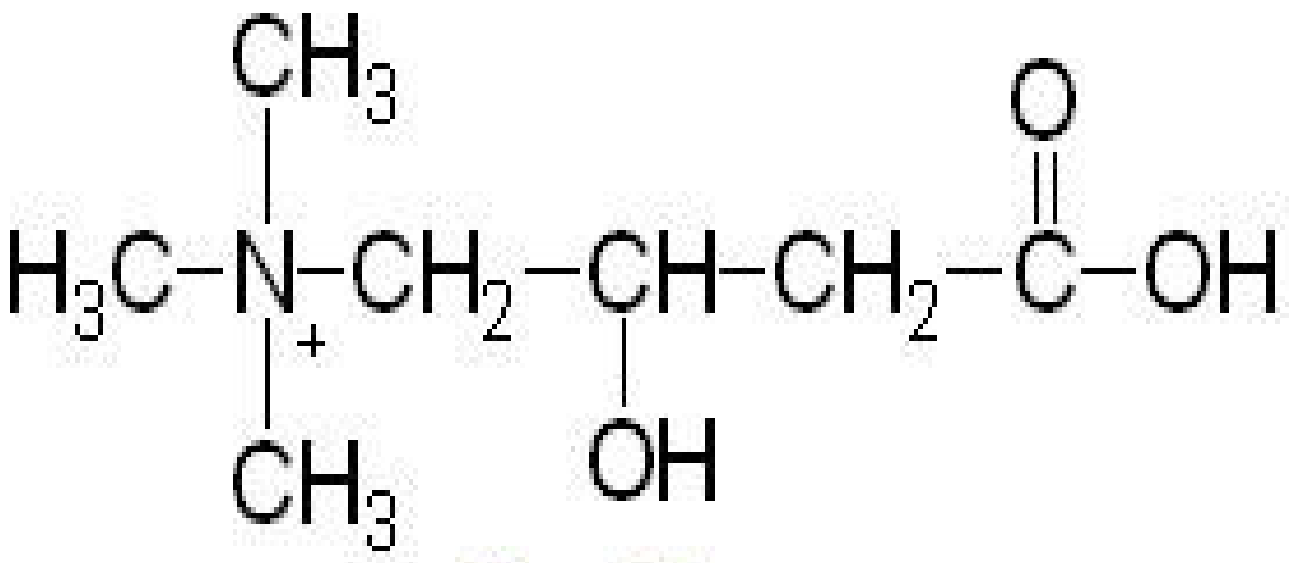
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Carnitine chemically is

β Hydroxy- γ Tri Methyl Ammonium Butyrate

OR

3-Hydroxy 4- Tri Methyl Ammonium Butyrate

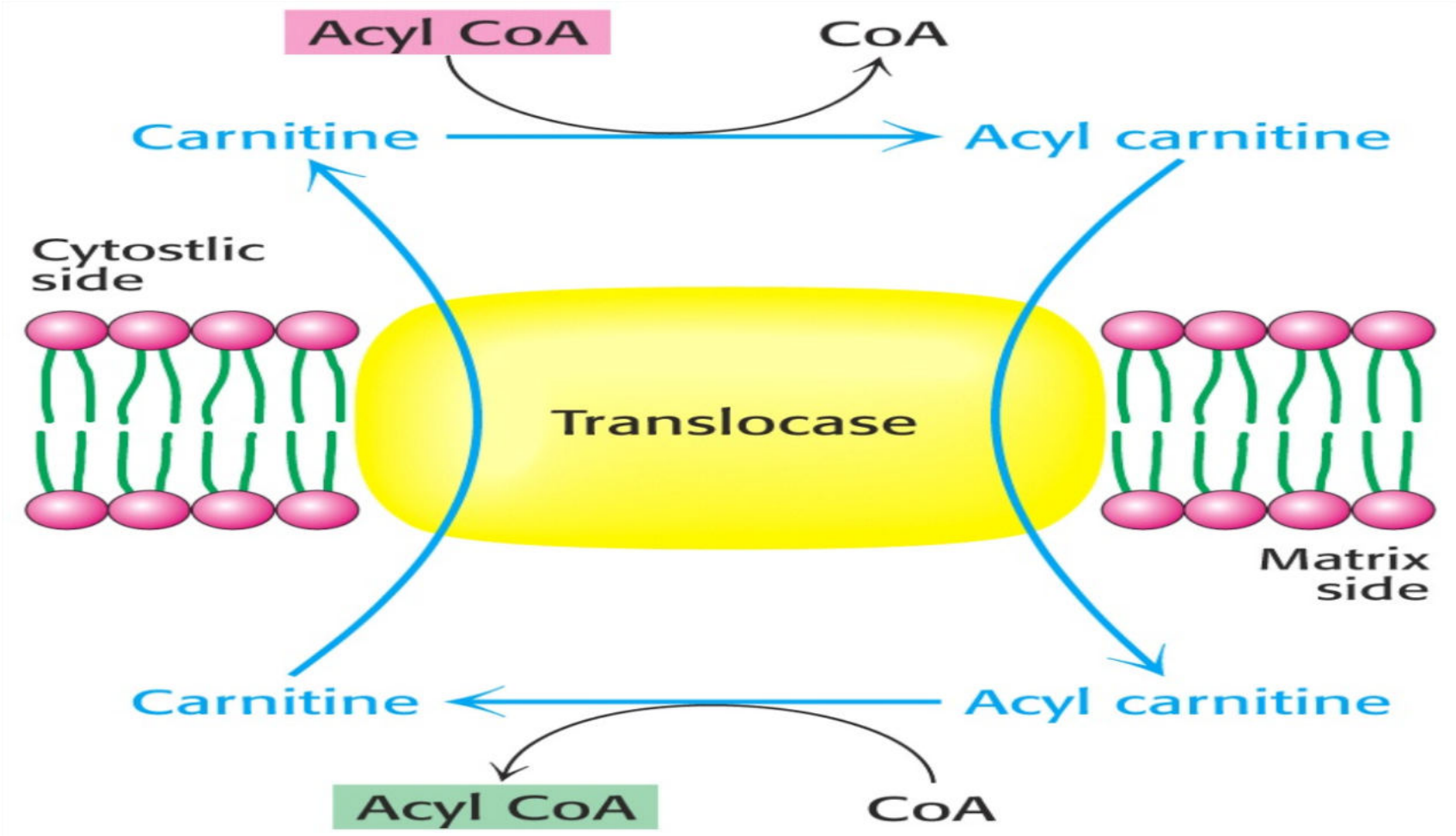


Carnitine

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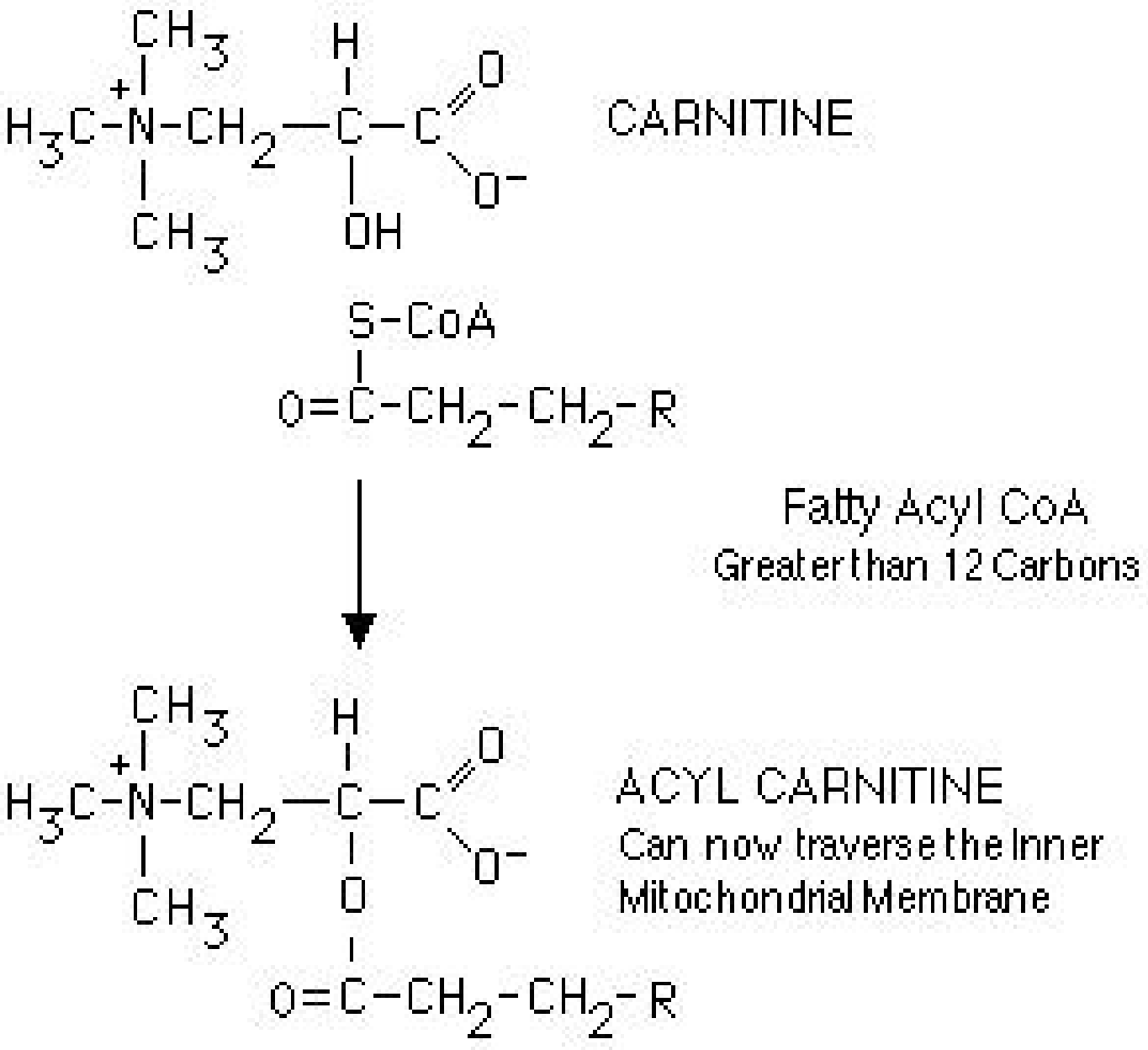
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- **Long chain Acyl CoA** traverses the inner mitochondria membrane with a special transport mechanism called **Carnitine Shuttle**.



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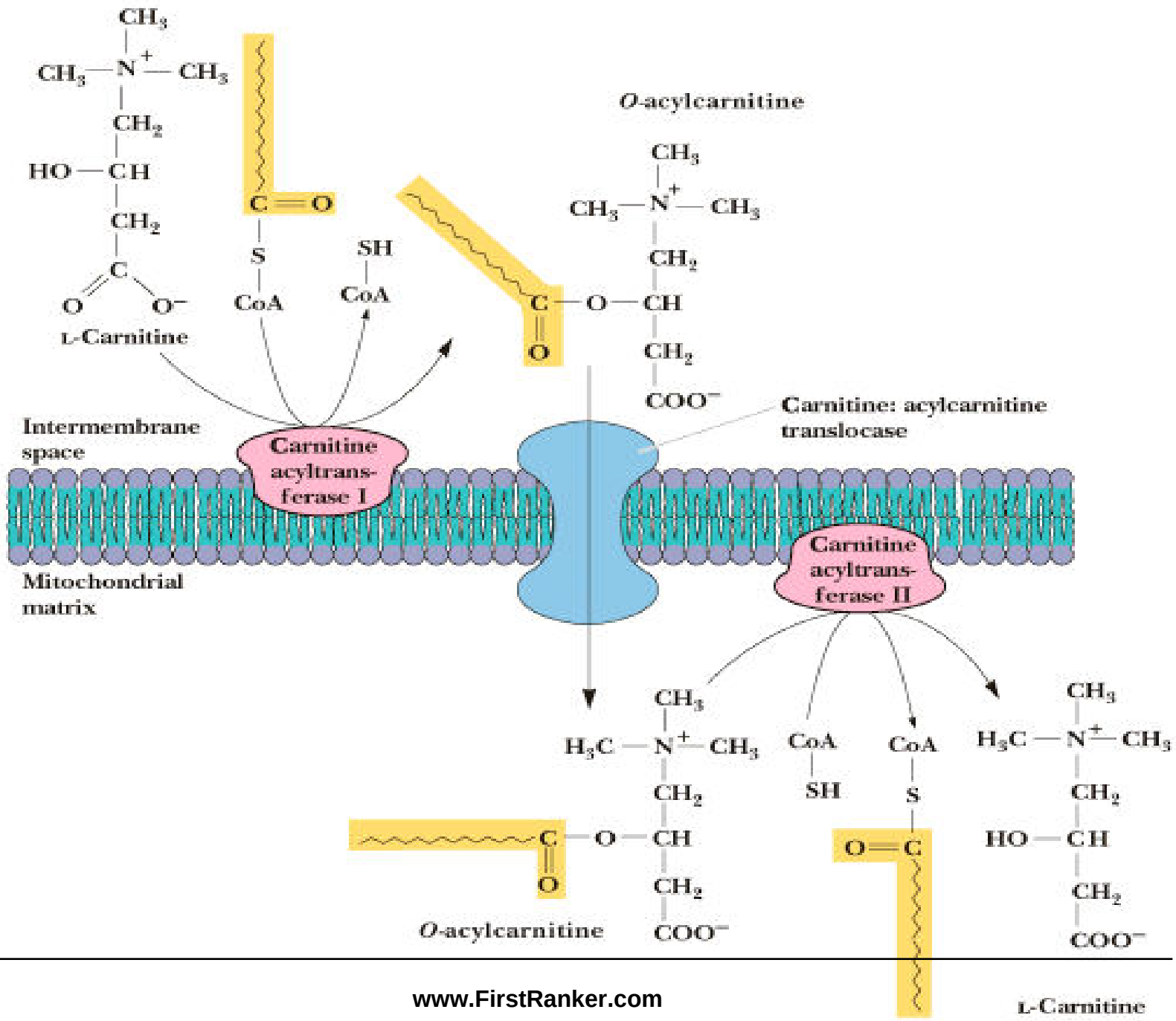
Mechanism Of Carnitine In Transport Of Fatty Acyl CoA From Cytosol To Mitochondrial Matrix

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- Acyl-CoA a high energy compound **cleave its high energy bond in the second stage.**

- The bond energy released is used up for **linking of Carnitine to Acyl chain to form Acyl-Carnitine.**



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- Long-chain FA are converted to Acyl Carnitine and are then transported
- Acyl-CoA are reformed inside the inner membrane of mitochondrial matrix.

- Acyl groups from Acyl COA is transferred to Carnitine to form Acyl Carnitine catalyzed by **Carnitine Acyl Transferase I,** in the outer mitochondrial membrane

- Acylcarnitine is then shuttled across the inner mitochondrial membrane by **a Translocase** enzyme.

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- The Acyl group is transferred back to CoA of Mitochondrial pool in mitochondrial matrix by **Carnitine Acyl Transferase II.**

- Finally, Carnitine is returned to the cytosolic side by **Protein Translocase**, in exchange for an incoming Acyl Carnitine.

Points To Remember

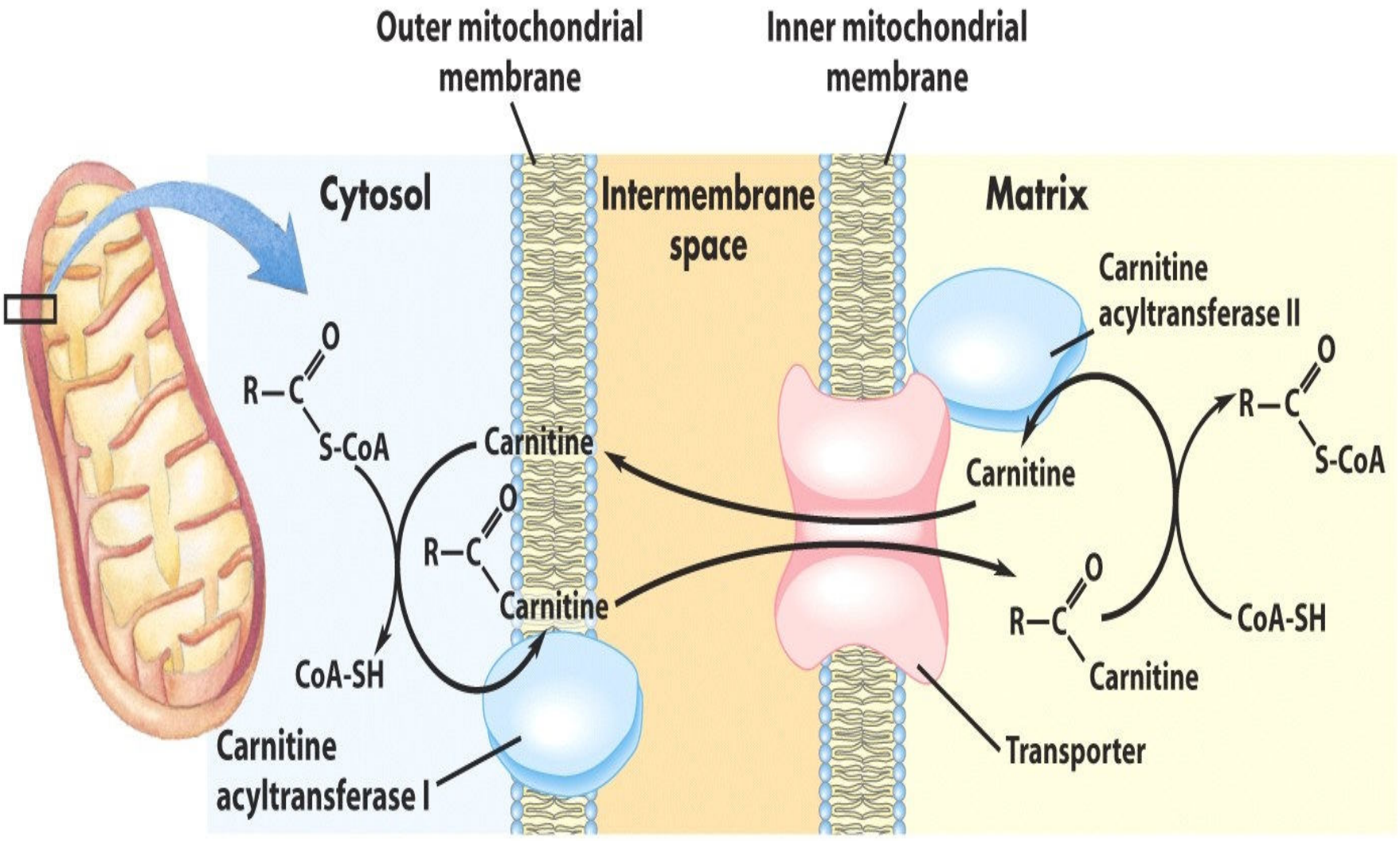
- Cell maintains two separate pools of Coenzyme-A:
  - **Cytosolic pool of CoA**
  - **Mitochondrial pool of CoA**

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- CoA is complex structure cannot transport across Mitochondrial membrane

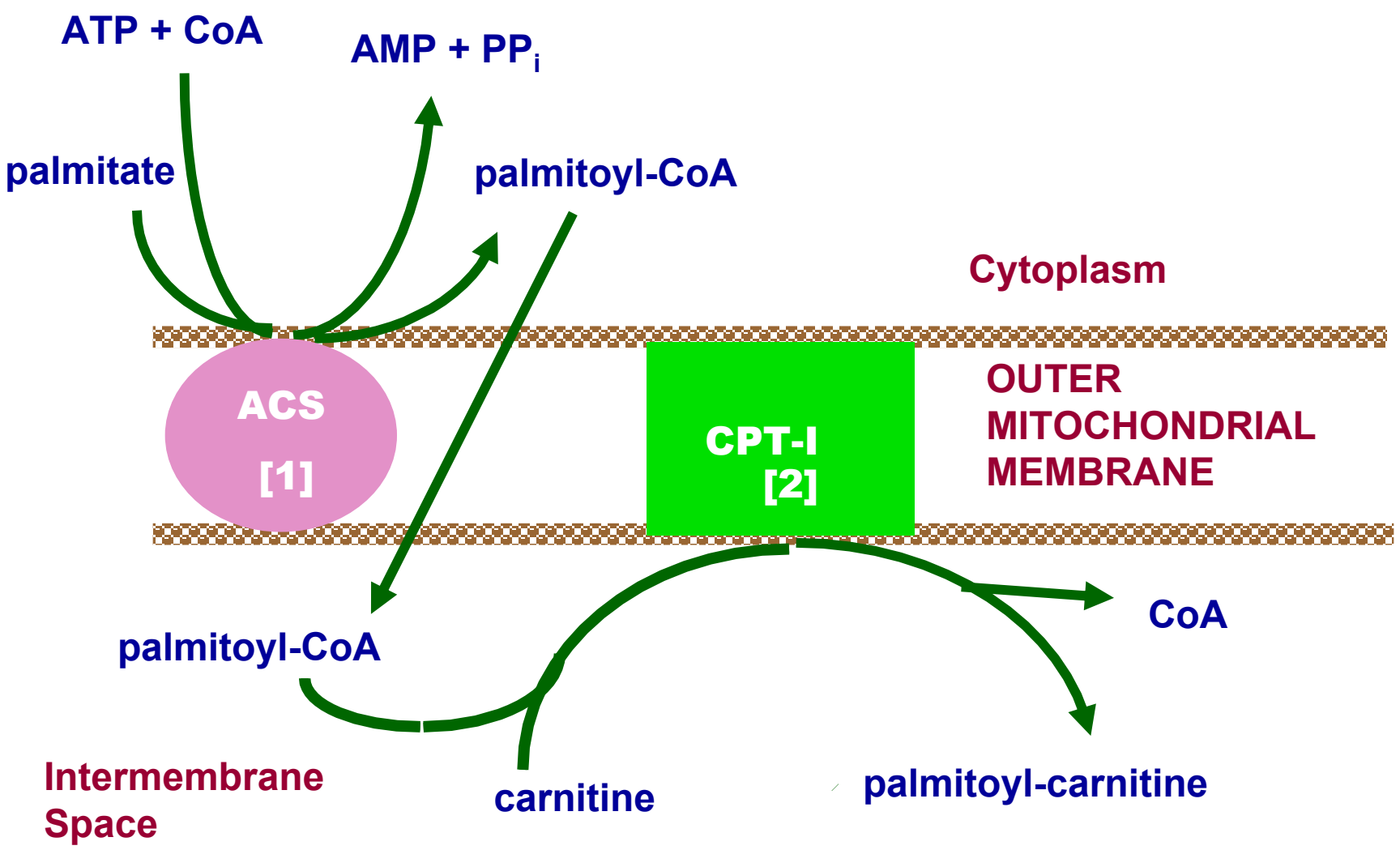
- CoA linked to Fatty acid in Mitochondria is different from that CoA used for Fatty acid activation.



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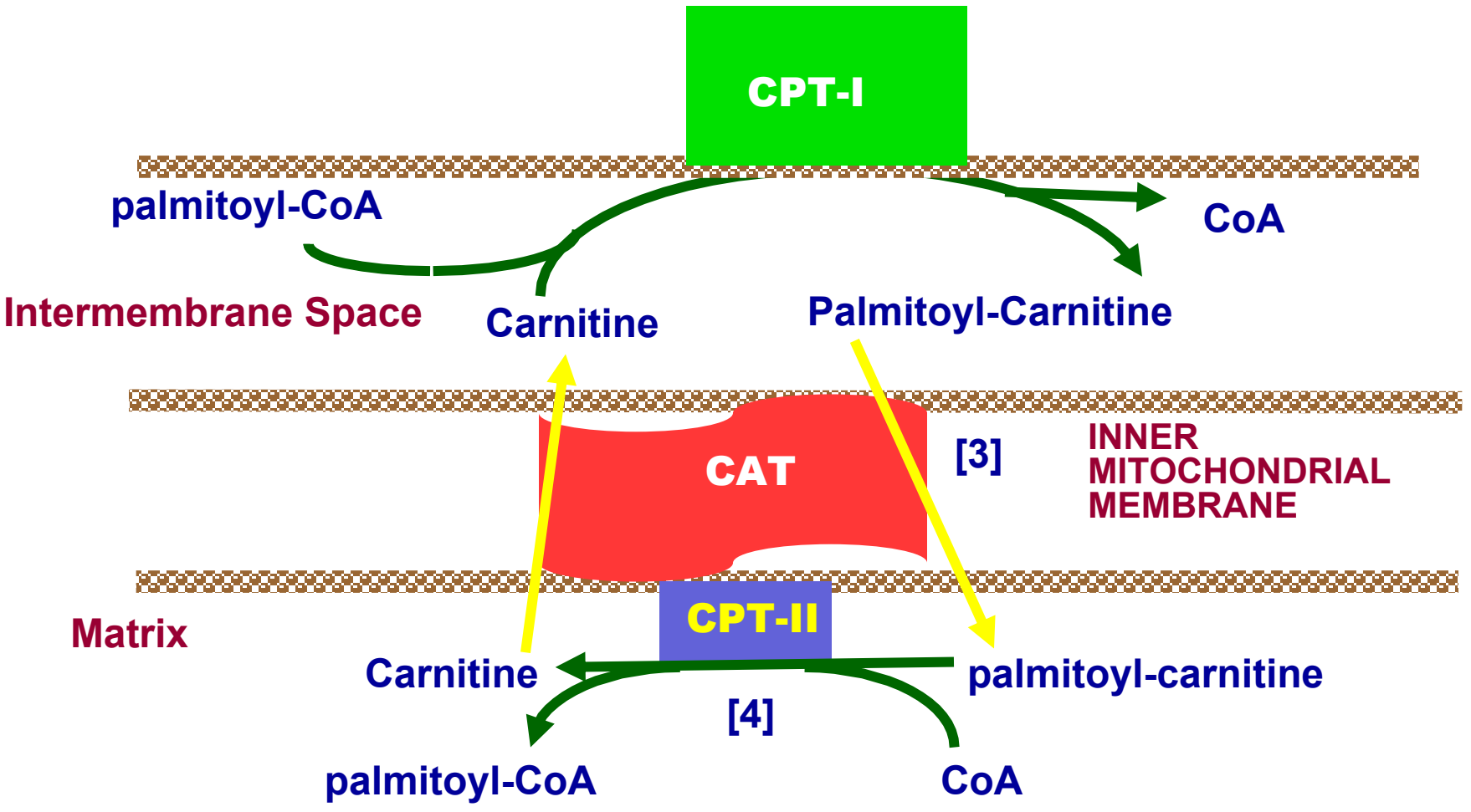
Translocation of Palmitoyl-CoA Across Mitochondrial Membrane



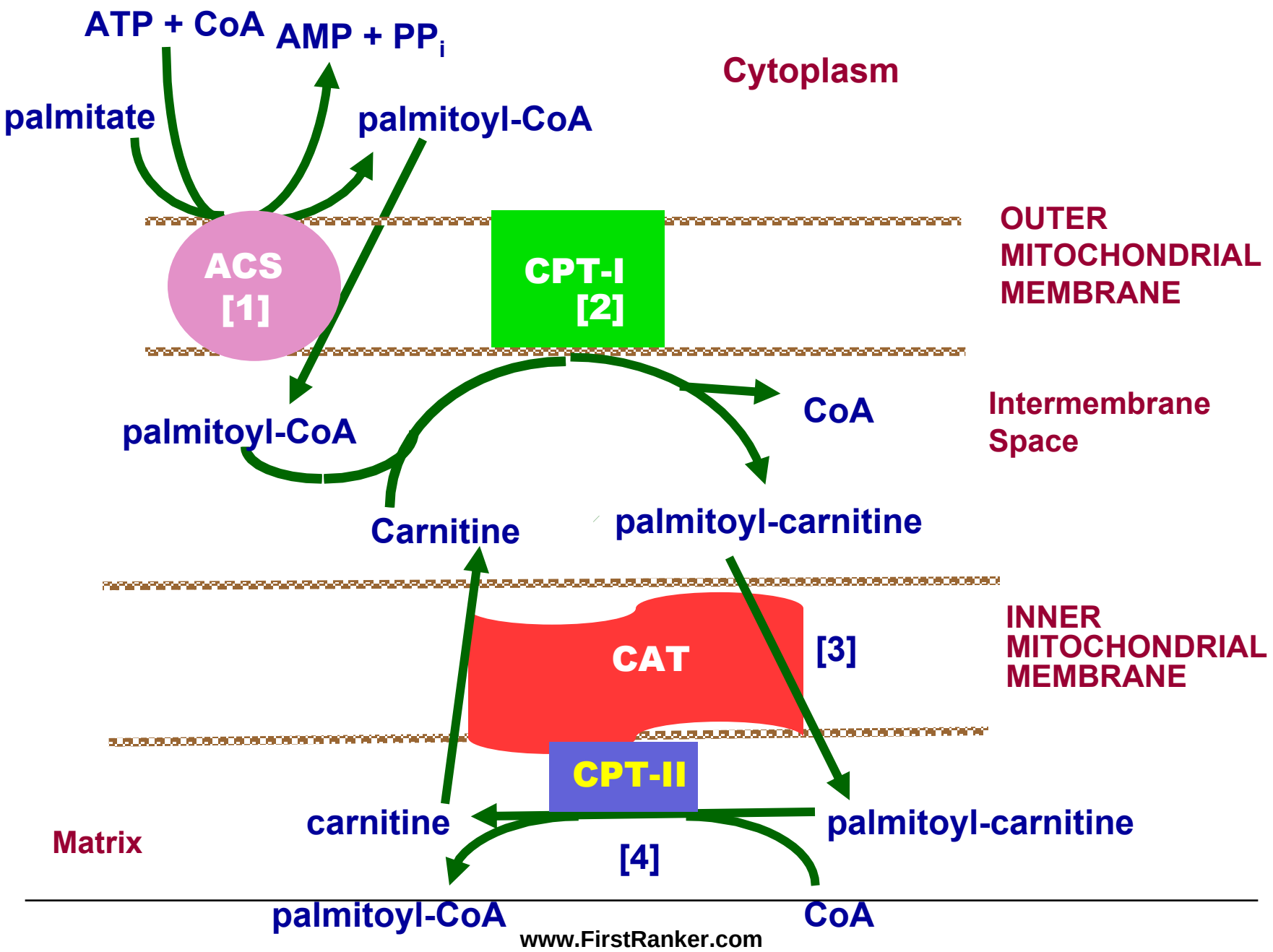
Activation of Palmitate to Palmitoyl CoA and conversion to Palmitoyl Carnitine

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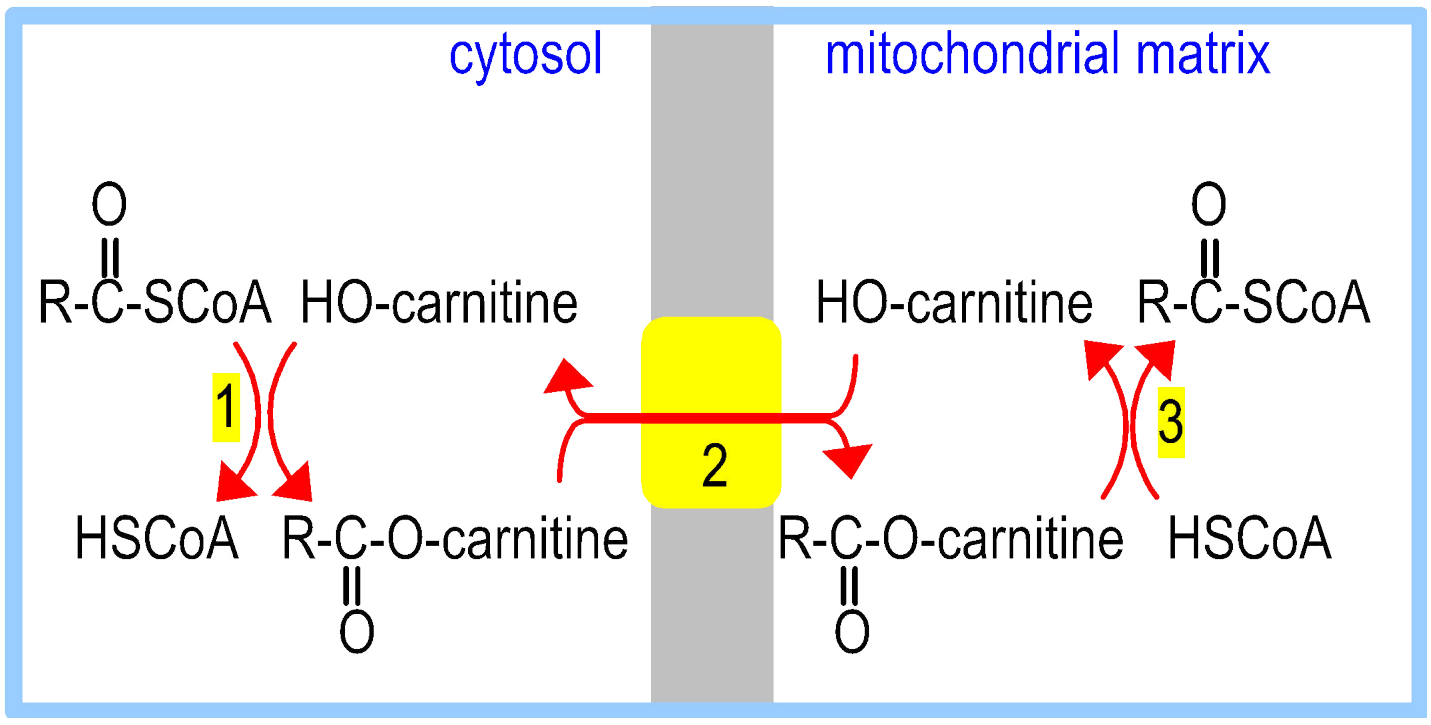


Mitochondrial uptake via of Palmitoyl-Carnitine via the Carnitine-Acylcarnitine Translocase (CAT)



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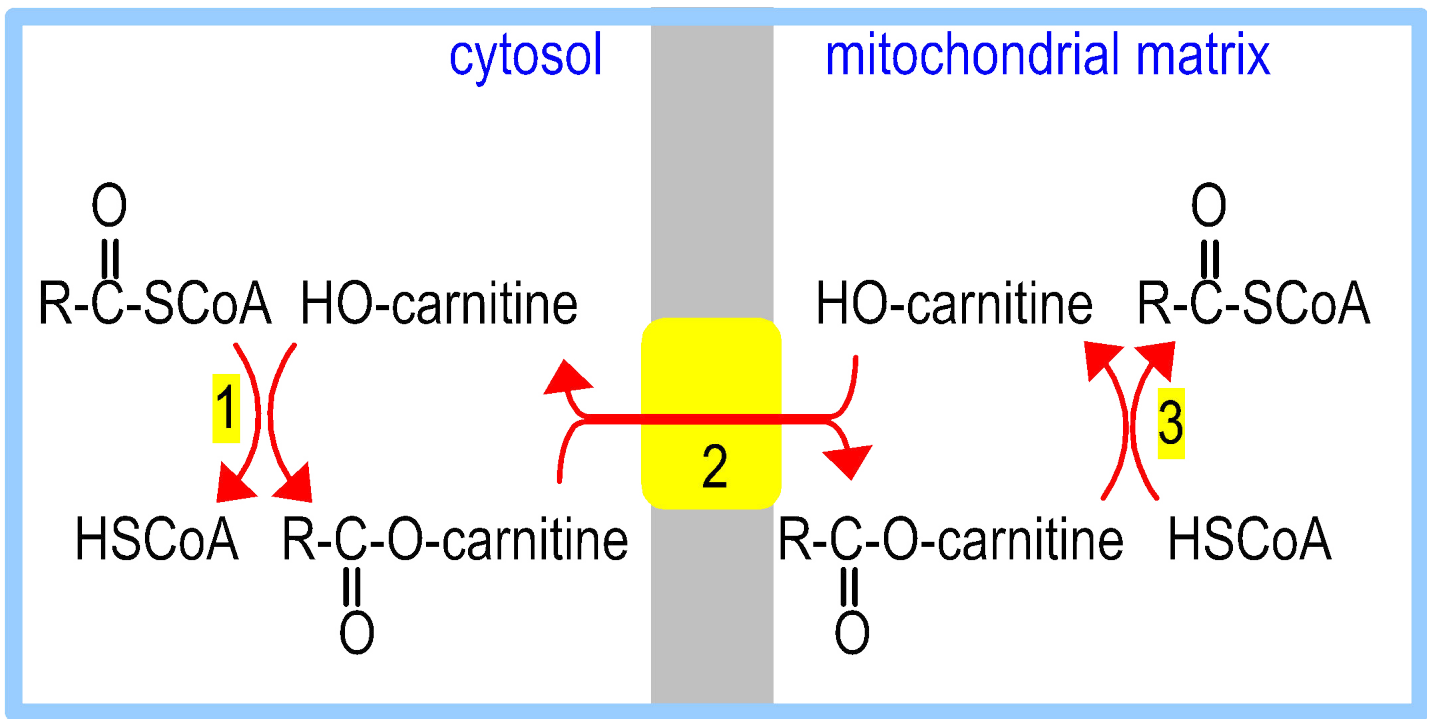
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Carnitine-mediated transfer of the fattyAcyl moiety into the mitochondrial matrix is a 3-step process:

1. **Carnitine Palmitoyl Transferase I**, an enzyme on the cytosolic surface of the outer mitochondrial membrane, transfers a fatty acid from CoA to the OH on Carnitine.

2. An **Translocase**/**Antiporter** in the inner mitochondrial membrane mediates exchange of Carnitine for Acylcarnitine.



3. **Carnitine Palmitoyl Transferase II**, an enzyme within the matrix, transfers the fatty acid from Carnitine to CoA. (Carnitine exits the matrix in step 2.)

The fatty acid is now esterified to CoA in the mitochondrial matrix.

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Stage III
Steps of Beta Oxidation Proper/Cycle In Mitochondrial Matrix

- **Oxidation Reaction**
- **Hydration Reaction**
- **Oxidation Reaction**
- **Cleavage Reaction**

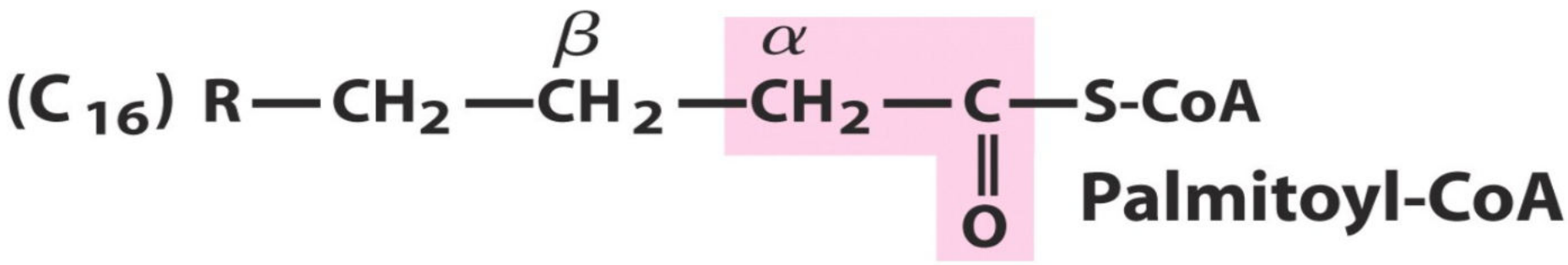
Site/Occurrence Of β – Oxidation Proper

- In the **Mitochondrial Matrix** of Cells.
- **After the reach of Acyl-CoA in Mitochondrial matrix.**

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Mechanism Of Reactions Of Beta Oxidation Proper of Palmitoyl-CoA



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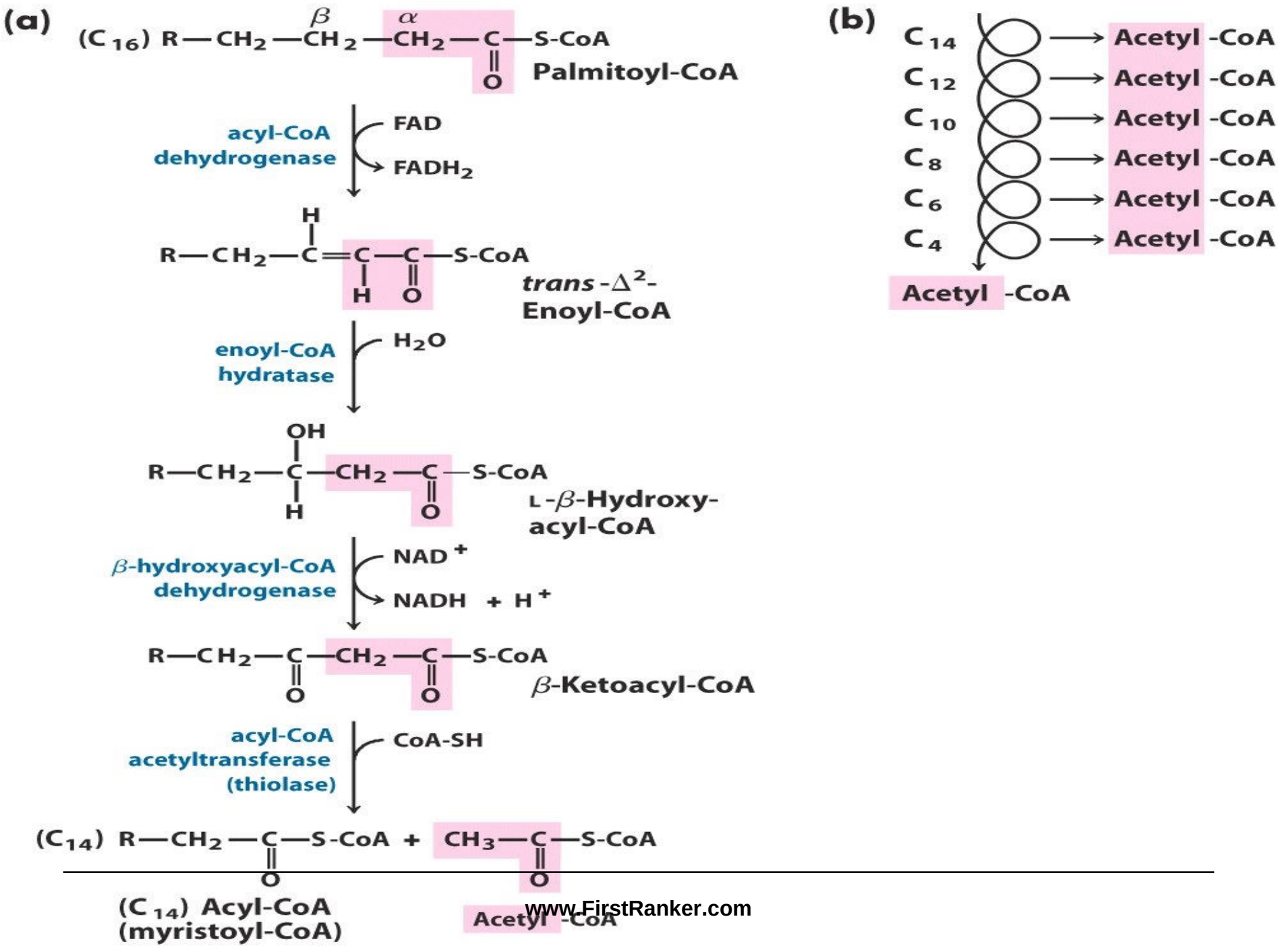
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Step I: Oxidation by ***FAD linked Acyl CoA Dehydrogenase***

Step II: Hydration by **Enoyl CoA Hydratase**

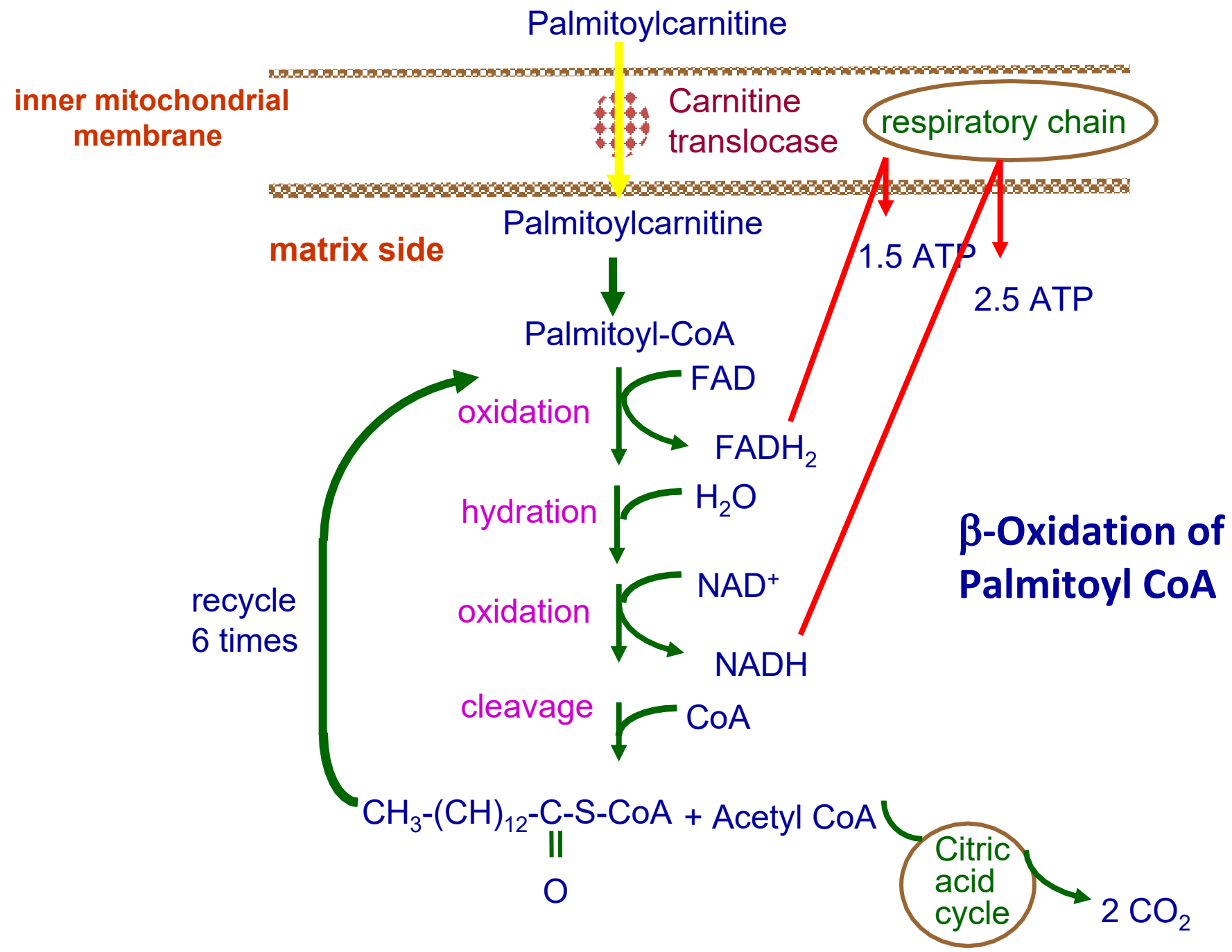
Step III: Oxidation by ***NAD linked Beta Hydroxy Acyl CoA Dehydrogenase***

Step IV: Thiolytic Clevage Keto Thiolase



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- Strategy of **First 3 reactions** of Beta Oxidation proper is to
- **Create a Carbonyl group** (C=O) on the **β-Carbon atom (CH2)** of a Fatty acid.
- This **weakens the bond between α and β Carbon atoms** of Fatty acid.

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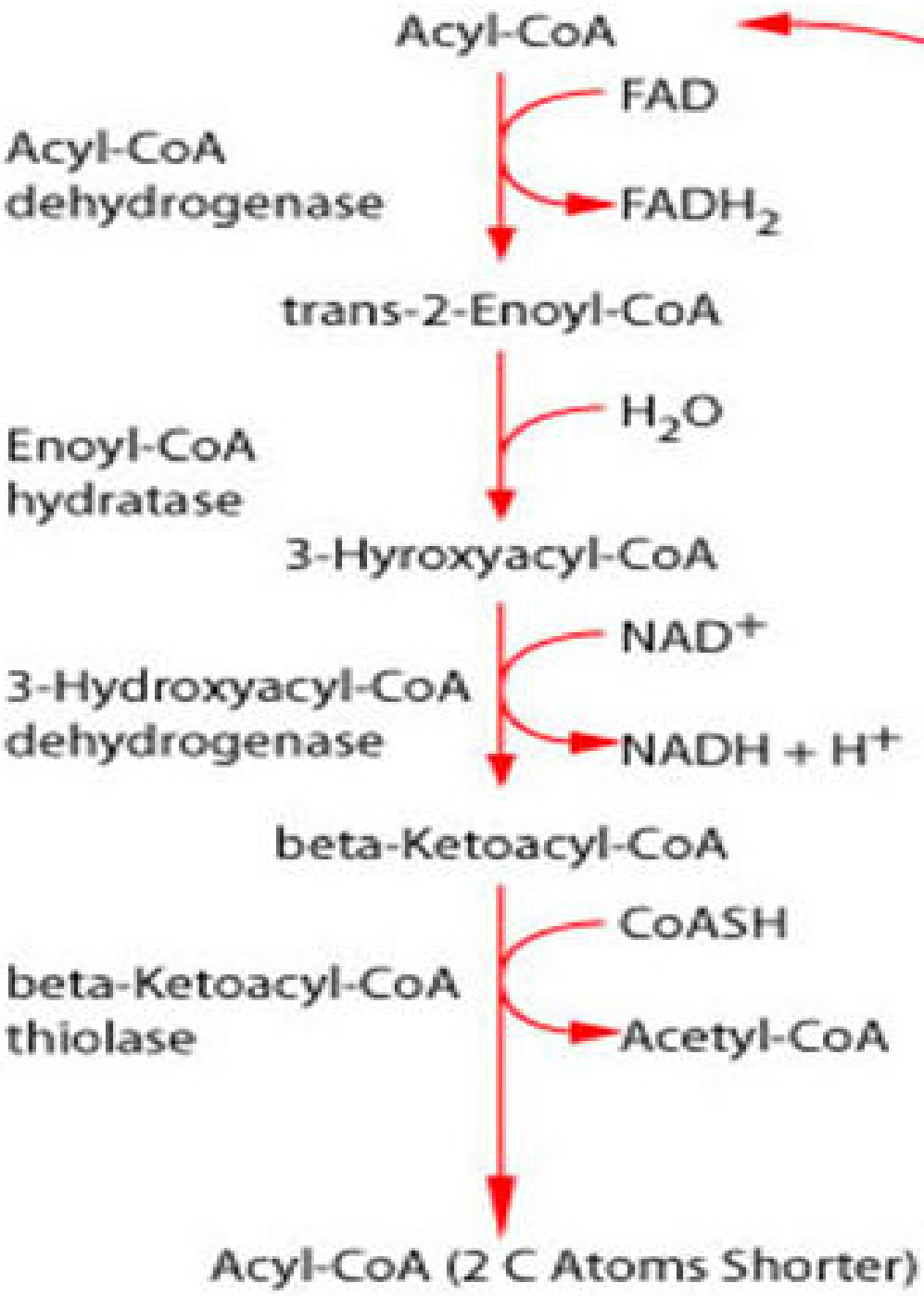
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- **Fourth reaction** cleaves the **"β-Keto ester"** in a **reverse Claisen condensation reaction.**

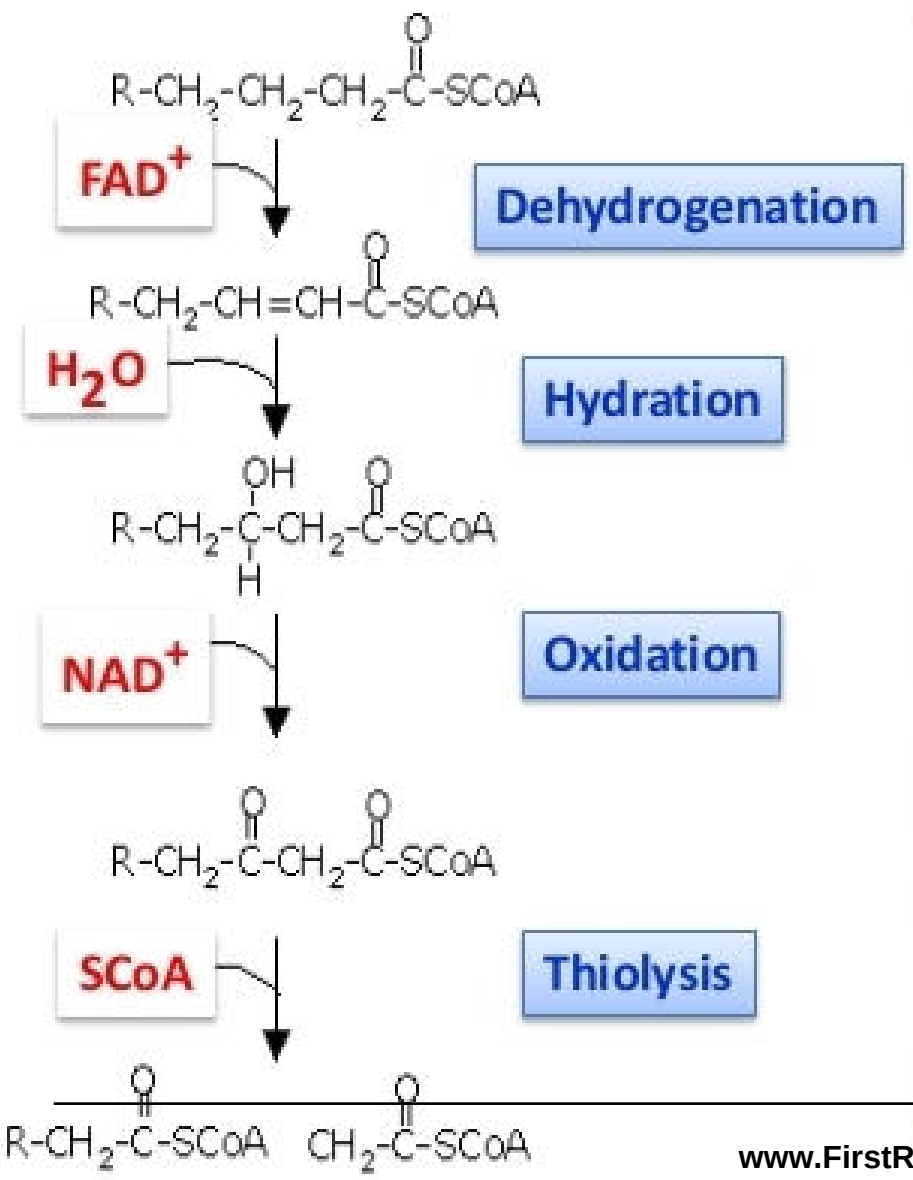
- **Products** of Each turn/cycle of **beta oxidation proper are** :
  - **Acetyl-CoA**
  - **Acyl-CoA** with **two carbons shorter**

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The Four-Step Beta-Oxidation Cycle of Fatty Acids



Each cycle through, releases a single acetyl-CoA molecule, reducing the initial fatty acid by two-carbon units.

Beta-oxidation can convert fatty acids having an even number of carbon atoms in their acyl chain, completely to acetyl-CoA.

For example, a fatty acid with 16 carbons in its acyl chain is converted to 8 acetyl-CoA molecules via beta-oxidation.

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Step 1

Role Of
Acyl-CoA Dehydrogenase
To Bring
Oxidation of the C_α-C_β bond
of Fatty acid

Acyl CoA Dehydrogenase is a
FAD linked Enzyme
(Flavoprotein)

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- Acyl CoA Dehydrogenase **catalyzes Oxidation reaction**
- Where there is a **removal of Hydrogen** from **alpha and beta carbon atoms** of Acyl-CoA.

- There **forms a double bond** between **C α-C β / C2 and C3** of Fatty Acid.
- The product of this oxidation reaction is **α-β Unsaturated Acyl CoA /Trans Enoyl CoA.**

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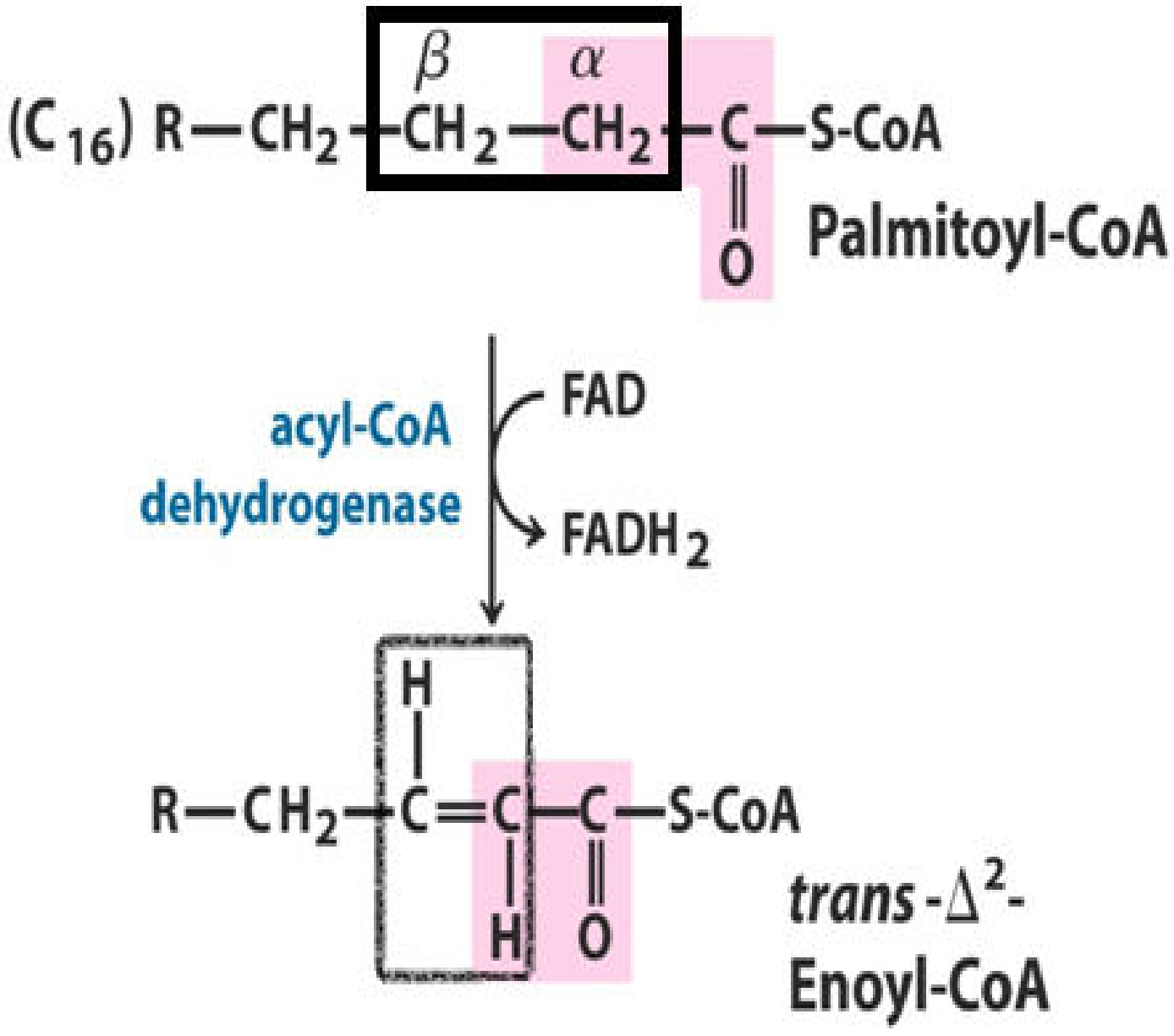
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- Coenzyme **FAD** is the **temporary hydrogen acceptor** in this oxidation reaction .
- The **reduced FADH2** is generated by oxidation reaction of Acyl CoA Dehydrogenase.
- **FADH2** is then **reoxidized**, after its enter into **Electron Transport Chain**

- **Mechanism of Acyl CoA Dehydrogenase involves :**
  - Proton **Abstraction/Removes Hydrogen**
  - **Double bond formation**
  - **Hydride removal by FAD**
  - Generation of **reduced FADH2**

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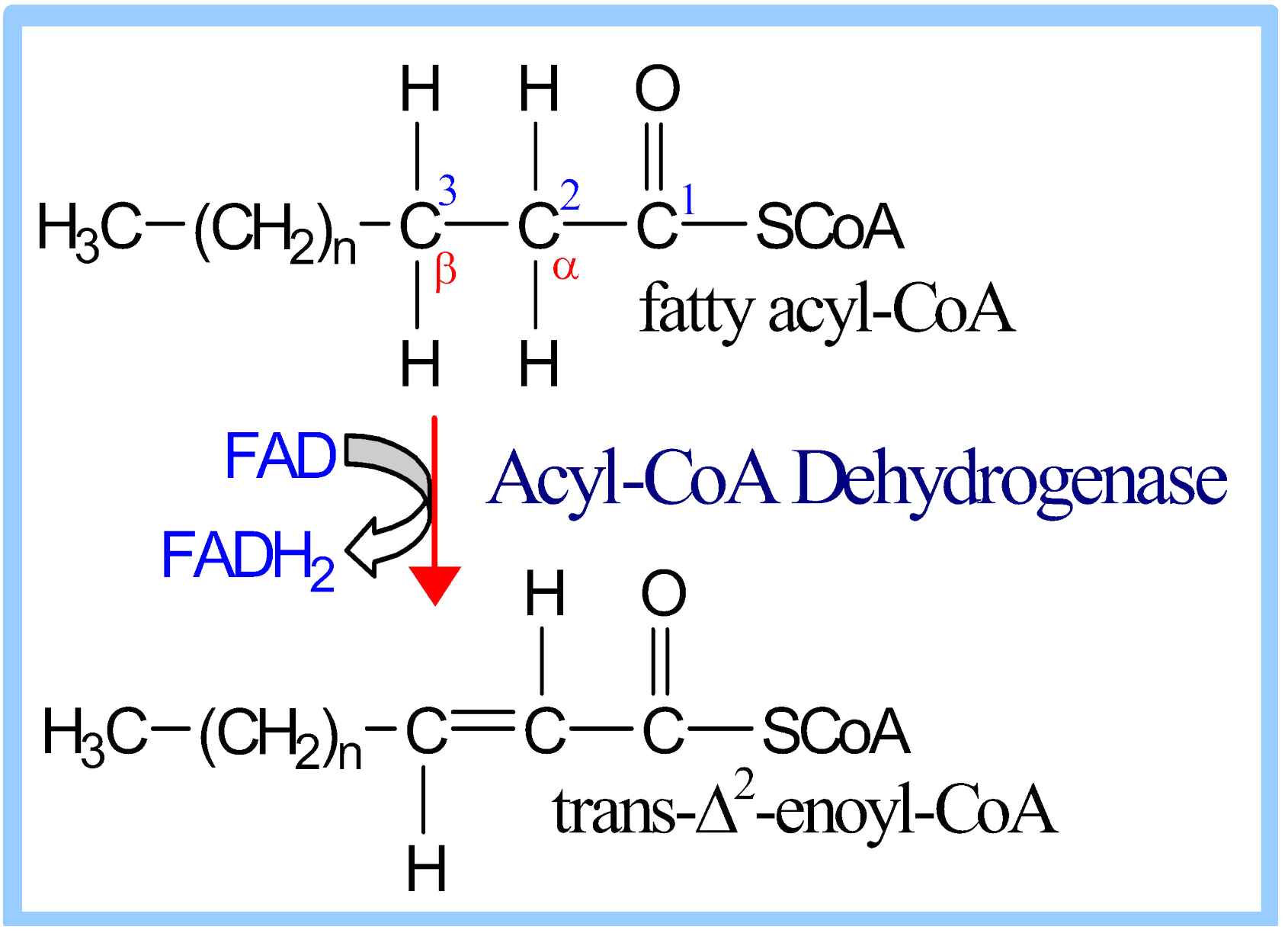


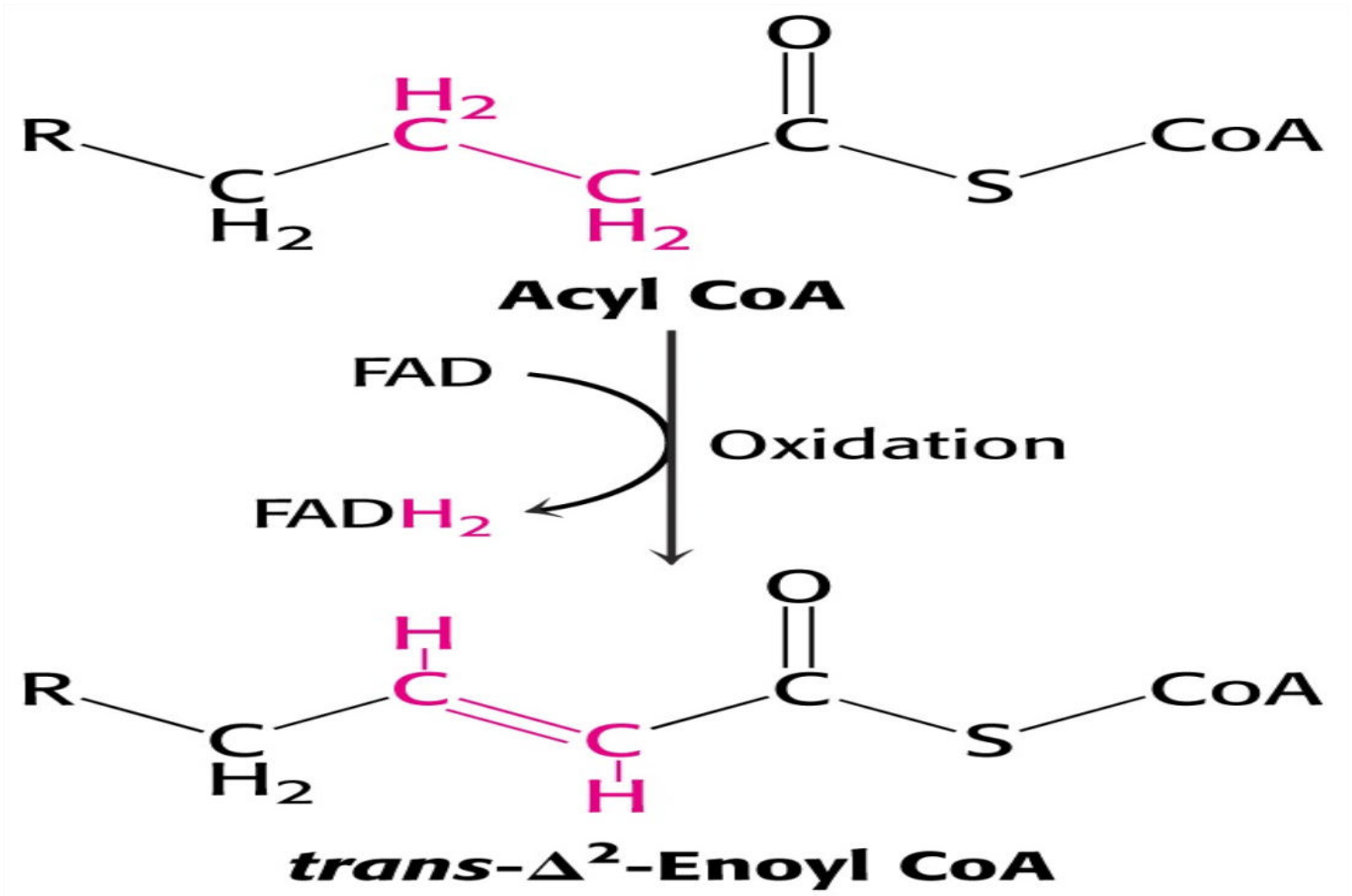
- FADH2 is oxidized by entering into **ETC.**
- Electrons from **FADH2 are passed to Electron transport chain components**,
- Coupled with phosphorylation to generate **1.5 ATP**

(By Oxidative Phosphorylation).

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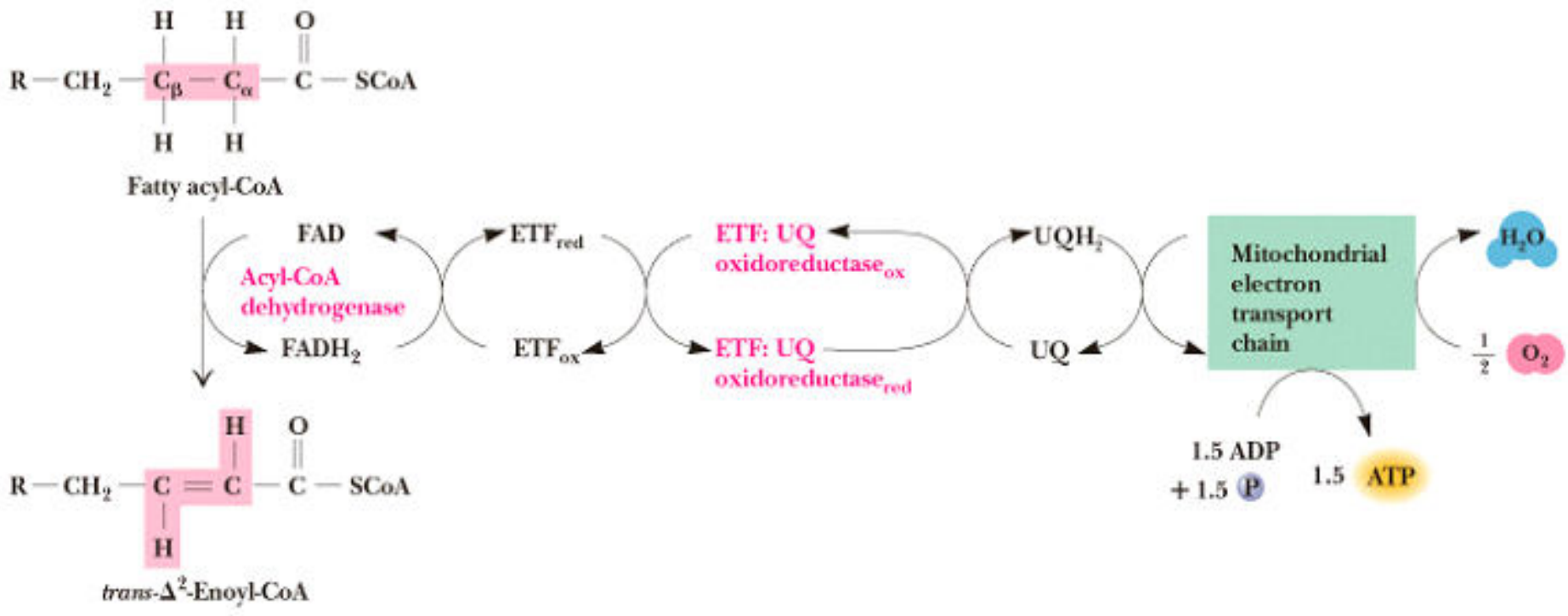




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Acyl-CoA Dehydrogenase



- There are **different Acyl-CoA Dehydrogenases :**
  - Short Chain Fatty acids (4-6 C),
  - Medium Chain Fatty Acids (6-10 C),
  - Long (12-18 C) and very long (22 and more)chain Fatty acids.

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Inhibitor Of
Acyl CoA Dehydrogenase

- Acyl CoA Dehydrogenase is **inhibited by** a **Hypoglycin** (from **Akee fruit**)

Step 2
Role Of
Enoyl CoA Hydratase

To add water across the double bond

Cα = Cβ of Trans-Enoyl-CoA

Saturate the double bond of Enoyl-CoA

Generate Hydroxyl group at beta carbon

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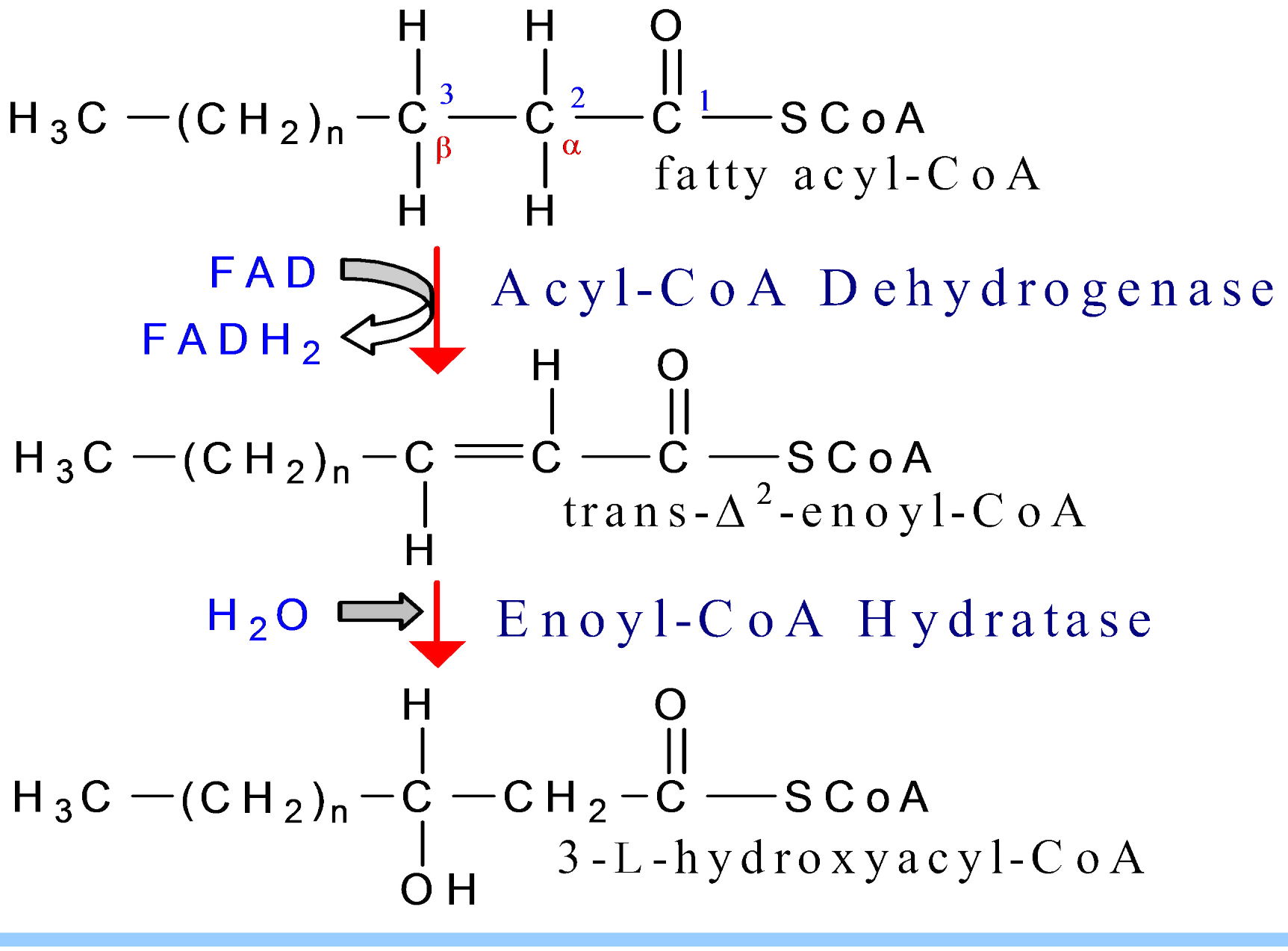
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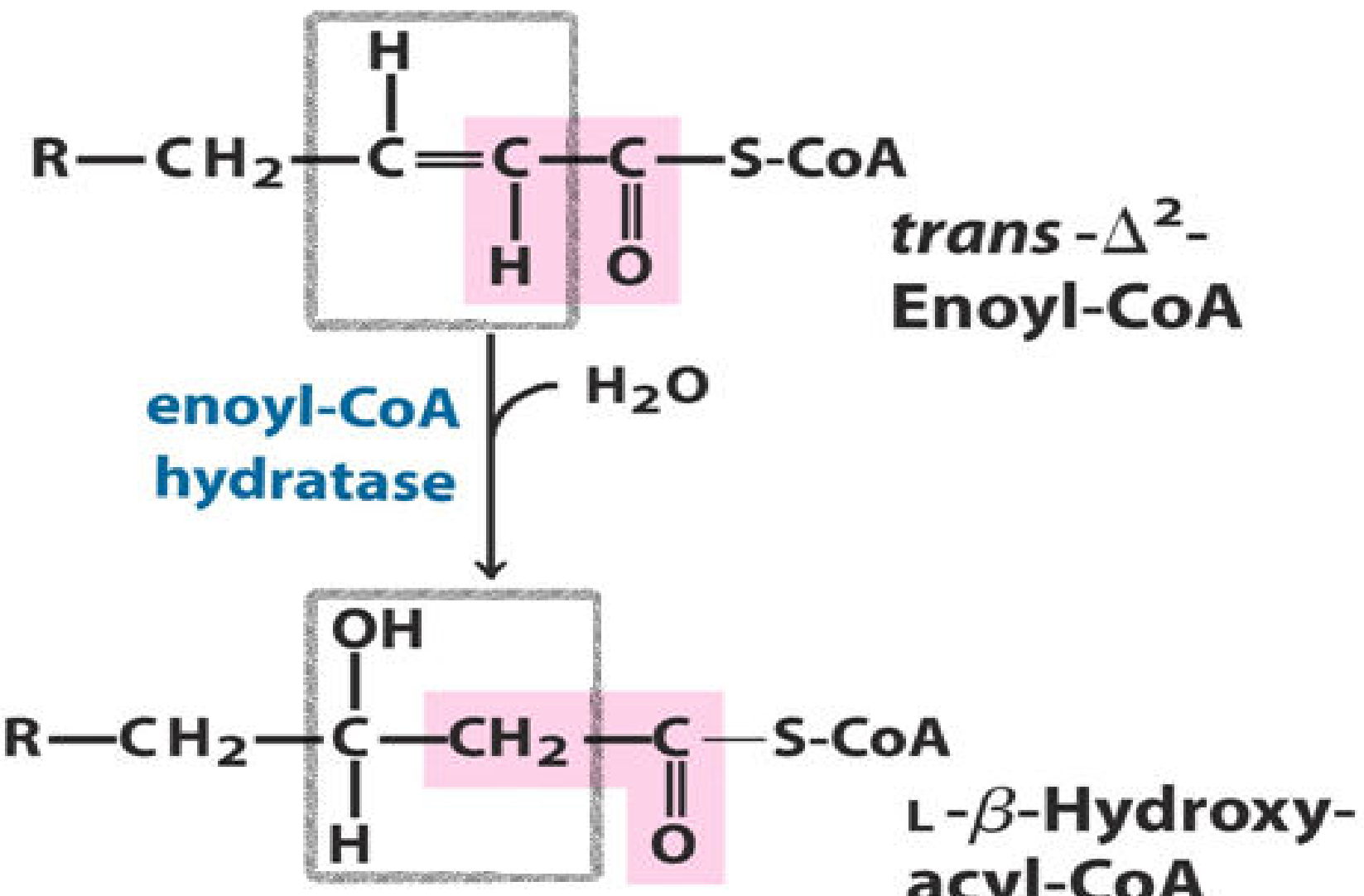
- **Enoyl-CoA Hydratase** catalyzes stereospecific **hydration** of the trans double bond
- It adds water across the double bond **at C2 and C3** of **Trans Enoyl CoA**

- This hydration reaction **generates Hydroxyl (OH) group** at beta carbon atom of FA
- **Converts Trans-Enoyl-CoA** to L **β-Hydroxyacyl-CoA**

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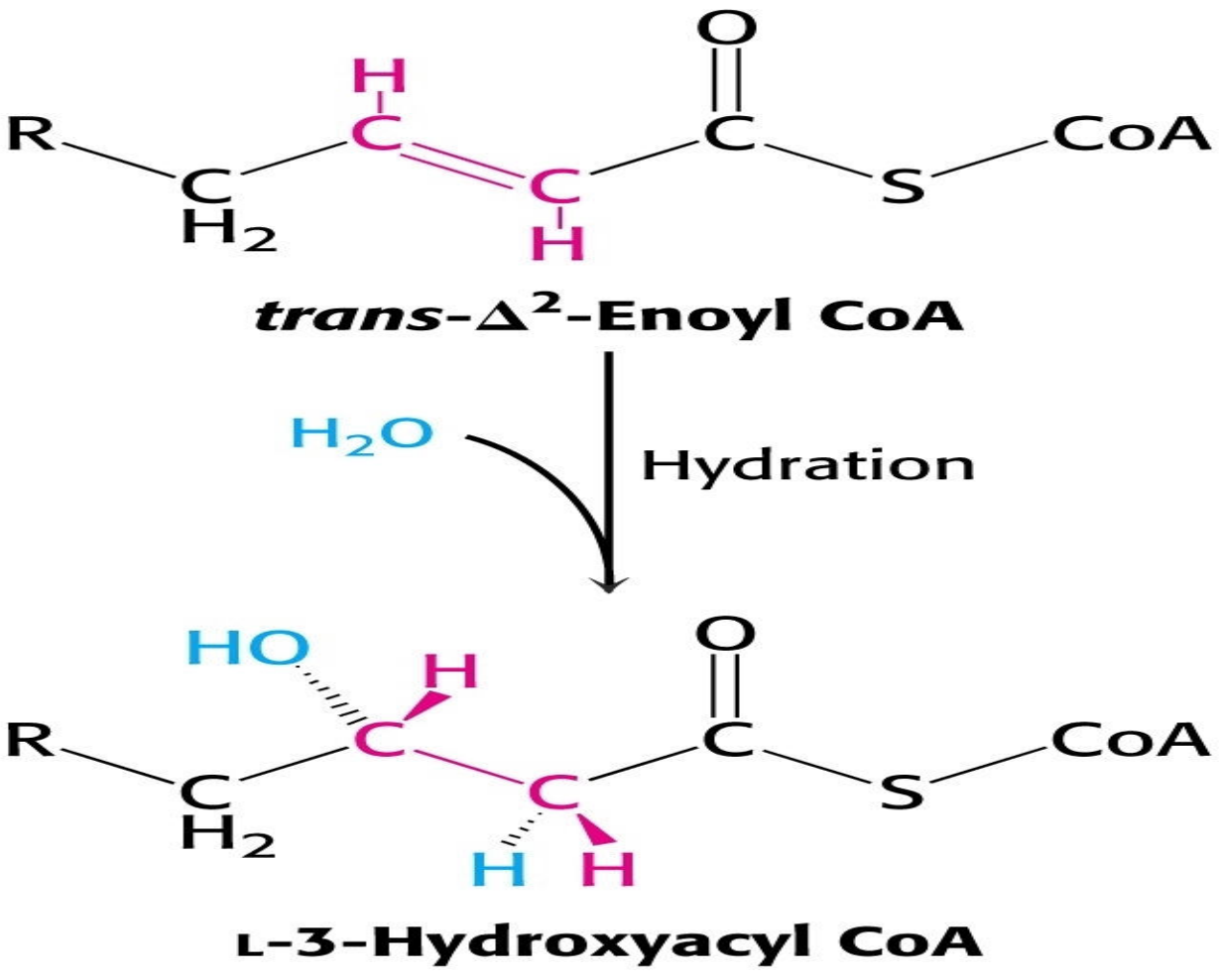
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Step 3
Role Of
Hydroxyacyl-CoA Dehydrogenase

To Oxidizes the β-Hydroxyl Group of β-Hydroxyacyl-CoA
And
Transform it into
β-Ketoacyl-CoA

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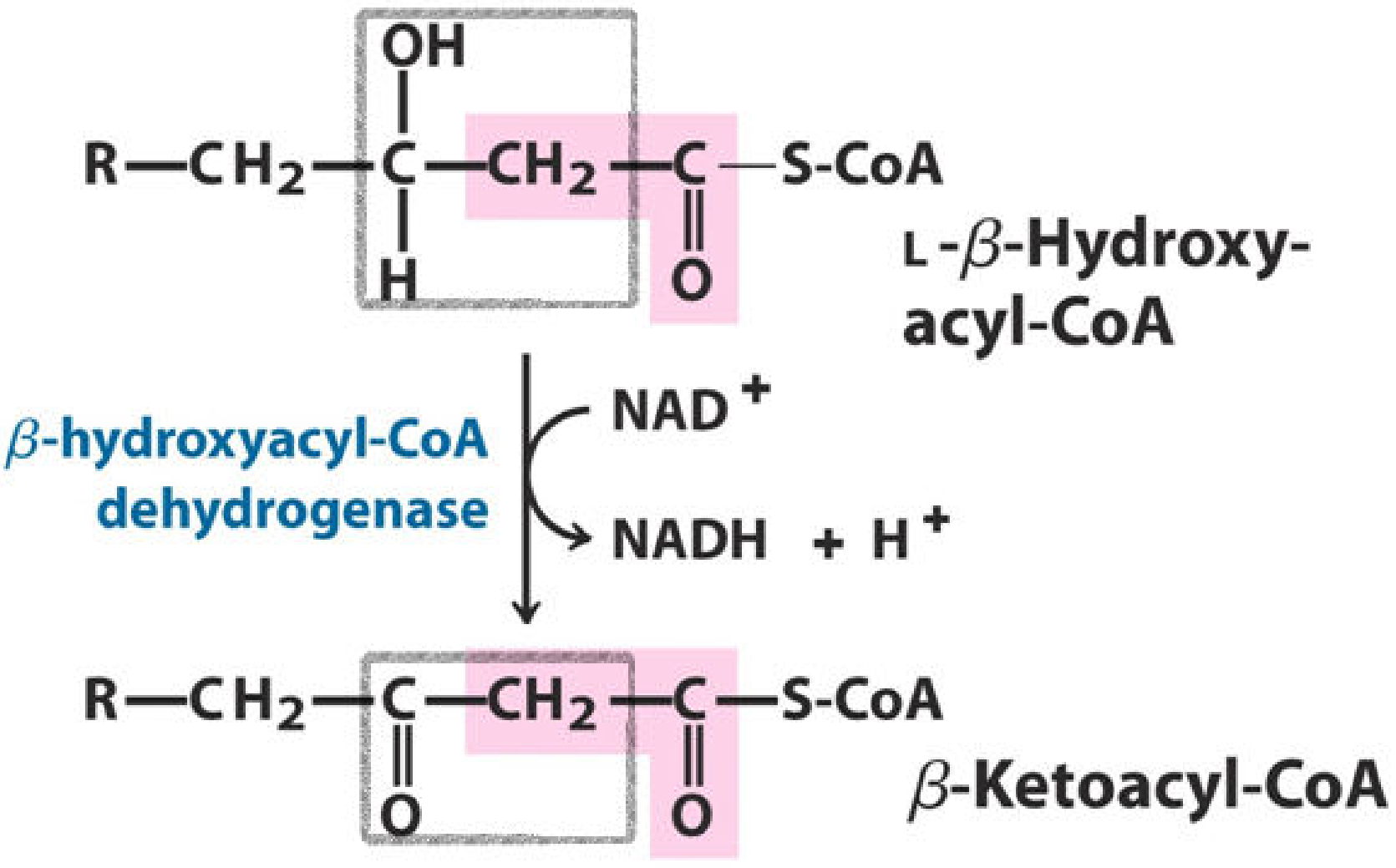
- **β-Hydroxyacyl-CoA Dehydrogenase is NAD^+ dependent**
- It catalyzes specific oxidation of the Hydroxyl group in the β position (C3) to form a ketone group.
- **NAD^+** is the temporary electron acceptor for this step which generates reduced form **$NADH+H^+$**

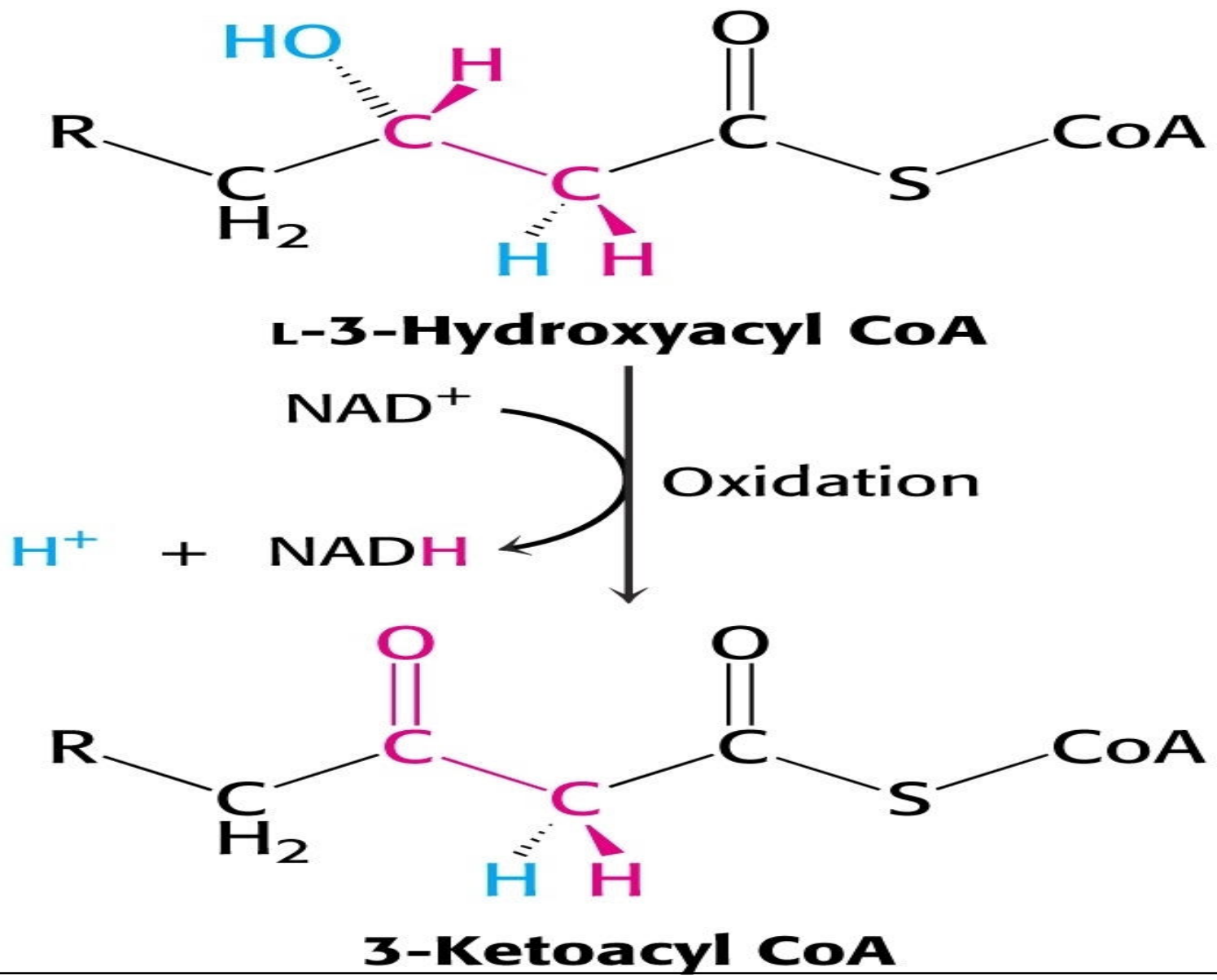
- **The oxidation** of

β-Hydroxyacyl CoA produces a product **β- Ketoacyl-CoA.**

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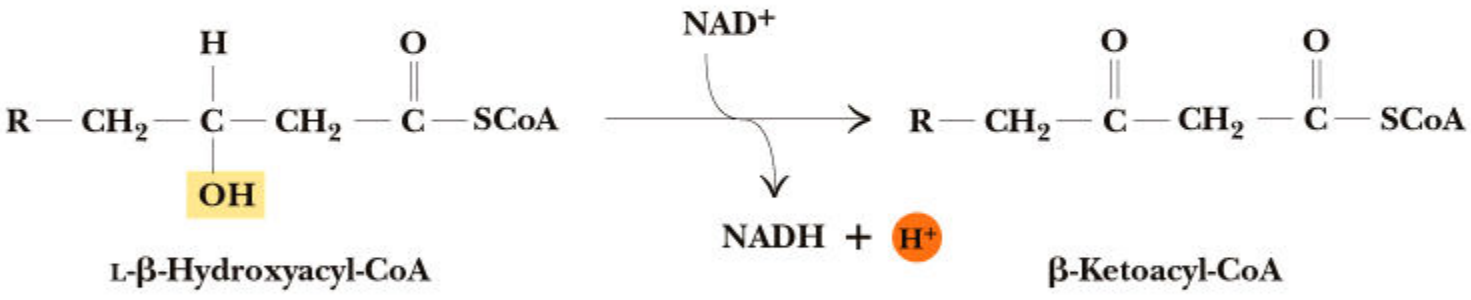




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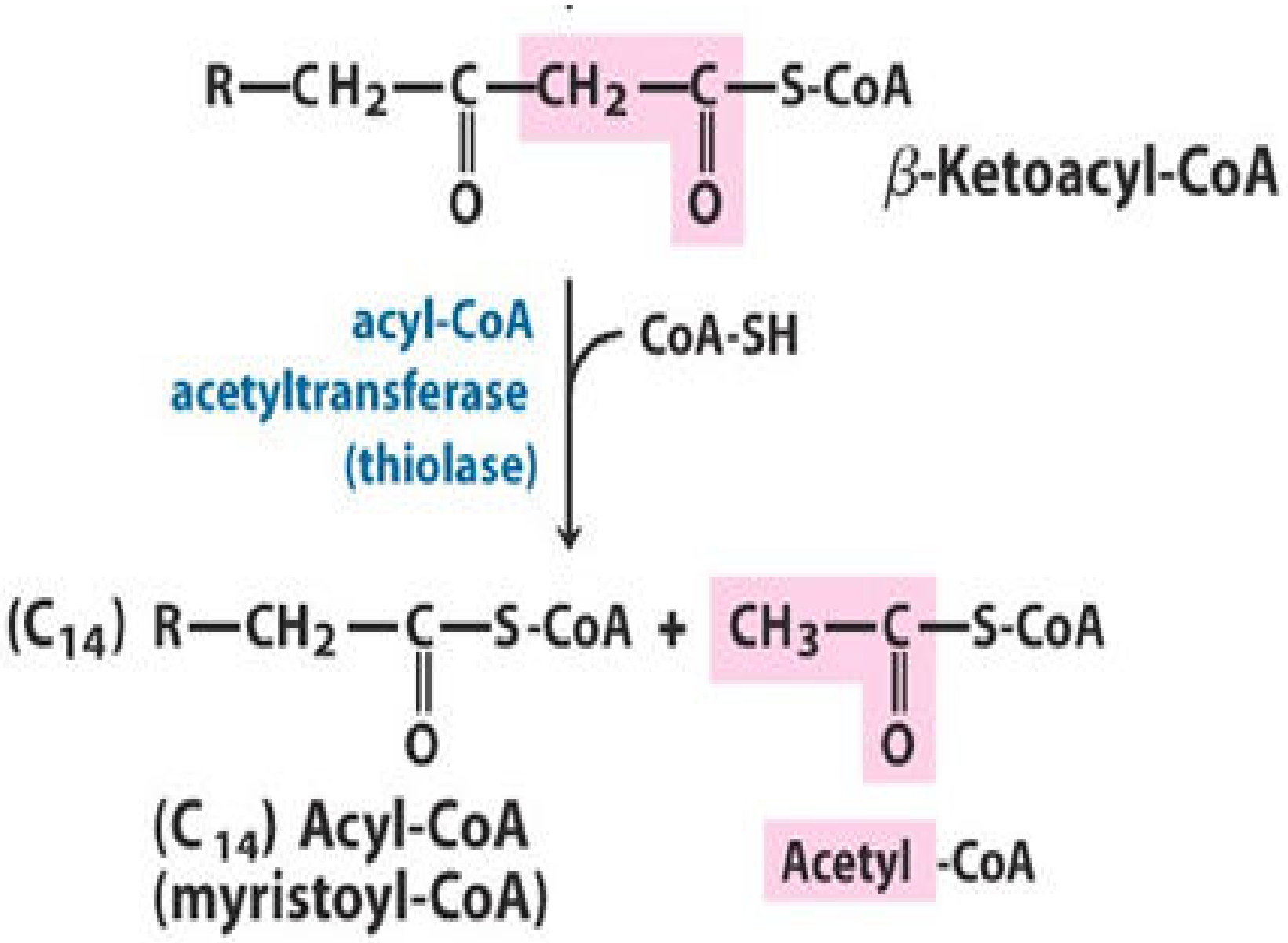
Step 4
Role Of β- Ketothiolase /Thiolase

Catalyzes Thiolytic cleavage of the two carbon fragment by splitting the bond between α and β carbons

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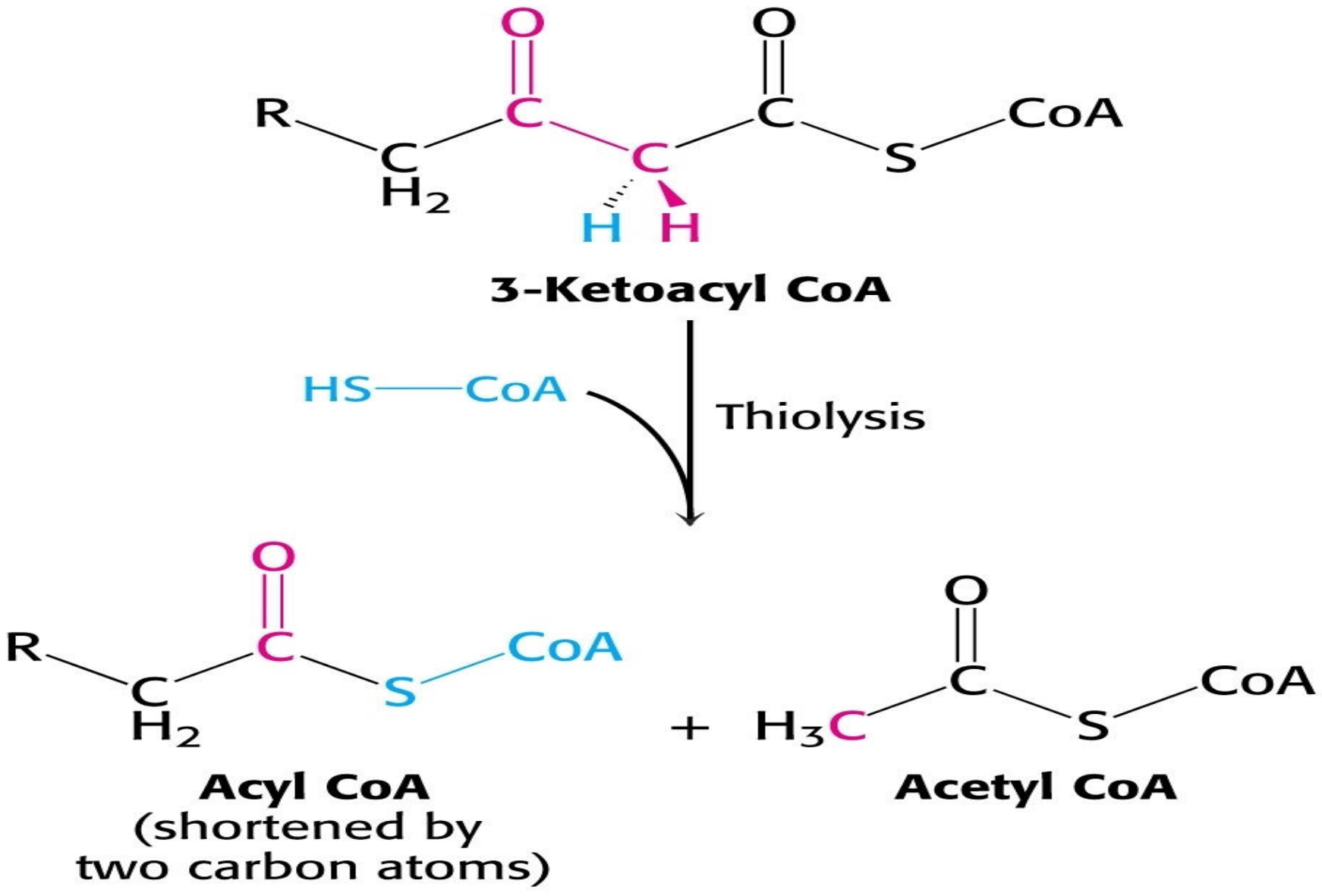
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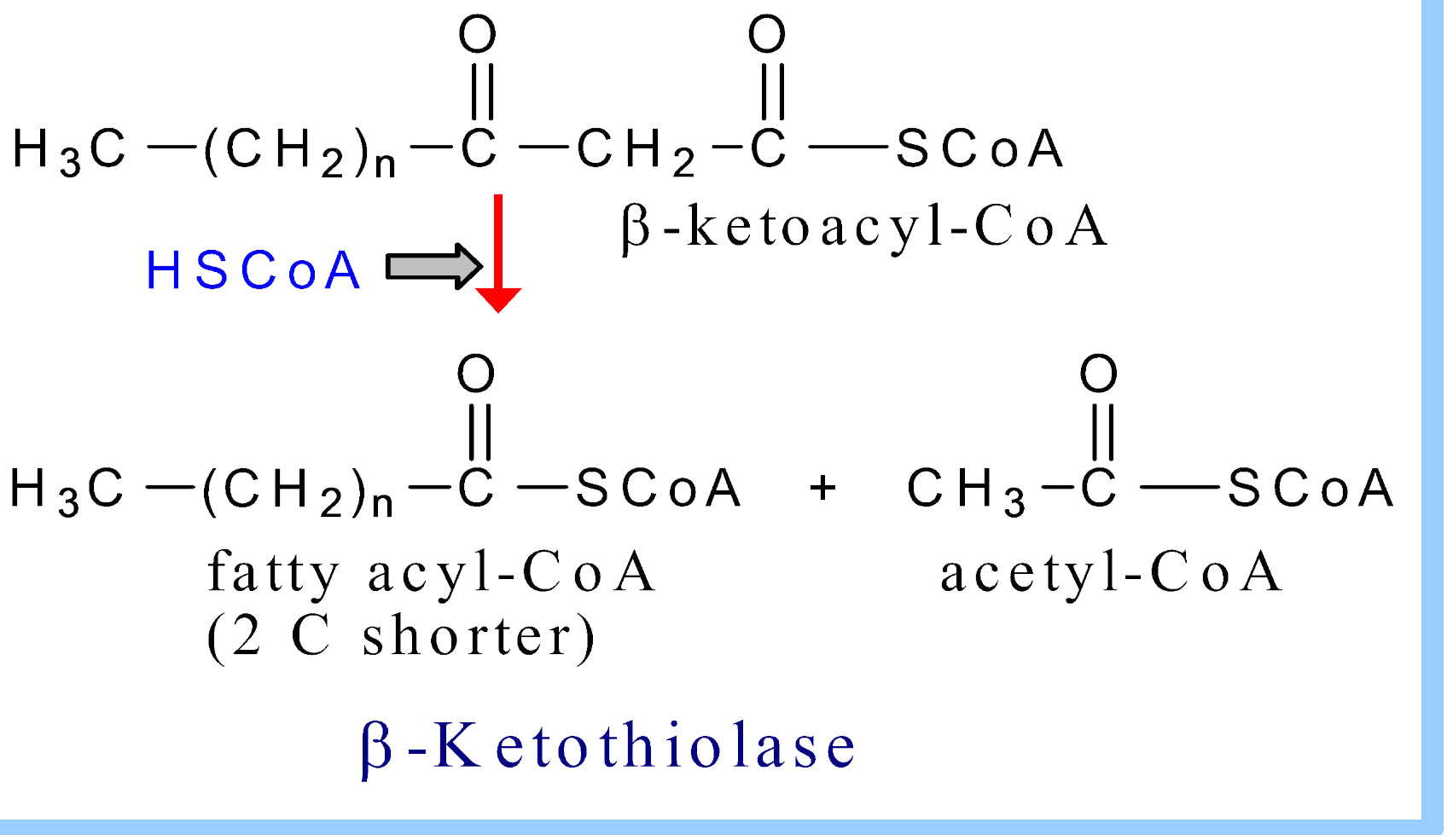
- An enzyme β–Keto Thiolase attacks the β-carbonyl group of β-Ketoacyl-CoA.
- This results in the **cleavage of the C_α-C_β bond.**
- Releases **Acetyl-CoA**(2C) and an **Acyl-CoA** (-2carbons shorter).



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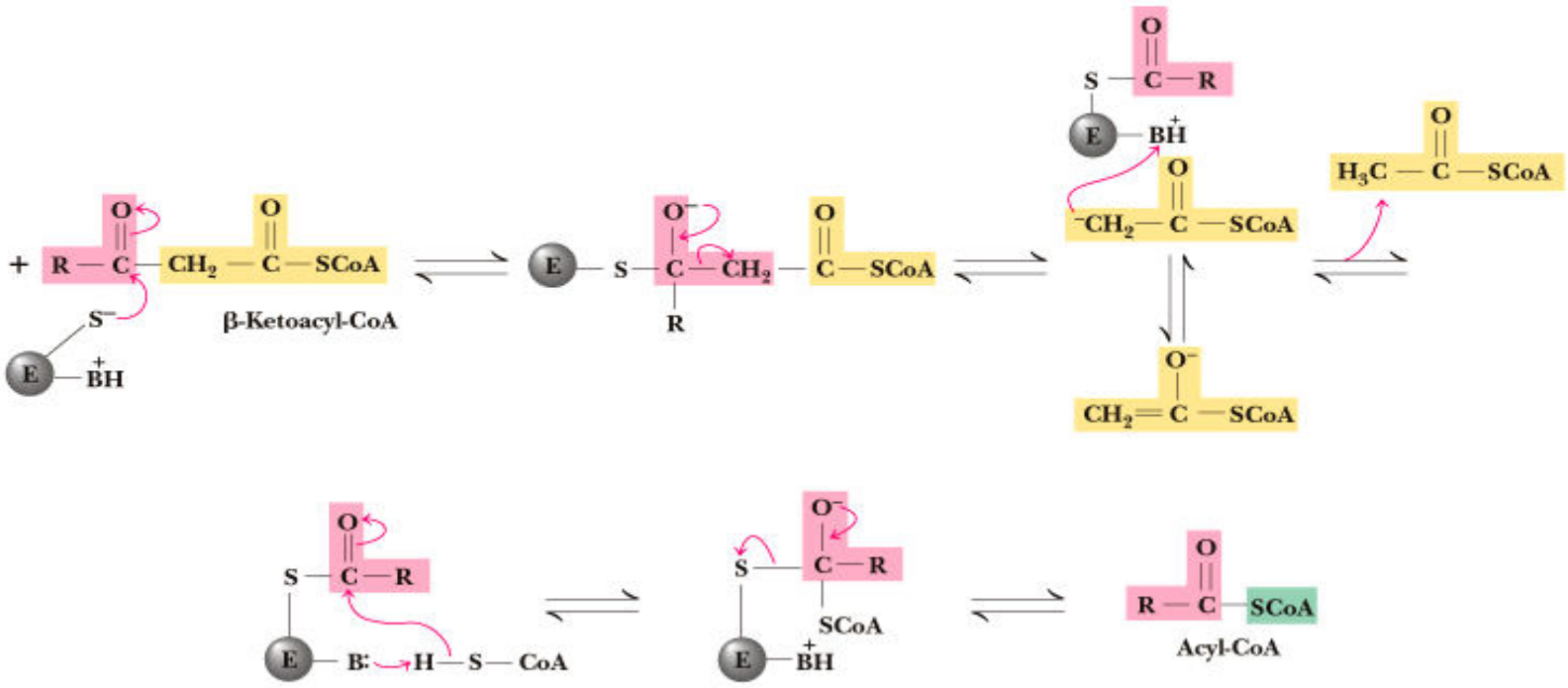




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Figure 24.17



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Repetitions Of 4 Steps Of Beta Oxidation Proper

- The β-oxidation proper pathway is **cyclic**.
- 4 Steps of Beta Oxidation proper are repeated
- **Till whole chain of Fatty acid is oxidized completely.**

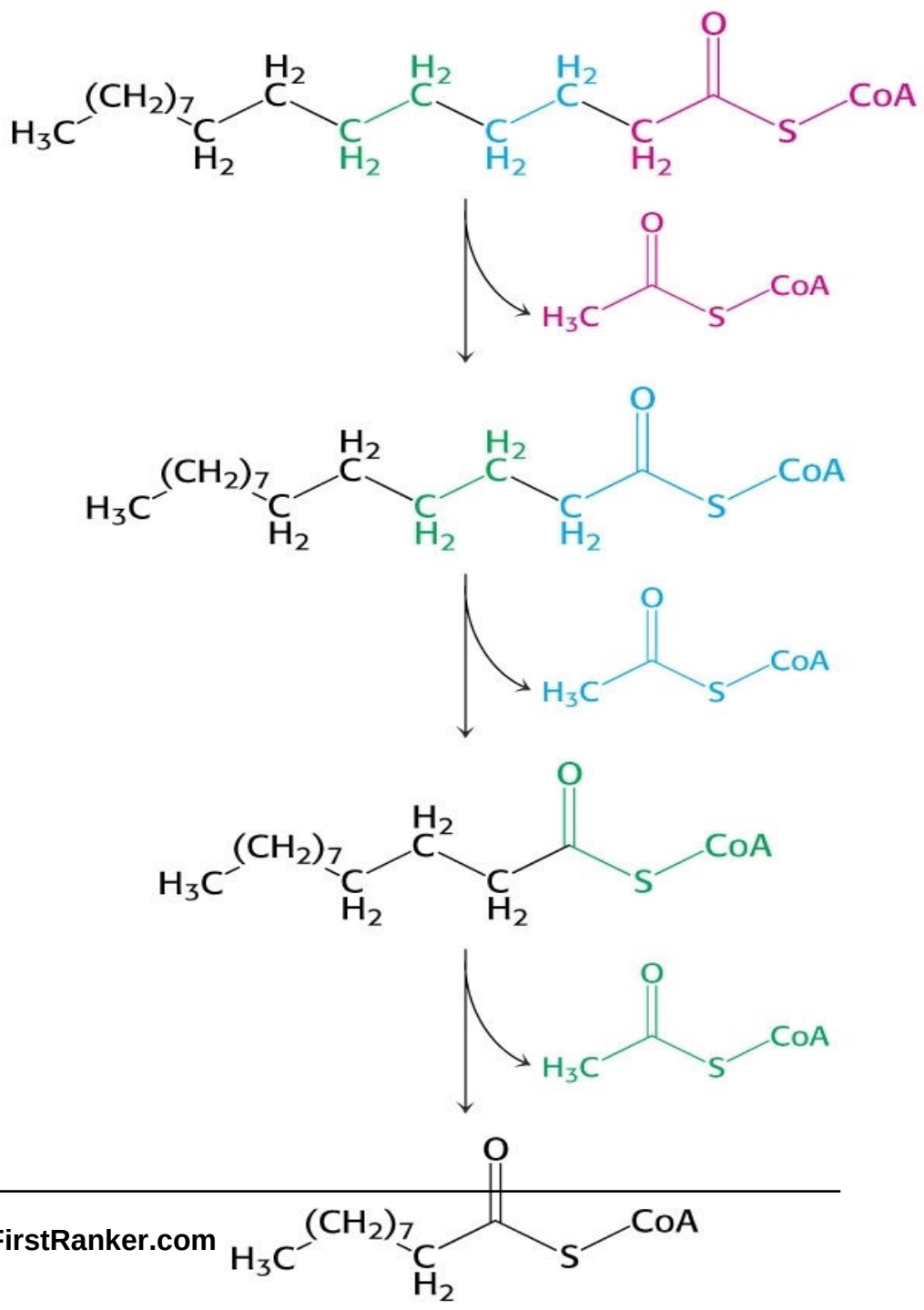
- The product, **2 carbons shorter Acyl -CoA**,
- **Is the input to another round/turn** of the beta oxidation proper pathway.

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- **Acyl CoA molecule released at end of Beta Oxidation**
- Is the **substrate for the next round** of oxidation starting with Acyl CoA Dehydrogenase.
- Repetition continues until all the carbon atoms of the original Fatty acyl CoA are converted to Acetyl CoA.

The shortened Acyl CoA then undergoes another cycle of beta oxidation



The number of beta oxidation cycles:

n/2-1, where n – the number of carbon atoms

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Products Of Each Turn Of Beta Oxidation Proper

- **Each turn/cycle** of **β oxidation proper** generates **one molecule each of:**
  - **$FADH_2$**
  - **$NADH+H^+$**
  - **Acetyl CoA**
  - **Fatty Acyl CoA (with 2 carbons shorter each round)**

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Steps Of β-Oxidation Proper of Fatty Acids Continues With A Repeated Sequence of 4 Reactions Till A Long Fatty Acyl Chain Is Completely Oxidized

- For an **oxidation of Palmitic acid** through beta oxidation
- **7 turns/cycles** of beta oxidation proper steps occur.

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Cycles of β-Oxidation

The length of a fatty acid:

- Determines the number of oxidations and
- The total number of acetyl CoA groups.

Carbons in Fatty Acid	Acetyl CoA (C/2)	β-Oxidation Cycles (C/2 –1)
12	6	5
14	7	6
16	8	7
18	9	8

Fates of the products of β-oxidation of Fatty Acid

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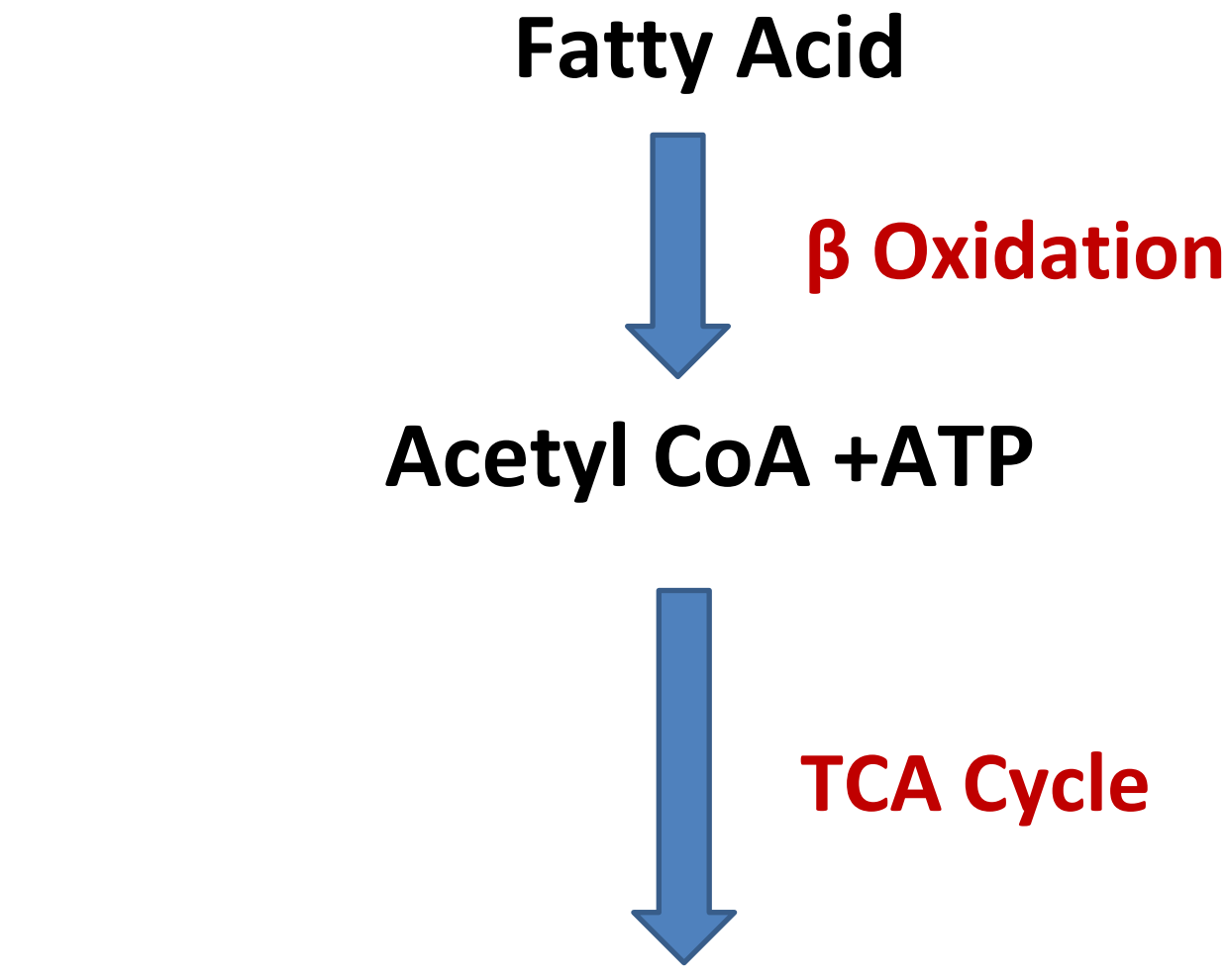
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- **$NADH+H^+$ and $FADH_2$** - are reoxidized in **ETC** to **generate ATP**
- **Acetyl CoA** - Enters the **Citric acid cycle(TCA cycle)** for its **complete oxidation.**
- **Acyl CoA** – Undergoes the **next turn/cycle of β oxidation proper**.

Complete Oxidation Of Fatty Acids

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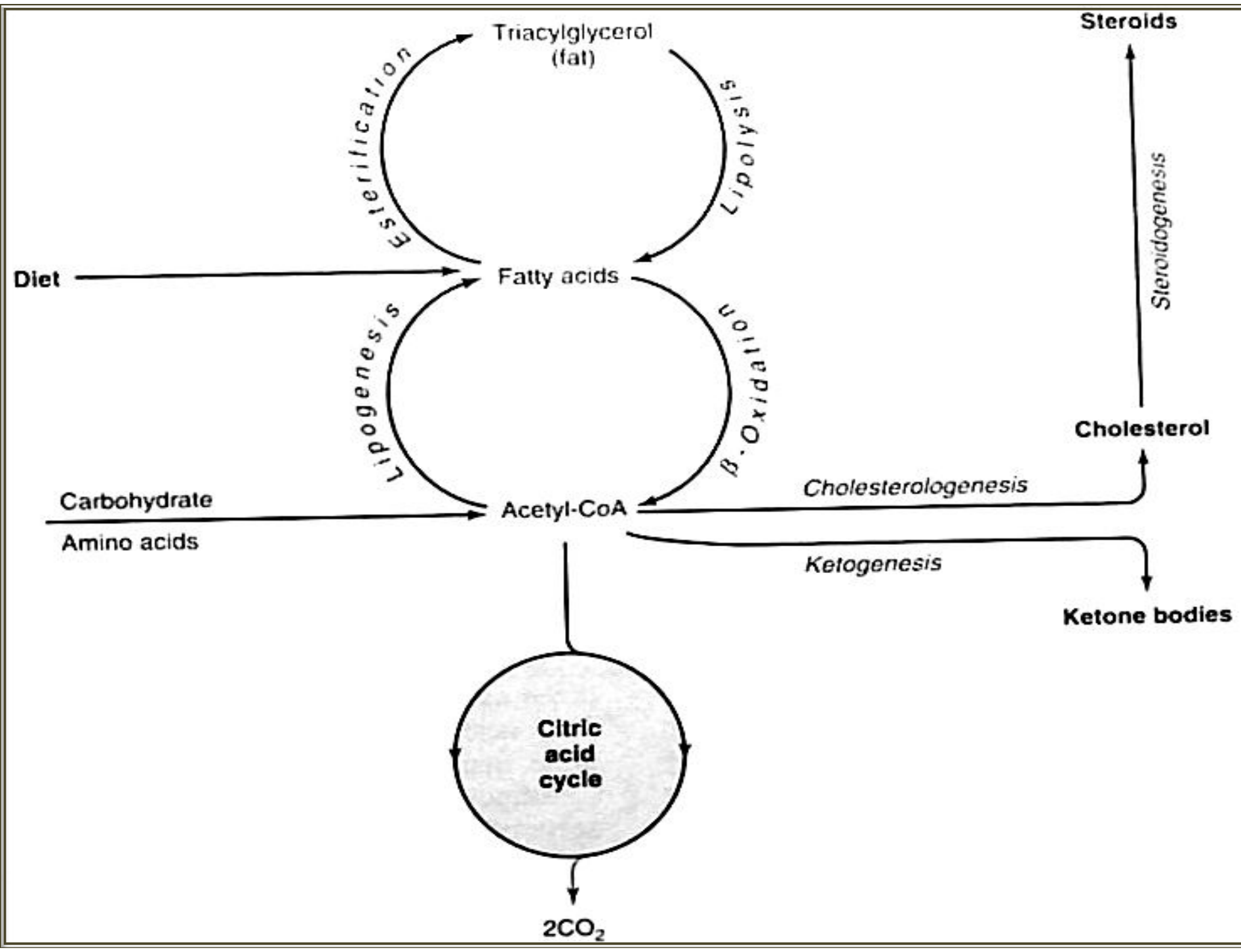
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- Fatty acid is activated and oxidized via **Beta Oxidation** in specific number of cycles depending upon chain length.
- **Acetyl CoA** an **end product** of Beta oxidation of Fatty acid
- Is further **completely oxidized** via **TCA cycle**.

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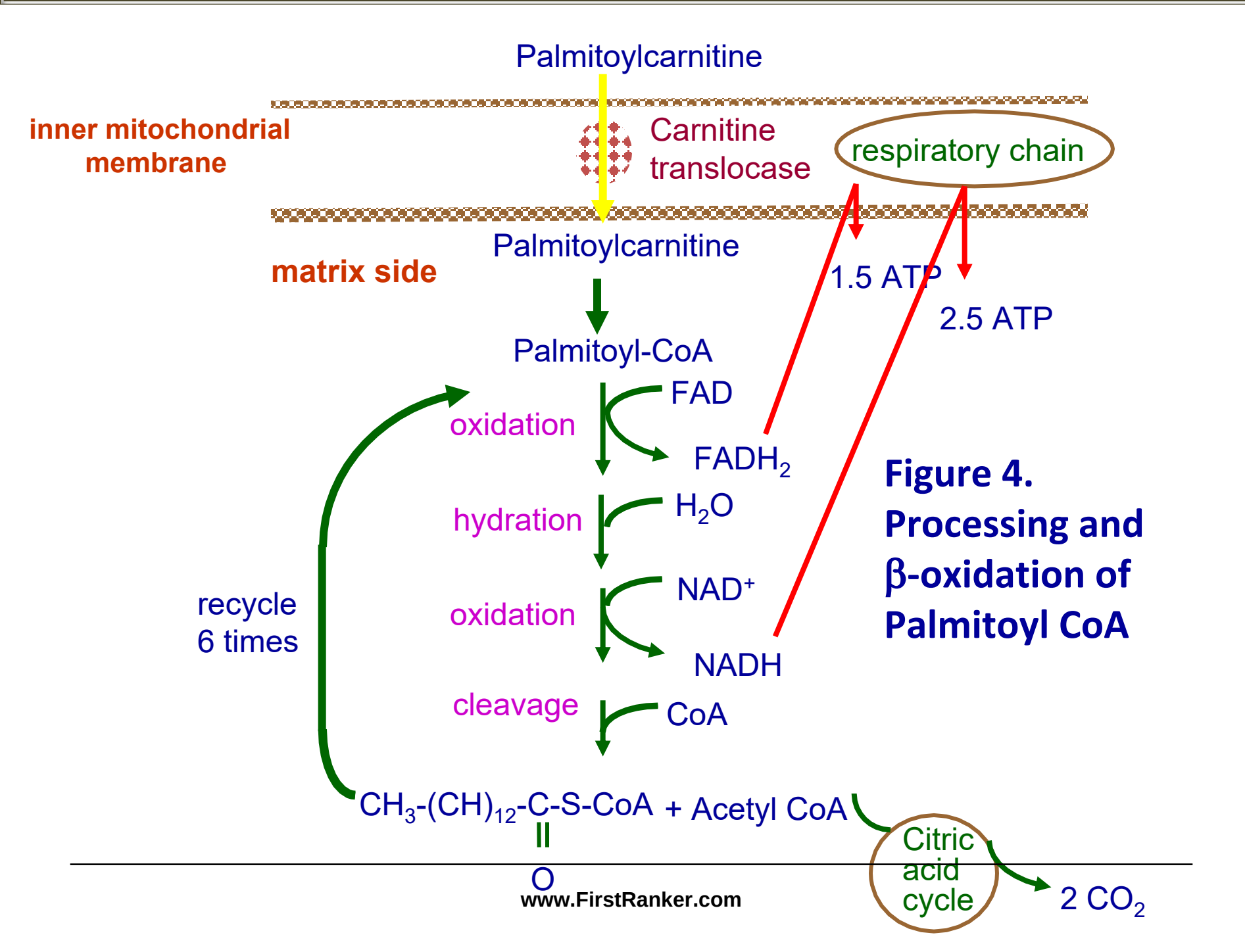
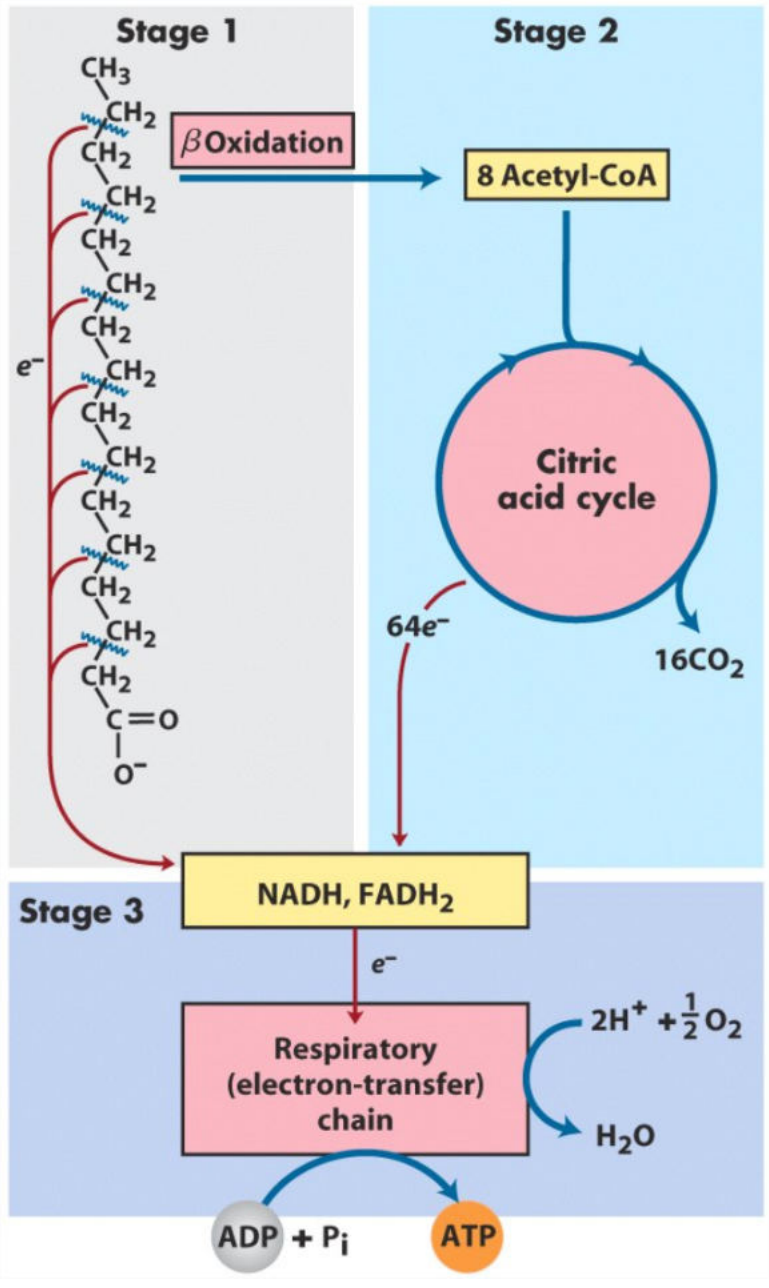


Figure 4. Processing and β-oxidation of Palmitoyl CoA

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B-Oxidation Overall Flow



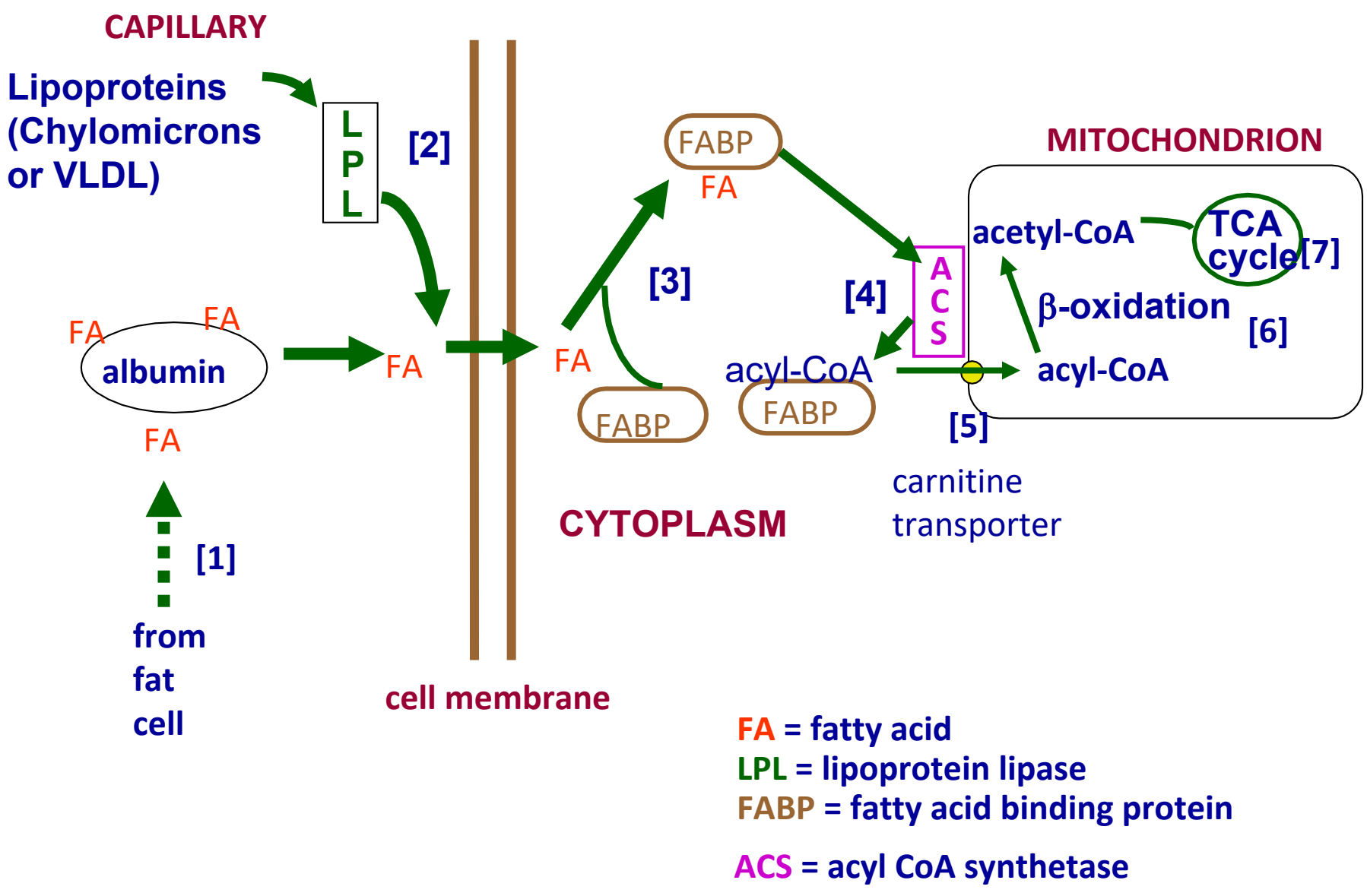


Figure 2. Overview of fatty acid degradation

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Energetics Of Beta oxidation Of Palmitate

- Oxidation of Palmitic Acid **C16** Number of turns of fatty acid spiral = **8-1 = 7 Cycles** of beta oxidation proper.
- **Generates 8 Acetyl CoA**

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During Electron Transport and Oxidative Phosphorylation Each FADH2 yield 1.5 ATP and NADH 2.5 ATP

Energetics of Fatty Acid Beta Oxidation e.g. Palmitic (16C):

1. β-oxidation of Palmitic acid will be repeated in **7 cycles** producing ***8 molecules of Acetyl COA*****.**

2. In each cycle 1 FADH2 and 1 $NADH+H^+$ is produced and will be transported to the respiratory chain/ETC
   - $FADH_2$ 1.5 ATP
   - $NADH + H^+$ 2.5 ATP

   - Thus Each cycle of β-oxidation **04 ATP**

- So 7 cycles of β-oxidation **4 x 7 = 28 ATP**

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1 Acetyl CoA yields 10 ATPs via TCA Cycle

- **Review ATP Generation –TCA/ Citric Acid Cycle which start with Acetyl CoA**
- Step ATP produced
- Step 4 (NADH+H to ETC) 2.5 ATP
- Step 6 (NADH+H to E.T.C.) 2.5 ATP
- Step 10 (NADH+H to ETC) 2.5 ATP
- Step 8 (FADH2 to E.T.C.) 1.5 ATP
- 1 GTP 01 ATP
- **NET per turn of TCA Cycle 10 ATP**

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1 ATP converted to AMP during activation of Palmitic acid to Palmitoyl-CoA is equivalent to 2ATPs utilized

3. Each Acetyl COA which is oxidized completely in citric cycle/TCA cycle gives 10 ATP
4. Hence 8 Acetyl CoA via TCA cycle (**8 x 10 = 80 ATP)**

5. 2 ATP are utilized in the activation of Fatty acid
6. Energy gain = Energy produced - Energy utilized
7. **28 ATP + 80 ATP - 2 ATP = 106 ATP**

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Thus On Complete Oxidation of One molecule of Palmitate

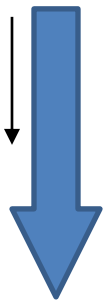
106 molecules of ATP are generated

ATP Generation from Palmitate Oxidation

Net yield of ATP per one oxidized Palmitate

Palmitate ($C_{15}H_{31}COOH$) - 7 cycles – n/2-1

Palmitoyl CoA + 7 HS-CoA + 7 FAD^+ + 7 NAD^+ + 7 H_2O



8 Acetyl CoA + 7$FADH_2$ + 7 NADH + 7 H^+

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	ATP generated
8 Acetyl CoA(TCA)	10x8=80
7 $FADH_2$	7x1.5=10.5
7 NADH	7x2.5=17.5
	108 ATP

ATP expended to activate Palmitate **-2 ATP**

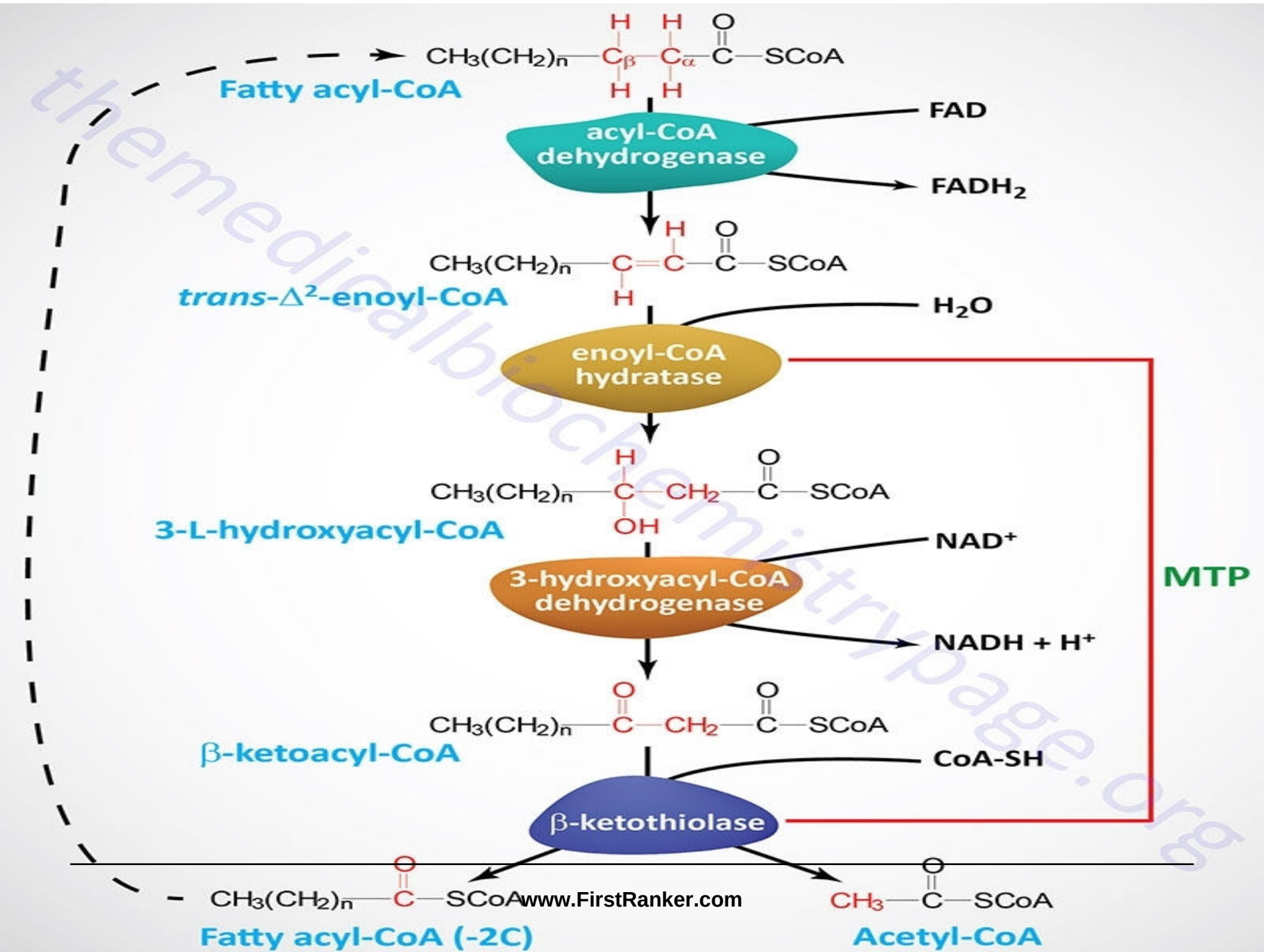
Net yield of ATPs with Palmitate Oxidation: 106 ATP

Total End Products
Of
Beta Oxidation
Of
1 molecule of a Palmitic Acid

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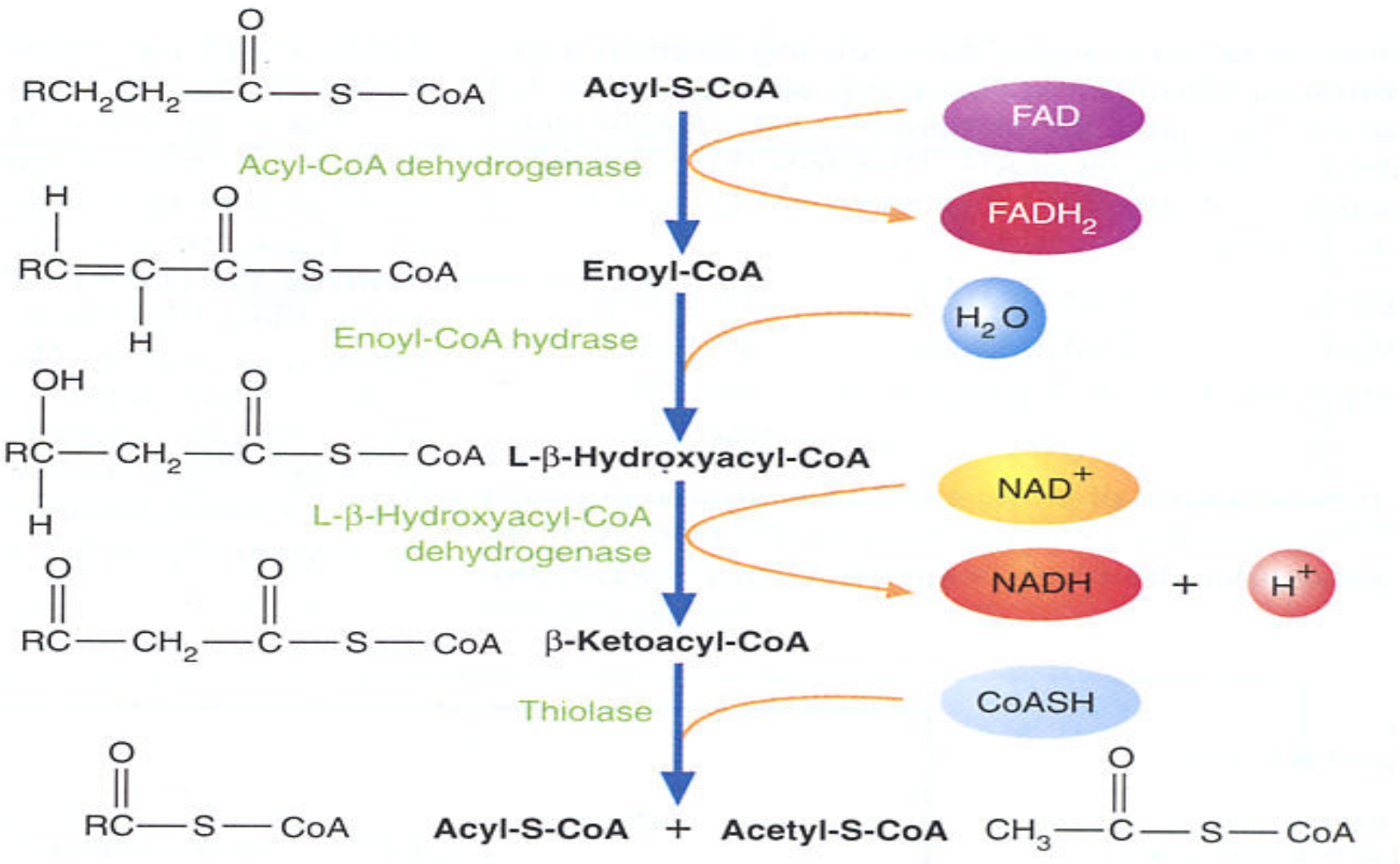
Palmitic acid
With 7 Turns of
Beta Oxidation Proper
Generates
8 Molecules Of Acetyl-CoA
7 FADH2+7 NADH+H+



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β-Oxidation Proper of Acyl-CoA



Summary of one round/turn/cycle of the β-oxidation pathway:

Fatty Acyl-CoA + FAD + NAD^+ + HS-CoA

↓

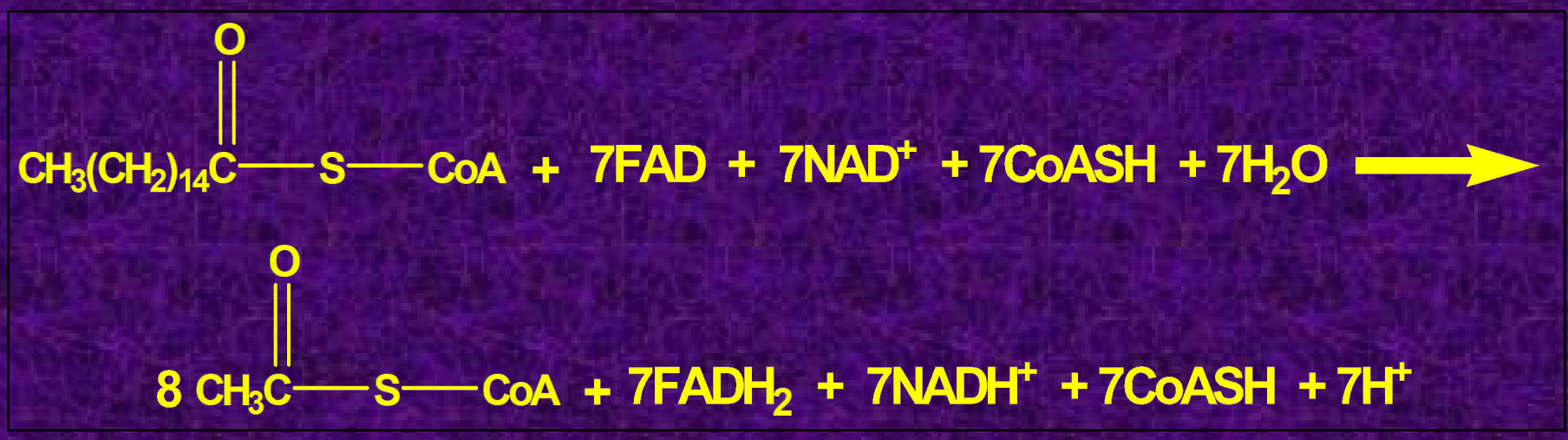
+Acetyl-CoA

Fatty Acyl-CoA (2 C less) **+ $FADH_2$ + NADH + H^+**

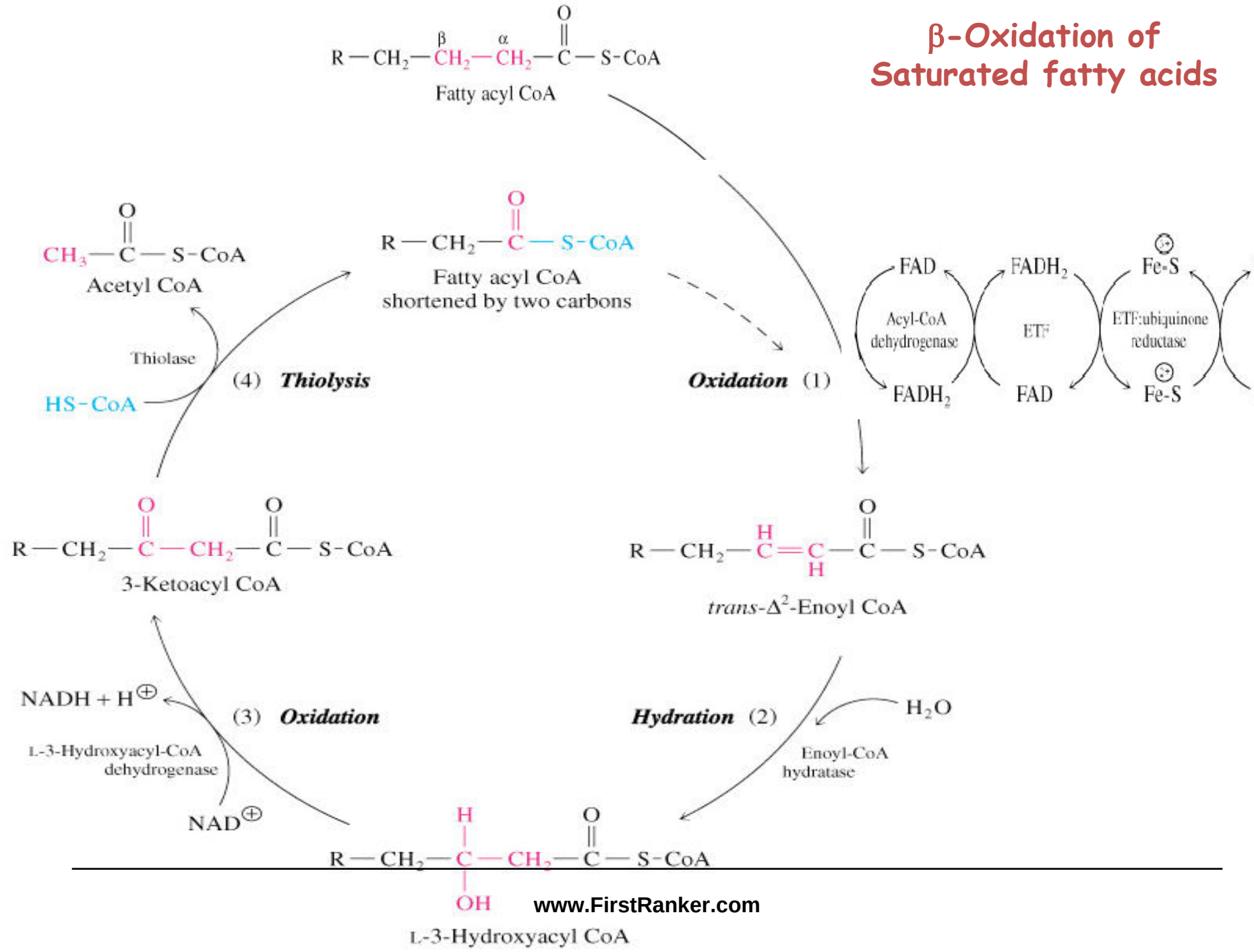
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Stoichiometry for Palmitic Acid Oxidation



β-Oxidation of Saturated fatty acids



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Regulation Of Beta Oxidation Of Fatty Acids

- The Lipolysis and

β Oxidation of Fatty acids are well **regulated by Hormonal influence.**

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Insulin In Well Fed Condition

- **Insulin inhibits Lipolysis** of Adipose Fat (TAG) and mobilization of Free Fatty acids.
- **Insulin decreases β Oxidation of Fatty acids.**

Glucagon In Emergency Condition

- When Cellular or Blood Glucose lowers down there is secretion of Glucagon.
- **Glucagon and Epinephrine stimulates Lipolysis** in emergency condition.

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- **Glucagon stimulates the Enzyme Hormone sensitive Lipase** and hydrolyzes depot Fat(TAG).
- Glucagon mobilizes Free fatty acids out into blood circulation
- **Increases β Oxidation of Fatty acids.**

Regulation Of Beta Oxidation Of Fatty Acid At Two Levels

- **Carnitine Shuttle**
- **Beta Oxidation Proper**

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Transport of Fatty Acyl CoA from Cytosol into Via Carnitine Shuttle Mitochondrial Matrix

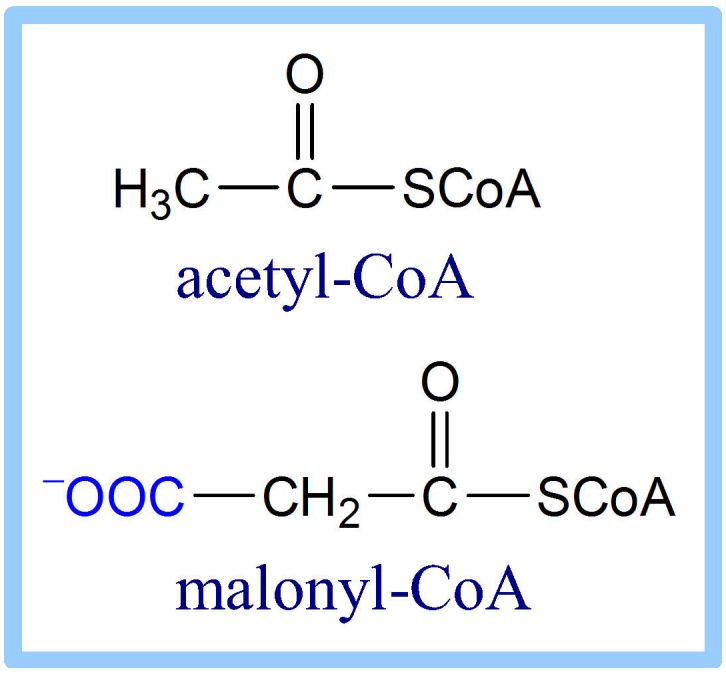
Is a Rate-limiting step

Malonyl-CoA Regulates Beta Oxidation At Carnitine Transport Level

Malonyl-CoA Is an Inhibitor Of Carnitine Acyl Transferase I

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Malonyl-CoA is produced from Acetyl-CoA by the enzyme **Acetyl-CoA Carboxylase during Fatty acid biosynthesis.**

Malonyl-CoA (which is a precursor for fatty acid synthesis) **inhibits Carnitine Palmitoyl Transferase I**.

This Control of Fatty acid oxidation is exerted mainly at the step of **Fatty acid entry** into mitochondria.

Acyl-CoA Dehydrogenase is Regulatory or key Enzyme of Beta Oxidation Of Fatty Acids

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Significance Of Beta oxidation of a Fatty acid

- Beta oxidation cycles helps in **cleaving and shortening of a long chain Fatty acid**

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- Oxidation of Beta carbon atom of a Fatty acid **transforms the stronger bond between alpha and beta carbon atom to a weaker bond**.

- Transformation to a weaker bond helps in easy cleavage between alpha and beta carbon
- During β oxidation there is dehydrogenation of beta carbon atom (CH2 to C=O)

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- The **Hydrogen atoms removed during beta oxidation** are
- Temporarily accepted by the oxidized coenzymes (FAD and NAD^+) to **form reduced coenzymes**
- Reduced coenzymes then **finally enter ETC and get reoxidized**
- The byproduct of ETC is **ATP**

- Thus **Beta oxidation** of Fatty acid
- Metabolizes a long chain fatty acid with **liberation of** chemical form of energy **ATP** for cellular activities.

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Summary of β-Oxidation

Repetition of the β-Oxidation Cycle yields a succession of Acetate units

- Palmitic acid yields **eight Acetyl-CoAs**
- Complete β-oxidation of one Palmitic acid yields **106 molecules of ATP**
- Large energy yield is consequence of the **highly reduced state of the carbon in fatty acids**
- This makes **fatty acid the fuel of choice for migratory birds and many other animals**

Disorders OF Beta Oxidation Of Fatty Acids

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Deficiencies of Carnitine OR Carnitine Transferase OR Translocase Activity Are Related to Disease State

Carnitine Shuttle Defects

- Affects the normal function of **Muscles, Kidney, and Heart**.

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- **Symptoms** include **Muscle cramping,** during exercise, **severe weakness** and death.

- **Muscle weakness occurs** since they are related with **Fatty acid oxidation** for **long term energy source.**

- **Note people with the Carnitine Transporter Defect**
  - Should be **supplemented with a diet with medium chain fatty acids**
  - Since the **MCFAs** do **not require Carnitine shuttle to enter Mitochondria**.

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Sudden Infant Death Syndrome (SIDS)

SIDS

- SIDS is a **congenital rare disorder** with an incidence of **1 in 10,000 births**.
- **Cause:** Due to the **deficiency** of Enzyme **Acyl-CoA Dehydrogenase** a regulatory enzyme of β Oxidation of Fatty acid.

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• Consequences Of SIDS

- Deficiency of Acyl-CoA Dehydrogenase
- **Blocks the β Oxidation** of Fatty acid.
- **Stops liberation** and supply of energy in the form **of ATPs in fasting condition**
- Leads to **unexpected death of an infant.**

Symptoms in defective Beta Oxidation of Fatty acids include:

- **Hypoglycemia**
- **Low Ketone body** production during fasting
- **Fatty Liver**
- **Heart and/or Skeletal muscle defects**
- **Complications of pregnancy**
- **Sudden infant death** (SID).

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- Hereditary deficiency of **Medium Chain Acyl-CoA Dehydrogenase** (MCAD),
- The **most common genetic disease** relating to fatty acid catabolism, has been **linked to SIDS.**

Jamaican Vomiting Sickness

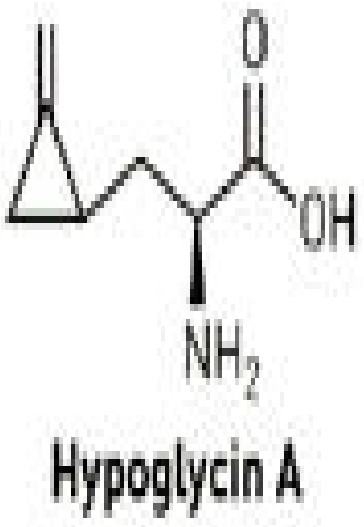
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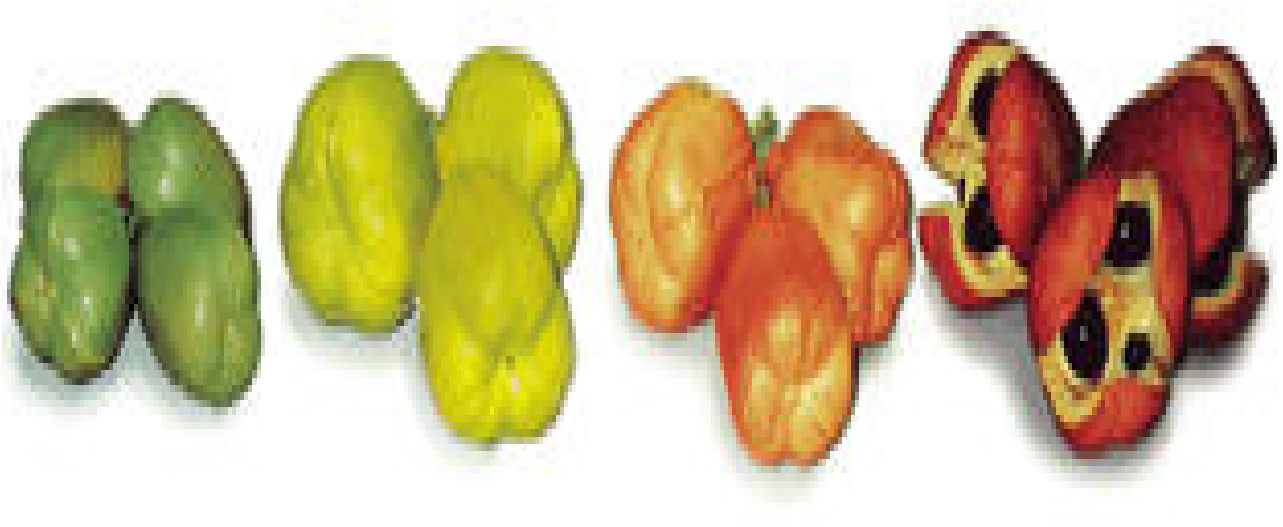
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- Jamaican Vomiting Syndrome is due to **ingestion of unripe Ackee fruit by people in Jamaica**

(Jamaica-Country of Caribbean**)**

Ackee Fruit





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- The Ackee fruit is rich in **Hypoglycin –A**

- **Hypoglycin is an inhibitor of** regulatory Enzyme β Oxidation Proper **Acyl-CoA Dehydrogenase.**

- The Jamaican Vomiting Disease leads to complications characterized by :
  - **–Severe Vomiting**
  - **–Hypoglycemia**
  - **–Convulsions**
  - **–Coma**
  - **–Death**

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Beta Oxidation
Of
Odd Chain Saturated Fatty Acids

β-OXIDATION
OF
ODD-CHAIN FATTY ACIDS

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- Odd chain carbon Fatty acids are **less common in human body.**

- Formed by **some bacteria in the stomachs** of ruminants and the **human colon.**

- β-oxidation of odd chain Fatty acid occurs **same as even chain Fatty acid oxidation**

- **Until the final Thiolase cleavage**
- Which results in a **3 Carbon Acyl-CoA /Propionyl-CoA**

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- **Odd-carbon Fatty acids are metabolized same as even carbon chain Fatty acid** via steps of β oxidation, **releasing Acetyl CoA (2C) in every turn.**

- In the **last turn of β oxidation proper** of **odd chain fatty acid**

- Releases **last three-C fragment as Propionyl-CoA (3 C).**

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End Products Of Odd Chain Fatty Acid Oxidation

- **End products of β-oxidation of an odd-number** Fatty acid is :
  - **–Acetyl-CoA(C2)**
  - **–Propionyl-CoA(C3)**

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Fate Of Acetyl-CoA

- Acetyl CoA released from beta oxidation of odd chain fatty acid
- **Enter in TCA cycle** and get **completely oxidized**.

Fate Of Propionyl-CoA

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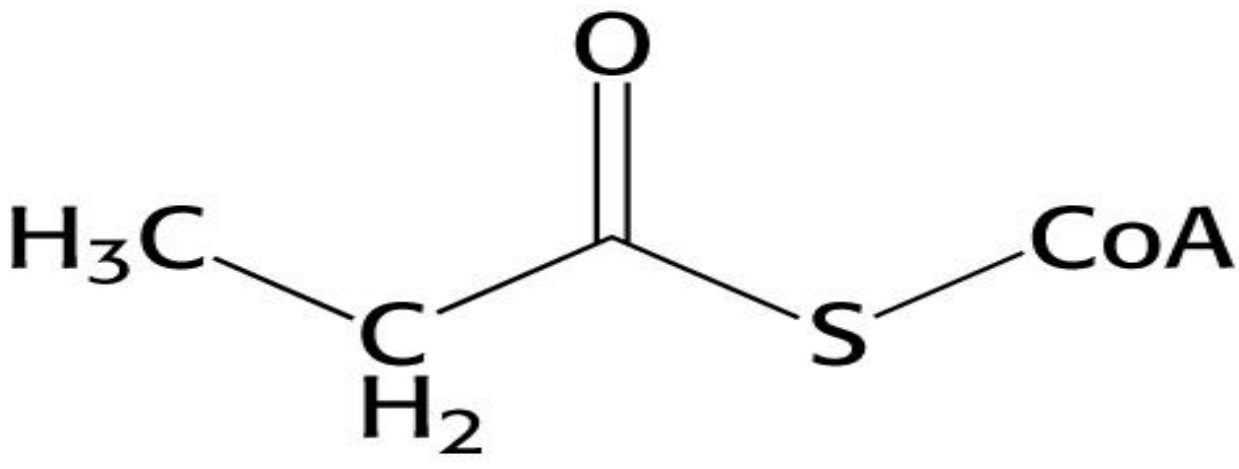
Metabolism Of Propionyl CoA

Propionyl CoA
An End Product Of Odd Chain Fatty Acid

Is Converted into
Succinyl CoA
A TCA intermediate

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Propionyl CoA

- **Metabolism of Propionyl-CoA**

- The Propionyl-CoA is **converted** to **Succinyl-CoA.**
- Which is **an intermediate of TCA/Citric acid cycle**

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- Propionyl CoA metabolism is **dependent on Vitamin B complex members:**
  - **Biotin**
  - **Vitamin B_{12}**

- Special **set of 3 Enzymes are required** to further oxidize Propionyl-CoA to Succinyl -CoA.

- Final Product **Succinyl-CoA enters TCA cycle and get metabolized.**

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- **Three Enzymes convert Propionyl-CoA to Succinyl-CoA:**

1. **Carboxylase**
2. **Racemase /Epimerase**
3. **Mutase**

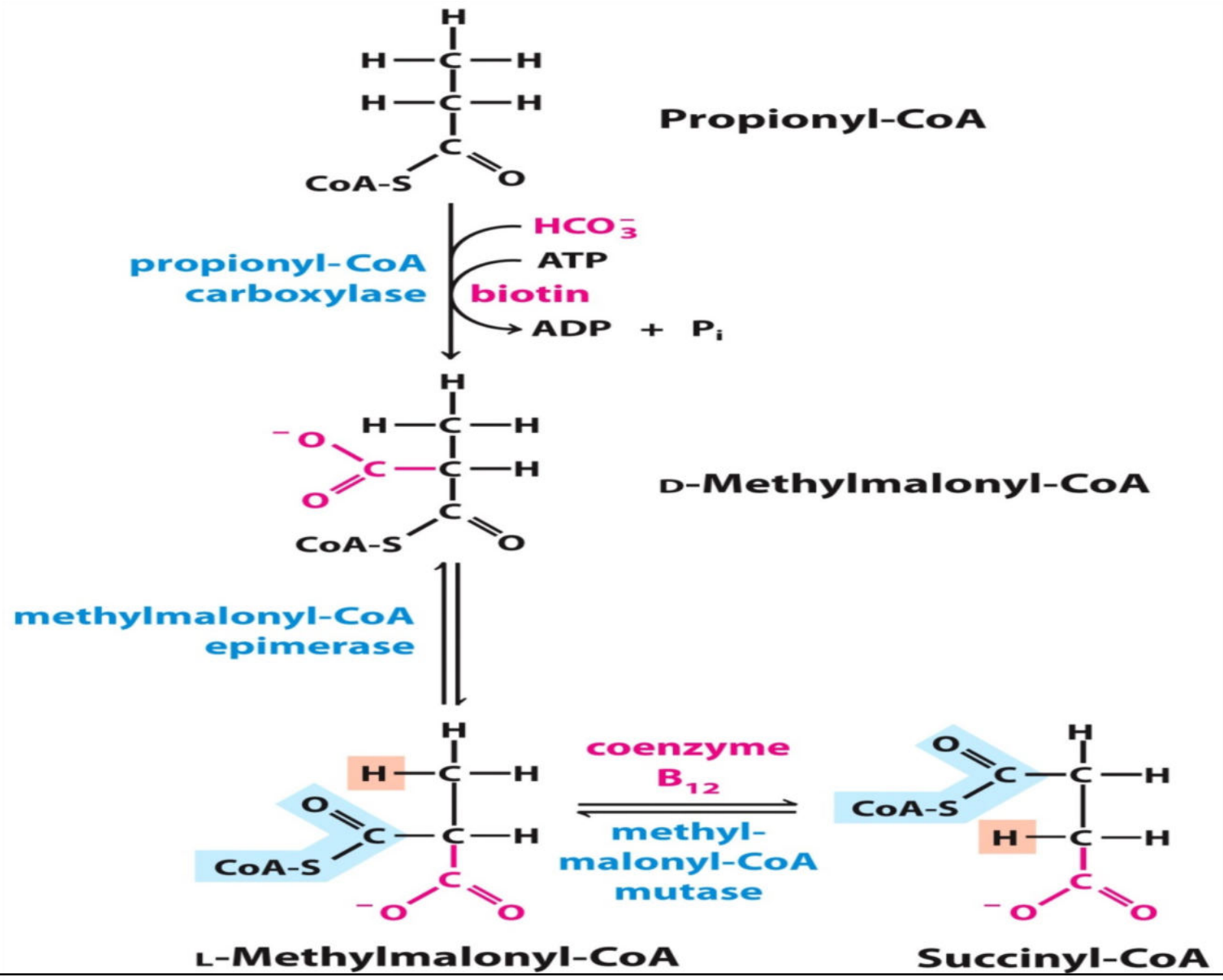
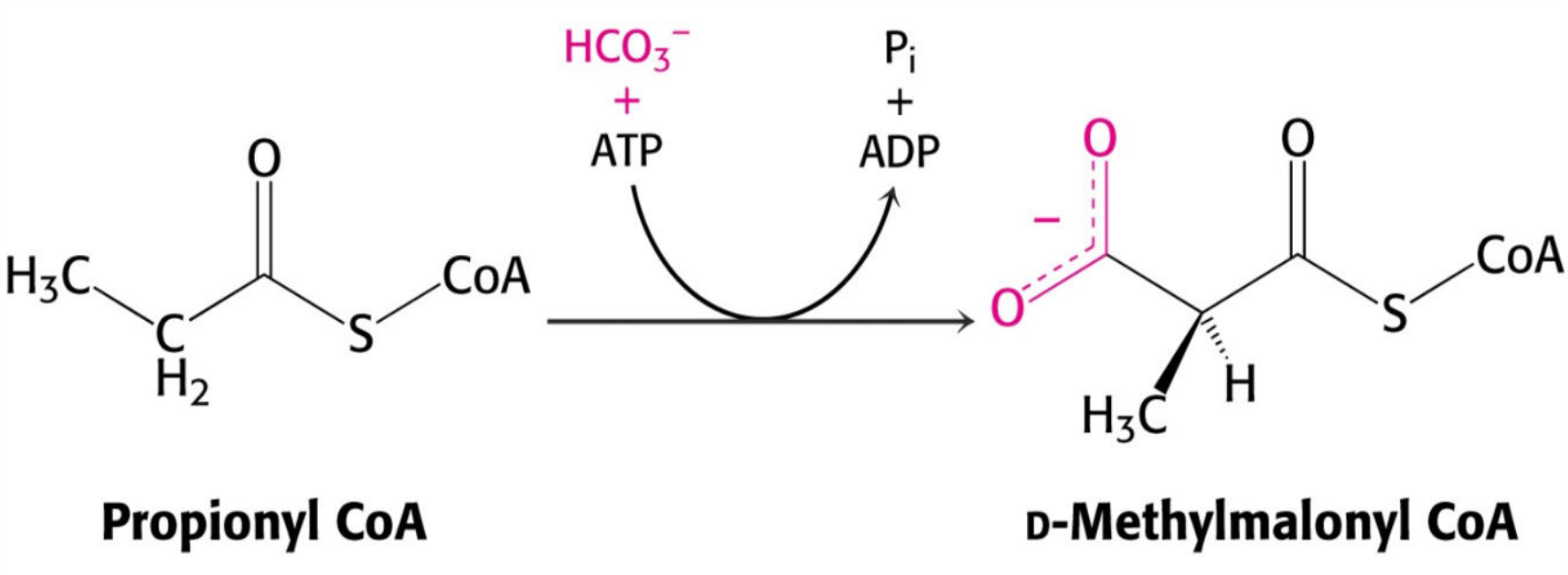


Figure 17-12
Lehninger Principles of Biochemistry, Sixth Edition
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Step1

- **Propionyl CoA** is **Carboxylated** to yield **D Methylmalonyl CoA.**
- Enzyme: **Propionyl CoA Carboxylase**
- Coenzyme: **Cyto Biotin**
- An **ATP is required**

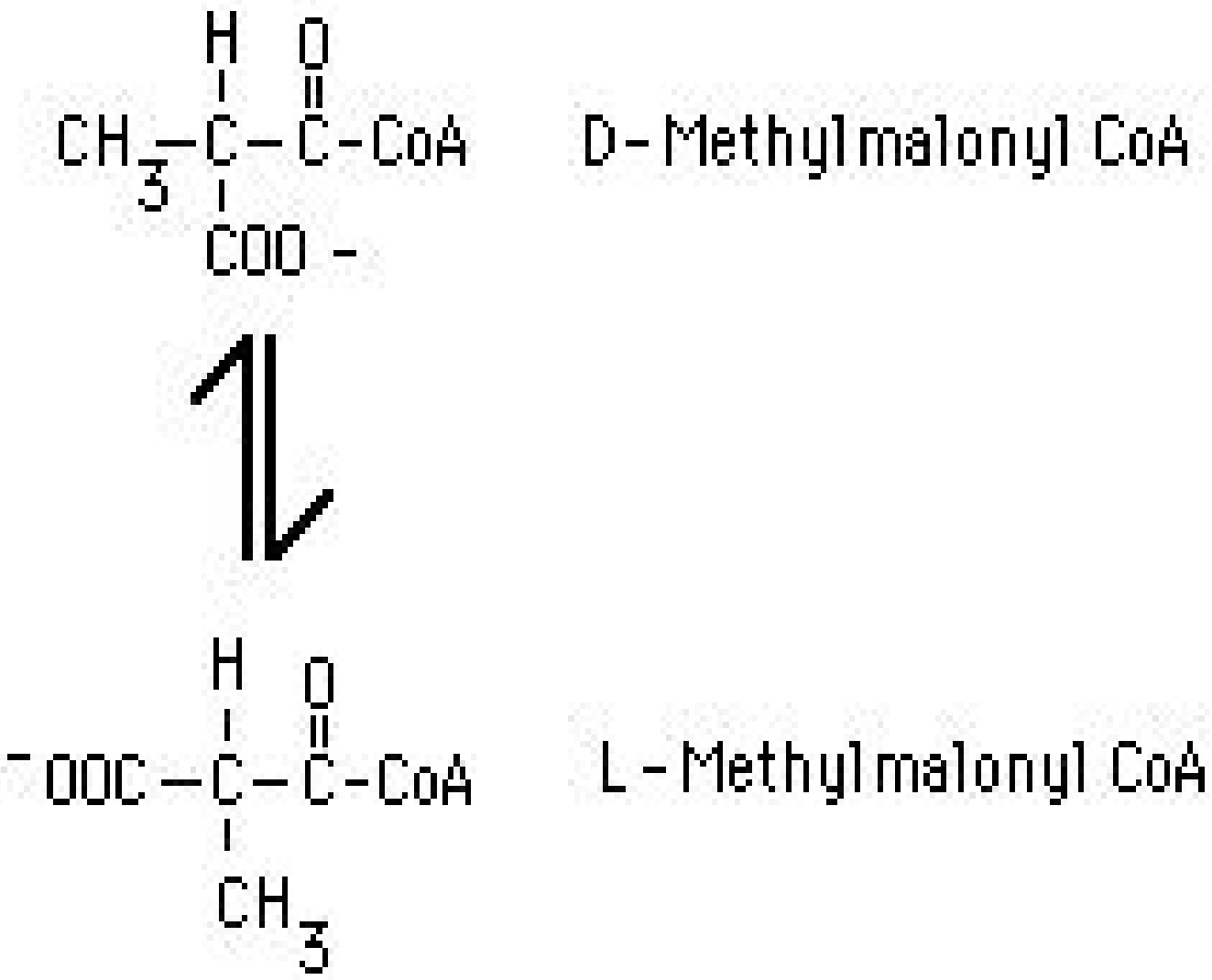


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Step2

- The D Methylmalonyl CoA is racemized to the L Methylmalonyl CoA.
- Enzyme: Methylmalonyl-CoA Racemase/ Epimerase

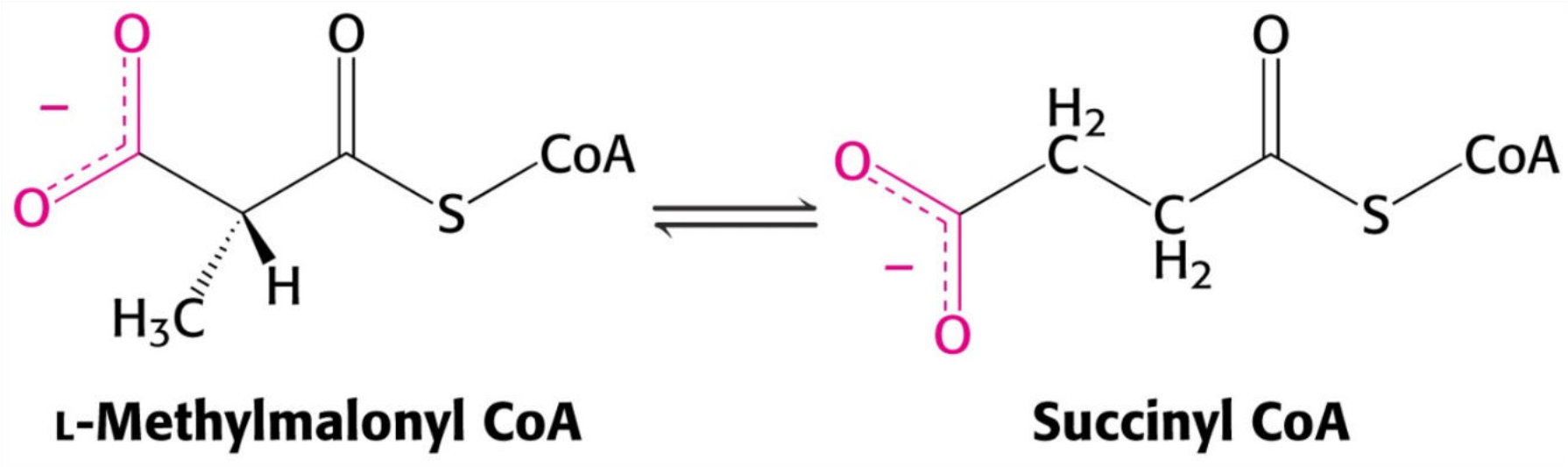


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Step 3

- **L Methylmalonyl CoA is converted into Succinyl CoA by an intramolecular rearrangement**
- **Enzyme: Methylmalonyl CoA Mutase**
- **Coenzyme of Vitamin B12 :Deoxy Adenosyl Cobalamin**



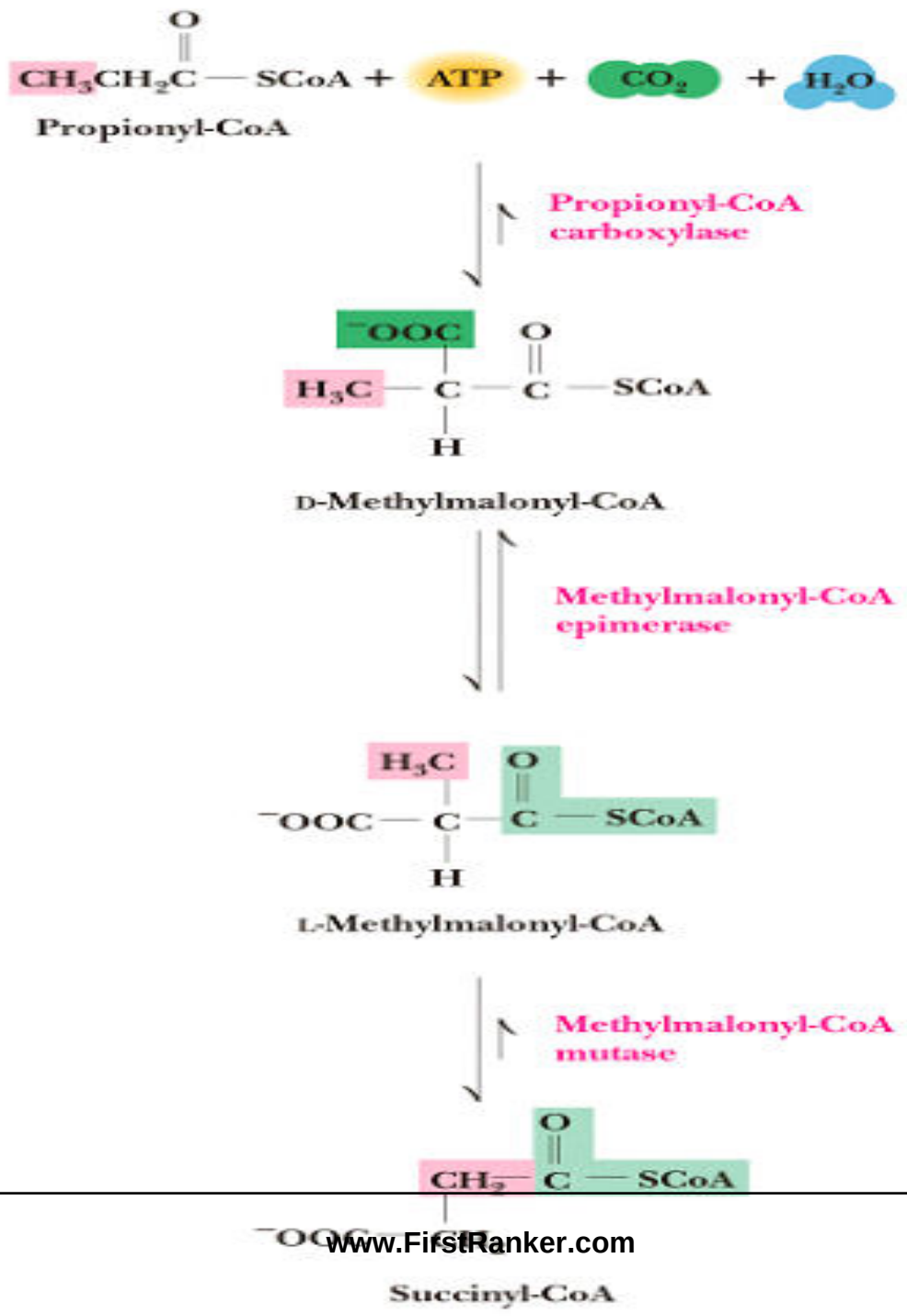
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Fates Of Succinyl CoA

- **Succinyl CoA**

- **Enters TCA cycle** and get metabolized
- Serve as **Glucogenic precursor** for Glucose biosynthesis in emergency condition
- Used as a **precursor for Heme biosynthesis**
- Involves in **Thiophorase reaction** of **Ketolysis**.

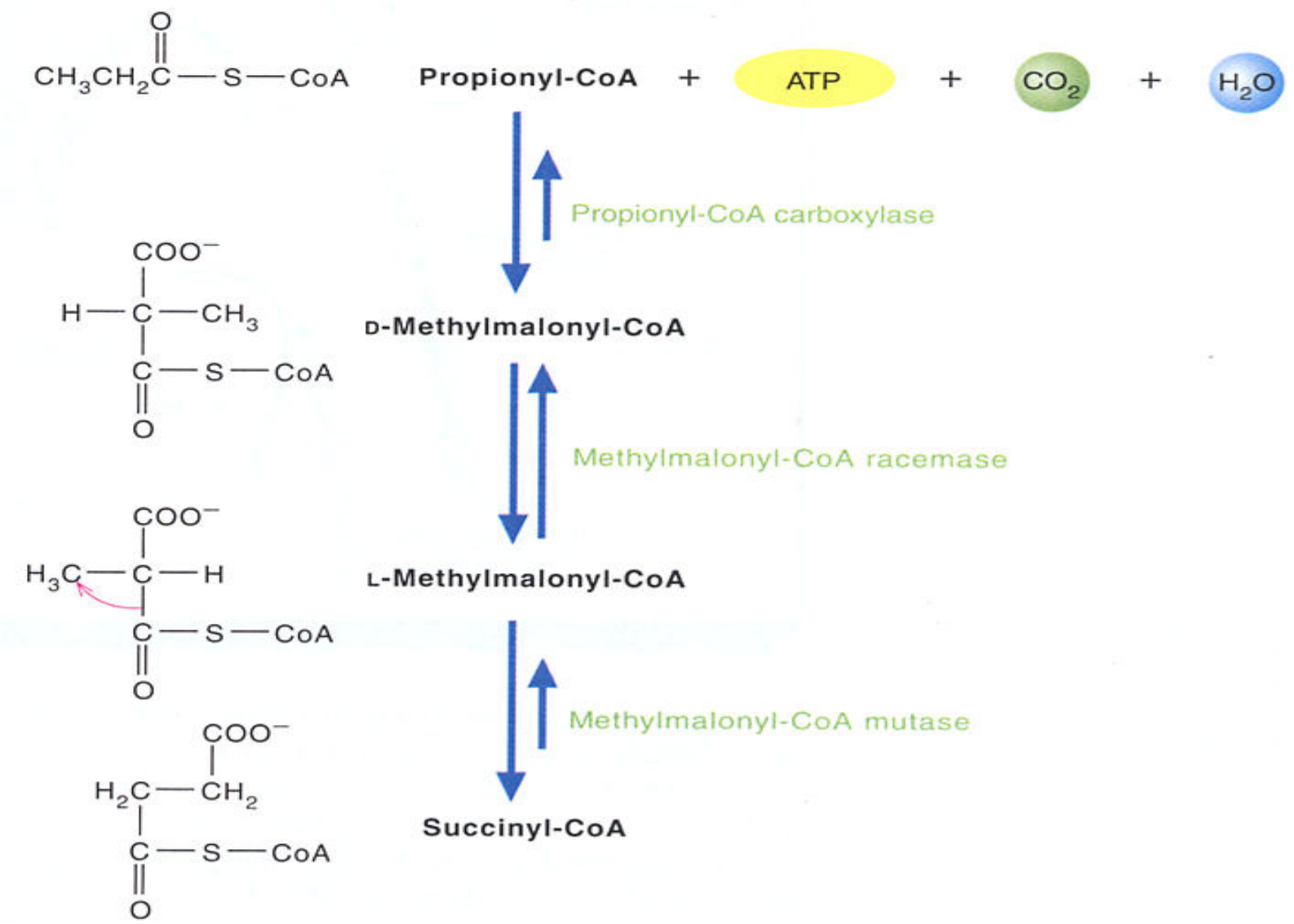


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Oxidation of Odd-chain Fatty Acids

Conversion of Propionyl-CoA to Succinyl-CoA



Defects In Propionyl CoA Metabolism

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- Deficiency of **Enzyme Propionyl-CoA Carboxylase** will block the metabolism of Propionyl-CoA.
- Accumulates Propionyl-CoA in blood leading to **Propionicacidemia.**

- **Deficiency** of **Vitamin B Complex members** affects Propionyl CoA metabolism to Succinyl –CoA.
- **Vitamin B12** deficiency **blocks** the **Mutase reaction**
- **Accumulates L-Methyl Malonyl-CoA** leading to **Methyl Malonylaciduria.**

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Alpha Oxidation Of Fatty Acid
OR
Oxidation Of
Branched-Chain Fatty Acid
OR

Phytanic Acid Oxidation

- The source of **Phytanic acid in human body** is through ingestion of **green leafy vegetables**.

- **Phytanic acid** is a **breakdown product of plant chlorophyll**.

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Why Phytanic Acid Does Not Initiate With Beta Oxidation Process?

- **Phytanic acid is a Branched chain FA.**
- Has **Methyl branches at odd -number carbons**.
- They are **not good substrates for β-oxidation.**

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- The branched chain Phytanic acid **contains Methyl (CH3)** group **at β Carbon atom.**

- Hence it **cannot get oxidized initially via β oxidation** pathway

- Thus initially Phytanic acid **follows α Oxidation**
- **Modify Phytanic acid to Pristanic acid** and
- **Further present it for Beta Oxidation process.**

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Occurrence Of Alpha Oxidation Of Phytanic Acid

Predominantly Alpha Oxidation Of Phytanic Acid Takes Place in Endoplasmic Reticulum of Brain Cells

Also In Peroxisomes

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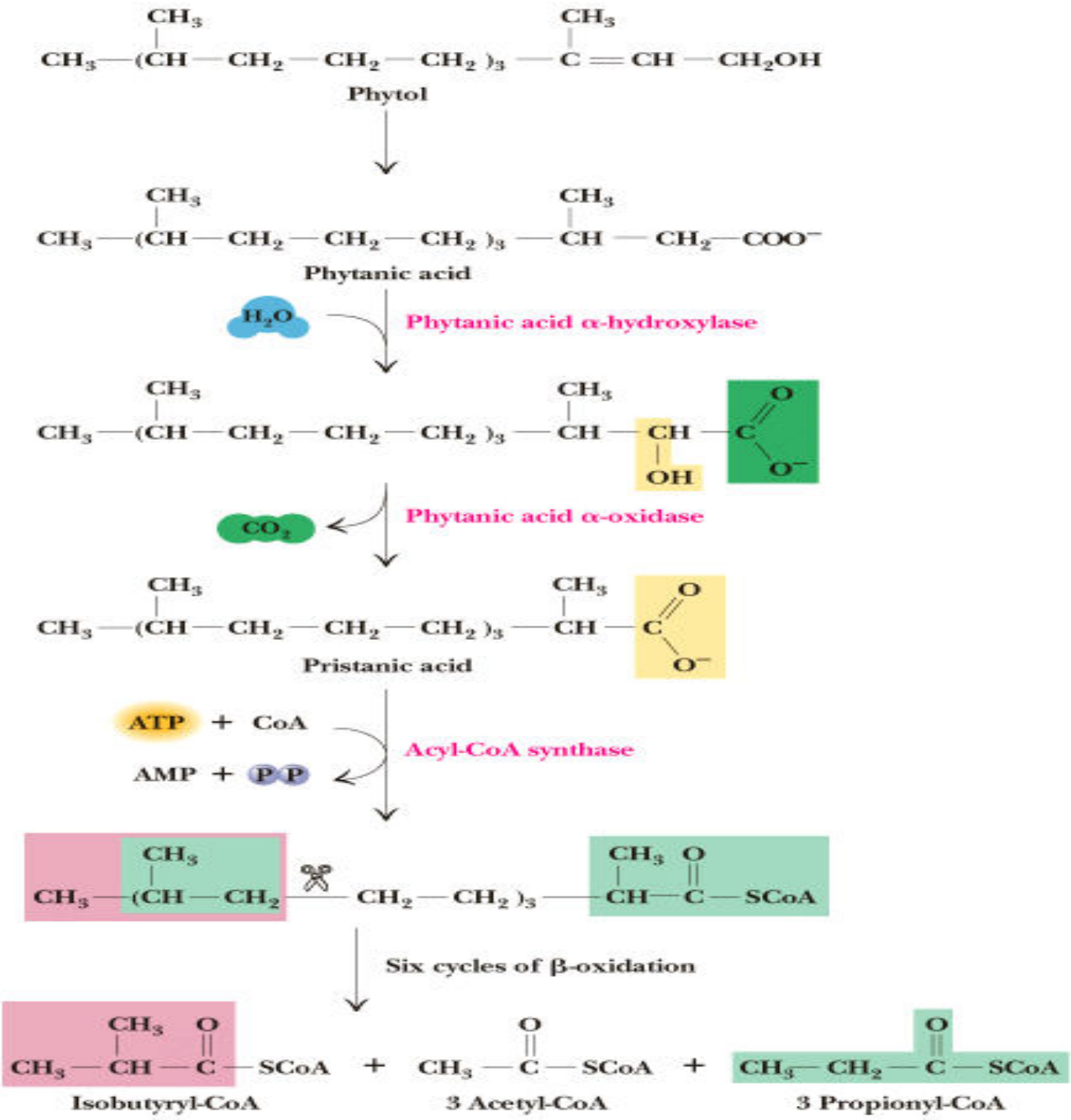
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Mechanism Of Alpha Oxidation Of Phytanic Acid

- Phytanic acid **3,7,11,15-Tetramethyl Hexadecanoic acid**
- Alpha oxidation **removes the Methyl groups** at beta carbon.
- **Later** making the Fatty acid ready for **beta oxidation process**.

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- **During α Oxidation there occurs:**

- **Hydroxylation at α Carbon** in presence of Enzyme **Hydroxylase or Monoxygenase .**

- This reaction is **Vitamin C dependent** forming **α Hydroxy Acyl-CoA.**

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- α Hydroxy Acyl-CoA is then oxidized to **α Keto Acyl-CoA**.

- The **Ketonic group at α Carbon** atom is decarboxylated

- **Yielding CO2 molecule** and a Fatty acid with one Carbon atom less.

- **Phytanic acid** on alpha oxidation is **converted to Pristanic acid**

- Which is **further metabolized via beta oxidation process** to generate Propionyl-CoA.

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Products of Phytanic Acid Oxidation

- **Alpha oxidation of Phytanic acid Generates**

–Acetyl-CoA

–Propionyl-CoA

–Isobutryl-CoA

Refsums Disease

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Disorders Associated With Defective α Oxidation Of Phytanic Acid

- **Refsums disease** is a **rare** but **severe neurological disorder.**
- Caused due to **defect in α Oxidation** of Phytanic acid

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The Enzyme Defects

- **Deficiency** of **Enzyme Phytanic acid α Oxidase/ Phytanol-CoA Dioxygenase** leads to Refsum's disease.

- **Biochemical Consequence Of Refsums disease Is:**
- No Oxidation of Phytanic acid
- **Accumulation of Phytanic acid in Brain cells and Other Tissues**
- **Dysfunction of Brain**
- **Manifesting Neurological disorder**

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- Management Of Refsums disease is :
- **Avoid eating diet containing Phytol /Phytanic acid.**

Omega Oxidation Of Fatty Acids

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- Omega Oxidation of Fatty acid is:

- **Oxidation of Omega Carbon atom (CH3) of a Fatty acid.**

When Does Omega Oxidation Of Fatty Acid Occurs?

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- Omega Oxidation takes place **when there is defect in β Oxidation of fatty acid.**

- **During ω Oxidation of Fatty acid**
- **ω Carbon atom (CH3) of a Fatty acid is** transformed to -**COOH**

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- The omega oxidation forms **Dicarboxylic acid**
- Which **further undergo oxidation**
- **Form more short Dicarboxylic acids Adipic acid and Succinic acid**
- **Which are more polar excreted out in Urine.**

ω-Oxidation of Fatty acids Occur in the Endoplasmic Reticulum of Liver Cells

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Mechanism Of ω Oxidation

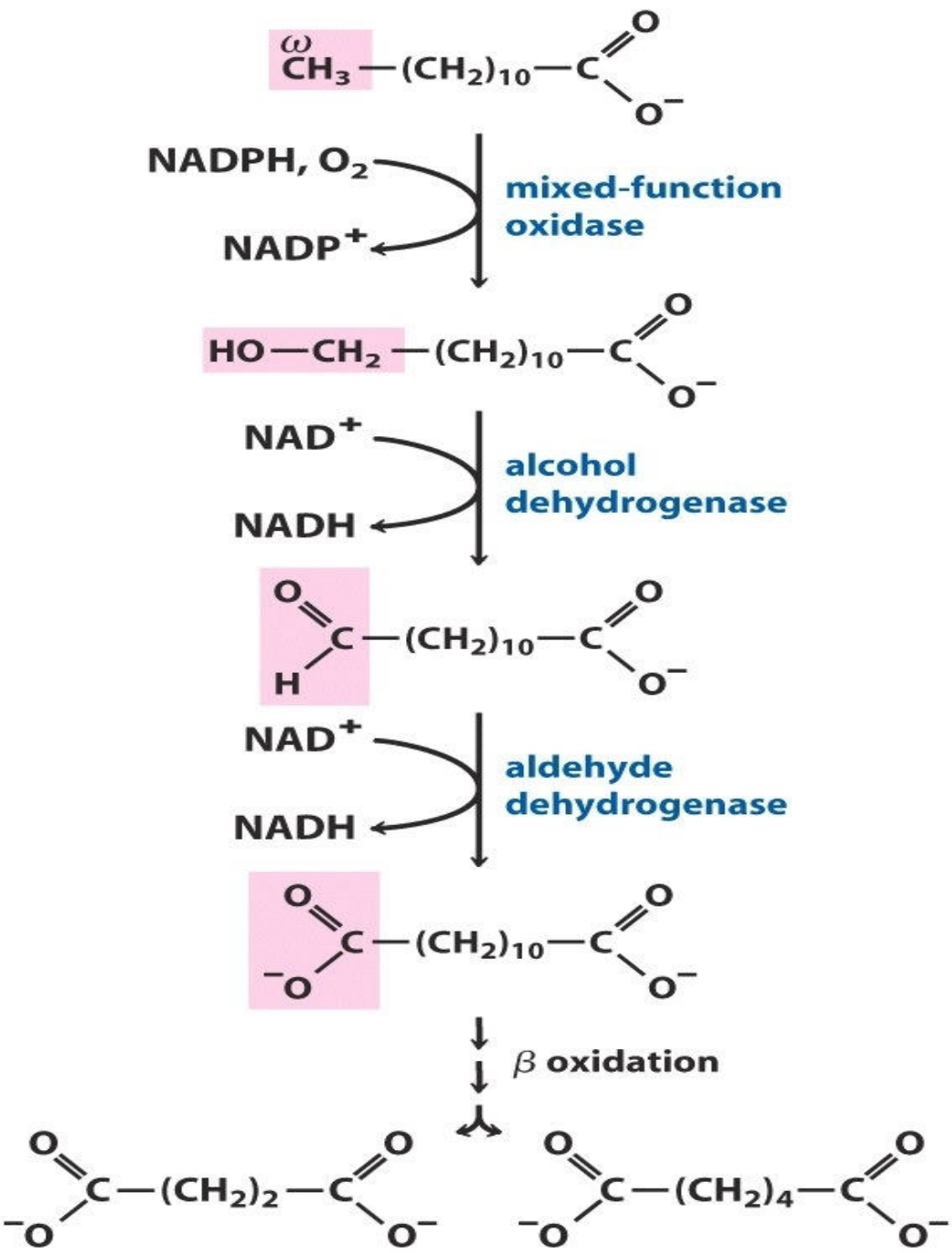
- ω Oxidation of Fatty acid is a **minor alternative oxidative Pathway.**

- Omega Oxidation of a Fatty acid takes place with:
  - **Hydroxylation Reaction**
  - **Oxidation Reaction**

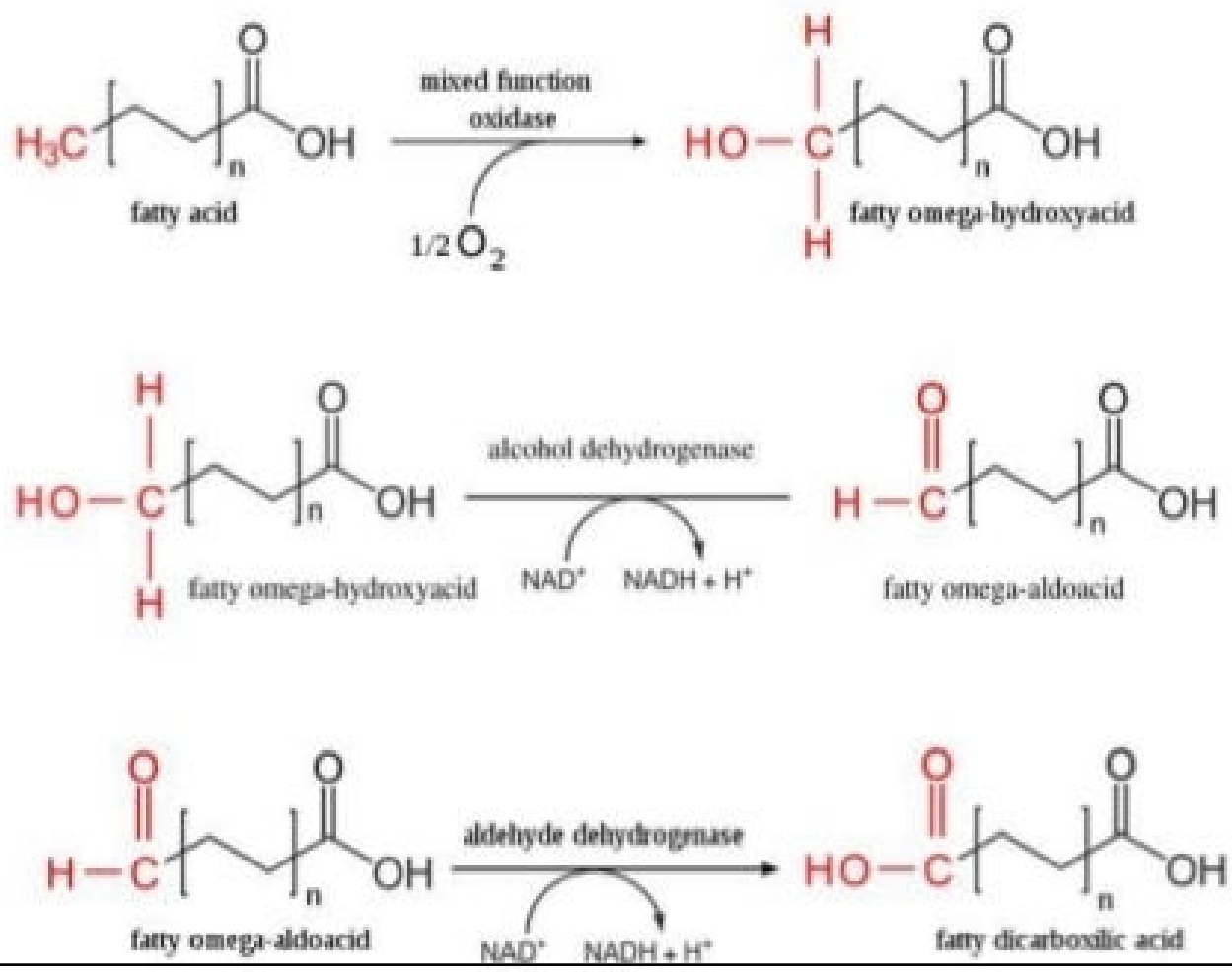
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ω = Omega, the last letter in the Greek alphabet



OMEGA OXIDATION OF FATTY ACIDS



Dicarboxylic acids so formed can undergo beta oxidation to produce shorter chain dicarboxylic acids such as Adipic acids(C6) and succinic acid (C4).

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- In ω Oxidation of Fatty acid there occurs **Hydroxylation at ω Carbon atom**
- **Converting** into **Primary terminal Alcohol (-CH2OH) group.**
- This reaction is catalyzed by NADPH+H^+ dependent **Cytochrome P450 system**
- **Next** the primary terminal Alcohol group is **oxidized to form -COOH group** .

- Further the **Dicarboxylic acid generated through Omega Oxidation** undergoes beta oxidation
- To **produce short chain Dicarboxylic acids as Adipic acid and Succinic acid**
- Which are **polar and excreted out through Urine.**

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Significance Of Omega Oxidation

- Omega Oxidation **transforms a non polar Fatty acid to polar** Dicarboxylic fatty acid.
- Omega Oxidation of fatty acid **facilitates excretion of accumulated fatty acids** due to defective normal β Oxidation in the cells.

Peroxisomal Oxidation Of Fatty Acids

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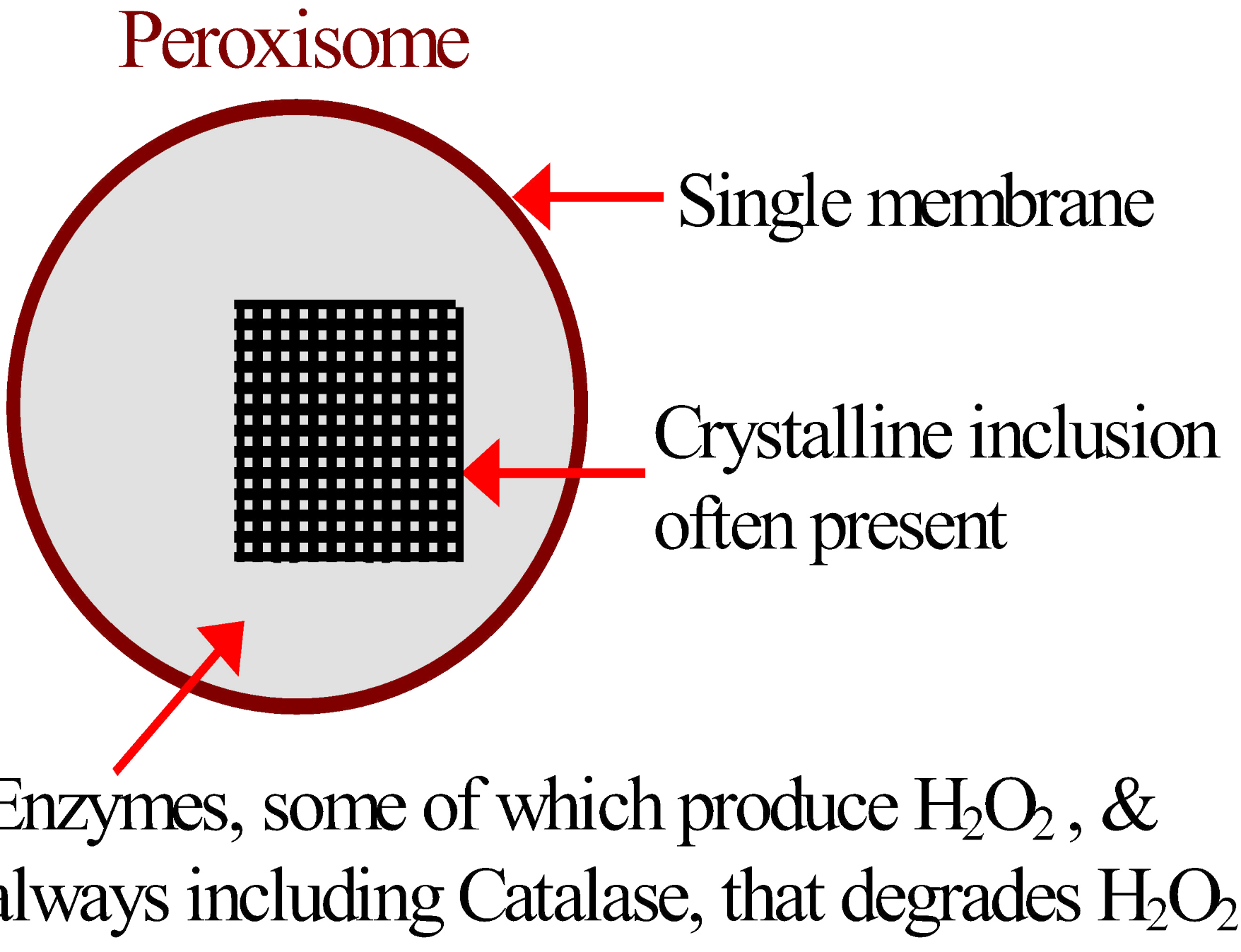
OXIDATION OF FATTY ACIDS IN PEROXISOMES

- **Peroxisomes** – Cell organelles containing Enzymes ***Peroxidase*** and ***Catalase***
- These Enzymes catalyzes the dismutation of **Hydrogen peroxide** into **water and molecular oxygen**

When ? Why? How?
Does
Peroxisomal Oxidation
OF
Fatty Acid Occurs?

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- **β-Oxidation of very long-chain fatty acids(>C22)** occurs within **Peroxisomes initially**
- **Later undergoes Mitochondrial β Oxidation .**

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- **Carnitine** is involved in transfer of Very long Chain Fatty acids (**VLCFAS >C22**) **into and out of Peroxisomes.**

- Peroxisomal Fatty acid oxidation is **induced by a high Fat diet with VLCFAs.**
- **To shortens the VLCFAs into LCFAs**
- Which are **further degraded by Beta oxidation process**.

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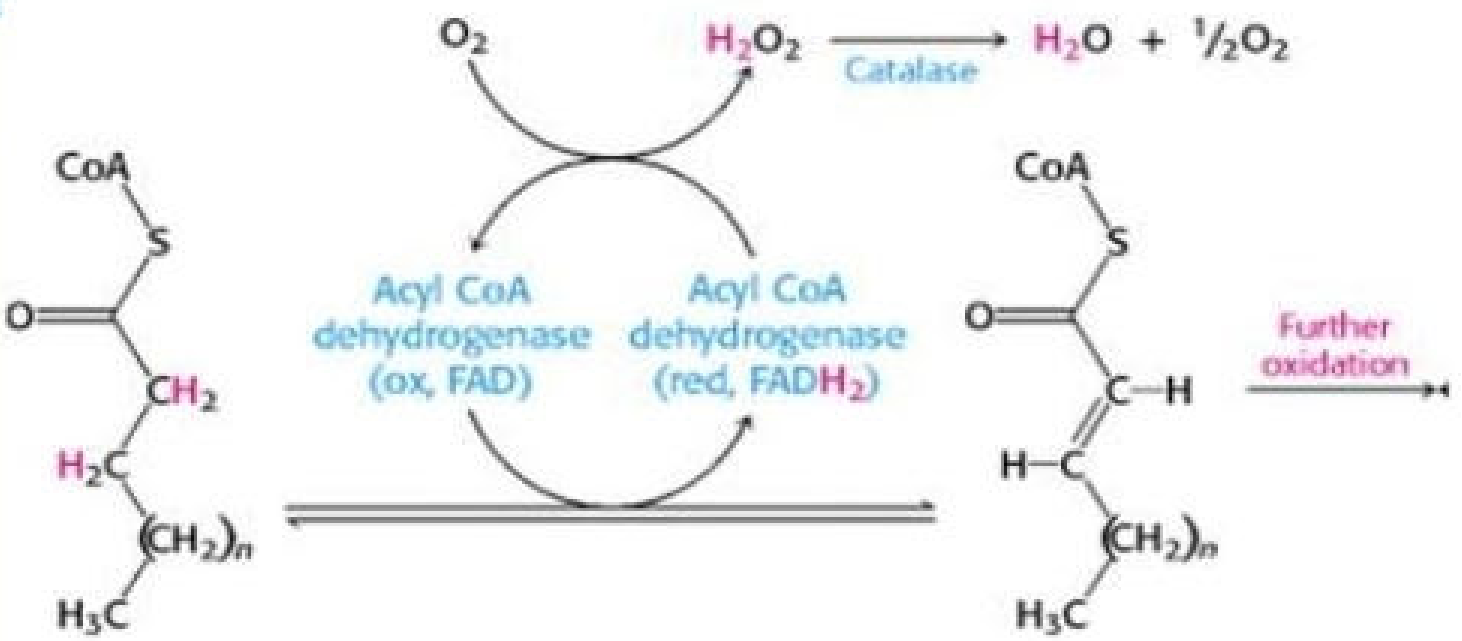
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Peroxisomal β-Oxidation

- Similar to Mitochondrial β-oxidation,

- Initial double bond formation is catalyzed by **Flavoprotein Acyl-CoA Oxidase**

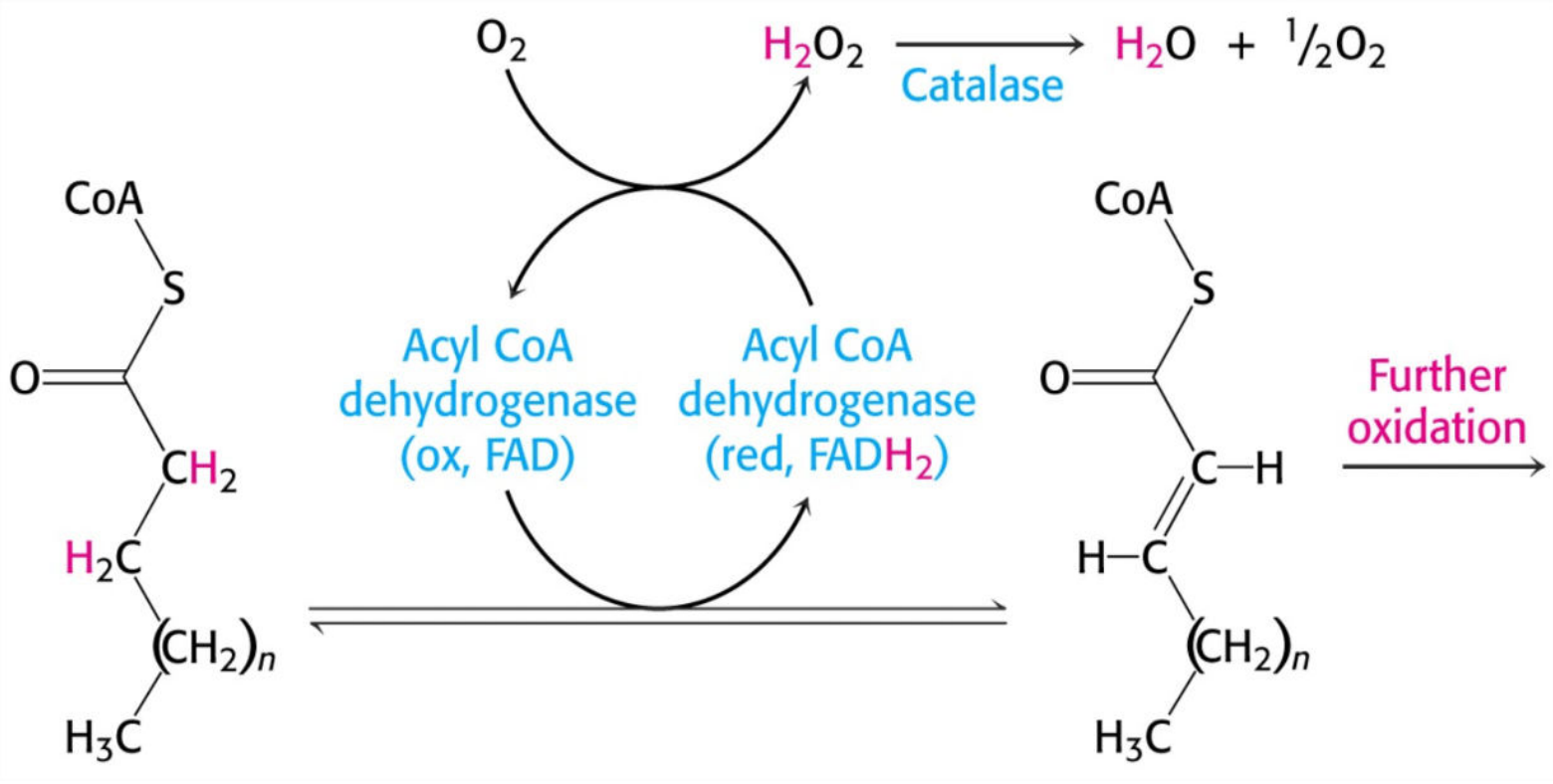
PEROXISOMAL OXIDATION OF VERY LONG CHAIN FATTY ACIDS



The specificity of the peroxisomal enzymes is for longer chain fatty acids. Thus peroxisomal enzymes function to shorten the chain length of relatively long chain fatty acids to a point at which beta oxidation can be completed in mitochondria.

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Acyl CoA Oxidase–FAD transfers electrons to O_2 to yield H_2O_2.

- **Coenzyme FAD** is e^- acceptor for Peroxisomal **Acyl-CoA Oxidase,** which catalyzes the 1st oxidative step of the pathway.

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- **FADH2 generated** at this step instead of transferring the high-energy electrons to ETC, as occurs in Mitochondrial beta-oxidation.
- Electrons of **FADH2 directly go to O_2 at reaction level to generate H2O2** in **Peroxisomes.**

- **Thus FADH2** generated **in Peroxisomes** by Fatty acid oxidation **do not enter ETC to liberate ATPs.**
- **Instead** the peroxisome, **$FADH_2$** generated by fatty acid oxidation by **Acyl CoA Oxidase** is **reoxidized producing Hydrogen peroxide**.

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$$FADH_2 + O_2 \rightarrow FAD + H_2O_2$$

The Peroxisomal enzyme **Catalase** degrades H_2O_2:

$$2\ H_2O_2 \rightarrow 2\ H_2O + O_2$$

These reactions produce **No ATP**.

- Once Very Long Chain Fatty acids are reduced in length within the Peroxisomes
- They may shift to the Mitochondrial beta oxidation for further catabolism of fatty acids.

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- Fewer ATPs result from Peroxisomal oxidation of VLCFAs.

- Steps of Peroxisomal Oxidation of Fatty acid **does not generate ATPs**
- Instead the **energy dissipated** in the **form of heat.**

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- Many **drugs** commercially available in market for **reducing obesity**
- **Stimulate Peroxisomal beta oxidation**
- Where the **Fatty acids are oxidized without much liberation of calories (ATPs).**

- Peroxisomal Oxidation of Fatty acid efficiently takes place in:
  - Obese persons
  - Persons taking Hypolipidemic drugs(Clofibrate).

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Peroxisomal β-Oxidation

- A second important difference between mitochondrial and peroxisomal β oxidation in mammals is in the **specificity for fatty acyl–CoAs**;
- The peroxisomal system is much more active on **very-long chain fatty acids such as hexacosanoic acid (26:0) and on branched-chain fatty acids such as phytanic acid and pristanic acid**
- The **inability of cells/patients** to make peroxisomes leads to neurological disorder called as **Zellweger syndrome**; and therefore lack all the metabolism unique to that organelle

Zellwegers Syndrome
OR
Cerebrohepatorenal Syndrome

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Peroxisomal Disorder

- Zellweger Syndrome
- Cerebro-Hepato-Renal Syndrome



Biochemical Causes

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- **Rare genetic autosomal recessive disorder.**
- Characterized by **absence of functional Peroxisomes.**

- Gene mutations in **PEX Genes** leads to Zellwegers Syndrome.

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Biochemical Alterations

- **No oxidation** of **very long chain Fatty acids** and **branched chain fatty acids** in **Peroxisomes**

- **Accumulation** of large abnormal amounts of **VLCFAs** in Peroxisomes of tissues.

- **No normal function of Peroxisomes**.

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- Progressive degeneration of **Brain/Liver/Kidney,** with **death ~6 month after onset.**

Signs and Symptoms

- **Defect** in normal function of **multiple organ system.**
- **Impaired** neuronal migration, positioning and **brain development.**
- Hypomyelination **affecting nerve impulse transmission.**
- **Hepatomegaly**
- **Renal Cysts**
- Typical **Dysmorphic facies.**

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Diagnosis

- **Detection of Increased levels of Serum Very Long Chain Fatty Acids-VLCFAs**

ZELLWEGER SYNDROME

- The **abnormally high levels of VLCFA(Very long chain fatty acids),** are most diagnostic.
- There is no cure for Zellweger syndrome, nor is there a standard course of treatment.
- Most treatments are **symptomatic and supportive.**
- Most infants do not survive past the first 6 months, and usually succumb to **respiratory distress, gastrointestinal bleeding, or liver failure.**

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Oxidation Of Unsaturated Fatty Acids

- **PUFAs** having **double bonds** in their structure **are unstable**.
- The **double bonds** are hydrolyzed and **metabolized faster** than **saturated bonds**.
- Thus dietary **intake of PUFA get readily metabolized**
- **Which reduces risk of ~~Atherosclerosis.~~**

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Mechanism Of Oxidation Of Unsaturated Fatty Acids

- **Initial and later** the **Oxidation of PUFAs** is by
- **Similar steps of β Oxidation** in the parts, of **saturated bonds**.

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- **The double bonds of UFAs are cleaved by the action of Following Enzymes:**
  - **Isomerase (Enoyl CoA Isomerase)**
    (For even numbered double bonds MUFAs)
  - **Reductase (2,4 Dienoyl CoA Reductase)**
    (For Odd numbered double bonds PUFAS)
  - **Epimerase**
    (Converts D Isomer to L Isomer)

- **Enoyl CoA Isomerase** handles **odd numbered double bonds** in MUFAs.
- **2,4 Dienoyl CoA Reductase** handles **even numbered double bonds** in PUFAs.

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- Usually natural unsaturated fatty acids have **cis double bonds.**
- Which is **transformed to *trans* *double bonds*** by the action of an **Isomerase .**
- As the next enzyme to act is **Enoyl Hydratase ,which acts only on *trans* double bonds.**

- **Enoyl-CoA Isomerase** converts Cis unsaturated Fatty acids to **Trans-** Δ^2 **Enoyl-CoA**

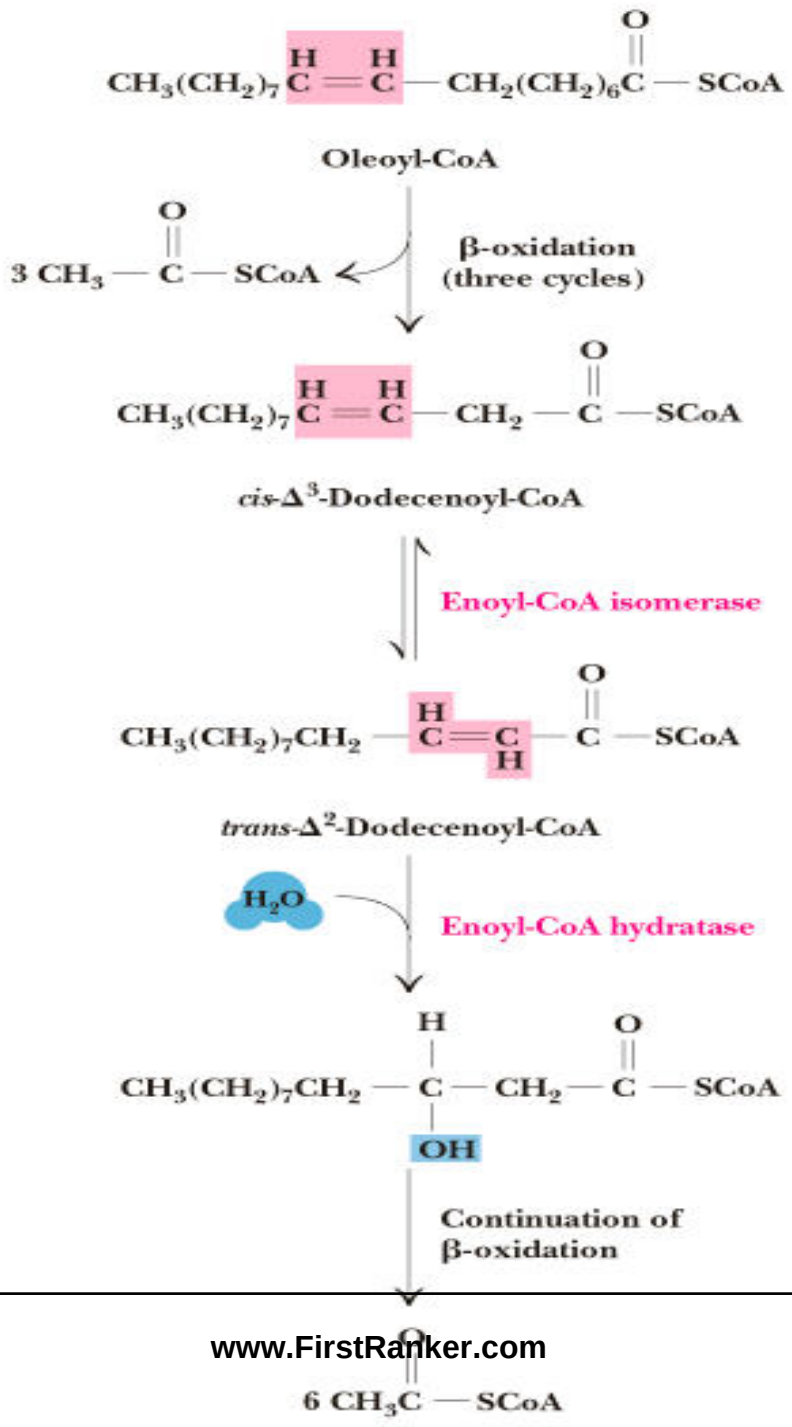
- Now the β-oxidation can continue on with the hydration of the trans- Δ^2-Enoyl-CoA by Enoyl CoA Hydratase

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Oxidation Of Monounsaturated Fatty Acids

- Oleic acid, Palmitoleic acid
- Normal β-oxidation for three cycles
- Cis-Δ^3 Acyl-CoA **cannot be utilized by Acyl-CoA dehydrogenase**
- **Enoyl-CoA Isomerase** converts this to trans- Δ^2 Acyl CoA
- β-oxidation continues from this point



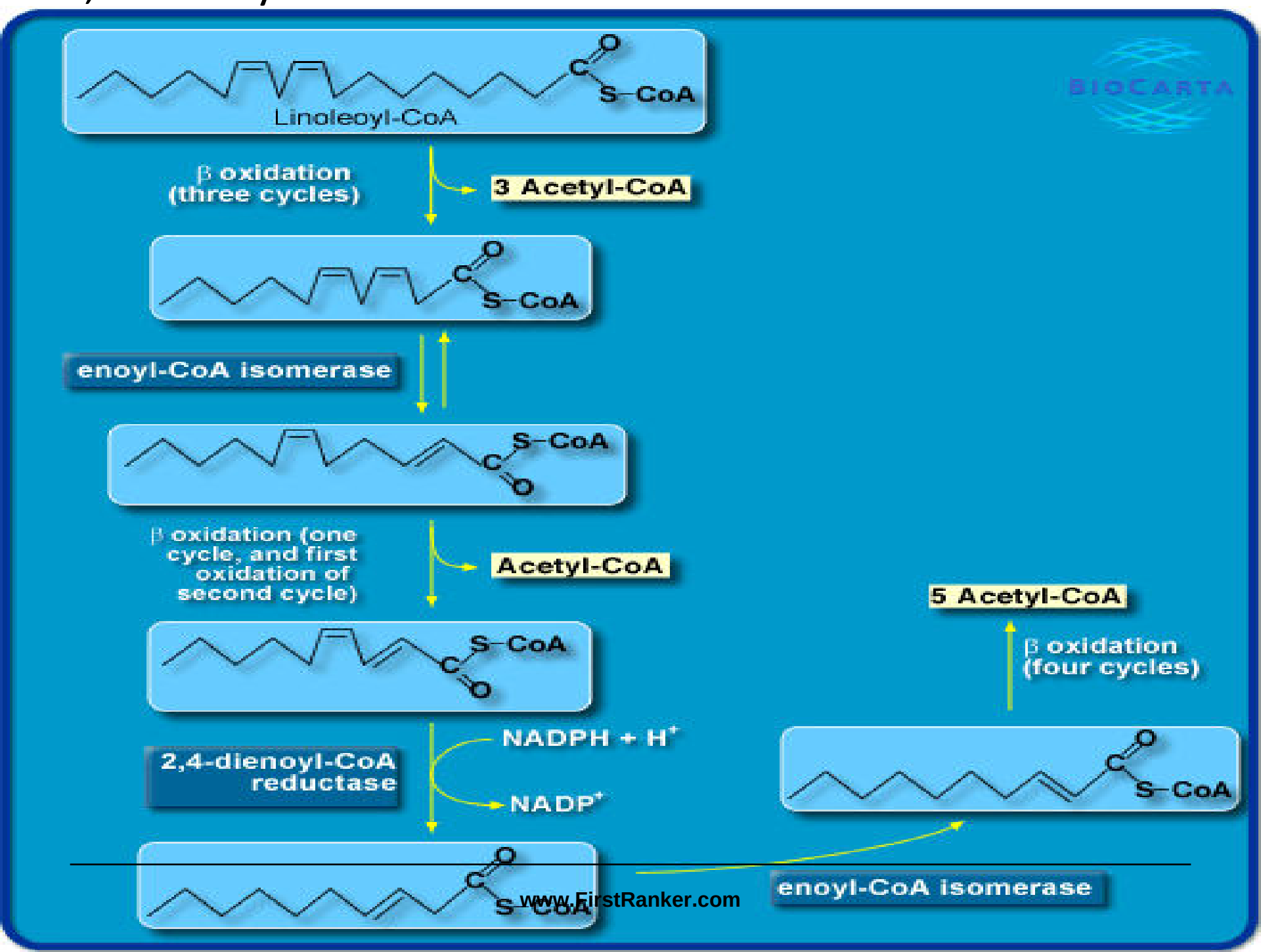
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Oxidation Of Polyunsaturated Fatty Acids

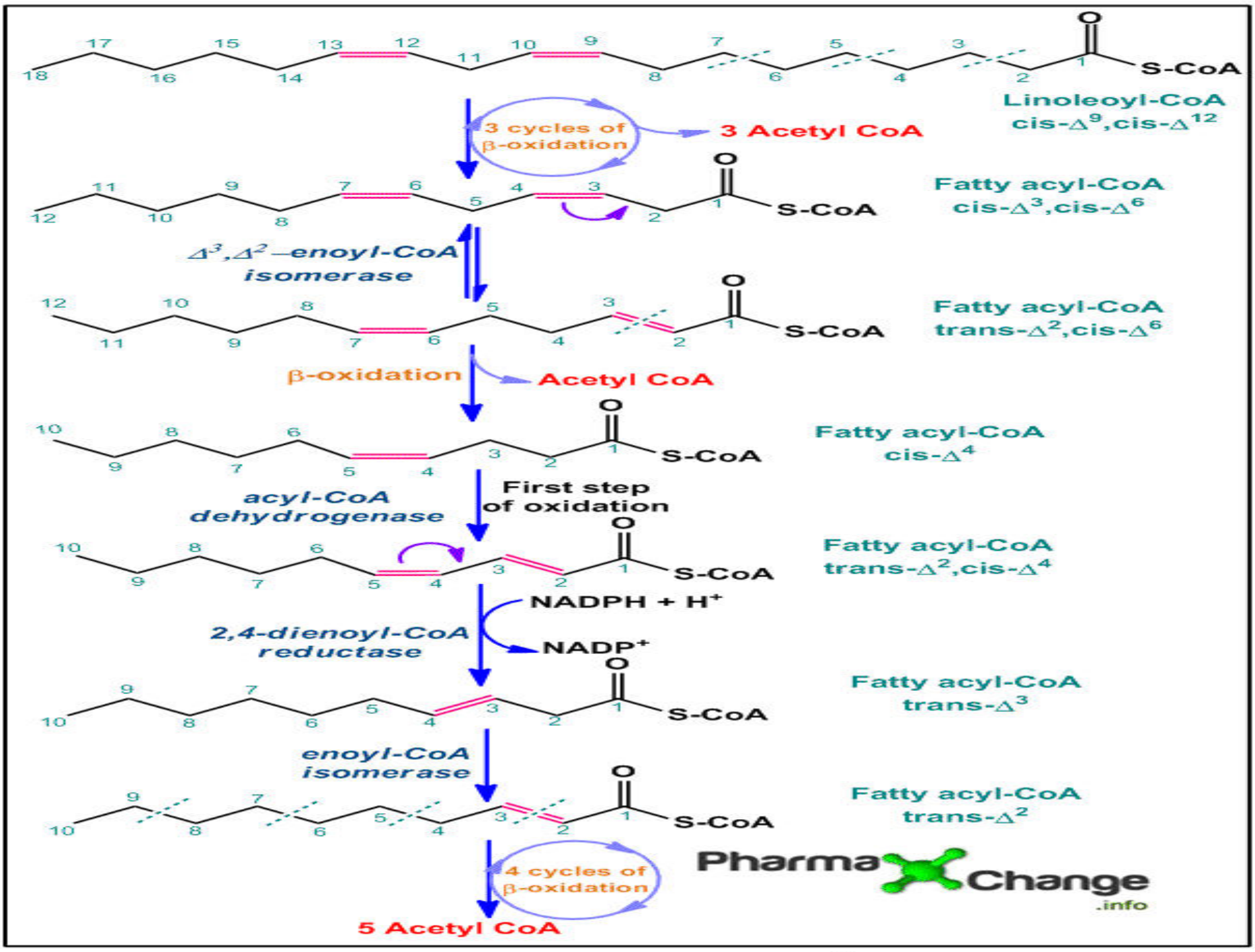
Slightly more complicated

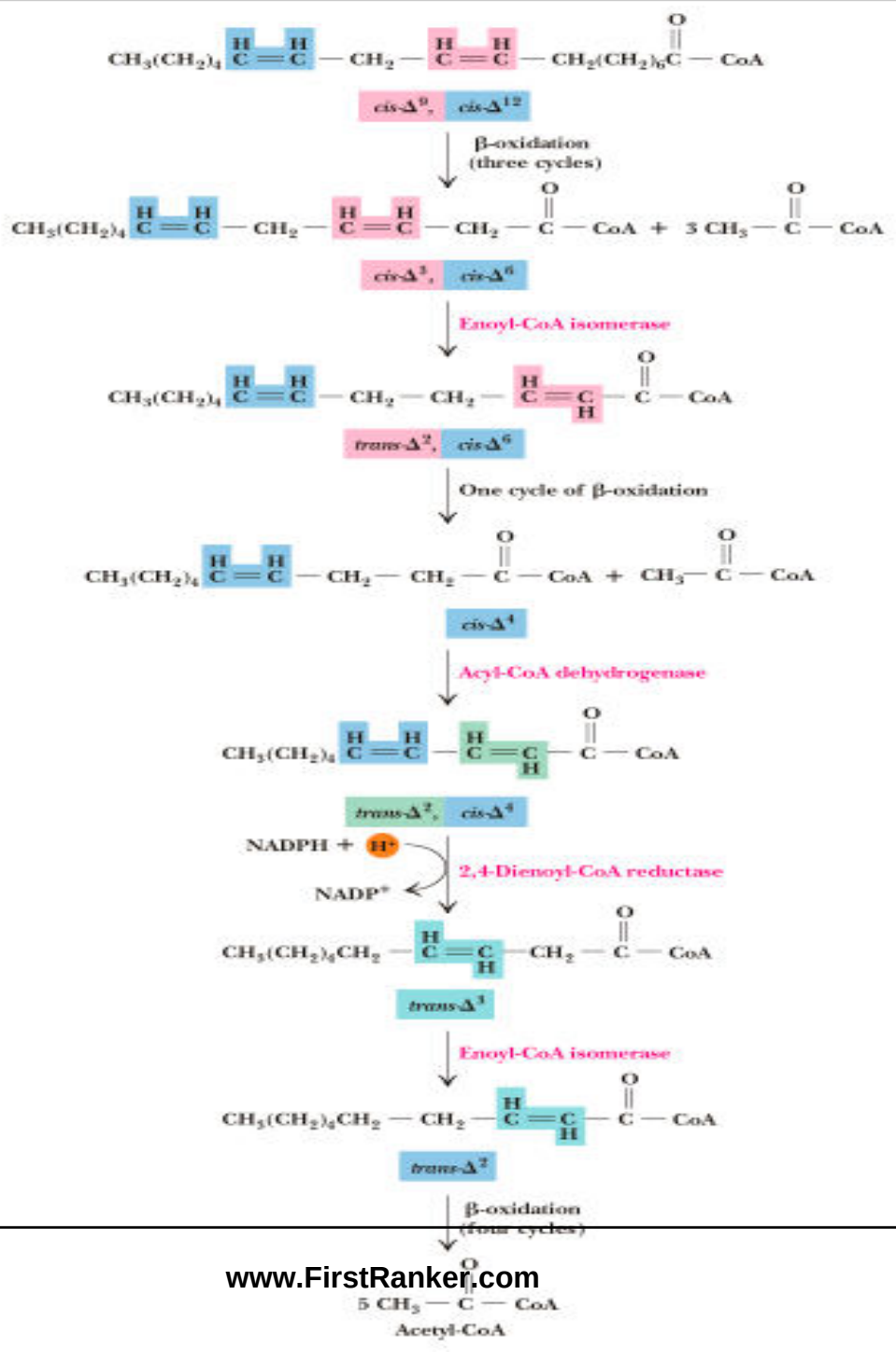
- Same as for Oleic acid, but only up to a point:
  - 3 cycles of β-oxidation
  - Enoyl-CoA Isomerase
  - 1 more round of β-oxidation
  - trans- Δ^2, cis- Δ^4 structure is a problem.
- 2,4-Dienoyl-CoA **Reductase** transform it to odd numbered.



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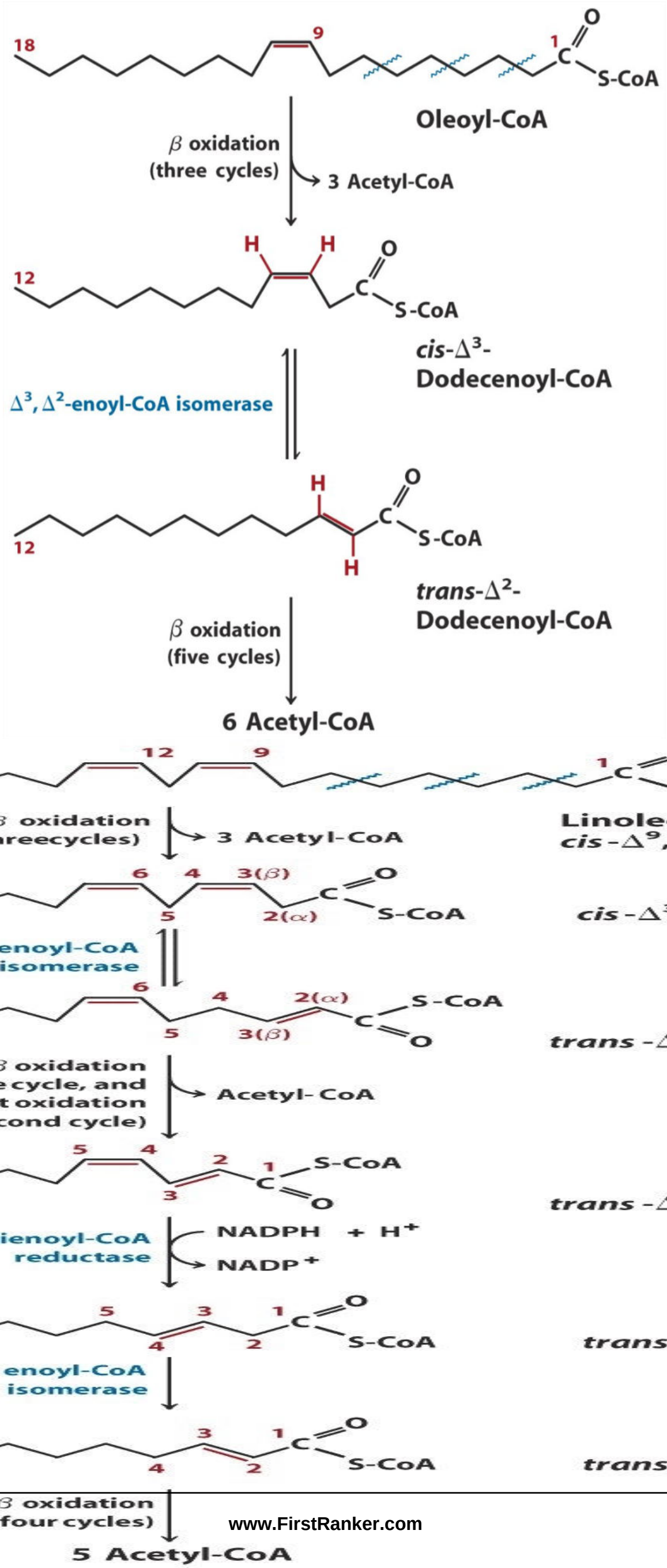




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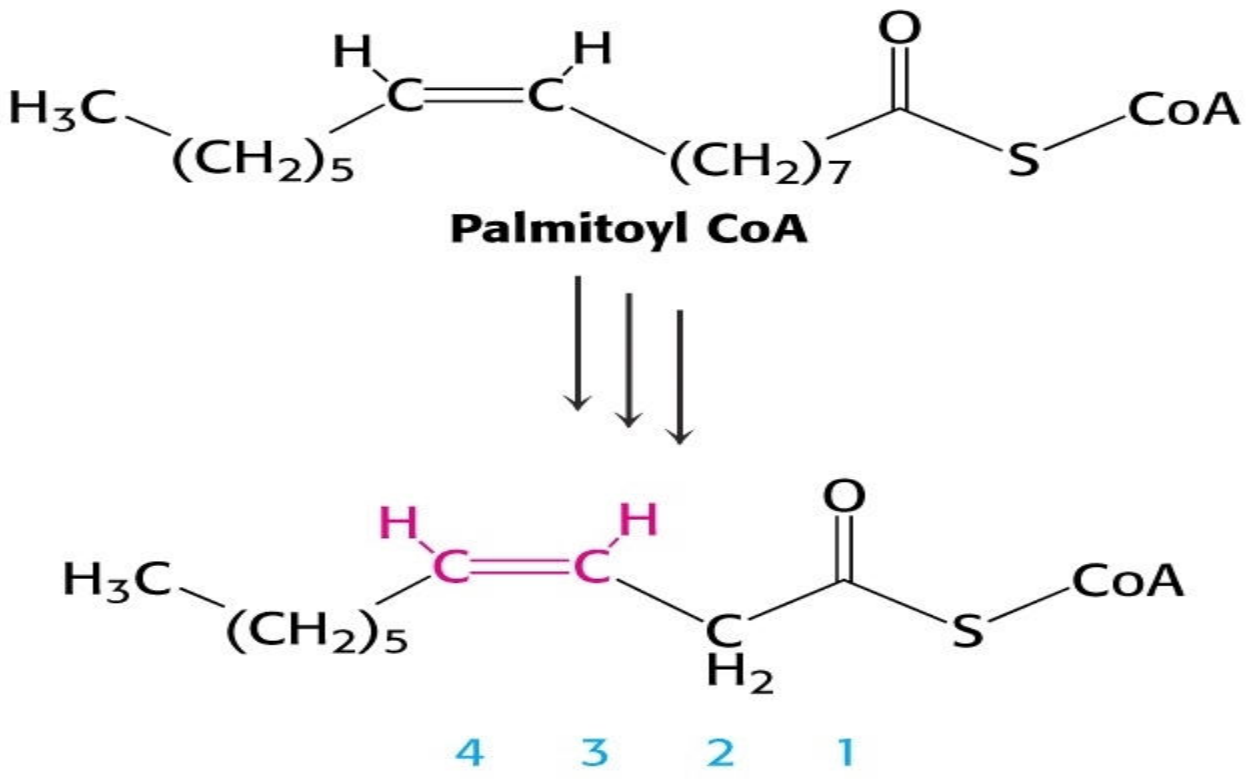
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Oxidation of Unsaturated Fatty Acids (Remember they are cis!)

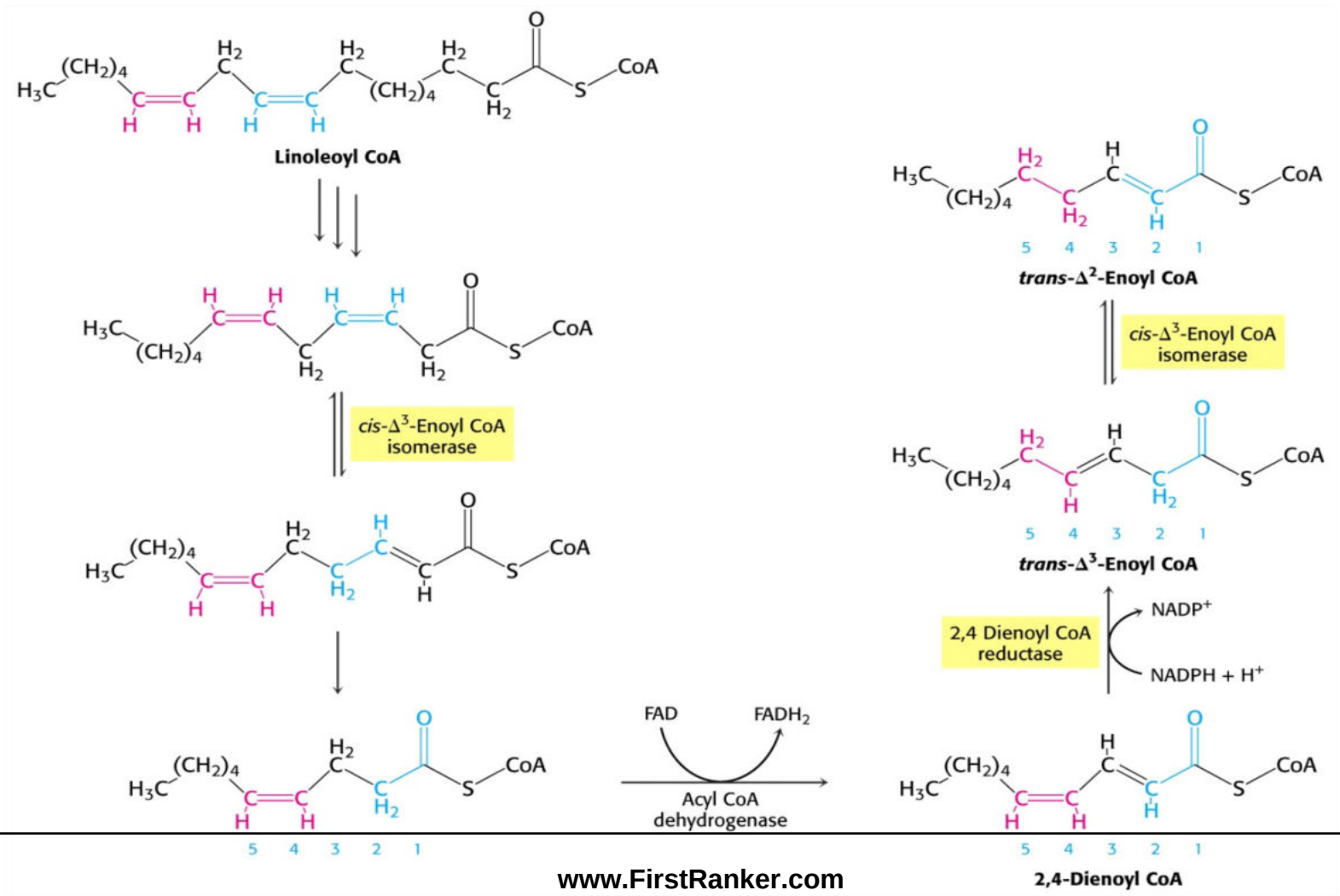


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β-oxidation of fatty acids with even numbered double bonds



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- The Oxidation of PUFAs **provide less energy** than saturated Fatty acids as they are **less reduced compounds**.
- At double bonds the Isomerase act and convert it into **Trans –Enoyl CoA.**
- This **bypasses the Acyl-CoA Dehydrogenase –FAD linked beta oxidation reaction**.
- 1.5 ATP less per double bond.

Ketone Body Metabolism

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Formation And Fates Of Ketone Bodies In Human Body

Ketogenesis And Ketolysis OR Formation And Breakdown Of Ketone Bodies

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What are Ketone Bodies ?

When ? Where? Why? and How?

Ketone Bodies are Formed In The Human Body???

Incomplete Oxidation Of Fatty Acids And There Products

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- **Ketone body Metabolism Includes:**

–**Ketogenesis** : Formation of Ketone bodies

–**Ketolysis**: Breakdown and Utilization of Ketone bodies

–**Ketosis:** Imbalance in Ketogenesis and Ketolysis.

Ketogenesis

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What Is Ketogenesis?

- **Ketogenesis is biosynthesis of Ketone bodies**
- **In emergency conditions at Mitochondrial matrix of Hepatocytes.**

Condition In Which Ketogenesis Occurs

- Ketogenesis efficiently occur **in Emergency conditions**

–Fasting/Starvation Phase

–Low Cellular Glucose Metabolism

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Site For Ketogenesis

OR

Where Does Ketogenesis Occurs ?

- **Ketone bodies are biosynthesized in** the **Liver/Hepatocytes at the Mitochondrial Matrix**
- **Formed Ketone bodies come out of Mitochondria**
- **Later they are diffused i**nto the blood and are
- **Transported to reach extrahepatic /peripheral tissues**

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Who Is The Precursor For Ketogenesis ?

- **Acetyl CoA is the precursor/starting material for Ketogenesis.**

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Source Of Acetyl-CoA For Ketogenesis

- Ketone bodies are formed from **Acetyl CoA ,obtained through increased beta oxidation of Fatty acids.**
- **Acetyl-CoA accumulated in Mitochondrial matrix due to underutilization via TCA cycle.**

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Biochemical Basis for Ketogenesis
OR
What Favors Ketogenesis ?
OR
Why Ketogenesis Occurs In Emergency Condition ?

What Factors

Promotes/Triggers Ketogenesis ?

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Biochemical Causes for Ketogenesis

- **In Emergency Condition**

–**Due to Cellular Glucose deprivation and its metabolism**

–**Low Cellular Oxaloacetate**

–**Low Operation of TCA cycle**

- **Normal Insulin** activity **do not promote Ketogenesis.**

- **Low Insulin** activity **promotes Ketogenesis.**

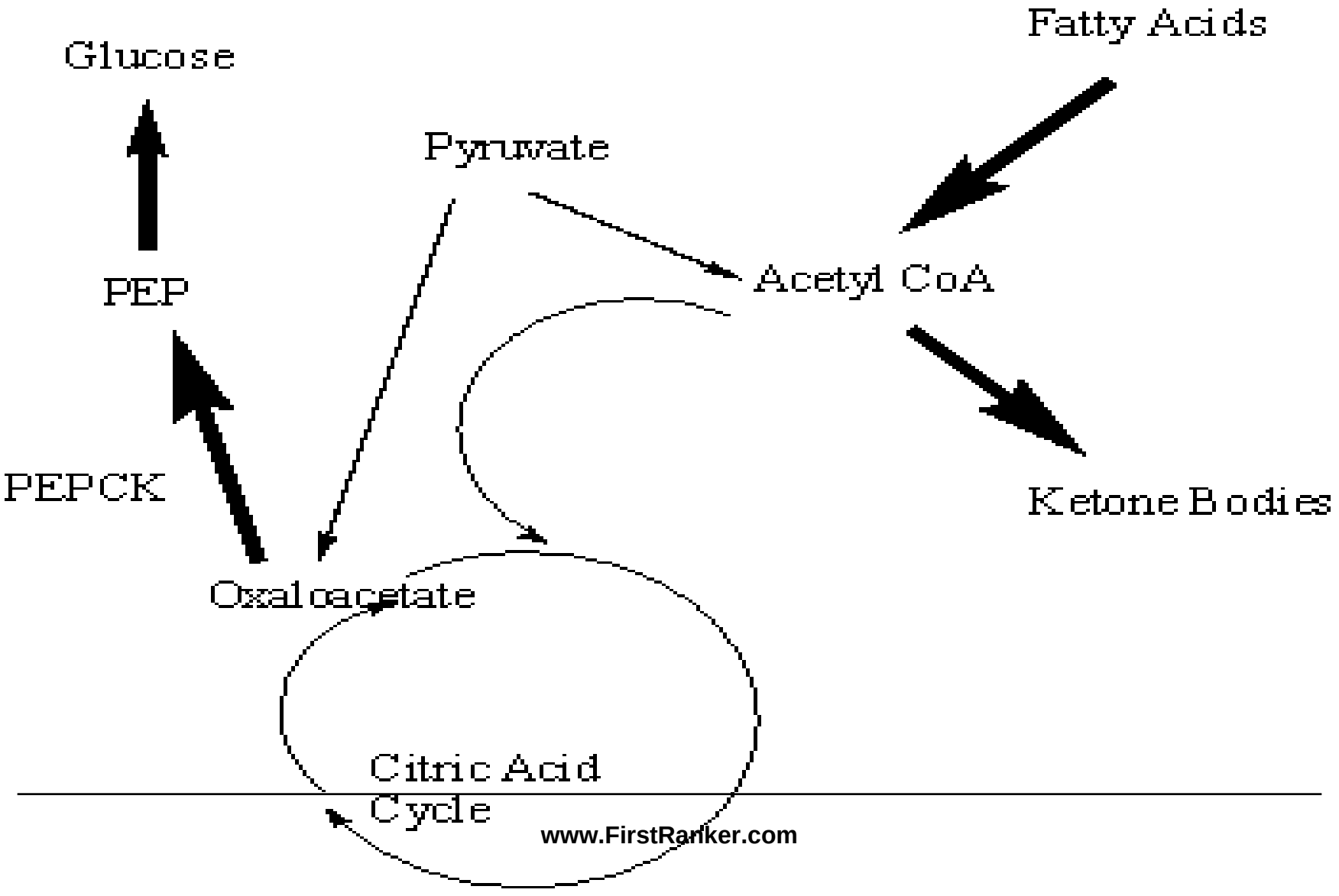
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Remember

- **Availability of Glucose in cells, do not promote Ketogenesis** and form Ketone bodies.
- **Unavailabity of Glucose in cells promote Ketogenesis** and **form Ketone bodies**

Way For KETOGENESIS



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REVIEW!

- When the body cells has **plenty of Carbohydrates (Glucose)** available as **primary energy source,**
- Glucose is **completely oxidized to CO2,H2O and ATPs**.

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–When the body has **excess Glucose available it is utilized as below:**

- Required amount of **Glucose is fully oxidized**
- **Stored as Glycogen**
- **Transformed to fatty acids and stored as TAG.**

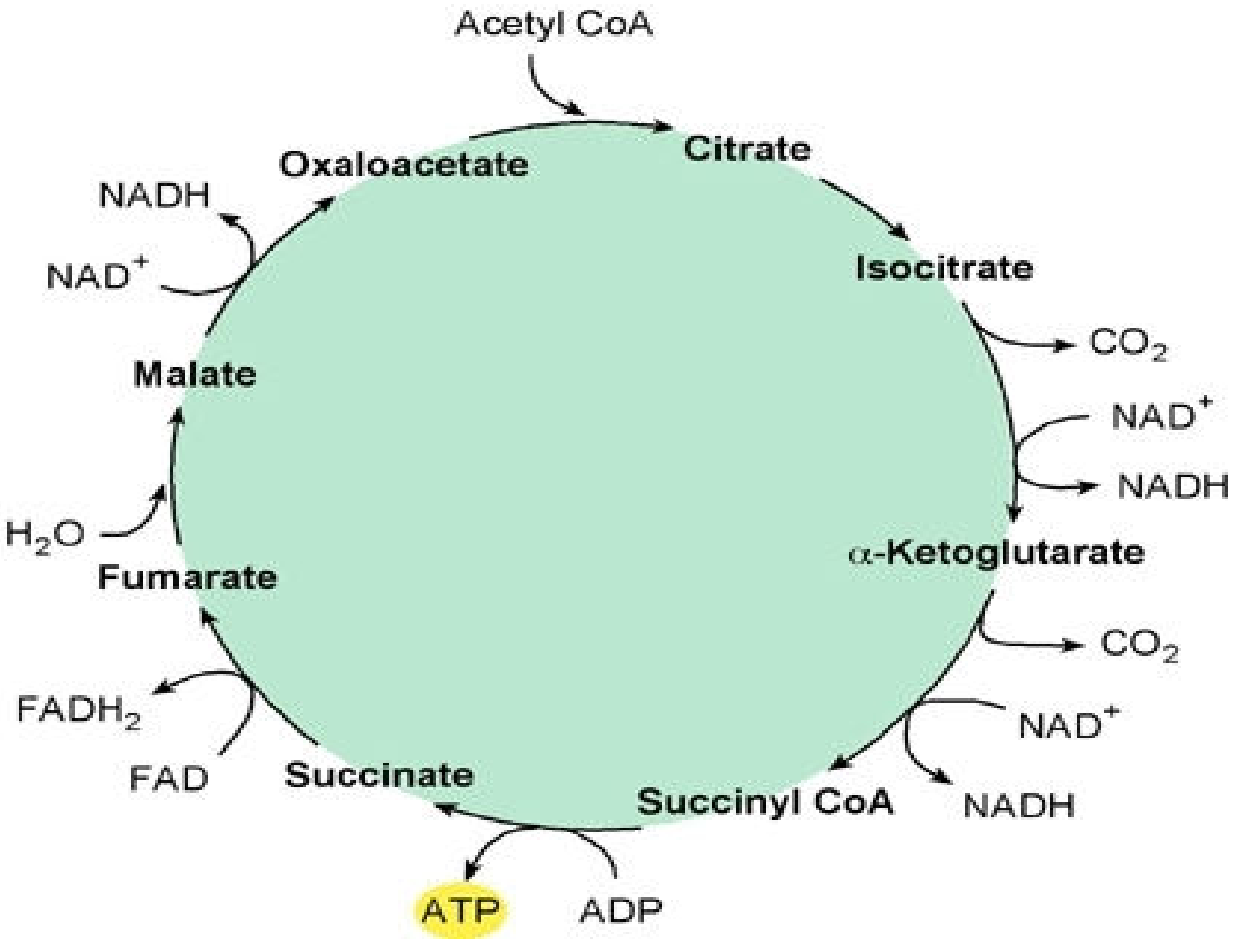
- When cell **Glucose go below sub normal**

- Fatty acids undergo **β-oxidation** to **form Acetyl-CoA.**

- Normally, **Acetyl-CoA is further oxidized via TCA cycle**.

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In Emergency
How Acetyl-CoA Gets Accumulated And Diverted For Ketogenesis ?

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- In Emergency Condition
- When **Cellular Glucose is low**

- In response to hormones **Glucagon and Epinephrine**

- There is **increased Lipolysis and beta oxidation Fatty acids.**

- In emergency conditions
- Cellular Glucose levels **decreases**
- **This decreases cellular Oxalo acetate (OAA).**
  - Since **source of OAA is Glucose**

    (By Pyruvate Carboxylation Rxn).
  - Also in emergency conditions **OAA is used for Gluconeogenesis which lowers cellular OAA.**

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- **OAA is the starting material required to initiate and operate TCA .**

- Due to **low levels** of **cellular OAA**, end product of Fatty acid oxidation- **Acetyl-CoA** is **not utilized via TCA cycle**.

- **The underutilized Acetyl-CoA in the Mitochondrial matrix of Liver gets accumulated.**

What Are The Steps Of Ketogenesis?

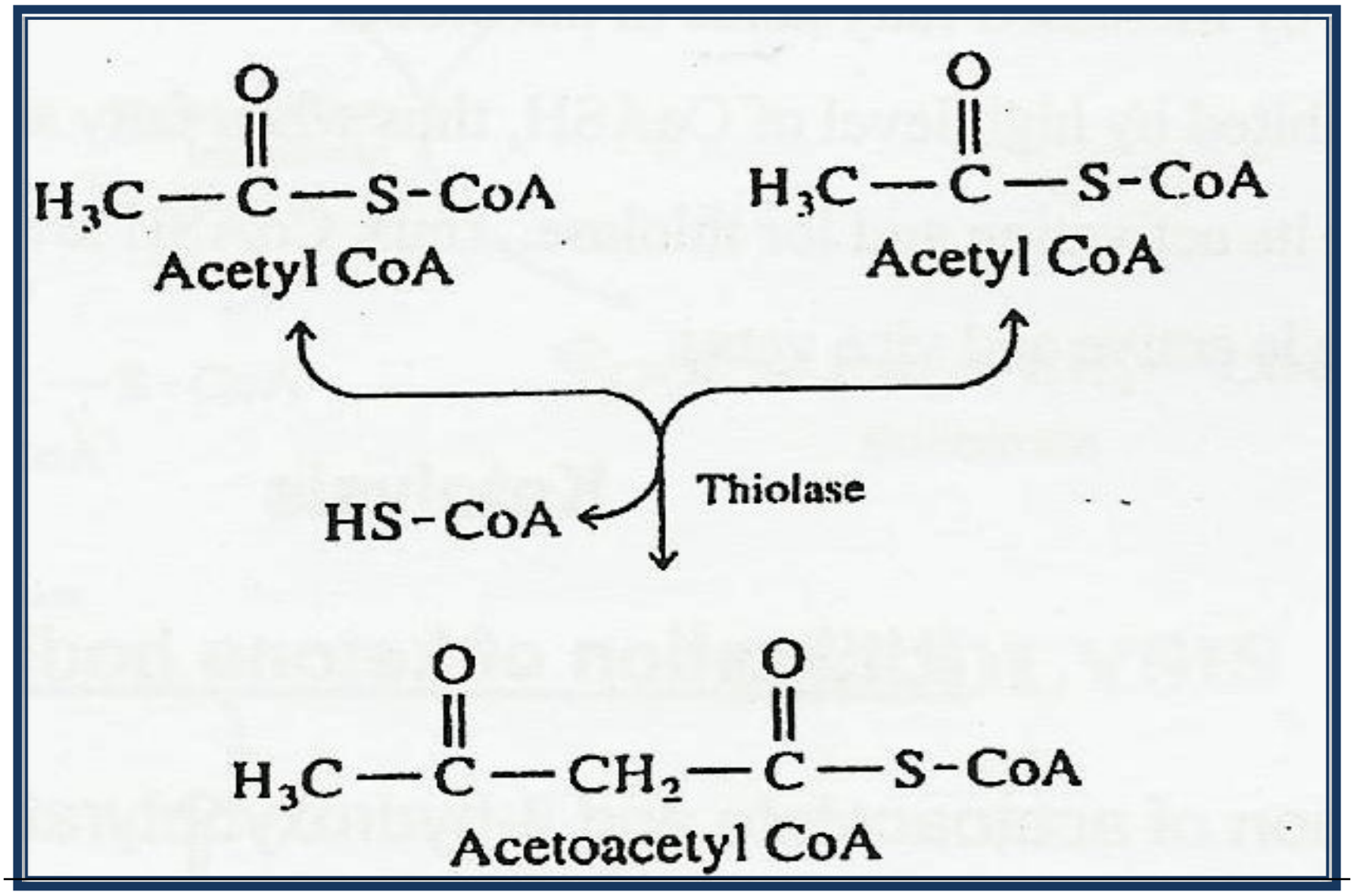
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Precursor For Ketogenesis

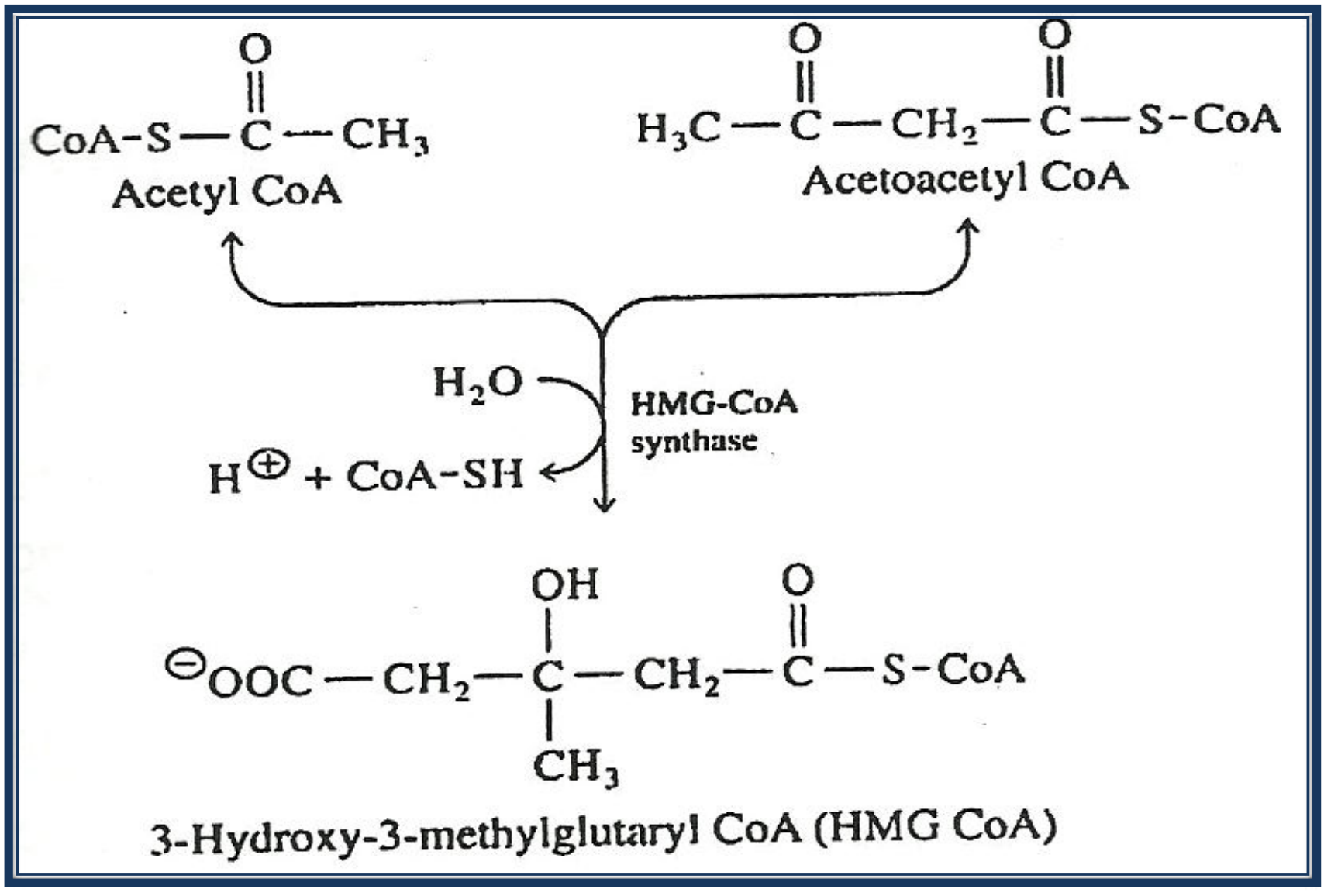
- **Is Acetyl-CoA**

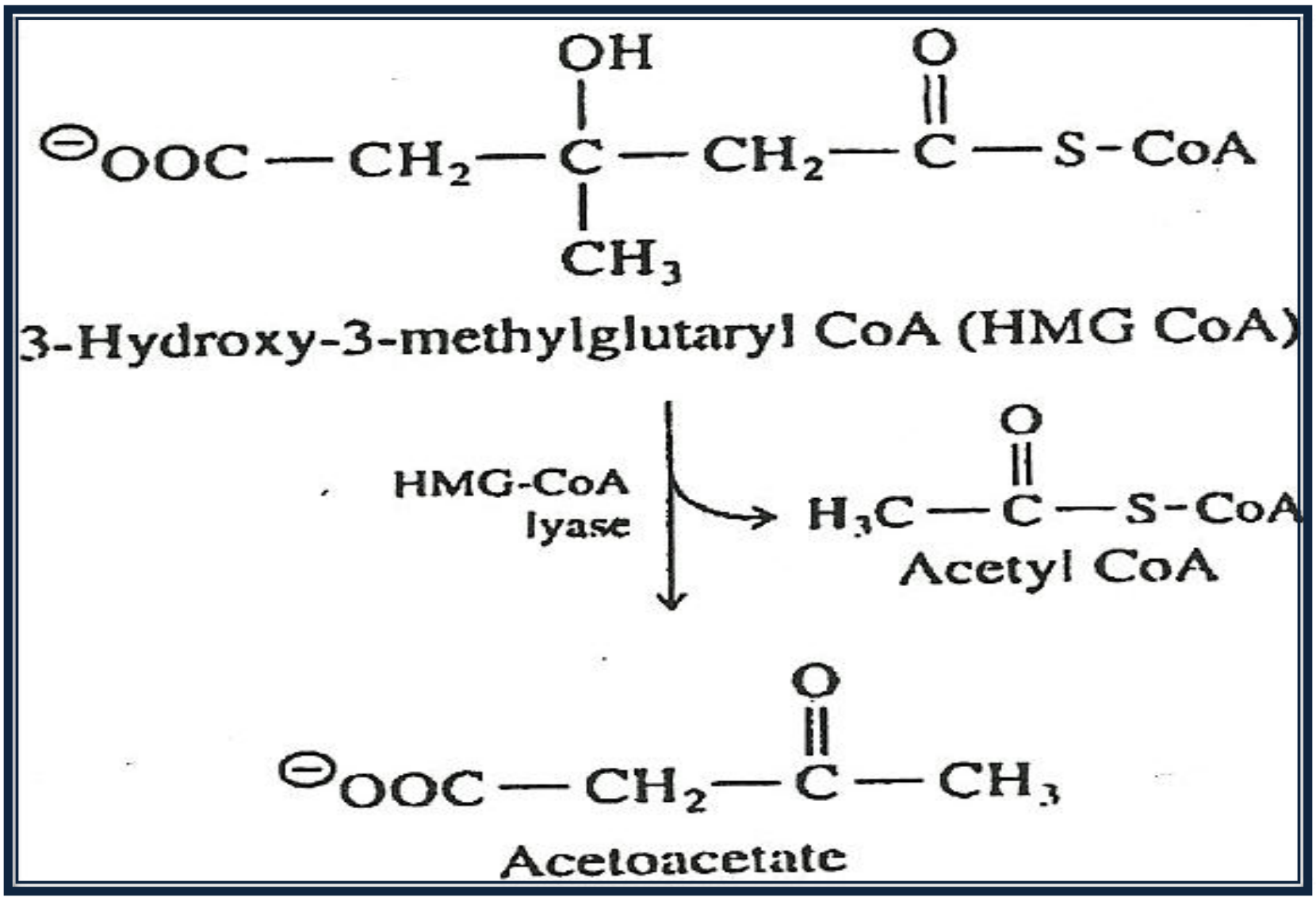
- **In Emergency condition**
- **Acetyl –CoA** obtained from increased **beta oxidation of Fatty acids** in **cellular Glucose deprived conditions**
- **Which accumulates Acetyl-CoA in Mitochondrial matrix due to low/no utilization of Acetyl-CoA via TCA cycle is** diverted for **Ketogenesis**.



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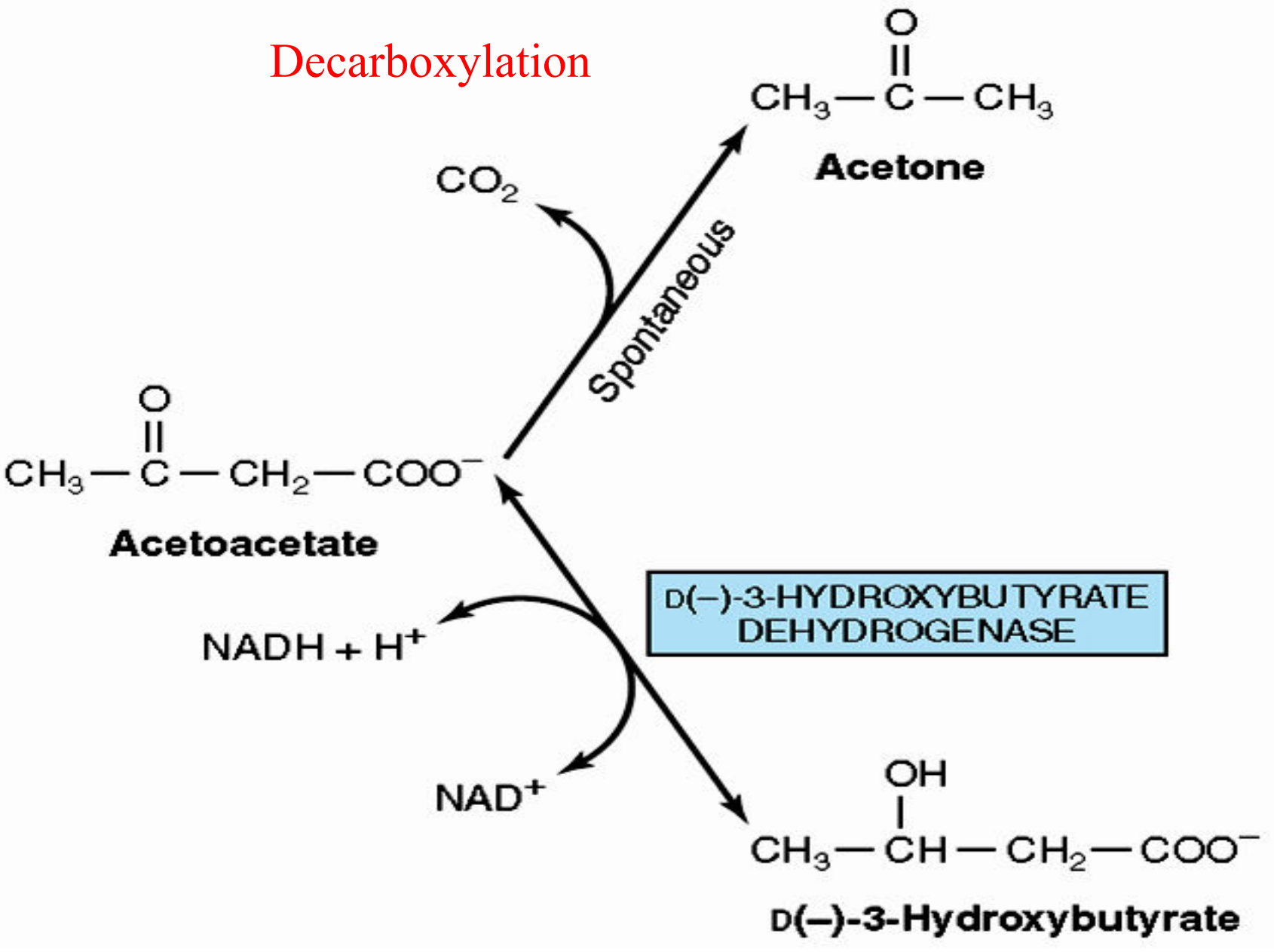




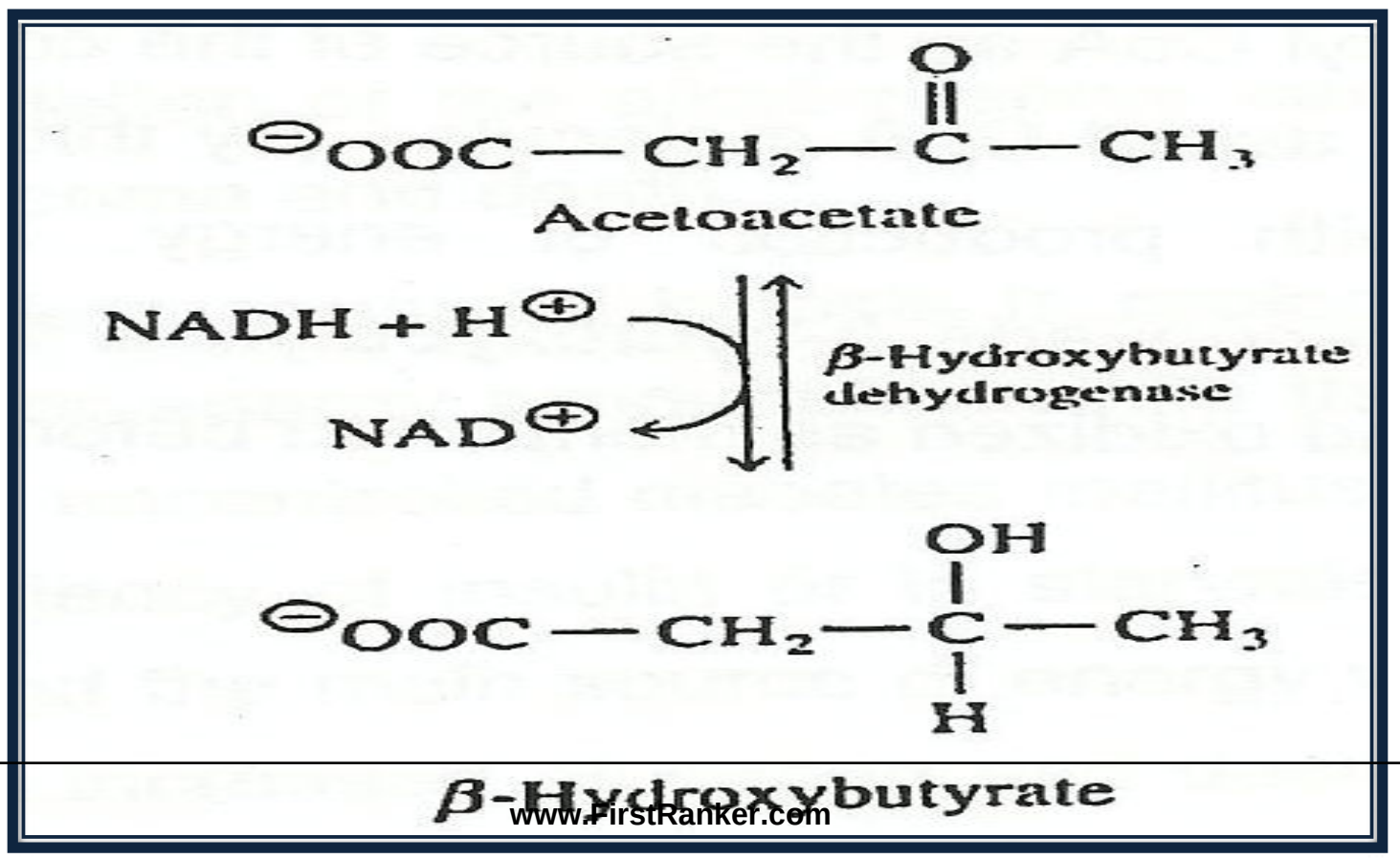
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Decarboxylation

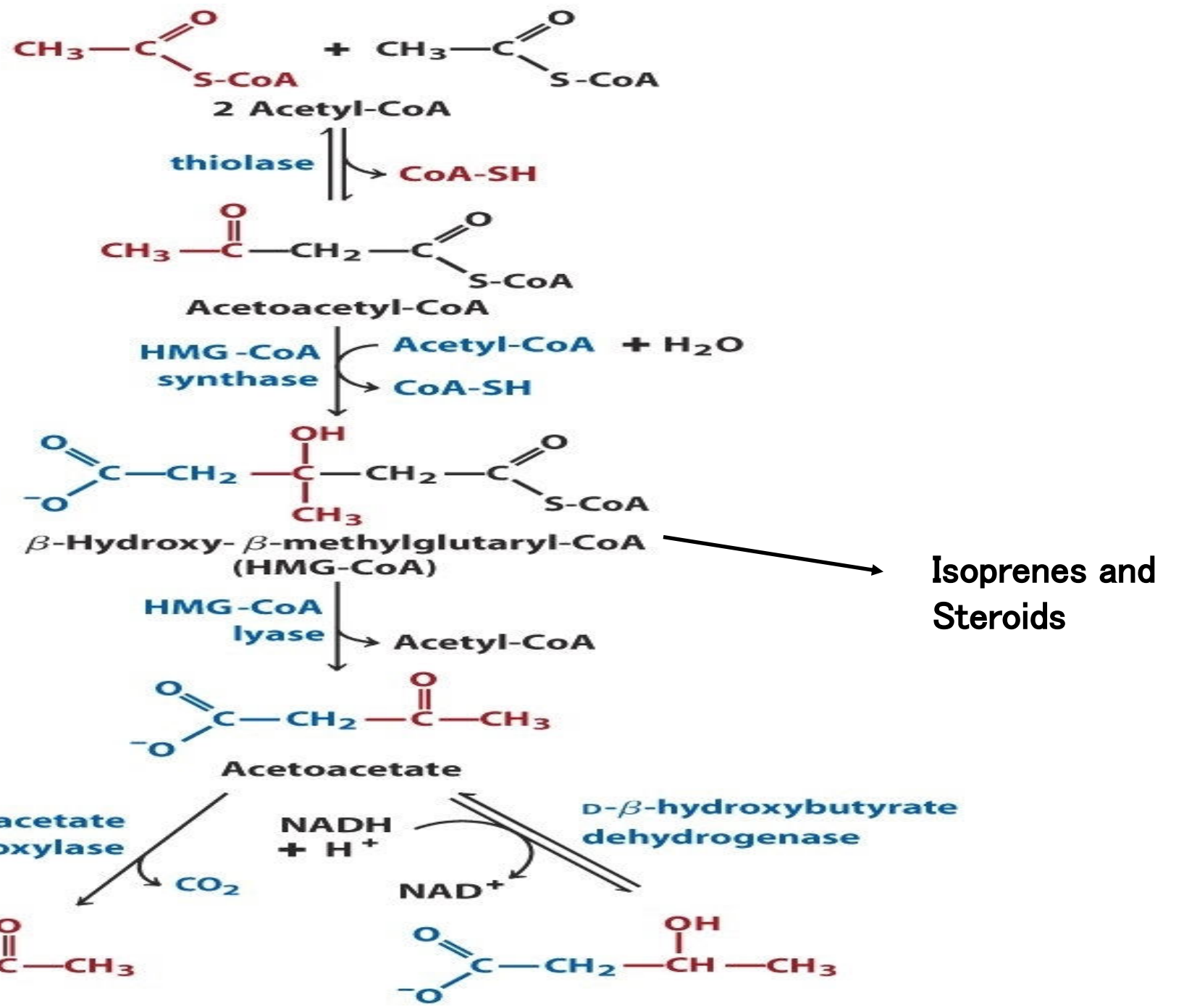


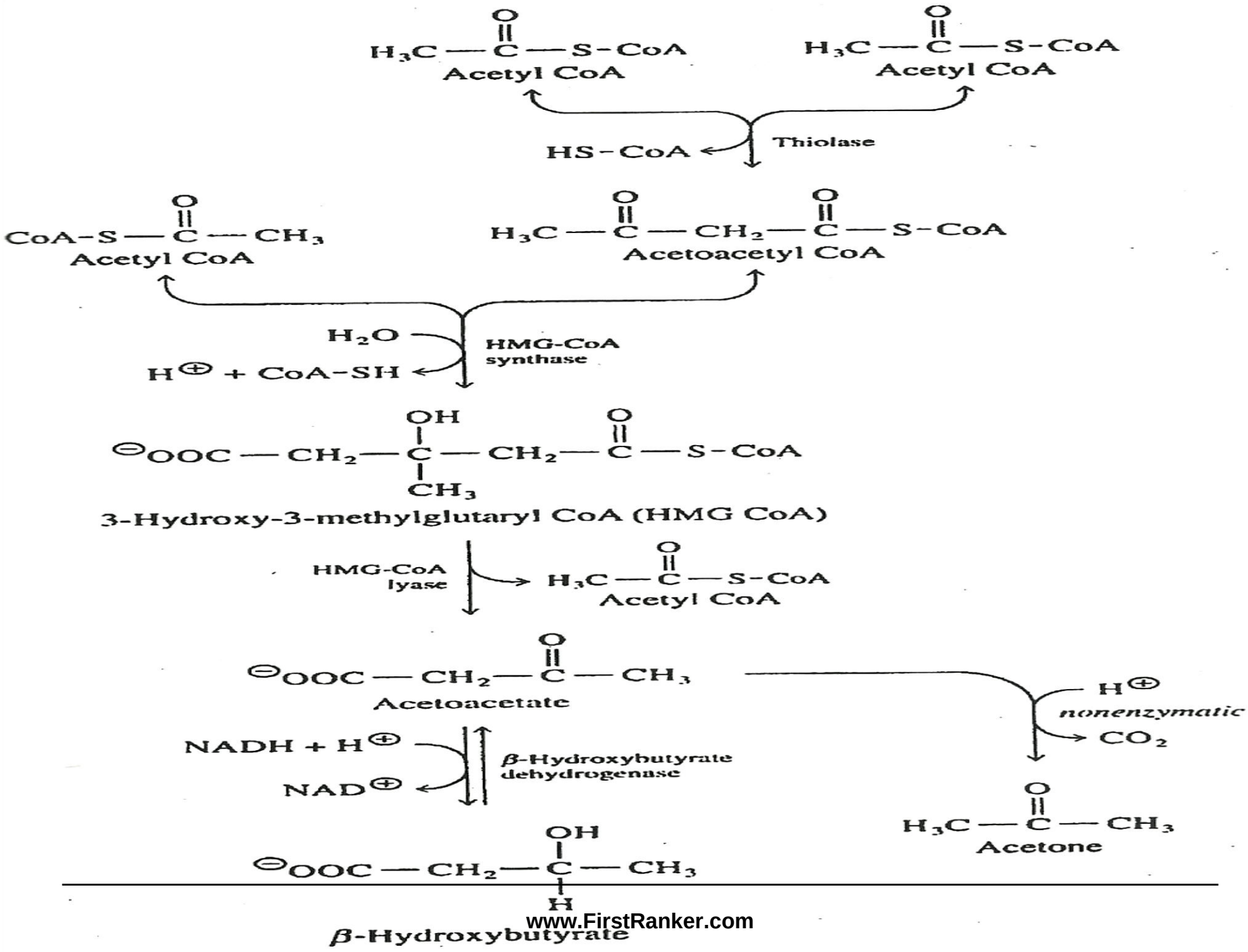
- **Acetoacetate** produces β-Hydroxybutyrate in a reduction reaction catalyzed by **β-Hydroxybutyrate Dehydrogenase i**n the presence **of NADH+H+**



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Fatty acid β-oxidation → 2 Acetyl CoA → *oxidation to CO_2* → Citric acid cycle

(excess acetyl CoA)

Thiolase

2 Acetyl CoA → CoA + Acetoacetyl CoA

acetyl CoA + Acetoacetyl CoA

HMG-CoA synthase

→ CoA + Hydroxymethylglutaryl CoA

MITOCHONDRIAL MATRIX

HMG-CoA-lyase

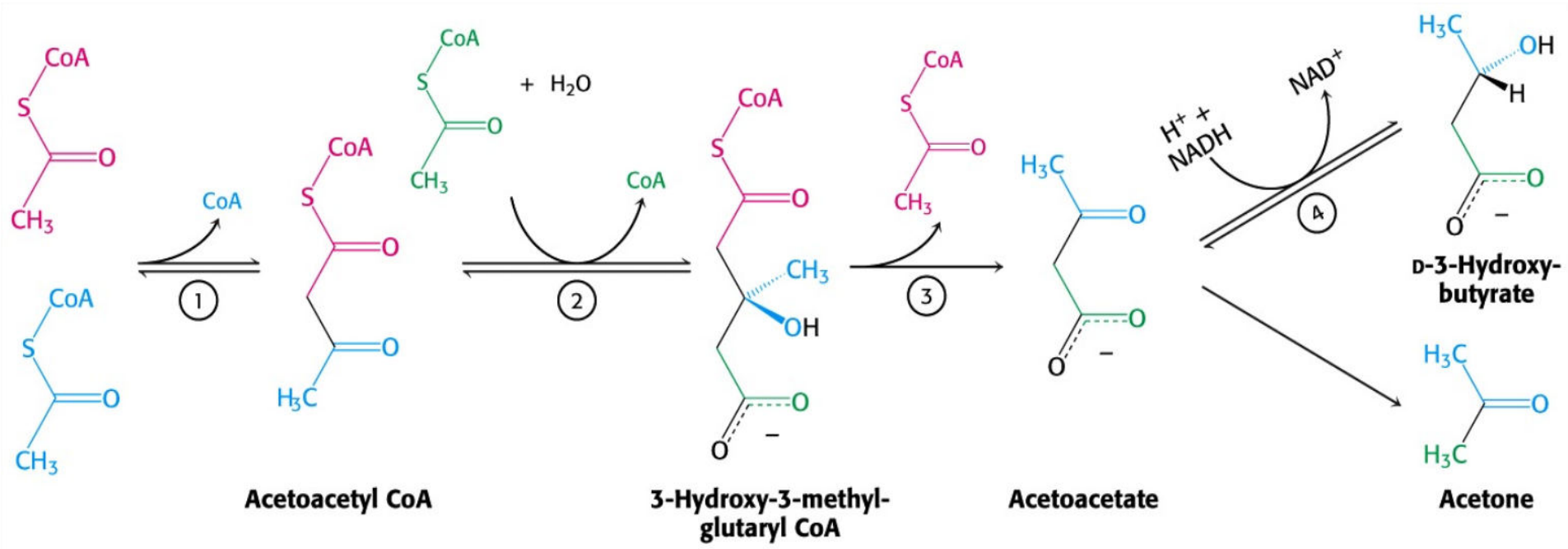
Hydroxymethylglutaryl CoA → acetyl CoA + Acetoacetate

(non-enzymatic)

Acetoacetate → Acetone

β-Hydroxybutyrate dehydrogenase

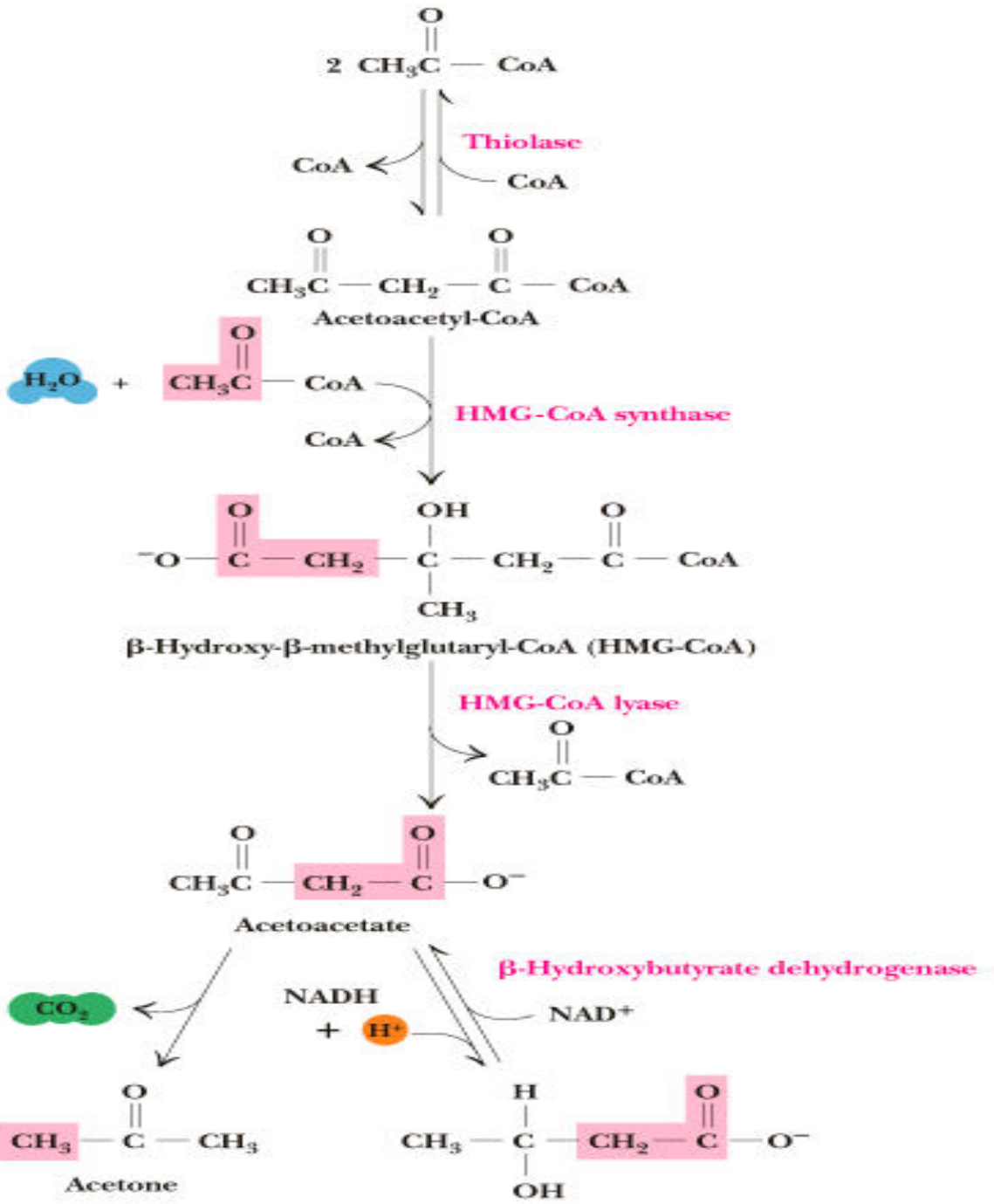
Acetoacetate + NADH → β-Hydroxybutyrate + NAD^+

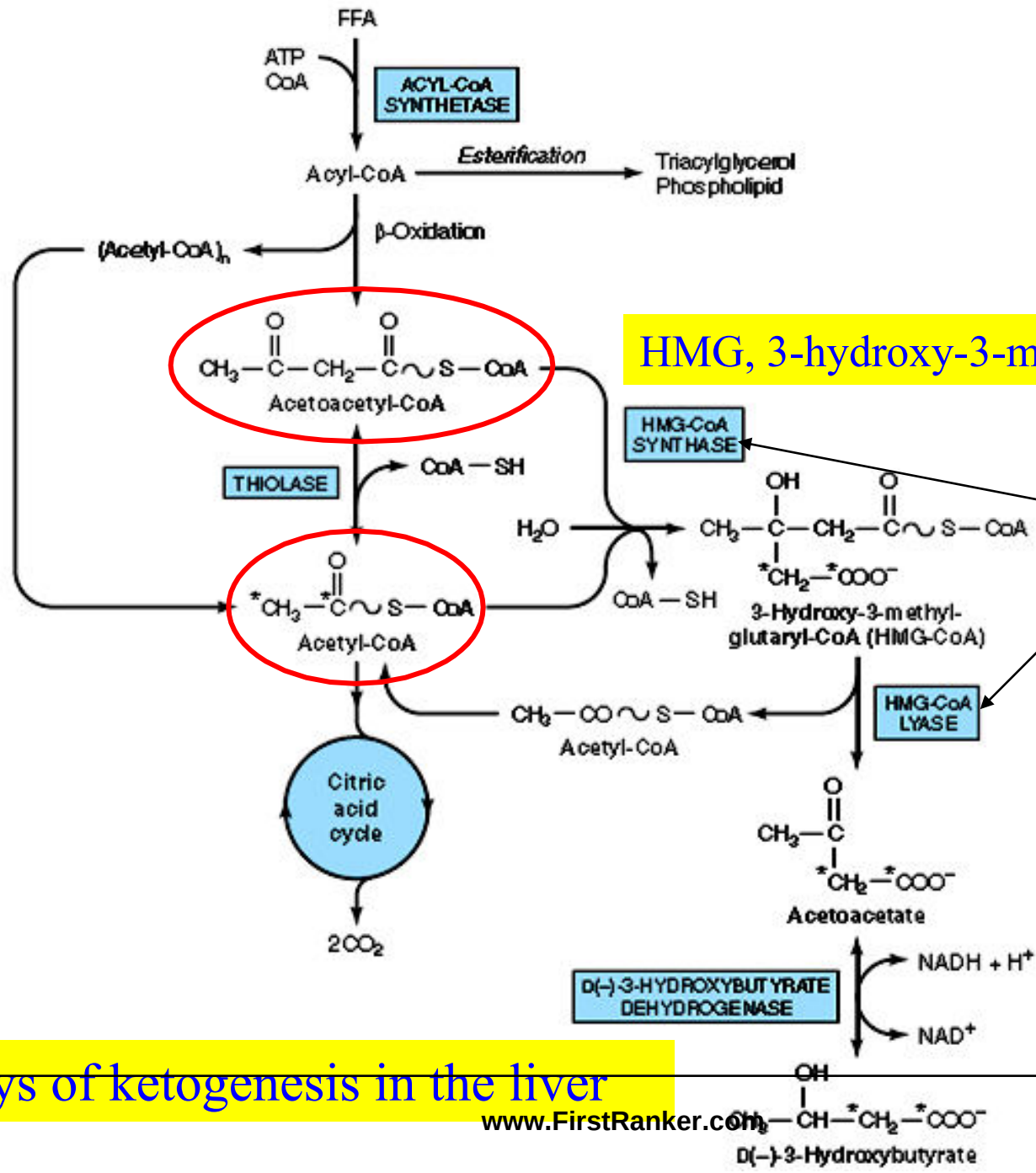


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Formation of ketone bodies





HMG, 3-hydroxy-3-methylglutaryl

Both enzymes must be present in mitochondria for Ketogenesis to take place.

Pathways of ketogenesis in the liver

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- **Three molecules of Acetyl-CoA** are involved during the steps of Ketogenesis.

- **Ketone bodies** can be **simply referred as**
- **Condensed** and **modified forms of Acetyl-CoA**

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- **Ketone Bodies** are **partially oxidized products of Fatty Acids (Half broken products of Fatty acids)**
- Obtained **through steps of Ketogenesis.**

- The end product of Beta oxidation of Fatty acid - **Acetyl-CoA,,** if **not completely oxidized and utilized via TCA cycle**
- The **complex ,impermeable, accumulated Acetyl-CoA is diverted for Ketogenesis and transformed to permeable Ketone bodies brought out of Mitochondria and cell into blood circulation.**

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Description Of Reaction Of Ketogenesis

- **Two molecules of Acetyl-CoA formed as an end product of β-oxidation condenses with one another to form Acetoacetyl – CoA**
- **This reaction is by a reversal of the Thiolase reaction by an enzyme Acetoacetyl-CoA Thiolase.**

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- **Acetoacetyl-CoA, which is the starting material for Ketogenesis,**
- **May also arises directly from the terminal four carbons of a fatty acid during β-oxidation.**

- **The further steps of Ketogenesis involves:**
- **Synthesis and breakdown of β Hydroxy β Methyl Glutaryl-CoA/ 3-Hydroxy-3-Methylglutaryl-CoA (HMG CoA) from Acetoacetyl-CoA.**
- **By two key Enzymes:**
- **HMG-CoA Synthase**
- **HMG-CoA Lyase**

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- **Subsequently in the second step a third molecule of Acetyl CoA is added to Acetoacetyl CoA.**

- Condensation of Acetoacetyl-CoA with another molecule of Acetyl-CoA to form 3-Hydroxy-3-Methylglutaryl CoA (HMG CoA)
- Catalyzed by **HMG-CoA Synthase.**

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- **These two steps are identical to the first two steps in the Cholesterol biosynthesis pathway.**

- **In the third step 3-Hydroxy-3-Methylglutaryl-CoA Lyase (HMG-CoA Lyase) split off HMG-CoA**

- **To release Acetyl-CoA and Acetoacetate.**

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- Both Acetoacetate and β-Hydroxybutyrate are permeable through mitochondrial membrane.
- Can be transported across the mitochondrial membrane and the plasma membrane of the Liver cells,

Ketone bodies enter to the blood stream to be used as a fuel by extrahepatocytes/other cells of the body.

6. **In the blood stream**, small amounts of Acetoacetate are spontaneously (non-enzymatically) **Decarboxylated to Acetone.**
7. **Acetone is a secondary ,volatile, Ketone body expired out by Lungs.**

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- **Acetone is soluble** and volatile and **cannot be detected** in the **blood** and **expired out by Lungs**.
- The odor of Acetone may be **detected in the breath**
- Also the urine of a person has high level of ketone bodies in the blood **(Ketonuria)**

- Condition where more **Acetone** is produced and expired out gives fruity odor also termed as **Acetone Breath/Kussmauls Breathing.**

- Acetone Breath is noted in persons with **Prolonged Starvation and Diabetic Ketoacidosis.**

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- **β Hydroxy Butyrate** is an **acidic compound.**
- **High levels** of β Hydroxy Butyrate in blood
- May **lower blood pH** and leads to a condition of **Metabolic Acidosis**.
- Acidosis due to increased Ketone bodies is termed as **Ketoacidosis.**

- Ketone bodies formed by Liver are **mobilized out**

- Circulated in blood and they may **enter extra hepatic tissues** for its use.

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What are Ketone Bodies?

Ketone bodies are
Ketone group containing compounds
Obtained from Acetyl-CoA
By Steps of Ketogenesis
Permeable, Soluble
Intermediate Products, of Incomplete
Oxidation of Fatty Acids
Produced in Emergency Conditions
At Mitochondrial Matrix Of Hepatocytes
~~Due to Cellular Glucose Deprivation~~

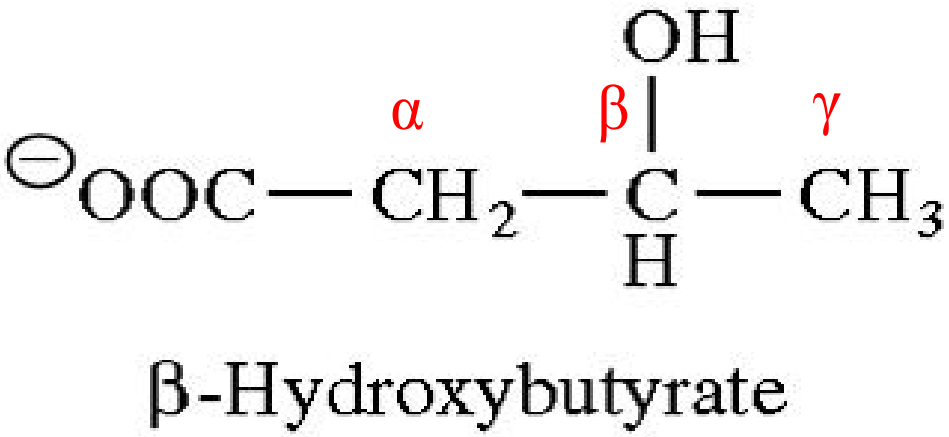
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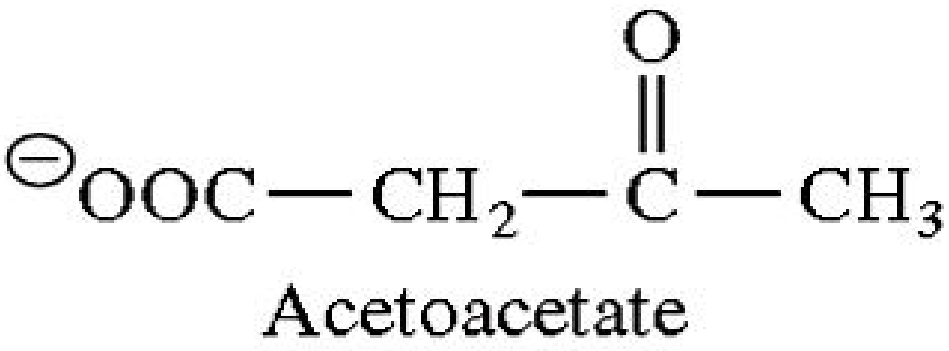
Name Three Ketone Bodies

- **The Three Ketone bodies present in human body are:**
  - **–Acetoacetate**
  - **–Acetone**
  - **–β- Hydroxybutyrate**

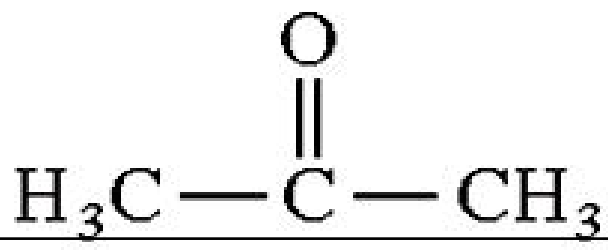
Structures Of Ketone Bodies



β-Hydroxybutyrate



Acetoacetate



Acetone

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Acetoacetate

Is the First Ketone body

To Be Formed

Hence Termed As

Primary Ketone Body

1)Primary Ketone Body:(First Formed Ketone Body)

CH_3-CO-CH_2-COOH **Acetoacetic Acid**

(Unstable Product)

2)Secondary Ketone bodies:(Derived From Primary Ketone Body)

CH_3-CHOH-CH_2-COOH **β-Hydroxybutyric Acid**

CH_3-CO-CH_3 **Acetone**

(Non-metabolized product)

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- **True Ketone Bodies:**

(Possess Ketone group in their structure)

- **Acetoacetate (Unstable)**
- **Acetone (Volatile)**

Significance Of Ketogenesis

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- **Ketogenesis** becomes of **great significant during starvation.**
- It **improves survival phase of vital organs.**

- **Ketone bodies formed by Ketogenesis** serve as an **alternative source of energy for extra Hepatocytes.**

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- **Brain adapts utilizing Ketone bodies** in **starvation conditions** where there is **poor availability of Glucose.**

- After the diet has been changed to **lower blood Glucose**
- **After 3 days** the Brain gets **25% of its energy from Ketone bodies**
- **After about 40 days**, this goes up to **70% energy source to Brain.**

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- Thus **Ketogenesis provides energy** for **vital organs and**

- **Maintain there minimal functions during prolonged starvation**

Aim Of Steps Of Ketogenesis
OR

What Happens During The Steps Of Ketogenesis?

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- Ketogenesis takes place to **transform impermeable Acetyl CoA** molecules (which are impermeable through mitochondrial membranes) t**o permeable Ketone bodies.**
  - **This is By:**
- **Condensation of Acetyl-CoA** molecules
- **Removal of complex impermeable CoA** from **Acetyl-CoA** moieties.
- Forming **permeable Acetoacetate** (Ketone body)

- The main aim to operate Ketogenesis in Mitochondria of Hepatocytes is:
  - **To remove the complex impermeable CoA** from carbon units of Acetyl–CoA
  - **Form permeable Acetoacetate(4C)** to mobilize out of Liver.

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- **Ketogenesis removes impermeable and accumulated Acetyl-CoA** out of **Liver Mitochondria** .

- Thus steps of **Ketogenesis prevent accumulation of Acetyl-CoA** in matrix of mitochondria.

- Ketogenesis **retains and recycle** the **CoA pool of Mitochondrial matrix .**

- And the **carbon units of Acetyl-CoA are removed as Acetoacetate.**

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- Formation of **permeable Ketone body Acetoacetate**
- **Significantly removes** the **accumulated carbon units** of **Acetyl-CoA**
- In the form of Acetoacetate (Ketone body) from Liver **Mitochondrial matrix.**

Regulation of Ketogenesis

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HMG COA Synthase

is the Regulatory Enzyme of Ketogenesis

- HMG-CoA Synthase activity is induced by **increased fatty acids** in the blood.

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- **CoA-SH levels regulate the Ketogenesis to retain CoA pool in Mitochondrial matrix.**

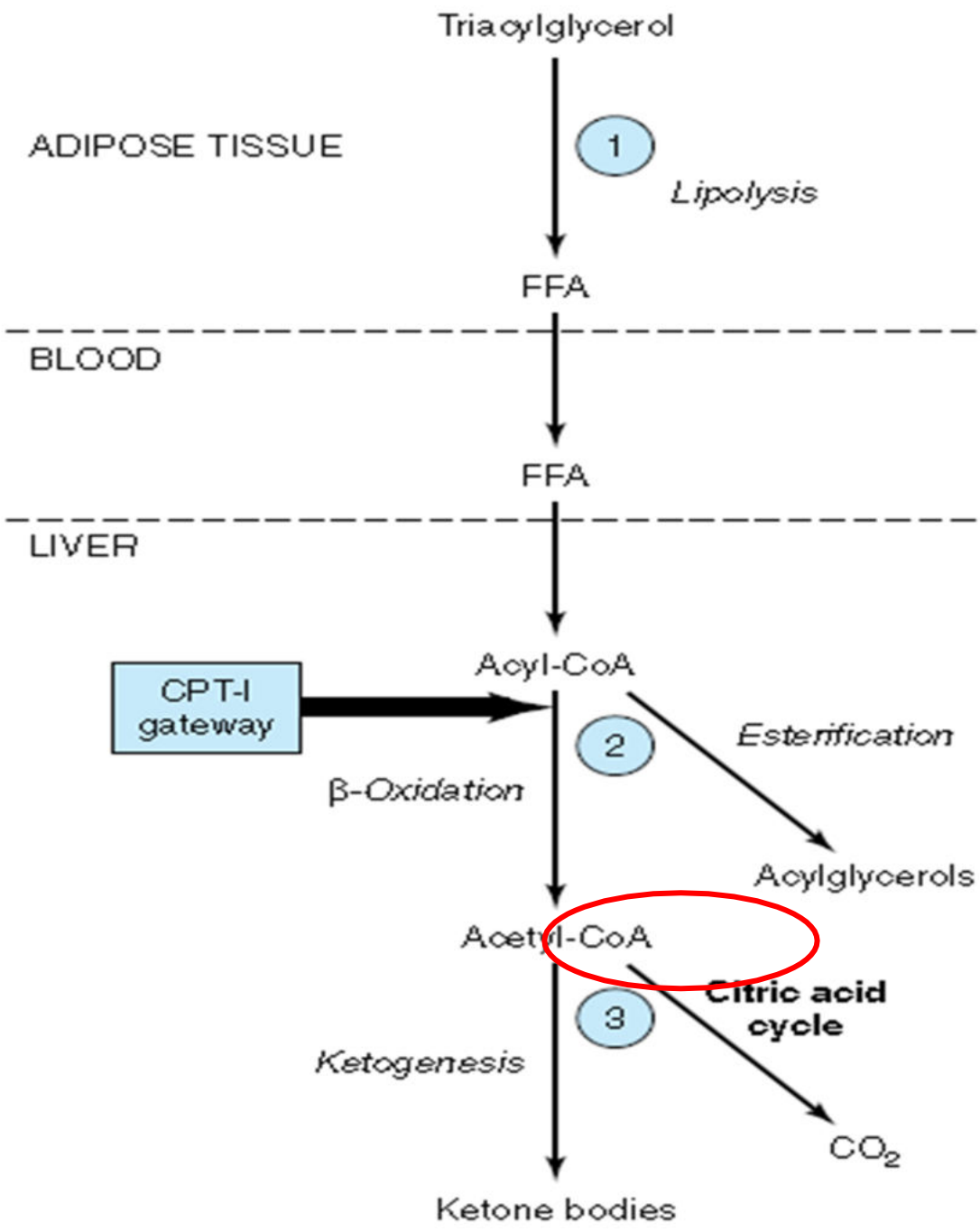
  – **Reduced CoA-SH** levels stimulates HMG CoA Synthase

  – **Increased CoA-SH** levels inhibits HMG CoA Synthase

- **Ketogenesis is regulated at three crucial steps:**
  - **Control of Free Fatty acid mobilization from Adipose tissue (Lipolysis)**
  - **The activity of Carnitine Palmitoyltransferase-I in Liver.**
  - **Partition of Acetyl-CoA between the pathway of Ketogenesis and the Citric acid cycle by OAA levels.**

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Regulation of Ketogenesis

Factors Responsible For Increased Ketogenesis

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- **Normally Ketogenesis takes place** to **small extent**.
- Ketone bodies are created at **moderate levels in our bodies,**
- Such as **during sleep and other times**
- When no Carbohydrates/Glucose are readily available in cells.

- The rate of Ketogenesis and its **efficiency directly depends upon:**
  - **The Insulin activity**
  - **Levels of Cellular Glucose**
  - **Levels of cellular OAA**

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- **Increased and incomplete oxidation of Fatty acids increases Ketogenesis.**

- The condition where there is **more cellular Glucose deprivation**
- **More is the efficiency of Ketogenesis.**

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- Thus **conditions which accumulates excess of Acetyl –CoA in Mitochondrial matrix**.
- Divert this Acetyl-CoA for Ketogenesis.

Which are The Conditions Which Deprives Cellular Glucose And OAA And Increases The Rate Of Ketogenesis ?

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- **Prolonged Starvation**
- **Diabetes Mellitus**
  Uncontrolled Condition of DM: **Diabetic Ketoacidosis**
- **Severe Vomiting**
- **Toxemia of Pregnancy**

– **Deprivation of Cellular Glucose**
– **High rates of Fatty acid Oxidation**
– **Low levels of cellular Oxaloacetate**
– **Under utilization of Acetyl CoA in TCA cycle**
– **Large accumulated amounts of impermeable Acetyl-CoA in mitochondrial matrix.**
– **Accumulated Acetyl-CoA diverted for Ketogenesis and**
– **Formation of soluble and permeable Ketone bodies which can be easily mobilized out of the Mitochondrial matrix.**

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Inter Relationship Of Carbohydrates And Lipid Metabolism

–Thus **low/non availability** of **Oxaloacetate** in cells in **emergency condition**

–Does not oxidize **Fatty acid Acetyl-CoA completely via TCA cycle.**

–This **results in accumulation of Acetyl-CoA** in **Mitochondrial matrix**

–Which then **activates and diverts Acetyl-CoA for Ketogenesis.**

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Fats Burns
In The Flame Of Carbohydrates

MEANS

For Complete Oxidation
Of Fatty Acids
There Needs Presence of
Sufficient Glucose In The Cells

- **Fat burns under the flame of Carbohydrates.**
- Complete oxidation of Acetyl-CoA obtained through Fatty acid oxidation
- **Requires sufficient Oxaloacetate** which is a **source from normal Glucose metabolism**.

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- Sufficient cellular **Glucose (Flame)** keeps the **availability** of **OAA**

- To **initiate and operate TCA cycle** and **completely oxidize** the end product of beta oxidation of Fatty acid **Acetyl CoA** to **CO2 ,H2O and ATP**.

- **The entry of Acetyl CoA** into the Citric acid cycle depends on the **availability of Oxaloacetate.**
- The concentration of Oxaloacetate is lowered
- If Glucose is unavailable (Starvation) or improperly utilized (Diabetes mellitus).
- Oxaloacetate is normally formed from pyruvate by *Pyruvate Carboxylase* (Anaplerotic reaction).

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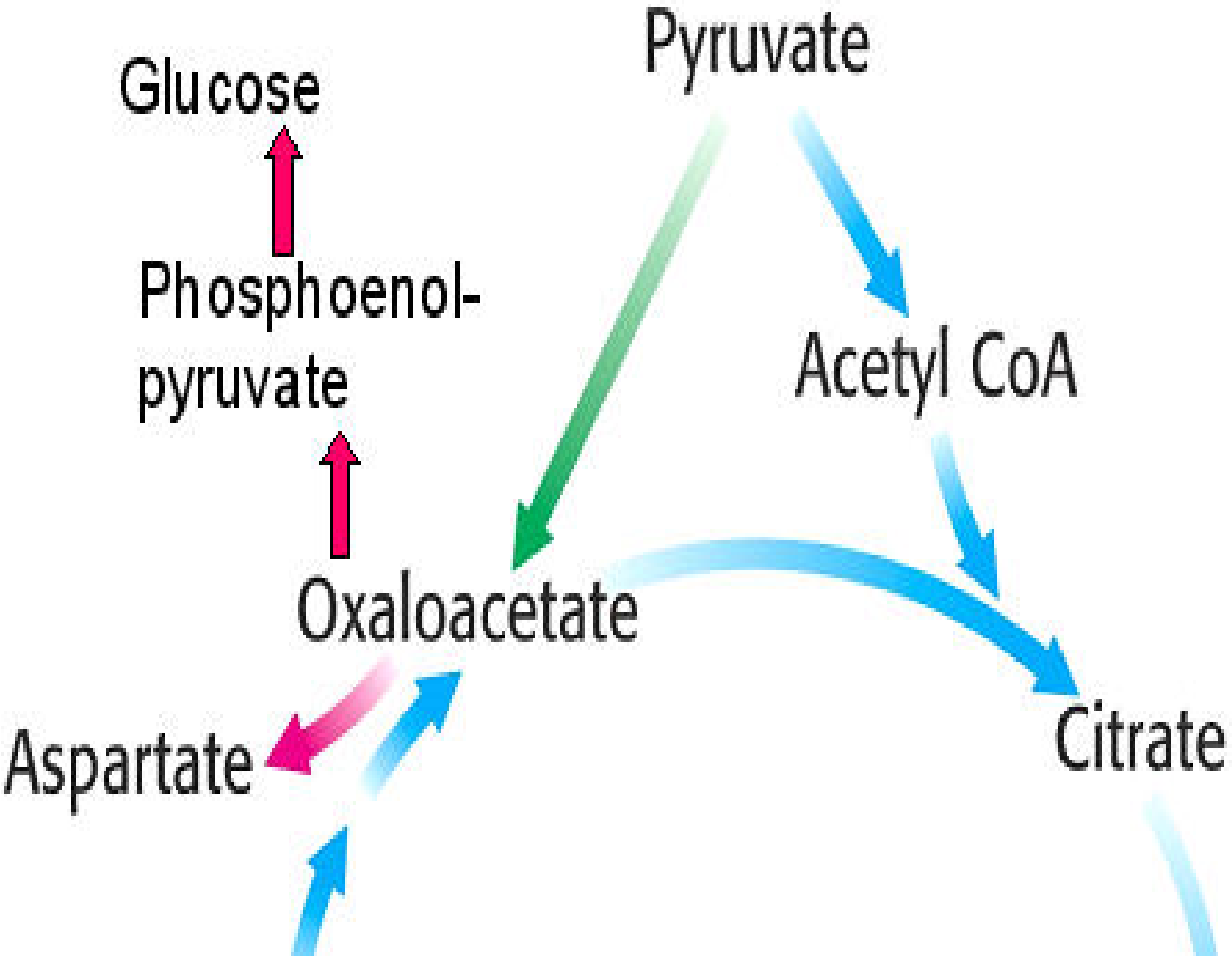
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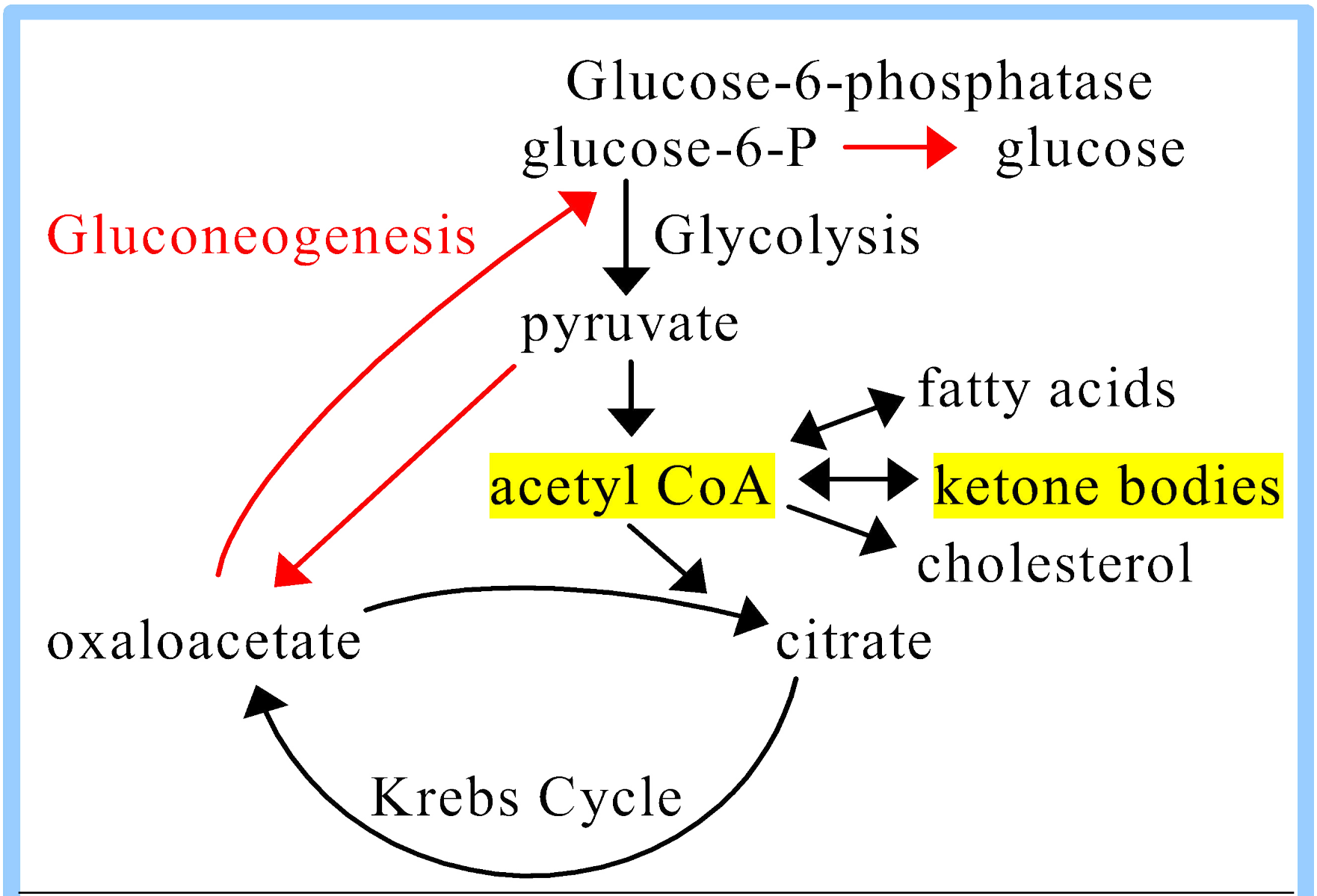
- In Starvation or Diabetes mellitus the Gluconeogenesis is activated and Oxaloacetate is consumed in this pathway.
- Fatty acids are oxidized **producing excess of Acetyl CoA** which is converted to **Ketone bodies**:

- **In deprivation of Glucose**
- **Acetyl CoA is under utilized** and incomplete oxidized via TCA cycle.

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Why Ketogenesis Occur?

The Main aim for the steps of Ketogenesis to occur is:

- To remove **the complex, impermeable ,accumulated Acetyl CoA** in **Mitochondrial Matrix**
- **By transforming Acetyl-CoA into permeable Ketone bodies by removing CoA moiety.**
- **Maintain the levels of free CoA pool of Mitochondrial matrix**

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- During emergency conditions due to low cellular Glucose.
- There is alternatively increased beta oxidation of Fatty acids, producing Acetyl-CoA.
- Deprivation of cellular Glucose also depletes the levels of Oxalo Acetate which is an initiator of TCA cycle.

- Low levels of cellular OAA under utilizes the Acetyl-CoA via TCA cycle.
- Acetyl-CoA which is obtained by Fatty acid oxidation is less utilized via TCA cycle .

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- This accumulates impermeable Acetyl-CoA in the Mitochondrial matrix.
- To remove the accumulated, impermeable Acetyl-CoA out from the Mitochondrial matrix, there occurs Ketogenesis .

Why Fatty Acids Are Not Completely Oxidized In Emergency Conditions?

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- Fatty acids in emergency conditions are not completely oxidized to CO2,H2O and ATP.
- Fatty acids in emergency undergo Beta oxidation and produce Acetyl-CoA
- But the produced Acetyl CoA is not further completely oxidized via TCA cycle.

- **The main facts to have incomplete oxidation of Fatty acids in emergency condition are :**
  - **Low levels of cellular Glucose and Oxaloacetate**

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What Makes The Cellular Oxaloacetate To Get Depleted In Emergency Conditions?

Remember

- In emergency conditions where the cellular Glucose is low
- Oxaloacetate levels also gets depleted

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- **Reasons for depletion of cellular OAA are:**
- Glucose is the main source of OAA
- OAA is, obtained by Pyruvate Carboxylase reaction
- Thus low availability of cellular Glucose brings low production of OAA from Glucose in cells.

- OAA is an emergency condition is **diverted for Gluconeogenesis** and transformed **to Glucose**.

- Which reduces the actual OAA levels in the cells.

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Remember

- OAA is an **initiator of TCA operation** and
- **OAA is required for complete oxidation for Acetyl-CoA.**

Fates Of Ketone Bodies
OR
Ketolysis/Breakdown Of Ketone Bodies

OR

Utilization Of Ketone bodies

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Fates of Three Ketone bodies

Uses Of Ketone bodies

- **Ketone bodies serves as a special and major source of fuel/energy**
- For certain tissues **in prolonged starvation phase.**

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- In the **starvation condition** where body has **low Glucose**.
- Ketone bodies are used to **generate energy** by **several extra hepatic tissues**

Fate Of Acetoacetate

- Acetoacetate may be oxidized and serve as a **source of energy** to **extrahepatocytes.**
- If not oxidized to form usable energy,

  it is **converted to next two Ketone bodies –Acetone and BHB**
- If it is not utilized Acetoacetate **excreted out through urine.**

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Fate of β-Hydroxybutyrate

- It is not technically a Ketone according to IUPAC nomenclature.
- It may be **used up for energy source** or excreted out through urine if not used.

Fate Of Acetone

- **Acetone** is **not used as an energy source,**
- But it is **instead exhaled or excreted as waste through expiration**.

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Acetone Do not Serve as Energy Source

- Acetone being volatile , is not catabolized and oxidized
- To liberate energy in the extra hepatocytes.

Ketolysis

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What Is Ketolysis ?

- **Ketolysis is breaking and utilization of Ketone bodies as energy source**

- In the Mitochondrial matrix of **Extra Hepatocytes.**

- **Ketone bodies have less potential metabolic energy than the fatty acids from which they are derived.**

- **They make up for this deficiency by serving as "water-soluble lipid derivatives" that can be more readily transported in the blood plasma.**

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- **During Starvation and in the bodies of uncontrolled Diabetes mellitus, Ketone bodies are produced in large amounts**

- **They become substitutes for Glucose as the principal fuel for Brain cells.**

Site Of Ketolysis

- Mitochondrial Matrix of **Extra Hepatic Tissues**.

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- **Thus primary tissues using Ketone bodies when available are :**
  - **Brain**
  - **Muscle**
  - **Kidney**
  - **Intestine**
  - **But NOT in the Liver**

- Ketolysis does not takes place in Liver
- Due **to absence of enzyme Thiophorase in Liver which is** required for Ketolysis.

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- **In early phase of starvation Heart and skeletal muscles primarily use Ketone bodies for energy**

- Thereby **preserving the limited Glucose and supply it for use by the Brain.**

- **Brain which normally depends on Glucose and do not have capacity to use Fatty acids.**
- **during starvation condition Brain adapts using Ketone bodies as major energy source for its survival**

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- **Heart Muscle** and the **Renal cortex** use **Acetoacetate** in preference to Glucose in **physiological conditions**.

- The **Brain** adapts to the utilization of **Acetoacetate** during **Starvation.**

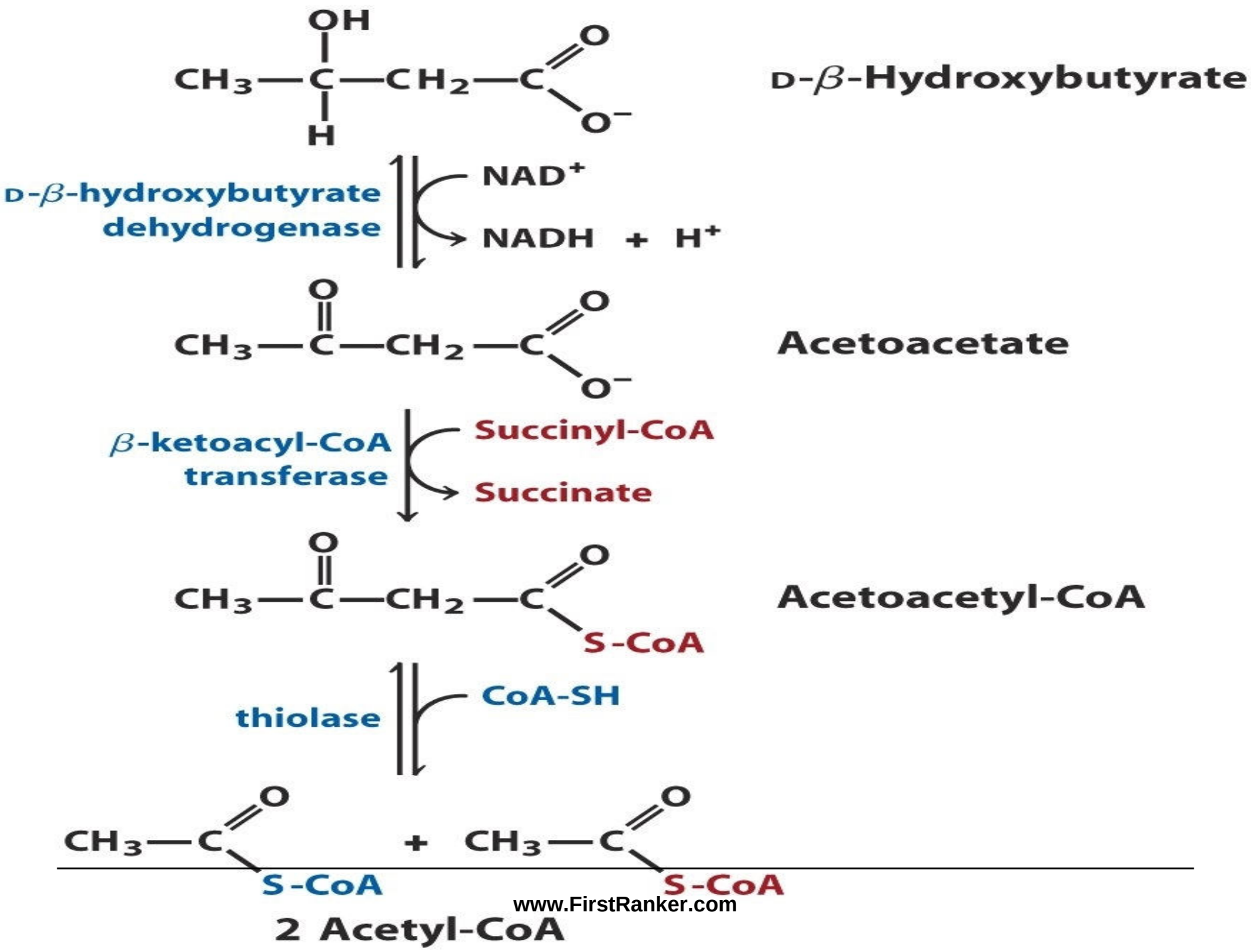
Steps Of Ketolysis

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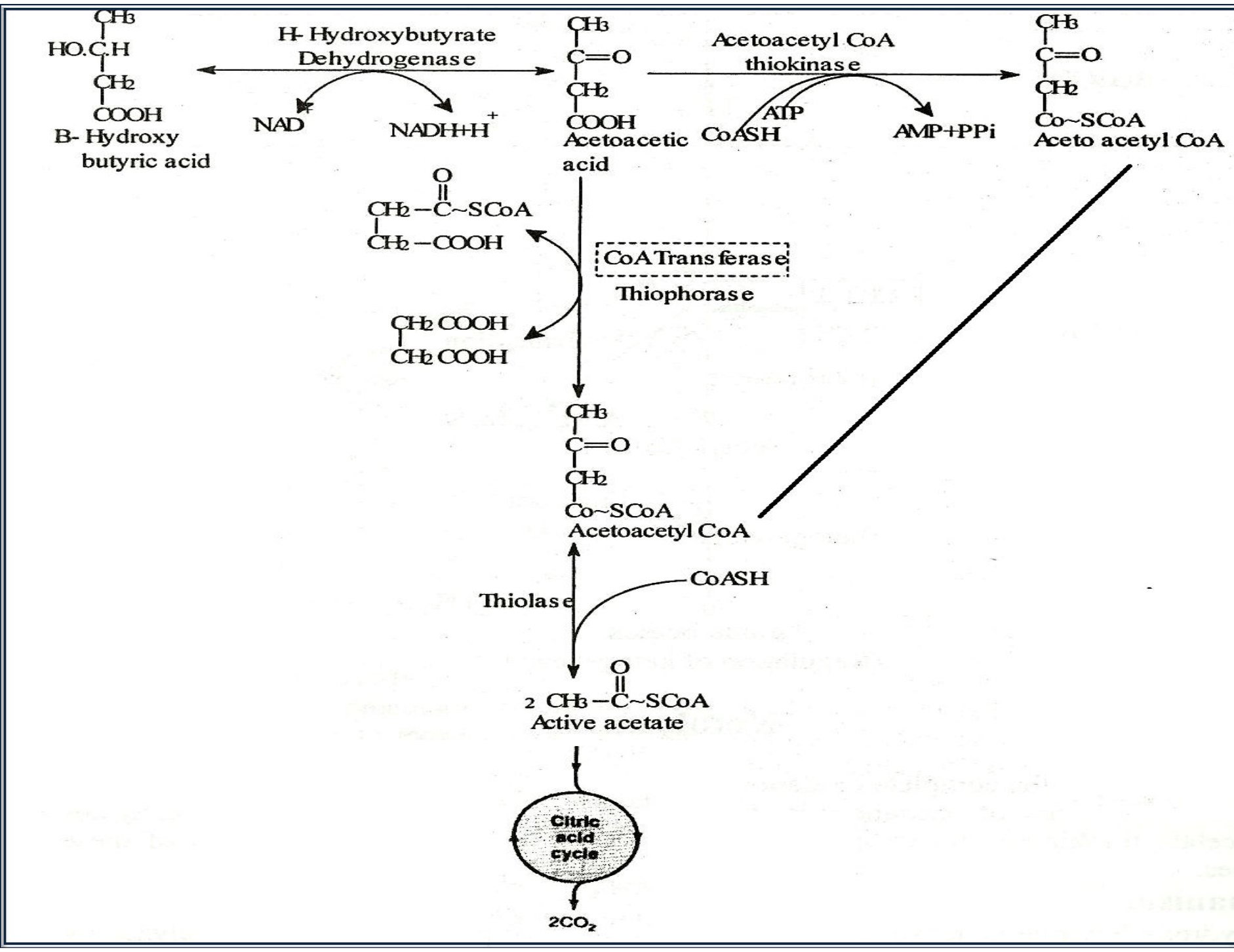
Remember

- Ketone bodies will be broken and utilized in only those organs/tissues/ cells
- Which **possess at least some content of Glucose and Oxalo acetate.**



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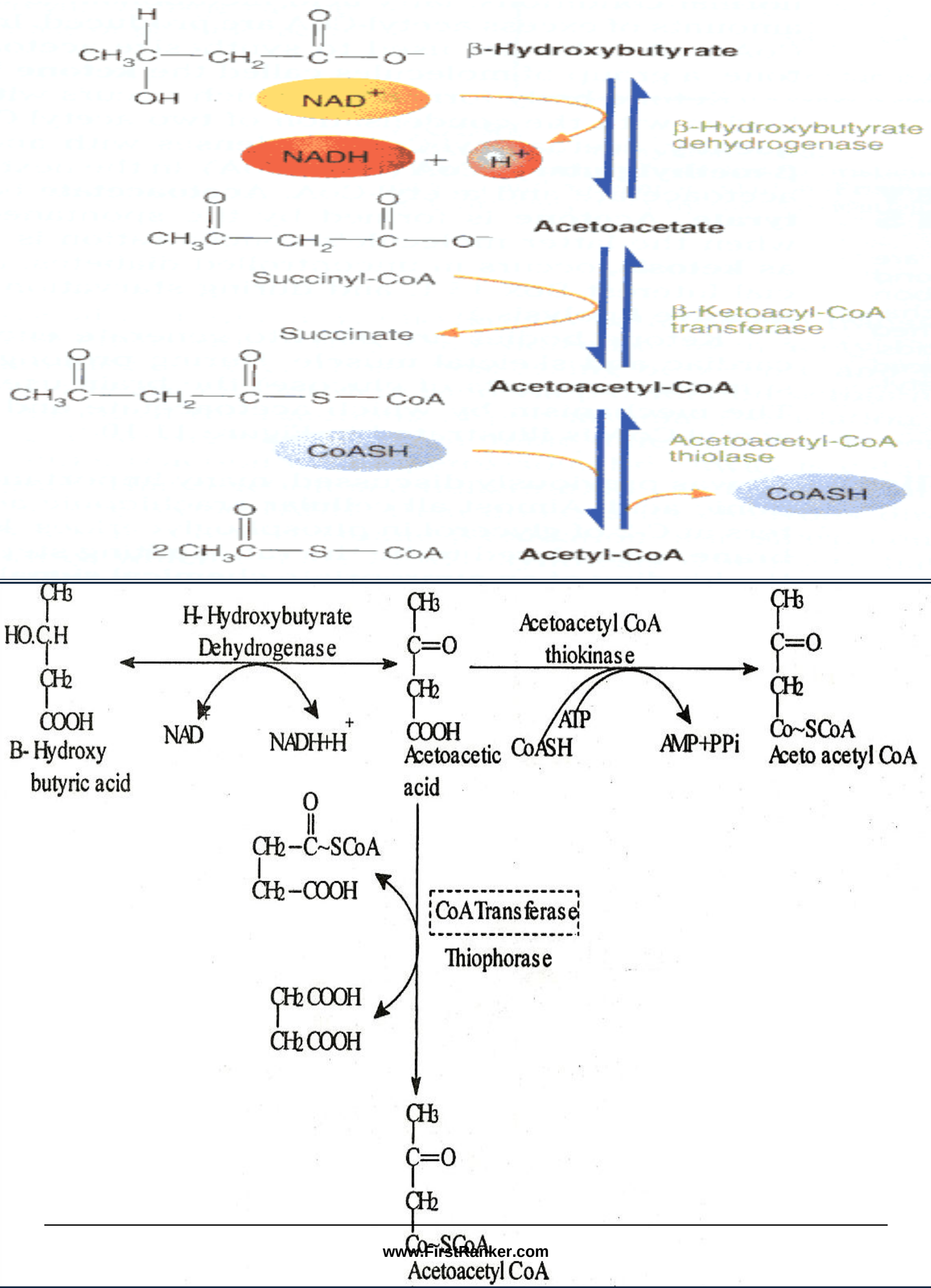


- Ketolysis breaks the Ketone bodies and **releases Acetyl – CoA**
- The released Acetyl-CoA is then **finally oxidized via TCA cycle** to **CO2,H2O and ATPs**.

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Conversion of Ketone Bodies to Acetyl-CoA



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- Ketone bodies as an energy source, β-Hydroxybutyrate and Acetoacetate
- Enter mitochondrial matrix of extra hepatocytes
- Where they are converted to Acetyl CoA,
- Which is further completely oxidized by the TCA/ Citric acid cycle.

- β-Hydroxybutyrate is oxidized to Acetoacetate in a reversible reaction catalyzed by an isozyme of β-Hydroxybutyrate Dehydrogenase of extrahepatocytes.
- Remember that this reaction enzyme is distinct from the Liver enzyme β-Hydroxybutyrate Dehydrogenase.

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Use Of Succinyl-CoA For Thiophorase Reaction In Ketolysis

- An Enzyme Thiophorase of Ketolysis requires Succinyl-CoA for its reaction.
- **Succinyl-CoA** in this step of Ketolysis is a **donor of Coenzyme A (–CoASH).**

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Enzyme Thiophorase Is Naturally Absent In Liver

- **Ketone bodies** are broken down only in non hepatic tissues
- Because enzyme **Thiophorase** is naturally present in all tissues **except Liver.**

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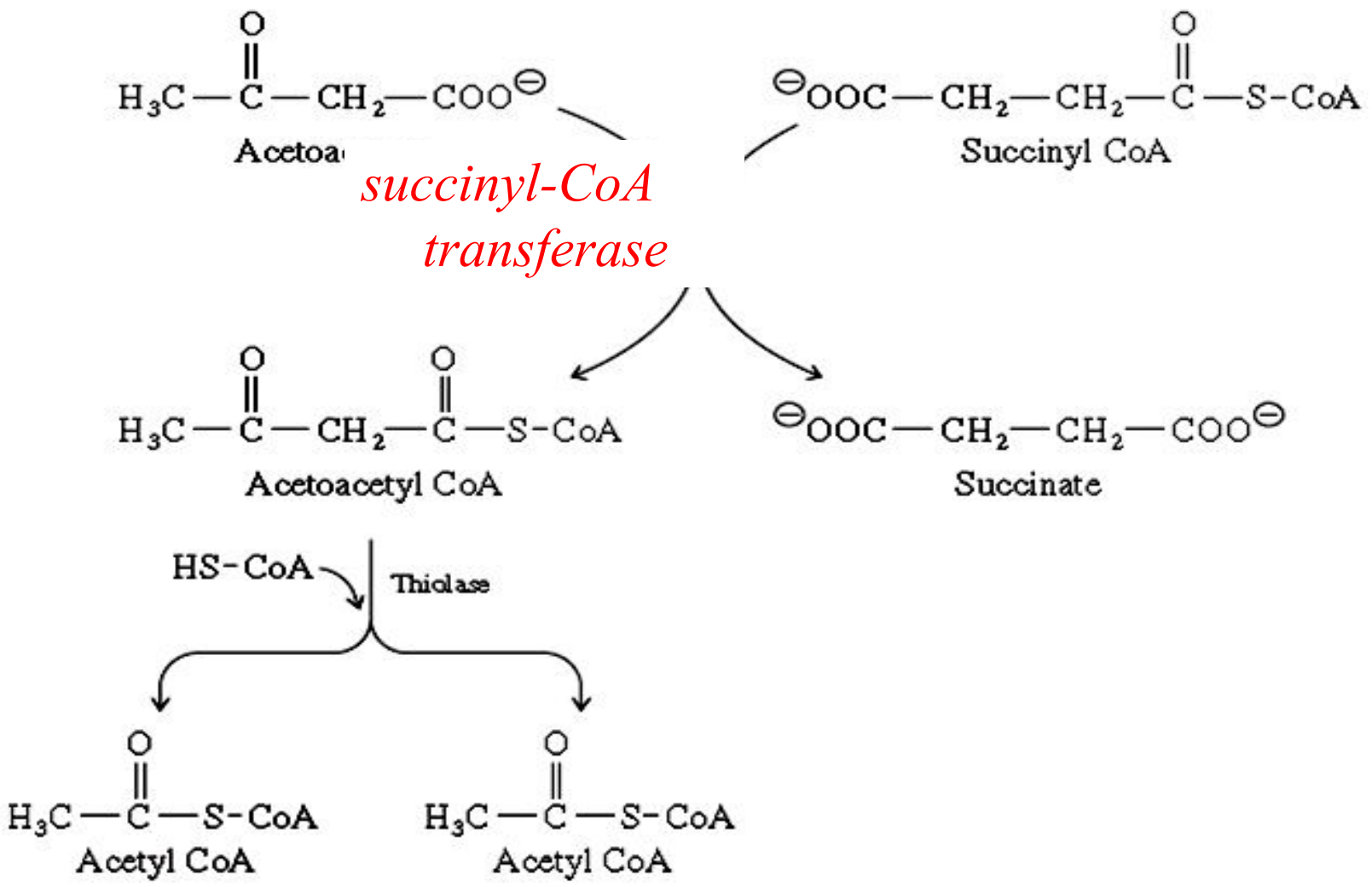
- **In extrahepatic tissues, Acetoacetate is activated to Acetoacetyl-CoA by Succinyl-CoA- by catalytic activity of Acetoacetate CoAtransferase/Thiophorase/Succinyl CoA Transferase.**
- **CoA is transferred from Succinyl-CoA to form Acetoacetyl-CoA.**

- **Acetoacetate reacts with Succinyl CoA to form Acetoacetyl CoA in a reaction catalyzed by *Succinyl-CoA Transferase/Thiophorase* .**

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- **The Acetoacetyl-CoA is split to Acetyl-CoA by Thiolase and oxidized in the Citric acid cycle.**



Conversion of Acetoacetate to Acetyl CoA.

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Significance Of Ketolysis

- **Ketone Bodies Serve as a Fuel for Extrahepatic Tissues on its oxidation in extra hepatocytes in Starvation condition.**

Calorific value of Ketone bodies is 7 Cal/gram

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Calculation Of Energetics From Degradation of Ketone bodies in Peripheral tissue

1. **Acetoacetate** is oxidized into **2 Acety1 CoA,** which enter the Citric acid cycle.

- Activation of Acetoacetate **consumes 1 ATP** , and **the total amount of ATP** from metabolism of 2 Acety1 CoA via TCA cycle is **20 – 1 = 19 ATP**

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2. Conversion of β- Hydroxybutyrate back into Acetoacetate generates 1 NADH ,

which produces an additional 2.5ATP total ATP produce = 22ATP)

(19 +2.5) = 21.5 ATP

After entering the electron transport chain .

Balance and Imbalance In Ketone Body Metabolism

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- In **normal physiological conditions**.
- There occurs **balance in Ketogenesis and Ketolysis**

- **When the cellular Carbohydrates and Lipids are in proper proportionate.**

- Then the **formation and utilization** of **Ketone bodies** in the body is **balanced and low.**

- There is balance in Ketogenesis and Ketolysis
- A very **low levels of blood Ketone bodies** are present in **normal physiological healthy condition.**

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- **Normal blood levels of Ketone bodies** is approx. **less than 1 mg%.**

Levels Of Ketone Bodies Increases As The Starvation Phase Prolongs

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–**3 days starvation**

[KB]=3mM

–**3 weeks starvation**

[KB]=7mM

Rate Of Ketolysis

- Rate of Ketolysis in **extra hepatocytes** is **dependent upon** :
  - –**The cellular levels** of **Glucose** and **Oxaloacetate** in **extrahepatic tissues .**

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- **Rate of Ketolysis decreases**
- In **more deprived conditions** of cellular Glucose and OAA.

Imbalance In Ketone Body Metabolism

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- Imbalance in Ketone body metabolism is
- **Increased Ketogenesis and decreased Ketolysis.**

- **No/Low Ketolysis** in body cells
- **Accumulates the Ketone bodies** in the body.
- Which leads **to Ketonemia and Ketonuria.**

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Ketosis

Ketosis

- Ketosis is a **collective term** used to refer **Ketonemia** and **Ketonuria .**

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- **Ketosis** is a **result of imbalance in Ketone body metabolism.**

- **Ketosis** is a condition where there is **increased Ketogenesis and decreased Ketolysis**.

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Ketonemia

- **Ketonemia** is an **abnormal increased levels of circulating Ketone Bodies in Blood more than 1 mg%.**

Ketonuria

- **Ketonuria** is an **abnormal excretion of Ketone bodies in Urine.**

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- If the blood levels of Ketone bodies **crosses more than the renal threshold levels of KB (3mg%)** it causes-**Ketonuria.**

Ketoacidosis

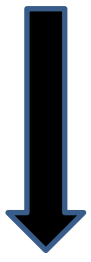
- **Ketoacidosis is Acidosis caused due to increased Ketone bodies.**
- **Ketoacidosis is a type of Metabolic Acidosis .**
- **It is caused due to imbalance in Ketone bodies metabolism.**

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- **During KETOACIDOSIS**
- **Excessive build-up of Ketone bodies results in Ketosis eventually**
- **Leading to a fall in blood pH due to the acidic Ketone bodies.**

Ketosis (Ketoacidosis)



Acetone odor in the breath

Acetoacetate and Acetone in urine

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Biochemical Basis Of Ketosis

- Cellular Deprivation Of Glucose
- Low Insulin Activity

Conditions Of Ketosis

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Conditions Of Ketosis

- **Prolonged Starvation**
- **Diabetic Ketoacidosis**

(Uncontrolled Diabetes Mellitus)

- **Hyperemesis gravidarum**

  (Severe Vomiting in first trimester)
- **Unbalanced diet i.e. high fat, low carbohydrate diet**
- **Renal Glycosuria**
- **Alcoholics after binge drinking and subsequent starvation**

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Consequences Of Ketosis

- **Ketone bodies accumulation** in the body
- May result to **negative long term effects.**

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- **Ketosis create more load on Lungs and Kidneys**

- **To expire and excrete out the Ketone Bodies.**

- Ketoacidosis **lowers blood pH affects the Enzyme activities**
- **Deranges the Metabolism**
- **Affects Normal energy metabolism**
- **Affects Water and Electrolytes Balance**

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- Increased Ketone bodies in blood is neutralized by the alkali reserve (blood buffers HCO3-)
- Very excess of Ketone bodies in blood exhaust $HCO3^-$,this leads to **Metabolic acidosis.**

- **If Ketone bodies are far high than the capacity of alkali reserve** to neutralize them they will result in acidemia –
- **Uncompensated acidosis** with a decrease in blood pH **(Acid Base Imbalance)** which is a serious that **results in death if not treated**.

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Clinical Features Of Ketosis

Acid Base Imbalance

- **Metabolic Ketoacidosis**
- **Reduced Alkali reserve**(HCO_3^-)
- **Kussamaul's Respiration**
  (**Acetone Breath**)

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Water and Electrolytes Imbalance

- **Osmotic Diuresis** (Loss of water and electrolytes along with Ketone bodies)
- **Dehydration**
- **Sodium Loss (Hyponatremia)**
- **Coma**
- **Death**

Diagnosis Of Ketosis
Detection Of Ketone Bodies

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- Volatile Ketone Body ,**Acetone** is **expired** out through Lungs,
- It can be smelled in **Ketotic persons as Acetone breath (With Fruity odor)**

- Ketone bodies excreted in Urine can be detected by carrying **Rothera's Test on Urine specimen.**
- **Positive Rothera's Test with Magenta color ring** in the tube **confirms Ketonuria.**

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- Ketoacidosis is detected by analyzing :
- The **Blood pH, Bicarbonates**.

- A patient with **Diabetic Ketoacidosis shows:**
  - **Urine Benedicts Test- Positive**
  - **Urine Rothera's Test- Positive**
- A patient with **prolonged Starvation shows:**
  - **Urine Benedicts Test- Negative**
  - **Urine Rothera's Test- Positive**

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Management Of Ketosis

- **Increasing Cellular Glucose**
- Manages condition of Ketosis.

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- In Starvation **Oral or intravenous Glucose infusion**
- In Diabetic Ketoacidosis **infuse Insulin dosage with Check on Serum Potassium levels.**

Prevention Of Ketosis

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- **Avoiding cellular Glucose deprivation prevents Ketosis**.

- A Patient of Diabetes mellitus (Type I) to prevent **Ketosis should control his/her blood Glucose.**

- With **proper dosage of Insulin** and maintaining cellular Glucose in cells.

Ketogenic Substances

- Substances **Promoting Ketogenesis** and **increases Ketone bodies are:**
  - **Low Cell Glucose**
  - **Excess Fatty acids**
  - **Ketogenic Amino acids**
  - **High Glucagon**
  - **Low Insulin**

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Antiketogenic Substances

- Substances **inhibiting Ketogenesis and decreasing Ketone bodies:**
  - **–Sufficient Cellular Glucose**
  - **–Glucogenic Amino acids**
  - **–Glycerol**
  - **–Normal Insulin**

Diabetes and Ketoacidosis

Diabetic Ketoacidosis

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- **Diabetic Ketoacidosis** is an **Immediate complication** of **severe uncontrolled cases** of **Diabetes mellitus(Type I/IDDM)**

KETOSIS In Diabetes Mellitus

The Absence of Insulin in Diabetes mellitus

- Liver Glucose Metabolism Altered
- inhibition of glycolysis
- activation of gluconeogenesis

↓

- Deficit of oxaloacetate

- activation of fatty acid mobilization by adipose tissue

↓

- Large amounts of acetyl CoA which can not be utilized in Krebs cycle

↓

- Large amounts of **ketone bodies** (moderately strong acids)

↓

- Severe Acidosis **(ketosis)**

↓

Impairment of the tissue function, most importantly in the central nervous system

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In Diabetic patients events that can lead to ketosis are:

⇧ Relative or absolute deficiency of insulin

↓

⇧ Mobilization of free fatty acids (from adipose Lipolysis)

↓

⇧ Increased delivery of free fatty acids to the liver

↓

⇧ Increased uptake and oxidation of free fatty acids by the liver

↓

⇧ Accelerated production of ketone bodies by the liver

- When there is not enough Insulin in the blood in cases of IDDM
- Cellular Glucose deprivation affects its efficient use to produce energy.
- Thus, the body utilizes the Lipids for its energy.
- Excessive Lipid degradation with low Glucose contents , leads to ketones build up in the blood .

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- Ketone bodies then spill over into the urine so that the body can get rid of them.
- Acetone can be exhaled through the lungs. This gives the **breath** a **fruity odor.**
- Ketones that build up in the body for a long time lead to serious illness and coma. (Diabetic Ketoacidosis)

- **Ketone bodies Acetoacetate and Beta Hydroxy Butyrate are acidic**
- **When produced in excess over long periods in Diabetes, causes Diabetic ketoacidosis.**

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- In a case of **severe Diabetic Ketoacidosis**
- The **Ketone bodies** in the **blood and urine may reach Life threatening concentrations.**

- **Blood Ketone bodies may be up to 100 mg% (Normal1mg%)**
- **Urinary** excretion of **Ketone bodies** may be as high as **5 gm /day**.

(Normal 125 mg/day)

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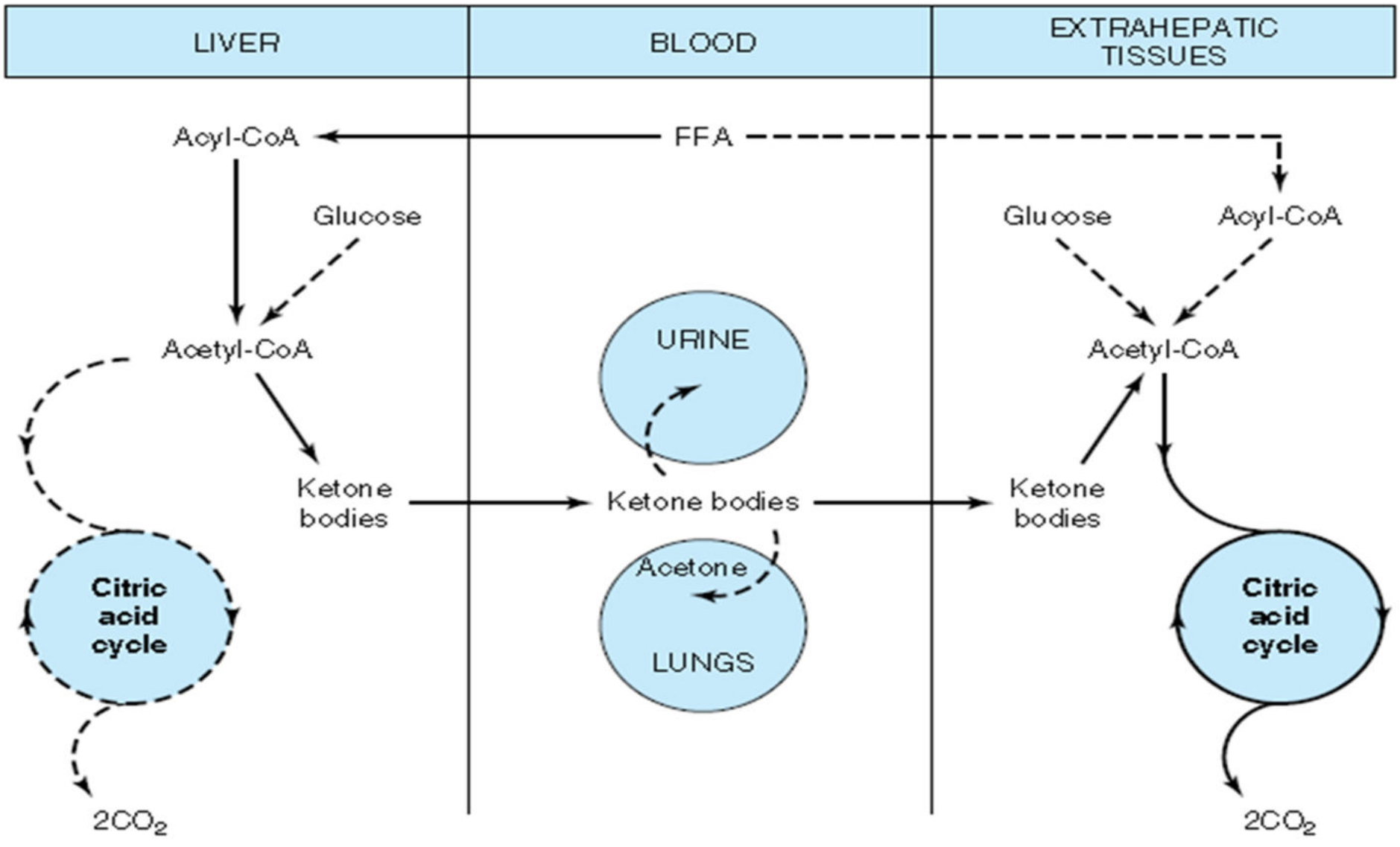
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Clinical Features OF DKA Creates Medical Emergency

- Hyperglycemia
- Metabolic Ketoacidosis
- Kussmaul’s Respiration
- Severe Dehydration /Water Imbalance
- Electrolyte Imbalance
- Acid Base Imbalance
- Coma
- Death

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Formation, Utilization, and Excretion of Ketone bodies

Lipogenesis

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What Is Lipogenesis?

- Lipogenesis is the **biosynthesis of various forms of Lipids in human body.**

When Lipogenesis Occurs?

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- **Lipogenesis occurs in a well fed condition** at **Cytosol of body tissues.**

Conditions Favoring Lipogenesis

- **Excess of Free Excess Glucose** after heavy Carbohydrate meals.
- **Insulin** promotes Lipogenesis

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Forms Of Lipid Biosynthesized In Human Body Tissues

LIPID BIOSYNTHESIS

- Fatty acid Biosynthesis
- Triacylglycerol Biosynthesis
- Cholesterol Biosynthesis
- Phospholipids Biosynthesis
- Glycolipids Biosynthesis
- Eicosanoids Biosynthesis

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Where Does Lipogenesis Occur?

Site Of Lipogenesis

- **Liver Cytoplasm** is the **predominant site** for Lipogenesis.

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- **Intestine ,Mammary glands** are **other tissues for Lipogenesis**

- **The endogenously biosynthesized Lipids in Liver** are

- **Gathered and mobilized out** in the form of **Lipoprotein VLDL to extrahepatic tissues.**

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- **VLDL** carries **endogenous Lipids** from **Liver to extra Hepatocytes.**

- **TAG is stored** as reserve food material in **Adipose tissue in unlimited amount.**

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Precursors For Lipogenesis

Precursors For Lipogenesis

- **Acetyl-CoA** serve as a **precursor for Fatty acids and Cholesterol biosynthesis.**
- This Acetyl-CoA comes **from excess and free Glucose Oxidation in a well fed condition.**

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- Phospholipid biosynthesis **needs Lipotropic factors.**

Why Lipogenesis Takes Place?

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Reasons For Lipogenesis

- **Free excess Glucose cant be stored** in body cells and tissues **as it is** .

- Free excess Glucose is **first converted and stored in the form of Glycogen**

- **Storage of Glycogen is limited**

- In a well fed condition **after limited storage of Glycogen**
- **When still there remains Free excess Glucose**
- This free excess Glucose is Oxidized to Pyruvate via Glycolysis
- Further Pyruvate to **Acetyl-CoA via PDH complex reaction**
- **The formed Acetyl-CoA when excess is then diverted for Lipogenesis.**

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- Thus **Lipogenesis occur** in a **well fed condition**
- **To transform the free excess Glucose/Acetyl-CoA in the body tissues into**
- Storage able form of Lipid (TAG).
- TAG in the Adiposecytes can be stored in unlimited amounts.

Hormonal Influence On Lipogenesis

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- **In a well fed condition**

- Hormone **Insulin stimulates Lipogenesis**.
- Hormone **Glucagon inhibits Lipogenesis.**

De Novo Biosynthesis Of Fatty Acids

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- Fatty acid biosynthesis is a **reductive biosynthetic mechanism**.
- To form **reduced molecules** of **Fatty acid (Palmitate).**

- De novo biosynthesis of Fatty acids is a **new biosynthesis of Fatty acids.**

- Using simple carbon units **Acetyl-CoA** and **NADPH+H$^+$** to a long chain fatty acids.

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- Palmitic acid (16:0) can be **further modified to higher Fatty acids .**

Site For Fatty Acid Biosynthesis

Organs Involved For Fatty Acid Synthesis

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- In humans, Fatty acids are biosynthesized in **Cytosol** of:
  - **Liver (Predominantly)**
  - Adipose tissue
  - Intestine
  - Lungs
  - Brain
  - Renal Cortex
  - Mammary glands during lactation

Reductive Biosynthesis Of Fatty acids

Extra Mitochondrial/Cytosolic Biosynthesis of Fatty acids

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- The biosynthetic pathway of Fatty acids involves
- The use of **reducing equivalents NADPH+H$^+$** in the **reduction steps.**

- To form the **reduced molecule** of **fatty acids,**
- **Hence** it is **termed as reductive Synthesis of Fatty acids**.

- Fatty acids biosynthesized are used up for biosynthesis of :
  - **Triacylglycerol**
  - **Phospholipid**
  - **Glycolipid**
  - **Cholesterol Ester**

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- **Fatty acids are stored as Triacylglycerol,** especially **in Adipose tissue.**

Biosynthesis Of Palmitic Acid/Palmitate (C16)

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Requirements Of De novo Biosynthesis Of Fatty acids

- **Precursor for Fatty acid biosynthesis is Acetyl-CoA**

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Species comparison of fatty acid synthesis

Species	Principal Tissue Site	Carbon Source
Poultry	Liver	Glucose
Human	Liver	Glucose
Pig	Adipose	Glucose
Mouse	Adipose	Glucose
Sheep	Adipose	Acetate
Cattle	Adipose	Acetate

- **Requirement of $HCO3^-$** (Bicarbonate Ions) : Provides $CO2$ **for Acetyl-CoA Carboxylation Reaction.**

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- **Enzymes Involved:**

–Acetyl-CoA Carboxylase

–FAS Multi Enzyme Complex

Coenzyme Required

- **Reducing Equivalent :**

–$NADPH+H^+$

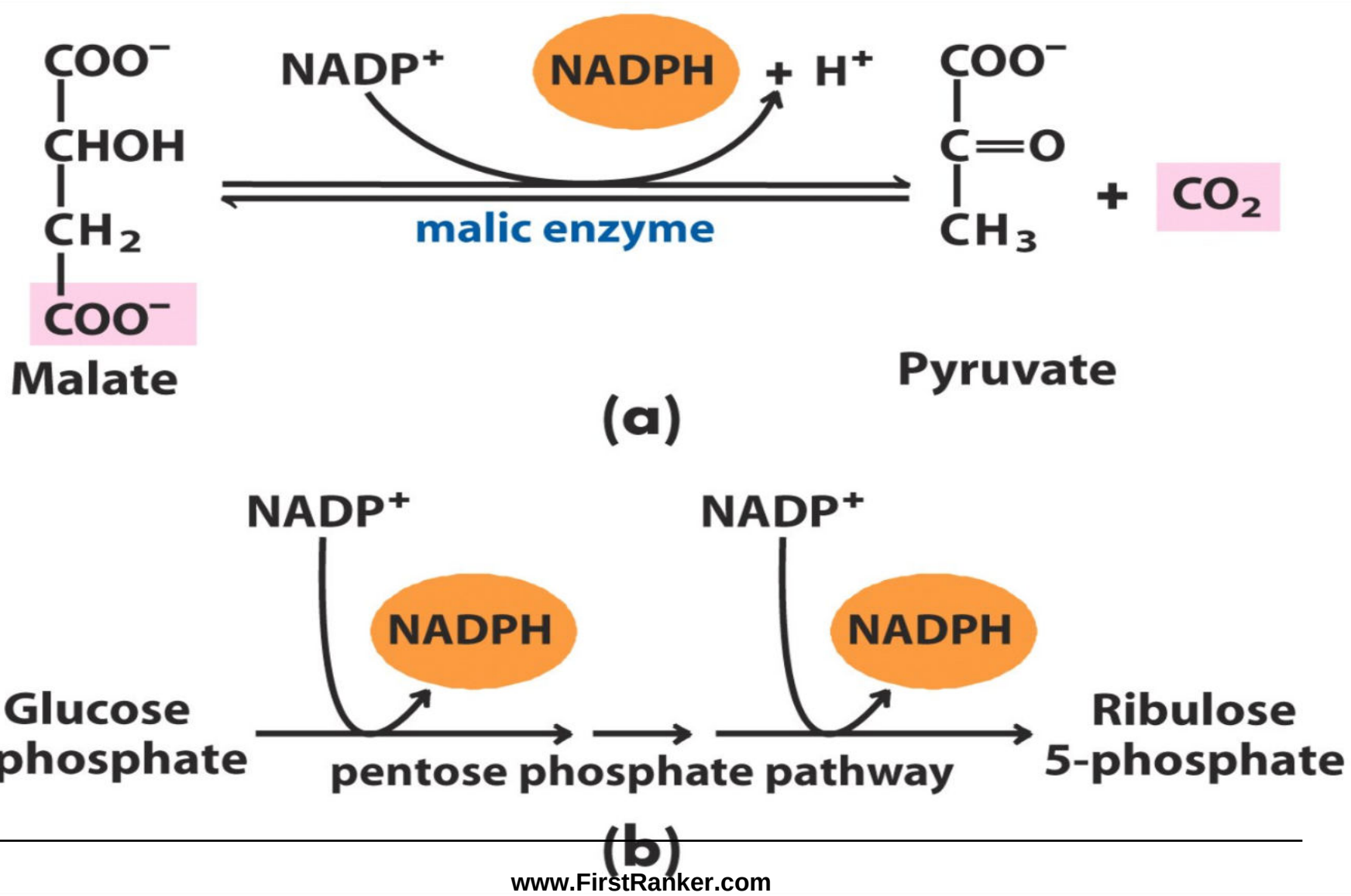
- The main source of **$NADPH+H^+$** is mainly by the **Pentose Phosphate Pathway.**

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- The **Malic enzyme activity** converts Malate to Pyruvate which is **another source of NADPH+H$^+$**

Production of NADPH+ H$^+$



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- **NADPH+H$^+$** serves as an electron donor in the two reactions
- **Involving substrate reduction in De Novo Fatty acid biosynthesis.**

Who Is The source Of Acetyl-CoA for Fatty acid Biosynthesis ?

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- **Free and Excess Glucose** in a **well fed condition**

- Is the **major source of carbon for** the **De novo fatty acid biosynthesis**.

- **Free and excess Glucose** remained **after limited Glycogen storage**

- Is used for **Acetyl-CoA production** and **diverted for the Fatty acid biosynthesis**.

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- **Glucose** is oxidized **to** **Pyruvate** via **Glycolysis.**

- **Pyruvate**(3C) is then **oxidatively decarboxylated**

- To a high energy compound **Acetyl-CoA** (2C)in **Mitochondria** by **PDH Complex.**

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- The **excess of Acetyl CoA** formed and **present in Mitochondrial matrix**

- Is **diverted for Denovo Biosynthesis of Fatty acids**.

- **8 molecules of Acetyl-CoA** (C2) are **required**

- **For the biosynthesis** of **1 molecule** of **even carbon Palmitate (C16).**

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- Eight Acetyl-CoA's are involved.
- To grow a Fatty acid Chain of 16-carbons

Fatty Acyl Synthase (FAS) Multi Enzyme Complex

For De Novo Biosynthesis Of Fatty Acids

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Fatty Acyl Synthase (FAS) Complex

- **FAS** is a **Multi Enzyme Complex Used in De Novo Biosynthesis of Fatty acids.**

- Structurally **FAS is a Homodimer**
- **Two alike monomeric subunits**
- **Linked together** in **head to tail fashion (Anti Parallel)**

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Structural Aspects Of FAS

- FAS is Composed of 8 Components
  - 7 Enzymes and 1 Protein

Three Subunits/Domains Of FAS Complex

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1.Condensation Unit
Has 3 Enzymes

- Acetyl Transacylase
- Malonyl Transacylase
- Beta Keto Acyl Synthase

2. Reduction Unit

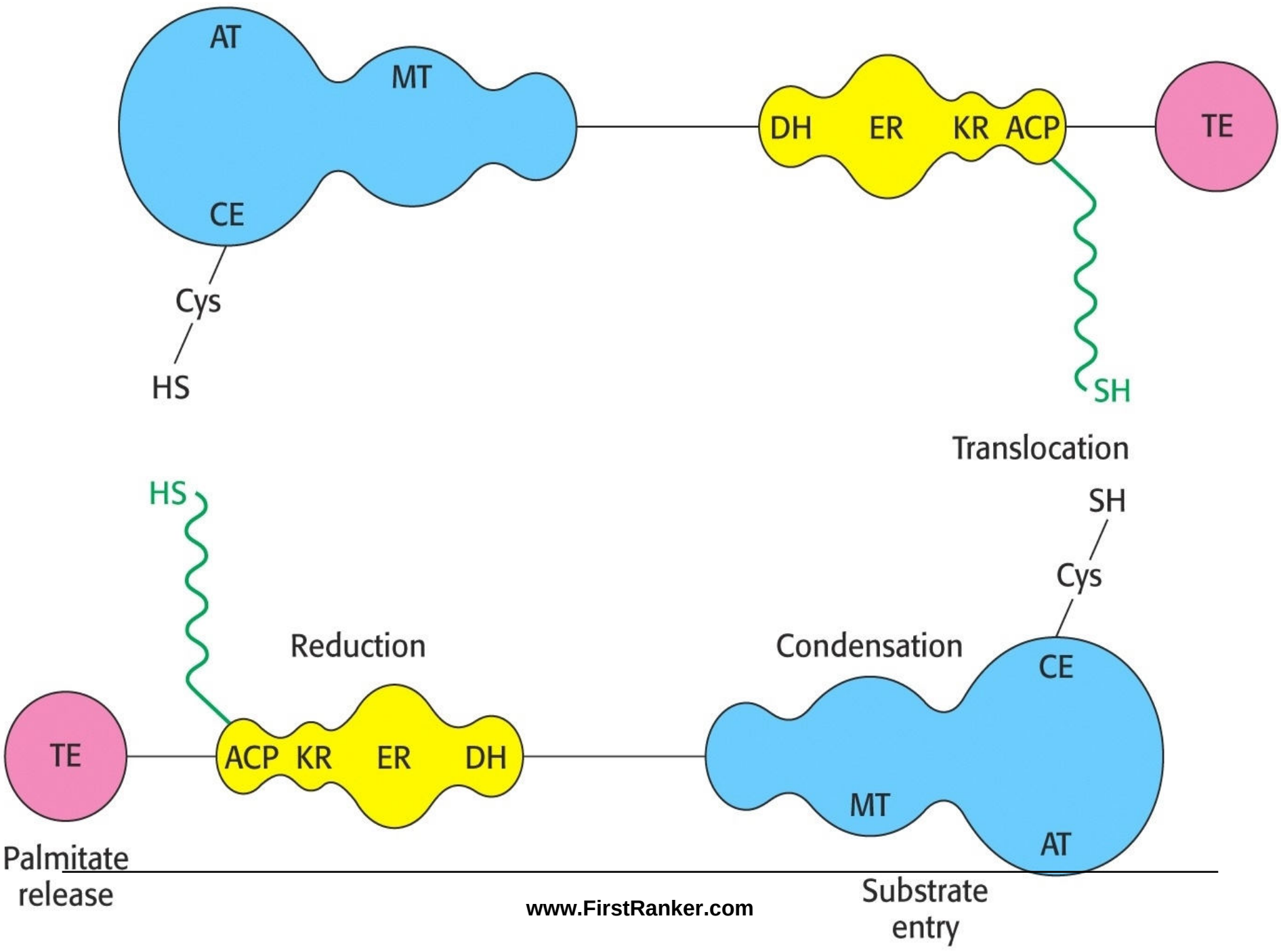
- ACP- (Acyl Carrier Protein)
- Beta Keto Acyl Reductase
- Dehydratase
- Enoyl Reductase

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3. Cleavage /Releasing Unit

- **Thioesterase (Deacylase)**



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ACP Of FAS Complex

- **Acyl Carrier Protein** (ACP) of FAS complex is a **carrier of growing Acyl chain**
- During **De novo biosynthesis of fatty acids.**

The Acyl Carrier Protein

Carrier of Intermediates in Fatty acid synthesis

- Discovered by **P. Roy Vagelos.**

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- **ACP** is a **Conjugated Protein component of FAS complex.**
- ACP is a part of **Reduction unit** of **FAS complex.**

- **4- Phospho Pantethene** serve as a **prosthetic group of ACP.**

- **4-Phospho Pantethene** is a **derivative of Vitamin B 5-Pantothenic acid.**

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- **4 Phosphopantetheine** (Pant) is covalently linked to **Serine hydroxyl** of Protein domain of ACP via a **phosphate ester linkage .**

- ACP has **–SH group (Thiol)** as **functional group**.

- **-SH group of ACP** is **an acceptor of Acetyl-CoA and Malonyl-CoA** during De novo biosynthesis of a Fatty acids.

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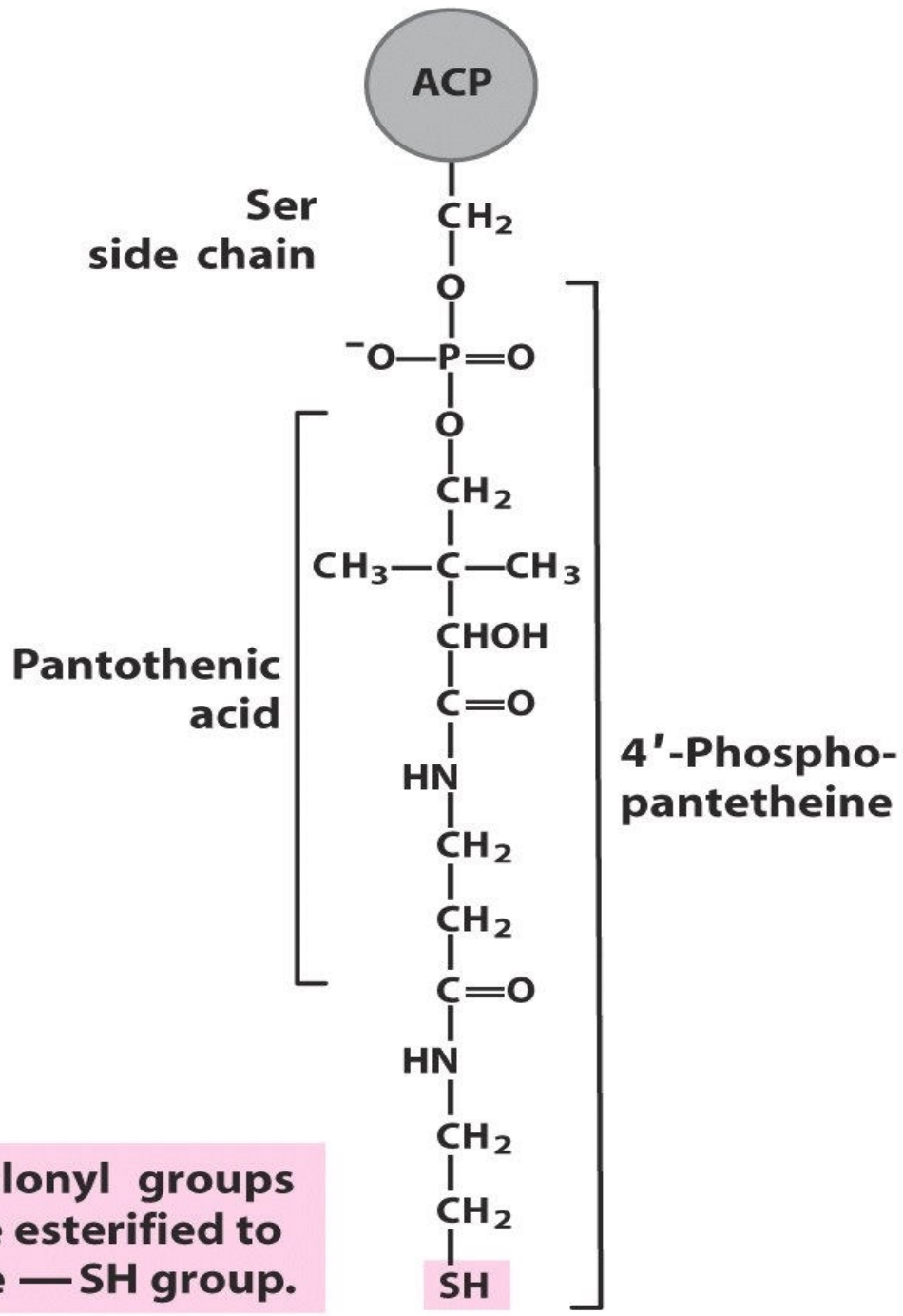
- At the **end of Denovo Fatty acid biosynthesis**

- The **complete chain** of **Fatty acid** is **linked to ACP** of FAS complex.

- The **long flexible arm** of Phosphopantetheine **helps its Thiol**
- **To move from one active site to another within the FAS complex.**

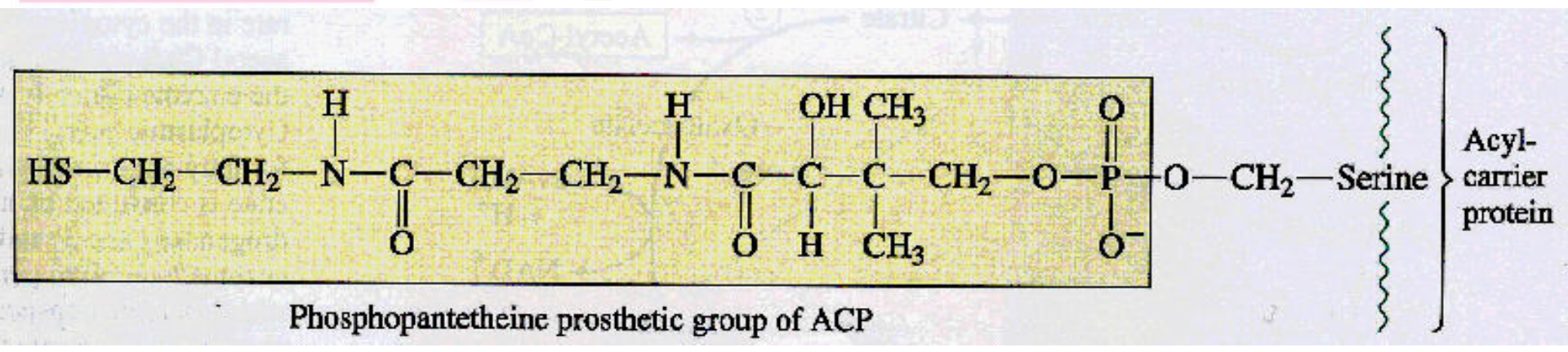
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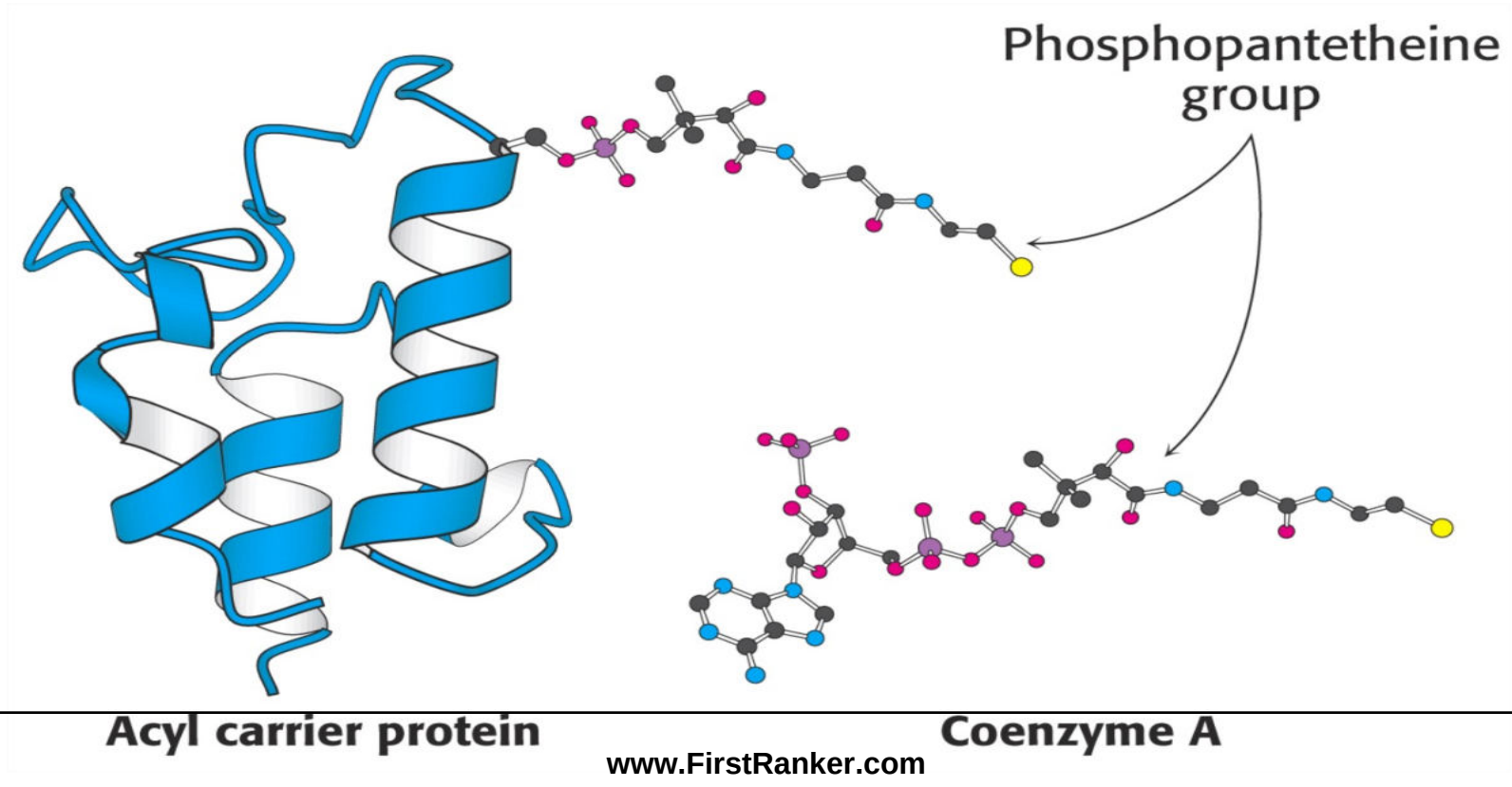


Key Player: Acyl Carrier Protein(ACP)

- "Macro" CoA, carries growing fatty acid chain via Thioester



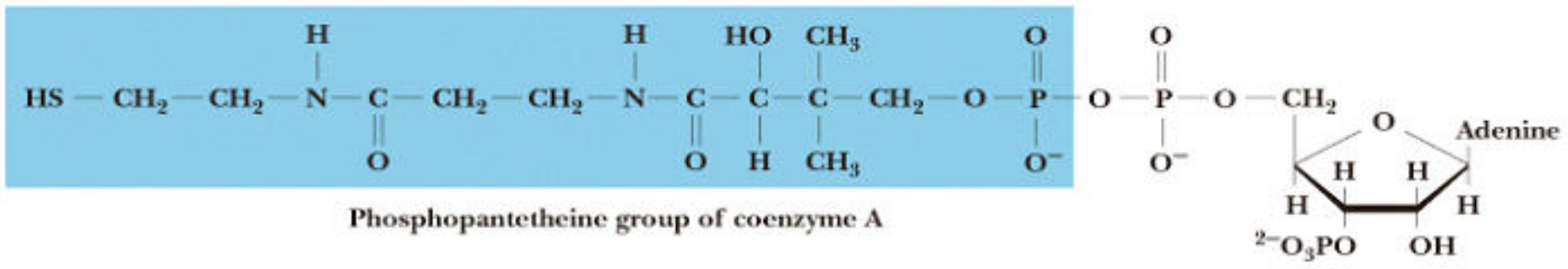
Phosphopantetheine prosthetic group of ACP



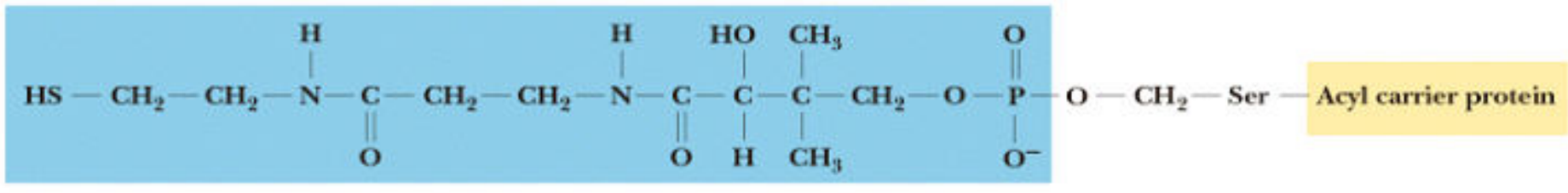
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ACP vs. Coenzyme A



Phosphopantetheine group of coenzyme A



Phosphopantetheine prosthetic group of ACP

- Intermediates in synthesis are linked to -SH groups of Acyl Carrier Proteins (as compared to -SH groups of CoA)

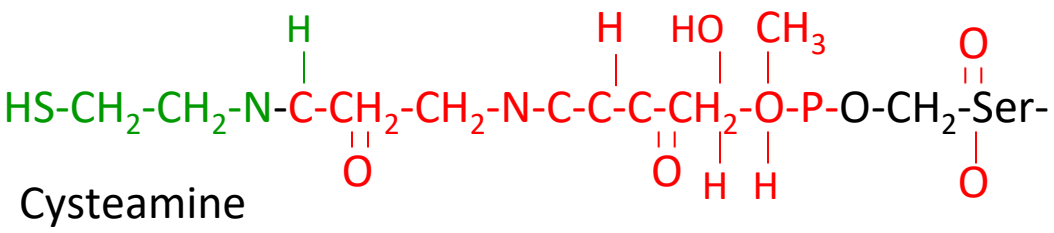
- In terms of function, **ACP is a large CoA.**

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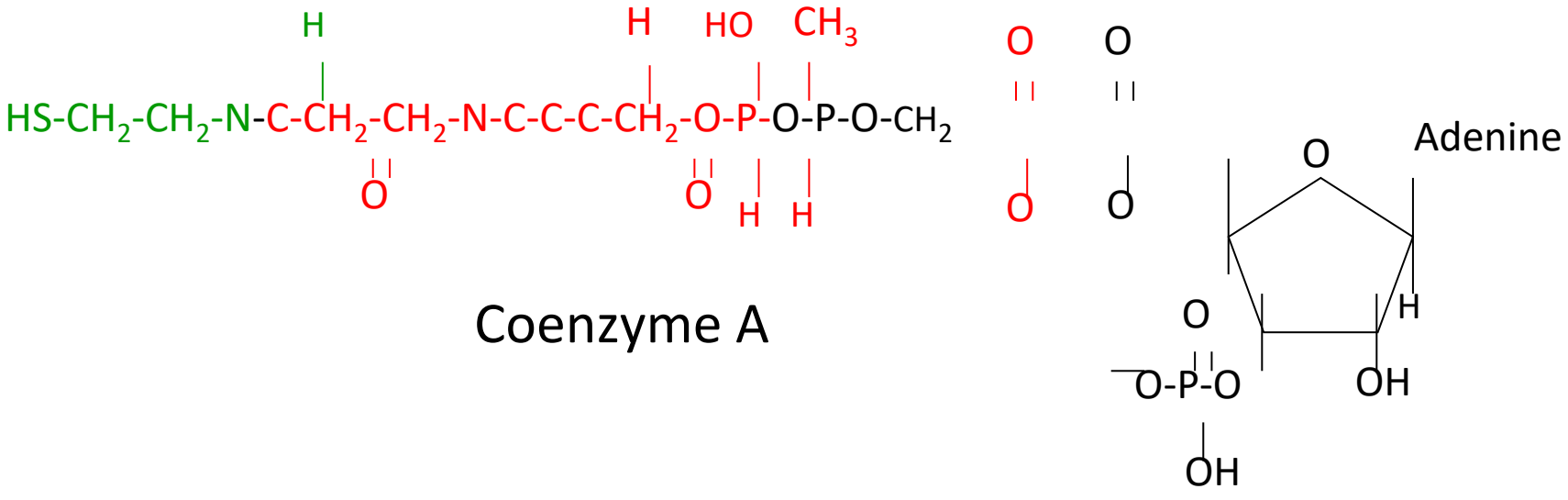
Acyl Carrier Protein

Phosphopantetheine





Acyl carrier protein
10 kDa



Coenzyme A

FAS Complex Is Coded By Single Gene

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Location Of FAS Complex

- **Cytosol**
- **Extra mitochondrial**

Hormones Regulating FAS Complex

- **Insulin**- Stimulates FAS Complex
- **Glucagon**-Inhibits FAS Complex

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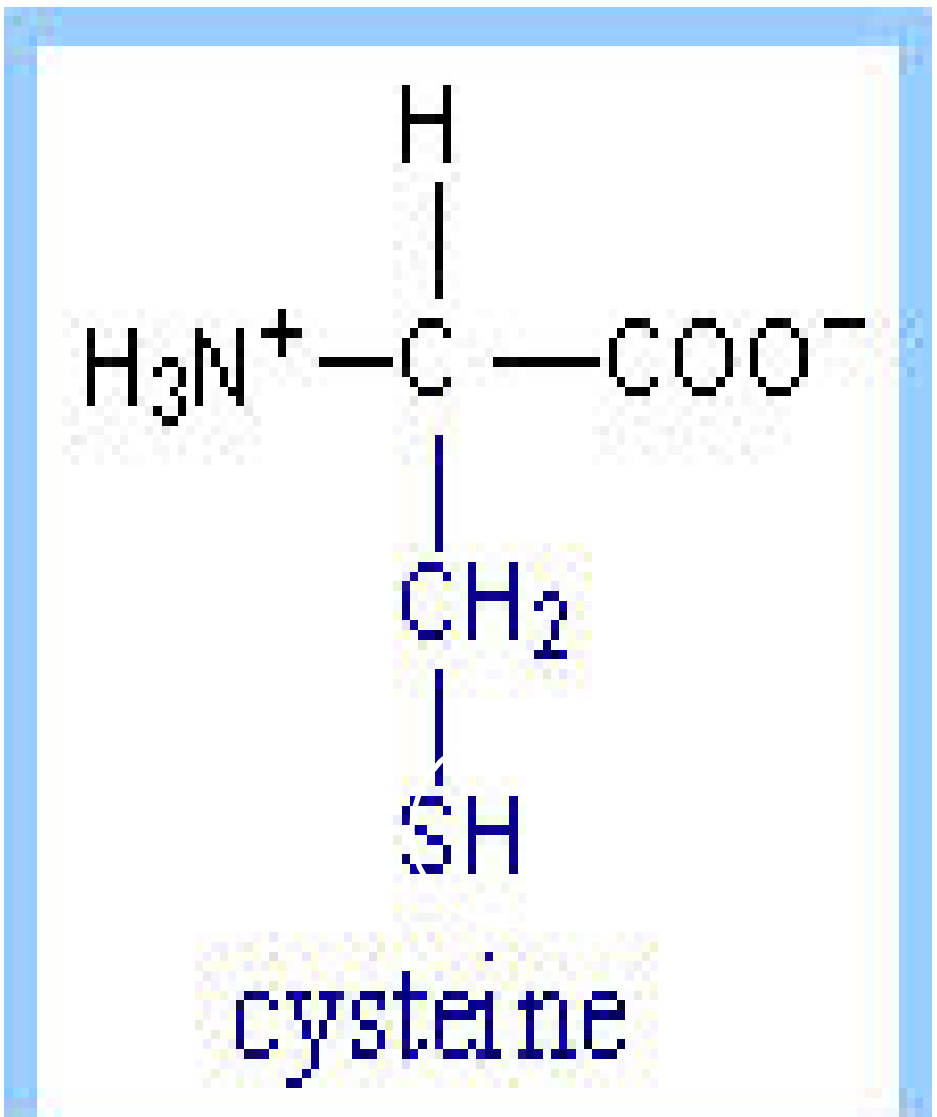
Functional Parts Of FAS Complex

- **FAS complex** being dimer **has two functional Units.**
  - —-**SH (Thiol) group of Cysteine** of condensation Enzyme **β Keto Acyl Synthase.**
  - —-**SH (Thiol) group of 4 Phospho Pantethene of ACP**.

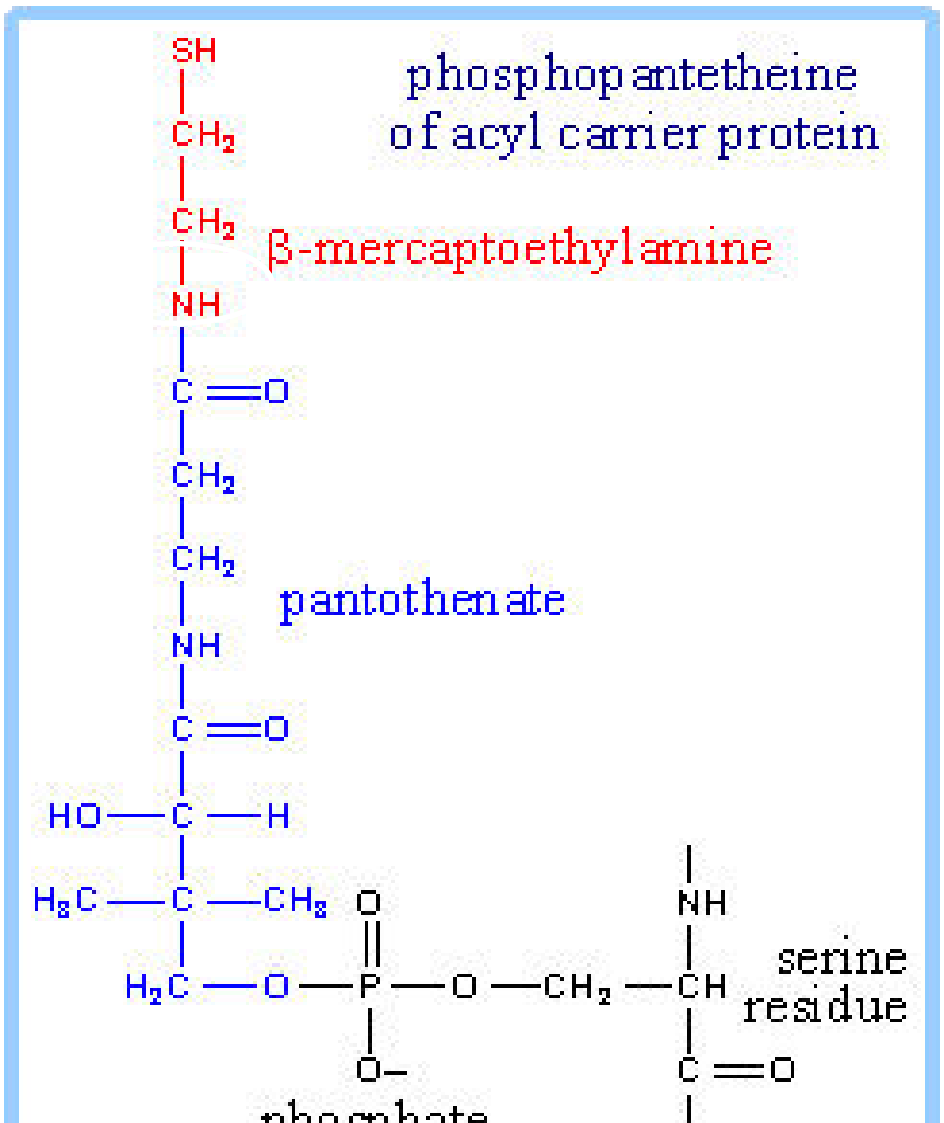
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Thiol Cysteine residue



Thiol of Phosphopantetheine



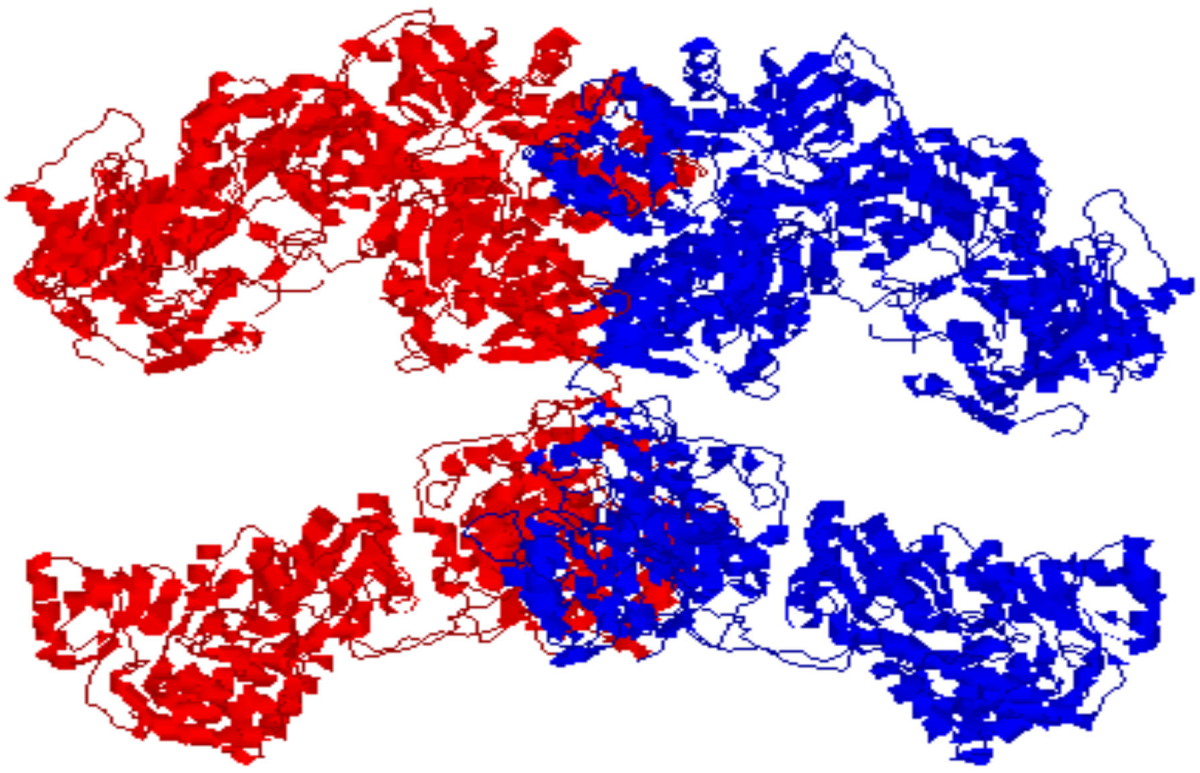
- As there are **two functional units**
- When **FAS complex operates at a time**
- There is **biosynthesis of two Fatty acids (Palmitate) molecule.**

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- **Rate of Fatty acid biosynthesis is high in the well-fed state.**

X-Ray crystallographic analysis at 3.2 Å resolution shows the Dimeric Fatty Acid Synthase to have an **X-shape**.



Fatty Acid Synthase PDB 2VZ8

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Fatty Acid Synthase Complex

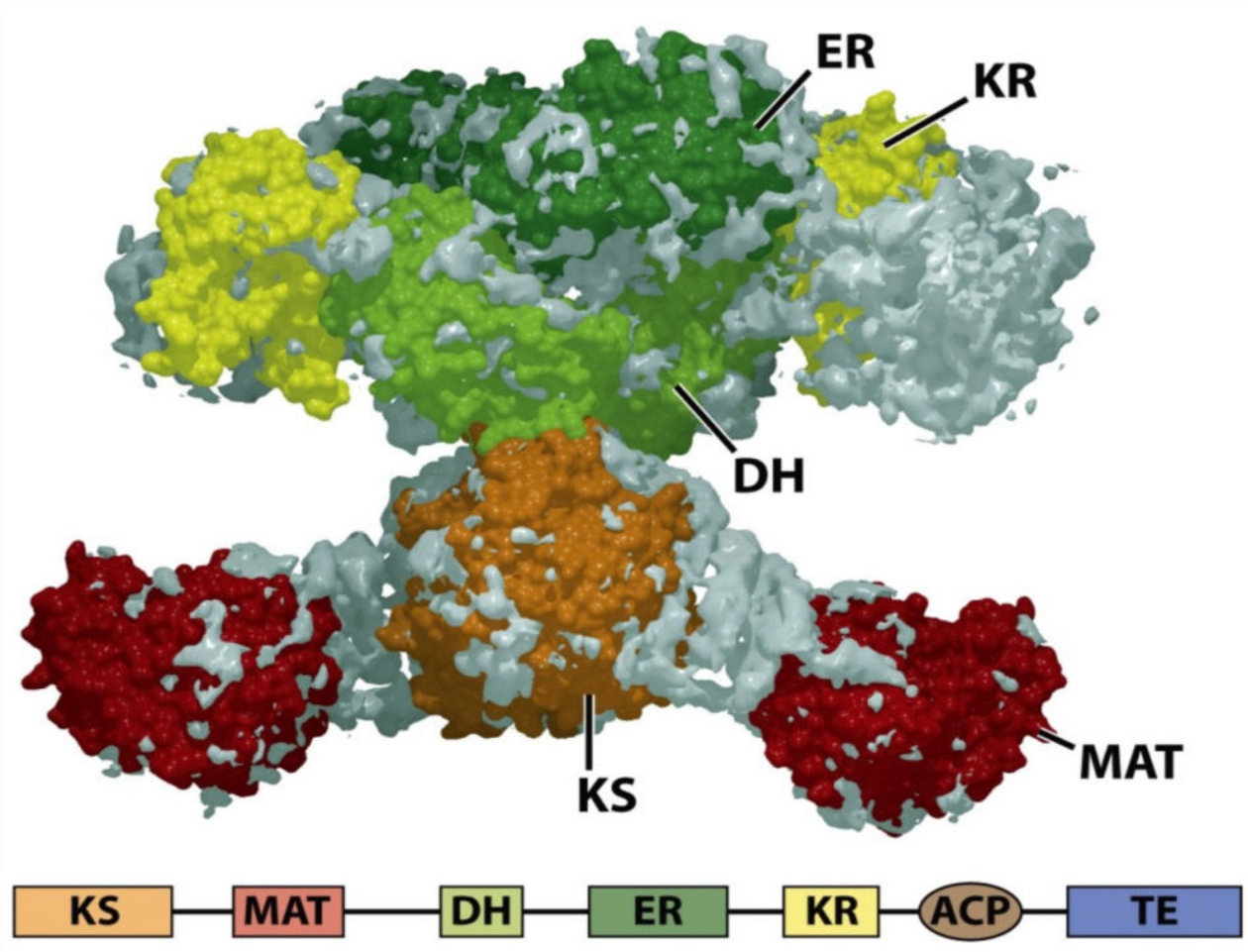
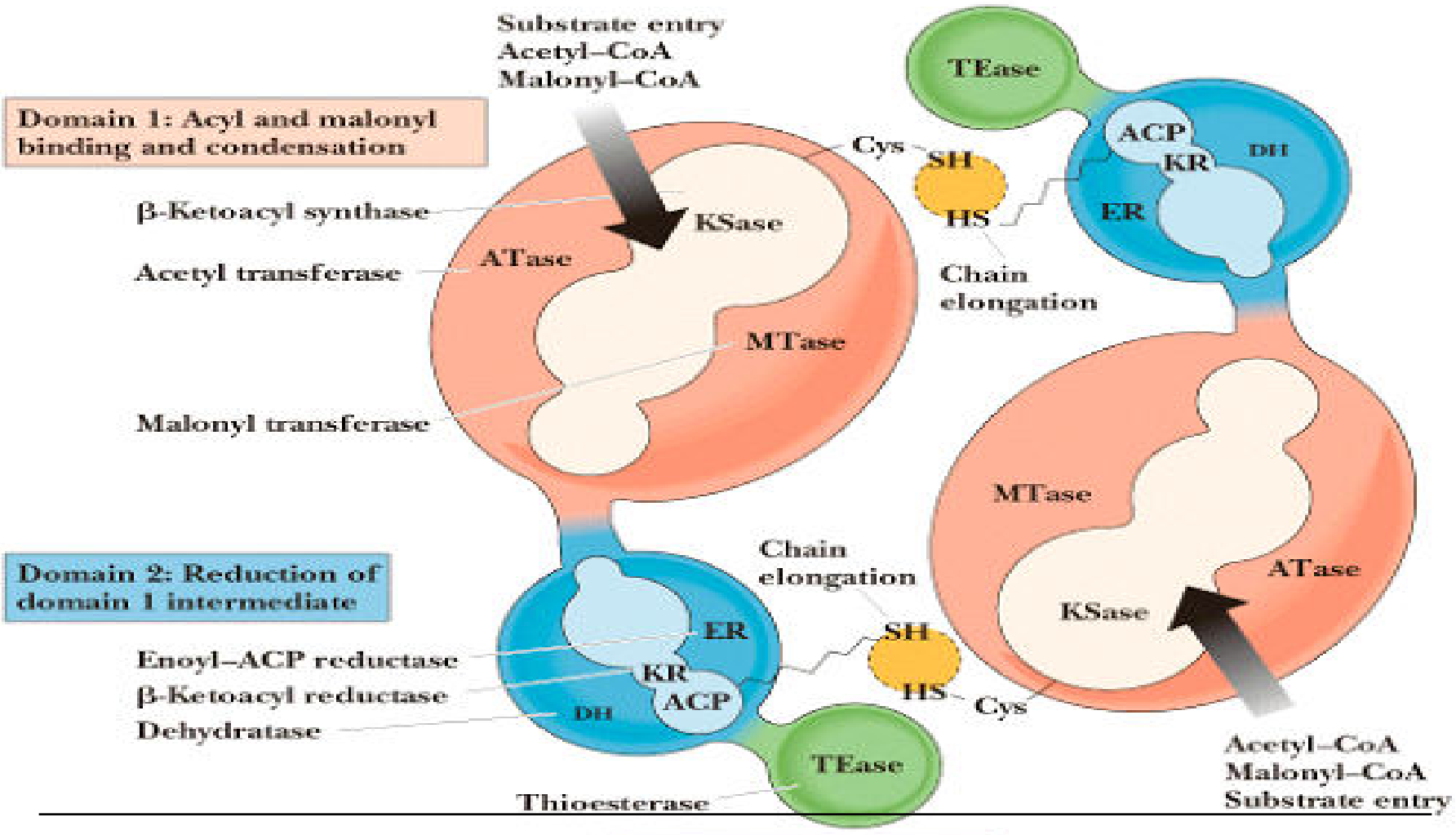


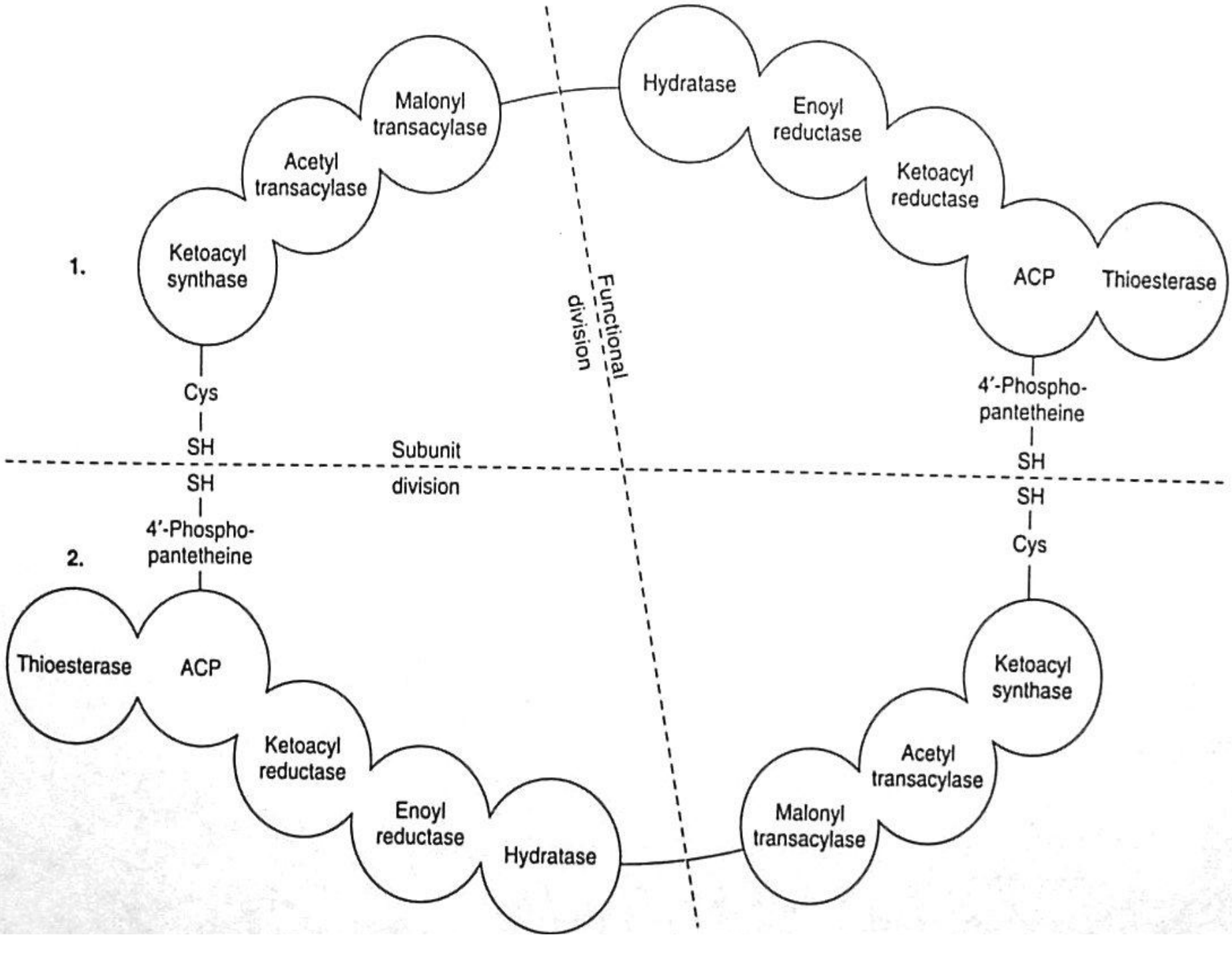
Figure 21-3a
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Fatty Acid Synthase Complex



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Stages And Steps Of De Novo Biosynthesis Of Fatty Acids

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Three Stages Of De novo Biosynthesis Of Fatty acid

I. Translocation of Acetyl-CoA from Mitochondria to Cytosol.

II. Carboxylation of Acetyl-CoA to Malonyl-CoA

III. Reactions of FAS Complex

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Stage I

Translocation of Acetyl-CoA from Mitochondria to Cytosol

Transport Of Mitochondrial Acetyl-CoA To Cytosol

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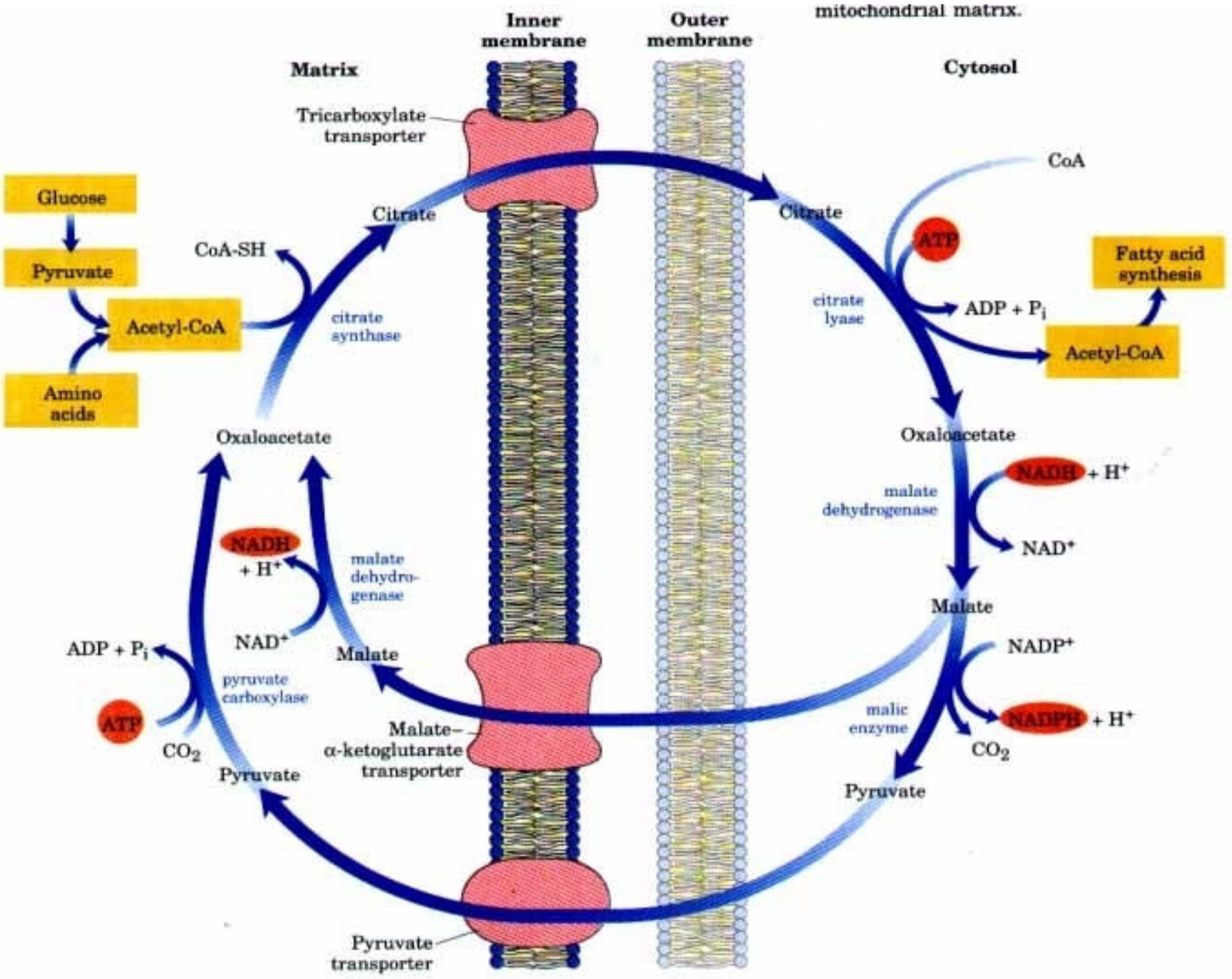
Since
Fatty Acid Synthesis
Occurs in the Cytosol
Mitochondria Acetyl-CoA
Is to be translocated In Cytosol

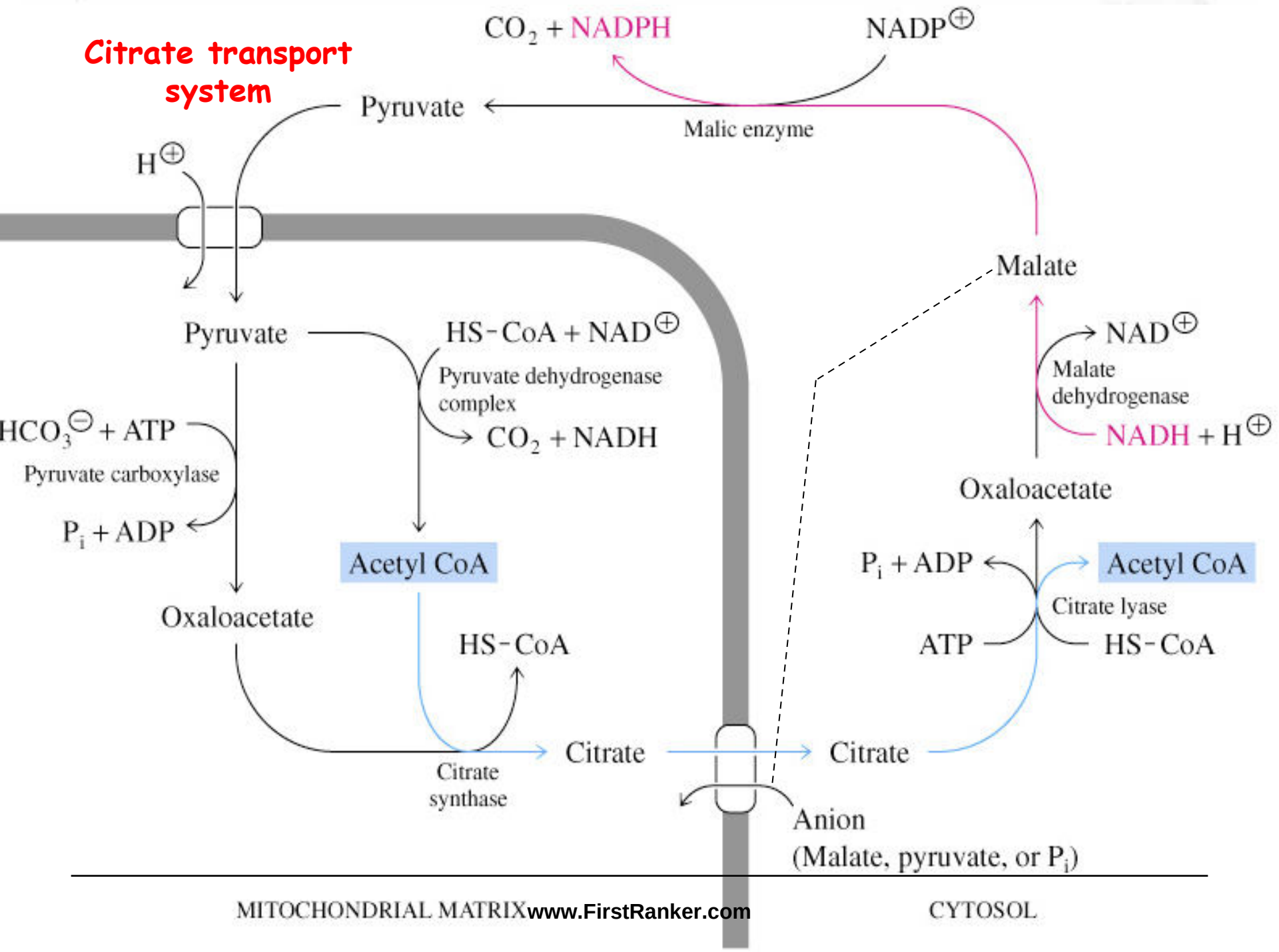
Translocation Of Acetyl-CoA
Through
Citrate Shuttle
Citrate Malate Pyruvate
Transport System

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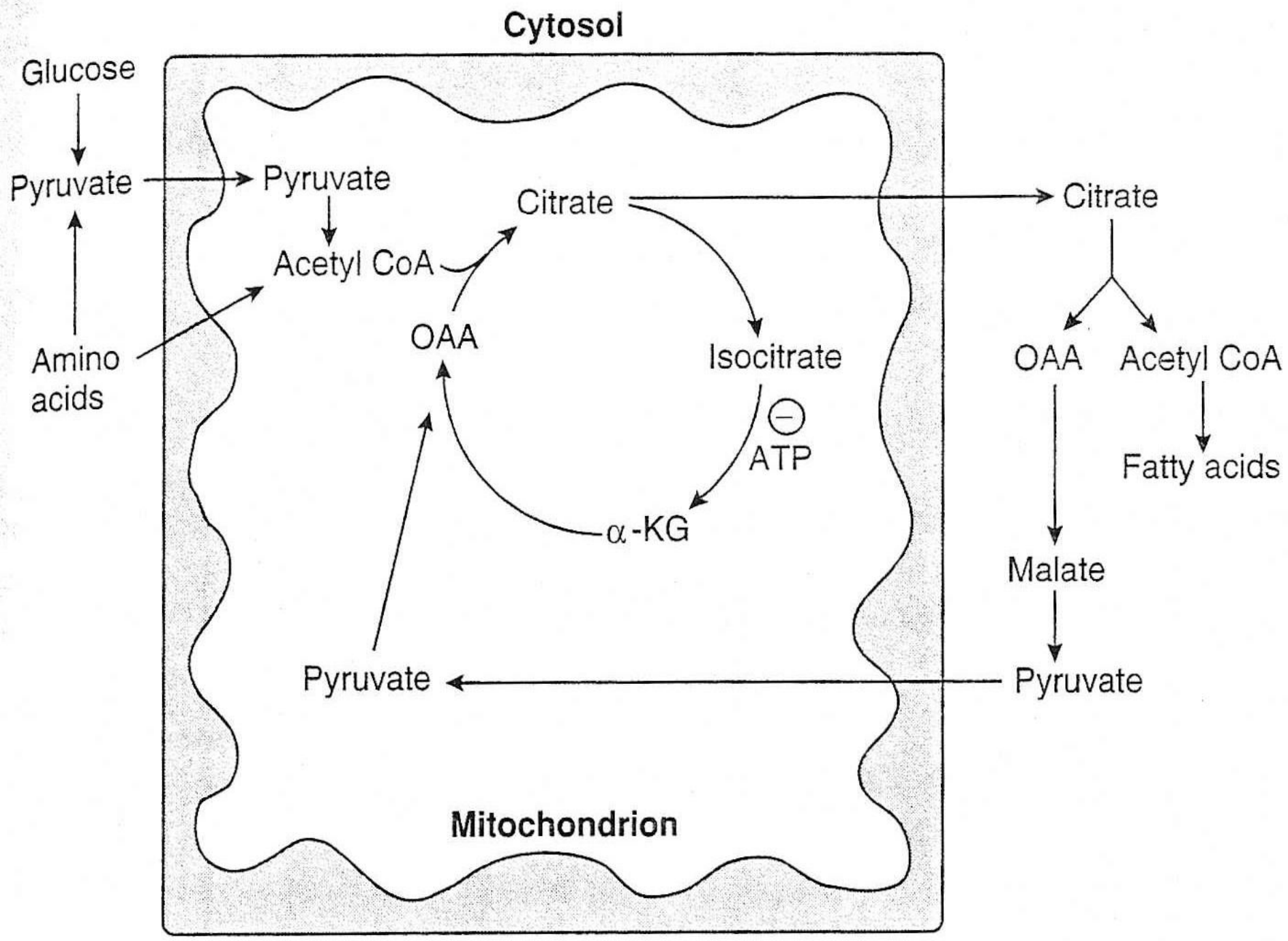
mitochondrial matrix.





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- The Mitochondrial **Acetyl CoA** is **impermeable** due to the **complex CoA** .
- Impermeable Acetyl CoA is transformed to **permeable Citrate** by **Citrate Synthase.**

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- Citrate is translocated out in the cytosol.
- Citrate in cytosol is cleaved by **Citrate Lyase** to **liberate Acetyl-CoA in cytosol.**

- **Thus Citrate-Malate-Pyruvate shuttle provides:**
  - **Cytosolic Acetyl CoA**
  - **Reducing equivalents NADPH+H+**
- **For De novo Fatty acid biosynthesis**

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- **Acetyl CoA** from **catabolism of Carbohydrates and Amino acids** is **exported from Mitochondria** via the **Citrate transport system**
- **2 ATPs are required during work of this system.**

- Impermeable **Acetyl-CoA** is translocated out
- **From Mitochondrial Matrix into Cytosol** in the form of **permeable Citrate**.

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- **Acetyl-CoA**(impermeable) produced in the **Mitochondria** is condensed with **Oxaloacetate** to form **Citrate**(permeable) by **Citrate Synthase**.

- **Permeable Citrate** is then transported out into the **Cytosol**

- **Citrate Lyase in Cytosol act upon Citrate to regenerate Acetyl-CoA** and **Oxaloacetate** with consumption of **ATP**

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- **Most Acetyl-CoA used for FA synthesis comes from Mitochondria.**

Stage 2
Carboxylation of Acetyl-CoA to Malonyl-CoA In Cytosol

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Carboxylation of Acetyl-CoA(2C) to Malonyl-CoA(3C)

By

Acetyl CoA Carboxylase (ACC)

Acetyl-CoA Units Are Activated To Malonyl-CoA

For Transfer To Growing Fatty Acid Chain

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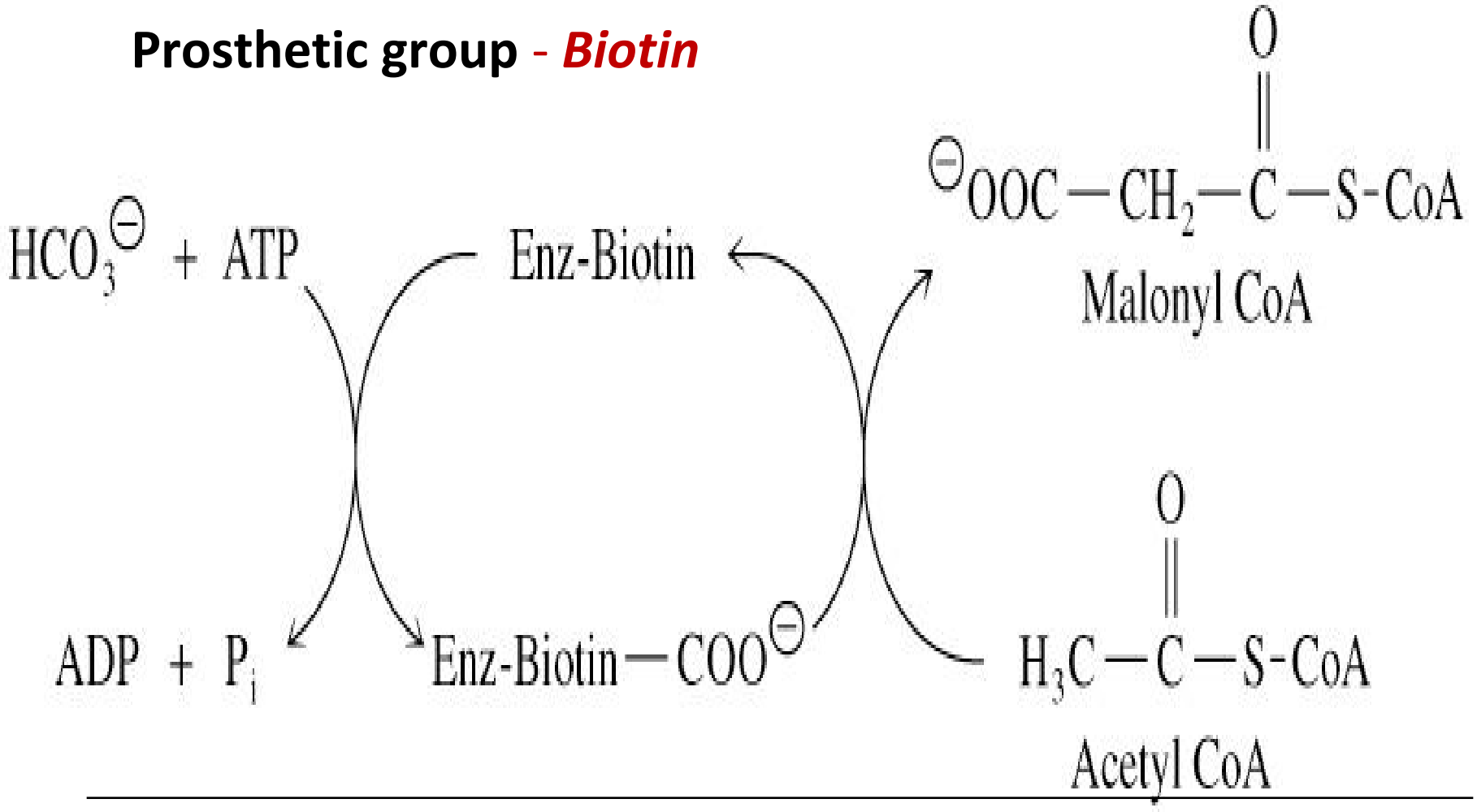
Malonyl-CoA Is a High Energy Compound

With a High Energy Bond In Its Structure

B. Carboxylation of Acetyl CoA

Enzyme: ***Acetyl CoA Carboxylase***

Prosthetic group - ***Biotin***



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- During **biosynthesis** of 16 C saturated **Palmitic acid**

- There **requires total 8 molecules of Acetyl-CoA**

- **During FAS complex** Fatty acid **synthetic steps**

- **Only one molecule of Acetyl-CoA** (C2) **enters as it is in the first step of Third Stage of Fatty acid biosynthesis.**

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- **Remaining 7 molecules of Acetyl-CoA are entered in the form of Malonyl-CoA (C3).**

- Thus **Seven Molecules** of **Acetyl-CoA** are
- **Transformed to Seven molecules of Malonyl-CoA.**

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- **Malonyl-CoA** is obtained from **carboxylation reaction** of Acetyl-CoA
- In presence of, enzyme **Acetyl Carboxylase** and **coenzyme Biotin and ATP.**

❖Conversion of Acetyl-CoA to Malonyl CoA , is by catalytic activity of **Acetyl CoA Carboxylase , Biotin and ATP.**

❖This is an Carboxylation reaction which **provides energy input.**

❖To form still more high energy compound **Malonyl-CoA(C3).**

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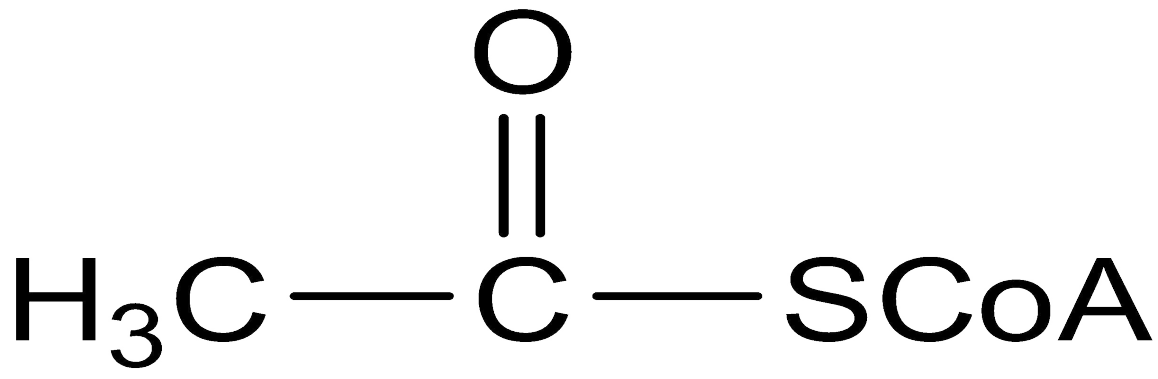
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- This carboxylation reaction after **use of high energy ATP**

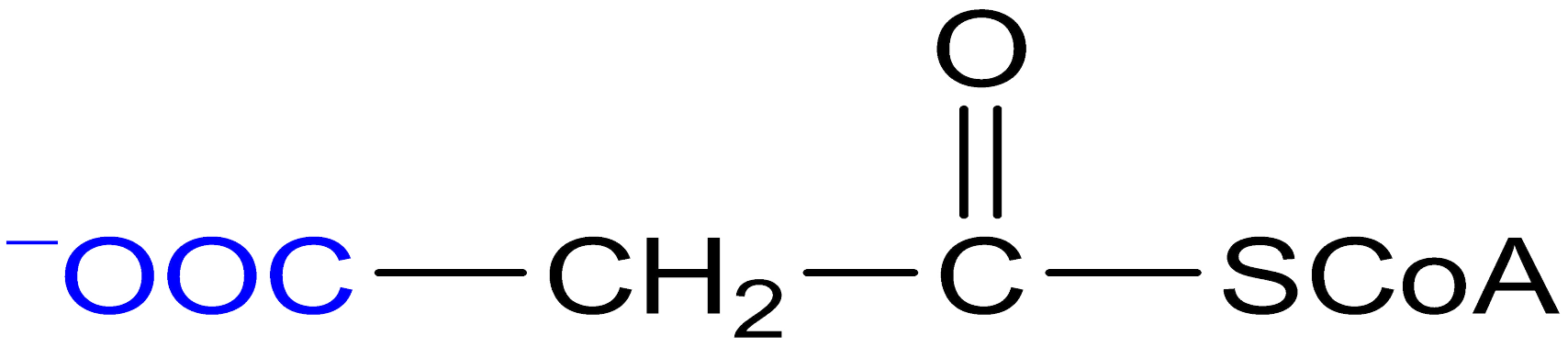
- Builds a high energy bond in a **high energy compound Malonyl-CoA.**

- The input of **Acetyl-CoA**, into Fatty acid biosynthesis is by its Carboxylation to **Malonyl-CoA**.

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acetyl-CoA



malonyl-CoA

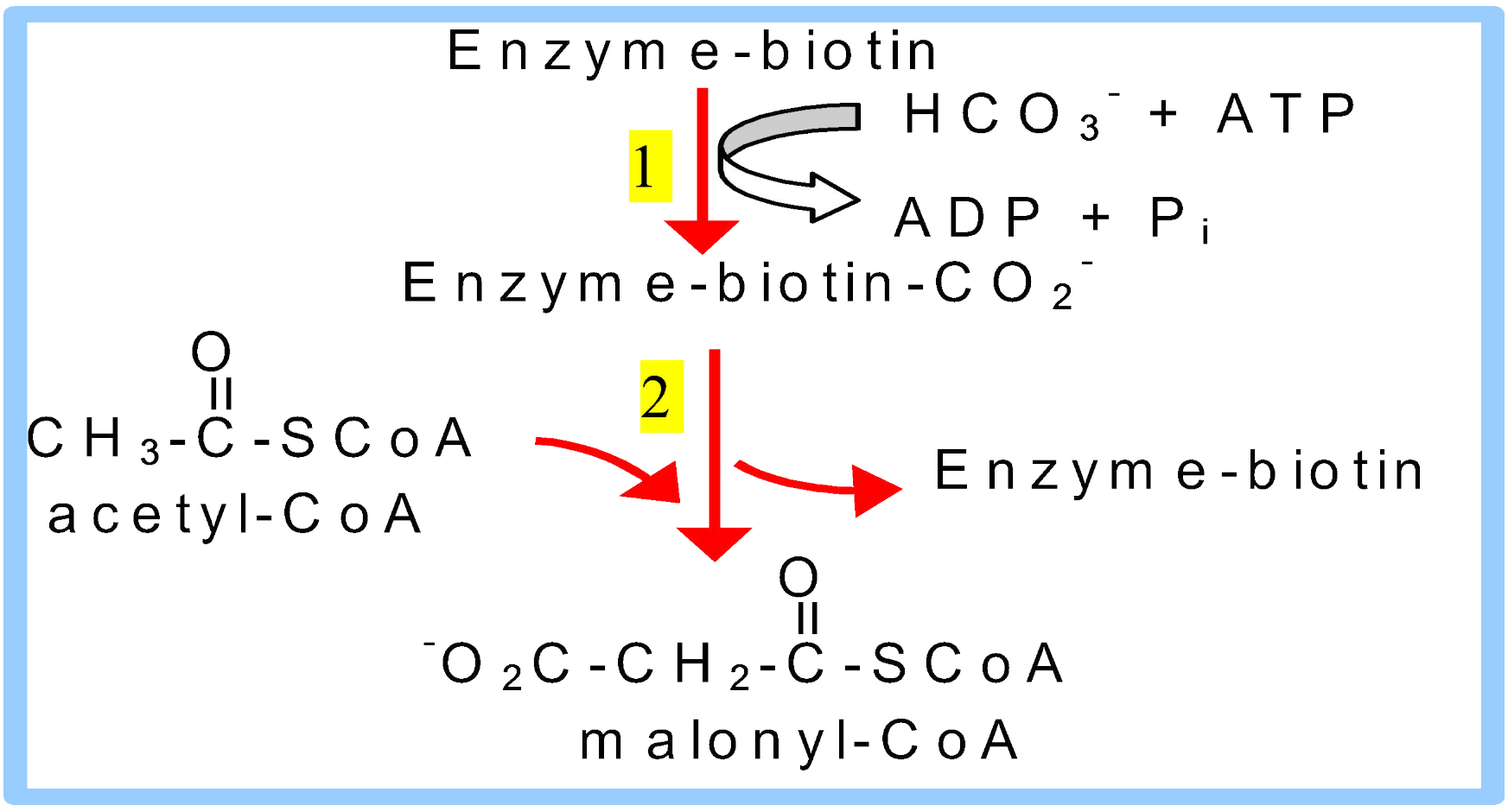
❖Later this **Malonyl CoA cleaves its high energy bond and looses** CO_2 and energy

❖This **released energy is used for the condensation reaction during third stage of Fatty acid biosynthesis** for the initation and growing of Fatty acid.

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- Thus the **spontaneous Decarboxylation** of **Malonyl-CoA**
- **Drives the condensation reaction of FAS complex.**



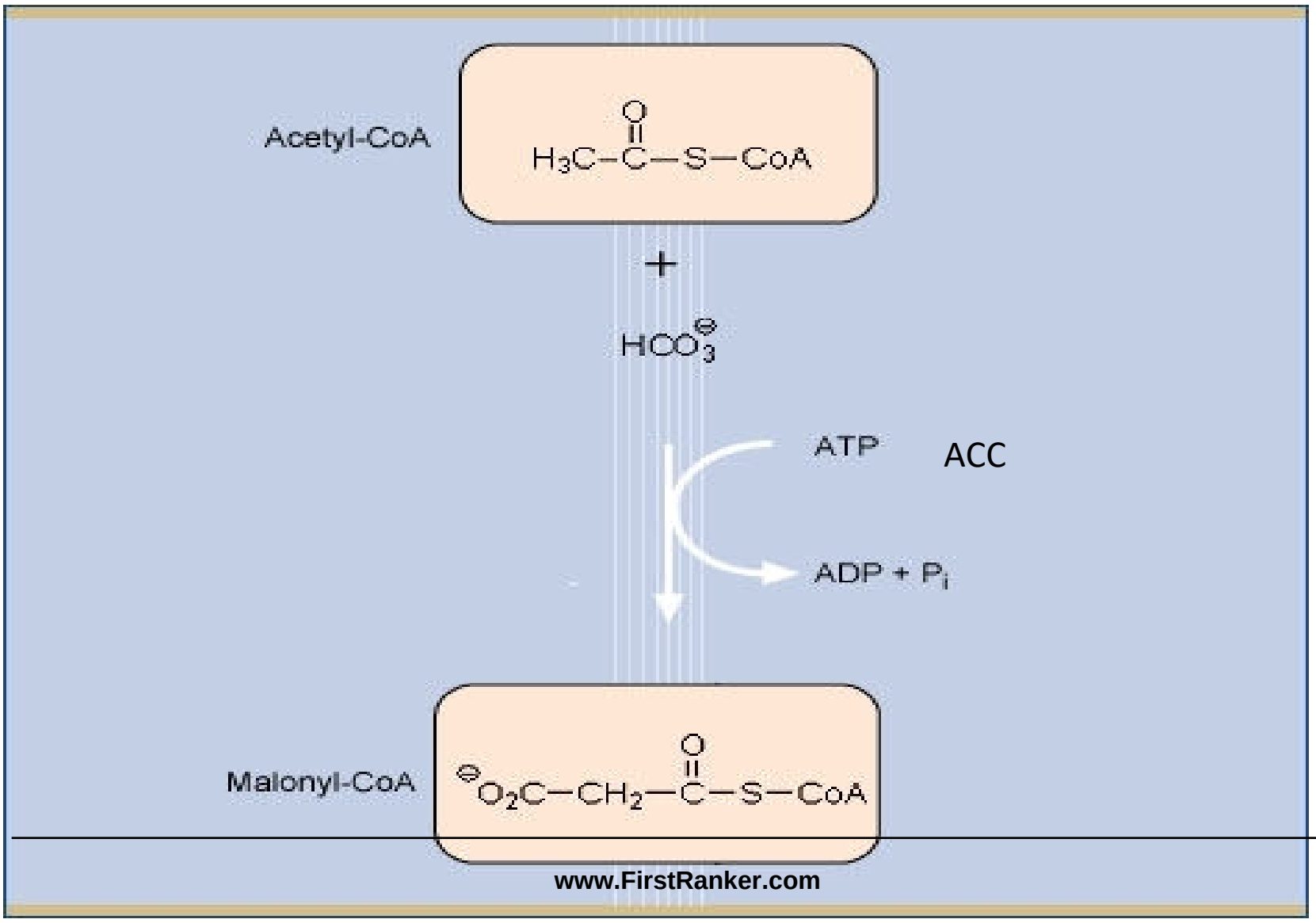
HCO_3^- + ATP + Acetyl-CoA → ADP + P_i + Malonyl-CoA

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$$\text{Acetyl-CoA} + HCO_3^- + ATP \xrightarrow{\text{ACC-Biotin}} \text{Malonyl-CoA} + ADP + P_i$$

Acetyl CoA Carboxylase (ACC)



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Formation of Malonyl-CoA

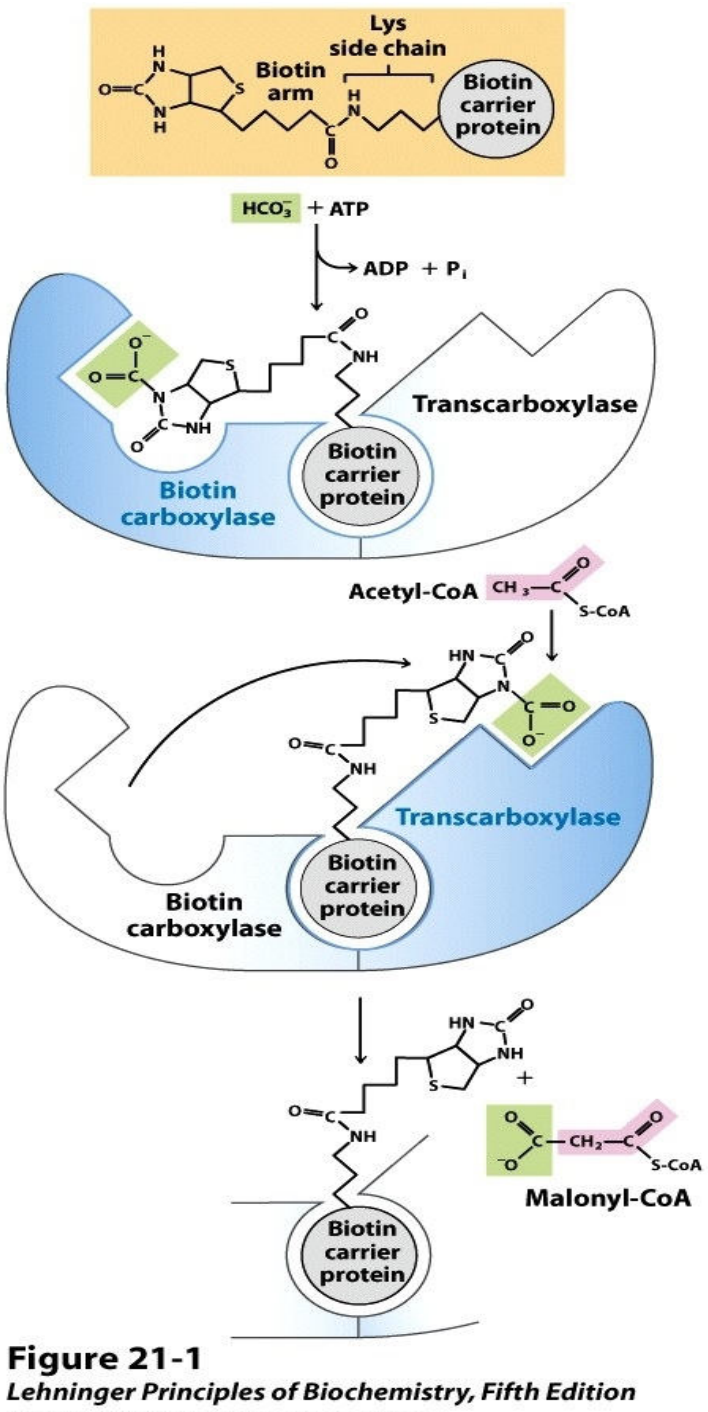


Figure 21-1

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- **Acetyl-CoA Carboxylase has three activities:**
  - ✓ **Biotin carrier Protein**
  - ✓ **Biotin Carboxylase**
  - ✓ **Trans Carboxylase**

Bicarbonate is Phosphorylated, then picked up by Biotin

Biotin swinging arm transfers CO_2 to acetyl-CoA

Significance Of Formation of Malonyl-SCoA

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Significance Of Formation of Malonyl-SCoA

- This Carboxylation reaction is **considered as activation step.**
- As the breaking of the CO_2 bond of Malonyl-SCoA releases lot of energy
- That **"drives" the reaction forward for condensation reaction of FAS complex.**
- The high energy bond of Malonyl-CoA is hydrolyzed later
- To liberate energy which is **used up** for **Condensation reaction** of FAS complex.

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- **Malonyl-CoA serves as activated donor of Acetyl groups** in FA synthesis.

- **Fatty acid synthesis**, from **Acetyl-CoA and Malonyl-CoA**,
- Occurs by a **series of reactions catalyzed by FAS complex.**

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Stage 3
Reactions Of FAS Complex During De Novo Biosynthesis Of a Fatty Acids /Palmitic Acid

- **Initation To Form An Acyl Chain**
  - I. **Loading of Precursors** –Acetyl-CoA at SH-ACP
  - II. **Translocation of Acetyl –S-ACP** to SH-Condensing Enzyme (SH-CE)
  - III. **Entry of Malonyl-CoA and Loading of Malonyl to SH-ACP**
  - IV. **Condensation of the Acetyl and Malonyl with decarboxylation**
  - V. **Reduction Reaction** to transform beta Keto group to Hydroxyl
  - VI. **Dehydration Reaction** to transform Hydroxyl group to Enoyl
  - VII. **Reduction Reaction** to transform Enoyl
  - VIII. **Translocation of Butyryl** From S-ACP to SH-CE
- **Elongation and Growing of Acyl Chain**
  - –By Six Time Repetitions of Steps III-VIII
  - –Entry Of 6 Malonyl-CoA's at SH-ACP
  - –1 Malonyl-CoA in each cycle to ACP-SH
- **Cleavage of Fatty acid/ Palmitate**
  - –By Thioesterase activity to release Palmitate and FAS

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Step I-Step III

Loading Of Precursors
Acetyl CoA and Malonyl-CoA
On FAS Complex
By
Acetyl and Malonyl Transacylases

- The **Acetyl-CoA** (2C) primer molecule is **first taken** up by – **SH group of ACP of FAS complex**

- To form **Acetyl-S-ACP** catalyzed by **Acetyl Transacylase.**

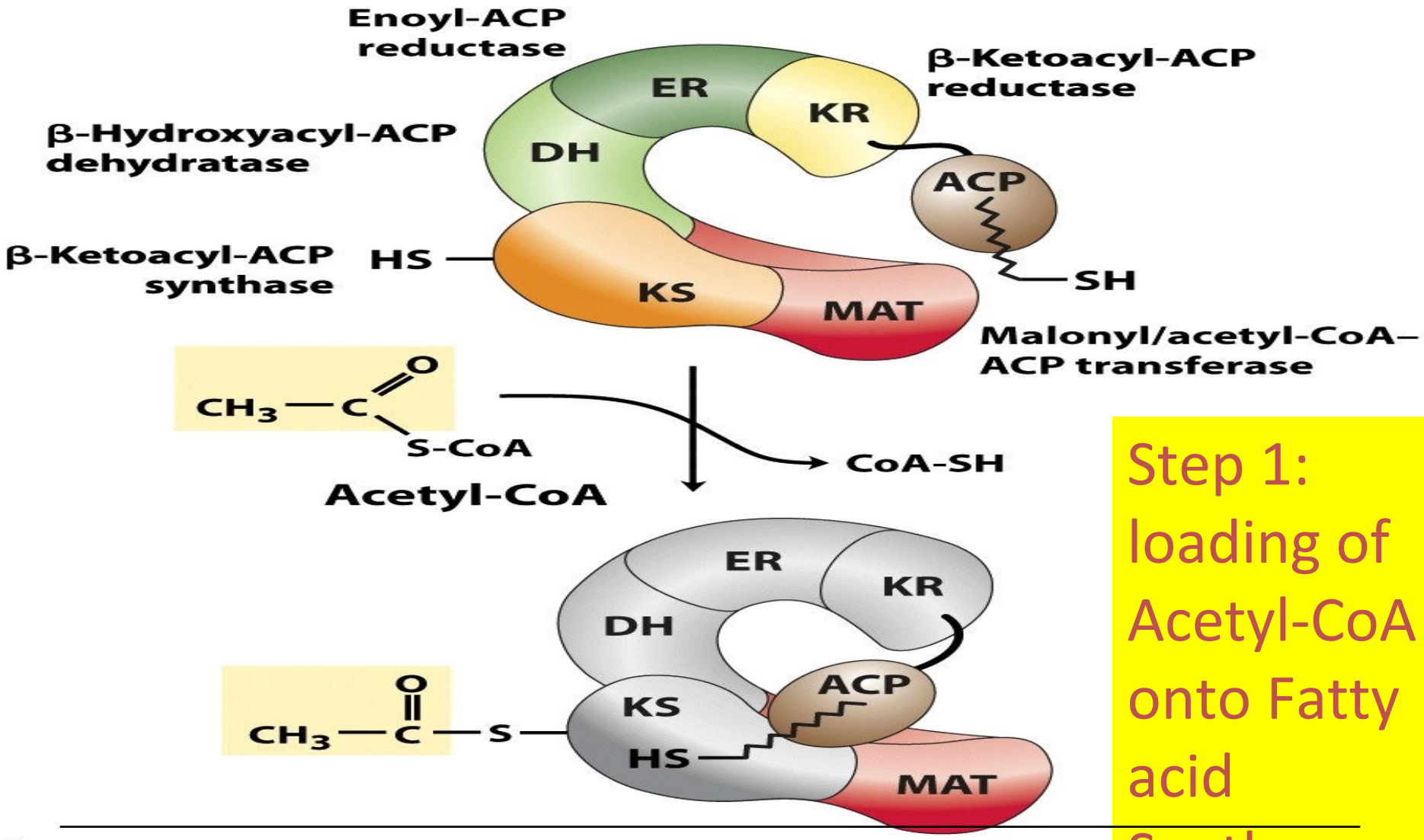
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- **Acetyl group from ACP** is shifted to Cysteine-SH of enzyme β Keto Acyl Synthase of FAS complex.

- To form **Acetyl-S-Enzyme β Keto Acyl Synthase** in presence of **Acetyl Transacylase.**

Loading Of Precursor Acetyl CoA



Step 1: loading of Acetyl-CoA onto Fatty acid Synthase

Figure 21-6 part 1
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- Malonyl-CoA (3Carbon unit) enters and is **taken up by**

-SH of ACP of FAS complex

- To form **Malonyl-S ACP** catalyzed by **Malonyl Transacylase.**

Entry Of Malonyl-CoA

Step 2: loading of Malonyl-CoA onto Fatty acid Synthase

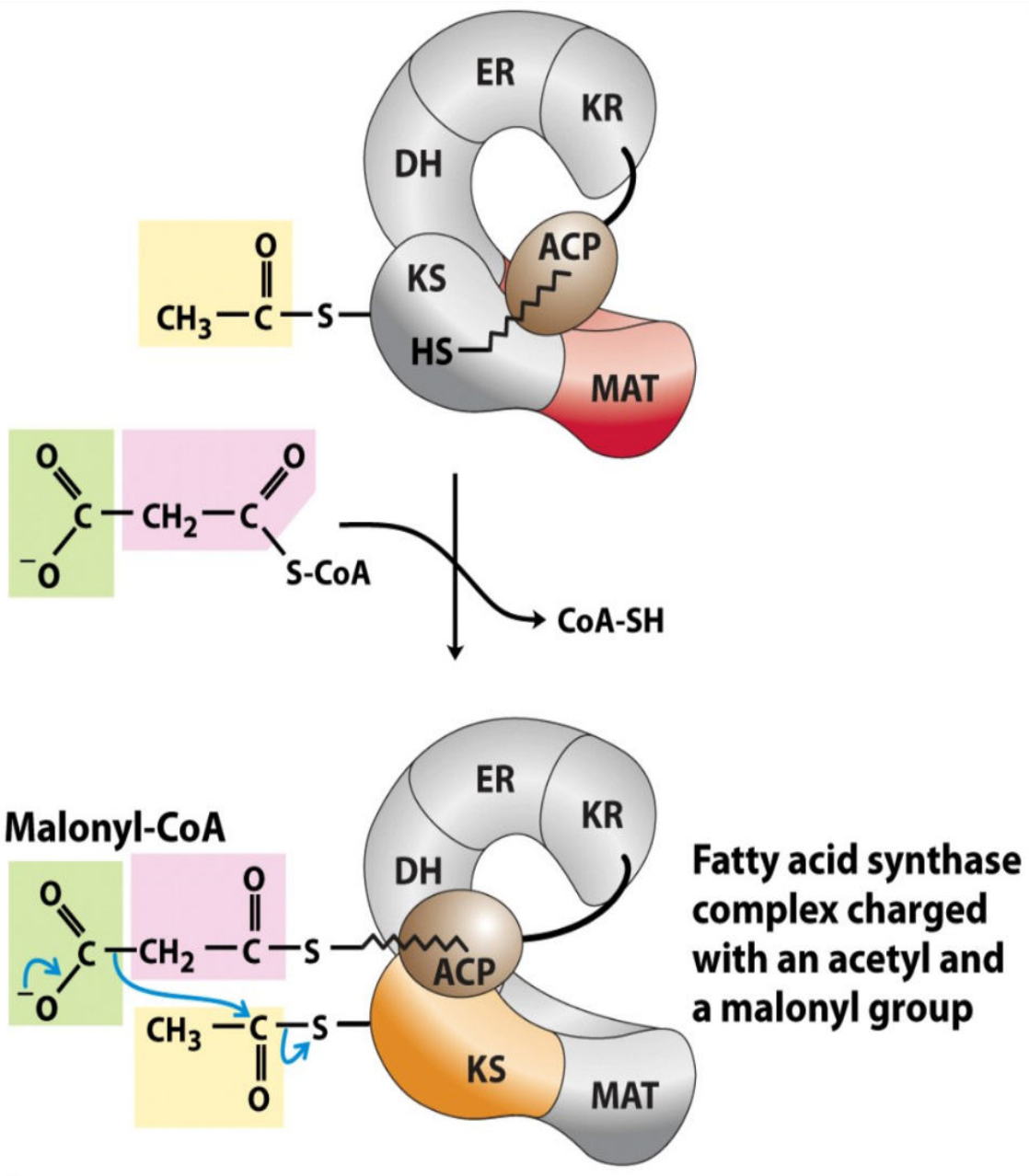
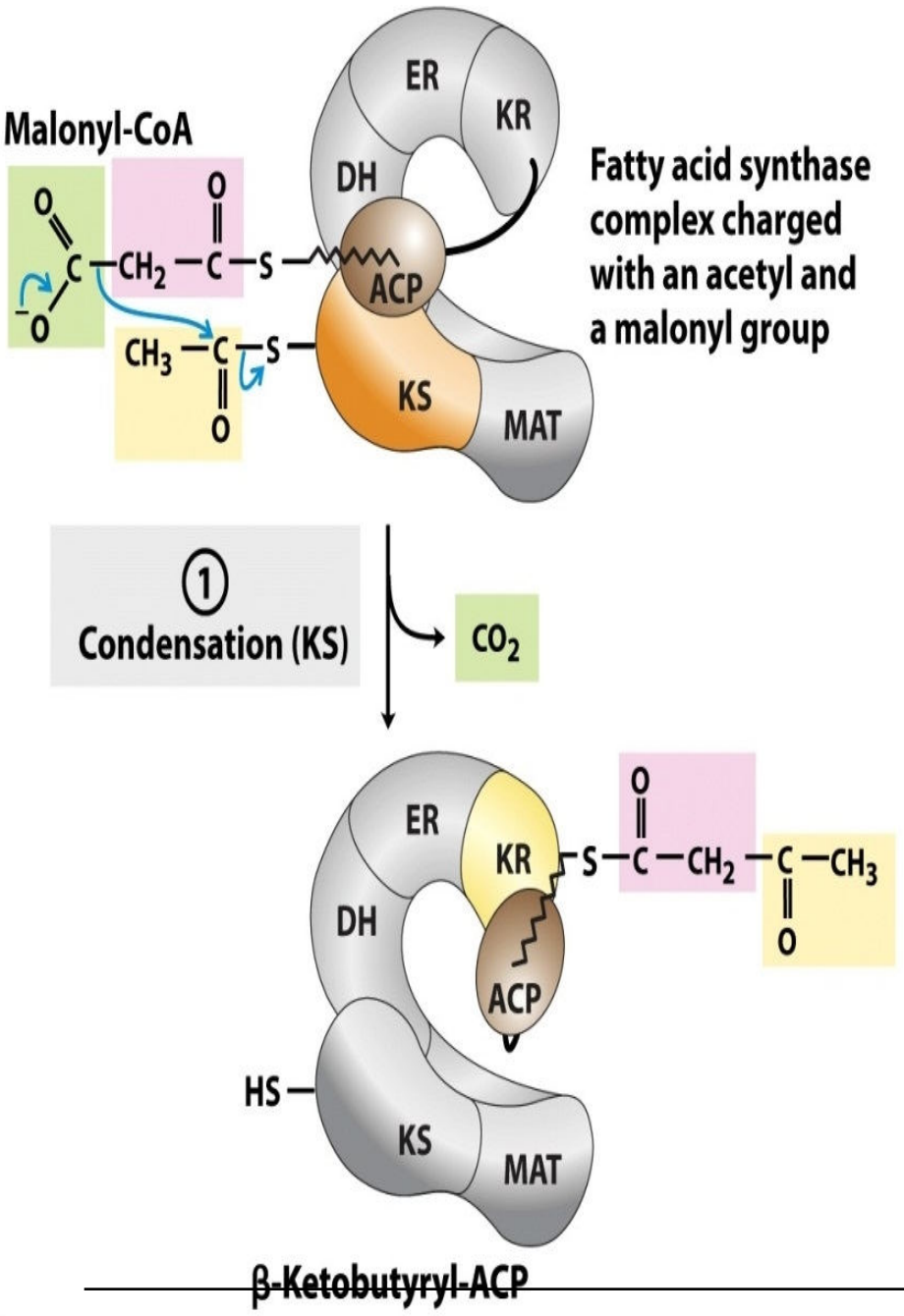


Figure 21-6 part 2
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Step IV
Condensation Reaction
Catalyzed By
Beta Keto Acyl Synthase
To Generate
Keto group
At Beta Carbon Atom



Step 2: Condensation

- Reaction of Malonyl group with Acetyl group to form Acetoacetyl- ACP
- Loss of CO_2 and energy from decarboxylation of Malonyl-CoA.

Figure 21-6 part 3
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- The Malonyl Group is **decarboxylated releasing** CO2 and **high energy**

- **W**hich is **used for bond building and condensation reaction**.

- During condensation reaction there is linking of 2C units of Acetyl and 2C units of decarboxylated Malonyl carbon units
- To form a 4 C **Beta Keto Butyryl ACP/β Keto Acyl ACP**.

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Step V
Reduction Reaction
By
Keto Acyl Reductase
To
Generate Beta Hydroxyl group

Step 3: Reduction of beta Keto group to form beta Hydroxyl group

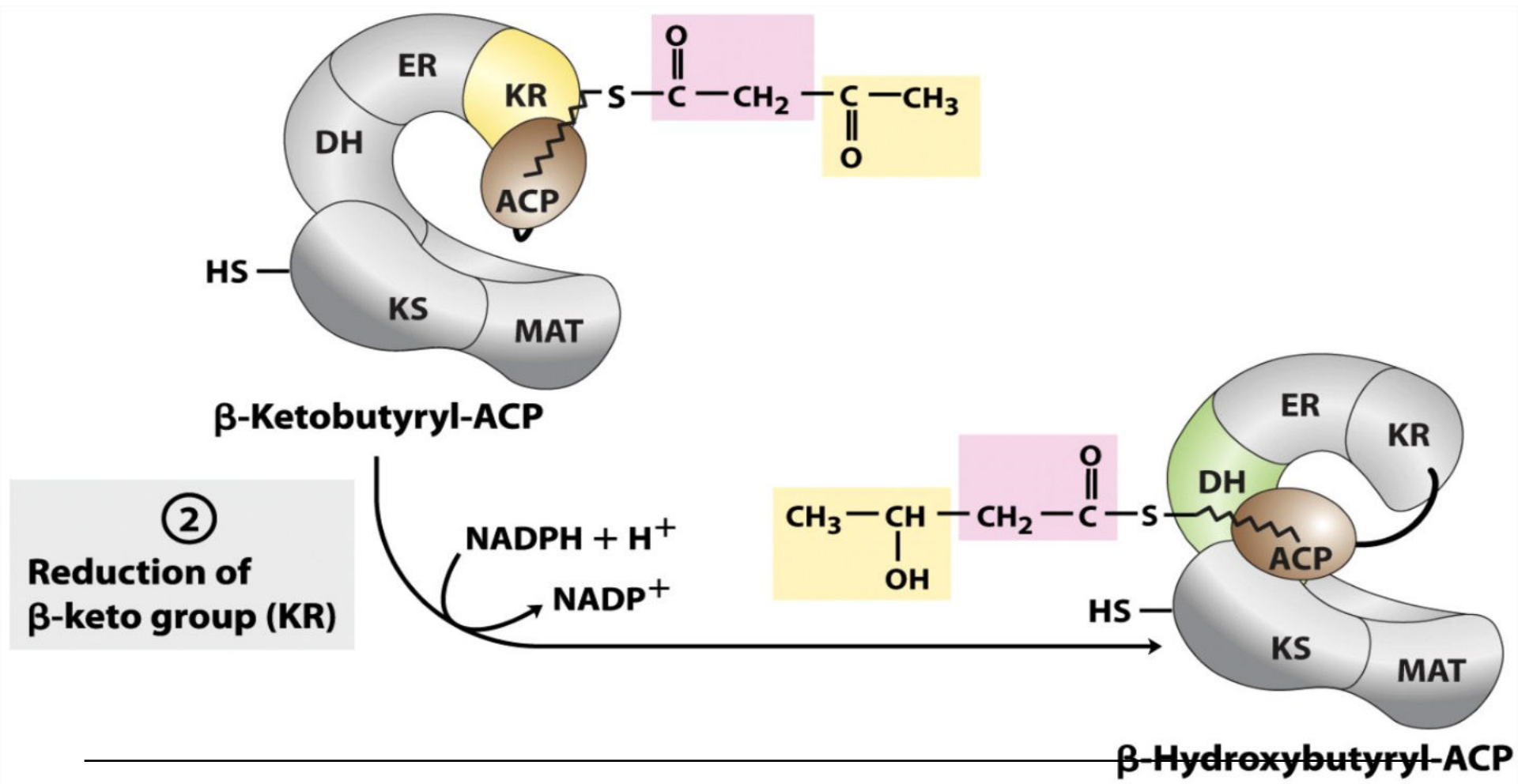


Figure 21-6 part 4
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Reduction Of β Keto Acyl- ACP

- **β Keto Acyl- ACP** is reduced to **β Hydroxy Acyl- ACP**
- In presence of reducing equivalents **NADPH+H+ and Enzyme β Keto Acyl Reductase.**

Step VI
Dehydration Reaction
By
Dehydratase
To
Develop Double Bond

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Step 4: Dehydration Reaction

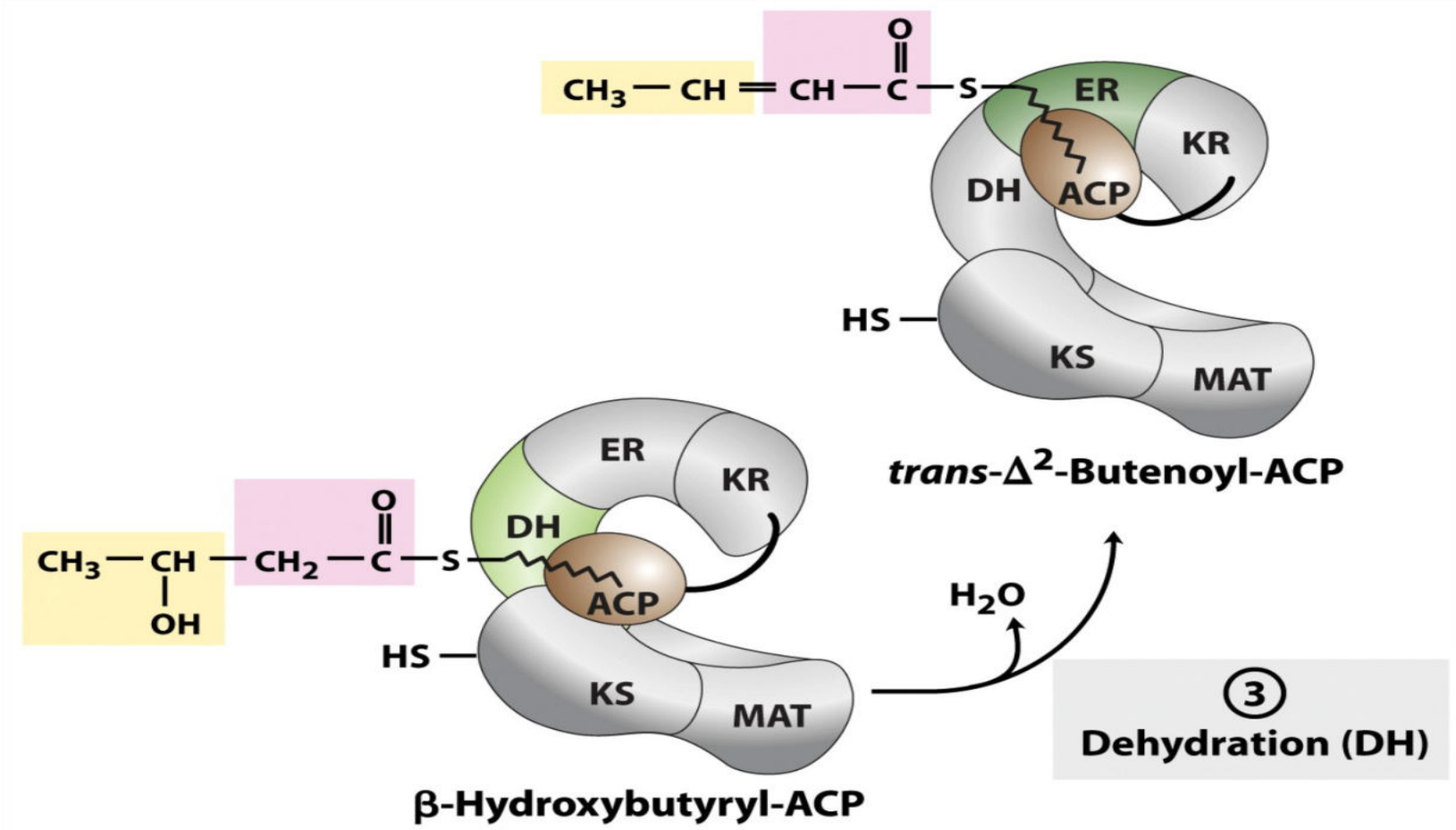


Figure 21-6 part 5
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- **β Hydroxy Acyl- ACP** is dehydrated to **Enoyl CoA/α –β Unsaturated Acyl ACP** by the catalytic action of **Dehydratase.**

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Step VII
Reduction Reaction
By
Enoyl-CoA Reductase
To Generate
Saturated Bond

Step 5: Reduction of double bond to Single bond

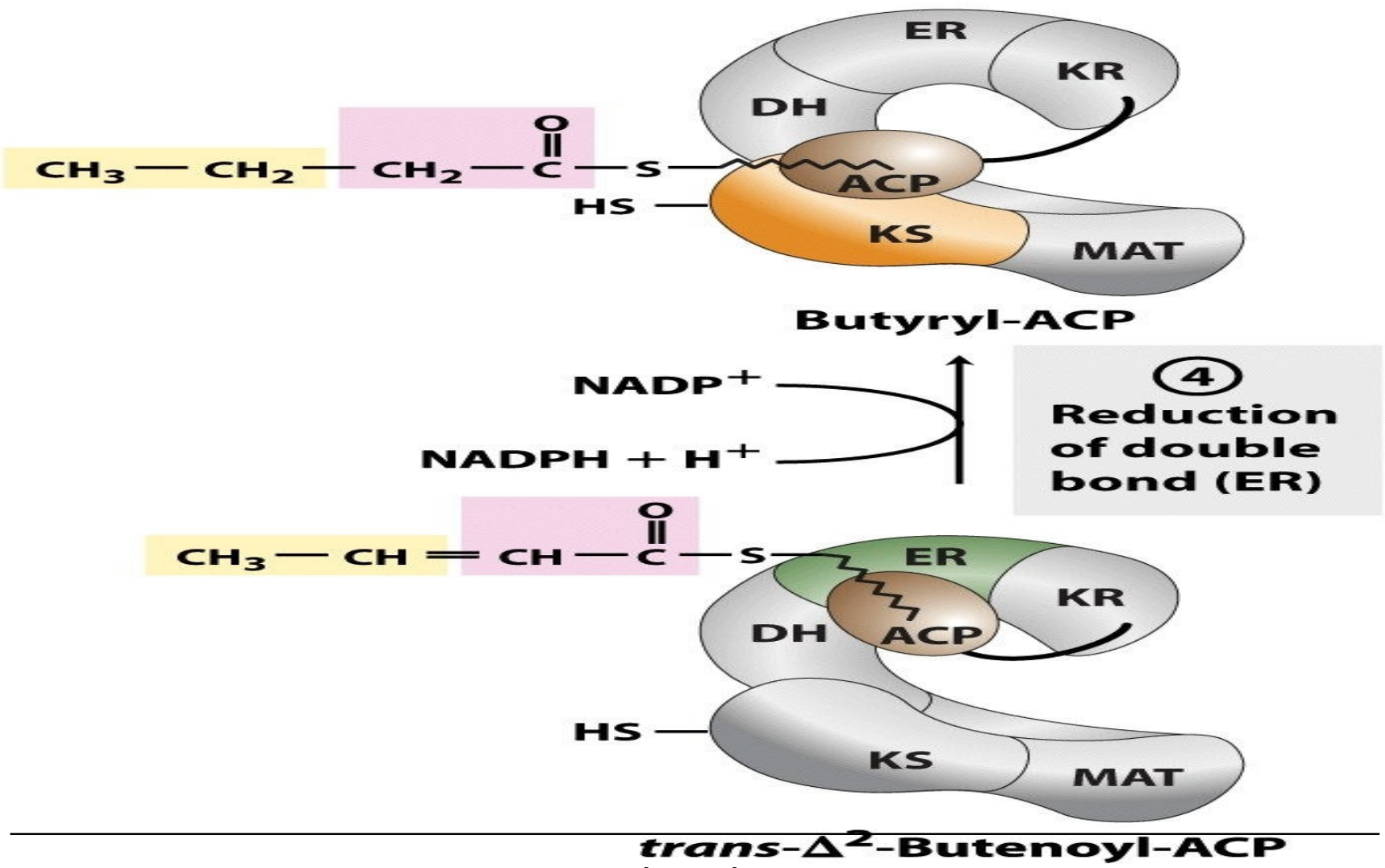
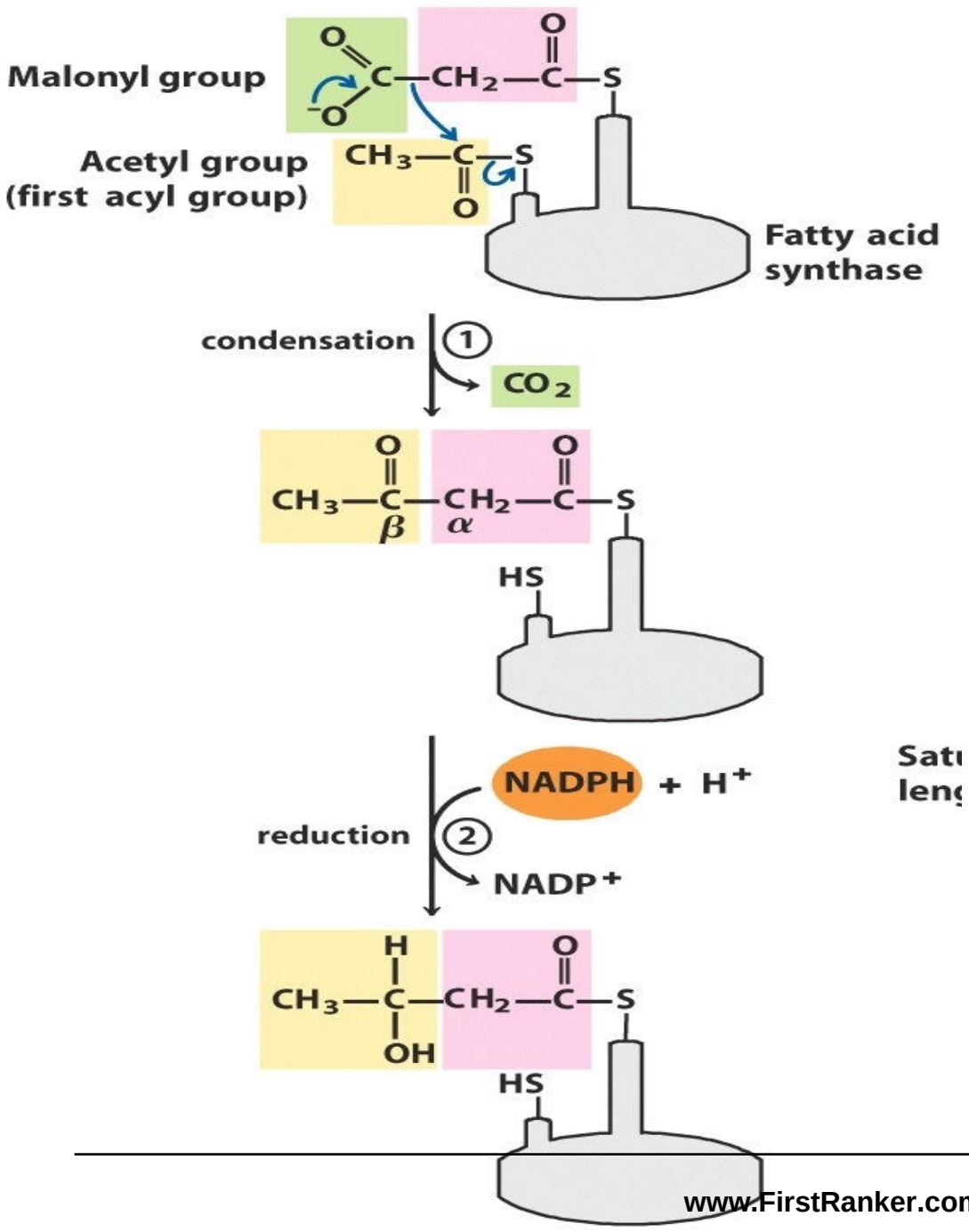


Figure 21-6 part 6
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- **α – β Unsaturated Acyl ACP is reduced to Butyryl –S-ACP**
- **By NADPH+ H+ and enzyme Enoyl Reductase.**



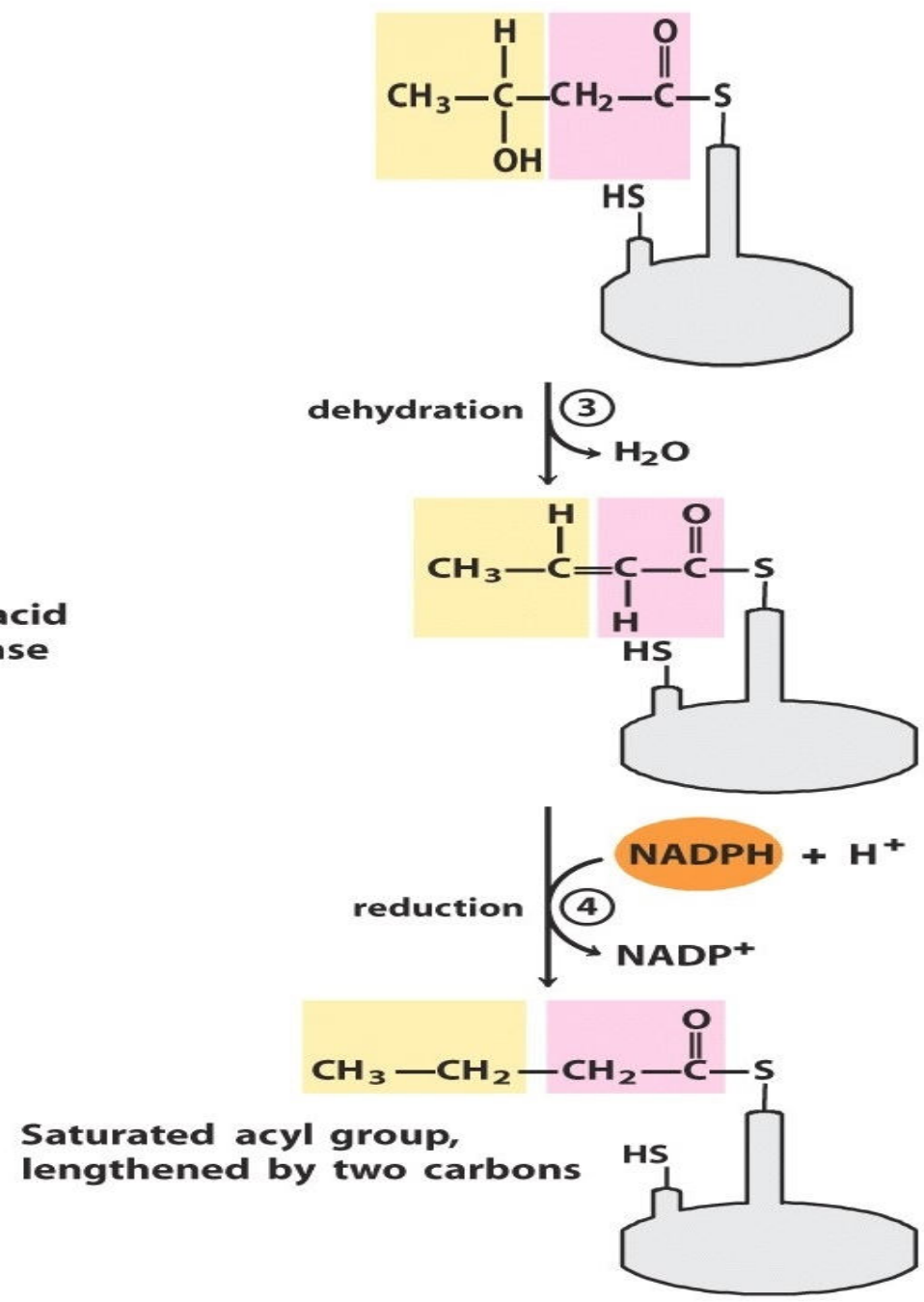
Overview of *Assembly Stage*

4 steps:

- ★ **Condensation**
- ★ **Reduction**

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Overview of Assembly Stage

- ★ Dehydration
- ★ Reduction

Step VIII
Translocation Of Butyryl-S CoA to SH group of Condensing Enzyme Beta Keto Acyl Synthase

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Transfer of Butyryl Chain to SH group of Beta Keto Acyl Synthase

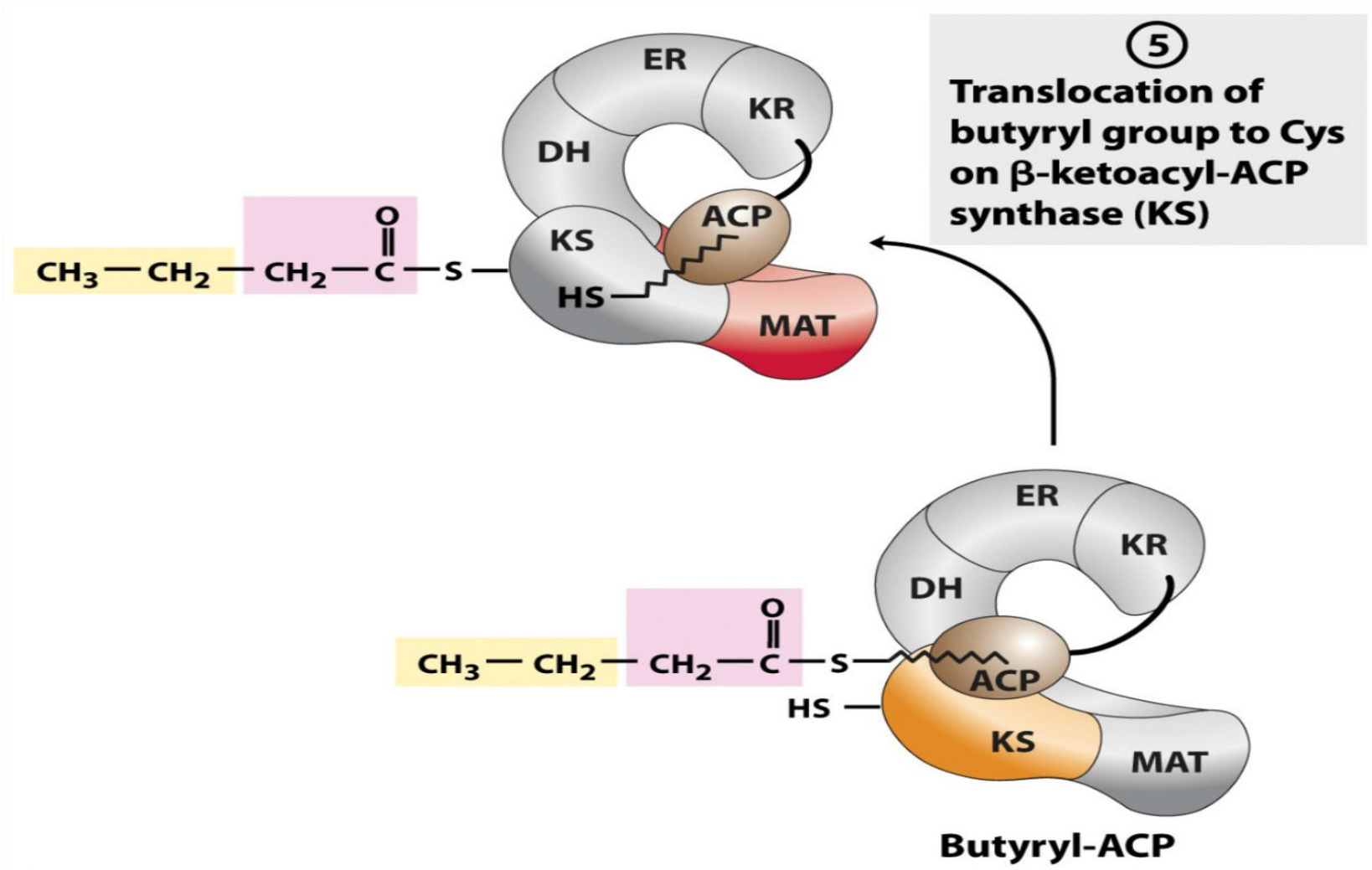


Figure 21-6 part 7

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Elongation and Growing Of Fatty Acid Chain

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To Elongate the Fatty Acid Chain To 16 Carbon Palmitate

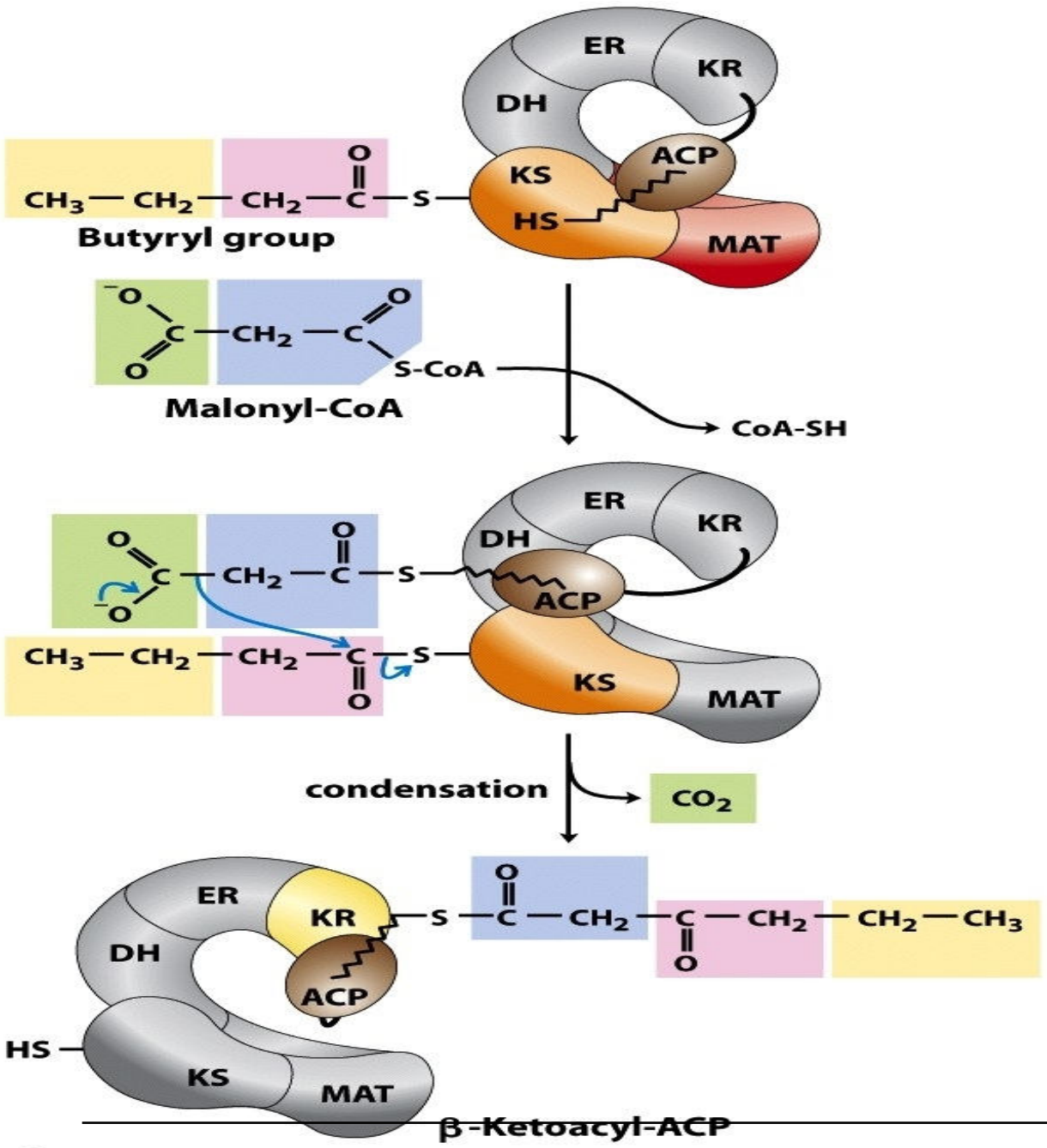
There Should Be Entry

Of

6 More Molecules of Malonyl CoA

By Six Time Repetitions of Steps III-VIII

1 Malonyl-CoA entry each Time



Next cycle begins

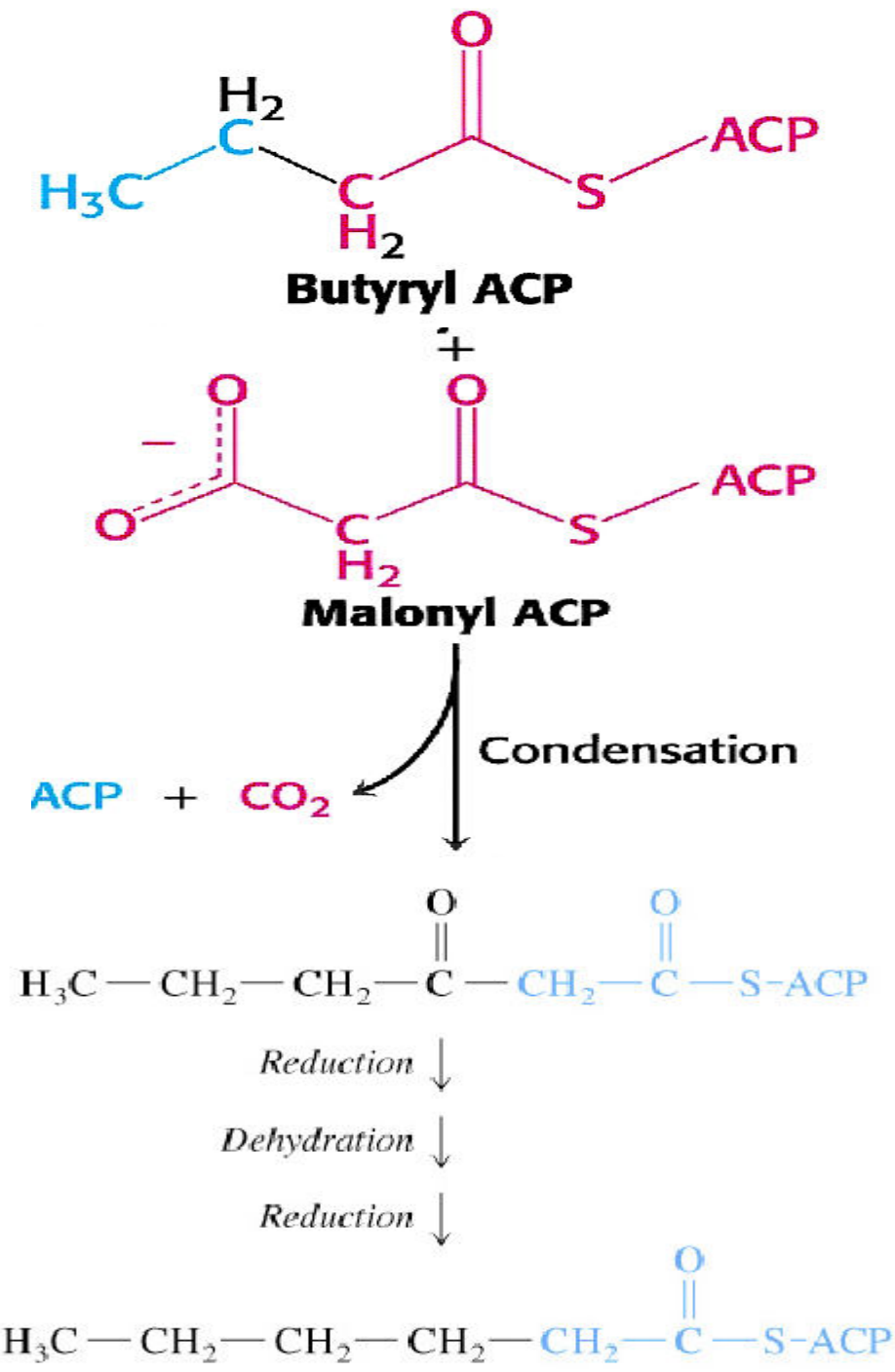
- Another Malonyl group is linked to ACP

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Repetitions Of 6 More Cycles With 5 Steps



- Following **transfer** of the growing fatty acid from Phosphopantetheine to the Condensing Enzyme's Cysteine sulfhydryl.
- the **cycle begins again**, with another Malonyl-CoA.

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- Elongation of Fatty Acyl chain occurs by addition of Malonyl-CoA after every cycle.
- Every time a new Malonyl – CoA enters and taken up by SH-ACP.

- **There are total 7 cycles** to utilize
- **1 Acetyl-CoA** and **7 molecules of Malonyl-CoA** and
- Elongate the Fatty Acid Chain to 16 Carbon Palmitate.

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Remember

- At **Each turn one Molecule of Malonyl CoA enters**
- **Accepted by ACP-SH** to form **Malonyl – SACP.**
- Then the repetitions of **Condensation ,Reduction , Dehydration and Reduction Reactions** takes place.

- **Decarboxylation of Malonyl-CoA and**
- **Reducing power of $NADPH+H^+$ drive fatty chain growth.**

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- **Butyryl group** (C4) is **shifted to SH of Cysteine of β Keto Acyl Synthase.**
- **SH of ACP** is free for accepting the second molecule of Malonyl CoA to form Malonyl-S-ACP.

- The steps of Condensation ,Reduction, Dehydration and Reduction repeats.
- The **aim of these steps is to convert a C=O group to CH2 group at β carbon of growing Acyl chain.**

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- After the completion of total 7 cycles
- There is Palmitate synthesized and is carried by **S-ACP of FAS complex**(Palmitoyl-S-ACP)

Cleavage Of Completely Biosynthesized Palmitate From ACP of FAS Complex
By Catalytic Activity Of Thioesterase
To Release
Free Palmitate and FAS Complex

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- The Cleavage enzyme **Thioesterase cleaves the Thioester linkage** and
- Releases **free Palmitic acid carried by S-ACP of FAS complex.**

- Since the **FAS complex is a dimeric unit** having **two functional units.**

- During its operation at a time **two molecules of Palmitic acid are biosynthesized and released**.

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Fatty Acyl Synthase

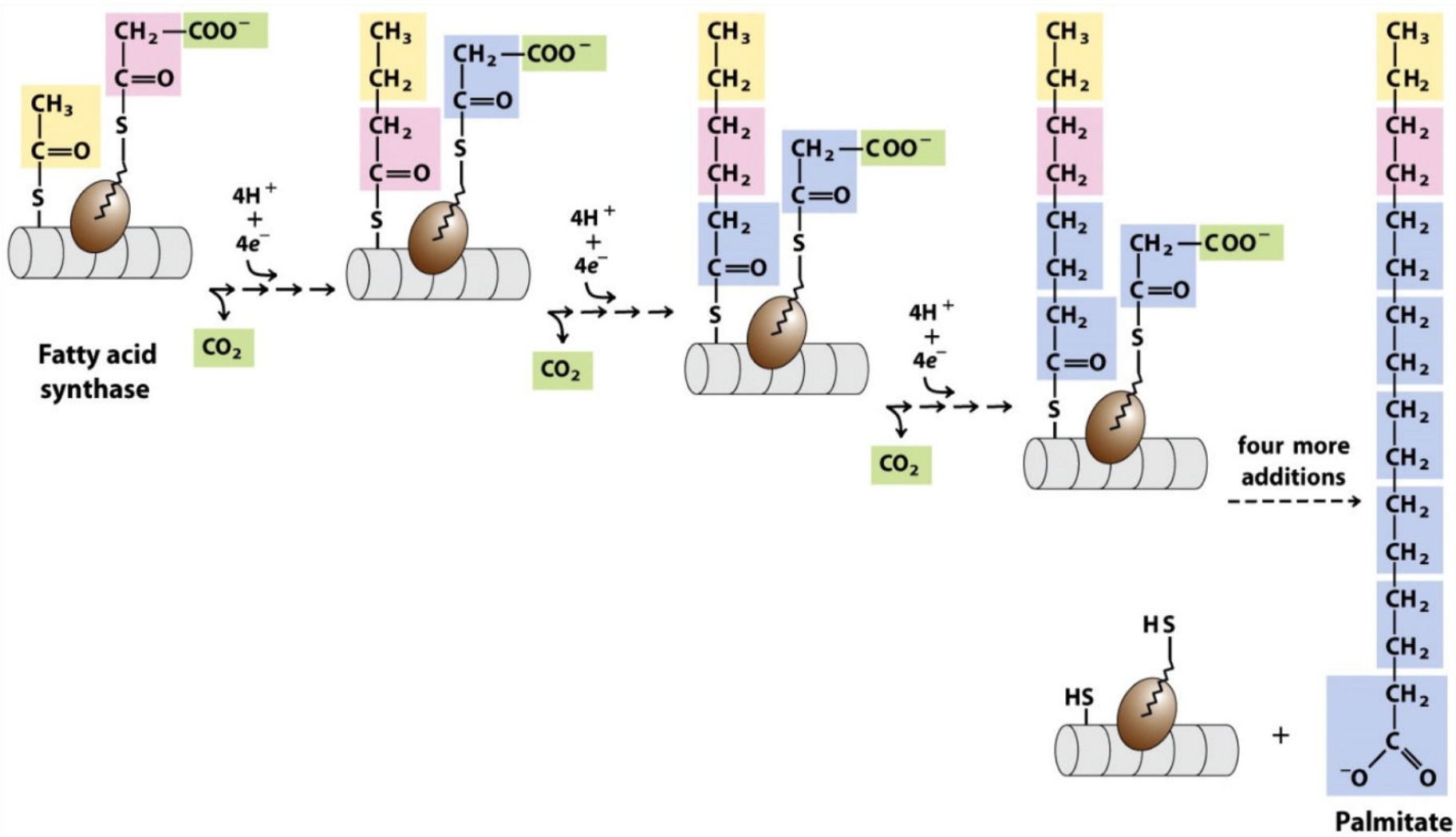
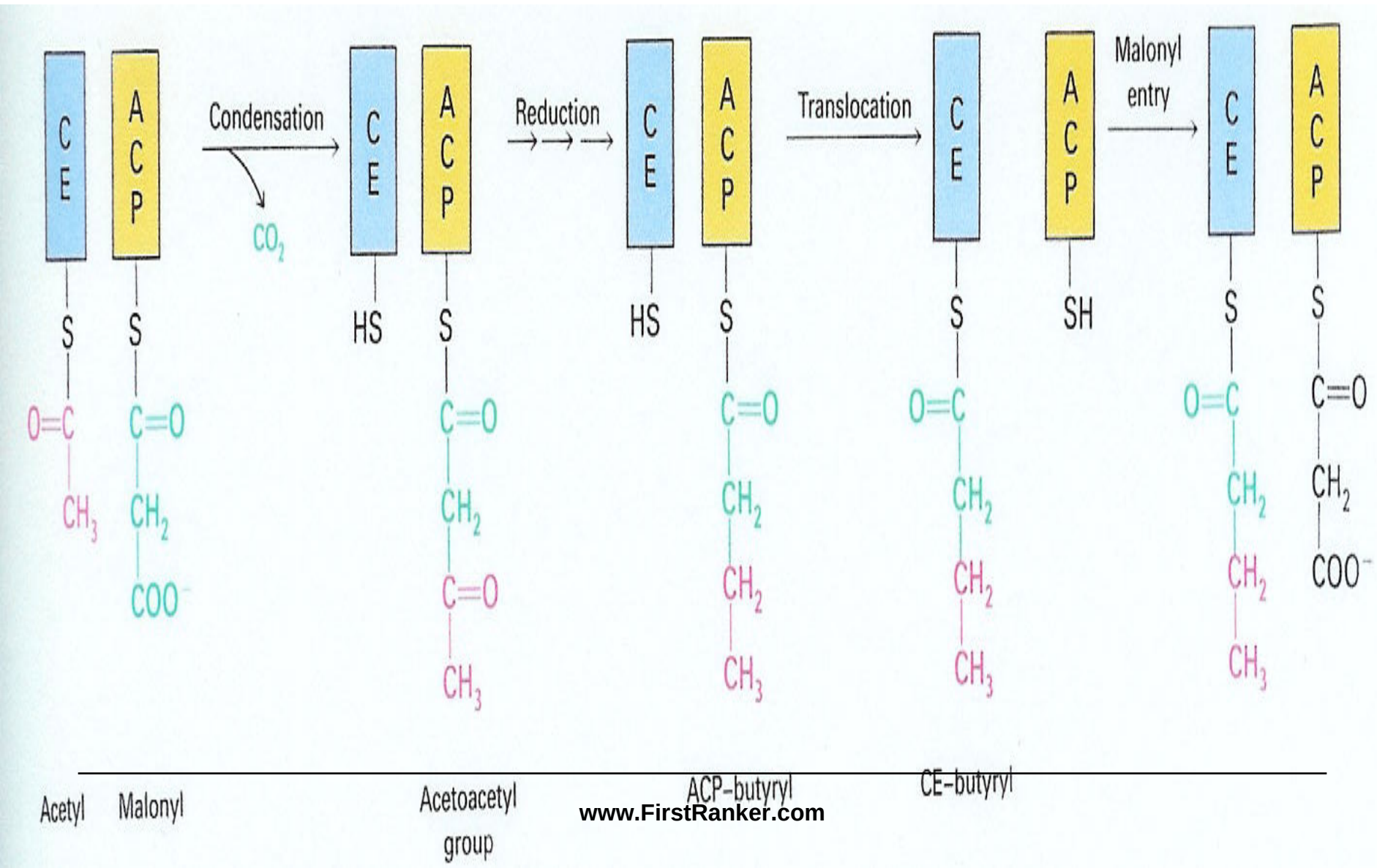


Figure 21-4

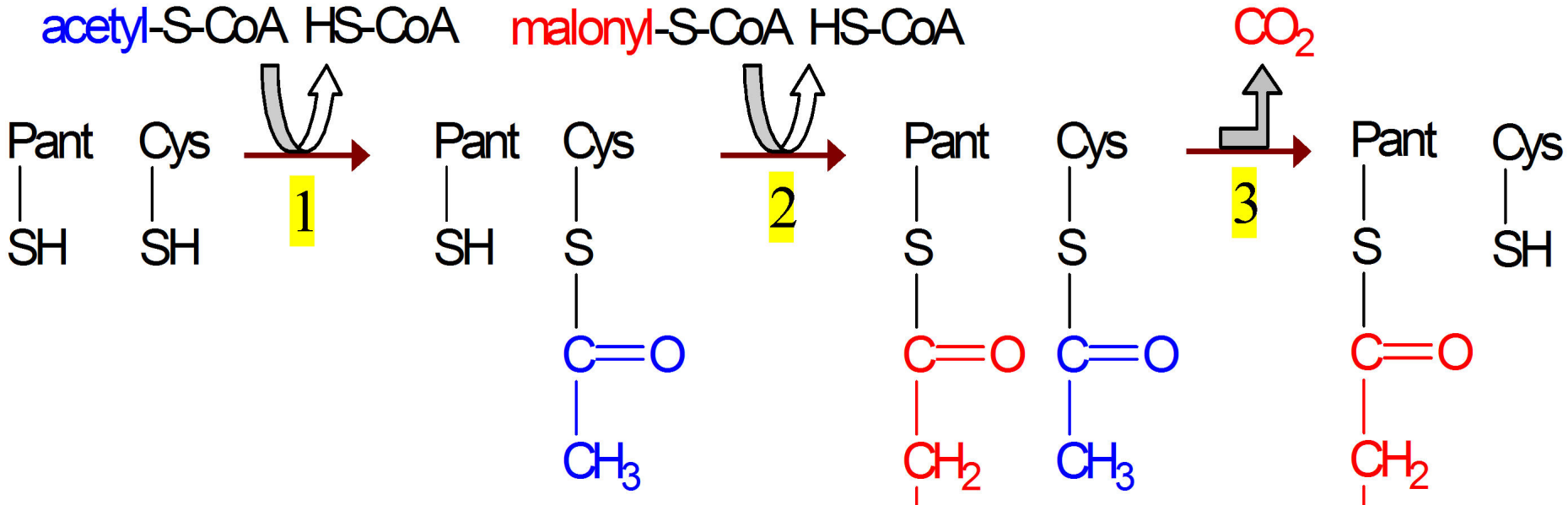
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The Steps in the De Novo biosynthesis of fatty acid



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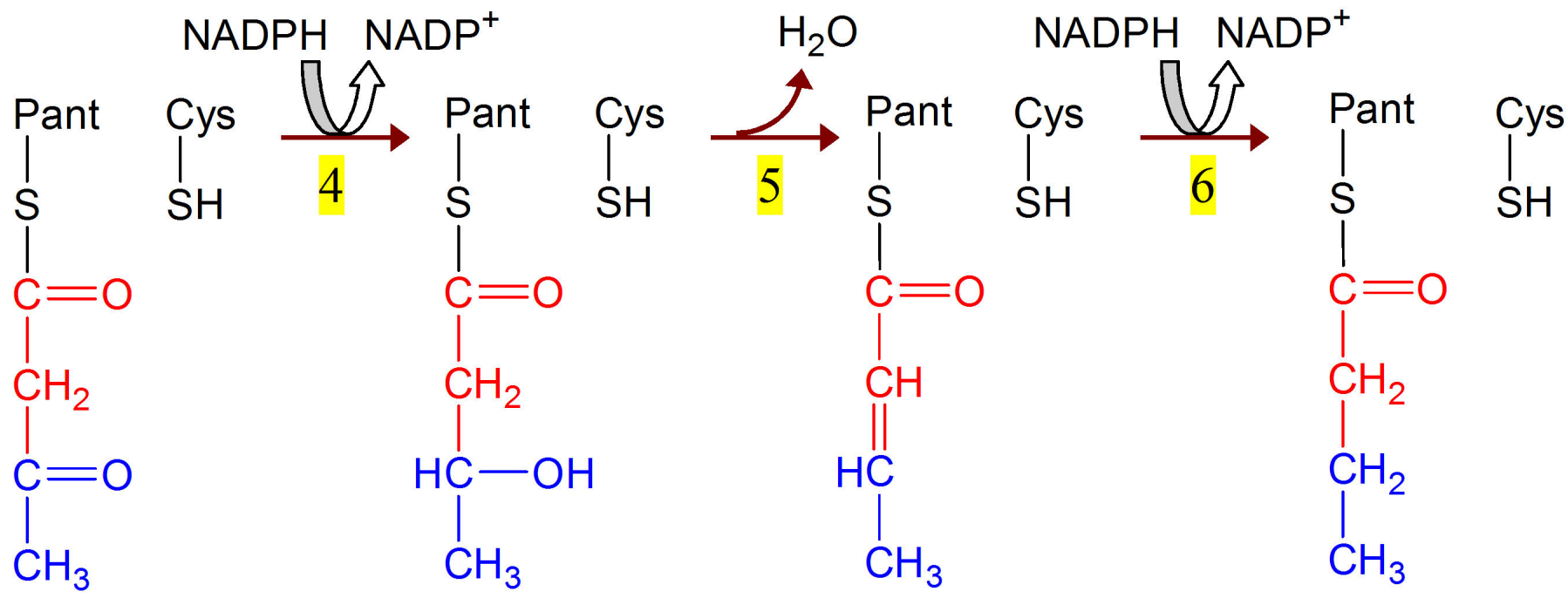
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1 Malonyl/acetyl-CoA-ACP Transacylase

2 Malonyl/acetyl-CoA-ACP Transacylase

3 Condensing Enzyme (β-Ketoacyl Synthase)



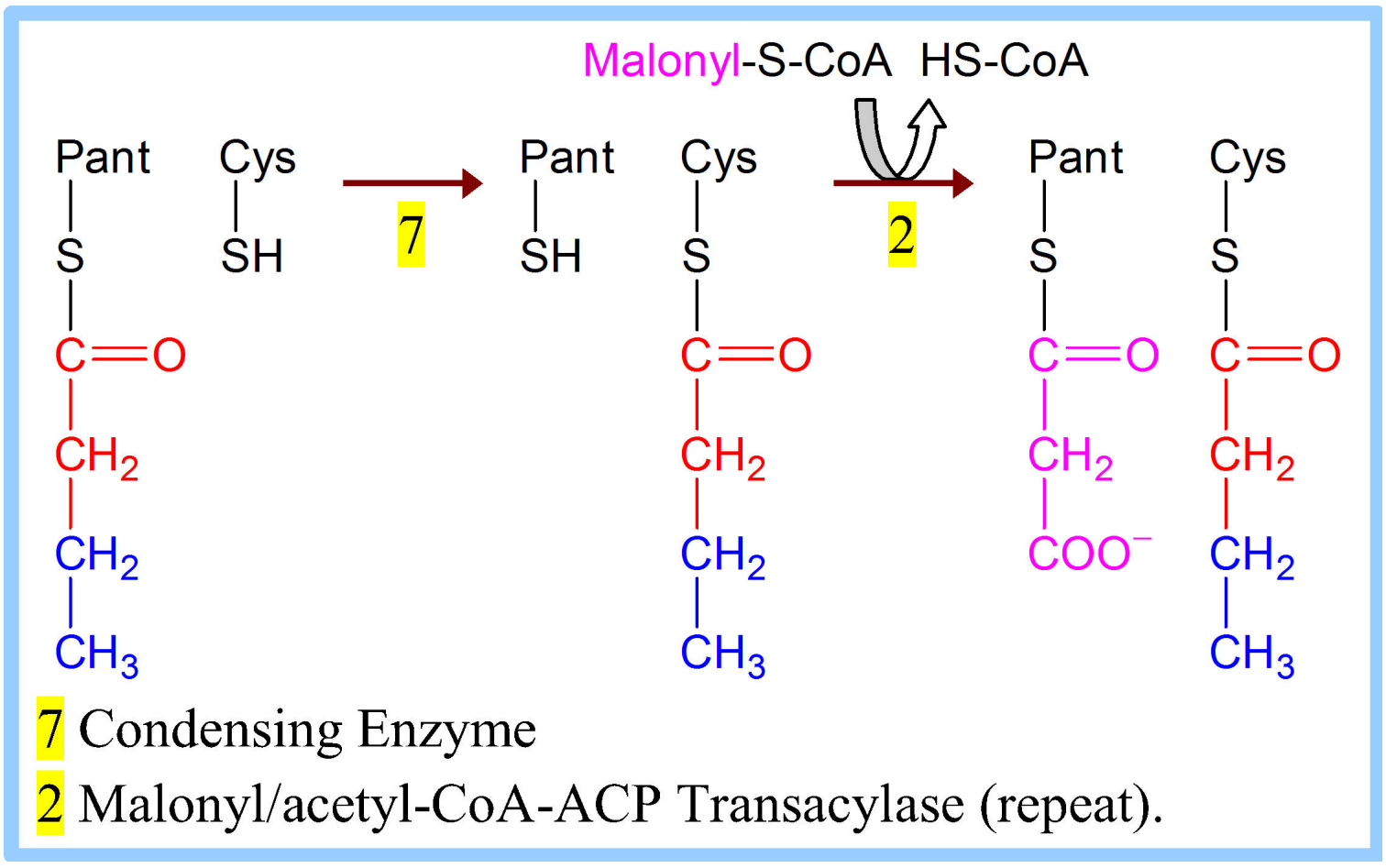
4 β-Ketoacyl-ACP Reductase

5 β-Hydroxyacyl-ACP Dehydratase

6 Enoyl-ACP Reductase

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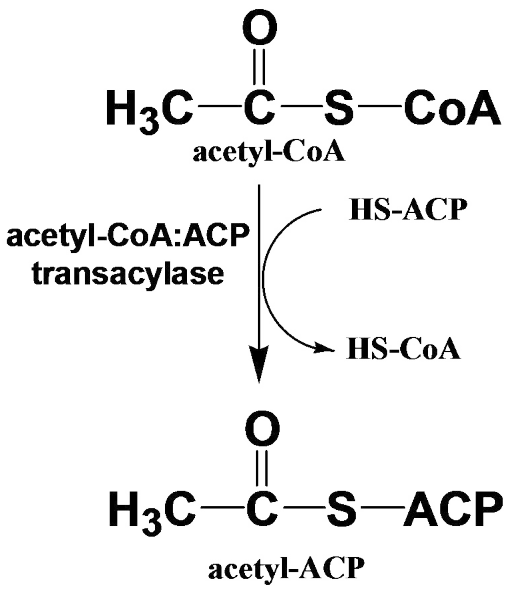
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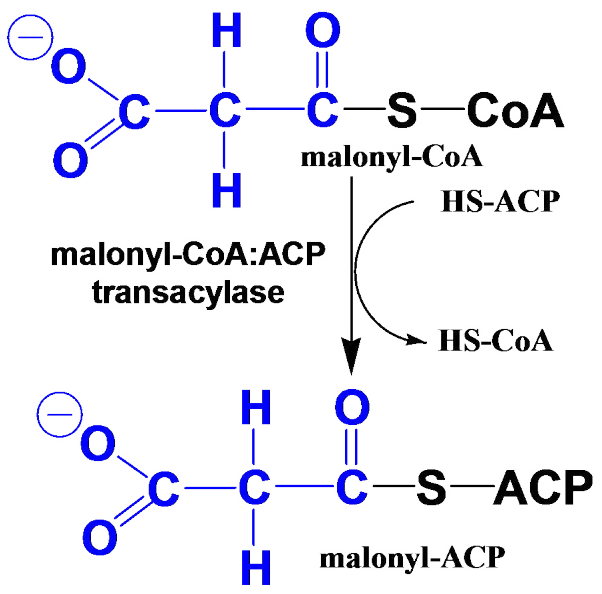


7 Condensing Enzyme

2 Malonyl/acetyl-CoA-ACP Transacylase (repeat).

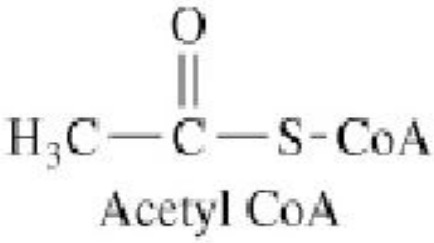
Step 1: Loading Reactions



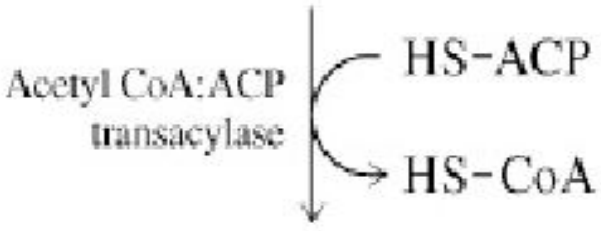


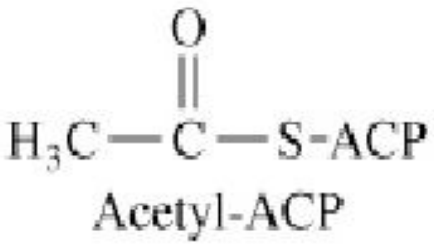
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Acetyl CoA





Acetyl-ACP



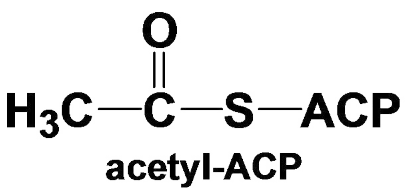
Malonyl CoA





Malonyl-ACP

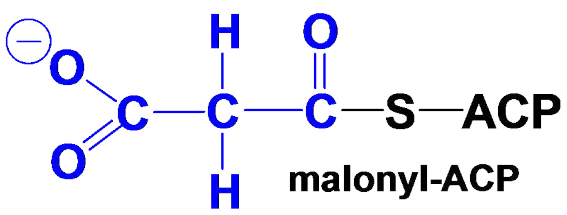
Step 2: Condensation Rxn



acetyl-ACP

HS-Ketoacyl-ACP Synthase

HS-ACP



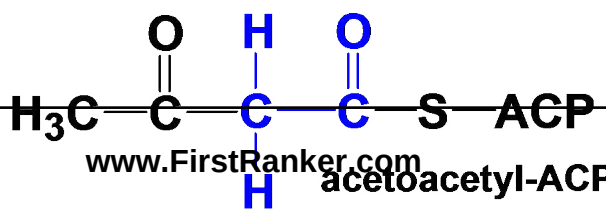
malonyl-ACP

+



keto-ACP synthase

CO_2

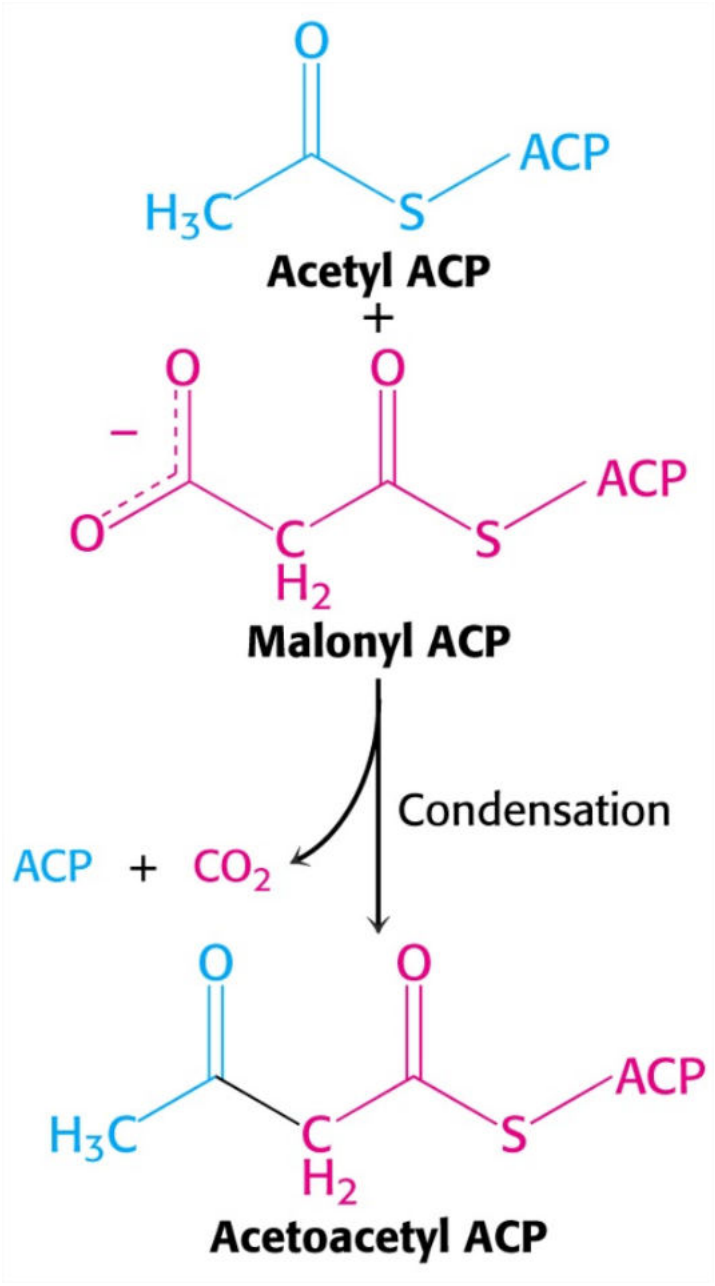


acetoacetyl-ACP

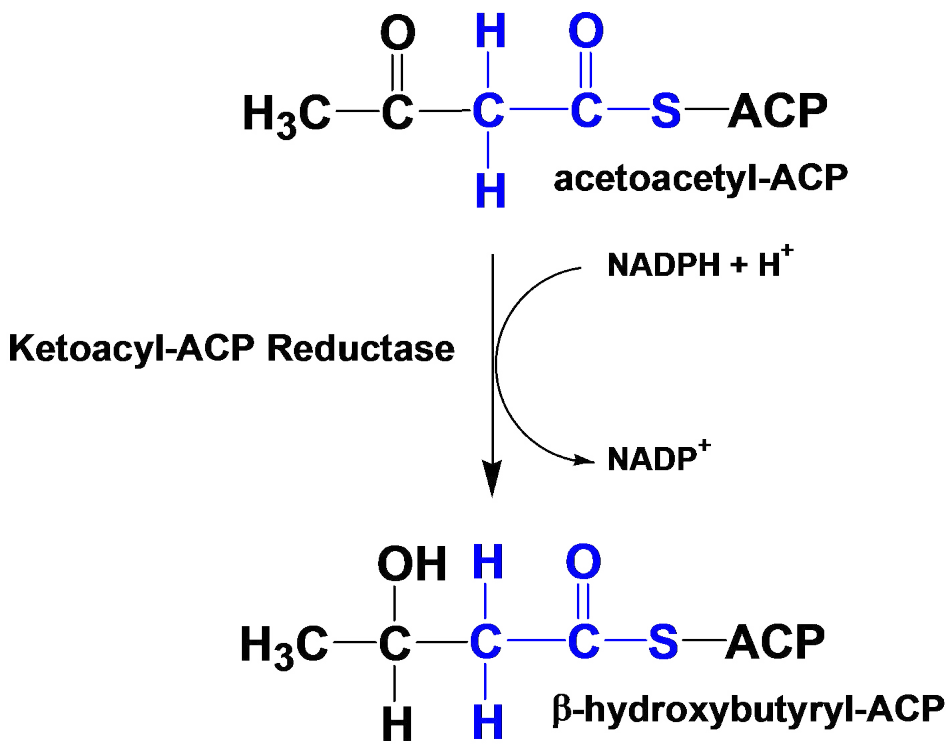
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Condensation reaction



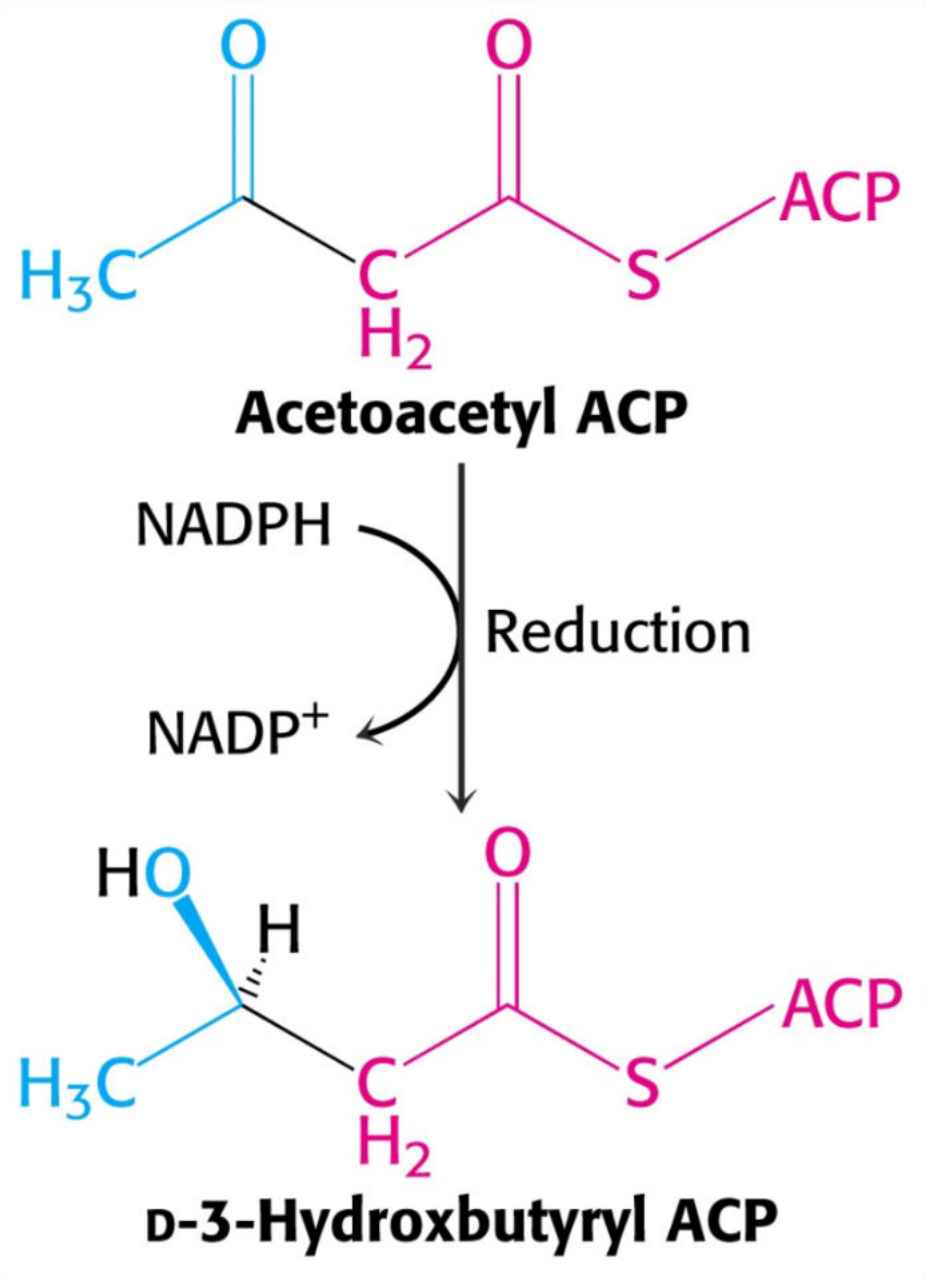
Step 3: Reduction



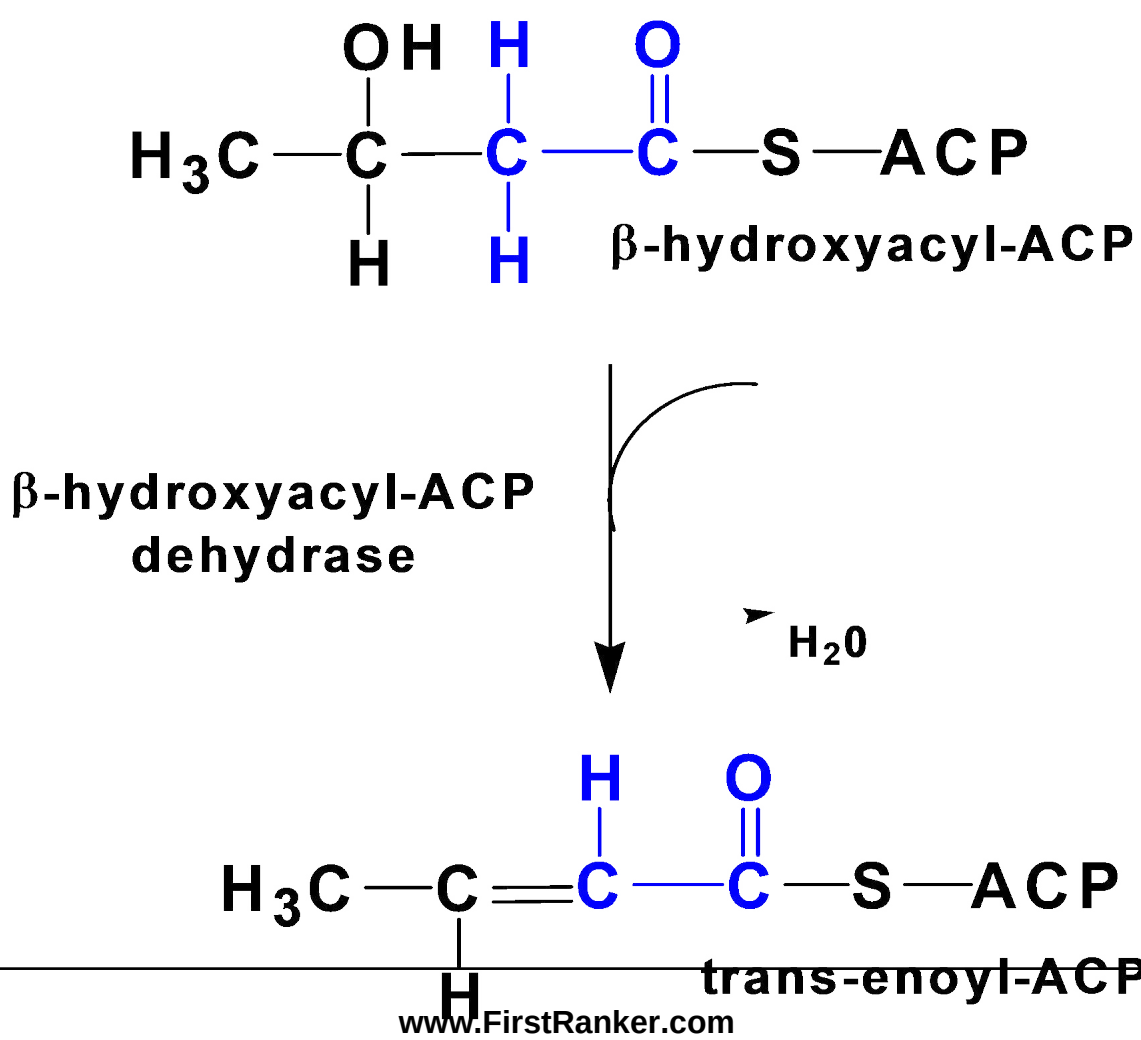
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Reduction Reaction



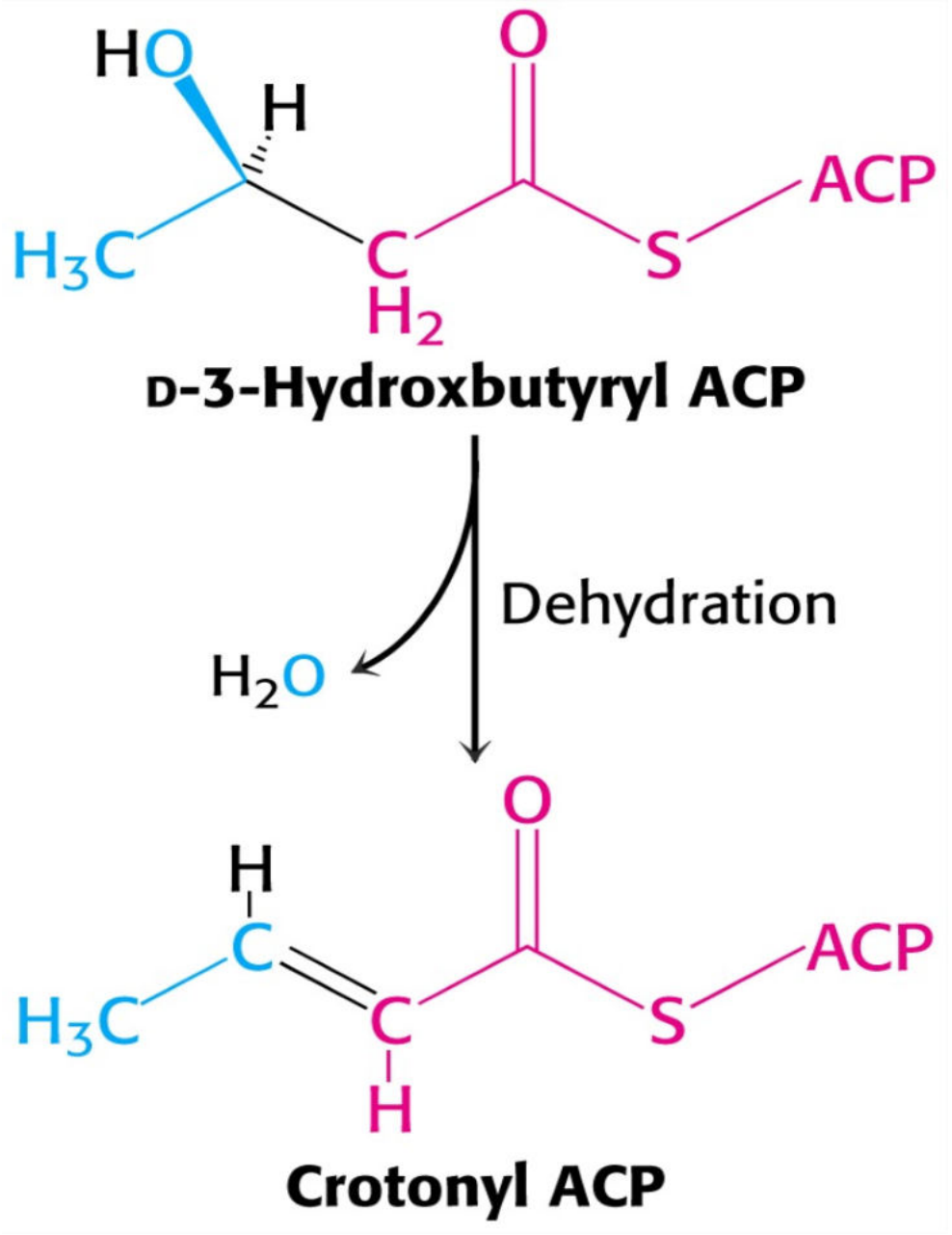
Step 4: Dehydration



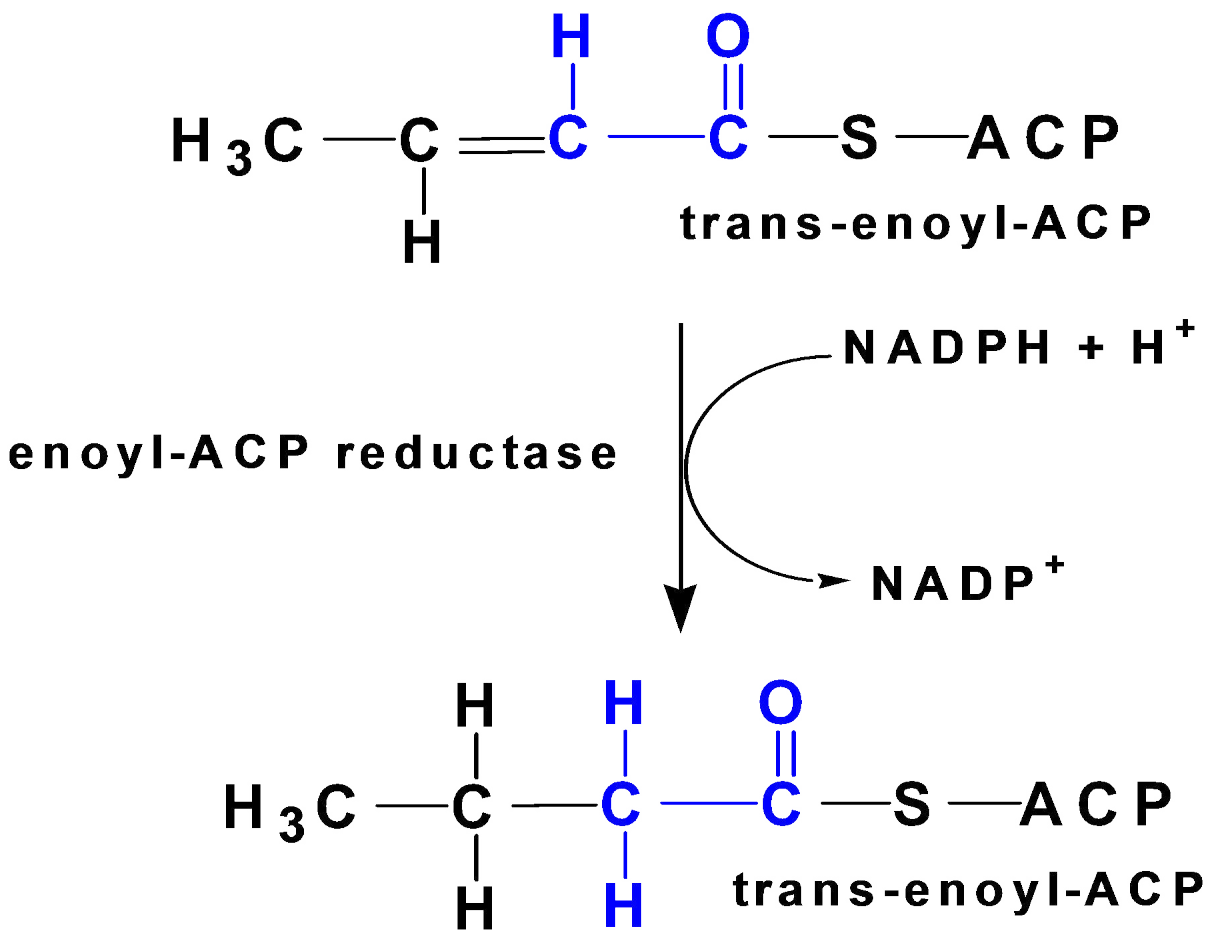
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Dehydration



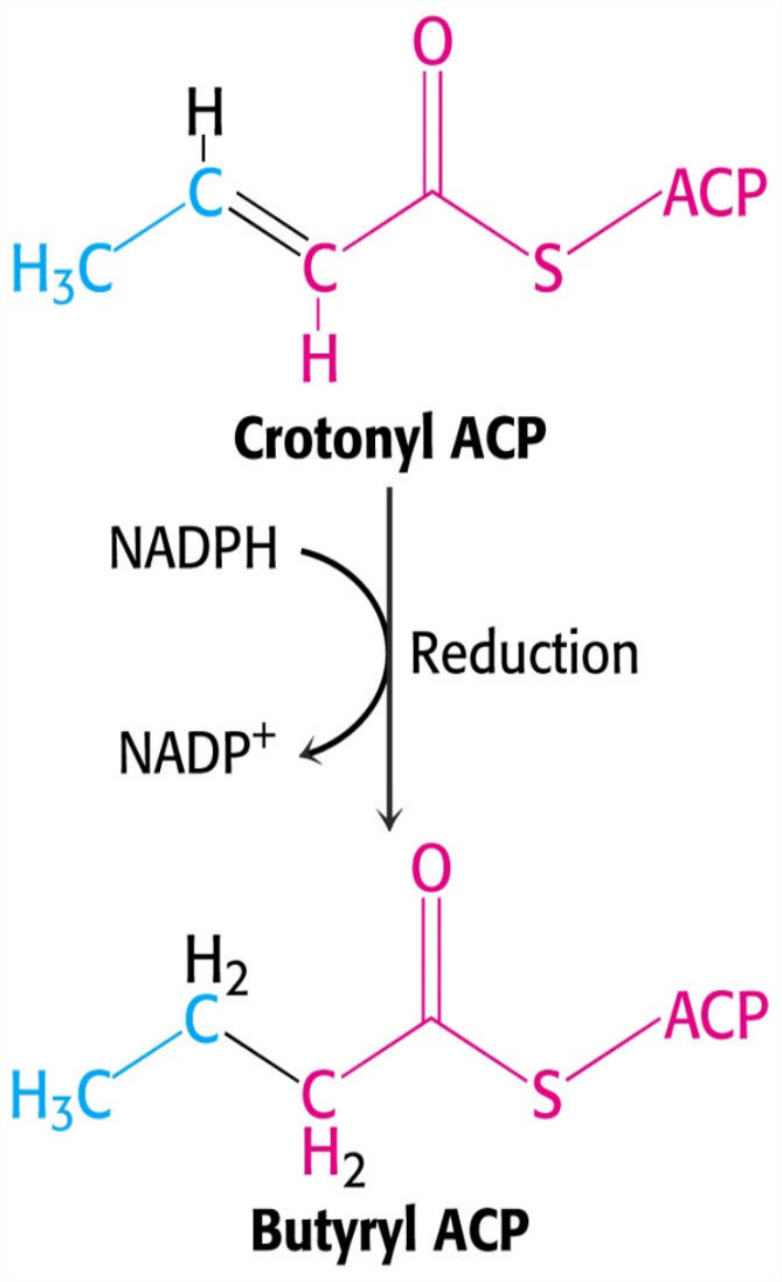
Step 5: Reduction



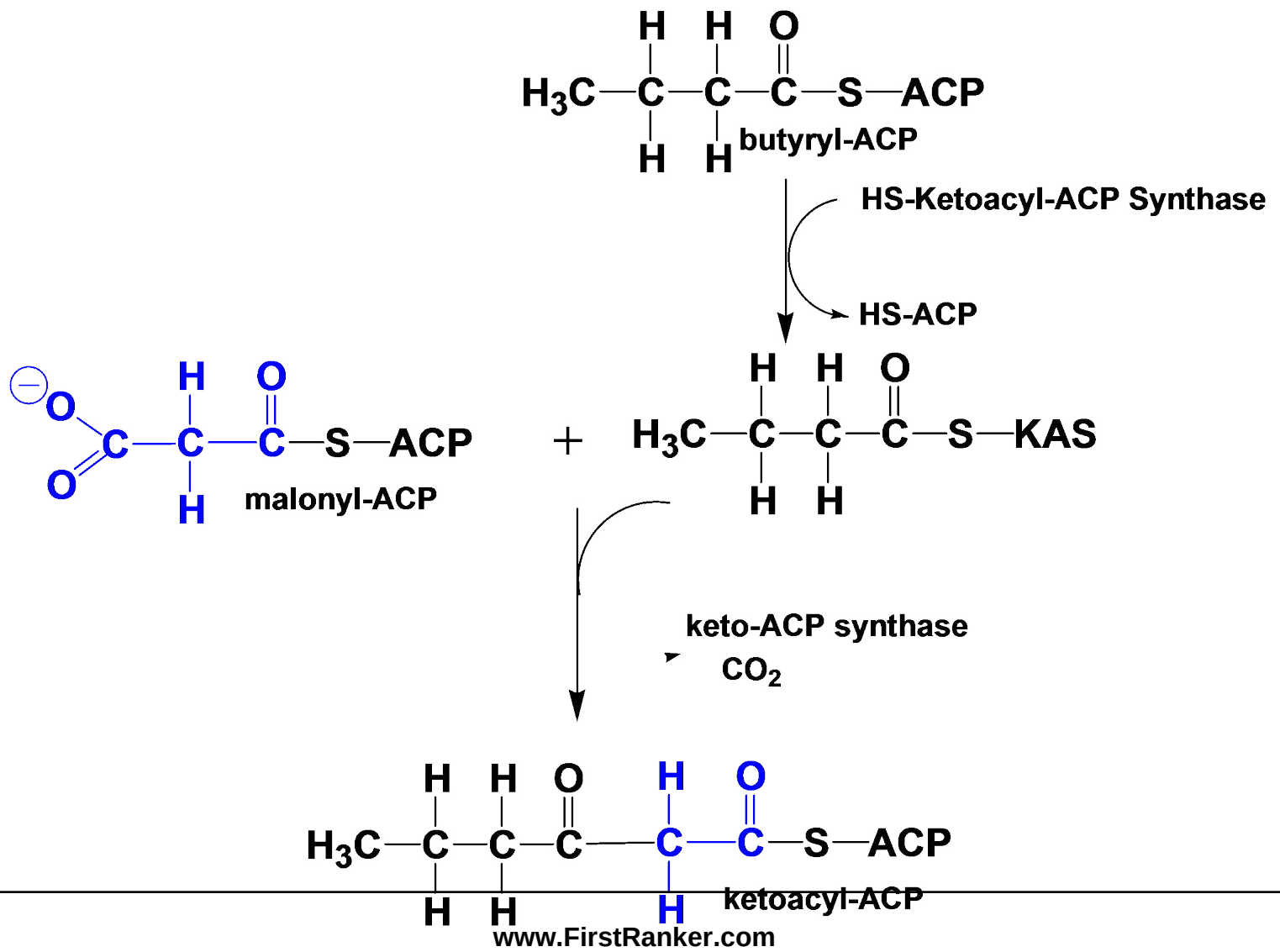
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Reduction



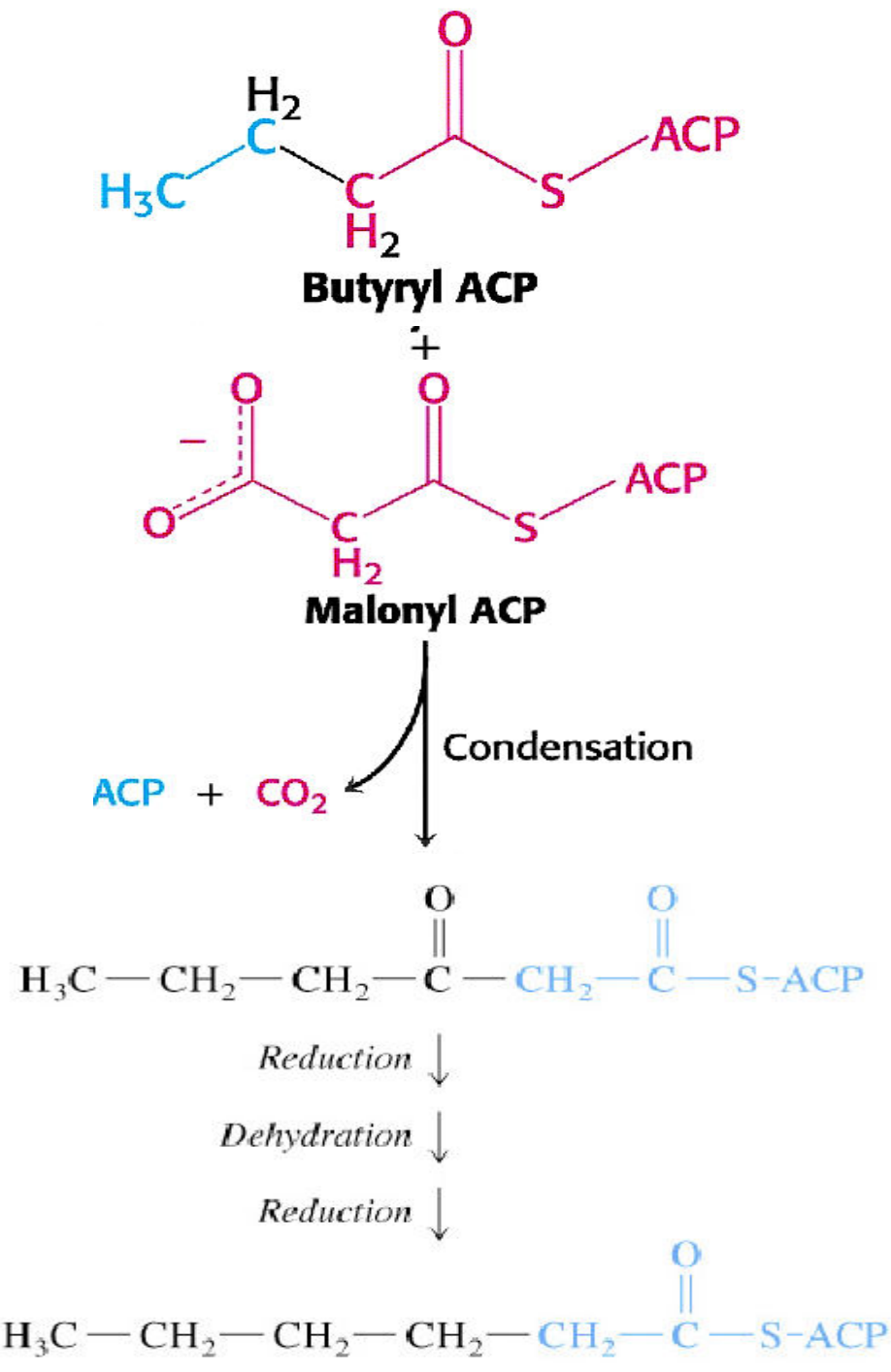
Step 6: Next condensation



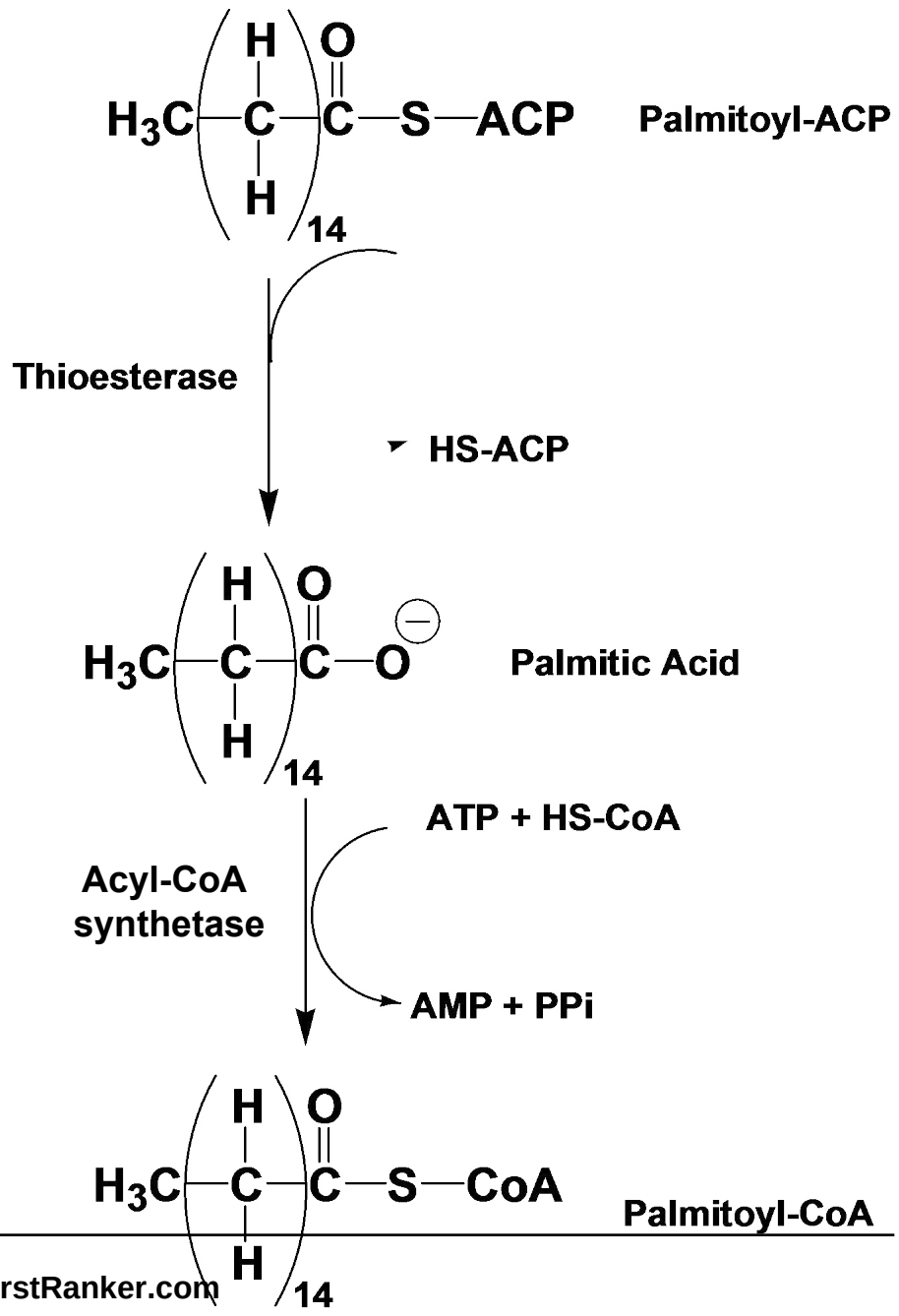
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Repetitions Of 7 Cycles



Termination of Fatty Acid Synthesis

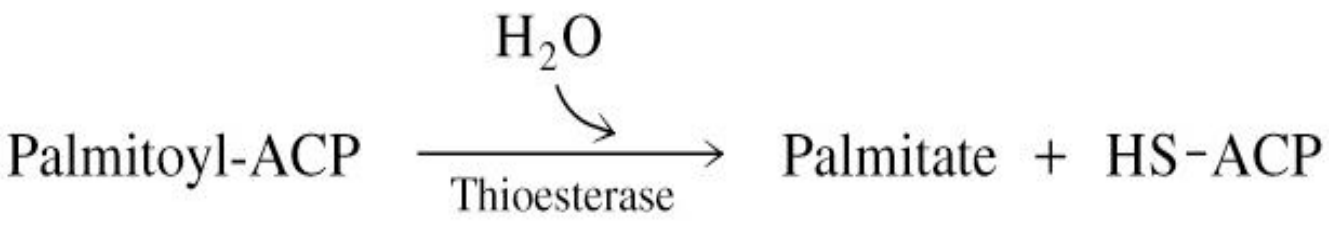


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Final reaction of FA synthesis is Cleavage

- Palmitoyl-ACP is hydrolyzed by a ***Thioesterase***



Overall Reaction of Palmitate Synthesis from Acetyl CoA and Malonyl CoA

Acetyl CoA + 7 Malonyl CoA + 14 NADPH + 14 H^+

↓

Palmitate + 7 CO_2 + 14 $NADP^+$ + 8 HS-CoA + 6 H_2O

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Principal reactions in fatty acid synthesis in bacteria

Step	Reaction	Enzyme
1	$Acetyl\ CoA + HCO_3^- + ATP \rightarrow malonyl\ CoA + ADP + P_i + H^+$	Acetyl CoA carboxylase
2	$Acetyl\ CoA + ACP \rightleftharpoons acetyl\ ACP + CoA$	Acetyl transacylase
3	$Malonyl\ CoA + ACP \rightleftharpoons malonyl\ ACP + CoA$	Malonyl transacylase
4	$Acetyl\ ACP + malonyl\ ACP \rightarrow acetoacetyl\ ACP + ACP + CO_2$	Acyl-malonyl ACP condensing enzyme
5	$Acetoacetyl\ ACP + NADPH + H^+ \rightleftharpoons$ D-3-hydroxybutyryl ACP + $NADP^+$	β-Ketoacyl ACP reductase
6	D-3-Hydroxybutyryl ACP $\rightleftharpoons$ crotonyl ACP + H_2O	3-Hydroxyacyl ACP dehydratase
7	$Crotonyl\ ACP + NADPH + H^+ \rightarrow butyryl\ ACP + NADP^+$	Enoyl ACP reductase

Summary based on Malonate as an input:

Acetyl-CoA + 7 Malonyl-CoA + 14 NADPH → Palmitate + 7 CO_2 + 14 $NADP^+$ + 8 CoA

Fatty acid synthesis occurs in the **cytosol**. Acetyl-CoA generated in mitochondria is transported to the cytosol via a shuttle mechanism involving **Citrate**.

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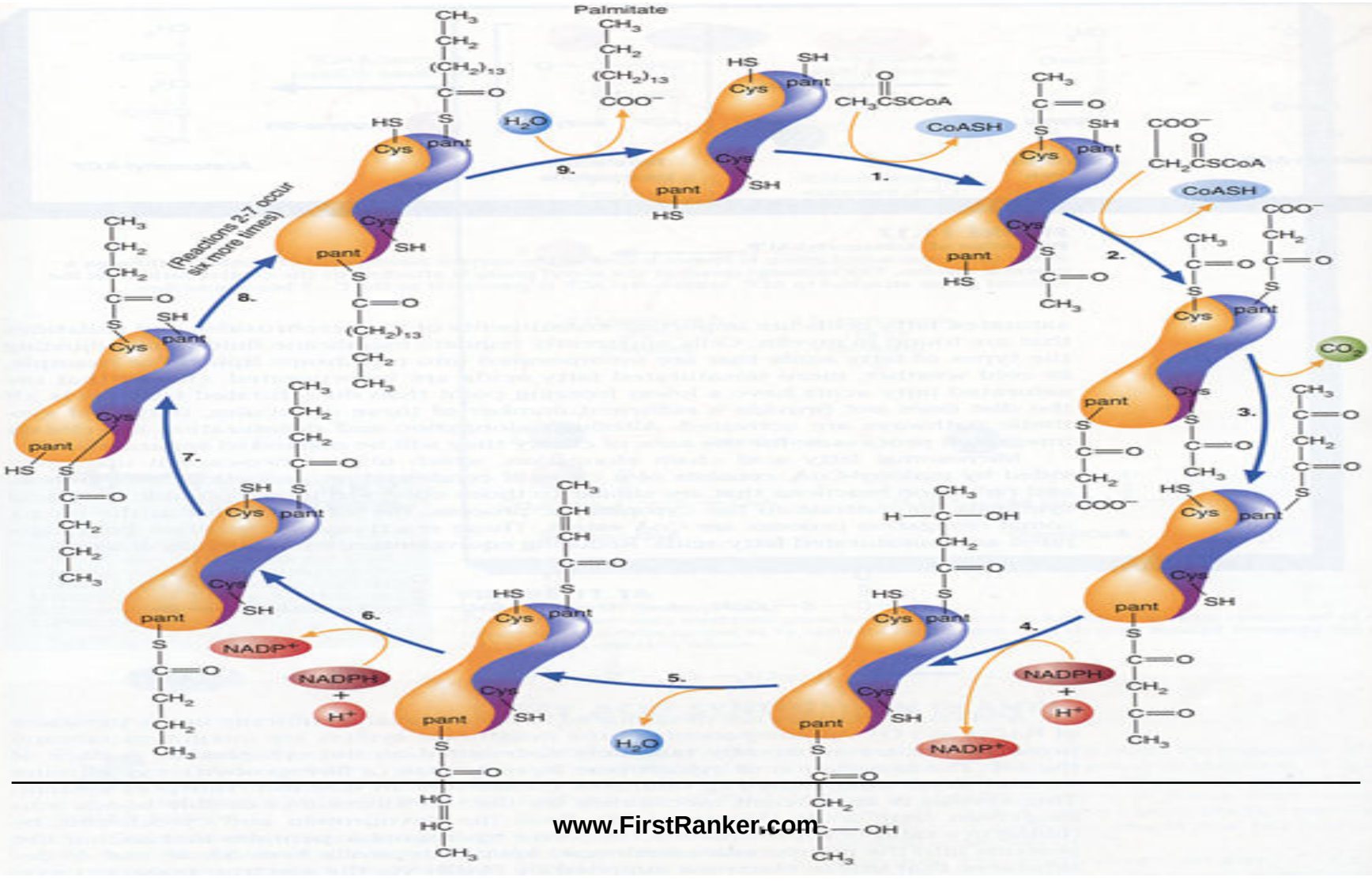
Stoichiometry for Palmitic Acid Synthesis

From acetyl-CoA

$$8\ CH_3\overset{O}{\overset{\|}{C}}{-}SCoA + 7CO_2 + 7ATP + 14NADPH + 14H^+ \longrightarrow$$

$$CH_3(CH_2)_{14}\overset{O}{\overset{\|}{C}}{-}OH + 14NADP^+ + 7CO_2 + 8CoASH + 6H_2O + 7ADP + 7Pi$$

Diagrammatic View of Fatty Acid Biosynthesis



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Energetics Of De Novo Synthesis Of Fatty Acids

- De Novo Fatty acid biosynthesis is an **Anabolic process involving use of ATPs.**

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- **Total 23 ATPs are utilized** for the biosynthesis of **one molecule of Palmitate.**

  - **2 ATPs** are used for **1 Acetyl-CoA** translocation through **Citrate transport** system
    - **For 8 Acetyl CoA translocation uses 16 ATPs**

  - **1 ATP** each is used for **Acetyl CoA Carboxylation** to Malonyl CoA.

    - To form **7 Malonyl CoAs** **7 ATPs** are utilized.

- **16+7 =23 ATPs Net utilized**

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Regulation Of Fatty Acid Biosynthesis

The Enzyme Acetyl Carboxylase
Is a
Regulatory ,Key Enzyme
Of
De Novo Fatty acid Synthesis.

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- **The Committed Step of Fatty Acid Synthesis**
  - Carboxylation of Acetyl CoA to Malonyl CoA
  - **By Acetyl CoA Carboxylase - Biotin**



- **Carboxylation of Acetyl-CoA to form Malonyl-CoA**

- **Is an Irreversible, committed step in Fatty acid biosynthesis**

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Modes Of Regulation Of Acetyl CoA Carboxylase of FA Biosynthesis

Acetyl-CoA Carboxylase is regulated by 3 modes:

1. **Hormonal Influence**
2. **Allosteric Control**
3. **Covalent Modification**

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1. Hormonal Influence

- **ACC is an Inducible Enzyme:**
  - –Induced by **Insulin**
    - **Insulin activates ACC**
  - –Repressed by **Glucagon**
  - **–Glucagon inhibits ACC**

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2. Allosteric Modifiers

- Citrate **Activates Acetyl-CoA Carboxylase** (Feed Forward)
- Fatty Acyl-CoAs **inhibit Acetyl-CoA Carboxylase**

Allosteric modification of Acetyl-Co A Carboxylase

- **Activated by**: Citrate
- **Inhibited by:** Long Chain Fatty Acid

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- Body with **high levels of cellular Citrate**
- Stimulate De novo biosynthesis of Fatty acids.

- Body on a **high fat diet** experience **little** if any **de novo fatty acid synthesis.**

3. Covalent Modification Of Acetyl-CoA Carboxylase

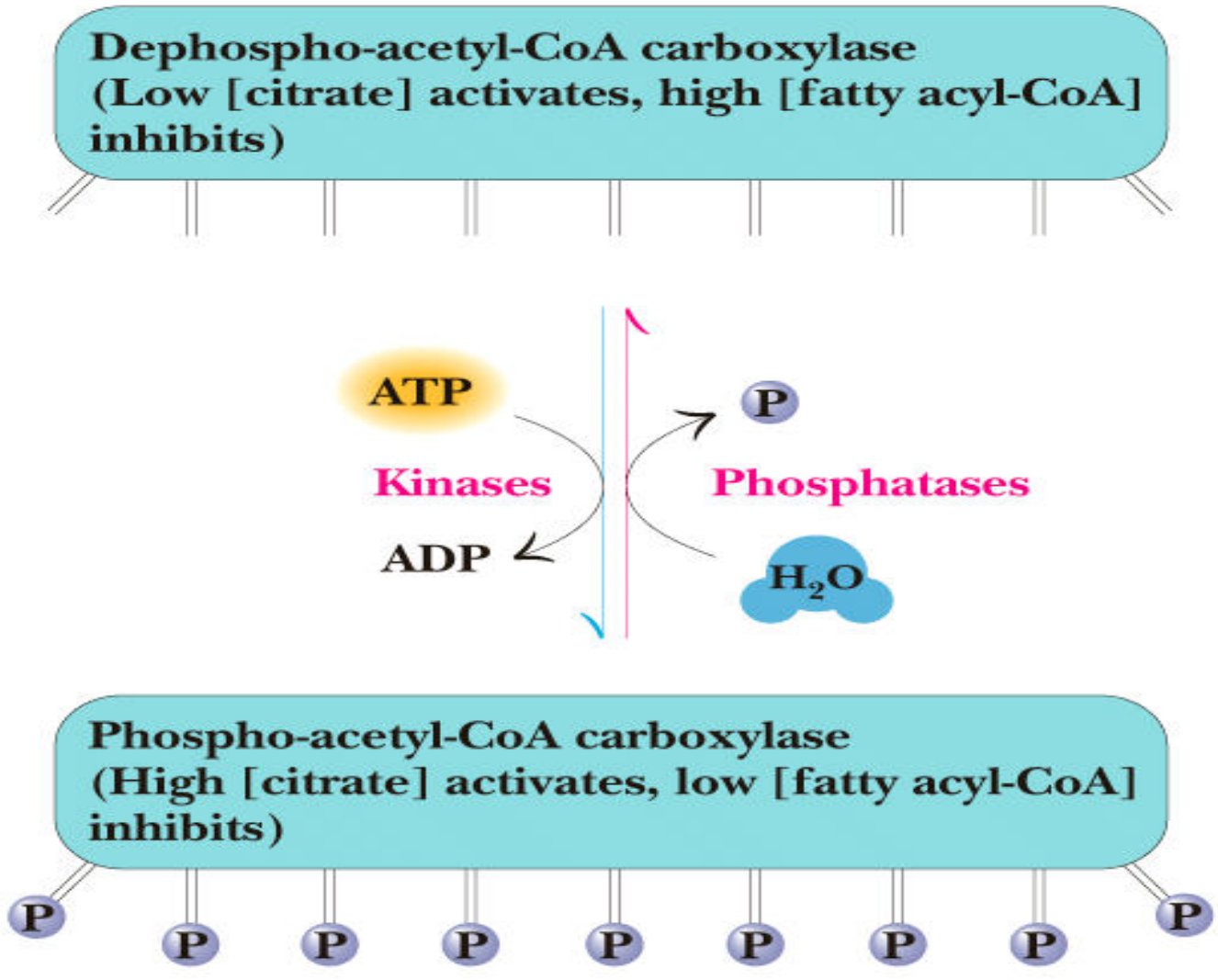
- **ACC is Activated by :**
  Dephosphorylation

- **ACC is Inhibited by:**
  Phosphorylation

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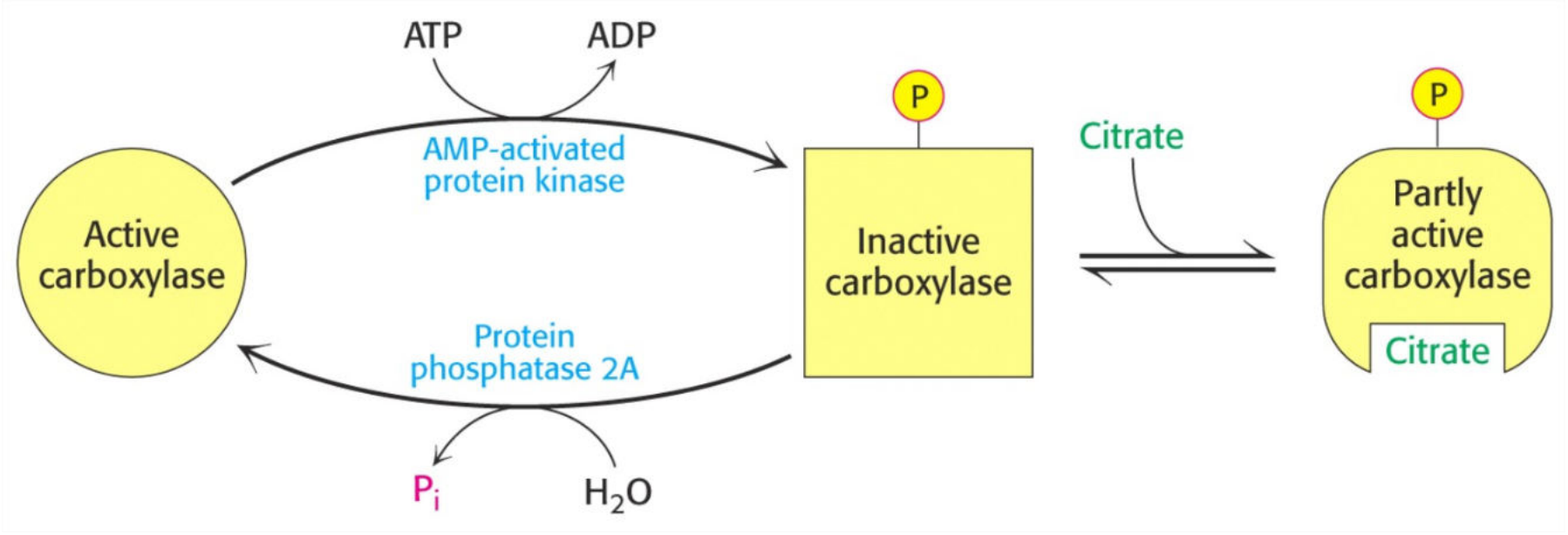
Covalent Modification Of ACC



Covalent Regulation OF Acetyl CoA Carboxylase

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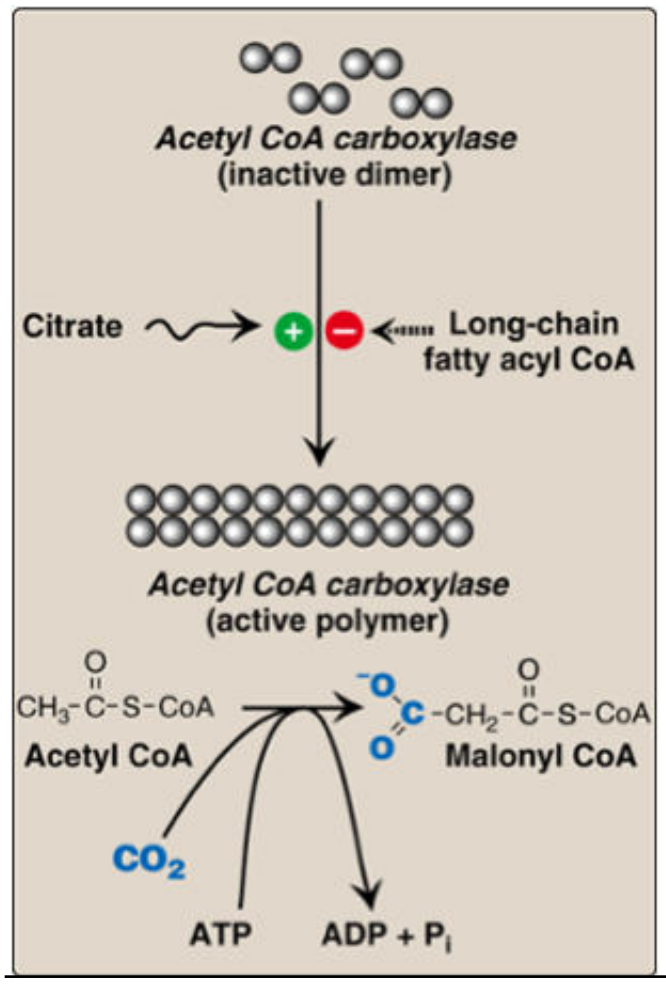
- **Activation of ACC**
- **In a well Fed state**
  - **Insulin** induces **Protein Phosphatase**
  - **Activates ACC by De phosphorylation**

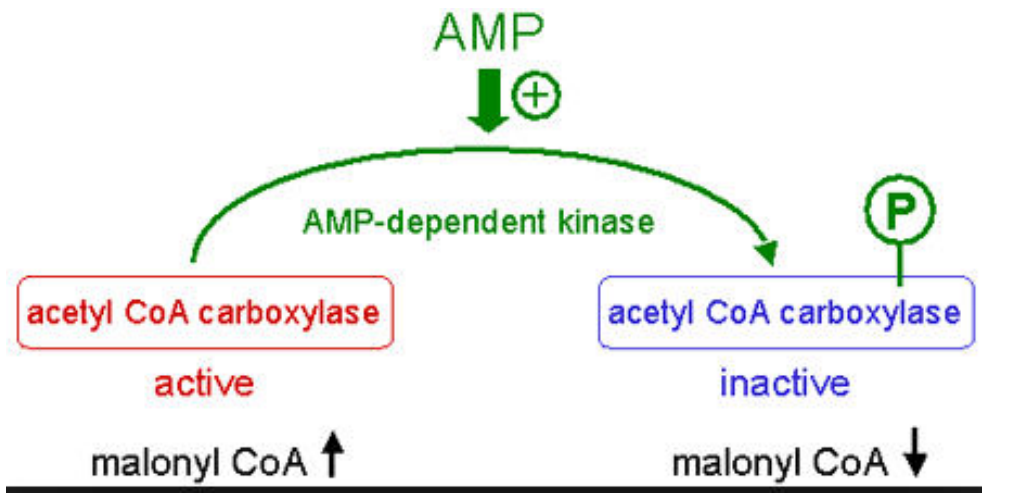
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- **Inactivation of ACC**
- **In a Starved state**
  - –Glucagon increases **cAMP**
  - –Activates **Protein kinase A**
  - –Inactivates ACC by **Phosphorylation**

Acetyl-CoA Carboxylase



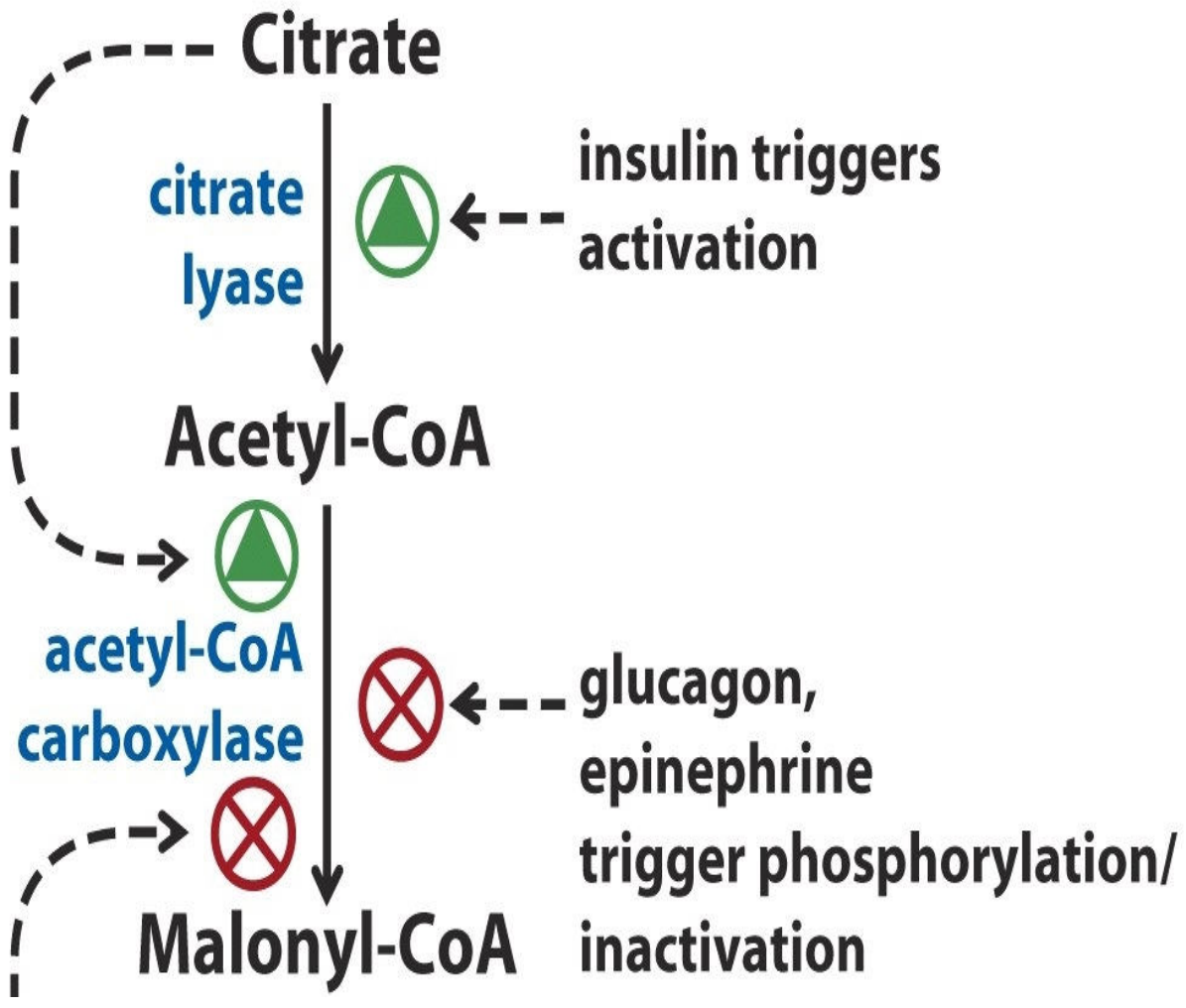


glucagon,
epinephrine
trigger phosphorylation/
inactivation

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Control of Fatty Acid Synthesis



Biosynthesis and Degradation of Fatty Acid are Reciprocally Regulated

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–**During Starvation**

–Epinephrine & Glucagon Stimulate Lipolysis

–Brings degradation of FA

–**Well Fed state**

❖ Insulin inhibits Lipolysis

❖Insulin Stimulates Fatty acid biosynthesis.

- **ACC also influences degradation of Fatty acids.**

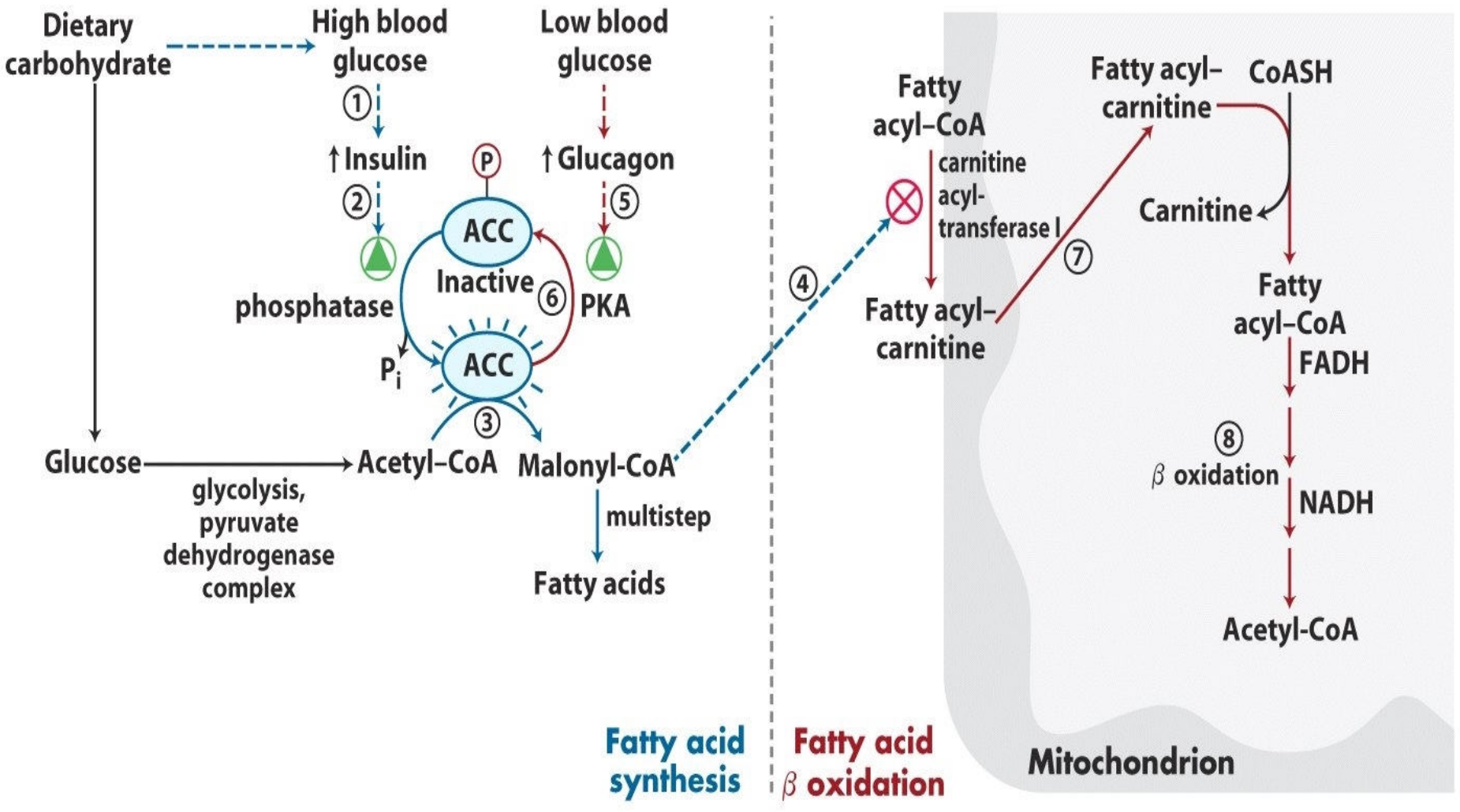
  –**Malonyl CoA** inhibits **Carnitine Acyltransferase I activity.**

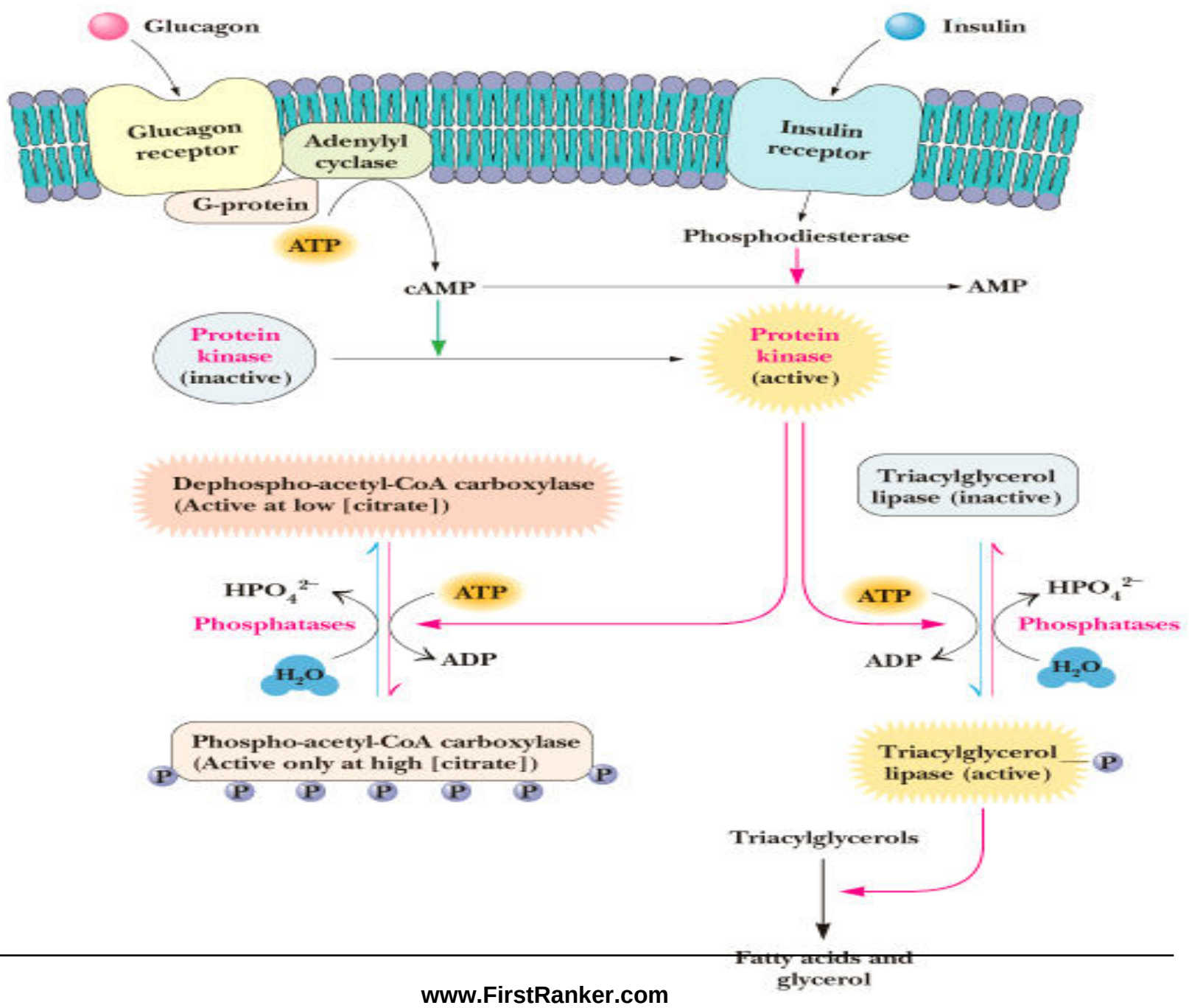
  –This **limits Beta oxidation of Fatty acids** in Mitochondrial Matrix.

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Reciprocal Control



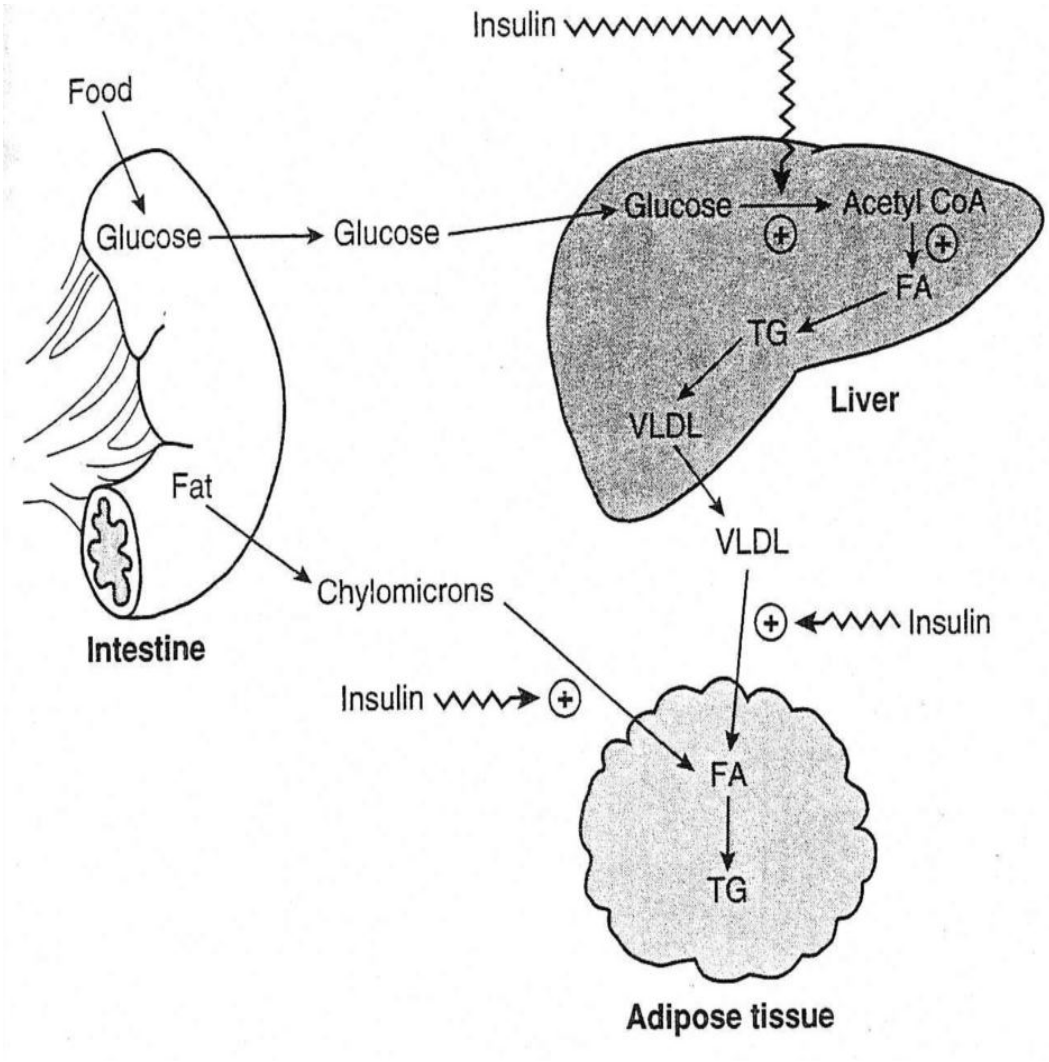


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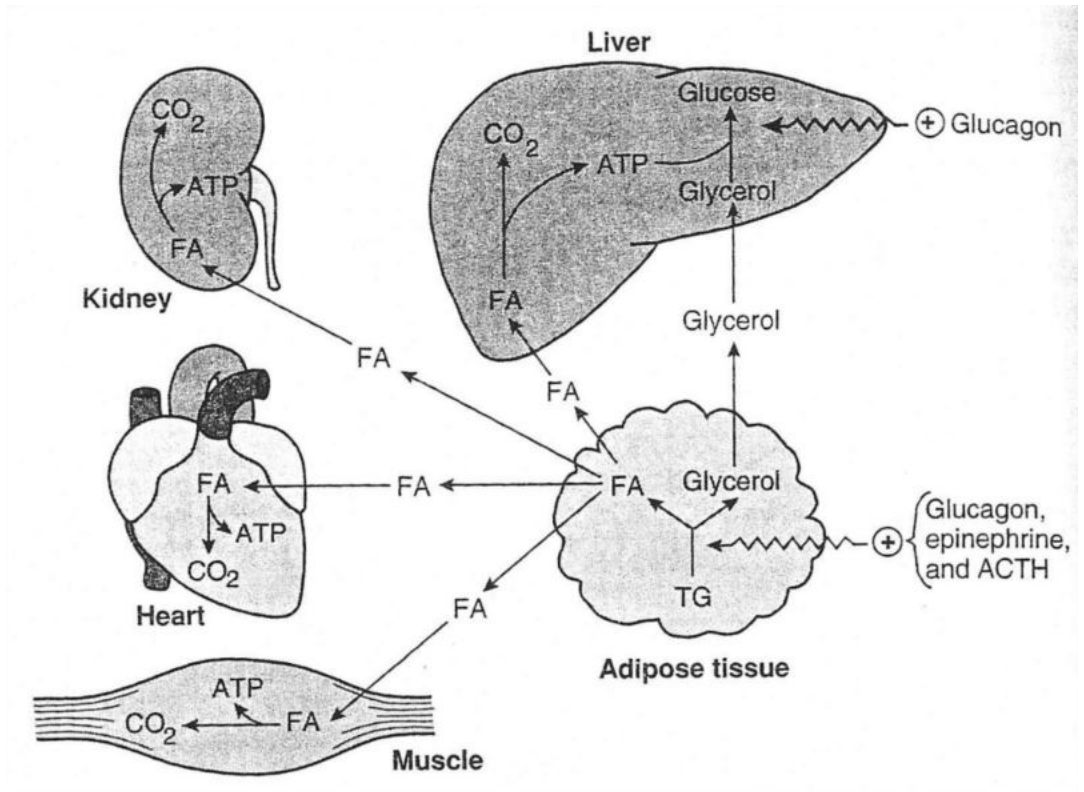
Overview of Fatty Acid Metabolism: Insulin Effects

- Liver
  - Increased fatty acid synthesis
    - Glycolysis, PDH, FA synthesis
  - Increased TAG synthesis and transport as VLDL
- Adipose
  - Increased VLDL metabolism
    - lipoprotein lipase
  - Increased storage of lipid
    - Glycolysis



Overview of Fatty Acid Metabolism: Glucagon/Epinephrine Effects

- Adipose
- Hormone-sensitive lipase Increased
  - Increased TAG mobilization
- Increased FA oxidation
  - All tissues Except CNS and RBC



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Post-Synthesis Modifications Of Biosynthesized Fatty Acids

- **C16 Saturated fatty acid (Palmitate) is the product which may undergo:**
  - Elongation
  - Unsaturation
  - Incorporation to form Triacylglycerols
  - Incorporation into Acylglycerol phosphates to form Phospholipids

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Chain Elongation Of Fatty Acids

Occurs In
Mitochondria
And
Smooth Endoplasmic Reticulum

Elongation Of Fatty Acids
In Microsomes /Mitochondria
To
Synthesize Long Chain Fatty Acids

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- Palmitate biosynthesized by **De Novo Biosynthesis in Cytosol by the activity of FAS Complex**

- Is further **elongated** to more higher Fatty acid either in **Mitochondria /Endoplasmic reticulum.**

Mitochondrial Chain Elongation

- Here **Acetyl-CoA is successively added** to Fatty acid chain lengthened
- In presence of reducing equivalents **NADPH+ H^+**
- The steps are **almost reversal of Beta Oxidation of Fatty acids.**

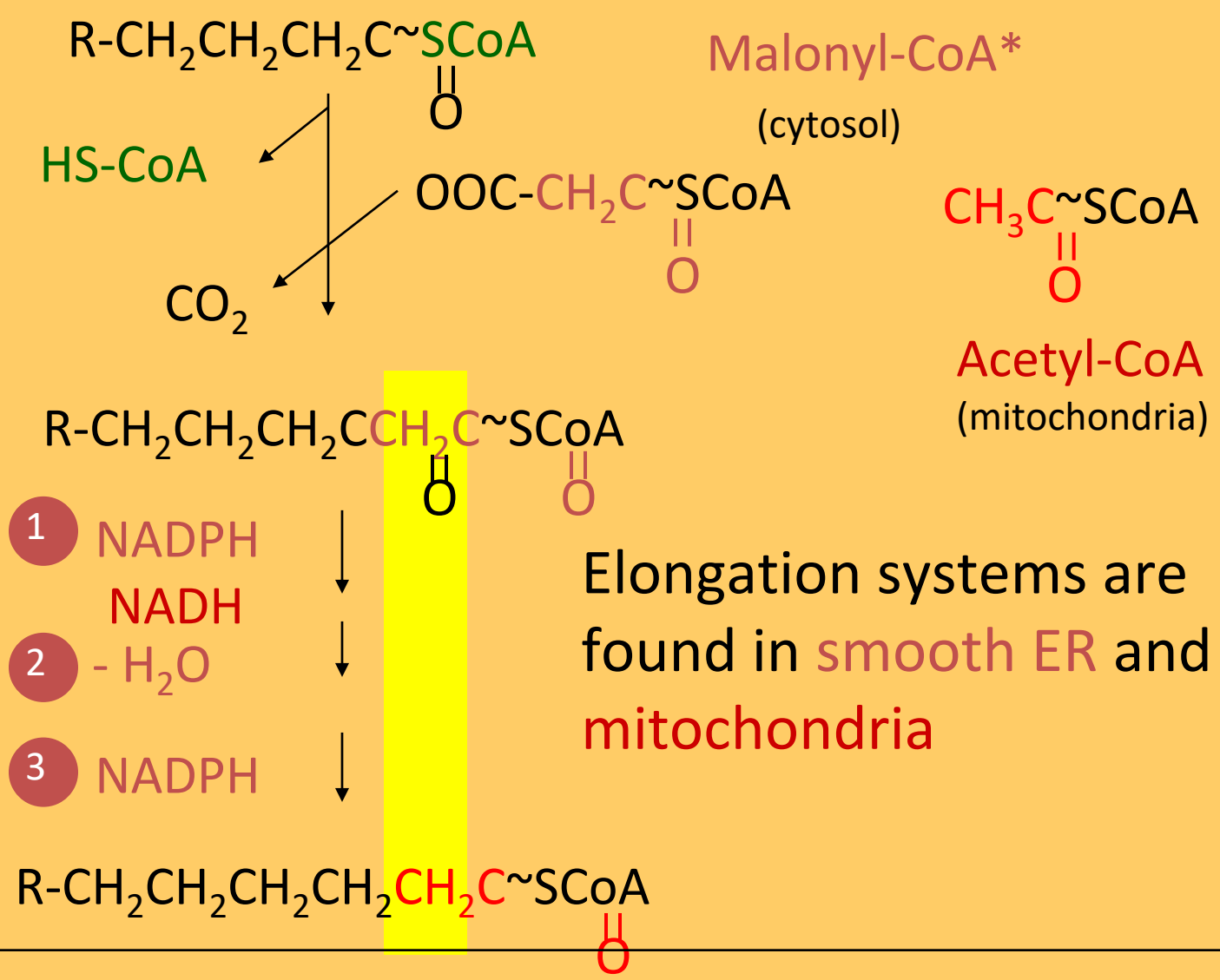
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Microsomal Chain Elongation Of Fatty Acid

- This is **more predominant way** of **Fatty acid Chain Elongation**.
- It involves **successive addition of Malonyl-CoA** with the participation of **NADPH+ H+** and enzyme **Elongases.**

Elongation of Chain (Two Systems)



Elongation systems are found in smooth ER and mitochondria

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Synthesis Of Unsaturated Fatty Acids

Mammals can Biosynthesize Long Chain And Unsaturated Fatty acids

Using Elongation And Desaturation

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Desaturation of Fatty Acid Chain In Microsomes

- Enzyme **Fatty Acyl-CoA Desaturase** which is a Flavoprotein
- Helps in **creating double bonds** and forming **Mono Unsaturated Fatty acids.**

- **Palmitic acid and Stearic acid** on **Desaturation**
- **Forms corresponding MUFAS Palmitoleic and Oleic acid respectively.**

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- Human body **lack the ability** to **introduce double bonds** **beyond carbon 9 and 10 of Fatty acids**.

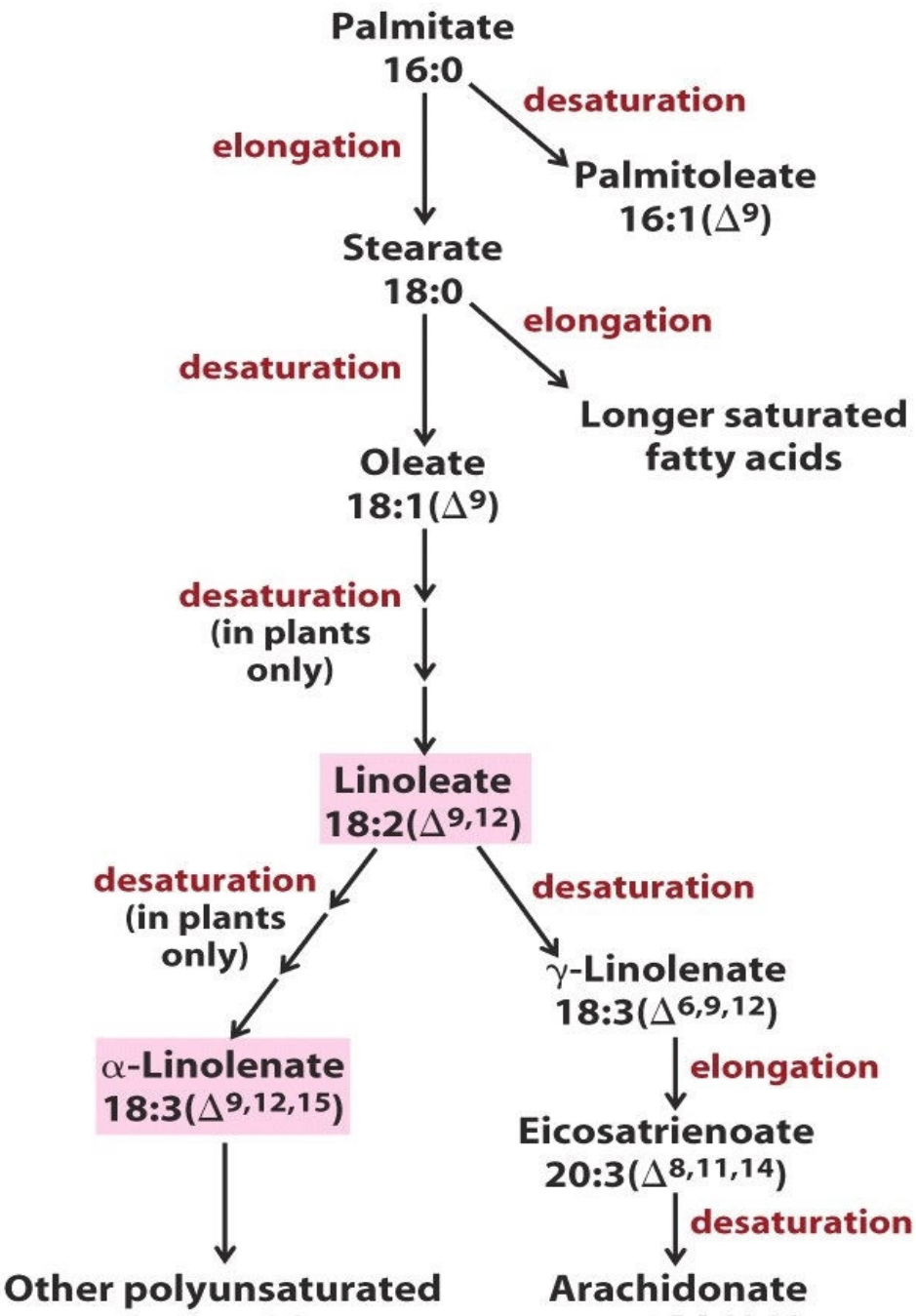
- Hence body **cannot biosynthesize Linoleic and Linolenic acid** and become dietary essential Fatty acids.

- However **Linoleic Acid by Chain Elongation and Desaturation**

- **Forms Arachidonic acid** in Human body.

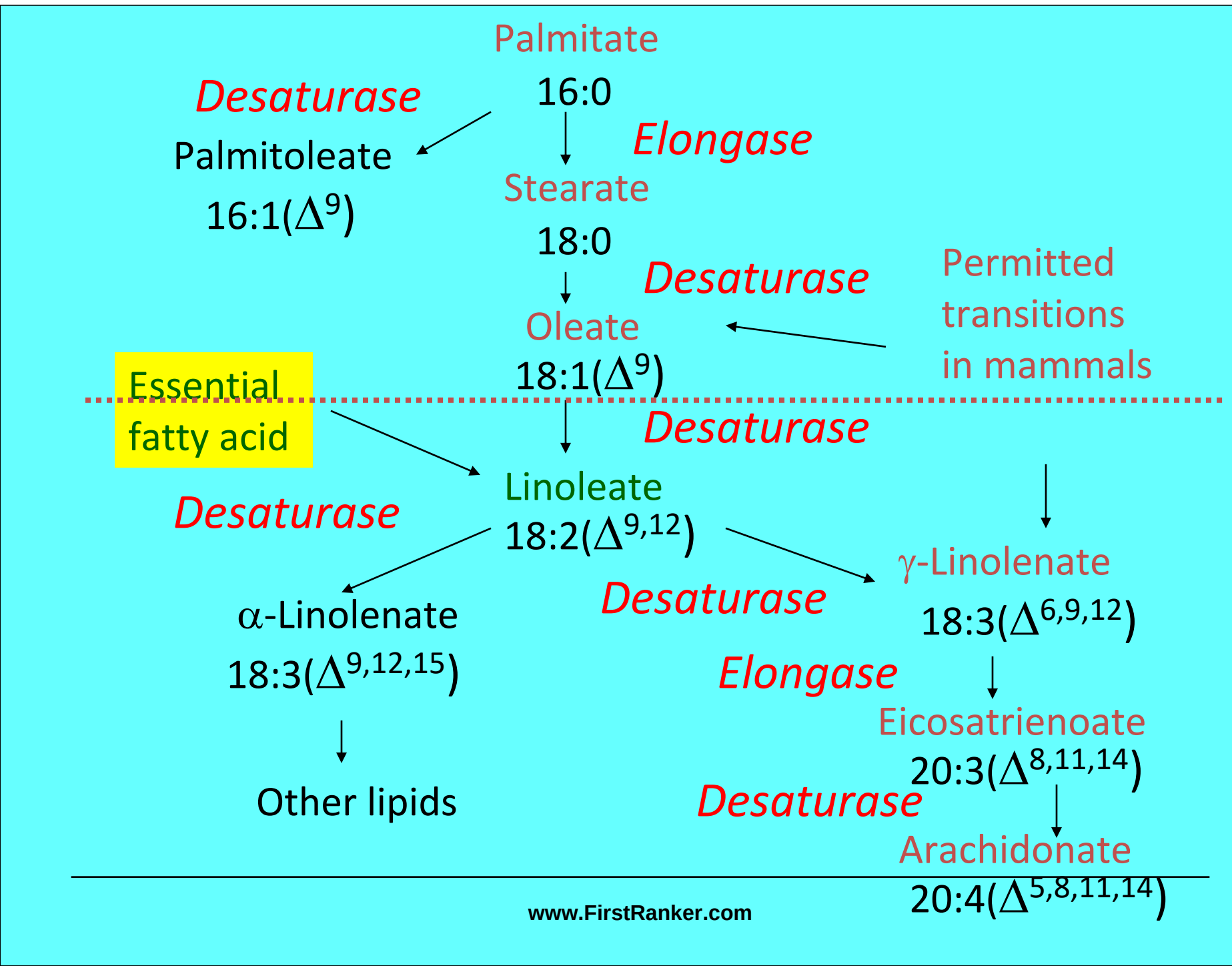
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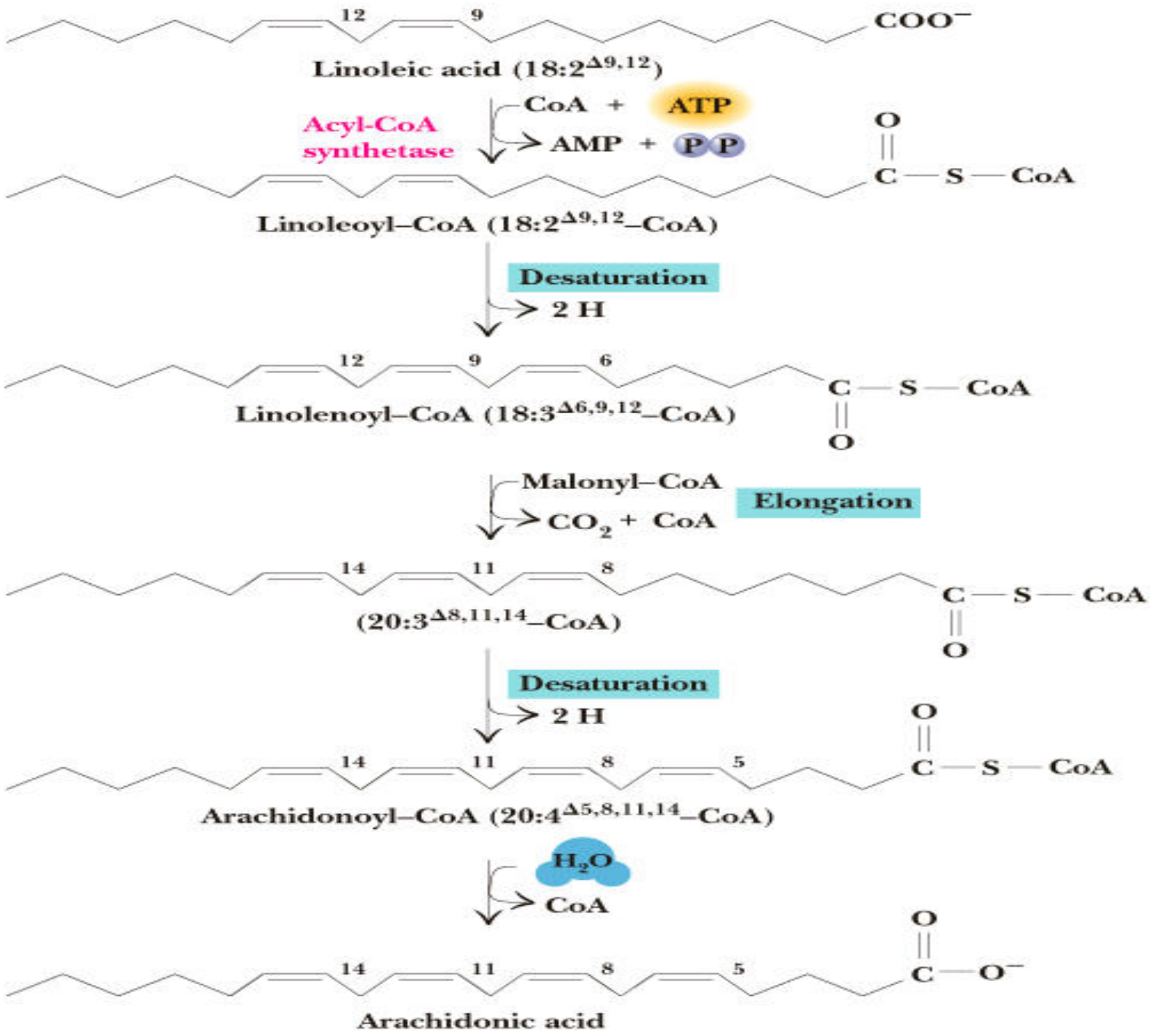
Palmitic acid modifications

- Cell makes a pool of palmitic acid that it can elongate and/or desaturate in the ER.
- Elongation system is very similar to synthesis: 2C units added from malonyl-CoA.



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Differences Between
Beta Oxidation Of Fatty Acid
And
De Novo Biosynthesis Of Fatty Acids

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The Biosynthesis and Degradation Pathways are Different

- The major differences between Fatty acid breakdown and biosynthesis are as:

Beta Oxidation Palmitic acid Pathway	De Novo Biosynthesis Palmitic acid Pathway
Catabolic /Oxidative	Anabolic /Reductive
Occurs In Mitochondria	Occurs In Cytosol
Acetyl CoA is an end product	Acetyl CoA is a precursor
Beta Carbon **CH2 is** transformed to **C=O**	Beta Carbon **C=O** is converted to **CH2**
Generates 106 ATPs	Utilizes 23 ATPs
Coenzymes FAD and NAD^+ are involved	Coenzymes NADPH $+H^+$ is involved
CoA is an Acyl Carrier	ACP is an Acyl Carrier

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Fatty Acid Synthesis

- C=O → -CH2

Fatty Acid Beta Oxidation

- CH2 → C=O

Triacylglycerol (TAG) Biosynthesis

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Site For TAG Biosynthesis

- TAG biosynthesis predominantly occurs in **Liver and Adipocytes**

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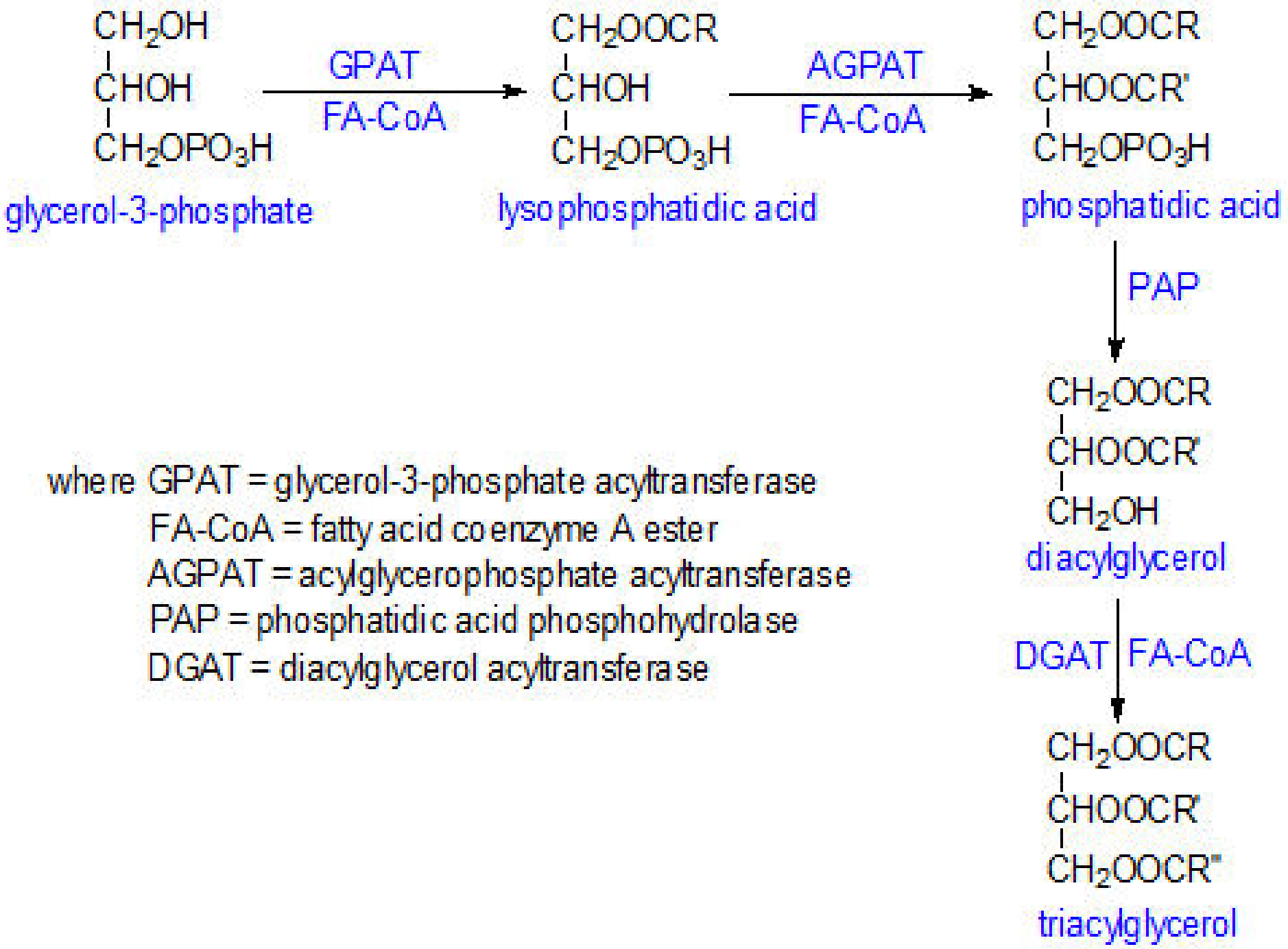
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TAG Biosynthesis Takes Place In Smooth Endoplasmic Reticulum

- **TAG biosynthesis takes place after De Novo Biosynthesis of Fatty acids.**
- **Fatty acids** and **Glycerol** are **activated** before TAG biosynthesis.
- Fatty acids are activated to **Acyl CoA by Thiokinase**
- Glycerol is activated to **Glycerol-3-Phosphate by Glycerol Kinase.**

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where GPAT = glycerol-3-phosphate acyltransferase
FA-CoA = fatty acid coenzyme A ester
AGPAT = acylglycerophosphate acyltransferase
PAP = phosphatidic acid phosphohydrolase
DGAT = diacylglycerol acyltransferase

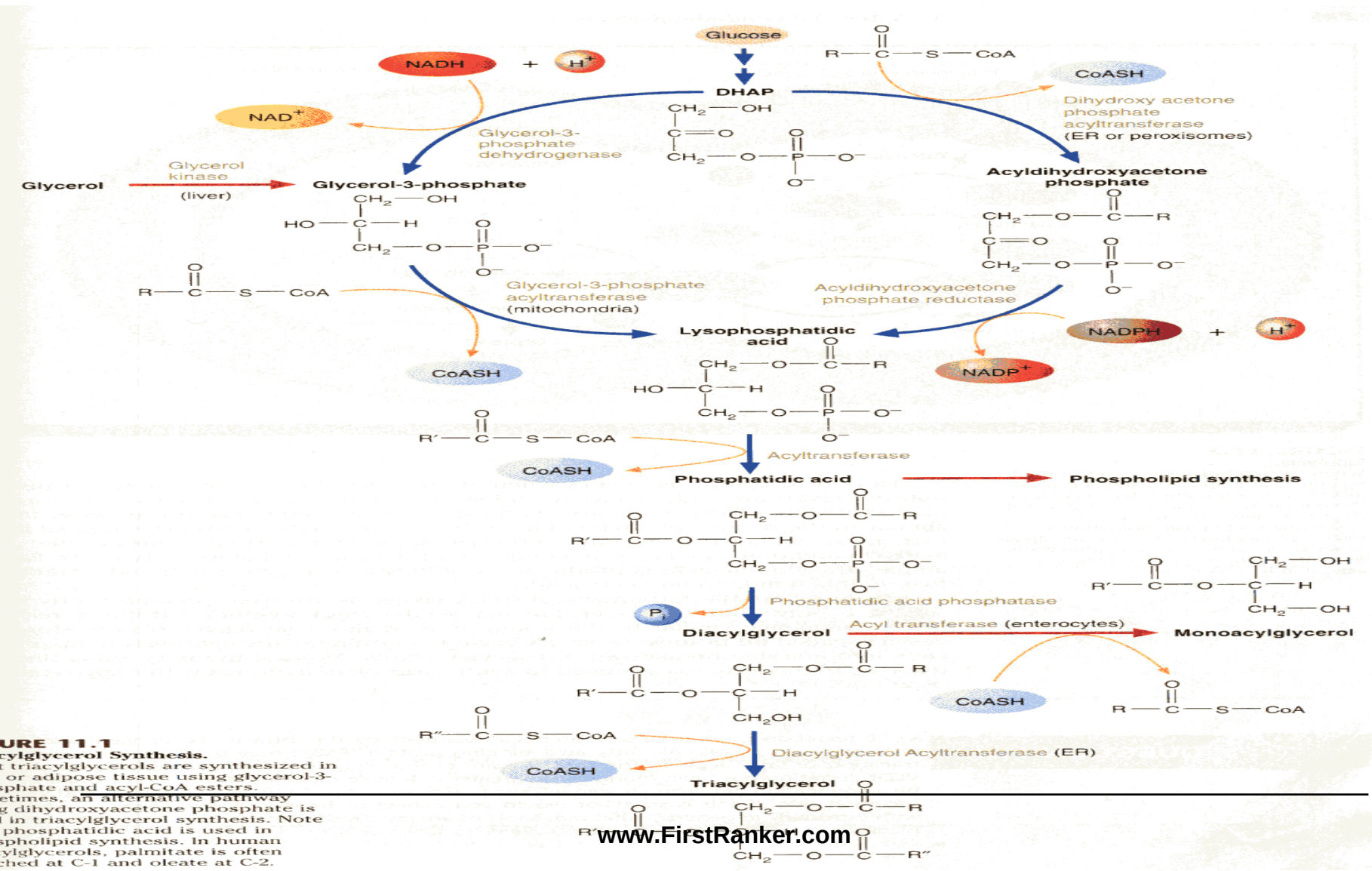
- An Acyl chain is transferred to Glycerol by **Acyl Transferase** producing **Lysophosphatidic acid.**
- Lysophosphatidic acid is transformed to **Phosphatidic acid** on addition of one more Acyl chain.

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- Phosphate group is removed from Phosphatidic acid to **generate Diacylglycerol**.
- The **addition of third Acyl chain to Diacylglycerol** finally **results in Triacylglycerol**.
- Usually a **mixed type of TAG** is synthesized in the body.

Triacylglycerol Synthesis



URE 11.1
cylglycerol Synthesis.
t triacylglycerols are synthesized in
or adipose tissue using glycerol-3-
sphate and acyl-CoA esters.
etimes, an alternative pathway
g dihydroxyacetone phosphate is
in triacylglycerol synthesis. Note
phosphatidic acid is used in
spholipid synthesis. In human
ylglycerols, palmitate is often
ched at C-1 and oleate at C-2.

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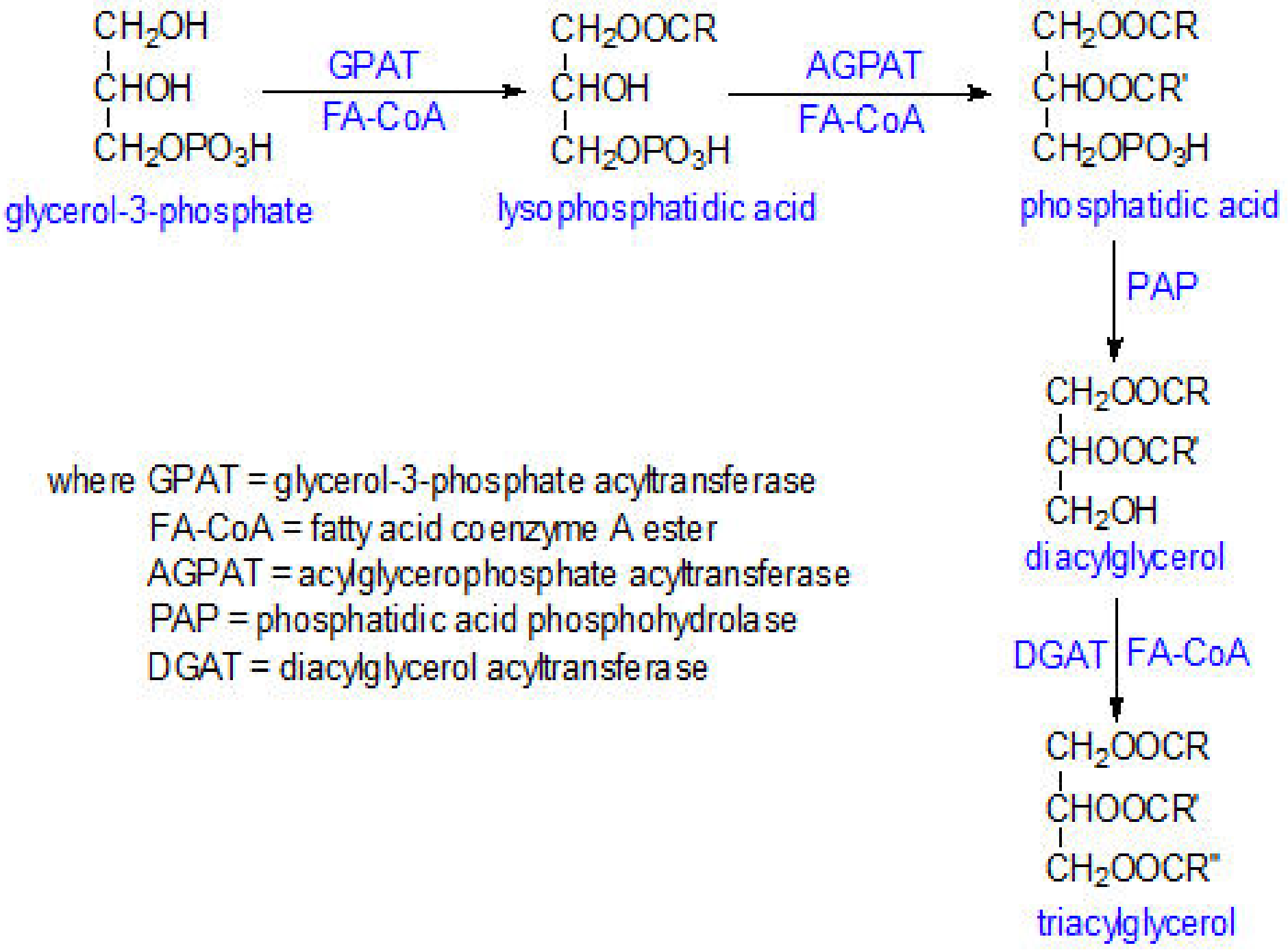
Phospholipid Biosynthesis

Glycerophospholipid Synthesis

- Glycerophospholipids are biosynthesized **from Phosphatidic acid and Diacylglycerol.**
- These are also intermediates of ~~TAG biosynthesis.~~

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where GPAT = glycerol-3-phosphate acyltransferase
FA-CoA = fatty acid coenzyme A ester
AGPAT = acylglycerophosphate acyltransferase
PAP = phosphatidic acid phosphohydrolase
DGAT = diacylglycerol acyltransferase

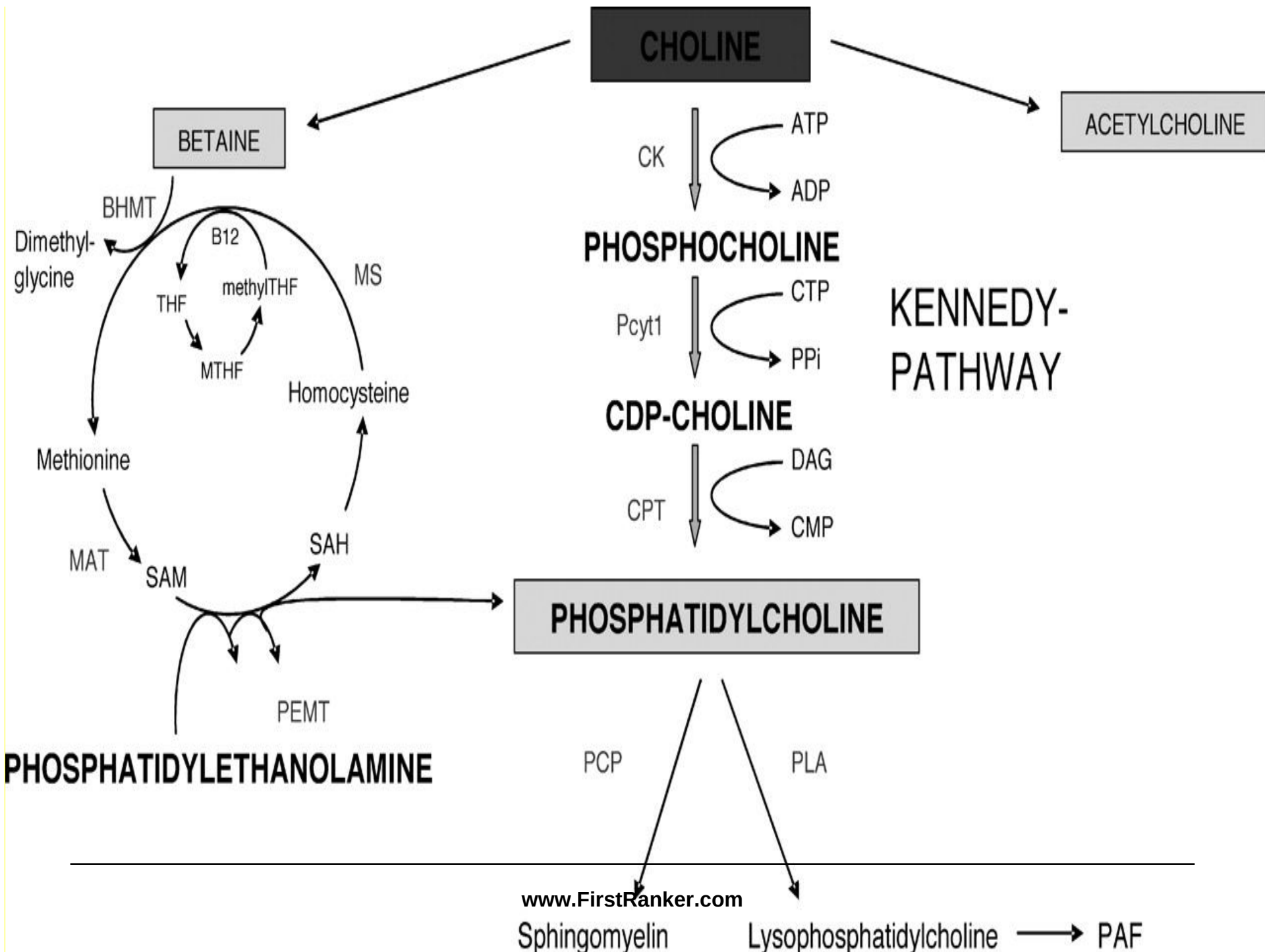
Synthesis OF Lecithin and Cephalin

- Nitrogenous bases **Choline** and **Ethanolamine** are **activated by CTP**
- To form **CDP-Choline and CDP-Ethanolamine.**
- These then **added to Phosphatidic acid** to **form Lecithin and Cephalin respectively.**

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- **Addition of Serine /Inositol** to Phosphatidic acid forms **Phosphatidyl Serine** and **Phosphatidyl Inositol**



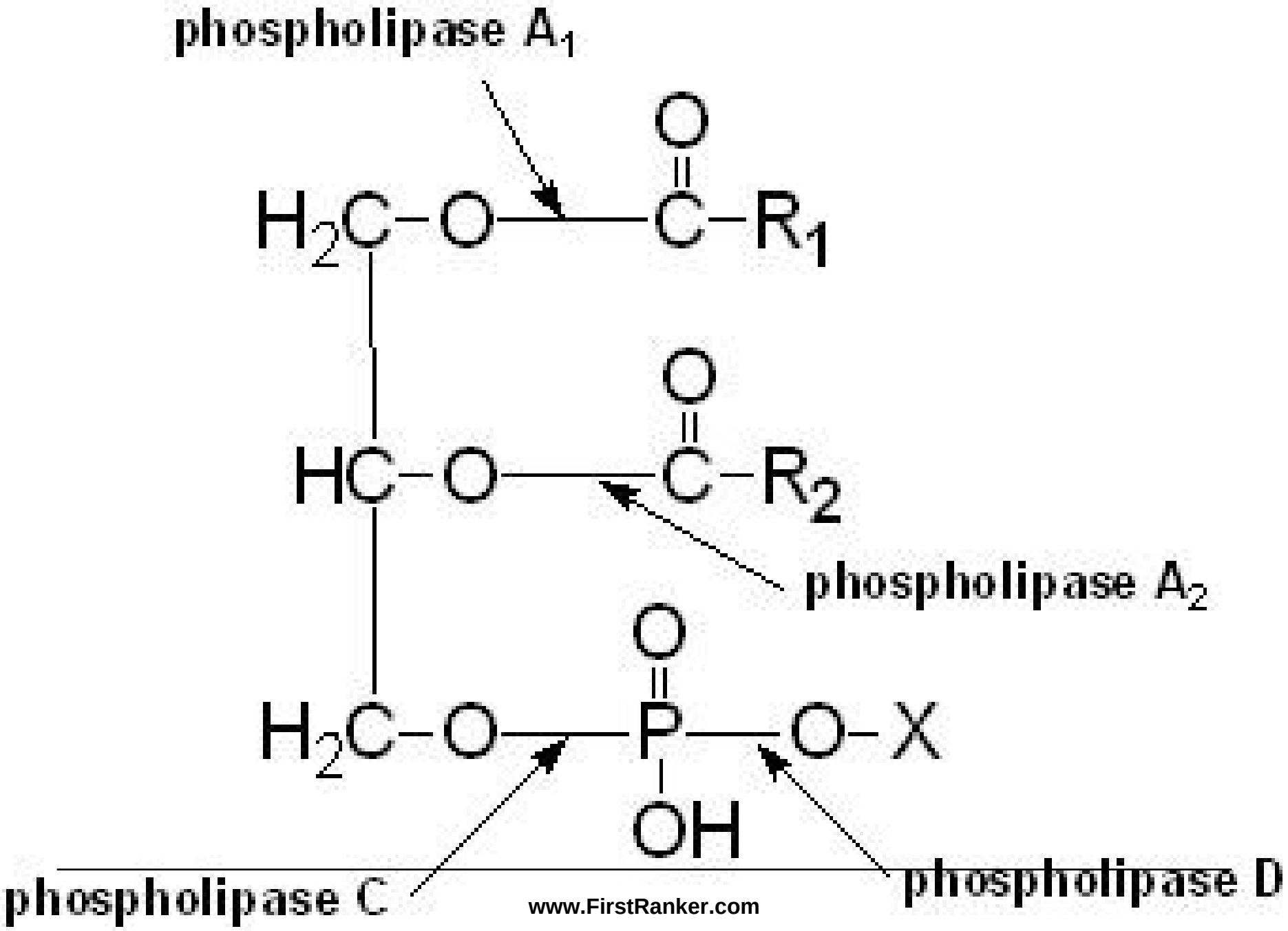
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Degradation Of Phospholipids By Phospholipases

OR

Different Types Of Phospholipases



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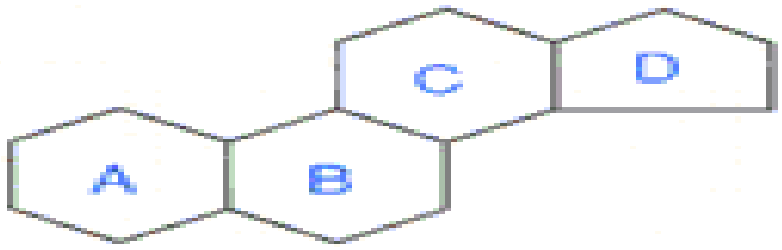
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Cholesterol Metabolism

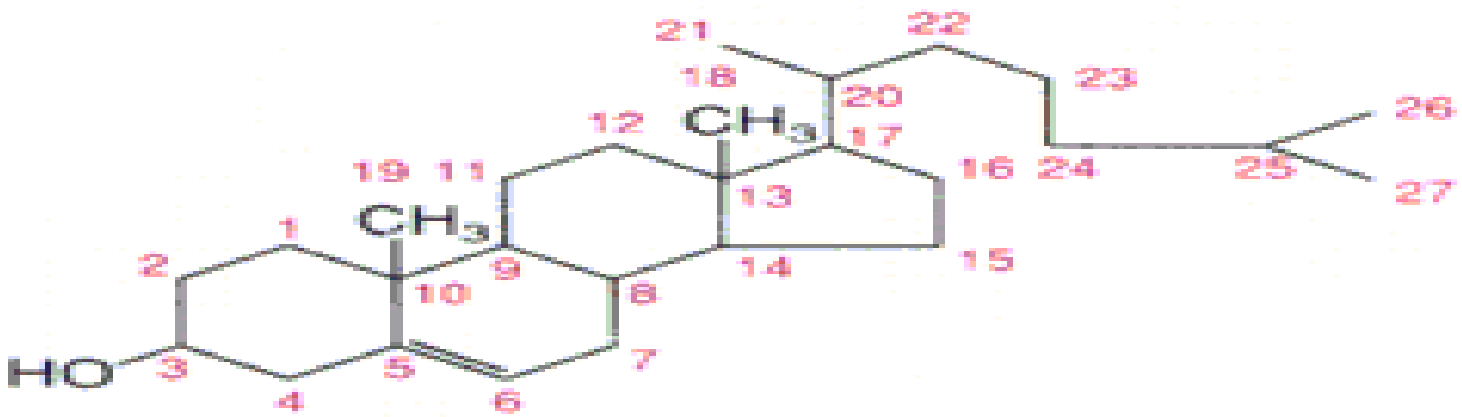
- **Cholesterol** is a **C27 compound**.
- Cholesterol has a parent nucleus **Cyclo Pentano Perhydro Phenantherene** Ring.

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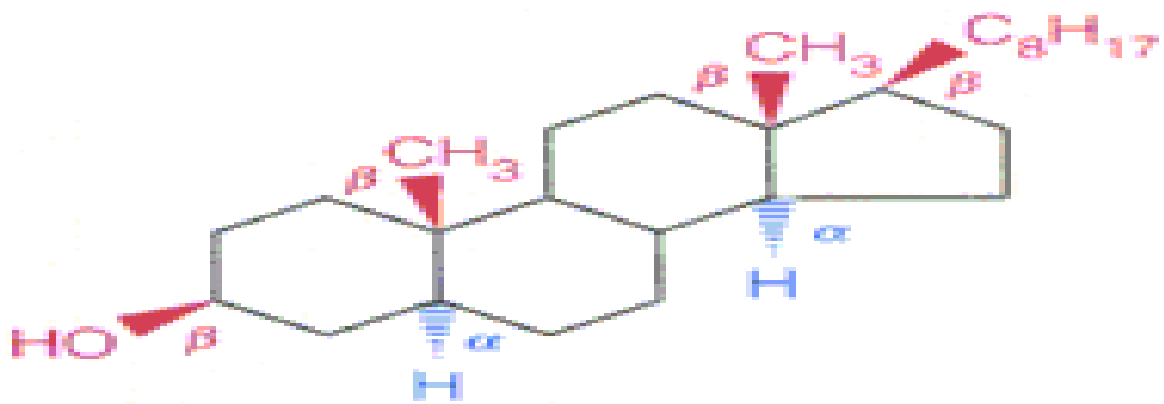
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(a) Perhydrocyclopentanophenanthrene



(b) Cholesterol



(c) Two-dimensional representation of cholestanol

Two Forms Of Body Cholesterol

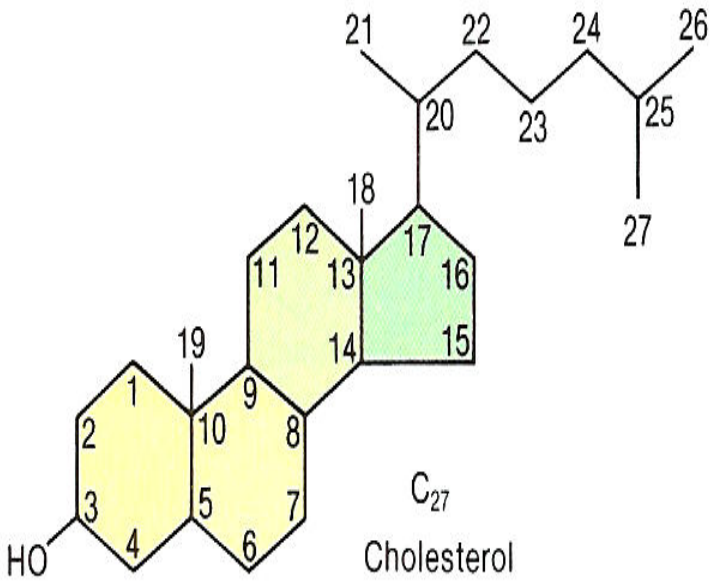
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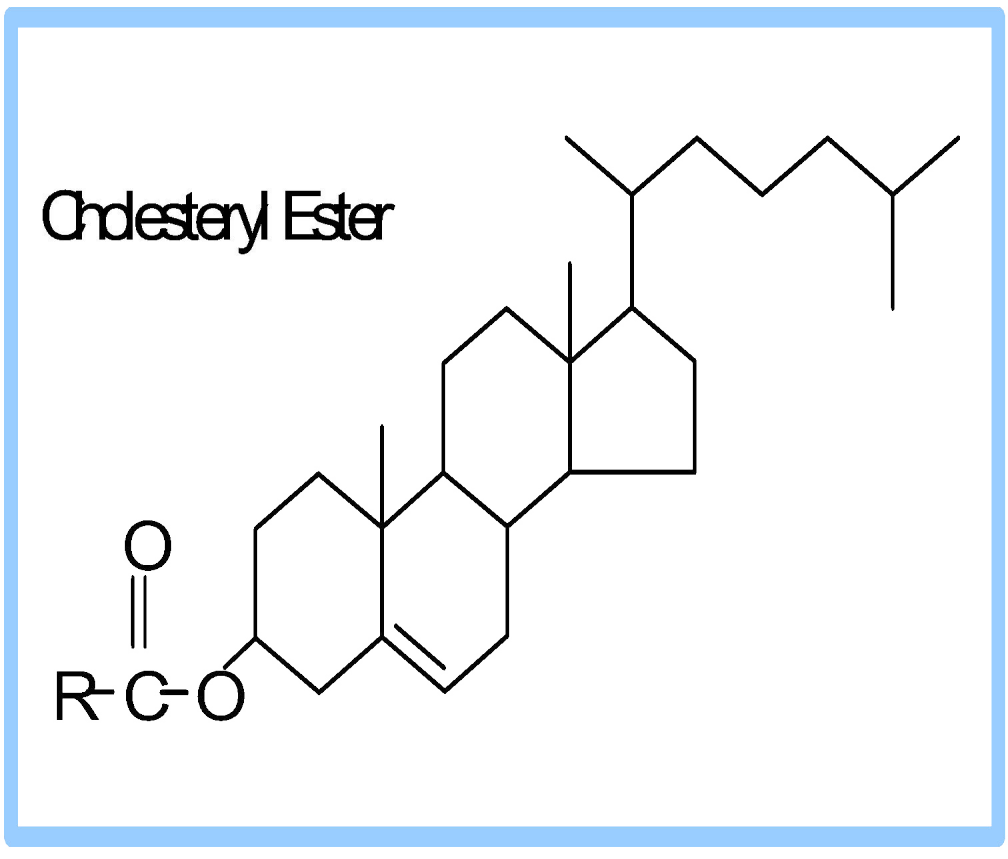
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- **Free Cholesterol** is a **derived Lipid**(30%)

- **Cholesterol Ester** is a simple Lipid and a body **Wax.** (70%)

Cholesterol





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- **Cholesteryl Ester** is a **storage and excretory form** of Cholesterol which is found in most tissues.

Functions Of Cholesterol

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Body Cholesterol Is An Essential

- Component of Biomembranes
- Nerve Impulse Conduction
- Precursor for:
  - **–Steroidal Hormone biosynthesis**
  - **–Bile acid/Bile Salts**
  - **–Vitamin D**

- Remember Cholesterol **is not an energy producing Lipid**.

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Cholesterol

Pregnenolone

Progesterone

Cortisol (glucocorticoid)

Affects protein and carbohydrate metabolism; suppresses immune response, inflammation, and allergic responses.

Corticosterone (mineralocorticoid)

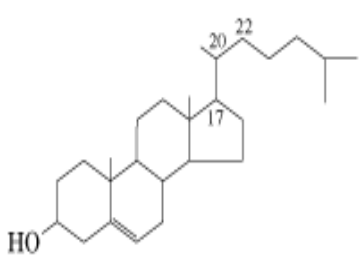
Aldosterone (mineralocorticoid)

Regulate reabsorption of Na^+, Cl^-, HCO_3^- in the kidney.

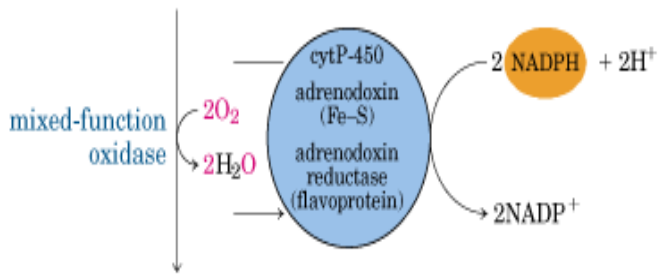
Testosterone

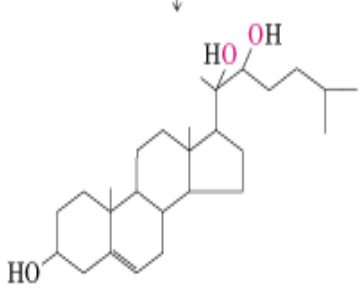
Estradiol

Male and female sex hormones. Influence secondary sexual characteristics; regulate female reproductive cycle.

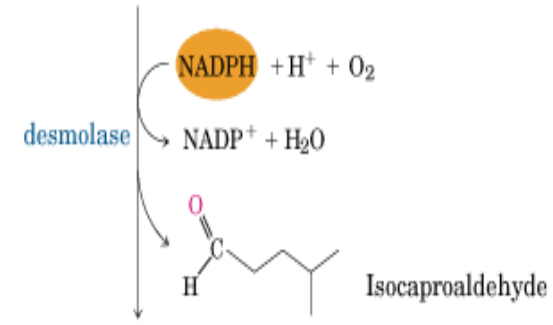


Cholesterol

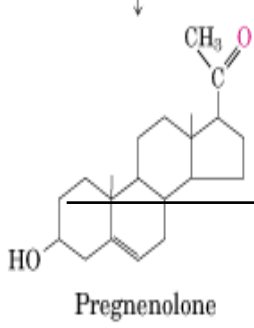




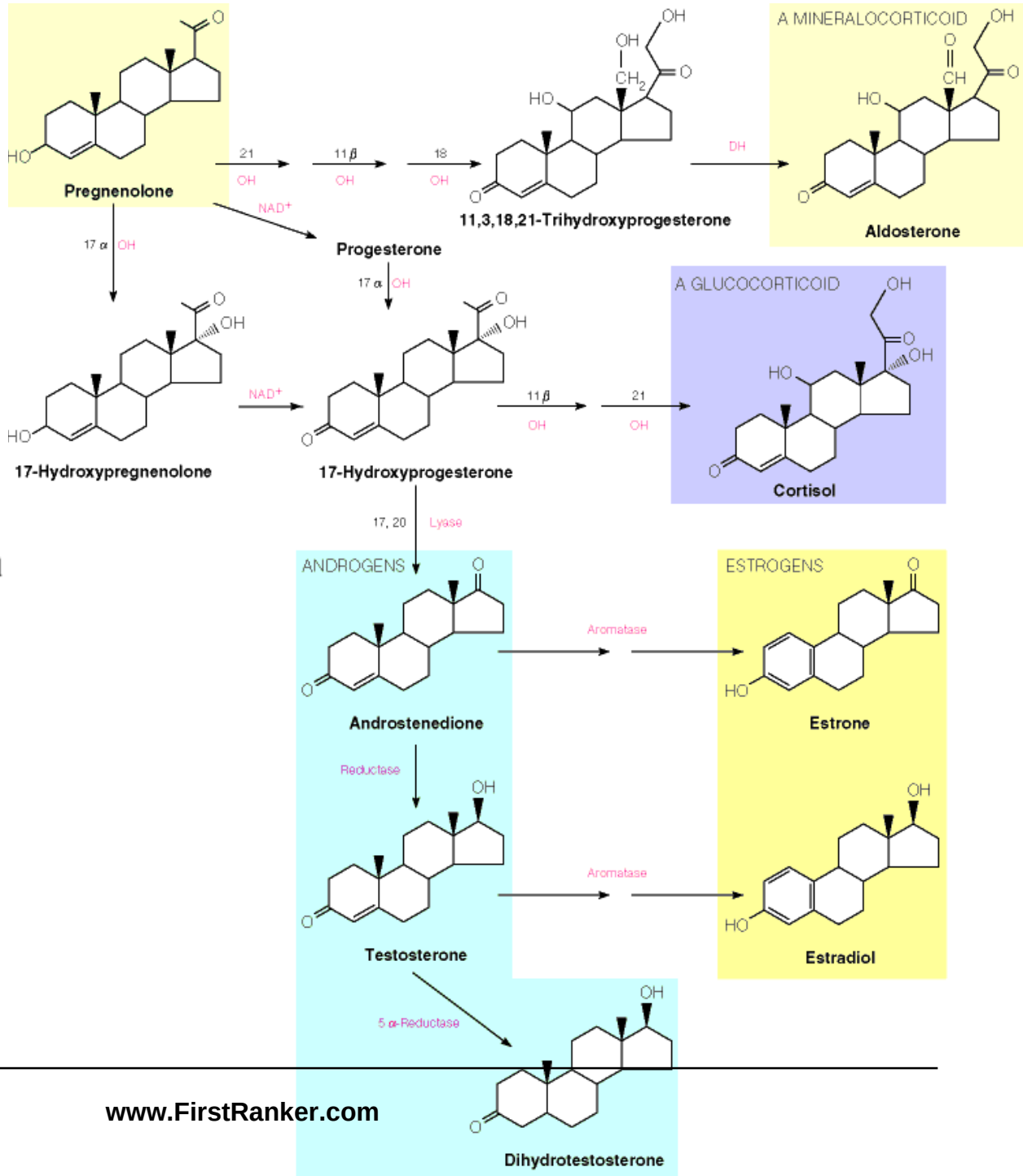
20,22-Dihydroxycholesterol



Isocaproaldehyde



Pregnenolone



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Sources Of Body Cholesterol

Endogenous And Exogenous Sources Of Body Cholesterol

- About 1 g/day originates by biosynthesis
- About 0.3 g/day extracted from food

✓ 80% Endogenously produced by the Liver (0.8 gram/day)

✓ 20% Exogenously comes from the digestive tract(0.3 gm/day)

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- Assume **400 mg** is an **intake** of dietary Cholesterol per day
- It **absorb about 50% Cholesterol**
- **200 mg** is **absorbed** from GIT
- **800 mg** of Cholesterol is from **de novo synthesis**

Dietary Cholesterol (Animal Sterol)

- Animal products – eggs
- Animal Brain
- Ghee
- Cheese

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Cholesterol Biosynthesis

Is

Endogenous Source Of Body Cholesterol

Amount Of Cholesterol Biosynthesis

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- **Endogenously about 1 gm/day** of Cholesterol is biosynthesized

- **Ingestion of excess of Carbohydrates elevates Cholesterol biosynthesis.**

Conditions Favoring For Cholesterol Biosynthesis

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- Biosynthesis of Cholesterol takes place:
  - **–In a well fed condition**
  - –In excess of **free cellular Glucose**
  - –On stimulation of **Insulin**

- The **amount of Cholesterol biosynthesis depends upon**
- **Availability of Acetyl-CoA obtained from Glucose metabolism in a well fed state.**

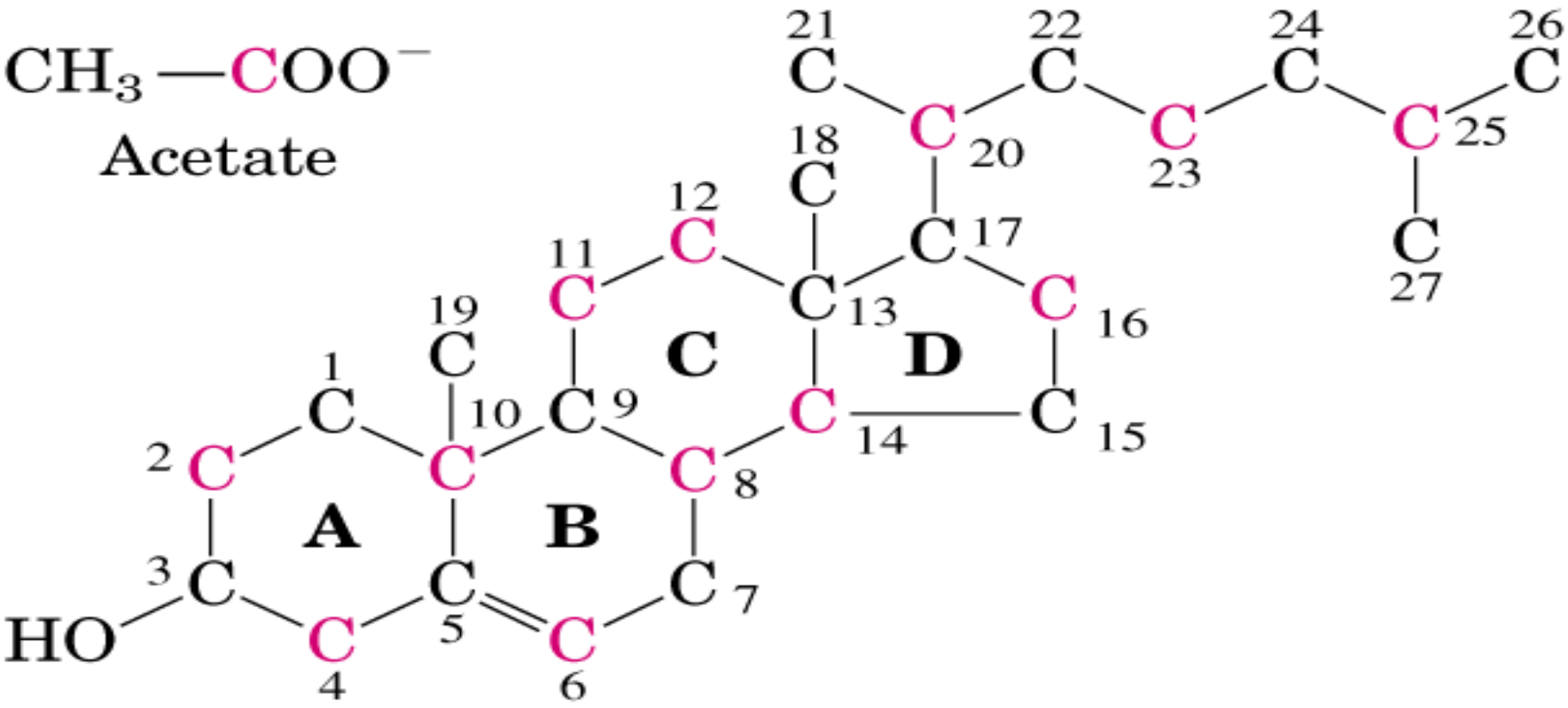
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- **Increased** free and excess of cellular **Glucose**

- **Increases the rate** of **endogenous Cholesterol biosynthesis**

Cholesterol Synthesis
Simplicity to Complexity



Cholesterol

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- All the **C27 carbon units** of Cholesterol Structure are biosynthesized using
- The **2 carbon Acetyl-CoA** units ,**obtained from Glucose metabolism**.

Site Of Cholesterol Biosynthesis

Organs and Cellular Site
For
Cholesterol Biosynthesis

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Organs Involved For Cholesterol Biosynthesis

- Liver (80%)
- Intestine (10%)
- Skin (5%)
- Adrenal Cortex
- Ovaries , Testes , Placenta
- Arterial walls (To some extent)

- Cholesterol Synthesizing Enzymes are **partly located in:**

  –**Cytoplasm**

  –**Endoplasmic Reticulum**

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Requirements For Cholesterol Biosynthesis

Requirements For Cholesterol Biosynthesis

- **Metabolic Precursor- Acetyl CoA** (Obtained from excess Glucose metabolism)
- **Enzymes ,Coenzymes and Cofactors**
- **16 NADPH $+H^+$** (Through HMP Shunt)
- **36 ATPs**

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Translocation Of Acetyl CoA From Mitochondrial Matrix To Cytosol

- Cholesterol is biosynthesized from **Cytosolic Acetyl CoA**
- Which is transported from Mitochondria via the **Citrate transport system.**

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Stages Of Cholesterol Biosynthesis

- **Biosynthesis of Cholesterol** is a very **complex process**
- **To understand divided in 5 Stages**
- Requires **more than 25 steps.**

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- **Stage 1.**
- **Acetyl-CoA forms HMG-CoA and Mevalonate.**

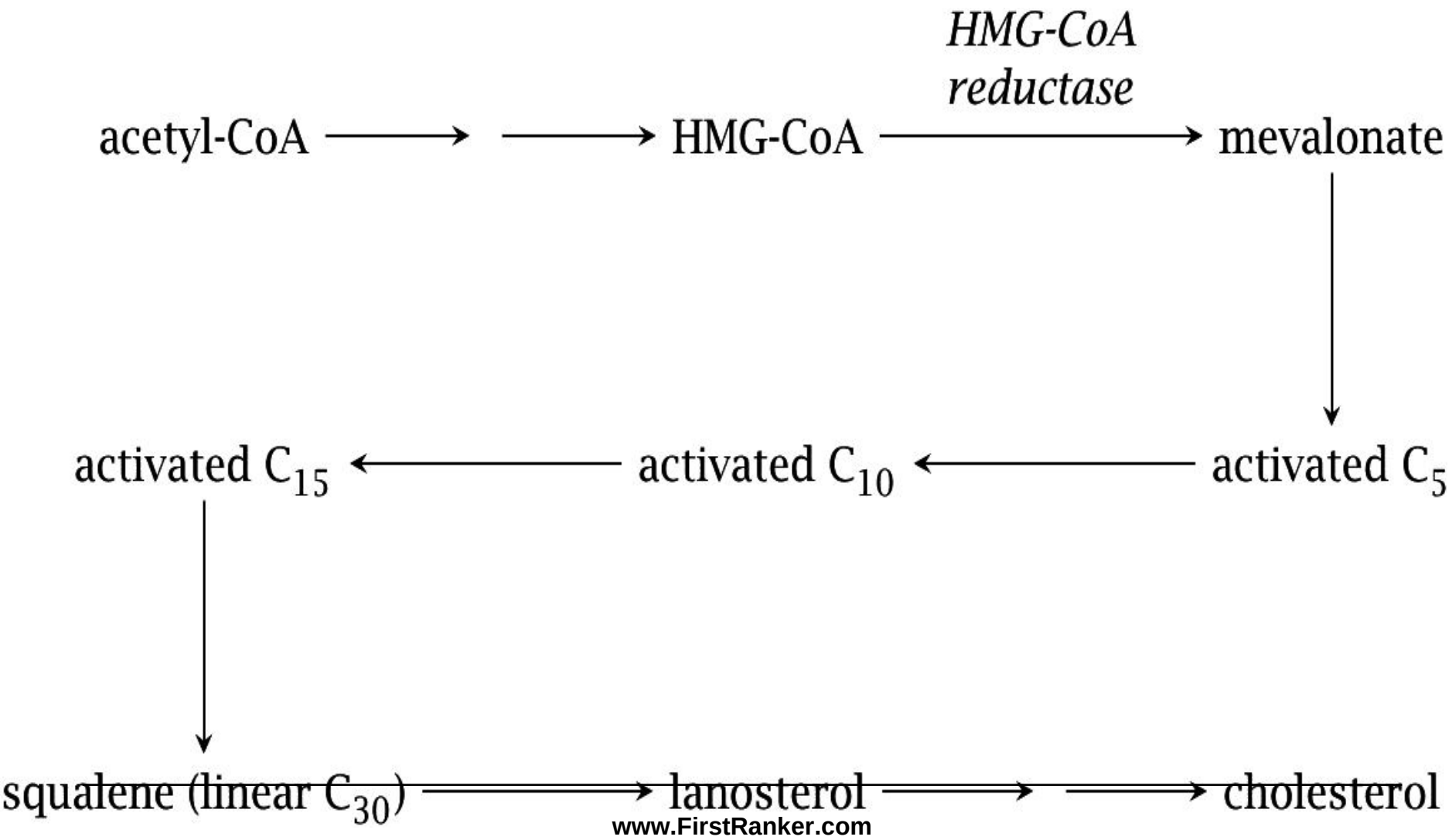
- **Stage 2.**
- **Mevalonate forms Active Isoprenoid units(C5)**

- **Stage 3.**
- **6 Isoprenoid units form Squalene (C30)**

- **Stage 4.**
- **Squalene is converted to Lanosterol**

- **Stage 5.**
- **Lanosterol is converted to Cholesterol(C27)**

Overview/Outline of Cholesterol Synthesis



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Acetyl-CoA → 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA)

Thiolase

Acetoacetyl-CoA

HMG-CoA synthase

HMG-CoA reductase
STATINS

Mevalonic acid

ATP

Mevalonate kinase

Mevalonate-5-phosphate

Phosphomevalonate kinase

Mevalonate-5-pyrophosphate

Isopentenyl-PP isomerase

CO_2

Mevalonate-5-pyrophosphate decarboxylase

Dimethylallyl-PP ← **Isopentenyl-5-pyrophosphate** (PP)

Farnesyl-PP synthase
BISPHOSPHONATES

Geranyl PP

Farnesyl-PP synthase
BISPHOSPHONATES

Geranylgeranyl-PP ← **Farnesyl-PP**

Geranylgeranyl-PP synthase

Squalene synthase

Squalene

Squalene monooxygenase

2,3 oxidosqualene

NADPH

Squalene epoxydase

Lanosterol

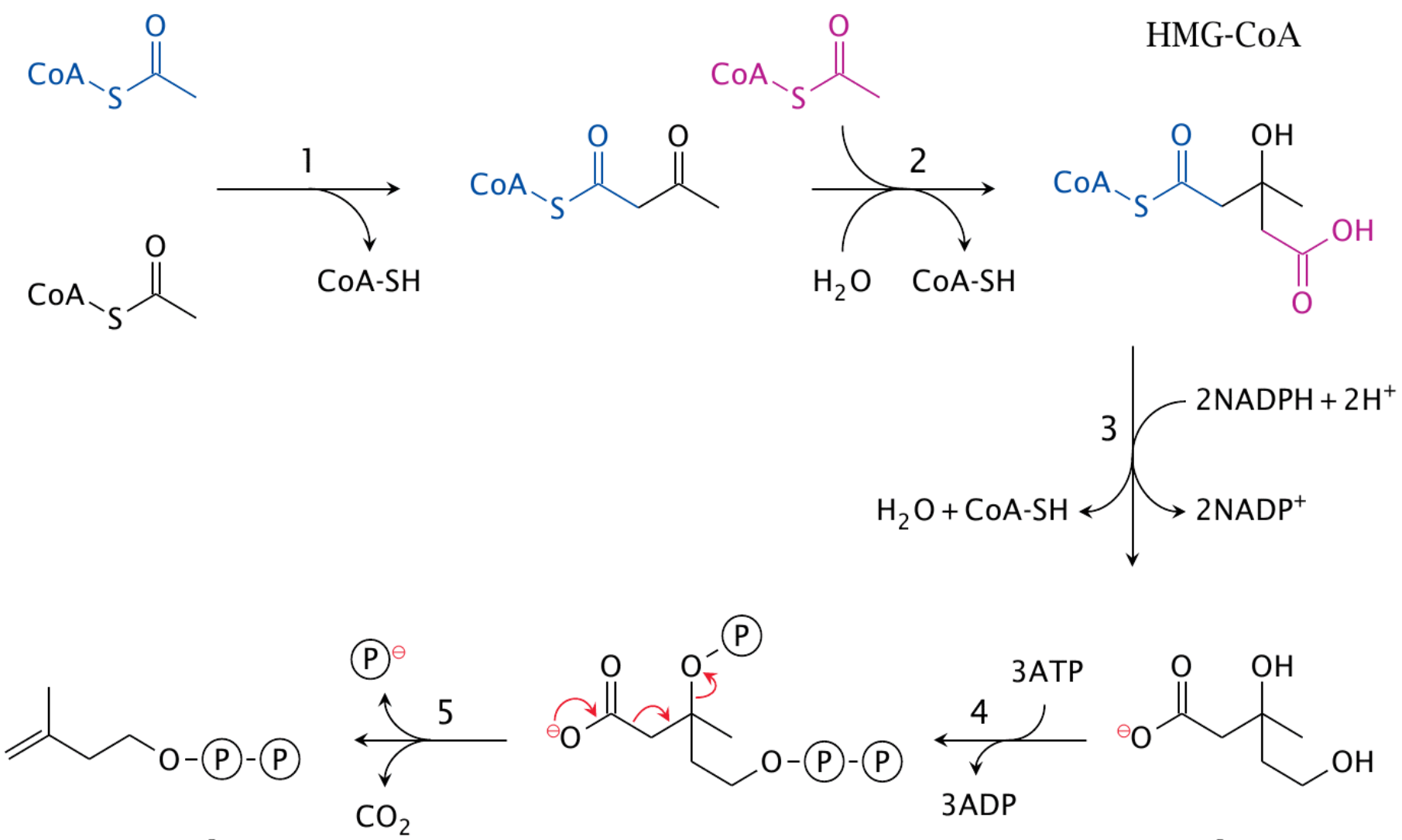
19 reactions

PRENYLATED PROTEINS

HEME A
DOLICHOL
UBIQUINON

CHOLESTEROL

Initial Activation Steps in Cholesterol Synthesis



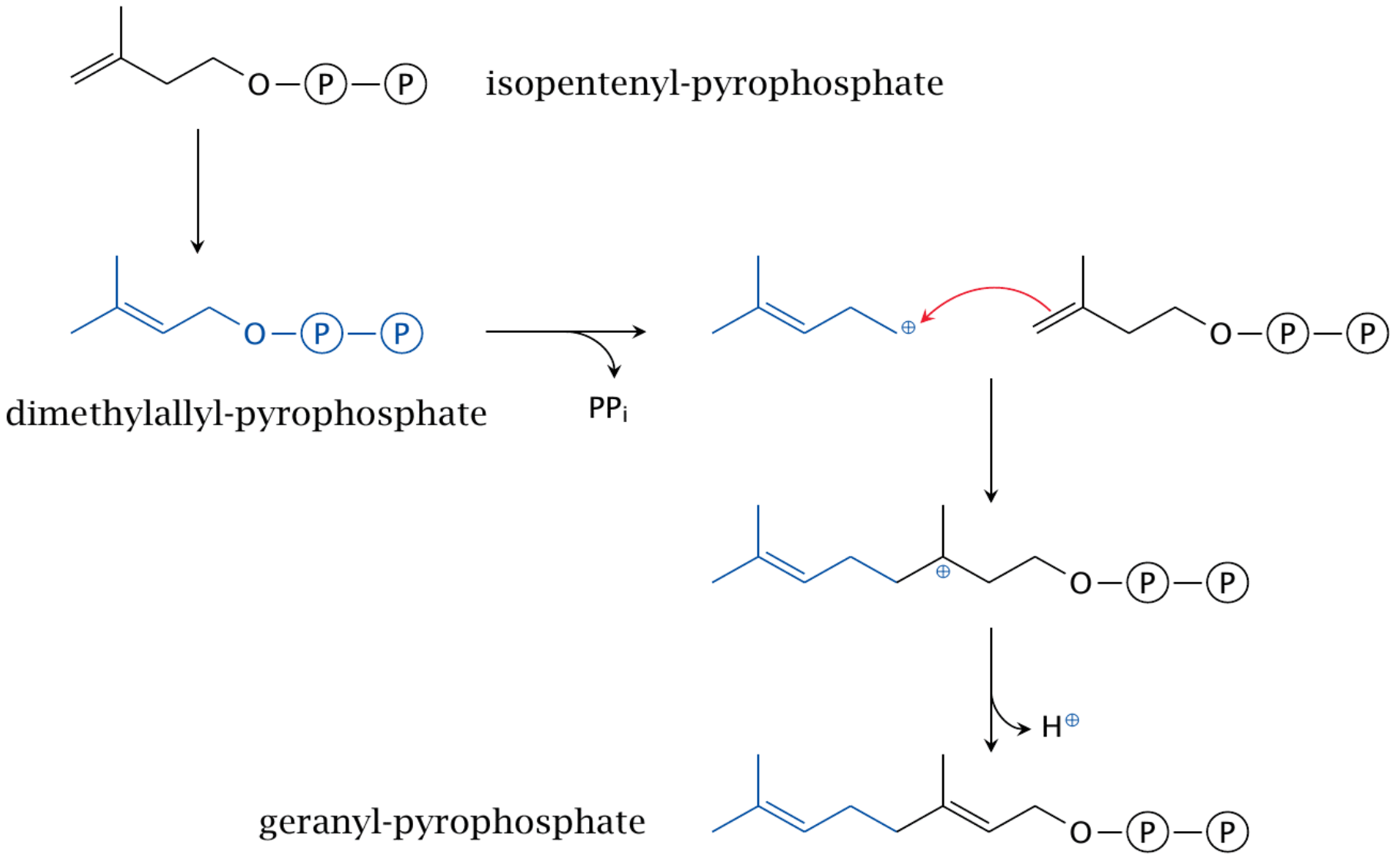
isopentenyl-pyrophosphate

mevalonate

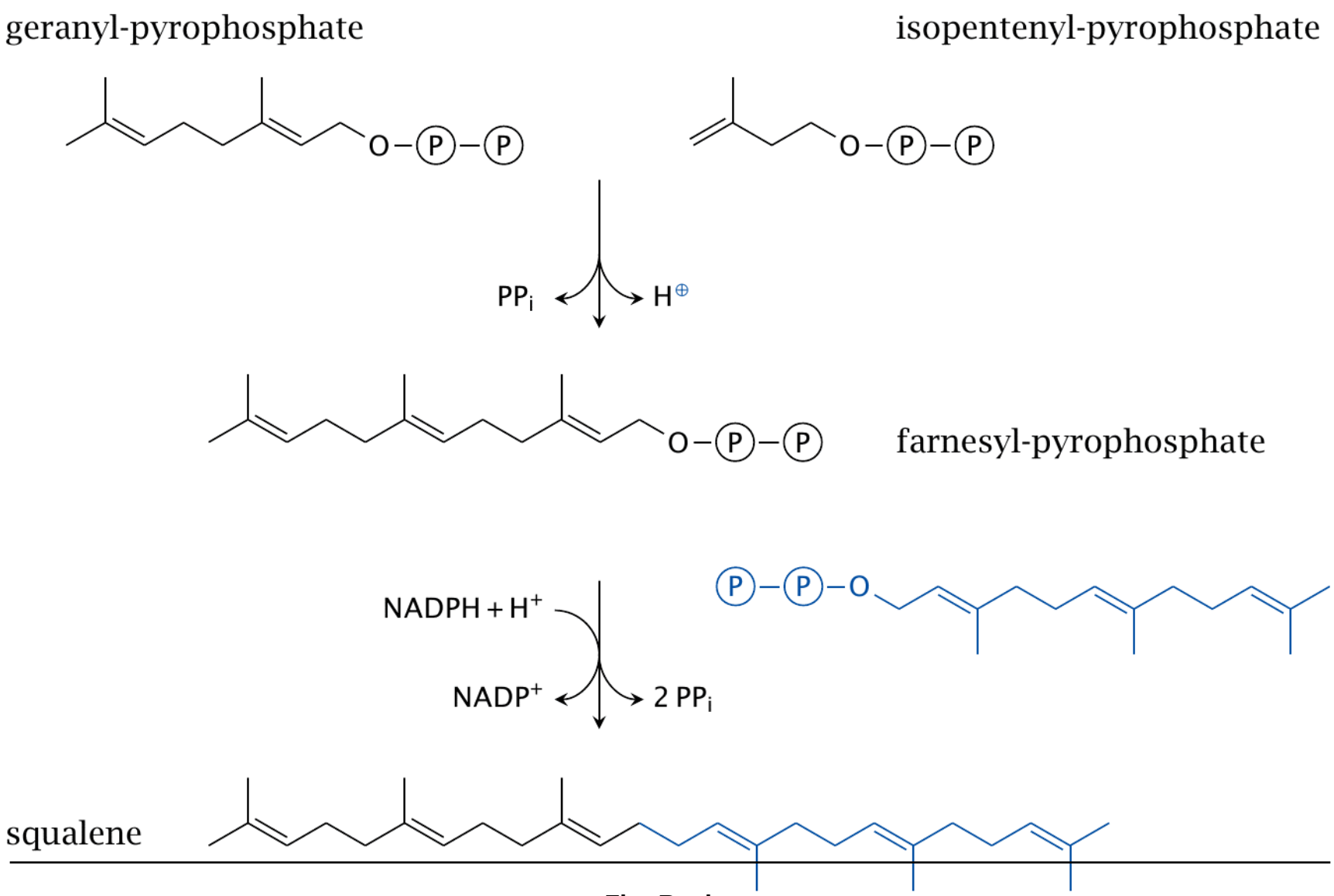
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Formation of a C_{10} intermediate GPP



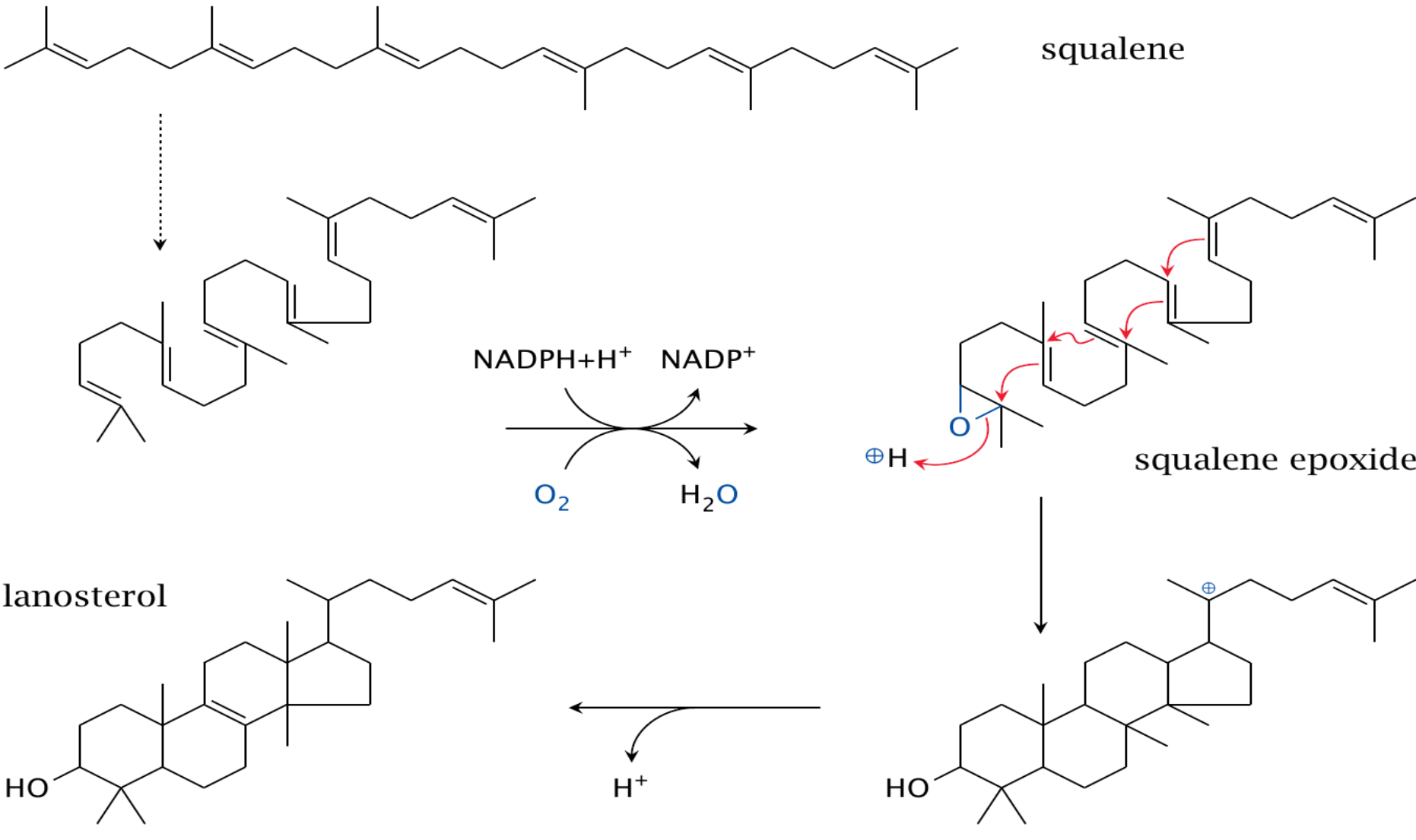
Formation of C_{15} and C_{30} intermediates



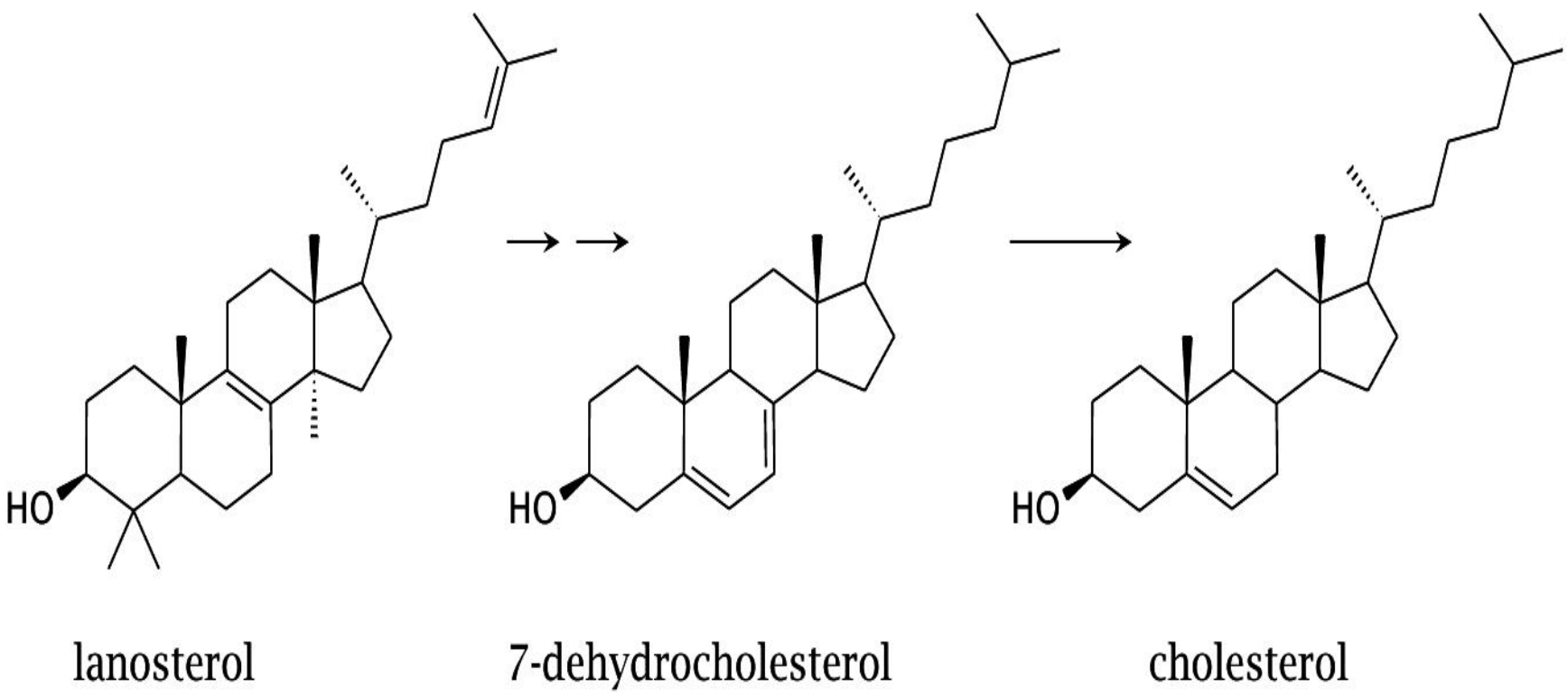
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Squalene cyclization yields the first sterol intermediate



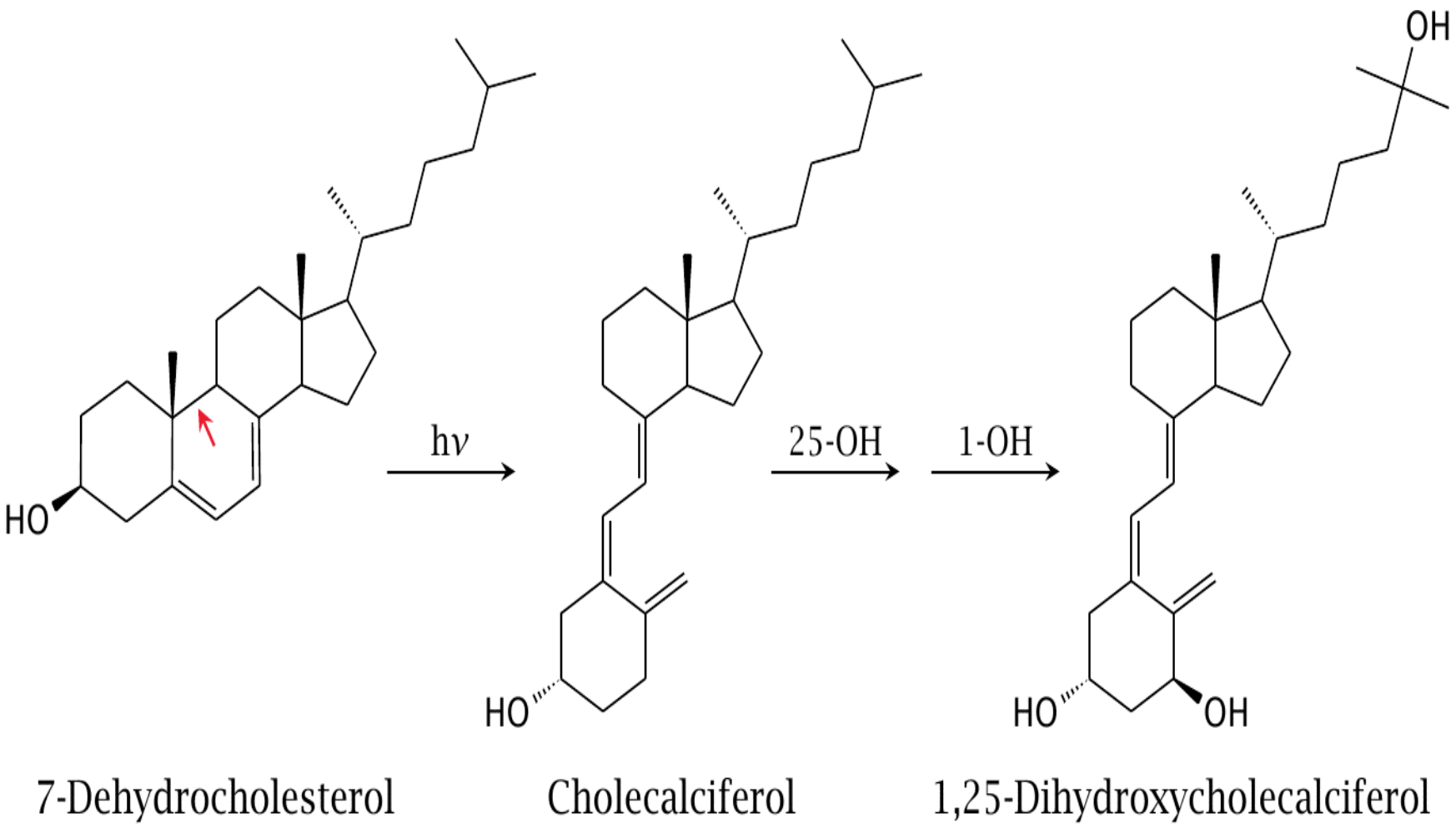
Demethylation, desaturation and saturation steps convert lanosterol to cholesterol



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UV-dependent synthesis of Cholecalciferol



7-Dehydrocholesterol Cholecalciferol 1,25-Dihydroxycholecalciferol

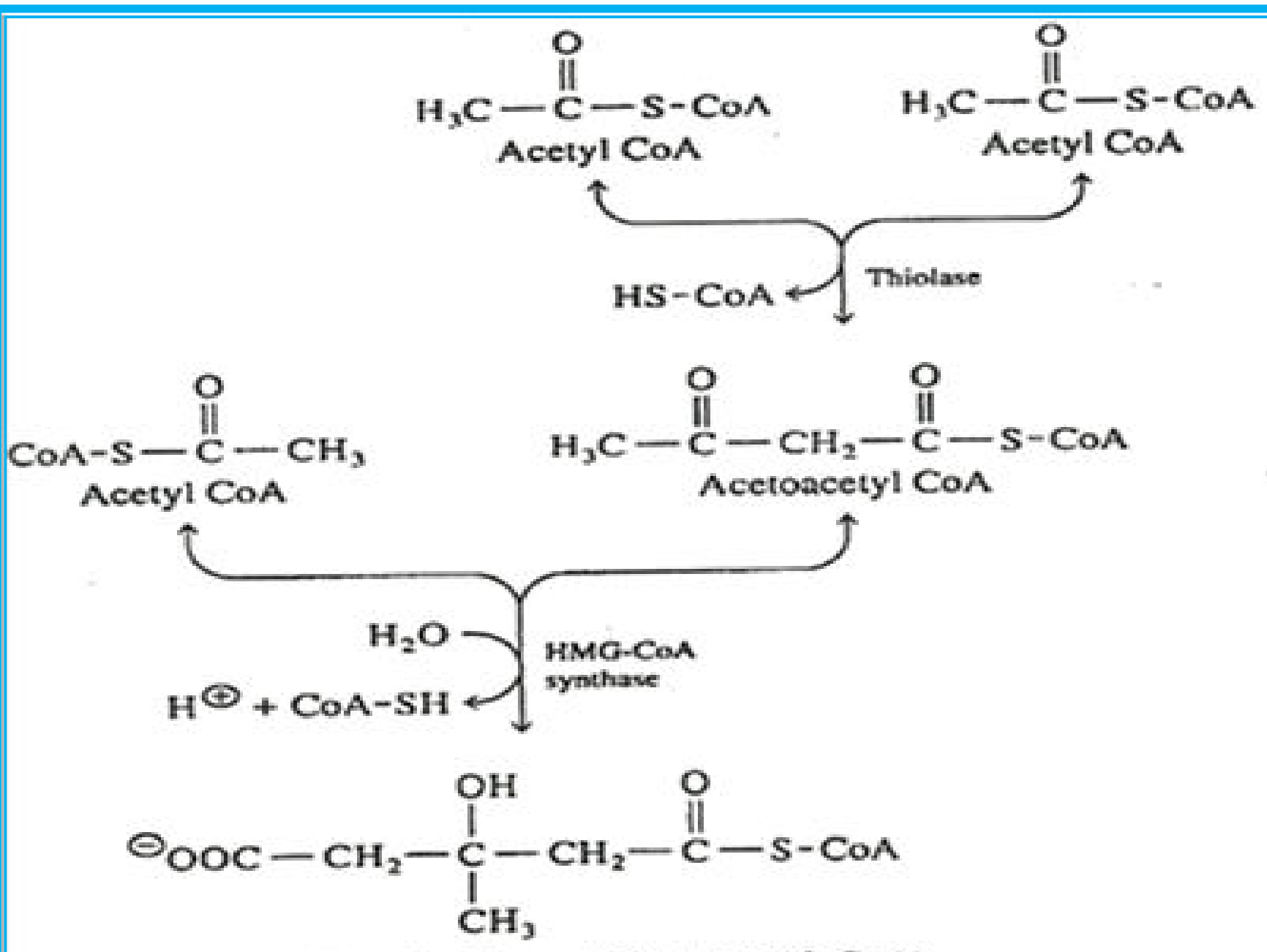
Stage I

Synthesis Of HMG CoA and Mevalonate

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It starts by the condensation of **three** molecules of **Acetyl CoA(C2)** with the formation of **HMG CoA (C6)** **by HMG CoA Synthase** **(As like In Ketogenesis)**



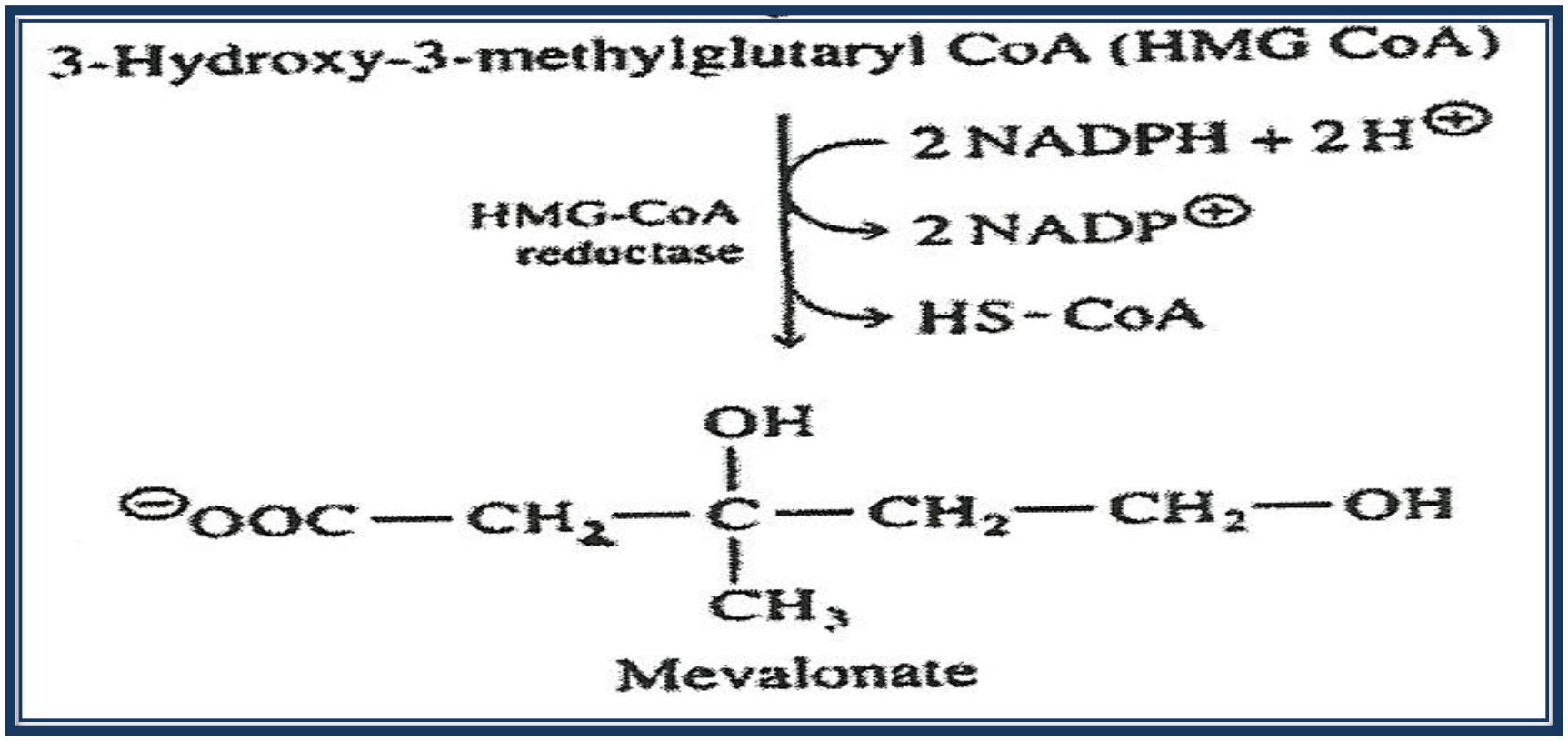
3-Hydroxy-3-methylglutaryl CoA (HMG CoA)

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HMG CoA is Reduced to Mevalonic acid (C6) by reaction requiring **NADPH+H+** and enzyme **HMG CoA Reductase.**

Two molecules of NADPH are consumed in the reaction.



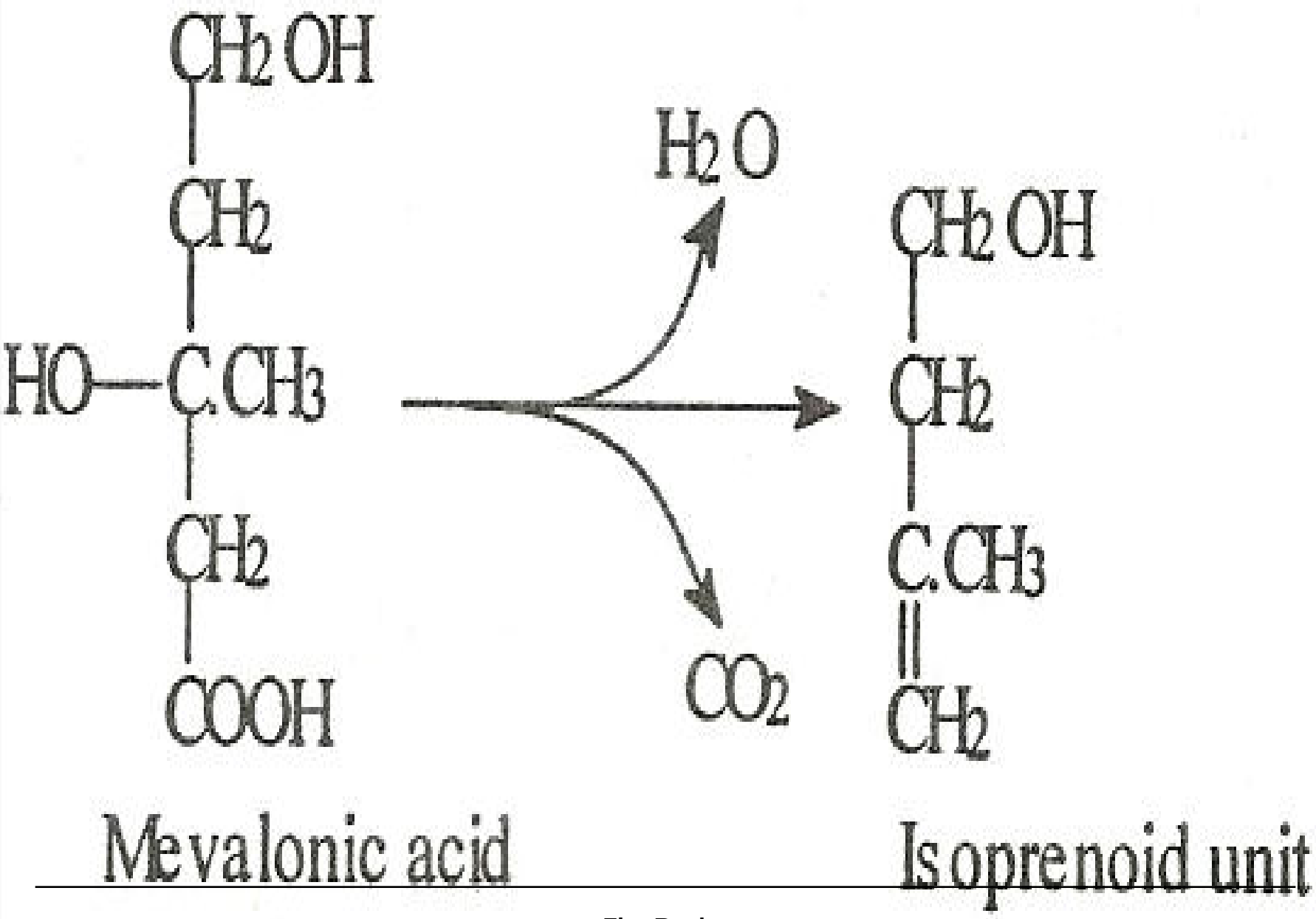
Stage 2
Formation Of Isoprenoid Unit Isopentenyl Pyrophosphate (IPP)

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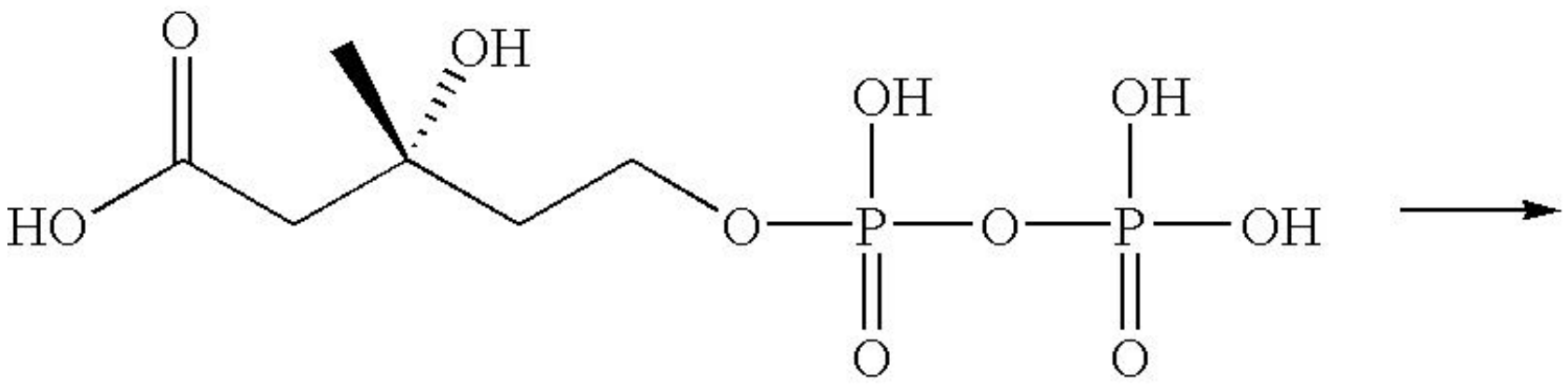
- **Mevalonate** in three subsequent steps is
  - **Phosphorylated with ATPs**
  - **Dehydrated and**
  - **Decarboxylated**

- To form Isoprenoid unit(C5)- **Isopentenyl pyrophosphate(IPP).**

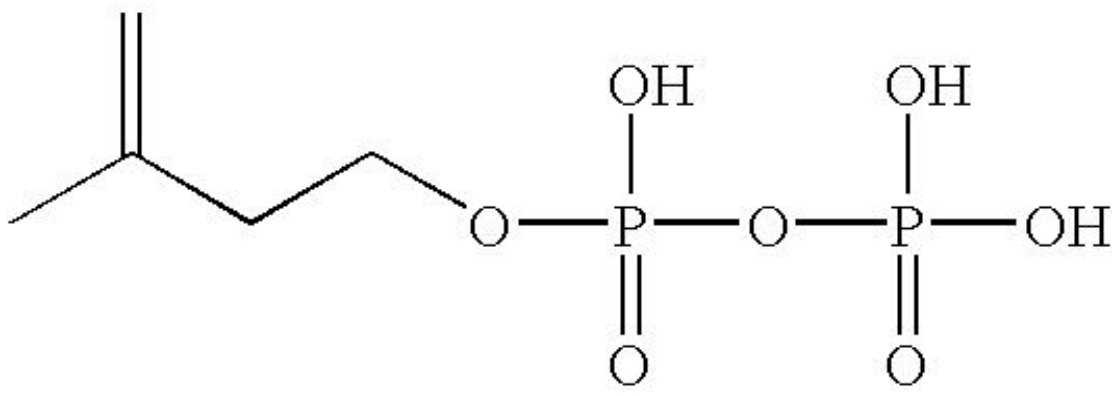


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Mevalonate 5-diphosphate



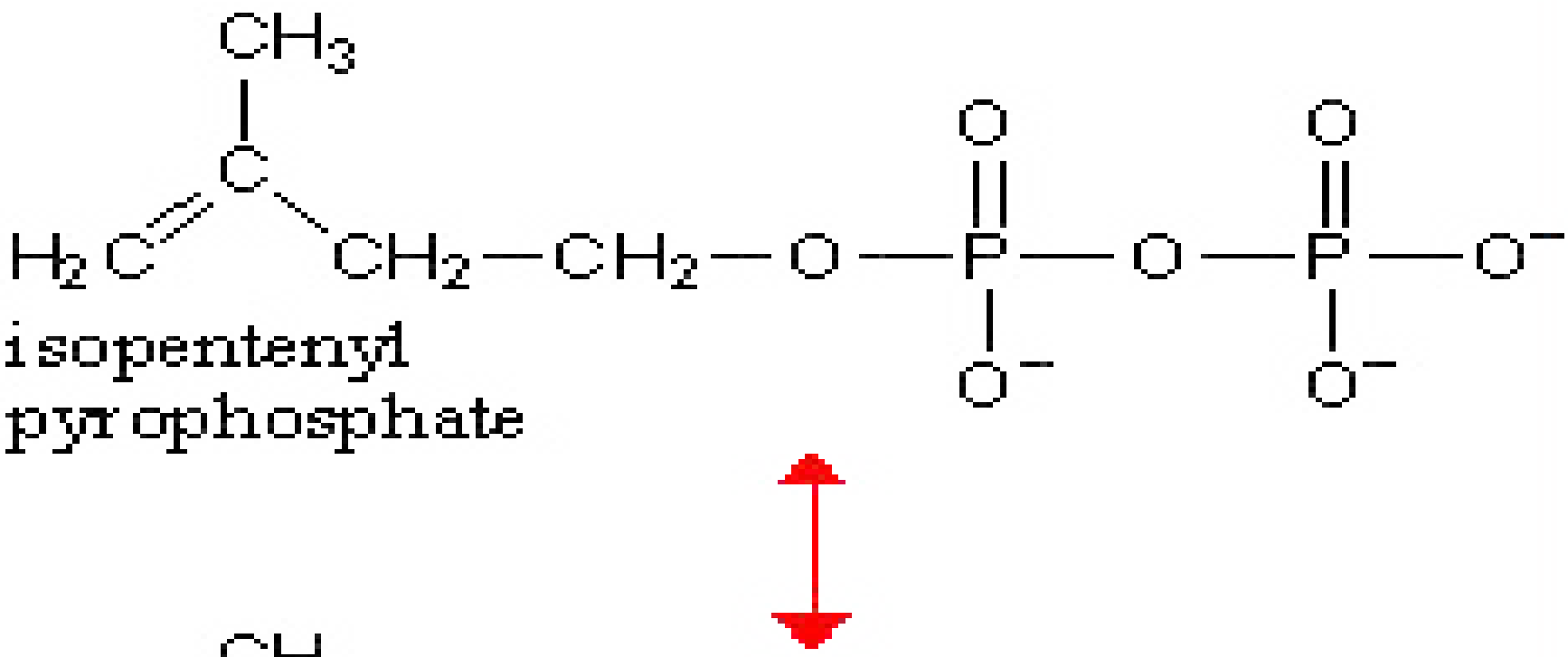
Isopentenyl pyrophosphate

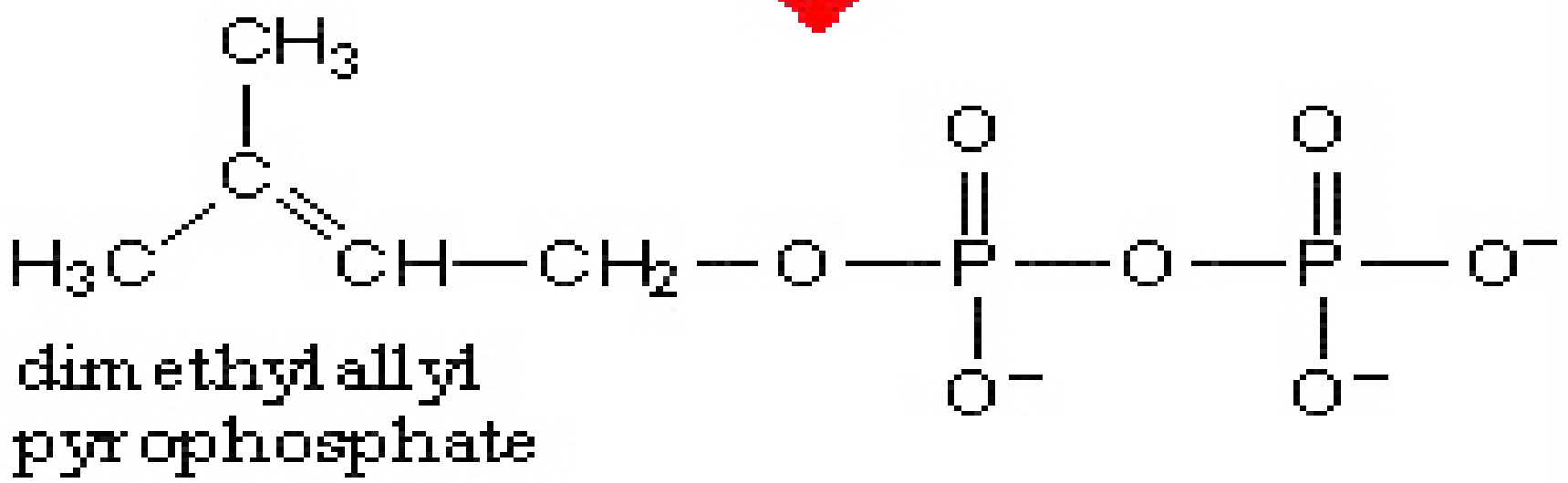
Isomerization Of IPP To DPP

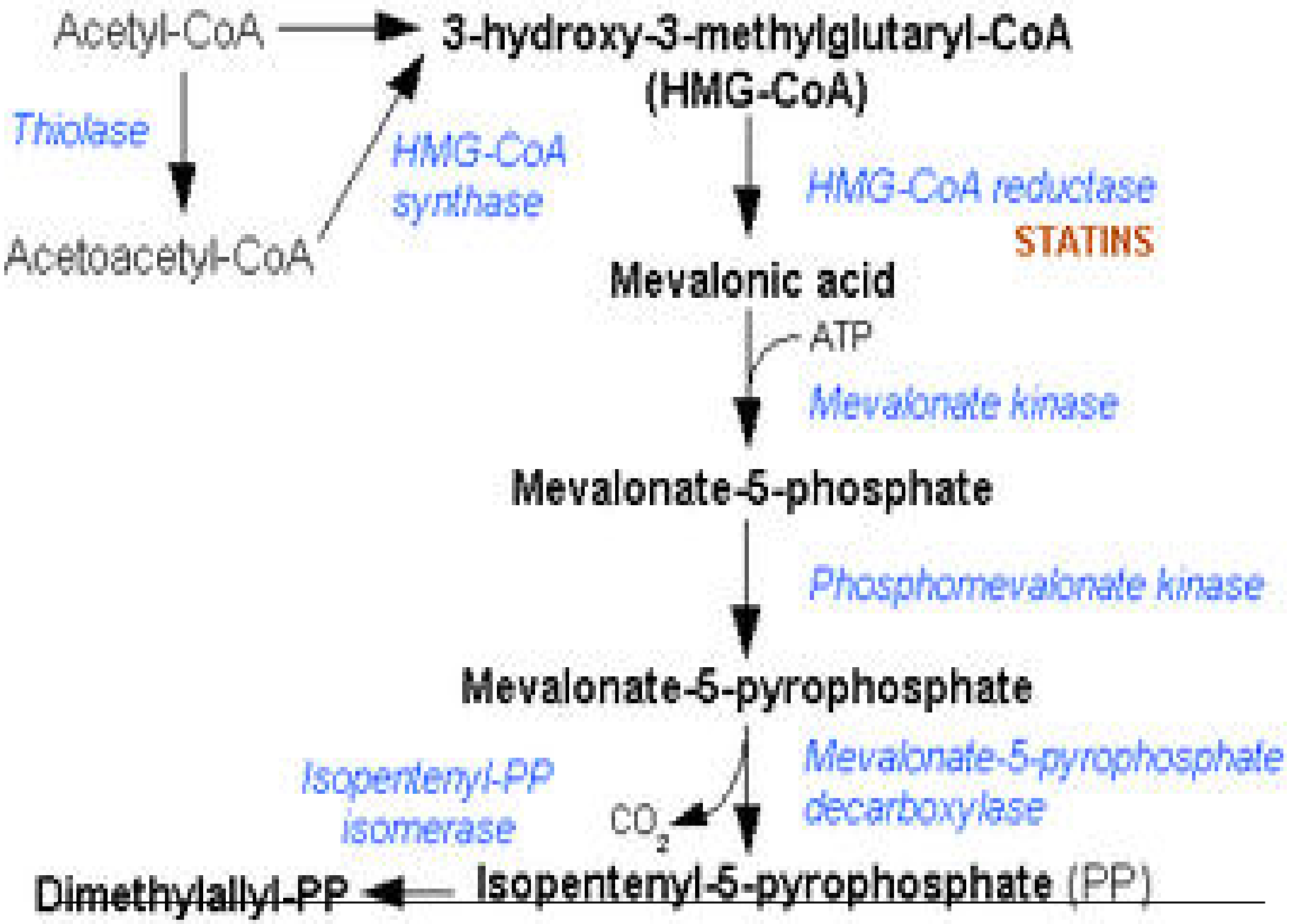
- Isopentenyl Pyrophosphate (IPP-C5) is **isomerized to** **Dimethylallyl Pyrophosphate** (DPP-C5) with the **Isomerase** activity

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Stage 3
Synthesis Of Squalene (C30)

Formation Of Geranyl Pyrophosphate (GPP-C10)

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- **IPP** (C5) and **DPP** (C5) get condensed to form **Geranyl Pyrophosphate** (GPP-C10)

Formation OF Farnesyl Pyrophospate (FPP- C15)

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- 1 molecule of **GPP condenses** with 1 molecule of **IPP** to form **Farnesyl Pyrophospahte** (FPP-C15)

Conversion Of FPP(C15) to Squalene (C30)

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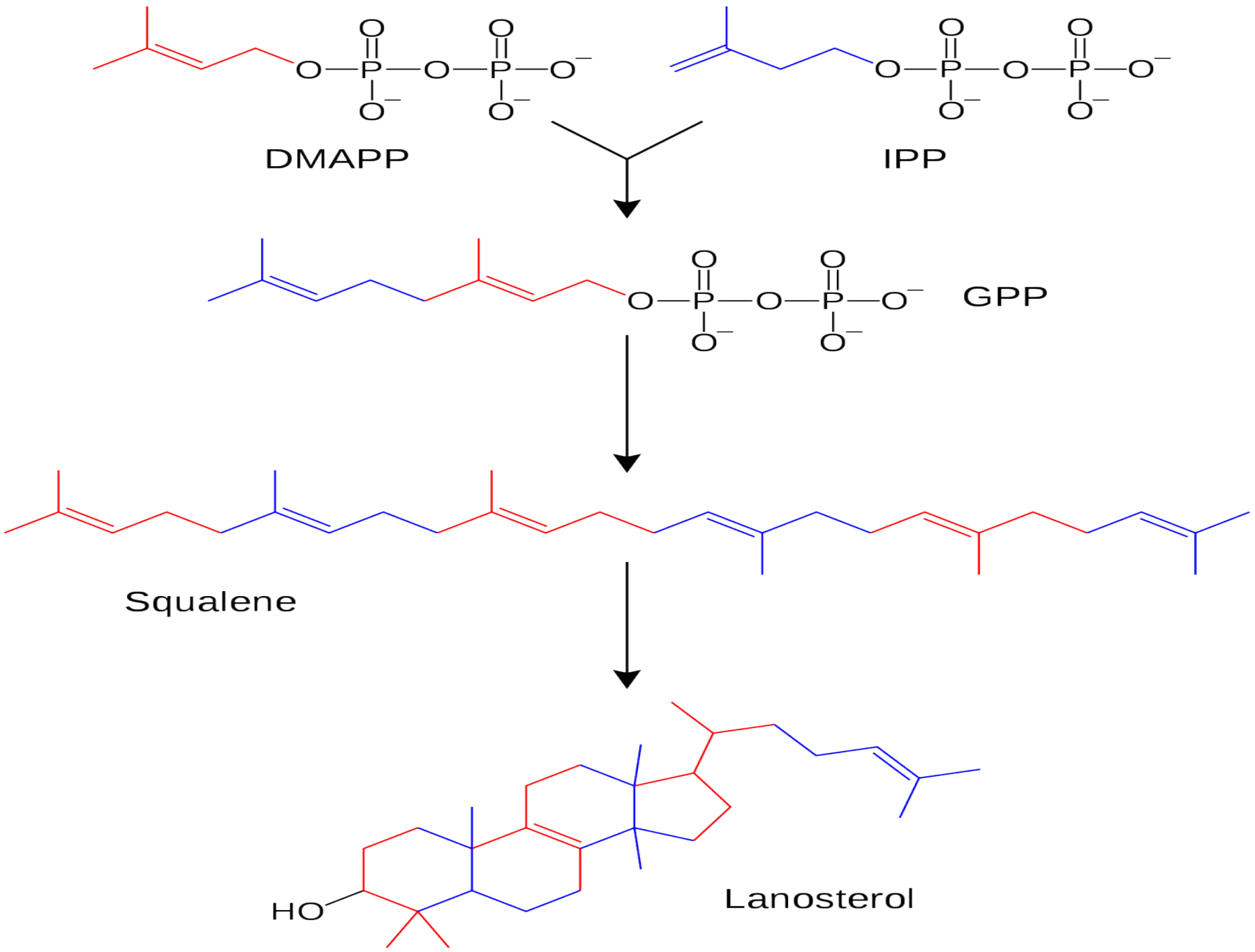
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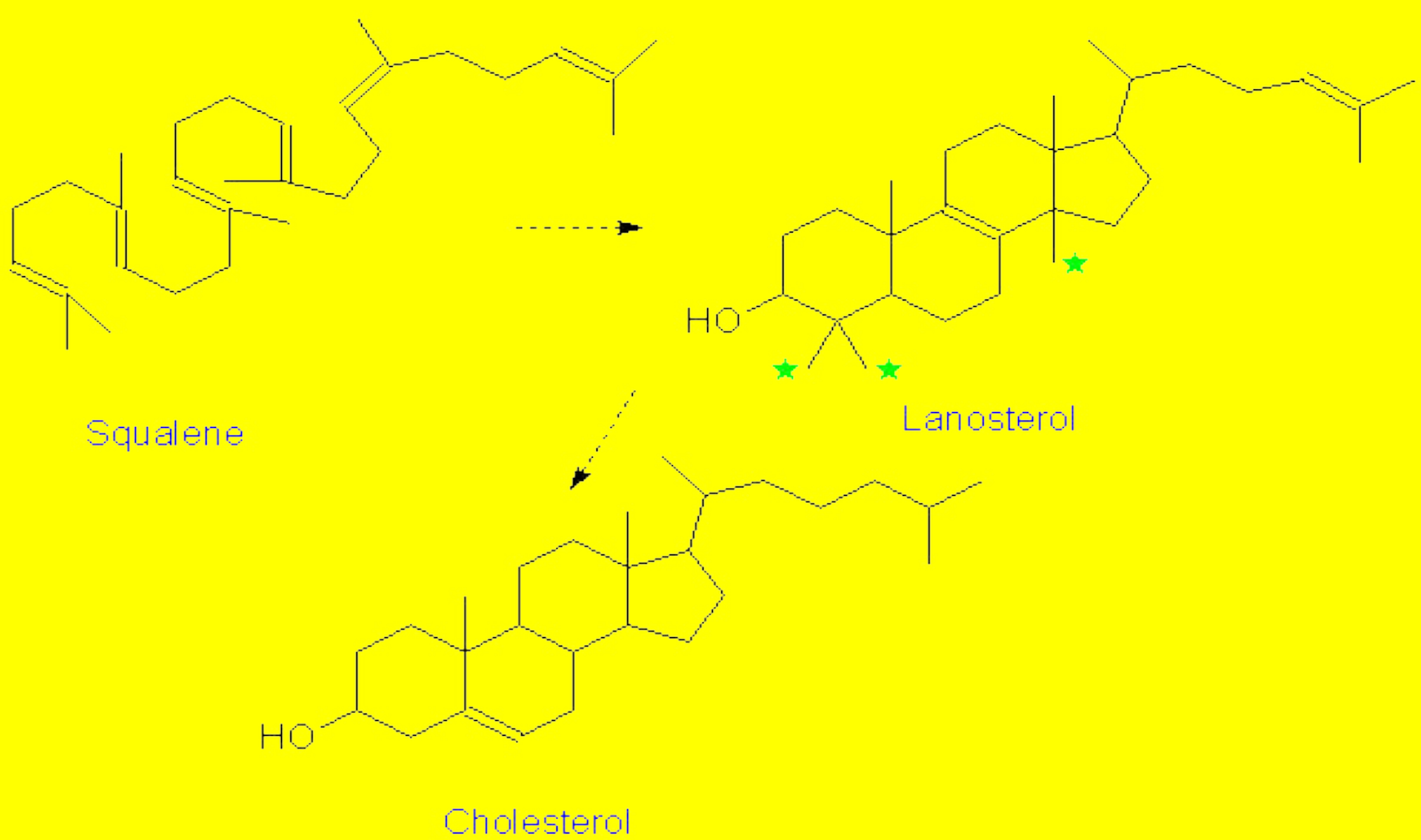
- Two molecules of FPP get condensed to **generate Squalene.**
- At smooth Endoplasmic Reticulum with the catalytic activity of **Squalene Synthase** Coenzyme **NADPH+H+** and Cofactors **Mg , Mn and Co**

Sage 4
Conversion Of Squalene To Lanosterol

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Stage 5
Transformation Of Lanosterol To Cholesterol

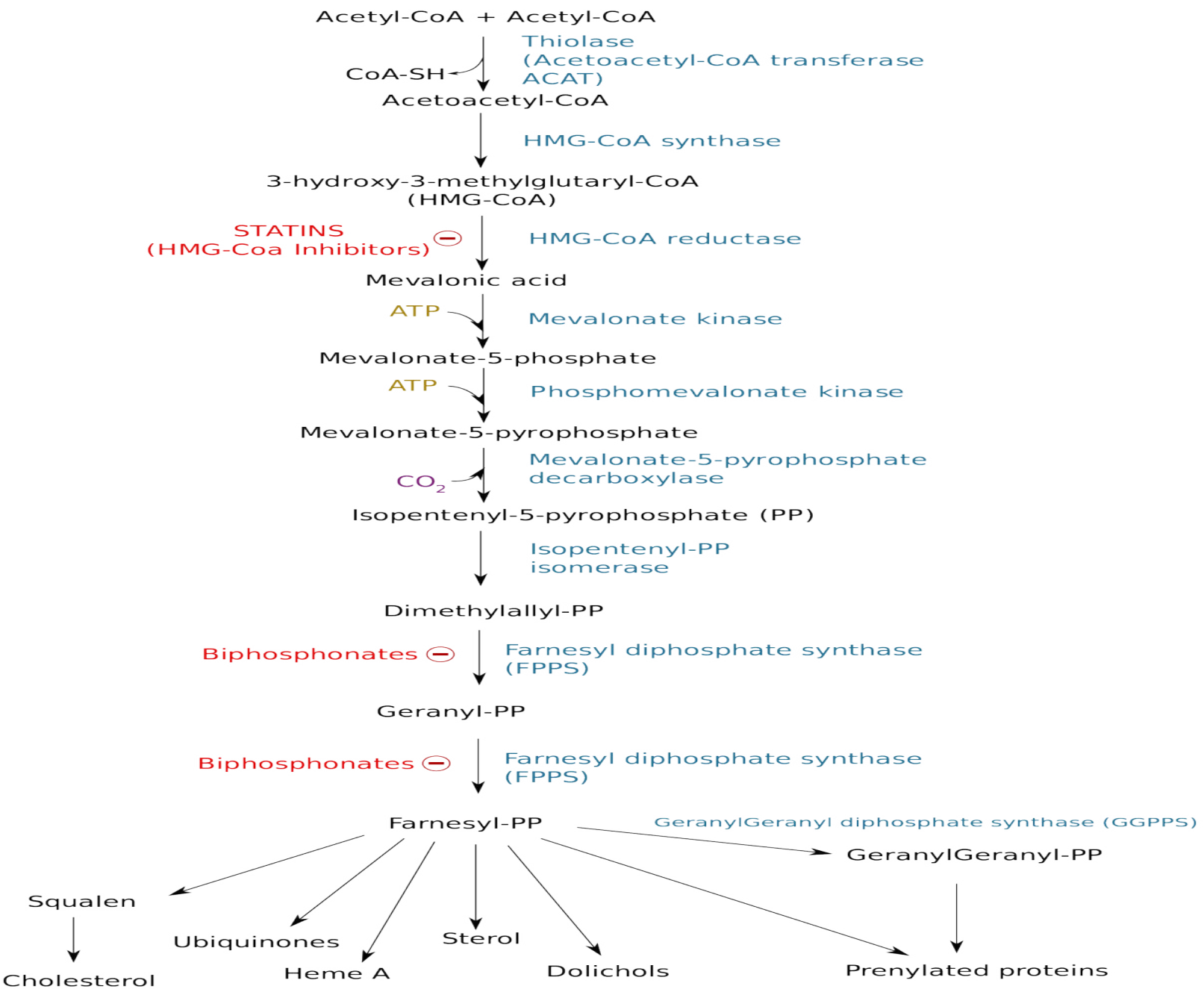
- Lanosterol is converted to Cholesterol with many sequential steps

- With an **intermediates Zymosterol and Desmosterol**

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Mevalonate pathway



Uses Of Body Cholesterol

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- **Cholesterol** after its biosynthesis may **serve as precursor for:**
  - **–Steroidal Hormones**
  - **–Bile Acids**
  - **–Vitamin D**

Fates Of Body Cholesterol

- Cholesterol in human body is **component of various biomembranes of cells.**
- **Cholesterol helps in nerve impulse conduction**
- Cholesterol is a **precursor for**
- Bile acids
- Vitamin D
- Steroidal Hormones-
  - – Aldosterone
  - – Estrogen
  - – Progesterone
  - – Testosterone

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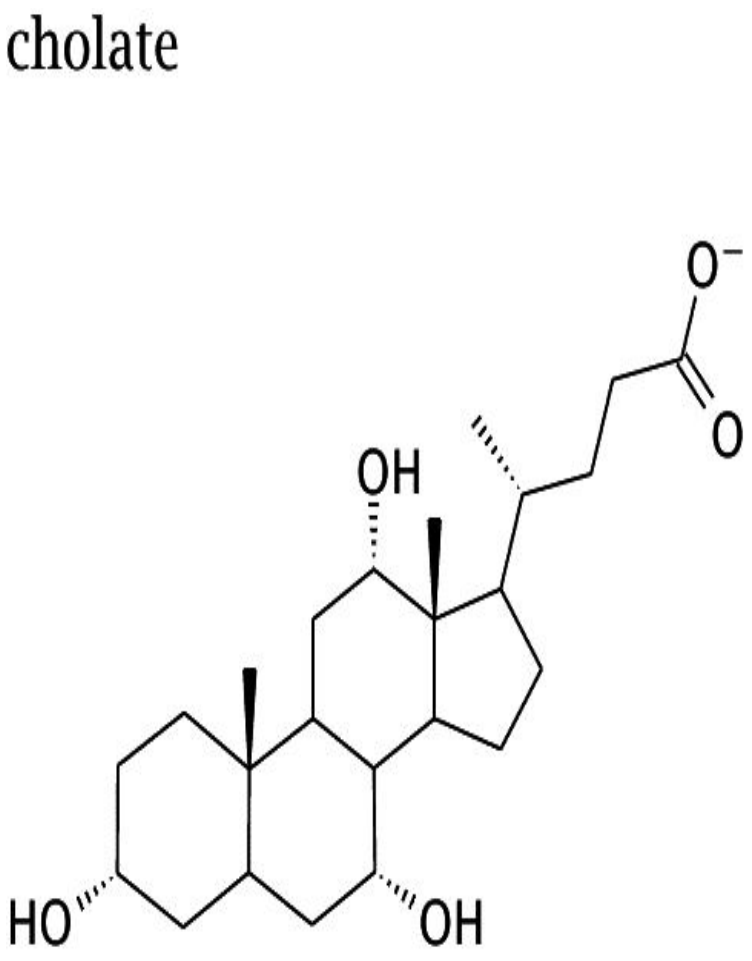
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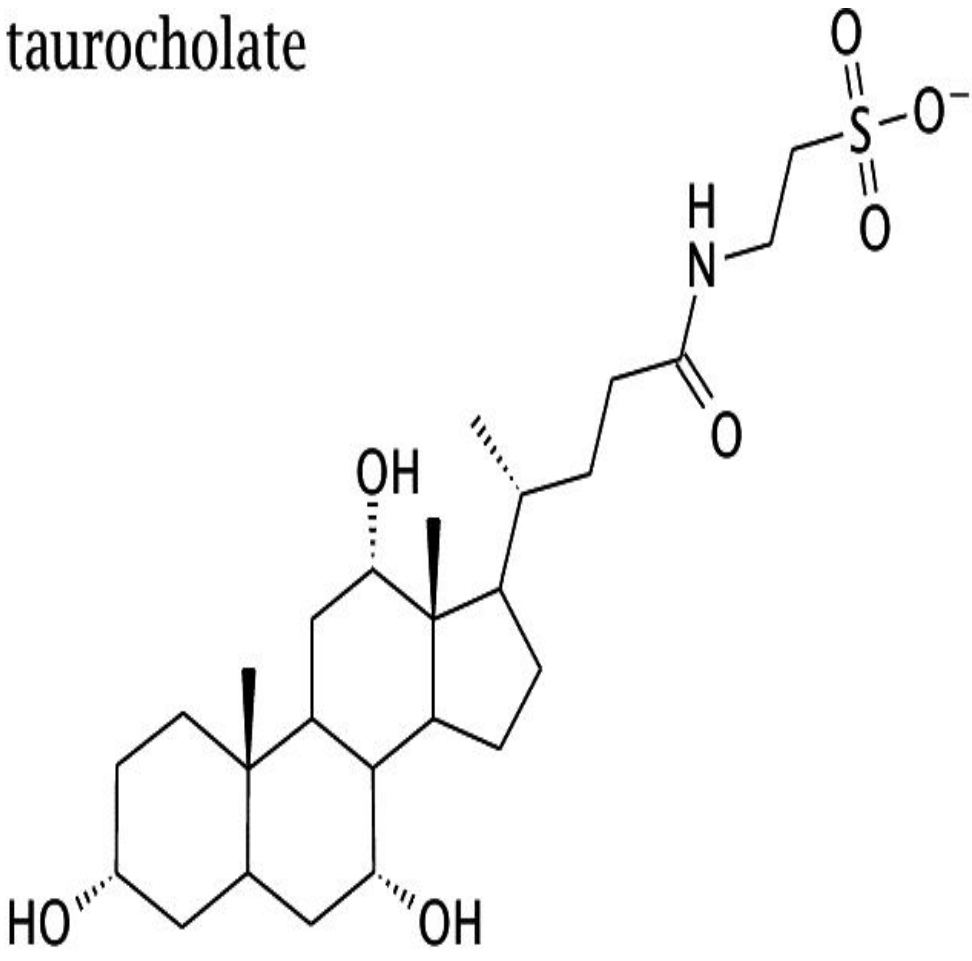
Bile Acids Formed From Cholesterol

- **Primary Bile Acids:**
  - Cholic Acid
  - Cheno Deoxy Cholic Acid

- **Secondary Bile Acids:**
  - Glycocholic Acid
  - Taurocholic Acid
  - De- Oxycholic Acid
  - Lithocholic Acid

Bile acids are Derived from Cholesterol





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- **Bile acids synthesized from Cholesterol** in the Liver are **carried through bile**

- **Released into the intestine** and reabsorbed in the Jejunum and Ileum.

Bile Acids are Transformed To Bile Salts

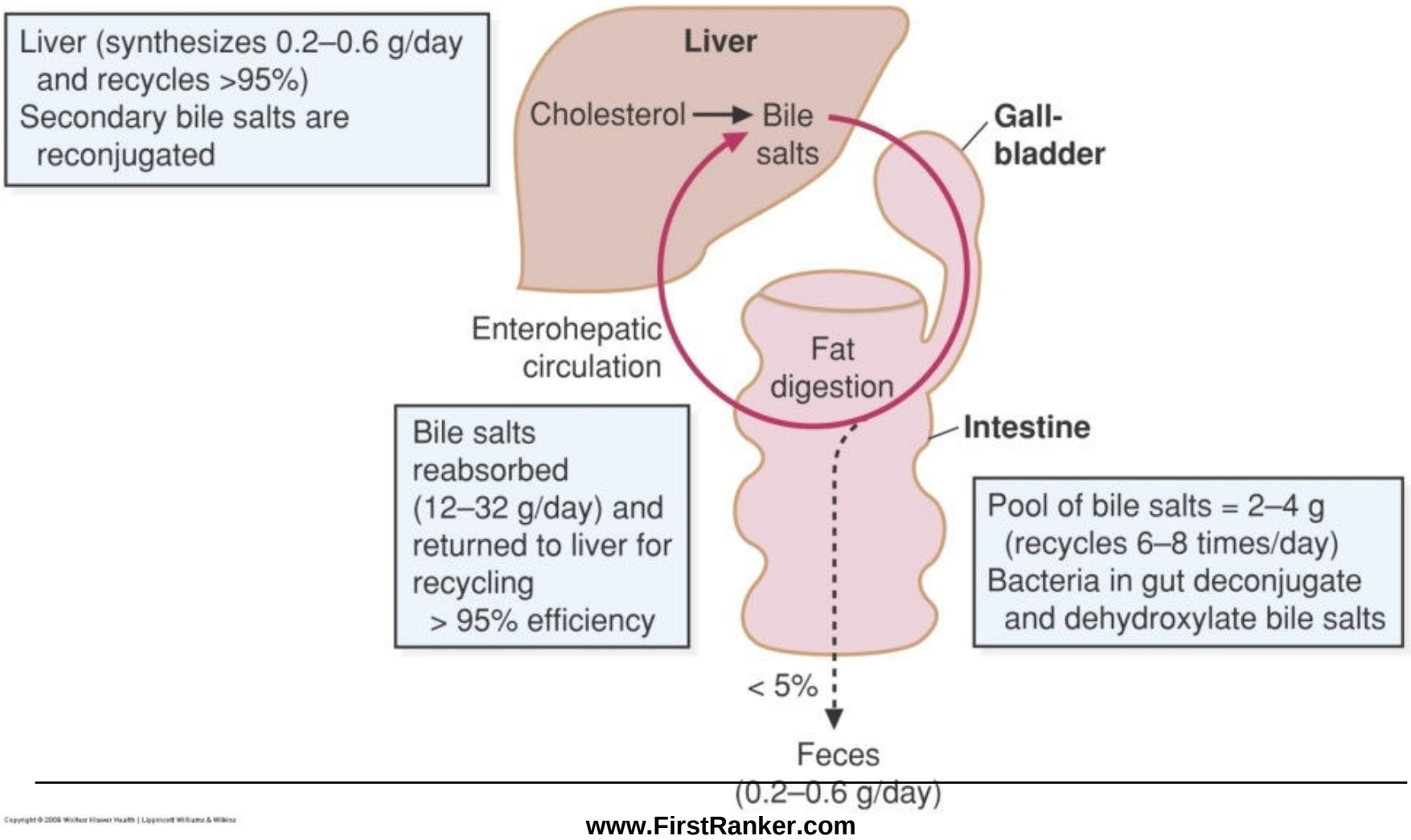
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Role Of Bile Salts

- Bile Salts are **effective detergents**
- They are biosynthesized in the Liver
- Stored & concentrated in the Gallbladder
- **Bile salts in Intestine facilitates in digestion and absorption of intraluminal lipids**
- Through **formation of emulsions and mixed micelles.**

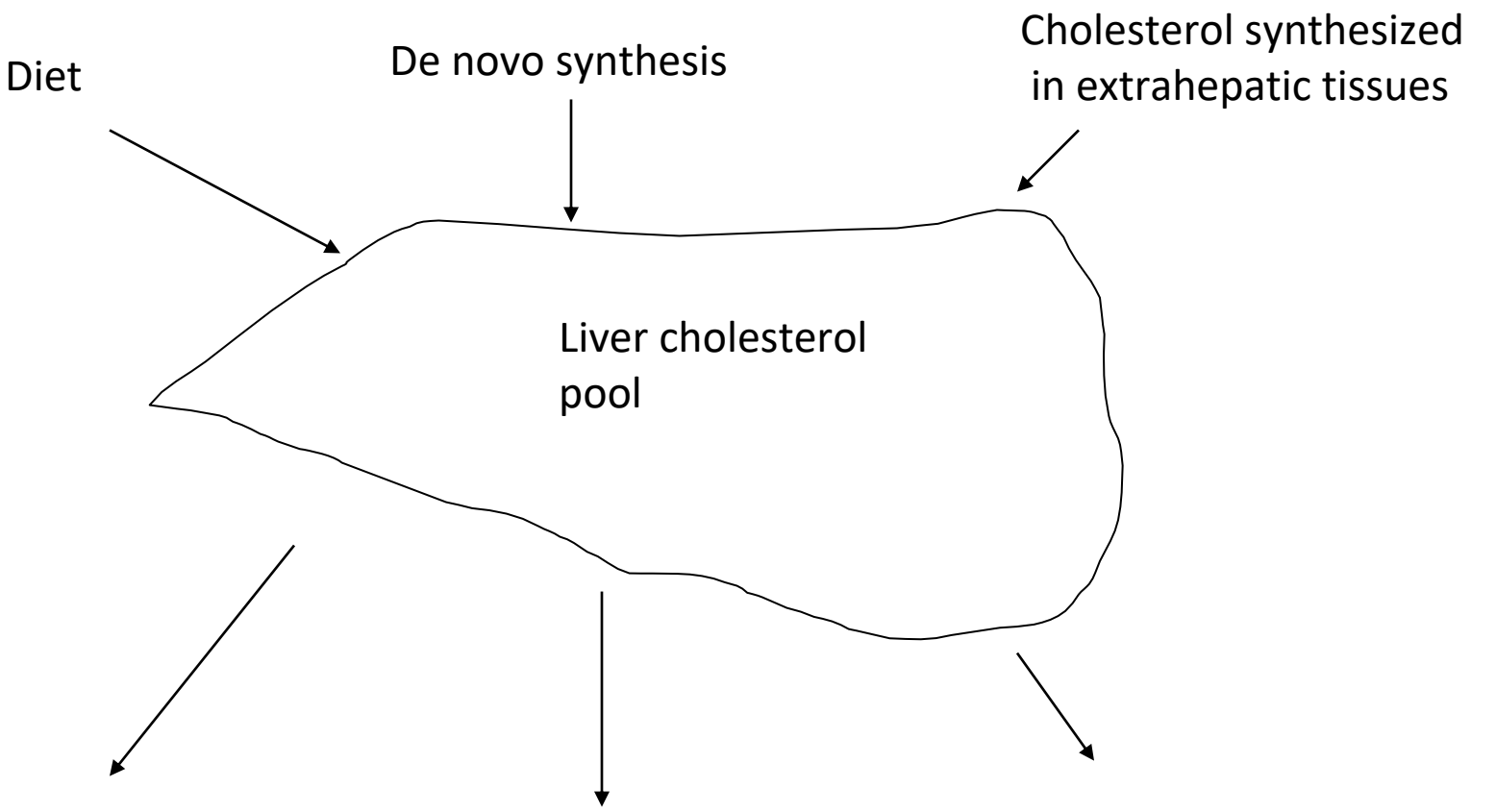
Fate of Bile Salts



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Fates of Cholesterol



Regulation Of Cholesterol Biosynthesis

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HMG-CoA Reductase

- Is the **regulatory/ key enzyme** of **Cholesterol Biosynthesis**.

- The enzyme is **stimulated and inhibited as per the requirement of bodies need.**

- **The enzyme HMG-CoA reductase has half-life of 3 hrs.**

- **Degradation of HMG-CoA reductase depends on Cholesterol levels.**

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Modes Of Cholesterol Regulation

- Hormonal Influence
- Covalent Modification
- Feedback Inhibition

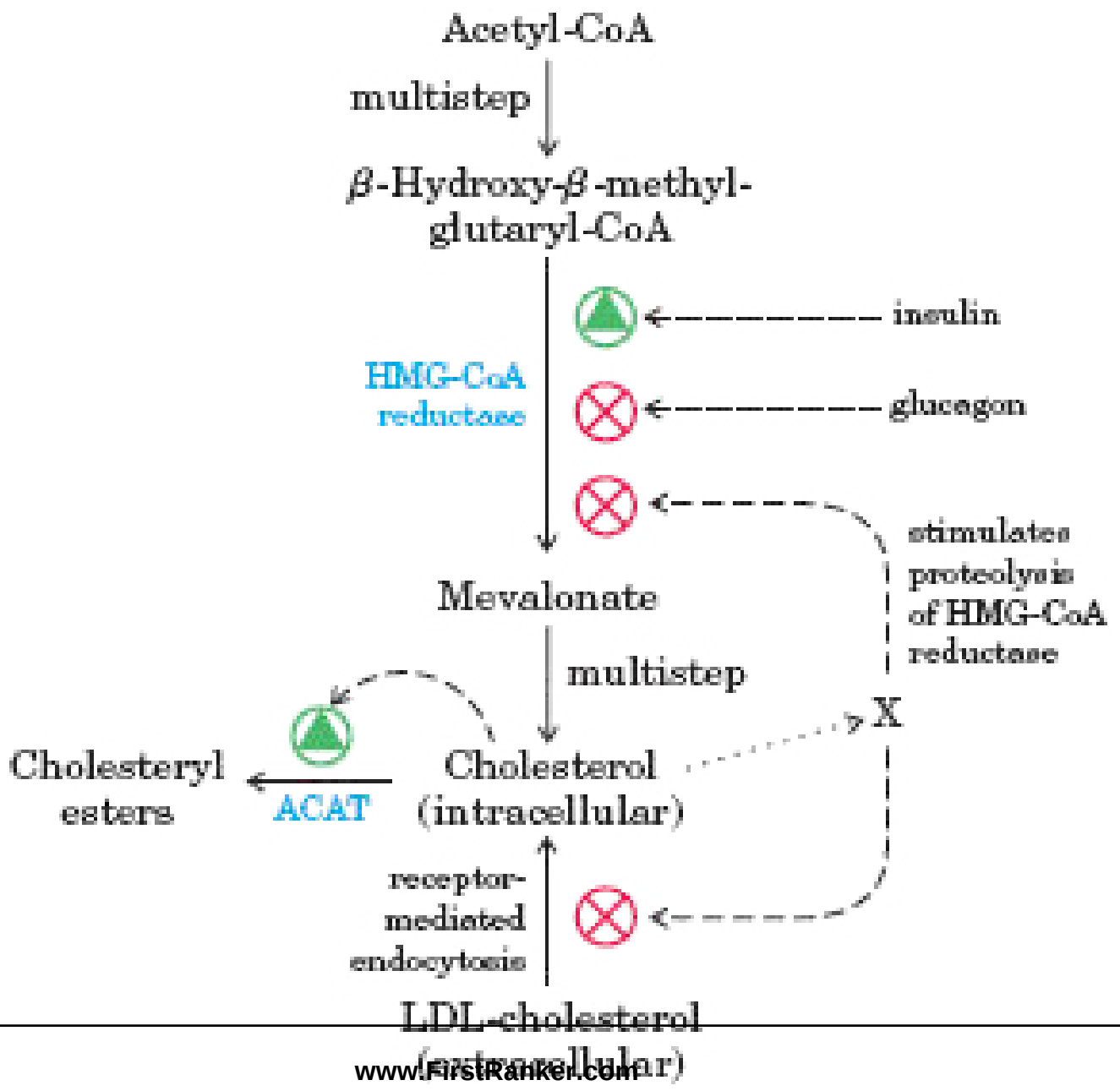
Hormonal Regulation

- **Insulin In well fed state:**
  - **Stimulates** and increases **HMG CoA Reductase**
  - **Increases** Cholesterol Biosynthesis

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- **Glucagon and Glucocorticoids in emergency states:**
  - **Inhibits** HMG CoA Reductase.
  - **Decreases** Cholesterol Biosynthesis.



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Covalent Modification Of Regulatory Enzyme HMG CoA Reductase

Phosphorylation And Dephosphorylation Of HMG CoA Reductase

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- **Short-term regulation** of Cholesterol biosynthesis is by
- **Phosphorylation & dephosphorylation** of Key enzyme **HMG CoA Reductase**

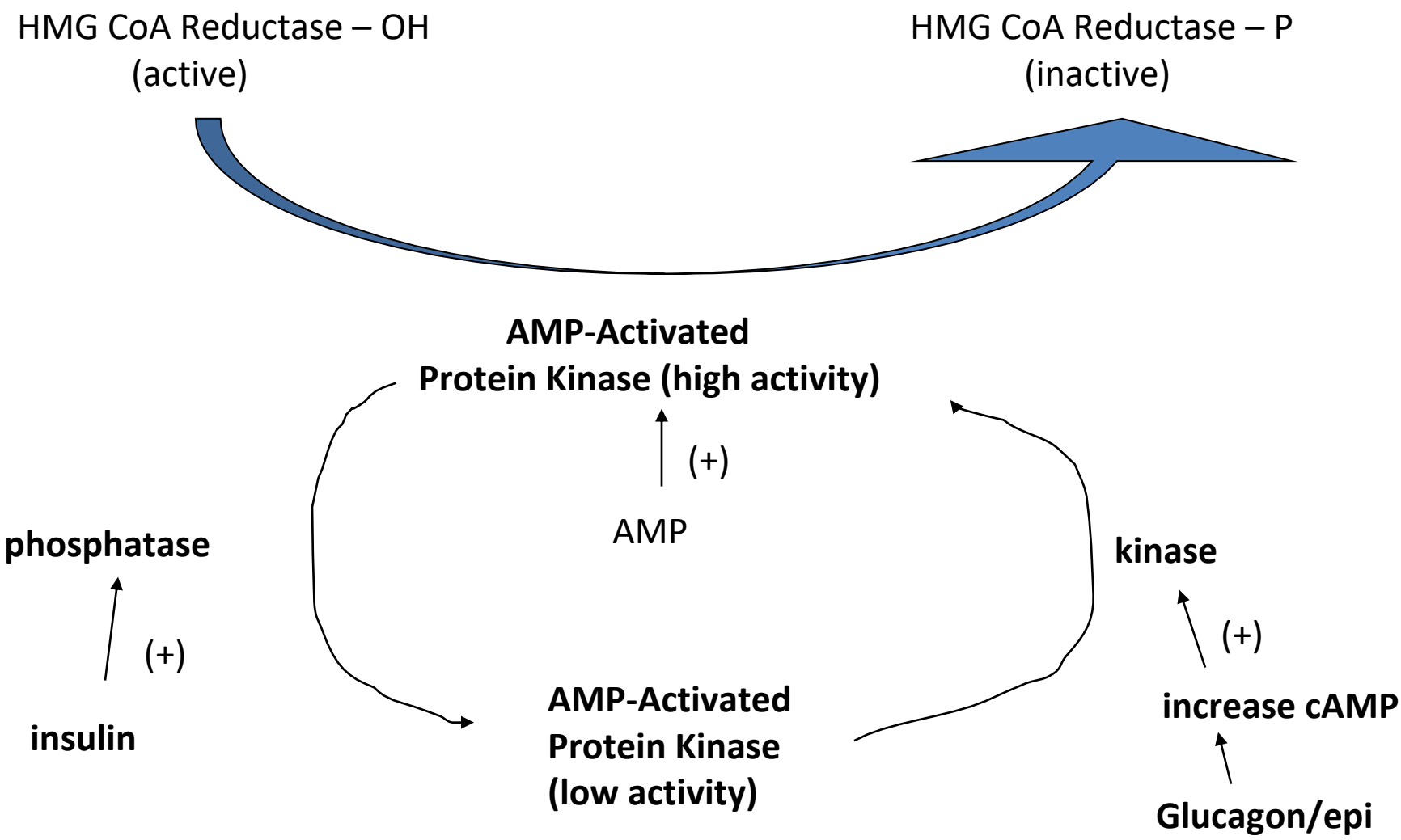
- **Phosphorylated –HMG CoA Reductase- Inactive Form**

- **Dephosphorylated-HMG CoA Reductase- Active form**

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HMG CoA Reductase - Phosphorylation



- Under influence of Hormone **Glucagon**
- **HMG CoA Reductase** is Phosphorylated by **cAMP-dependent Protein Kinases.**
- **Phosphorylation** of the Enzyme **inactivates HMG-CoA Reductase**
- **This inhibits Cholesterol Biosynthesis.**

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- Glucagon, Sterols, Glucocorticoids & low ATP levels
- **Inactivate HMG-CoA Reductase**.

- **Under influence of Hormone Insulin**
- **HMG CoA Reductase is Dephosphorylated**
- Which **activates HMG-CoA Reductase.**
- This **increases Cholesterol Biosynthesis.**

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- **Insulin, Thyroid hormone, high ATP levels**
- **Activate the key enzyme HMG-CoA Reductase.**

Feed Back Inhibition

- **Sufficient amounts of body Cholesterol** regulate its biosynthesis
- By **feed back inhibition** of **Enzyme HMG CoA Reductase.**

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- **Ingestion of Cholesterol inhibits endogenous cholesterol synthesis** (control exerted at both transcriptional and translational levels).
- **Gene expression (mRNA production) is controlled by Cholesterol levels**

Cholesterol Synthesis Transcription Control

- Rate of HMG-CoA Reductase mRNA synthesis is controlled
- By **Sterol Regulatory Element Binding Protein (SREBP)**

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Competitive Inhibitors Of Cholesterol Biosynthesis

- **Drugs like Statins- Lovastatin ,Simvastatin**
- **Competitive inhibitors** of key Enzyme **HMG CoA Reductase** of Cholesterol biosynthesis.
- **Decreases Endogenous Cholesterol Biosynthesis**

Lovastatin Inhibits Cholesterol Biosynthesis

- **Lovastatin (Mevinolin) blocks HMG-CoA Reductase activity and prevents biosynthesis of Cholesterol.**
- **Lovastatin is an (inactive) Lactone**
- **In the body, the Lactone is hydrolyzed to Mevanolinic acid, which is a competitive inhibitor of HMG CoA reductase.**

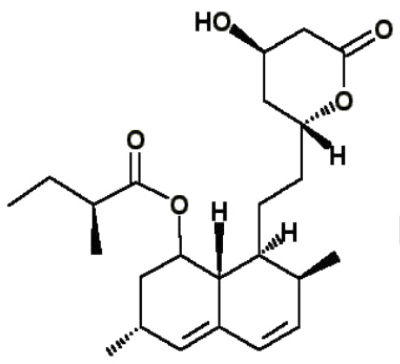
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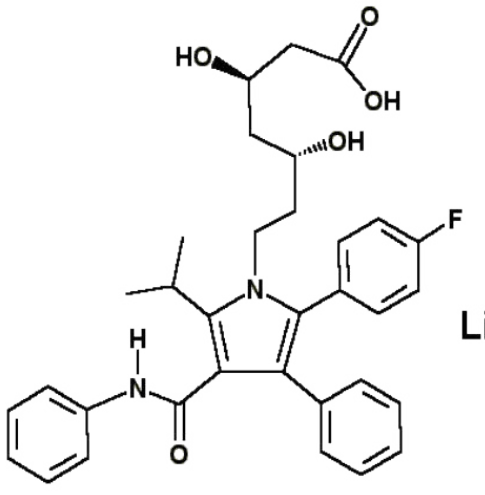
Drugs Lowering Cholesterol

- **Statins** – decrease HMG CoA Reductase activity

Statins



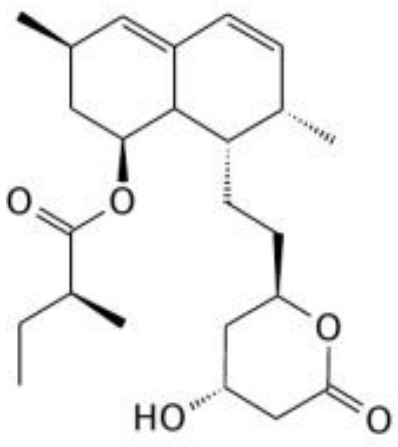
Mevacor (lovastatin)



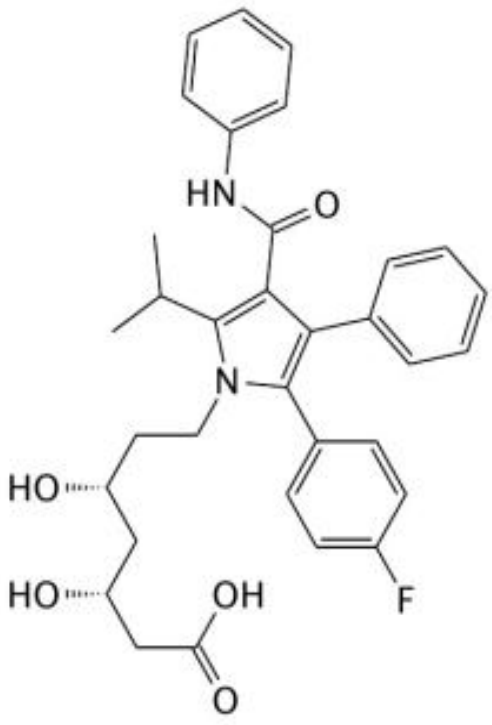
Lipitor

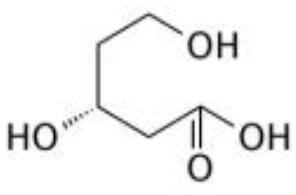
"Statins" Competitively Inhibit HMG-CoA Reductase

Mevastatin

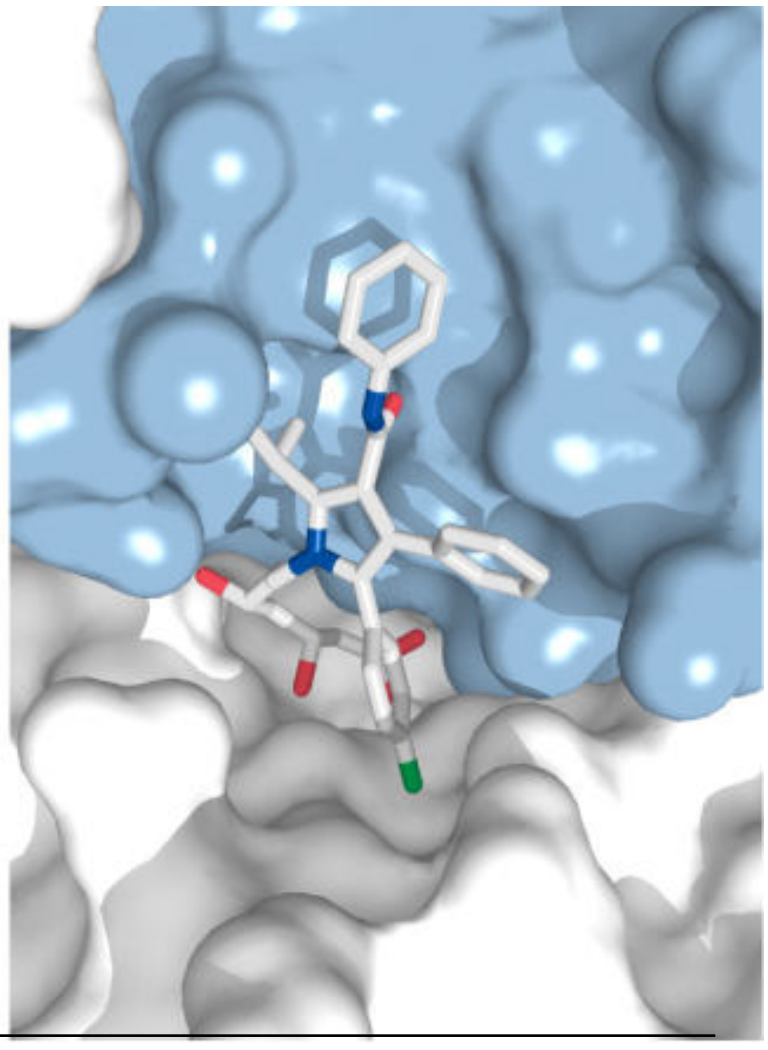


Atorvastatin





Mevalonate



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Effects Of "Statins"
(HMG-CoA Reductase Inhibitors)

- **Action: Competitively inhibits HMG-CoA reductase, the key enzyme for *de novo* cholesterol biosynthesis.**

- **Effects Of Statins in Human body:**
- **Cells express more LDL receptors**
- **Decreases serum LDL levels**
- **Increased HDL levels**
- **Increased HDL/LDL ratio**
- **Suppresses production of VLDL in Liver**

- **Advantages: Specific; Effective; Well-tolerated.**

- **Disadvantages: Hepatotoxicity; myopathy; most expensive; contradicted in pregnant and nursing women.**

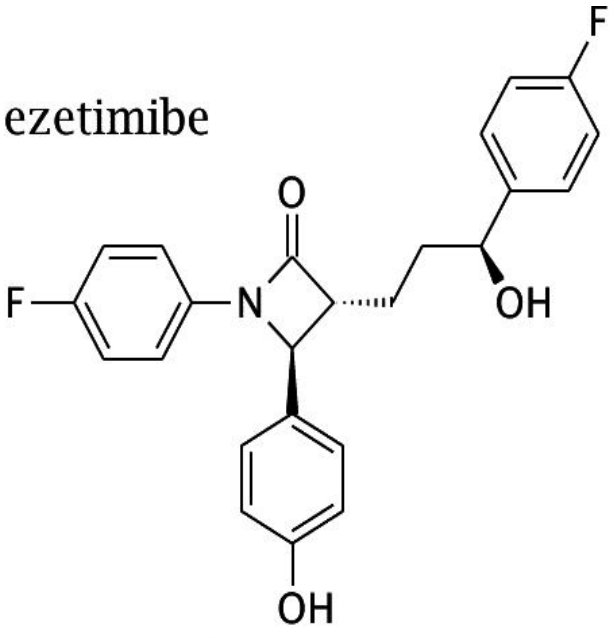
- **Bile salts** inhibit the **intestinal** HMG CoA Reductase.

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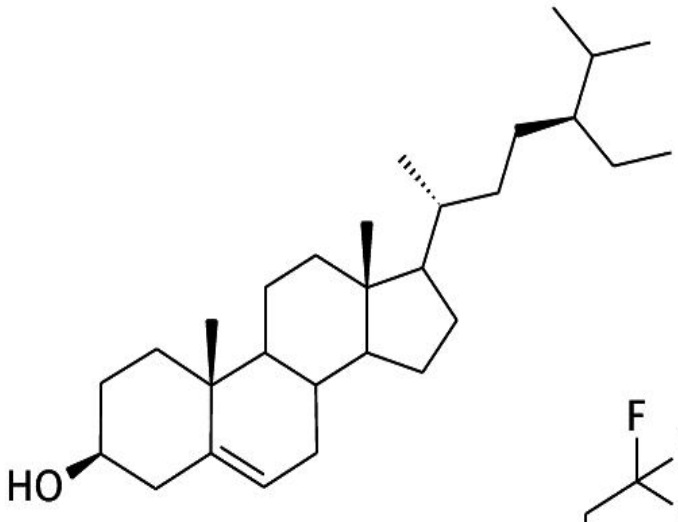
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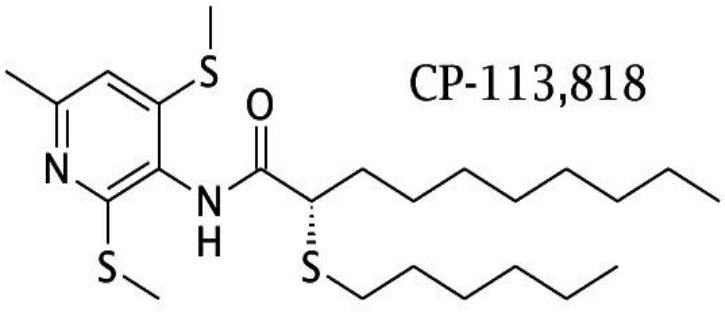
Drugs Inhibitors of Intestinal Cholesterol uptake

ezetimibe

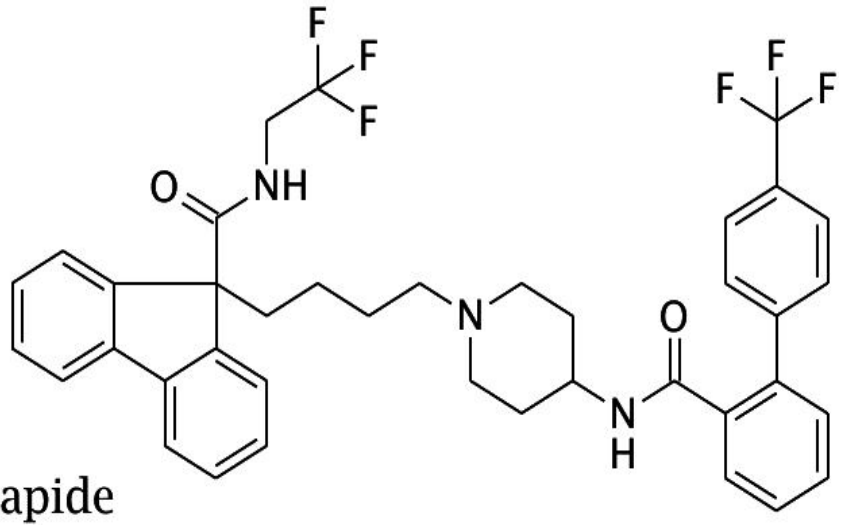


sitosterol





CP-113,818



lomitapide

Cholesterol Transport

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Lipoproteins Involved In Cholesterol Transport In Blood

- **Chylomicrons**
- **LDL**
- **HDL**

- **Chylomicrons transport the dietary Cholesterol**

- **From intestine to Liver** through lymph and blood

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- **LDL** transports **Endogenous Cholesterol**
- From **Liver to Extrahepatic tissues.**

- **HDL transports, Cholesterol for its excretion**
- **From Extrahepatic tissues to Liver.**

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Cholesterol Esterification

- In human body Cholesterol is present in two forms:
  - **Free Cholesterol (30%)**
  - **Esterified Cholesterol (70%)**
- Cholesterol esterification is by enzyme **ACAT and LCAT activity.**

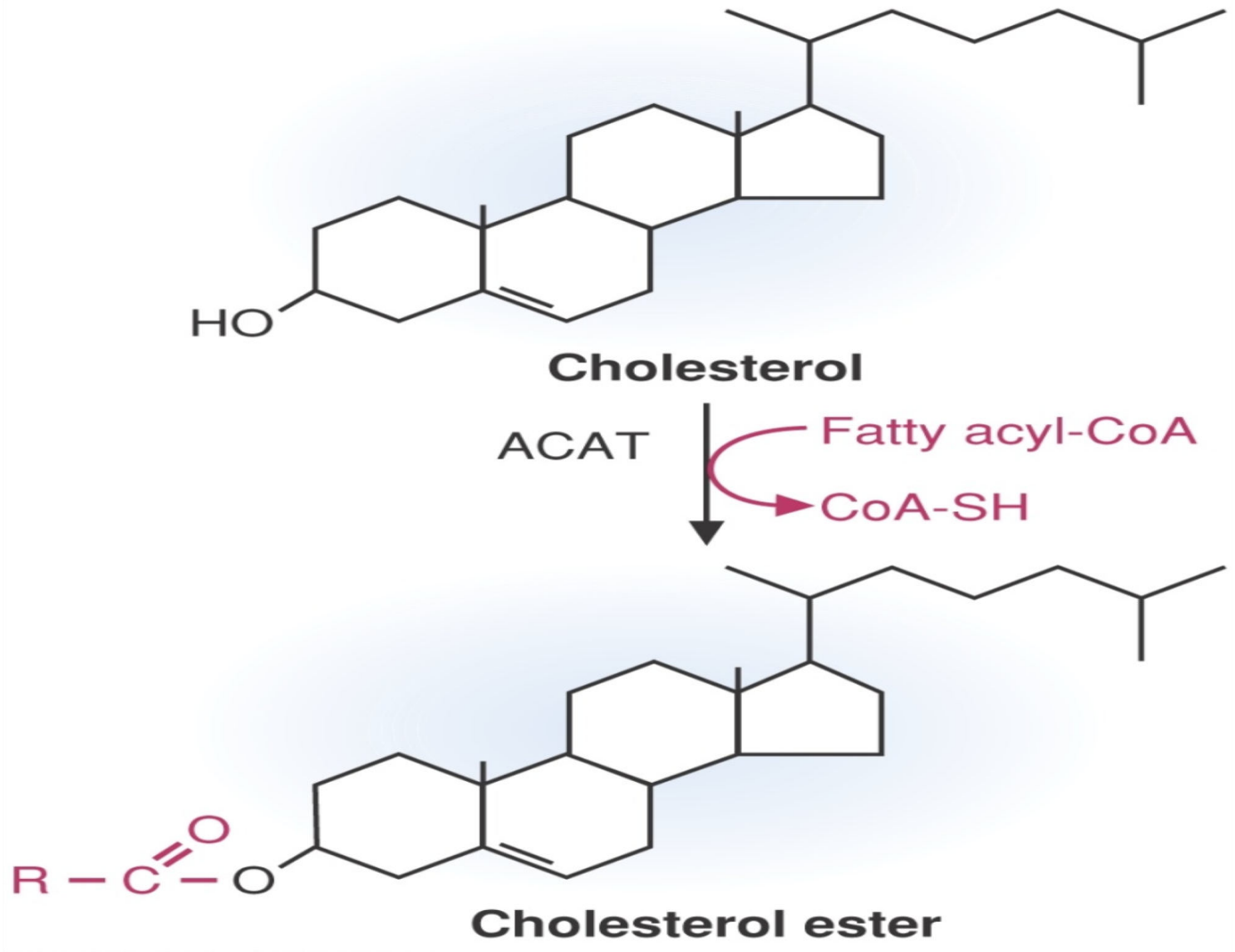
- **Cholesterol** when has to get **excreted out** of the body

- It gets esterified to **Cholesterol Ester** and transported for its excretion.

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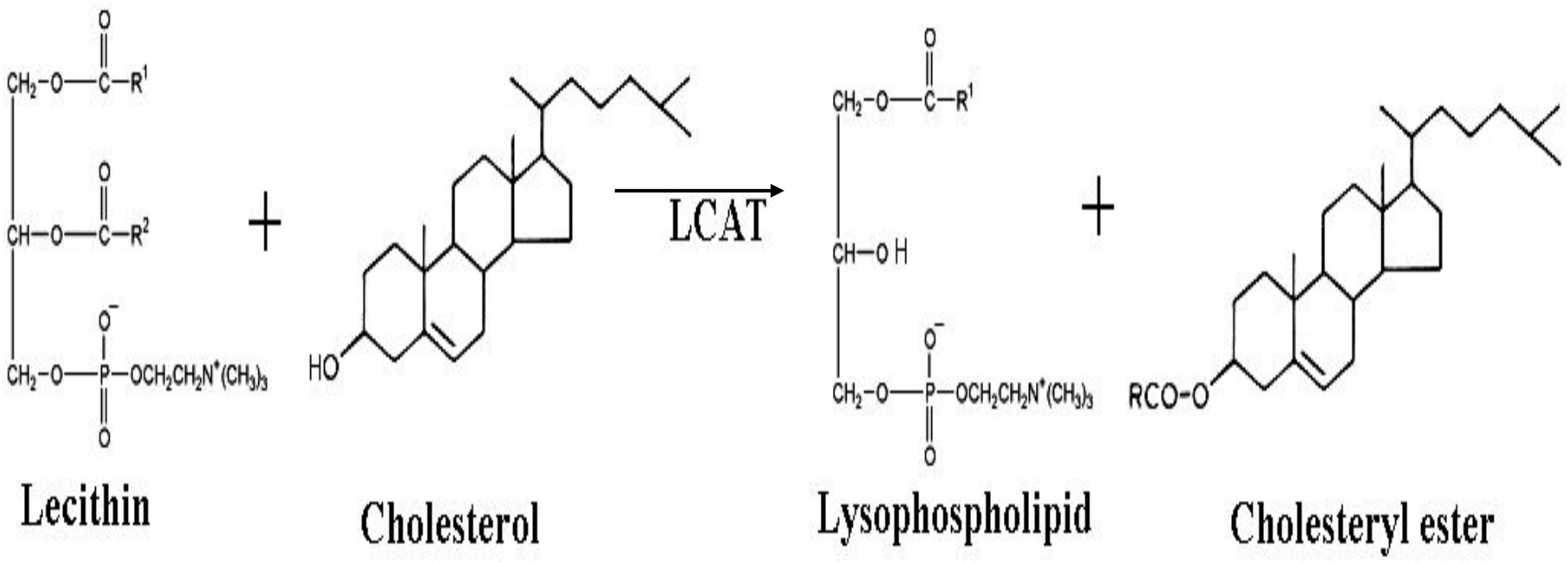
Cholesterol Esterification



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LCAT
(Lecithin: Cholesterol Acyltransferase)

Formation of Cholesterol Esters in Lipoproteins



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- Acyl-CoA: Cholesterol Acyl Transferase (ACAT) is an ER membrane protein
- **ACAT** transfers fatty acid of CoA to C3 Hydroxyl group of Cholesterol
- Excess Cholesterol is stored as Cholesterol esters in cytosolic lipid droplets

- The **LCAT activity** is associated to **Lipoprotein HDL.**
- **HDL is responsible for transporting of Cholesterol Ester from extra hepatocytes to Liver for its excretion.**

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Cholesterol Degradation and Excretion

- About **1 gram** of **Cholesterol** is **catabolized and excreted out** of body **via Bile.**

- Cholesterol is mostly converted to **Bile acids and Bile salts and excreted**.

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- **Thus Cholesterol** is **excreted** in the form of **Bile acids and Bile salts.**

- **Bile acids , Bile Salts and Cholesterol** are **carried through bile to intestine for its excretion**.

- Thus **half of the body Cholesterol is degraded to Bile acids** and **excreted through feces.**

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- **Cholesterol** is **modified** by **intestinal bacterial flora to**

- **Cholestenol and Coprostenol which are** then excreted out in feces.

- A person is **healthy when** there is a **perfect balance** between
  - **Cholesterol Biosynthesis**
  - **Cholesterol Utilization**
  - **Cholesterol Excretion**
- This **minimizes the chances of Cholesterol deposition in blood and tissues.**

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Note

- Increased intake of dietary Cholesterol

- Decreases absorption of Cholesterol

Blood Cholesterol And Its Clinical Significance

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Adult Reference Ranges For Lipid Profile

ANALYTE	REFERENCE RANGE
Total cholesterol	140-200 mg/dL
HDL cholesterol	40-75 mg/dL
LDL cholesterol	50-130 mg/dL
Triglyceride	60-150 mg/dL

OPTIMAL CHOLESTEROL LEVELS

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- Blood Cholesterol is associated to Lipoproteins in 2 forms:

  - **Free cholesterol (30%)**
  - **Esterified Cholesterol (70%)**

Classification of Plasma Cholesterol Concentrations

Total cholesterol (mg/dl)	Classification
< 200	Desirable
200 - 239	Borderline
≥ 240	High

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HDL Cholesterol

Less than 40 mg/dl
Low level. A major risk factor for CAD

40 to 59 mg/dl
The higher the level the better

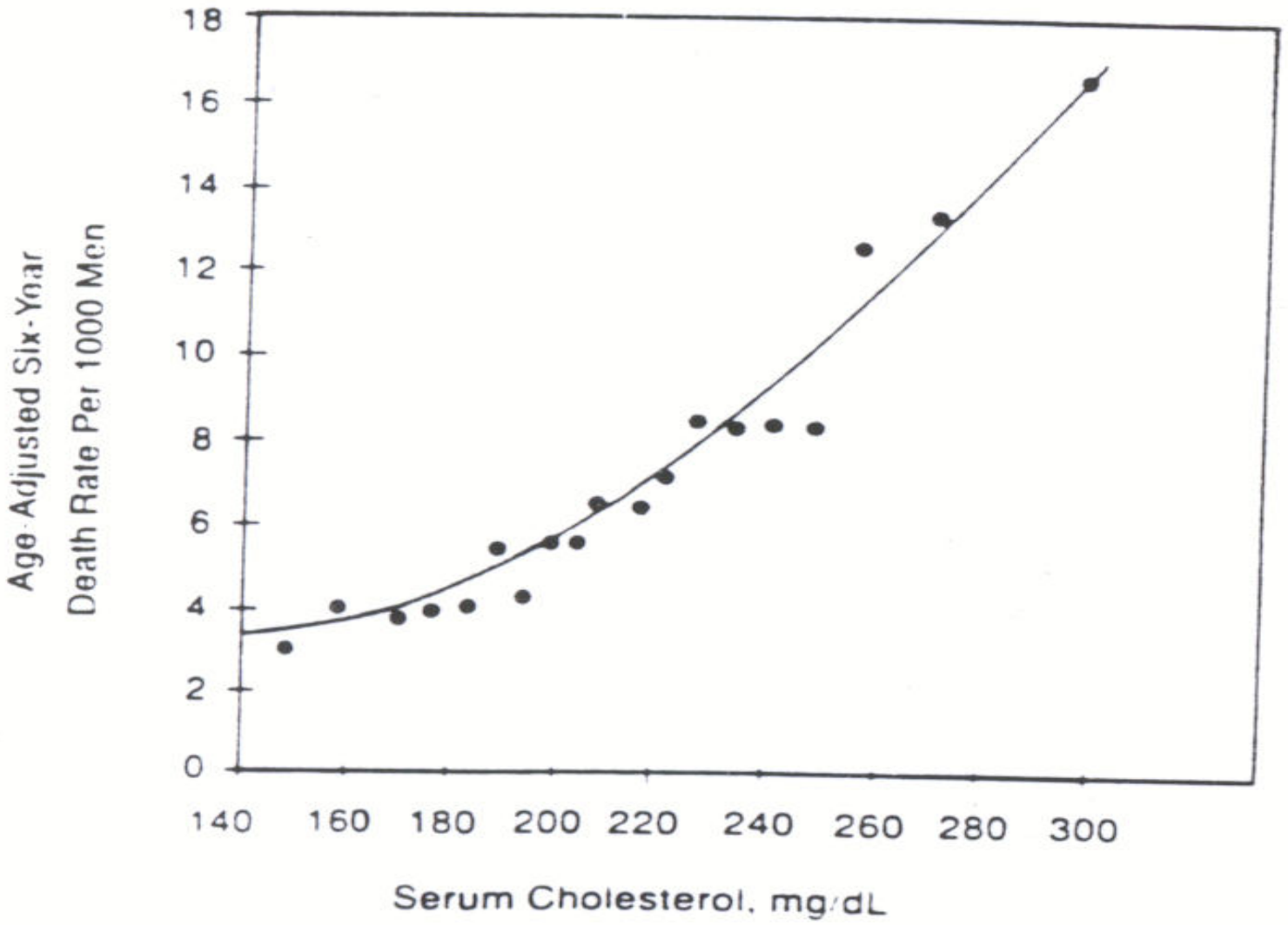
60 mg/dl and above
High level. Considered protective against CAD

LDL Cholesterol

- **Less than 100 mg/dl Optimal**
- **100 to 129 mg/dl Near or above optimal**
- **130 to 159 mg/dl Borderline high**
- **160 to 189 mg/dl High**
- **190 mg/dl and above Very high/ BAD Cholesterol**

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Hypercholesterolemia Causes, Conditions And Consequences

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Hypercholesterolemia

- **Abnormal high levels of Cholesterol more than the reference range** in blood circulation is termed as Hypercholesterolemia.

Conditions Of Hypercholesterolemia

- **Diabetes mellitus**

(Increased Intake /Biosynthesis)

- **Nephrotic Syndrome**

(Defective Lipoprotein metabolism which is not internalized)

- **Obstructive Jaundice**

(Bile duct obstruction and regurgitation of Bile in Blood)

- **Hypothyroidism**

(Decreased Catabolism and Excretion)

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Inherited Hypercholesterolemia

- Inherited Hypercholesterolemia is a **genetic cause**
- Caused due to **defective LDL receptors on tissues.**
- **Increases LDL –Cholesterol in blood**

Consequences Of Hypercholesterolemia

- Increased risk of **Atherosclerosis**
- Stimulates **plaque/thrombus formation**
- May **occlude arteries** and
- Leads to **tissue infarction**

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- **Infarction** is **irreversible damage to tissues due to absence of Oxygen and Nutrient.**
- **Infarction of Brain is Stroke**
- **Infarction of Heart is MI**

Hypocholesterolemia

- Abnormal **low levels of Cholesterol** in blood circulation is termed as **Hypocholesterolemia.**

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Conditions Of Hypocholesterolemia

- Malnutrition
- Malabsorption
- Hyperthyroidism
- Pernicious Anemia
- Hemolytic Anemia
- Liver Disorders

Consequences of High Cholesterol

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MORTALITY RELATED DUE TO HIGH CHOLESTEROL

- ✓ 1 cause of death: Cardio-vascular diseases
- ✓ 3 cause of death: Cerebro-vascular diseases
- ✓ 1 + 3 = ~ 40% of all deaths

(Higher risk for Alzheimer & Chronic Liver disease)

FACTORS INFLUENCING CHOLESTEROL LEVELS

- **Diseases :**
  - Hypothyroidism
  - Diabetes mellitus
- Lifestyle (Exercise, Stress, Smoking)

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- A Family History-Genetic defects
- Diet- High Fat and Carb diet
- Age
- Weight- Obese
- Gender (Men, Menopause)

HDL cholesterol levels lower than <40 mg/dl)
increase a person's risk of developing coronary artery disease, especially in people who also have high total cholesterol levels.

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- **HDL Cholesterol levels greater than 100 mg/dl**

- **Also increase the risk in developing coronary artery disease and Stroke.**

CHOLESTEROL PROFILE IMPROVEMENT STRATEGY

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- **IMPROVING DIET**
- **LIFE STYLE MODIFICATIONS**
  - **REGULAR EXERCISE**
  - **SMOKING, ALCOHILISM CESSATION**
  - **STRESS REDUCTION**
  - **WEIGHT CONTROL**
  - **BEHAVIOR CHANGE**

- When diet changes fail.
- **Hypolipidemic drugs** will reduce serum Cholesterol and Triacylglycerol.

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Therapeutic Principle: Lowering Blood Cholesterols

- **Inhibition** of **Cholesterol biosynthesis**

- **Inhibition** of **Cholesterol uptake from GIT**

- Inhibition of Bile acid reuptake

- LDL apheresis (Taking away)

- Inhibition of **Cholesterol Ester Transfer Protein (CETP)** to some extent increases HDL levels.

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- **Cholestyramine Resins:**

  Block reabsorption of bile acids.

- **Sitosterols:**

  acts by blocking the absorption of Cholesterol from the gastrointestinal tract.

- **Mevocore or Lovastatin:**

inhibitors of HMG-CoA Reductase

Lipoprotein Metabolism

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Role Of Lipoproteins In Health And Disease

Transportation Of Lipids

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Lipoprotein Metabolism And Related Disorders

What are Lipoproteins ?

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❖**Lipid compounds: Relatively insoluble in water**

❖**Therefore, they are transported in plasma and Lymph (aqueous phase) as Lipoproteins**

- Lipoproteins are **complex macromolecules**
- Biosynthesized by **aggregation of Lipids and Proteins.**

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- **Lipoproteins** are **compound Lipids/Conjugated Proteins.**

- Lipoproteins **acquire charge** and **made soluble** in aqueous phase.

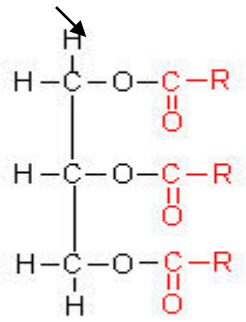
Structure Of Lipoproteins

- **Non polar Lipids** are **at center**
- **Polar Lipids** and **Apoproteins** are **present at periphery.**

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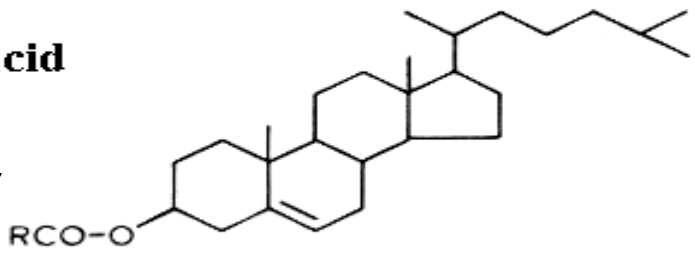
Glycerol Fatty acid



Triglyceride

Hydrophobic lipids

Fatty acid

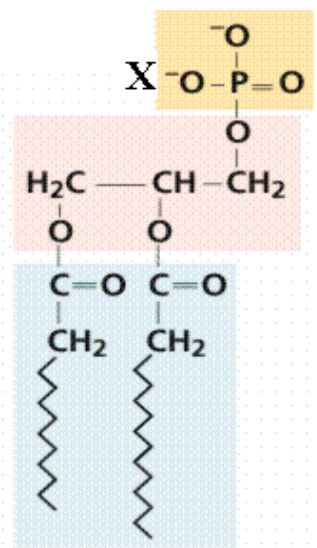


Cholesteryl ester

Phosphoric acid

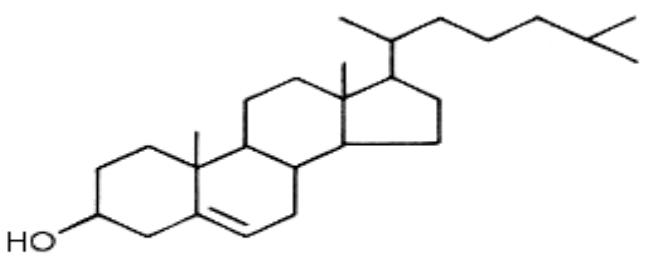
Glycerol

Fatty acid



Phospholipid

Amphiphilic lipids



Cholesterol

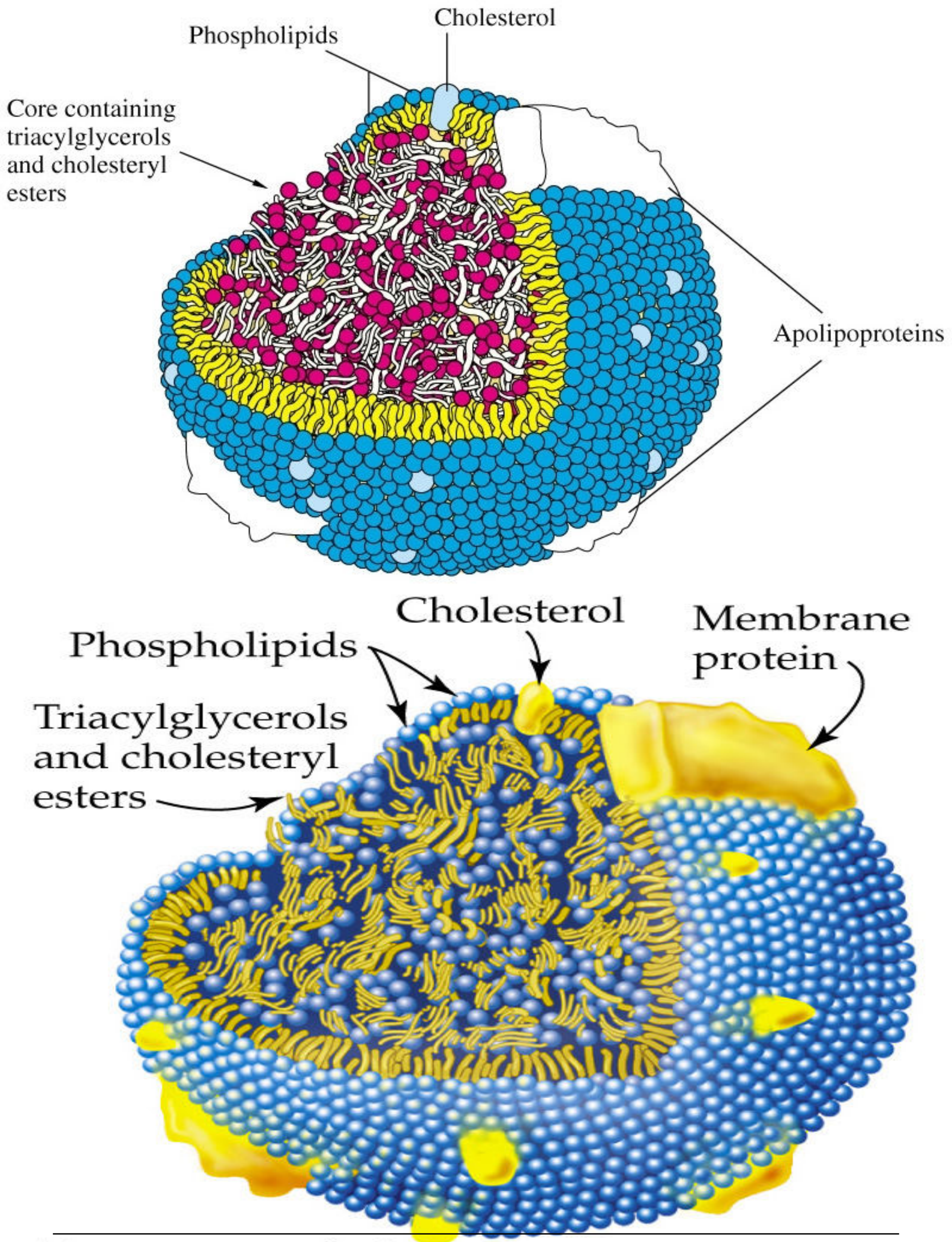
- Lipoproteins
  - Lipids
    - Hydrophobic lipds
      - Triglyceride (TG)
      - Cholesteryl ester (CE)
    - Amphiphilic lipids
      - Phospholipid (PL)
      - Cholesterol (C)
  - Proteins
    - Apolipoprotein (Apo)
      - ApoAs
      - ApoBs
      - ApoCs
      - ApoE
      - ApoD
      - Apoa
    - Other proteins



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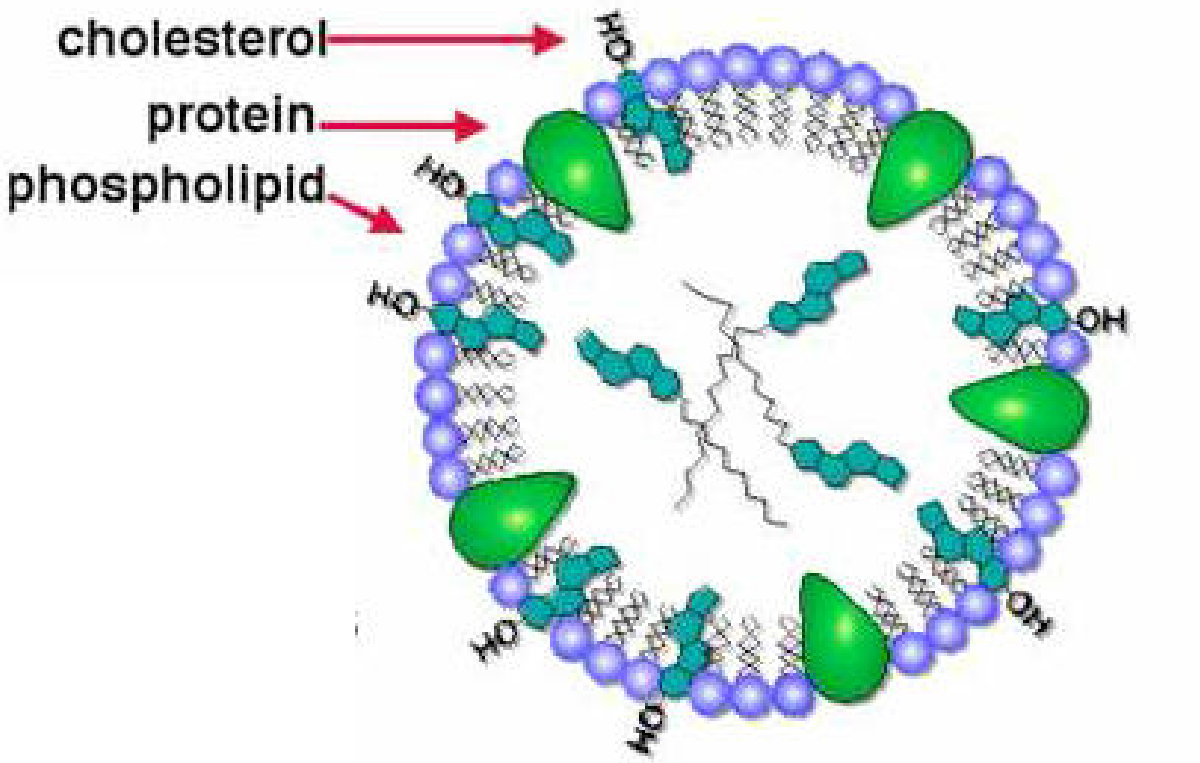
Structure Of Lipoprotein



(a) Structure of a lipoprotein

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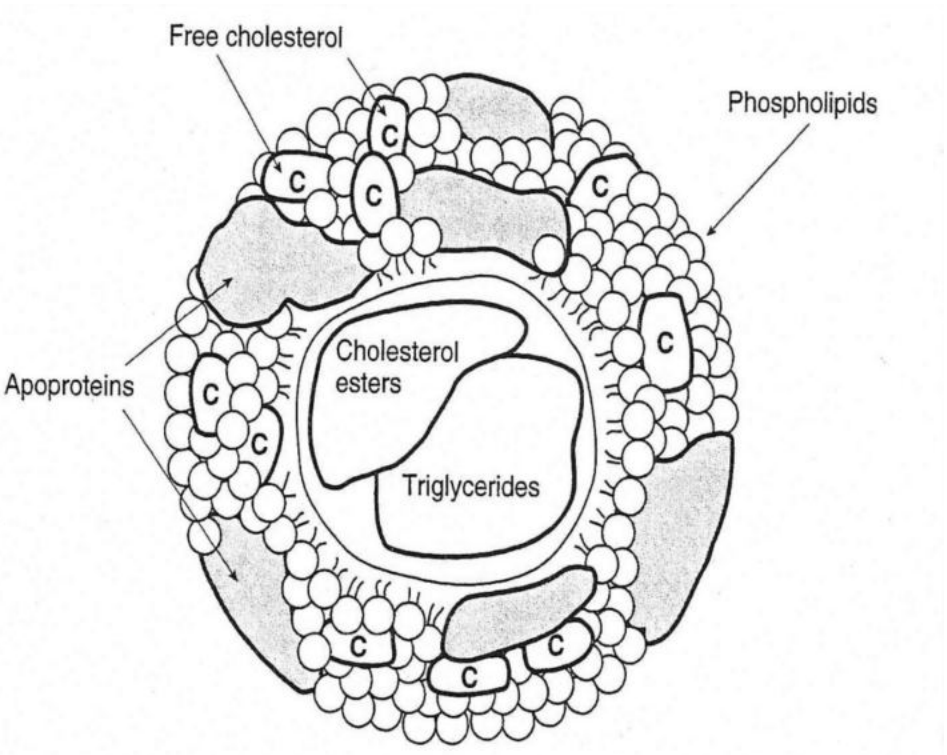


Structure of lipoprotein

Hydrophobic lipids (TAG, CE) in the core Amphiphilic lipids (C, PL) and proteins on the surface

Plasma Lipoproteins (Structure)

- Non-covalent assemblies of lipids and proteins
- LP core
  - Triglycerides
  - Cholesterol esters
- LP surface
  - Phospholipids
  - Proteins
  - Cholesterol



Function as transport vehicles for triacylglycerols and cholesterol in the blood

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Function/Role Of Lipoproteins

- **Lipoproteins function as transport vehicles**
- **For transportation of insoluble form of Lipids in blood plasma.**

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- Lipoproteins deliver the lipid components (Cholesterol and TAG etc.) **from one tissues to various tissues for their utilization**.

- Various **Lipoproteins** formed within the body cells
- **Serves in transportation of exogenous** (Dietary Source) and **endogenous** (Those Lipids biosynthesized)lipids
- **From one organ to another** through aqueous phase of Lymph and blood.

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Lipoproteins Role Facilitate

- Substrates for Energy Metabolism (TAG)
- Provide Essential components for cells (PL, C)
- Precursors for Hormones (Cholesterol)
- Carries Lipid soluble Vitamins
- Precursors for Bile acids and Bile salts (C)

Types Of Lipoproteins

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- **There are different types of Lipoproteins depending upon:**

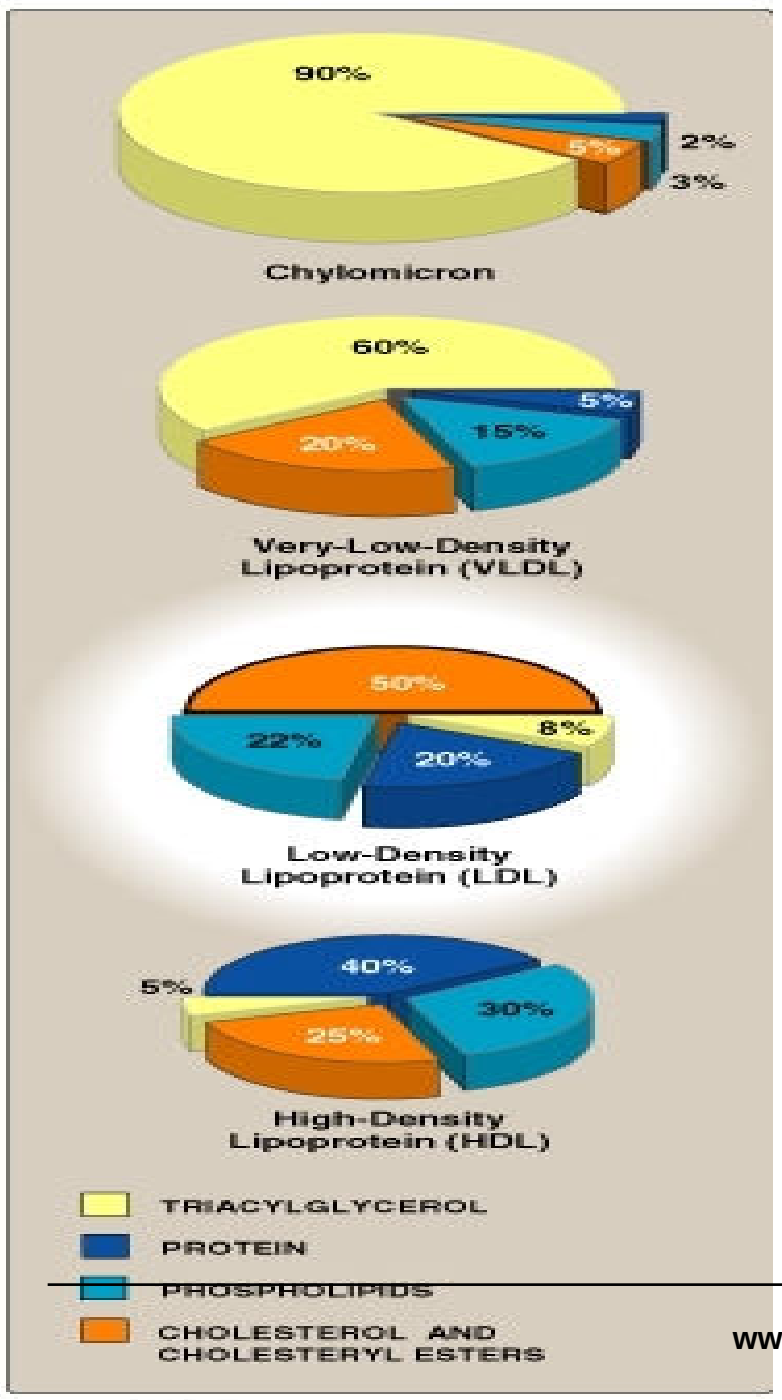
I. Site of Lipoprotein Biosynthesis
II. Lipid Contents
III. Apoprotein Contents and Type
IV. Diameter /Size
V. Transport Destination
VI. Ultracentrifugation
VII. Electrophoretic Pattern

Lipoproteins	Site Of Synthesis	Destination	Major Lipids	Biochemical Functions
Chylomicrons	**Intestine**	Liver	Exogenous Triacylglycerol	Deliver lipids of dietary origin to Liver and Adiposecytes
VLDLs	**Liver**	Extra Hepatic Tissues	Endogenous Triacylglycerol	Deliver endogenously produced Lipids to Extrahepatocytes
LDLs	Intravascular removal of Triacylglycerol from VLDL	Extra hepatic Tissues	Cholesterol	Deliver endogenously produced cholesterol to Extrahepatocytes
HDLs	Liver and intestine	Liver and steroid-hormone-producing glands	Phospholipid Cholesterol	Remove and degrade Cholesterol.

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	CM	VLDL	LDL	HDL
Density (g/mL	<0.96	0.96-1.006	1.006-1.063	1.063-1.21
Diameter (nm)	100-1000	30-90	20-25	10-20
Apolipoprotein	A,C,E,B48	A,C,E,B100	B100	A,C,D,E
Composition (%)				
Proteins	2	10	20	40
Lipids	98	90	80	60
Lipid composition (%)				
TAG	88	55	12	12
CE+C	4	24	59	40
PL	8	20	28	47
Free fatty acid	-	1	1	1



Chylomicrons

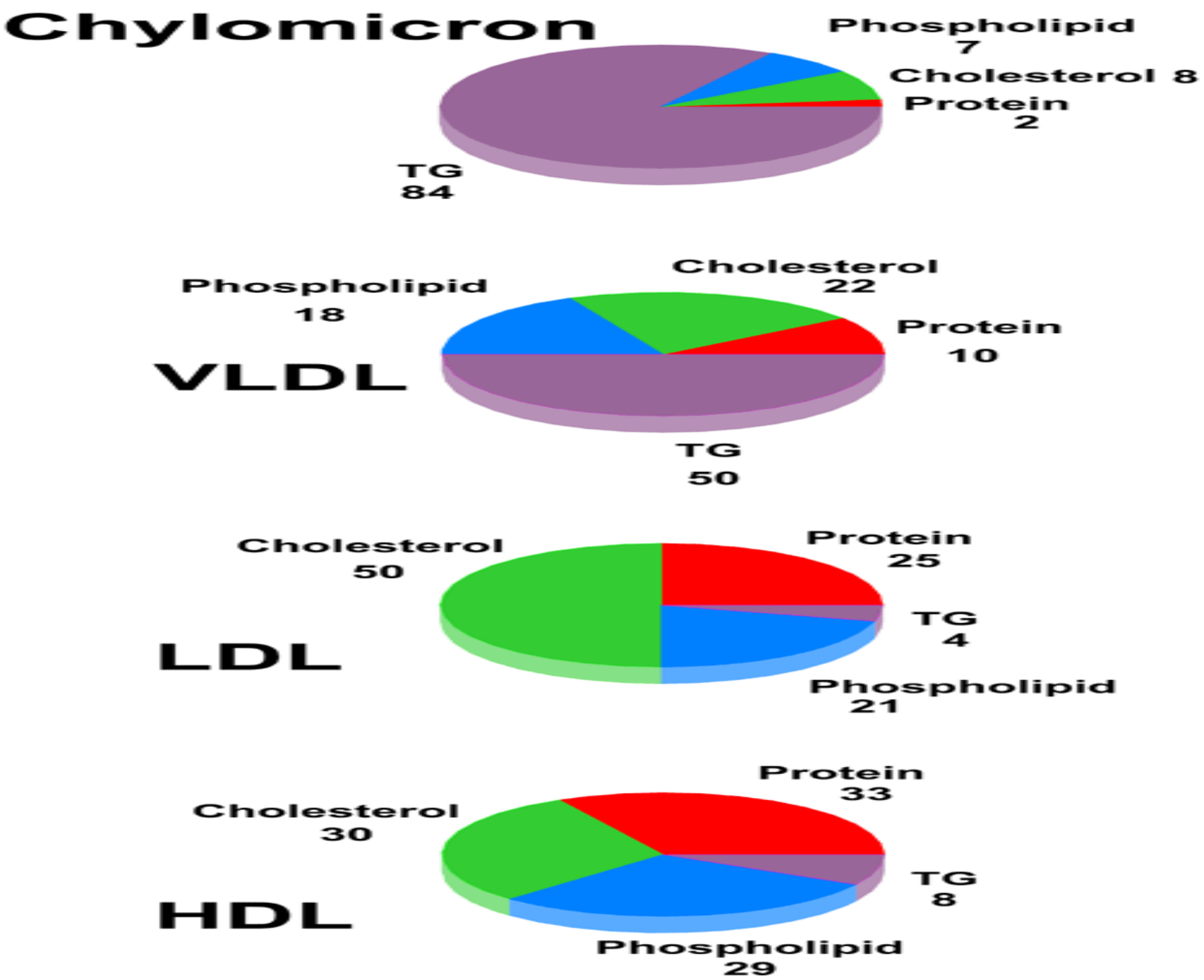
Very low density Lipoprotein (VLDL)

Low density Lipoprotein (LDL)

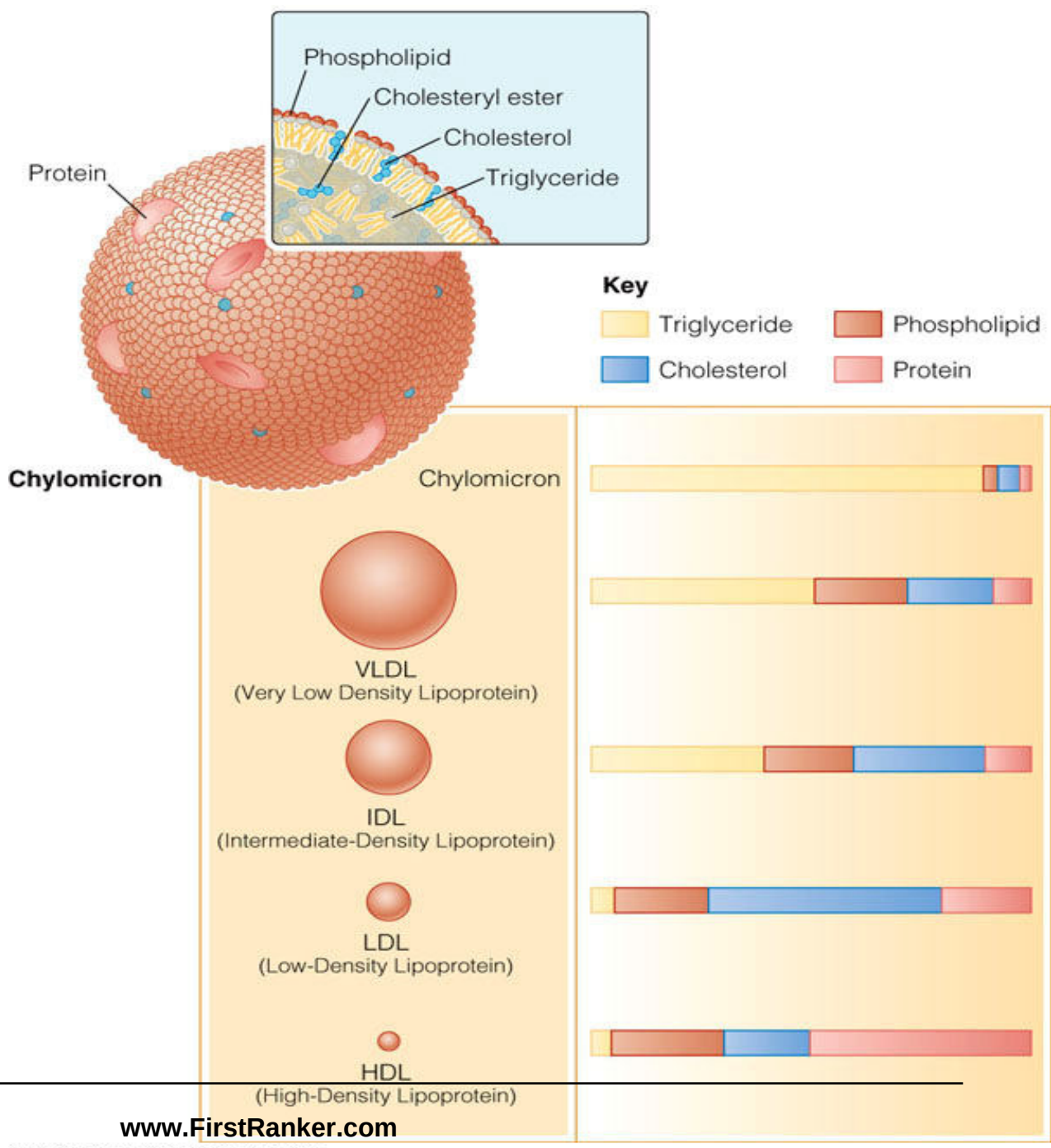
High density Lipoprotein (HDL)

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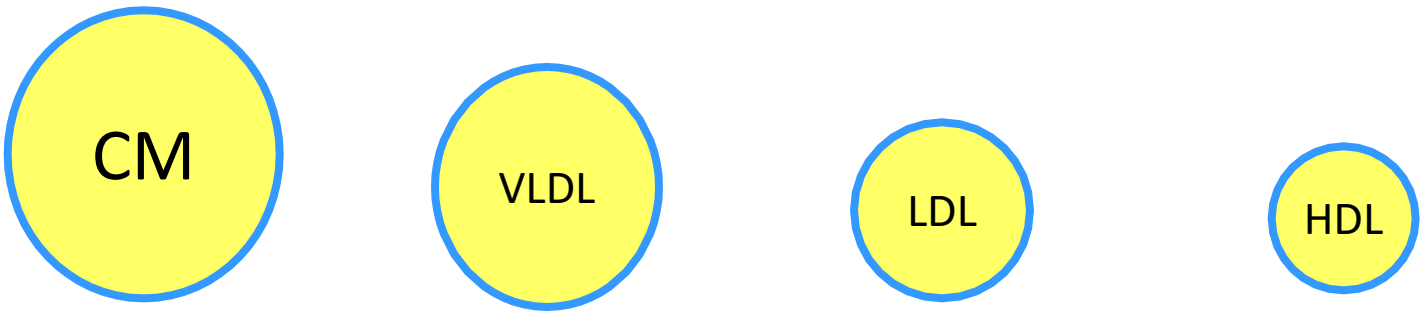
Lipoproteins



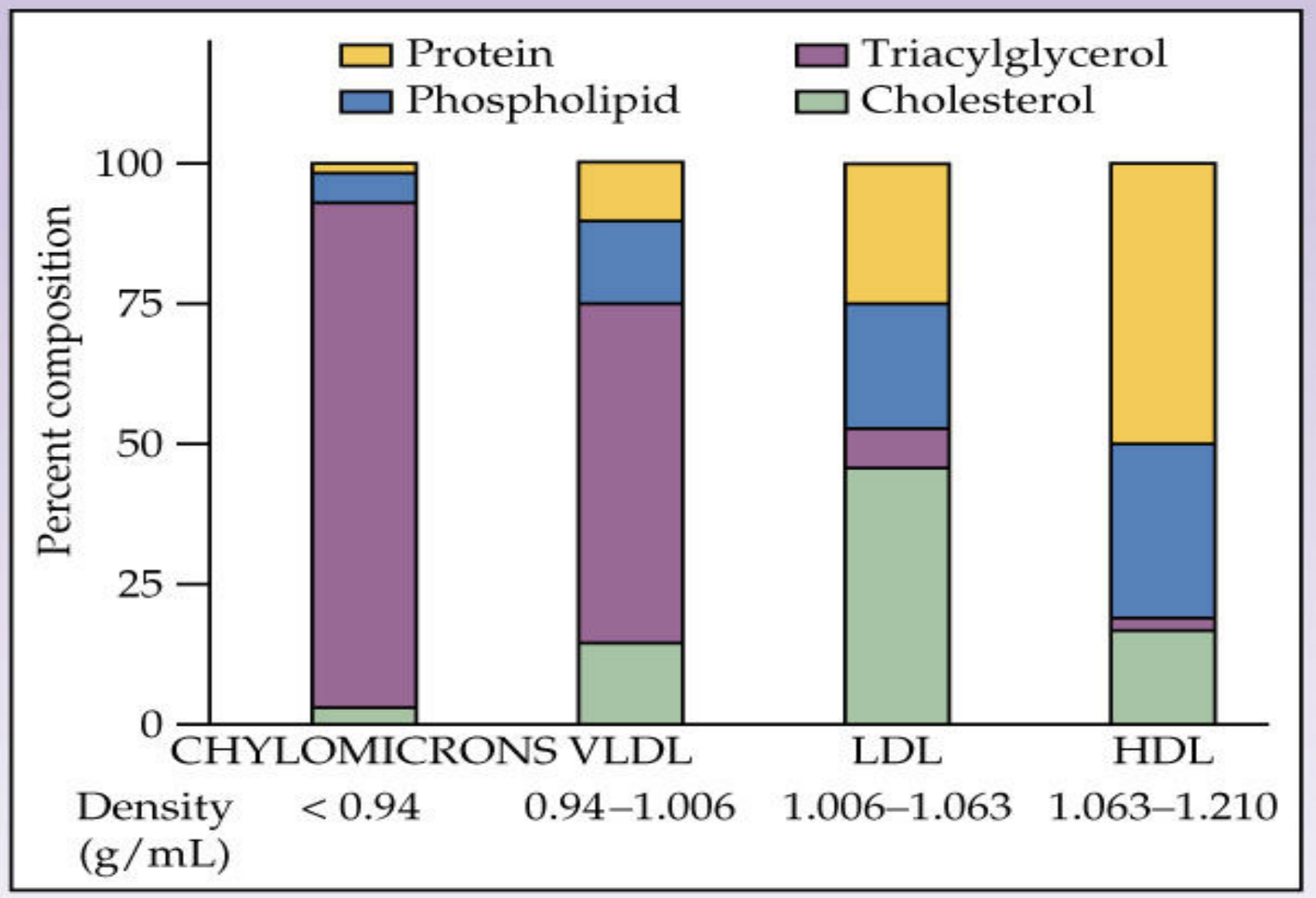
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Lipoprotein Nomenclature, Composition and separation



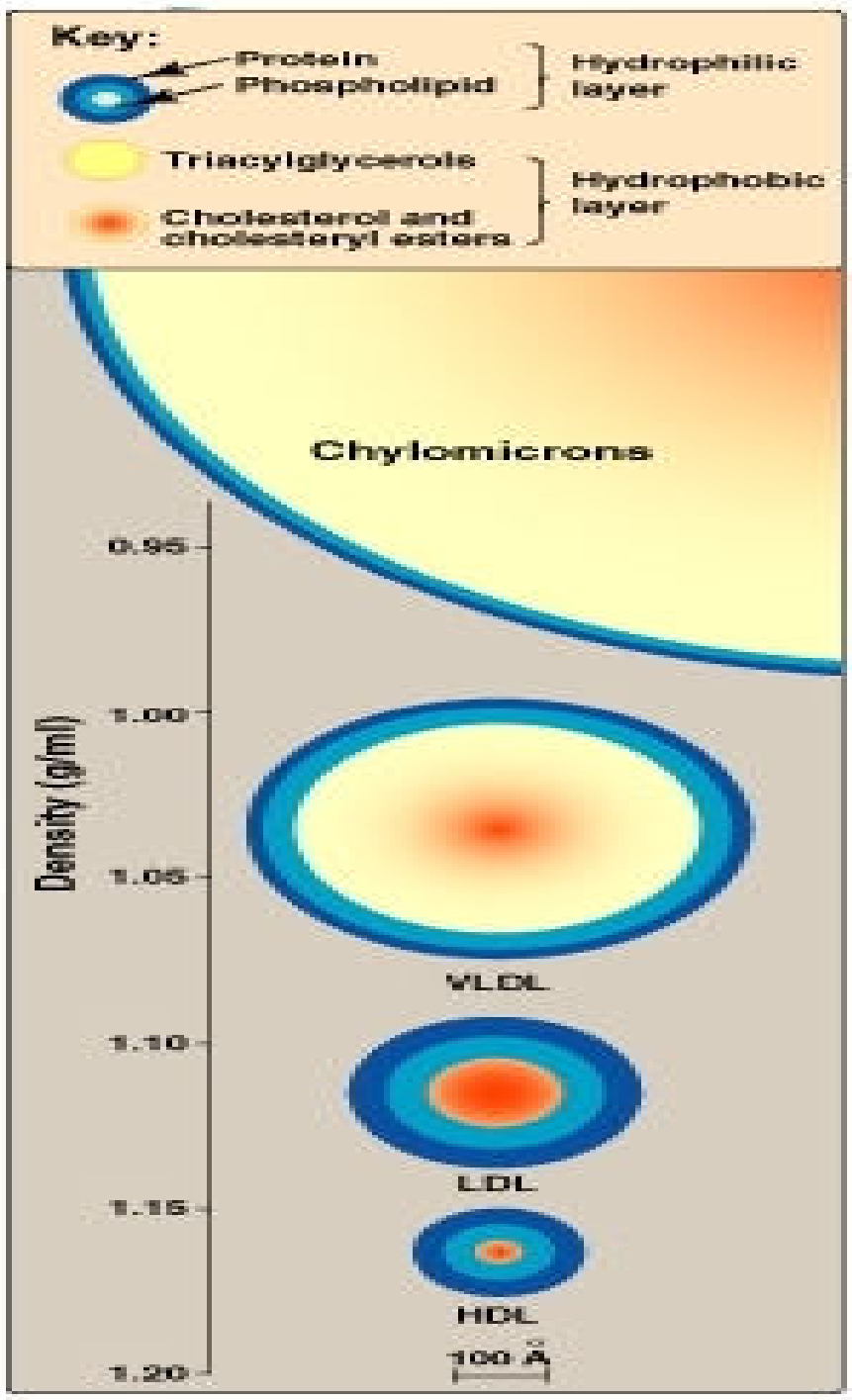
Major Protein	ApoB 48	ApoB 100	ApoB 100	ApoA-I
Major and CE Lipid	TAG	TAG	CE	PL



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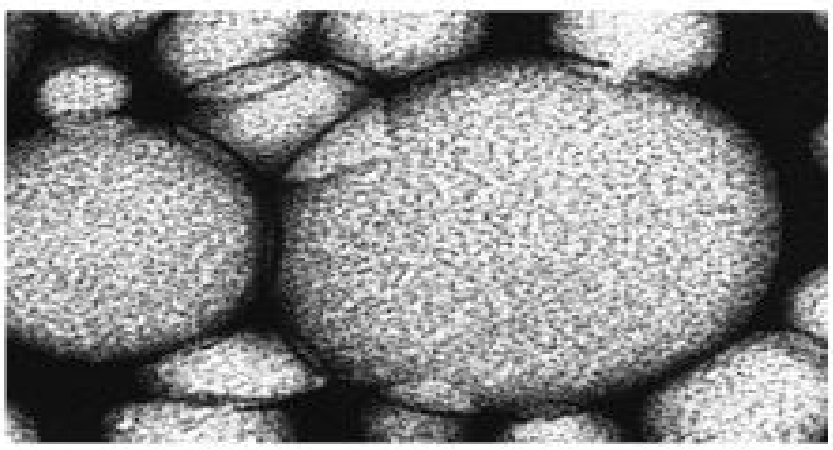
(b) Density and composition of lipoproteins

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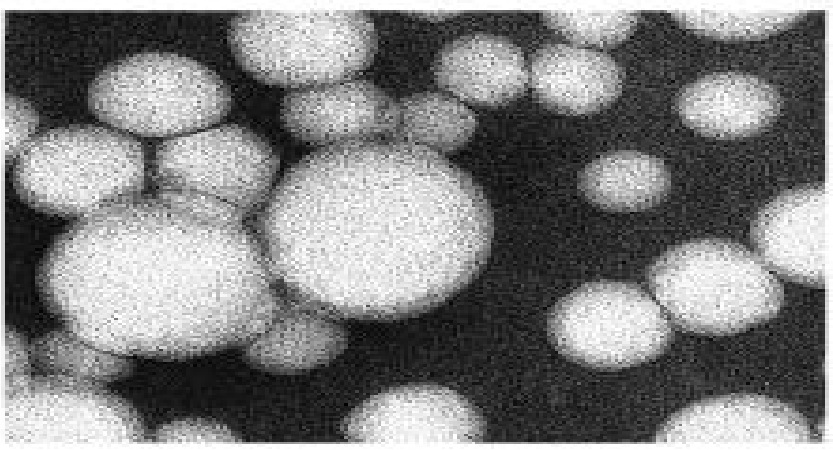


Ultracentrifugation of Lipoproteins

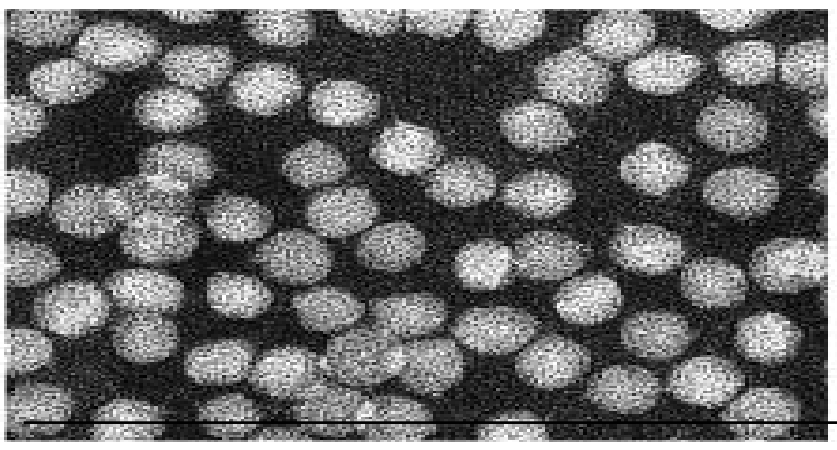
Lipoprotein Particles with distinct densities



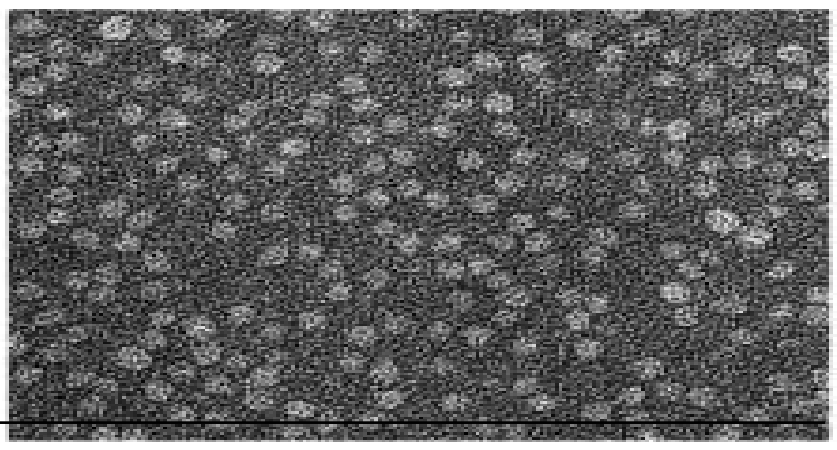
Chylomicrons (50–200 nm diameter)



VLDL (28-70 nm diameter)



LDL (20-25 nm diameter)



HDL (8-11 nm diameter)

(b)

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1.Electrophoresis method:

CM (chylomicron)

Slow

β-Lipoprotein

pre β-Lipoprotein

Fast

α- Lipoprotein

2. Ultra centrifugation method:

CM (chylomicron)

Slow

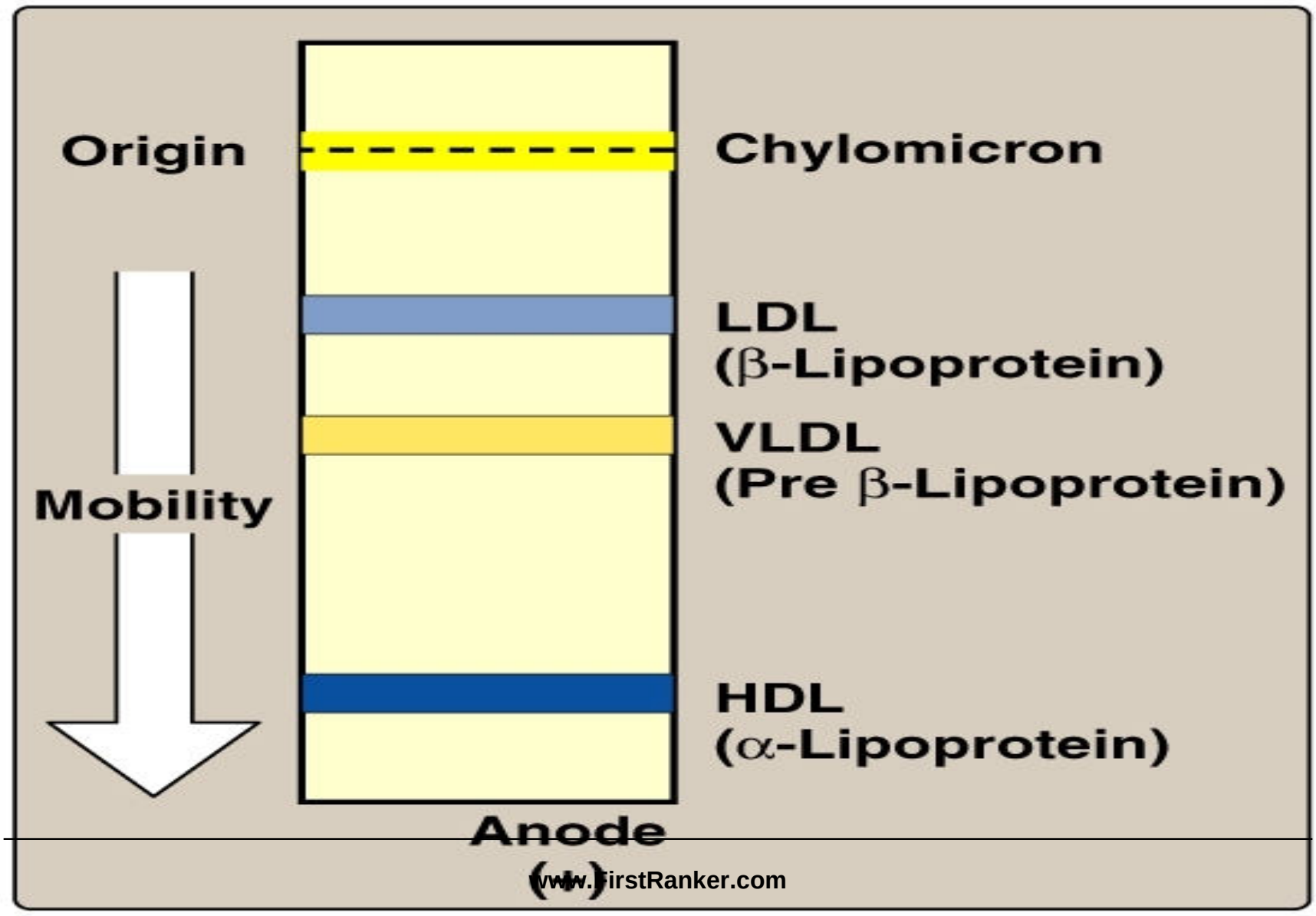
very low density lipoprotein (VLDL)

low density lipoprotein (LDL)

high density lipoprotein (HDL)

High

Lipoprotein Electrophoresis



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Figure 18.15

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TABLE 26.1 Properties of plasma lipoproteins

Lipoproteins	Major core lipids	Apoproteins	Mechanism of lipid delivery
Chylomicron	Dietary triacylglycerols	B-48, C, E	Hydrolysis by lipoprotein lipase
Chylomicron remnant	Dietary cholesterol esters	B-48, E	Receptor-mediated endocytosis by liver
Very low density lipoprotein (VLDL)	Endogenous triacylglycerols	B-100, C, E	Hydrolysis by lipoprotein lipase
Intermediate-density lipoprotein (IDL)	Endogenous cholesterol esters	B-100, E	Receptor-mediated endocytosis by liver and conversion into LDL
Low-density lipoprotein (LDL)	Endogenous cholesterol esters	B-100	Receptor-mediated endocytosis by liver and other tissues
High-density lipoprotein (HDL)	Endogenous cholesterol esters	A	Transfer of cholesterol esters to IDL and LDL

Plasma Lipoproteins

For Triacylglycerol Transport (TAG-rich):

- Chylomicrons: TAG of dietary origin

- VLDL:TAG of Endogenous (hepatic) synthesis

For Cholesterol transport (cholesterol-rich):

LDL: Mainly Free Cholesterol

HDL: Mainly esterified Cholesterol

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Important Enzymes and Proteins

Involved in

Lipoprotein Metabolism

Lipoprotein Lipase
OR
A Clearing Factor

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Lipoprotein Lipase (LPL)

.**LPL is located in the endothelial lining of blood vessels.**

Lipoprotein Lipase (LPL)

- **LPL is an extracellular enzyme, anchored by Heparan sulfate to the capillary walls of most tissues**

- **It is predominantly present in Adipose tissue, Cardiac & Skeletal muscle**

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- LPL requires Apo C-II for its activation
- LPL degrades TAG into Glycerol and free fatty acids by its activity.
- Insulin stimulates its synthesis and transfer to the luminal surface of the capillary.

Lipoprotein Lipases

- Lipoprotein Lipases in capillaries of adipose and muscle tissues hydrolyze TAG in VLDLs.
- VLDLs become IDLs
- IDLs looses more TAG and become LDLs.
- LDLs are less in TAG and rich in Cholesterol and Cholesterol-esters.

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- Lipoprotein Lipase **act upon TAG of Lipoproteins** and hydrolyze it

- **LPL Transforms the –**
  - **–Chylomicron to Chylomicron remnant**
  - **–VLDL to LDL**

- **LPL clear the circulating Lipoproteins from blood** hence it is termed as **Clearing Factor.**

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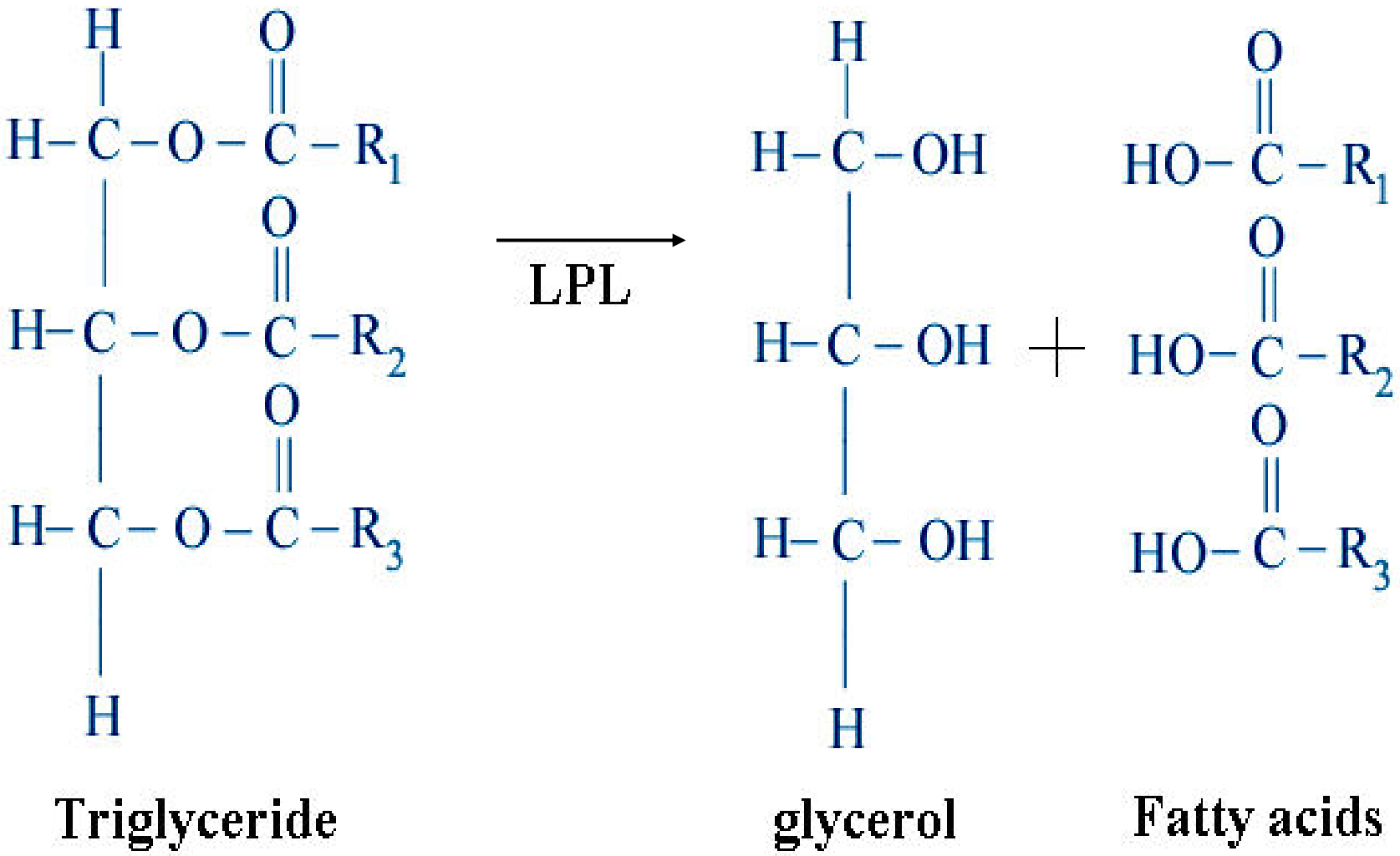
- **Type I Hypolipoproteinemia**
- **This is termed as Familial Lipoprotein Lipase deficiency**
- **Caused due to:**
  - **LPL defect**
  - **Apo C-II is defect**

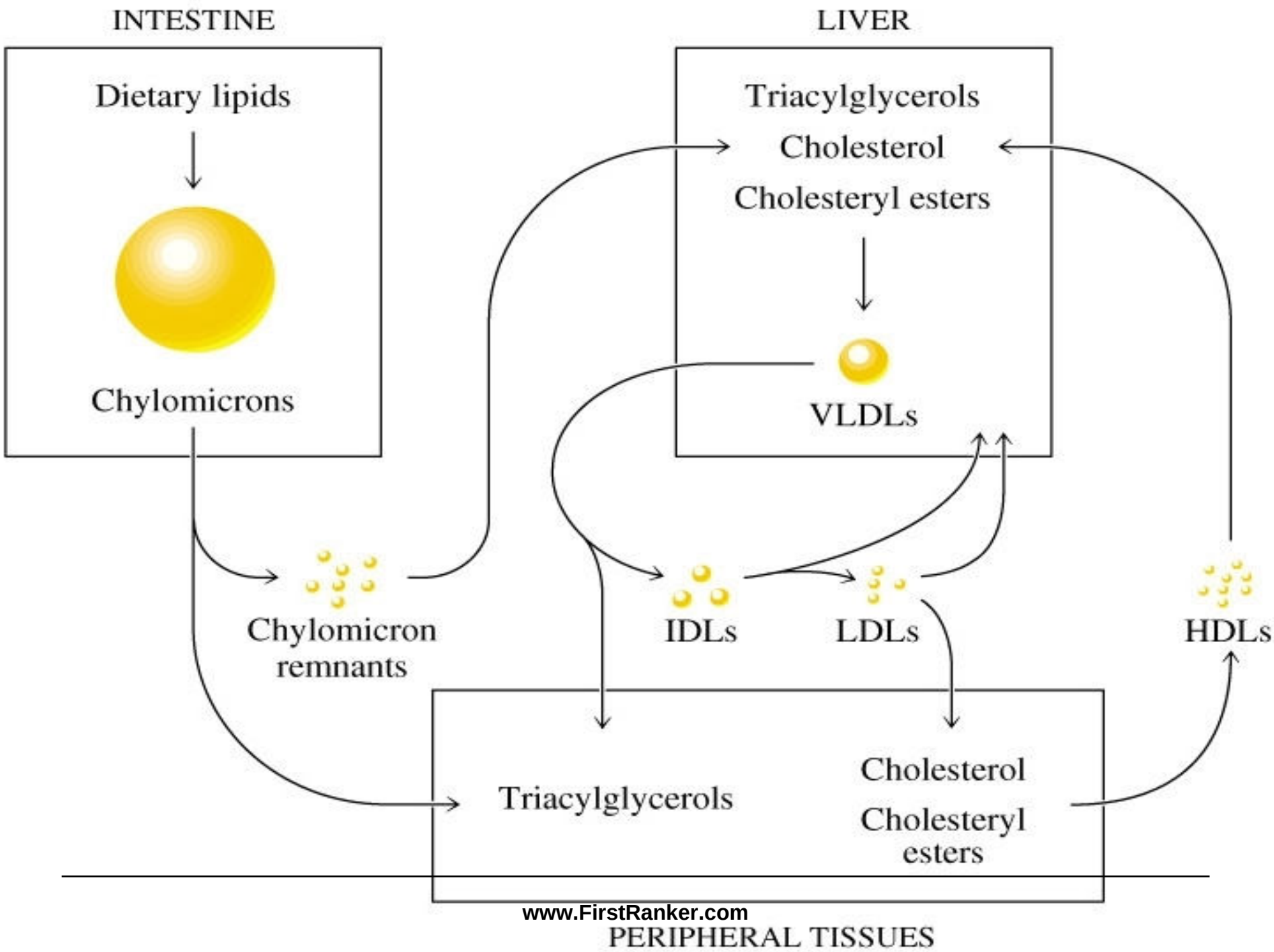
- **LPL Hydrolyzes Triacylglycerol (TAG) in the core of CM and VLDL to free Fatty acids and Glycerol.**

- **The released free fatty acids and Glycerol**
- **Then enter into the tissue, mainly adipose, heart, and muscle (80%), while about 20% goes indirectly to the Liver.**

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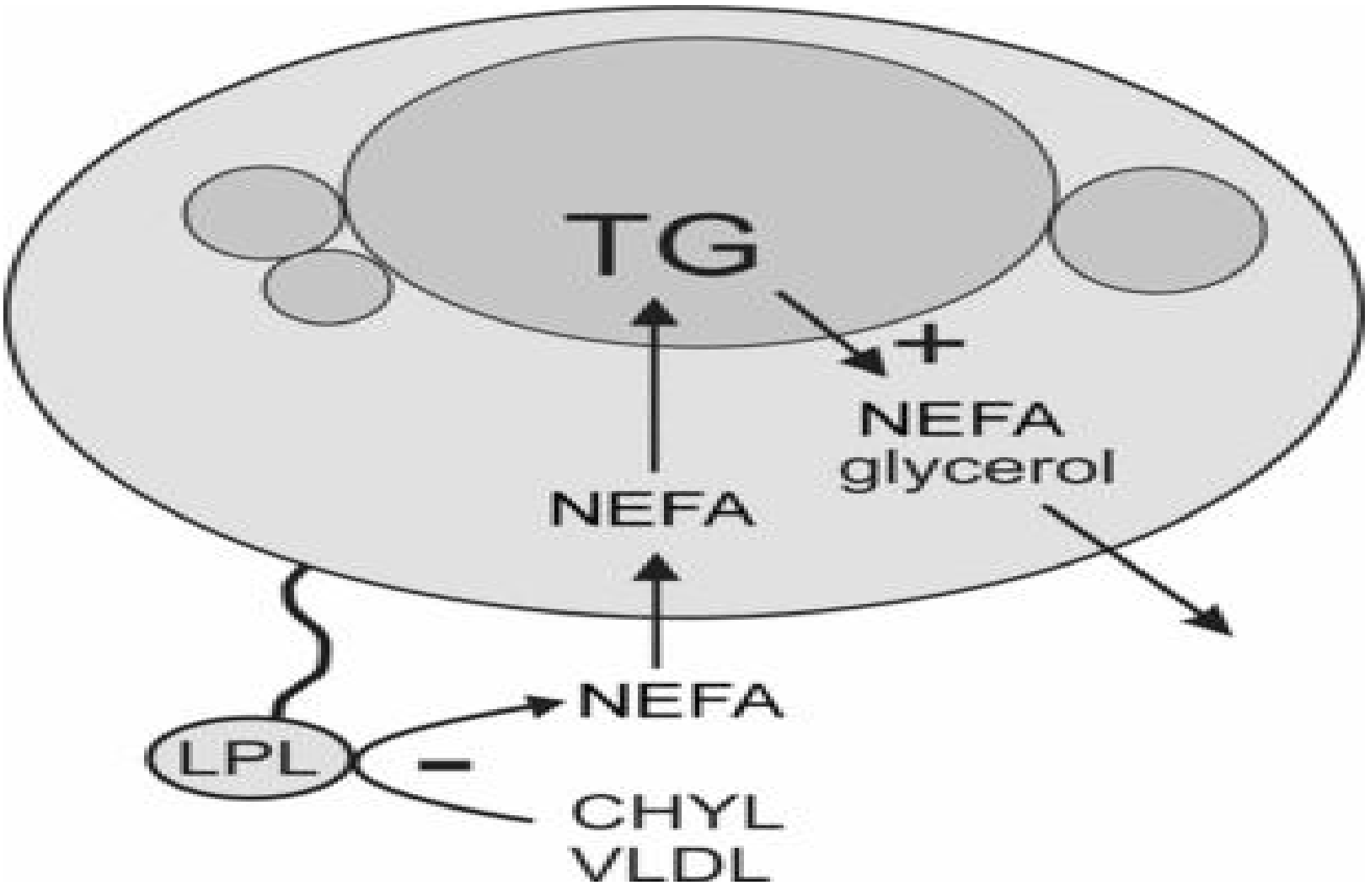




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LPL Mediated Fatty Acid Uptake



Hepatic Lipase (HL)

- **HL is bound to the surface of Liver cells**
- **Hydrolyzes TAG to free fatty acids and Glycerol**
- **HL is concerned with TAG hydrolysis in Chylomicron remnants and HDL coming to Liver.**

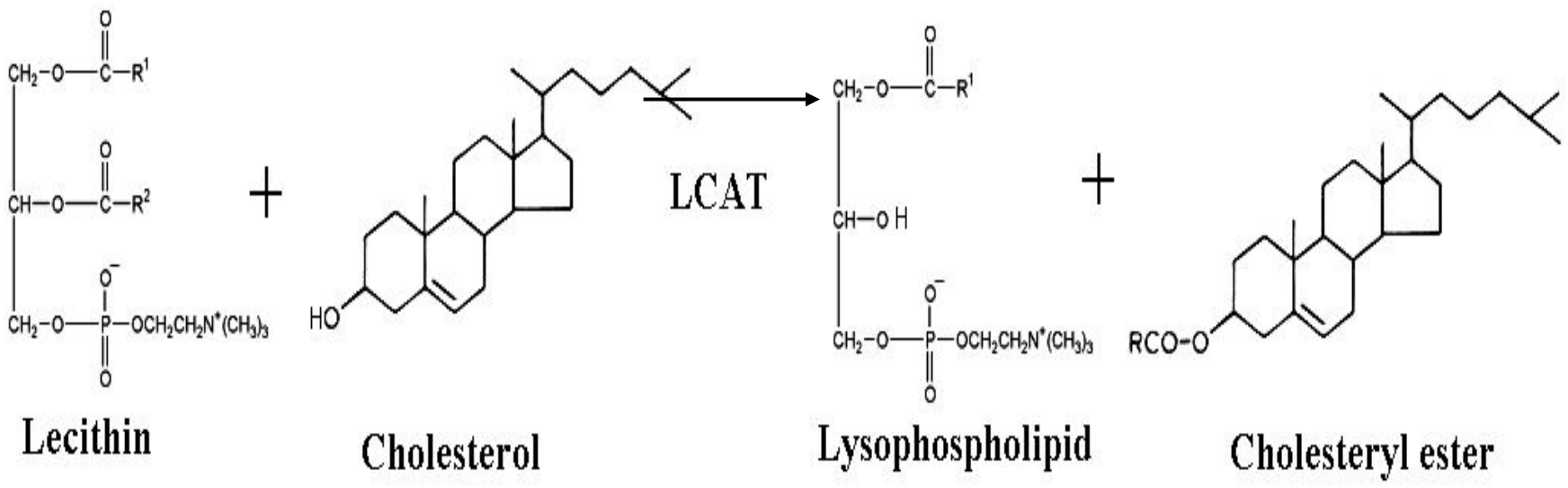
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LCAT

(Lecithin Cholesterol Acyltransferase)

Formation of Cholesterol Esters in Lipoproteins



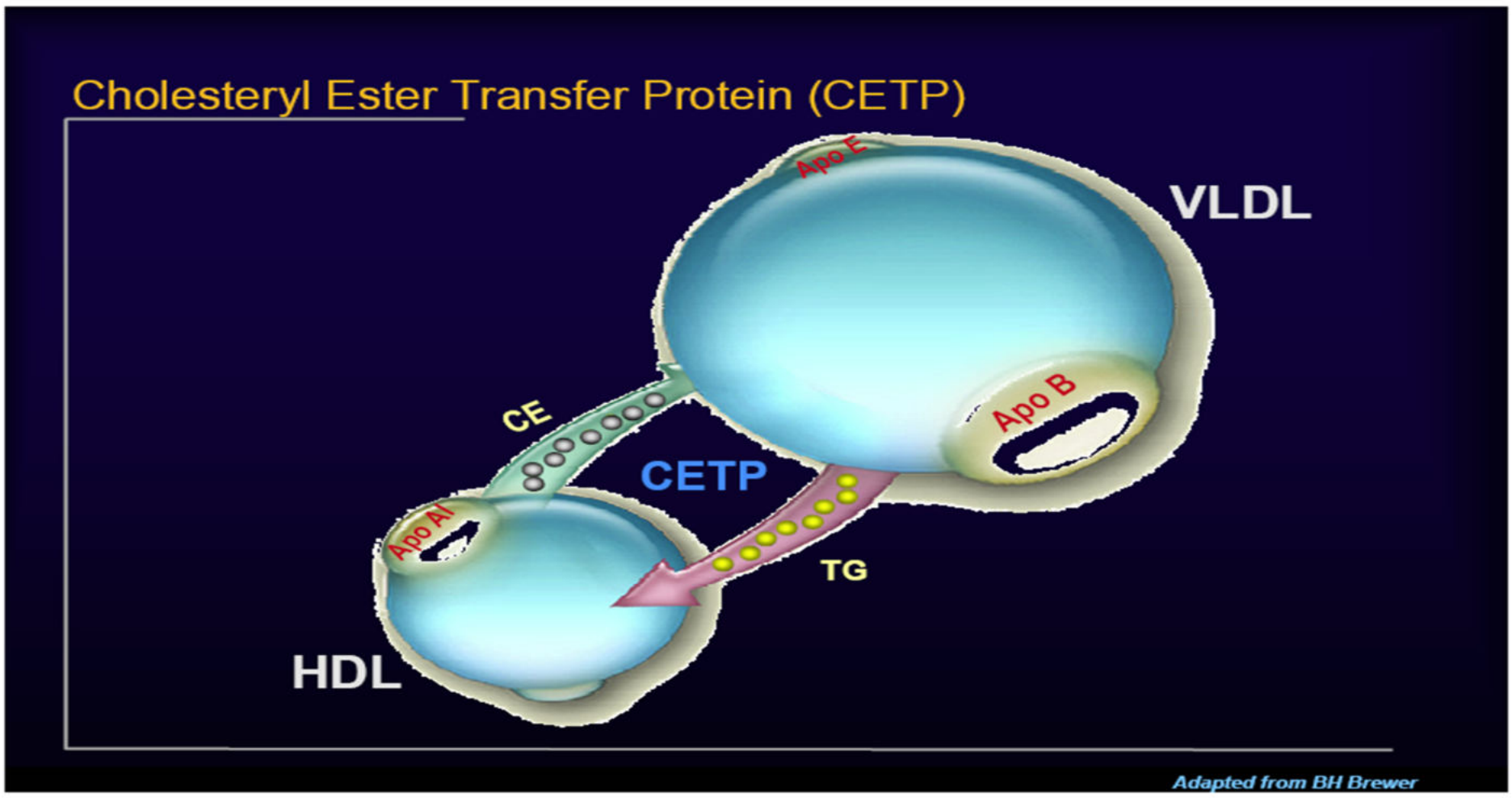
- **LCAT is associated** with **HDL Lipoprotein.**
- LCAT esterifies the Cholesterol and to HDL.

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CETP

(Cholesteryl Ester Transfer Protein)



Cholesterol Ester Transfer Protein

CETP

- **CETP is also termed as plasma lipid transfer protein.**

- **CETP exchanges Lipids from one Lipoprotein to another.**

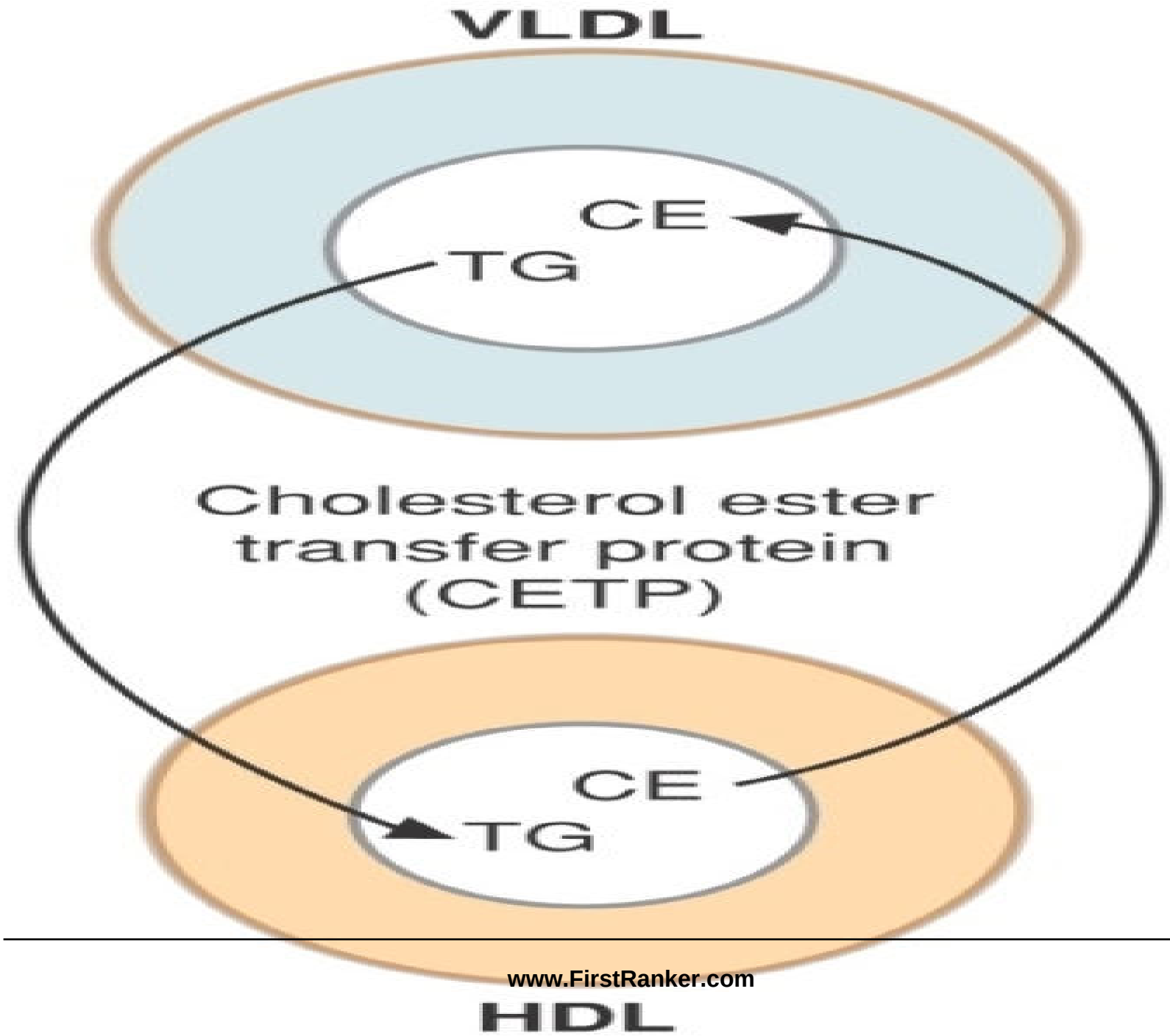
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CETP Activity

- CETP is a Plasma Protein that facilitates the transport of

- **Cholesteryl Esters** and **Triacylglycerol** between the Lipoproteins.



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- By CETP activity **Cholesteryl Ester May be transferred from HDL to:**
  - **VLDL**
  - **IDL**
  - **LDL**

- **CETP transfers TAG** from VLDL or LDL to HDL

- In exchange of Cholesteryl Esters from HDL to VLDL.

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- **HDL** either transfers **Cholesterol & Cholesterol esters.**

- **To Liver by means of CETP**

CETP by its activity Transforms HDL

HDL 3 to HDL 2

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Sub fractions Of HDL

HDL_2 and HDL_3

- **Prior to CETP activity HDL is** smaller particles termed as **HDL_3**

- **Post CETP activity HDL3** become larger TAG rich and termed as **HDL_2**

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- **HDL 3** is **Cholesteryl Ester rich** biomolecule.

- **HDL 2** is **TAG and CE containing.**

- **The receptors present on Hepatocytes** are for **HDL 2.**

- **HDL 2 is internalized in the hepatocytes** and get metabolized.

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Significance Of CETP Activity

- **Significance of CETP activity is to transfer**
- **The valuable functional compound Cholesterol from HDL to VLDL** and get transported to extrahepatocytes when it is required for its use.

- Hence **CETP activity is induced when there is need of Cholesterol to Extrahepatocytes.**

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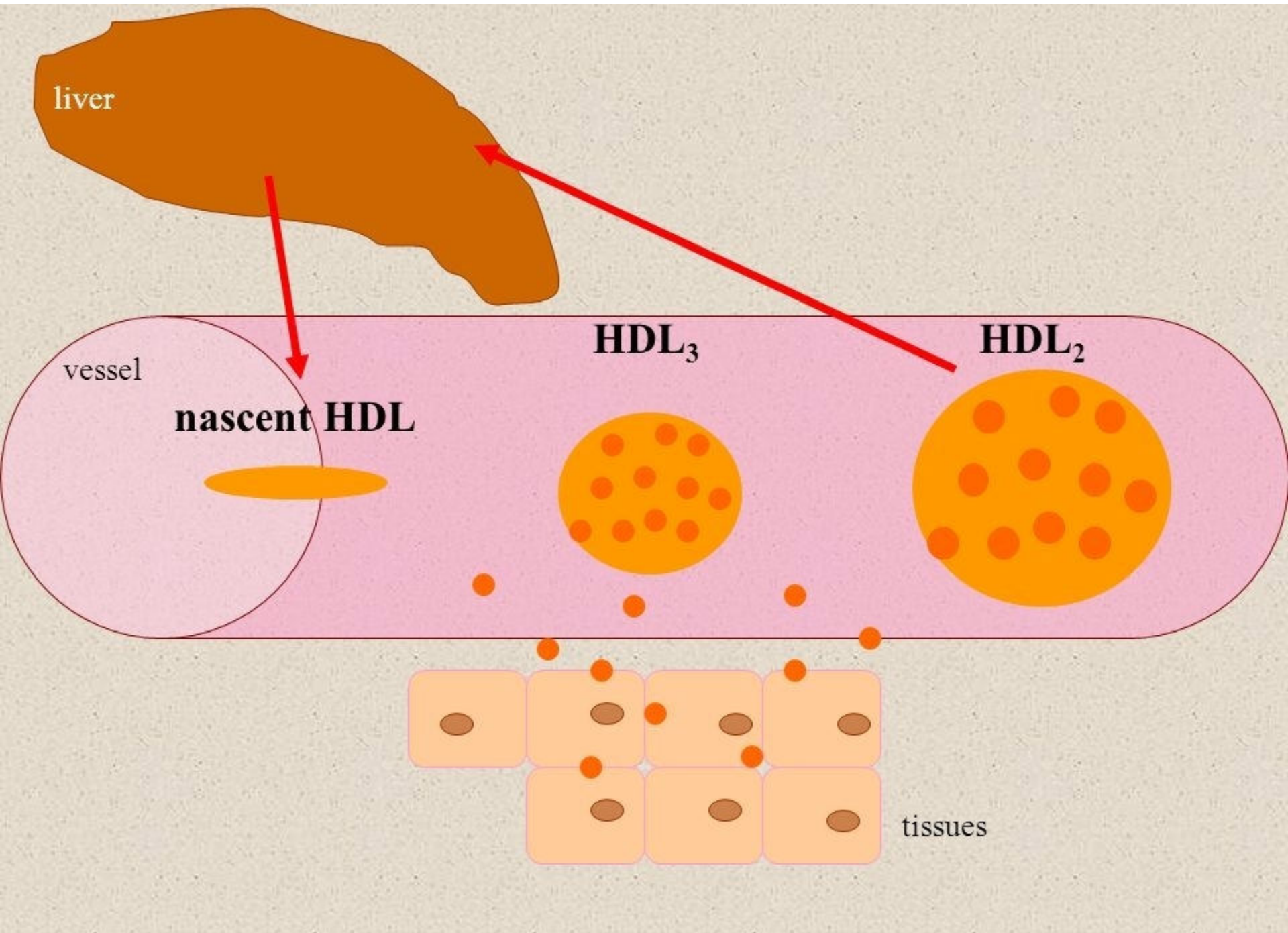
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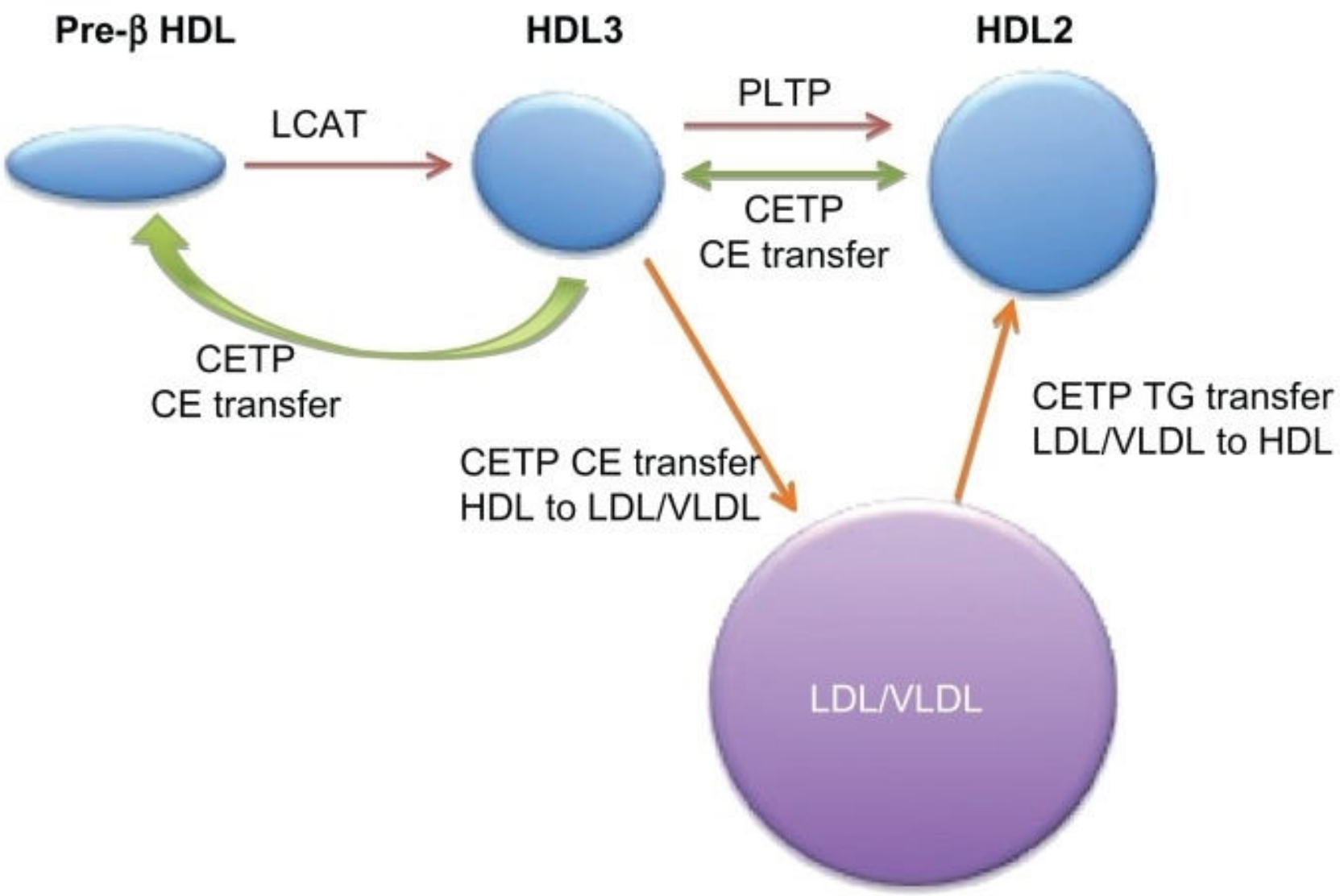
- **CETP activity reduces the content of Cholesteryl Ester of HDL.**

- **Low CE content of HDL** after CETP activity
- **Increases the HDL associated LCAT activity**.

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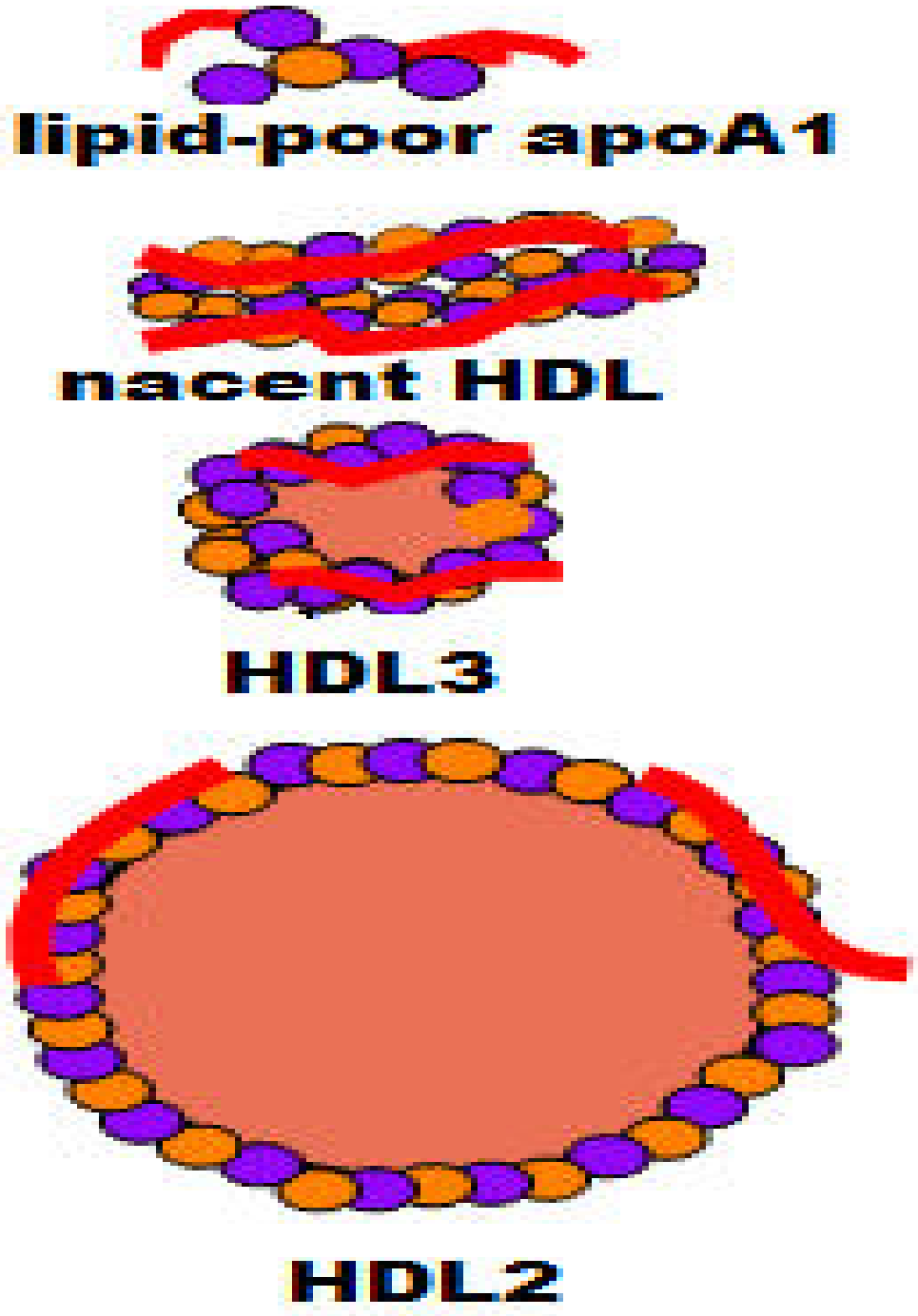
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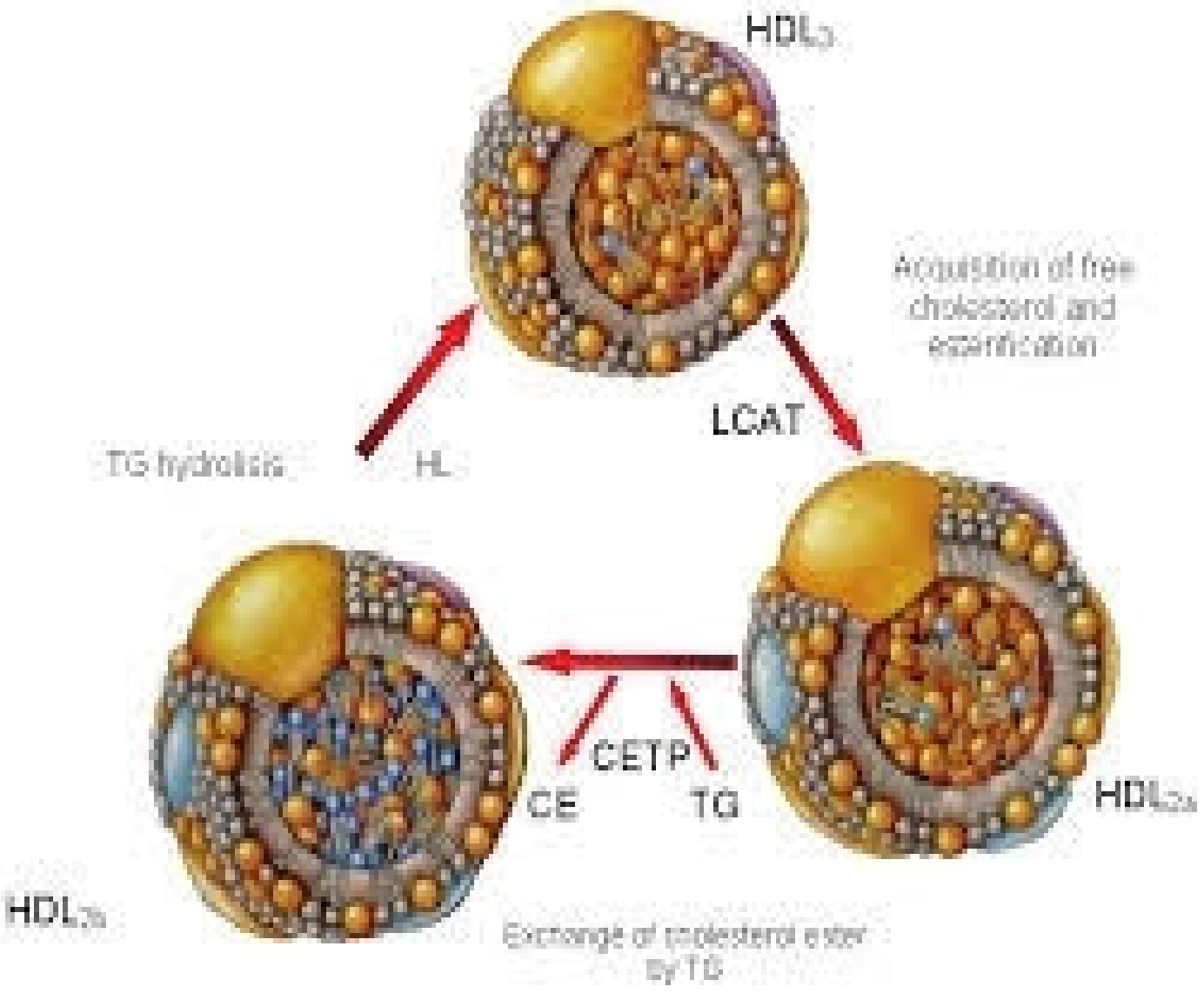




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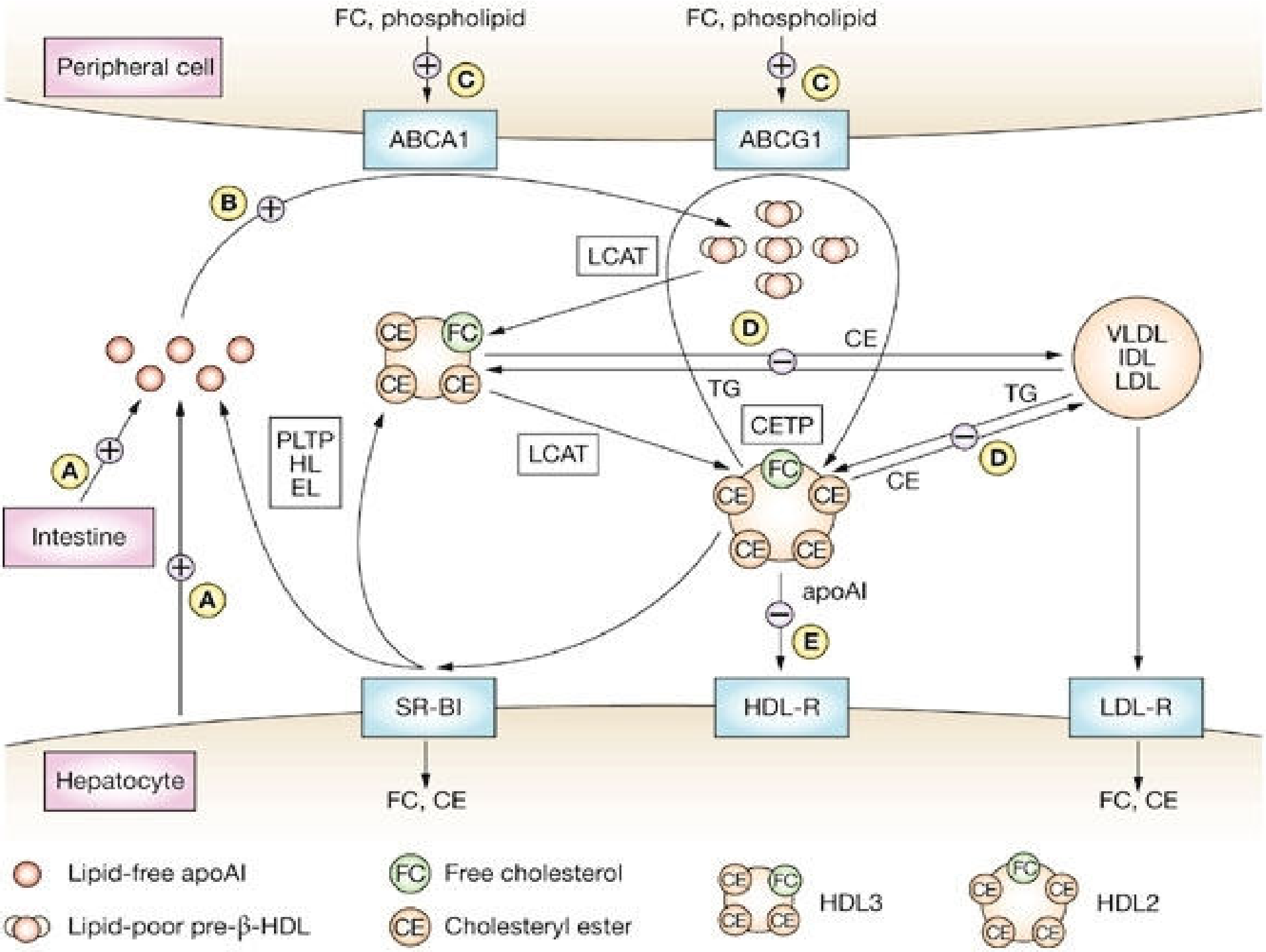
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Inhibition Of CETP Activity

Causes High HDL levels In Blood Circulation

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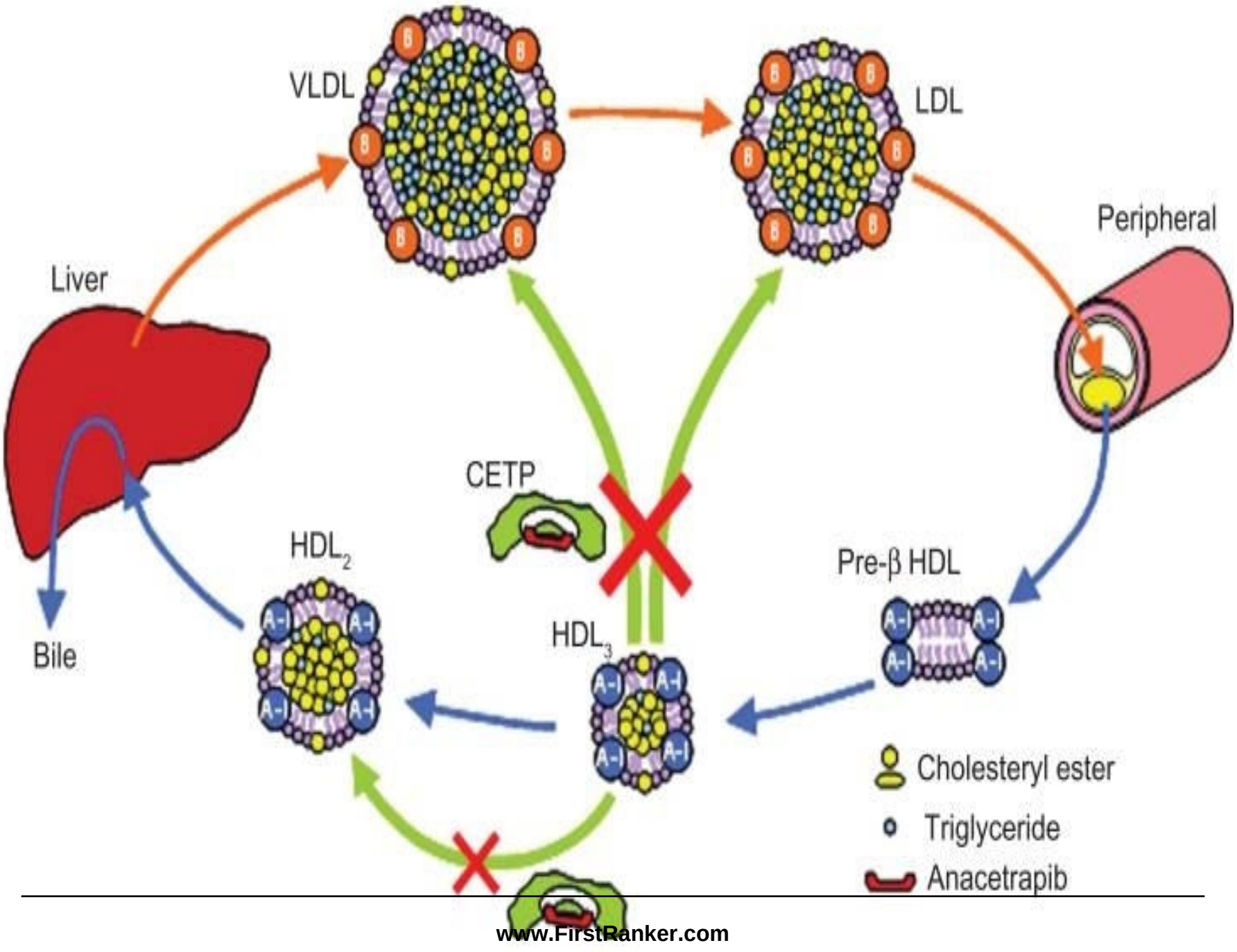
- **Inhibition of CETP** will not transfer the HDL Cholesteryl Ester to VLDL, for use in extra hepatocytes.
- **Not modify HDL3 to HDL2**
- **No internalization of HDL3 by hepatocytes**.
- This may **elevate the levels of HDL3 in blood.**
- **Defective Scavenging role of HDL**
- This leading to its **bad consequences of Atherosclerosis.**

- **Inhibition of CETP increases HDL3 levels.**
- But highly reduced CETP activity **accelerates very high HDL3 levels.**
- This **abnormal high levels of HDL3** evidenced showing **development of Atherosclerosis and Coronary Heart Diseases.**

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- Recent Studies have evidenced
- The **CETP inhibiting drugs**
- **Elevates the levels of HDL3** and
- **Increases the mortality rate.**

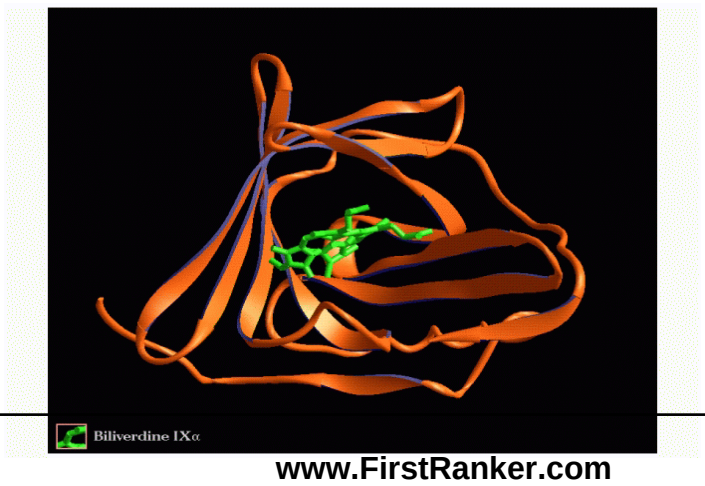


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Apolipoproteins

Functions of Apolipoproteins



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- Apoproteins are protein parts of Lipoprotein structure
- Apoproteins act as structural components of Lipoproteins
- Apoproteins are polar moieties which impart solubility to Lipoprotein structure.

- Apoproteins

- Recognizes the Lipoprotein receptors on cell membrane surface as ligand.
- Which further facilitates the uptake of LP by specific tissues.

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Apoproteins Activate /Inhibit Enzymes Involved in Lipoprotein metabolism.

- **Apo A I:** Activator LCAT
- **Apo C-I :** Activator of LCAT
- **Apo A-IV:** Activator of LCAT
- **Apo C-II:** Activator of LPL

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- **Apo C-III: Inhibitor of LPL**

- **Apo AII: Inhibitor of Hepatic Lipase (HL)**

- **Chylomicrons contain ApoB-48.**

- **VLDLs, IDLs and LDLs has ApoB-100.**

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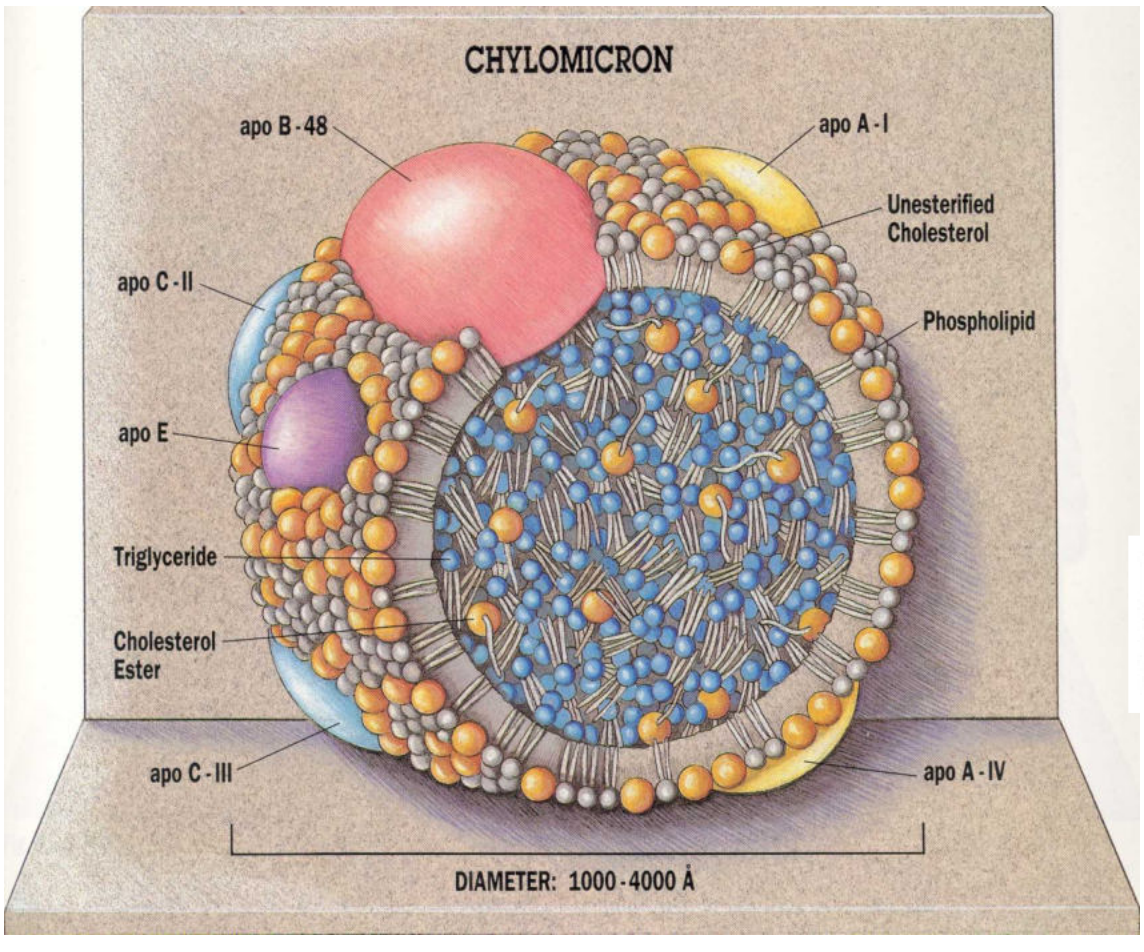
HDL transfers Apo E & Apo CII to Chylomicrons & VLDL

Chylomicron Metabolism

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Metabolism of Chylomicrons



Surface Monolayer
Phospholipids
Free Cholesterol
Protein

Hydrophobic Core
Triglyceride
Cholesteryl Esters

Chylomicrons

- **Assembled in intestinal mucosal cells**
- **Has lowest density**
- **It has largest size**
- **Highest % of lipids and lowest % proteins**

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- **Highest concentration of Triacylglycerol (dietary origin)**
- **Chylomicrons carry dietary lipids from intestine to Liver**
- **Responsible for physiological milky appearance of plasma (up to 2 hours after meal)**

- **Chylomicron** is a type of Lipoprotein
- **Formed in the intestinal mucosal cells**
- Due to aggregation of dietary digested and absorbed Lipids.

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- The Chylomicrons has 99% Lipids and 1% Proteins
- The predominant Lipid present in Chylomicrons is Triacylglycerol (TAG) of dietary origin.

- The Apoprotein of Chylomicron is B48
- Significant role of Chylomicron is to transport dietary Lipids from intestinal mucosal cell to Liver via Lymph and Blood.

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- Chylomicrons formed in intestinal mucosal cells are
- First released in lymphatic system
- Which then enters systemic blood circulation via thoracic duct.

- Chylomicrons in blood circulation are not moved inertly
- But **receives Apo C II and Apo E from the circulating HDL** and gets mature.
- ***Apo C II then stimulates the enzyme Lipoprotein Lipase*** present in endothelial lining of blood vessels of Adipose tissue and Cardiac tissue.

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- The stimulated Lipoprotein Lipase acts upon TAG of Chylomicrons ,

- Hydrolyze it into free fatty acids and Glycerol ,which then enters to adjacent adiposecytes.

- Entered Free fatty acids TAG and stored as reserve food material.

- The circulating Chylomicrons are continuously acted upon by Lipoprotein Lipase
- Most of the TAG is removed from it and transformed to Chylomicron remnant till they reach Liver.

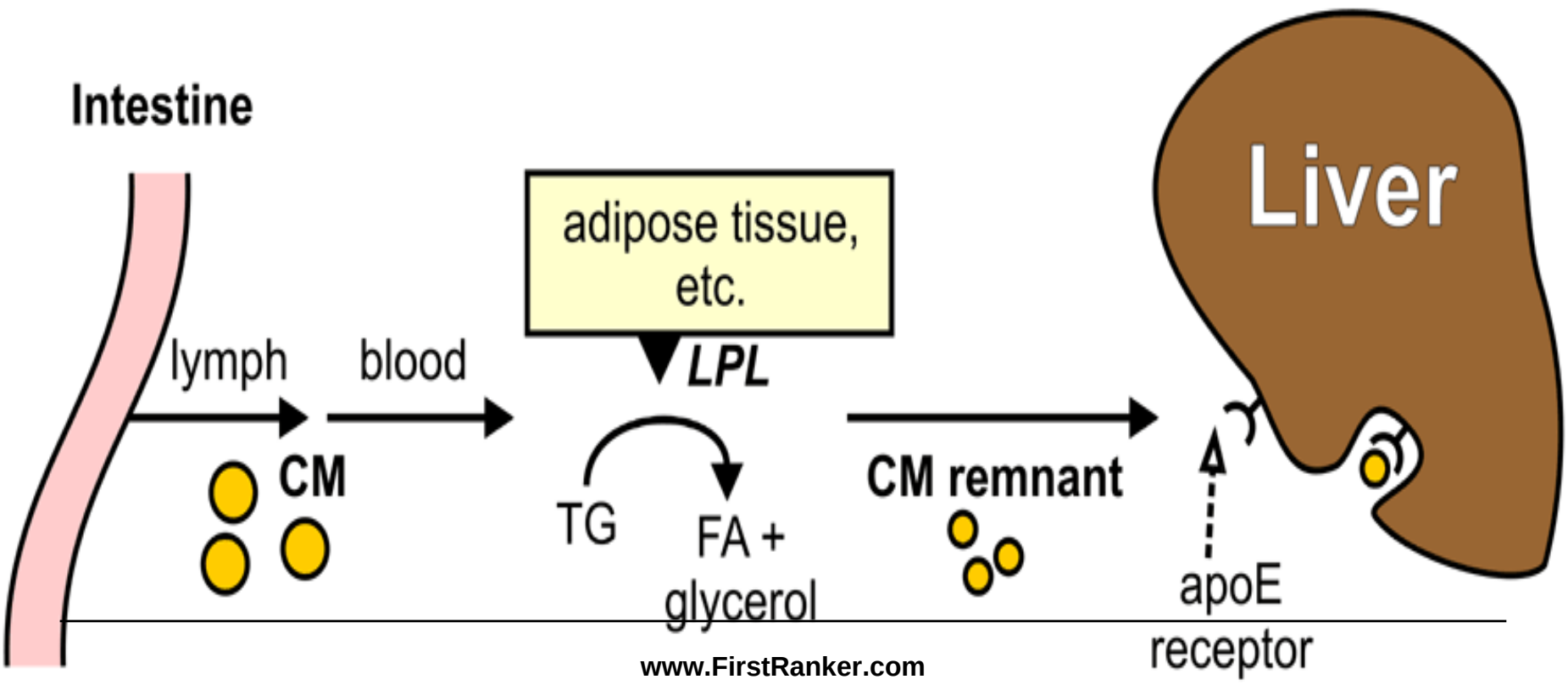
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- The **Liver has receptors for Chylomicron remnant.**

- Chylomicron remnant linked to receptors of hepatocytes are **internalized and metabolized in Liver.**

- **Chylomicrons transport dietary TAG and Cholesterol from the intestine to the peripheral tissues**



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- **Lipoprotein lipase (LPL) is activated by Apo C-II**

- **After most of the TG is removed, Chylomicrons become Chylomicron remnants. During the process, CM give ApoC and ApoA back to HDL**

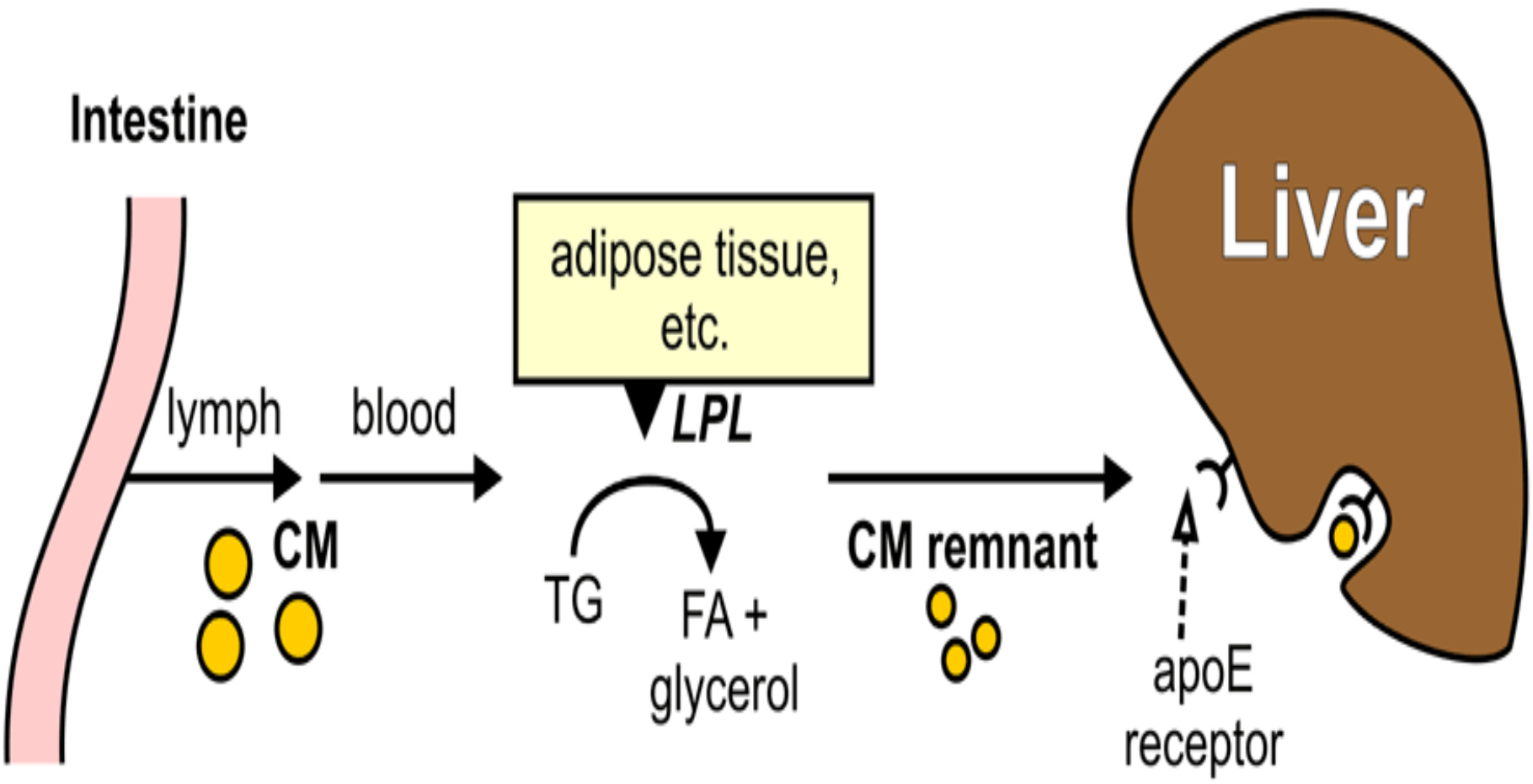
- **CM remnants bind to specific receptors on the surface of liver cells through apo E and then the complex is Endocytosed.**

- **Remnant receptor or ApoE receptor or LRP (LDL receptor-related protein)**

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- **Chylomicron remnants deliver dietary cholesterol and some cellular cholesterol (via HDL) to the liver.**
- **Half life of CM is short, less than 1 hour.**



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Chylomicrons

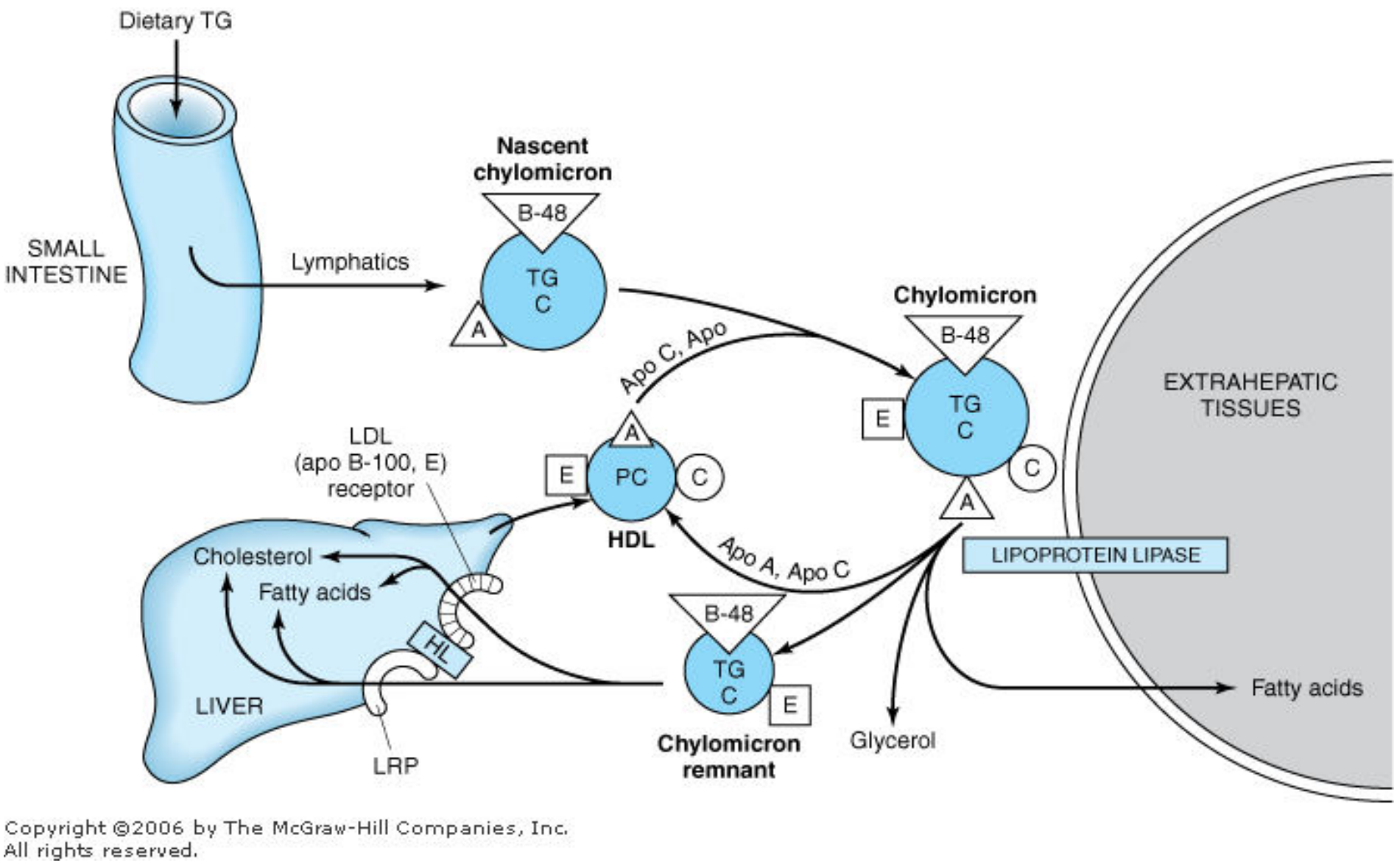
Nascent Chylomicron are formed in the intestinal and consists of rich in dietary TG + minimal amount of dietary cholesterol + Apo (B-48)

Mature Chylomicron after Nascent chylomicron passage to blood, addition of Apo C II and Apo E from HDL

Lipoprotein lipase hydrolyzes TAG present in Chylomicrons

Chylomicron remnant taken up by the liver through endocytosis.

Apo C removed and returns back to HDL



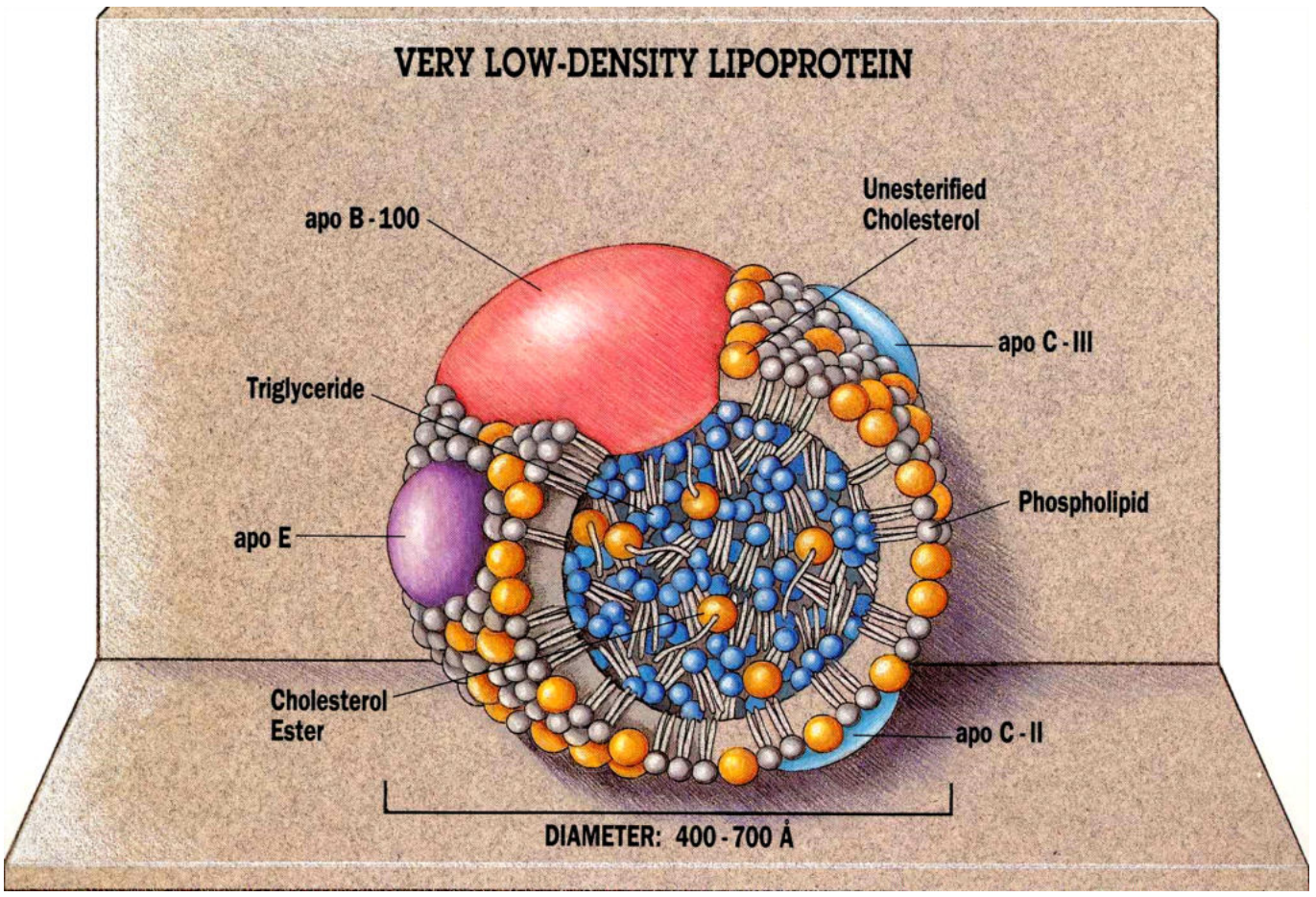
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Metabolic fate of chylomicrons. (A, apolipoprotein A; B-48, apolipoprotein B-48; , apolipoprotein C; E, apolipoprotein E; HDL, high-density lipoprotein; TG, triacylglycerol; C, cholesterol and cholesteryl ester; P, phospholipid; HL, hepatic lipase; LRP, LDL receptor-related protein.) Only the predominant lipids are shown.

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Metabolism of VLDL and LDL



Formation and Fate Of VLDL

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- **The Lipoprotein Very Low Density Lipoprotein (VLDL)**
- Biosynthesized in **Hepatocytes and Intestinal Mucosal Cells**.

- The **endogenously biosynthesized Lipids** are aggregated
- Along with **Apoprotein B-100** to **form VLDL.**

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- **VLDL predominantly contains Triacylglycerol of endogenous origin.**

Role Of VLDL

- VLDL facilitates in **mobilizing out the endogenously synthesized Lipids** in Hepatocytes and Intestinal mucosal cells.

- **VLDL transports endogenous Lipids from Liver to Extra Hepatocytes via blood**.

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- **Nascent VLDL accepts Apo CII and Apo E from HDL**
- This modify it to **mature VLDLs** in blood.

- **Nascent VLDL: contains Apo B-100**
- **Mature VLDL: Apo B-100 plus Apo C-II and Apo E (from HDL)**

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- **Apo C-II is required for activation of Lipoprotein lipase**

- **Lipoprotein lipase is required to degrade VLDL TAG into Glycerol and fatty acids**

- **Circulating VLDL on action by Lipoprotein Lipase hydrolyzes most of its TAG.**
- **VLDL gets modified to IDL and LDL.**

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- Thus **intermediate product of IDL and end product LDL are formed from VLDL**

- **In blood circulation by action of LPL on VLDL and removal of TAG from it.**

Normal VLDL Metabolism Prevents the person to Suffer from Fatty Liver

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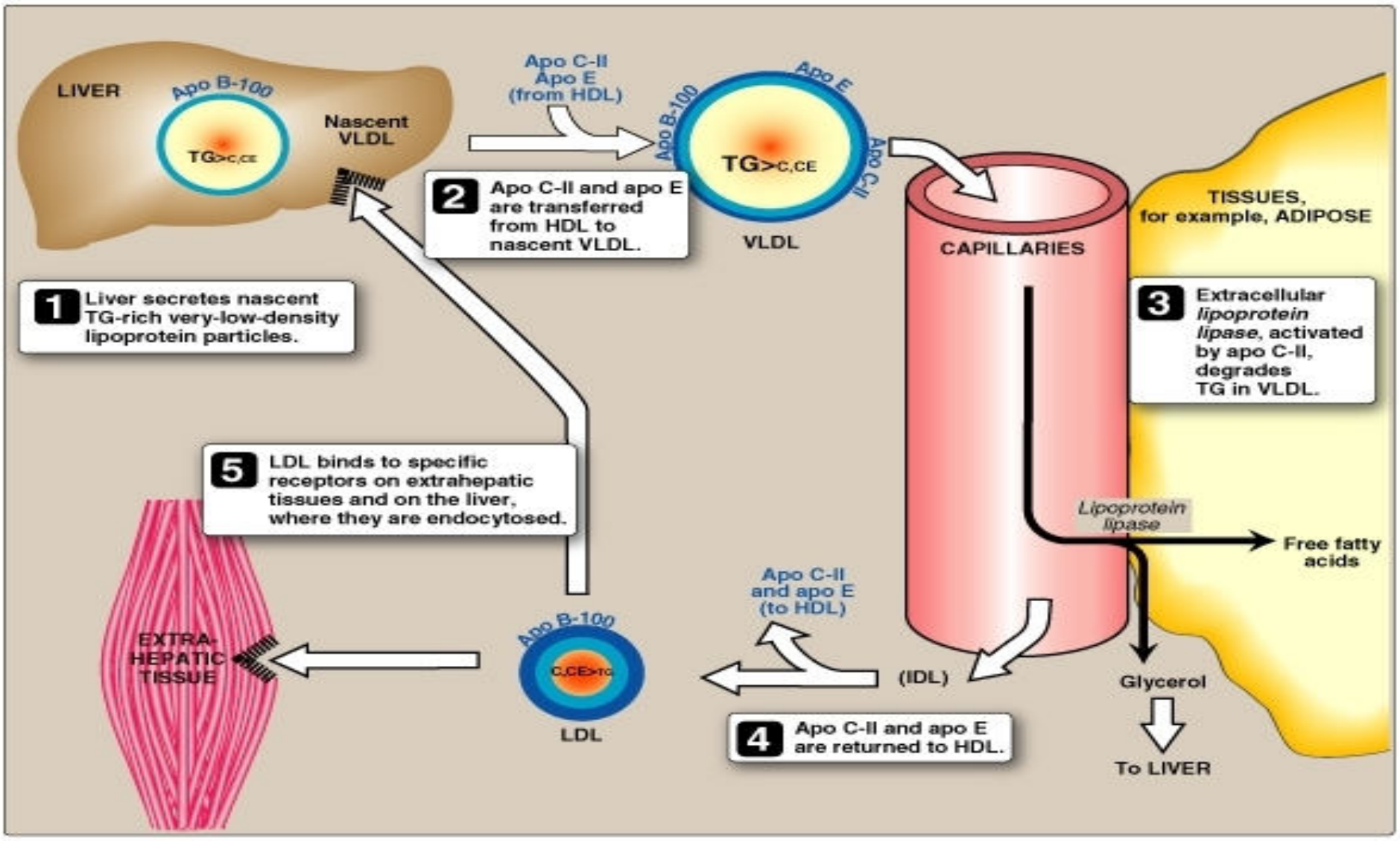
- **VLDL help in mobilizing out the endogenously biosynthesized Lipids of Hepatocytes.**
- **Normal Formation and mobilization of VLDL prevents from accumulation of excess Fat in the Liver and develop Fatty Liver.**

Modifications of Circulating VLDLs

VLDL → IDL (returns Apo E to HDL) → LDL

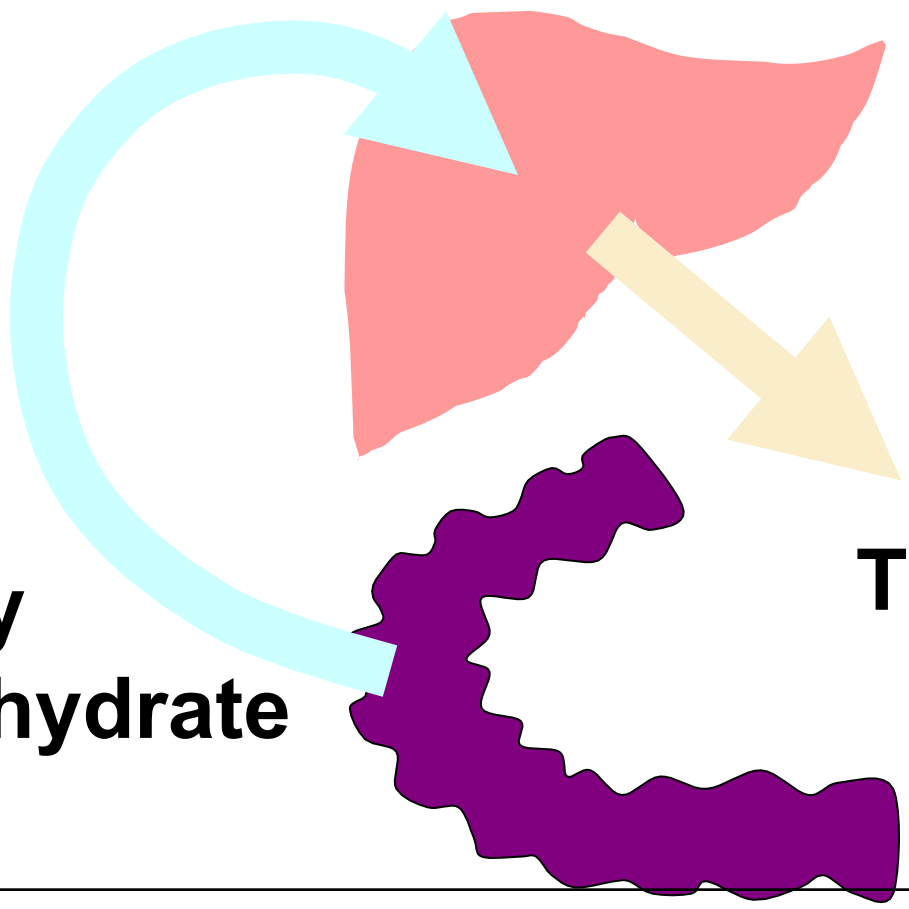
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VLDL Metabolism

Dietary Carbohydrate Increases VLDL Production



Dietary Carbohydrate

Plasma Triglyceride (VLDL)

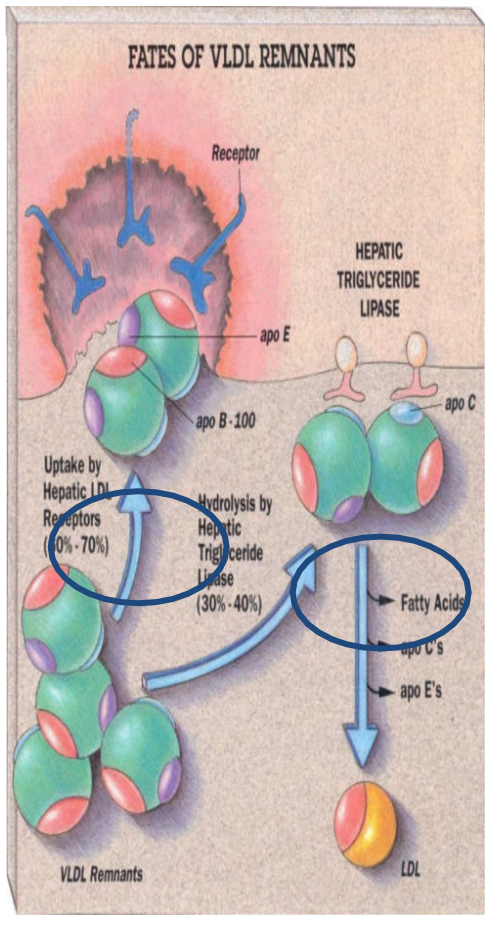
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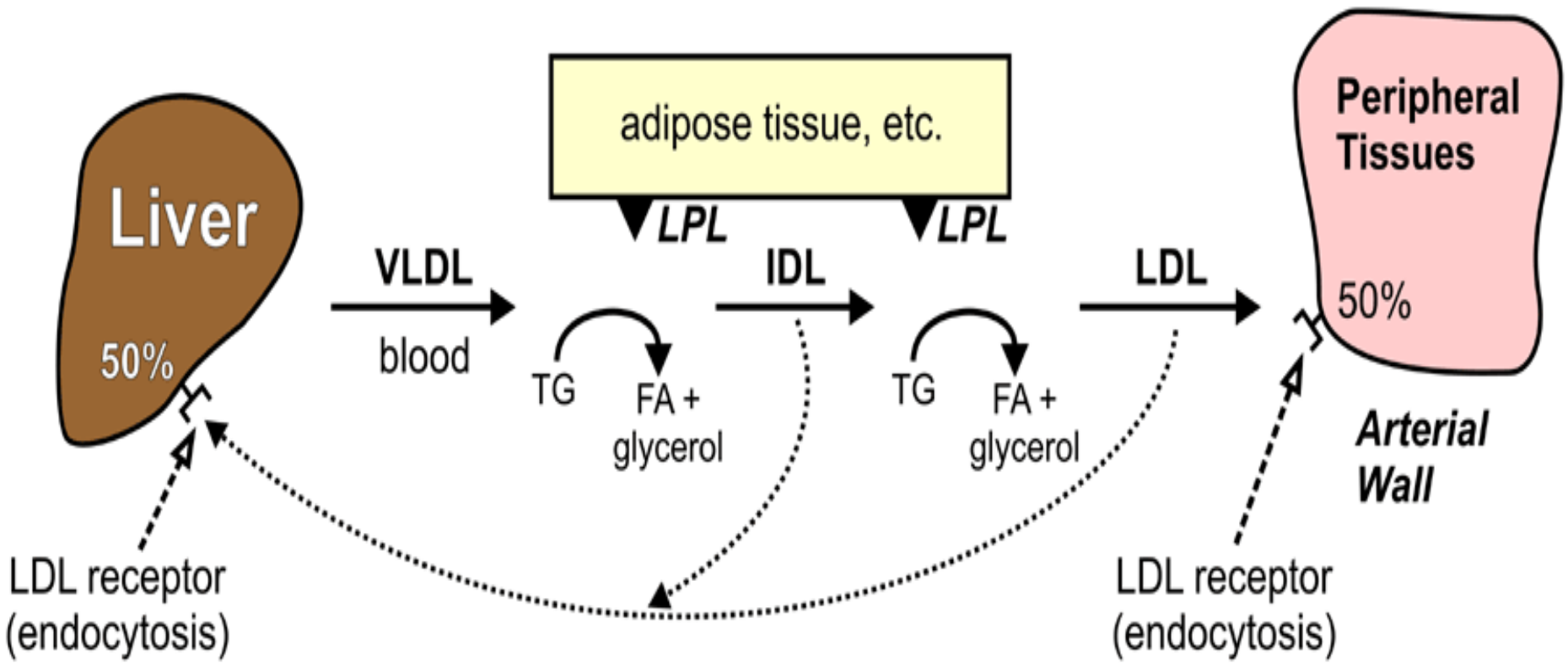
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VLDL Remnants

IDL and LDL

- **LDL results from loss of TAG in VLDL**
- **LDL contains relatively more Cholesterol esters**
- **LDL looses all Apo lipoproteins except ApoB100.**





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Very Low Density Lipoprotein (VLDL)

Nascent VLDLare formed in the liver and consists of endogenous TG + 17 % cholesterol + Apo (B-100)

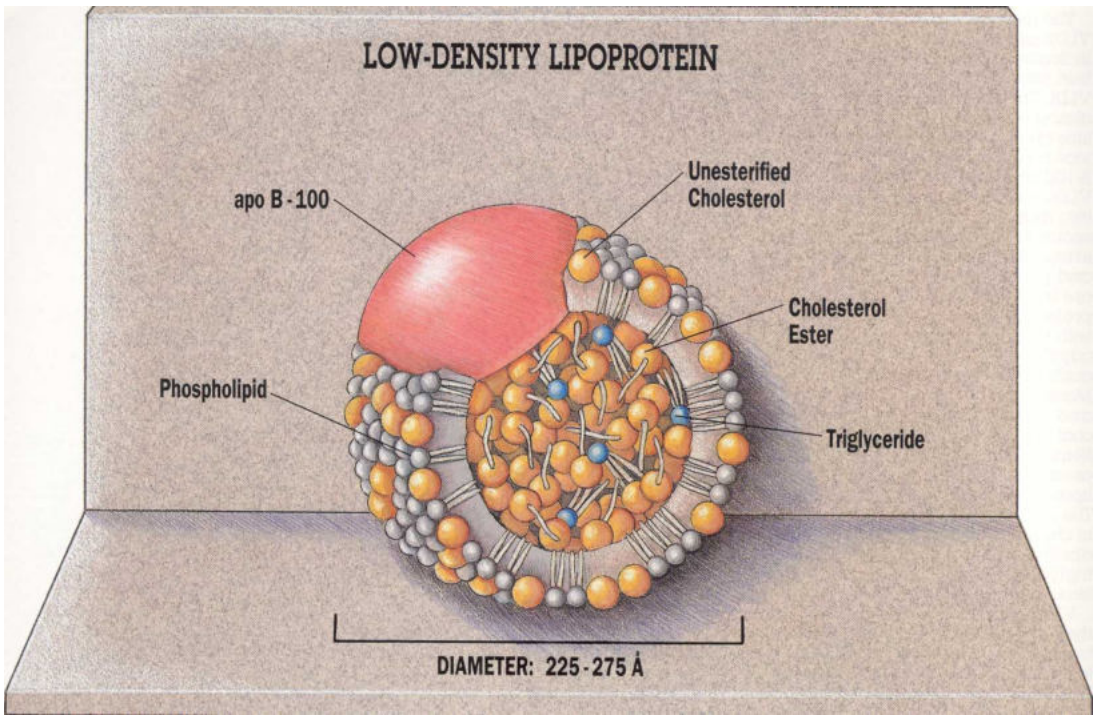
Mature VLDL after Nascent VLDL passage to blood, addition of ApoC II, ApoE and cholesterol esters from HDL

Lipoprotein lipase (LPL) hydrolyzes TAG present in VLDL

VLDL remnant containing less of TG and more of cholesterol and taken up by the liver through endocytosis.

Apo C removed and returns to HDL

LDL Metabolism



Most core lipid in LDL is Cholesterol ester.

ApoB100 is only Apolipoprotein in the surface.

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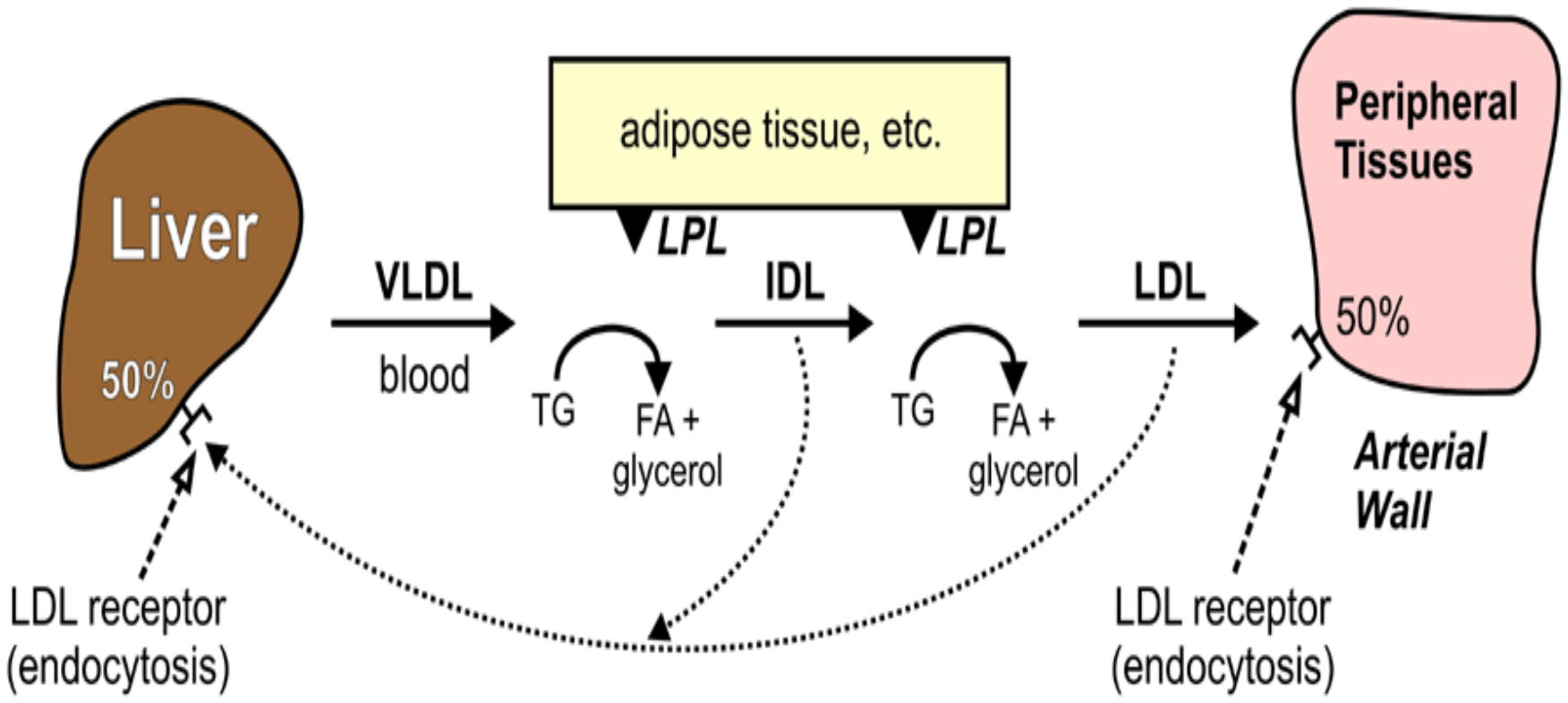
Formation and Fate Of LDL

- Low Density Lipoprotein (LDL) is a Lipoprotein **formed from VLDL in blood circulation.**
- VLDL in blood circulation receives Apo CII and Apo E from the circulating HDL.

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- **Apo CII then stimulates the Lipoprotein Lipase enzyme** present in the endothelial lining of blood vessels.
- Lipoprotein Lipase then acts upon TAG present in VLDL ,hydrolyze it to Glycerol and free fatty acids



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- **LDL is the modified form of VLDL** formed in blood circulation.
- **LDL is remnant of VLDL**

- LDL is mostly associated with **Cholesterol and Phospholipids with minimal TAG**
- Of endogenous origin mobilized out from Liver.

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- The **major Apoproteins** of **LDL is Apo B100**

- Same as VLDL **since LDL is derived from VLDL**

- **Function of LDL is to transport endogenously biosynthesized Cholesterol from Liver to the peripheral /extrahepatic tissues.**

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LDL Receptor

- LDL receptor is also named as ApoB100/ApoE receptors
- **Since ApoB-100 of LDL binds to LDL receptor.**
- The complexes of LDL and receptor are taken into the cells by endocytosis,
- Where LDL is degraded but the receptors are recycled

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- LDL receptors are found on cell surface of many cell types of extrahepatocytes.

- LDL is internalized by the tissues when LDL get fixed to the LDL receptors.

- LDL receptor mediates delivery of Cholesterol

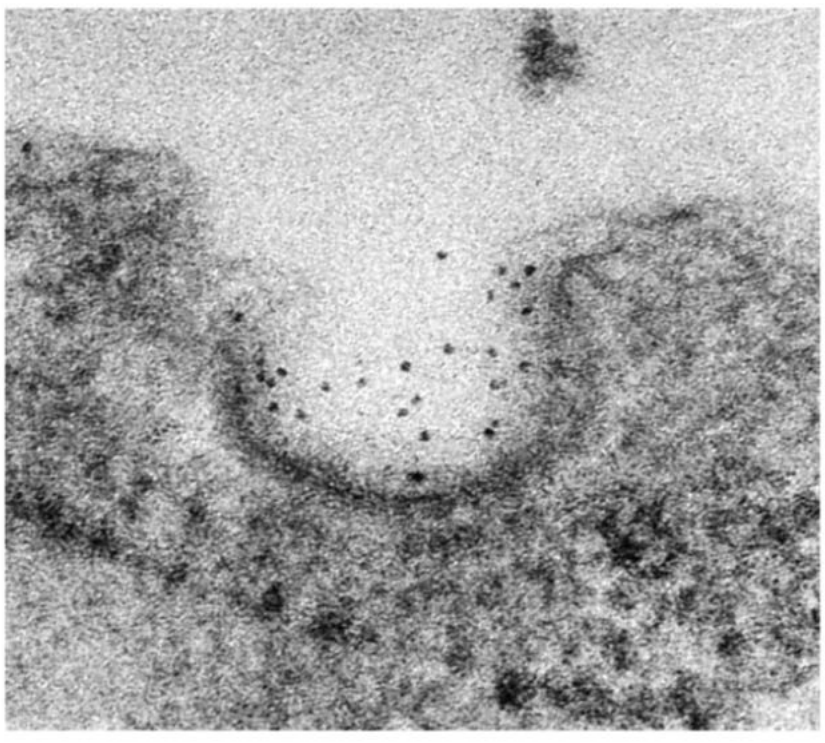
- By inducing endocytosis and fusion with Lysosomes.

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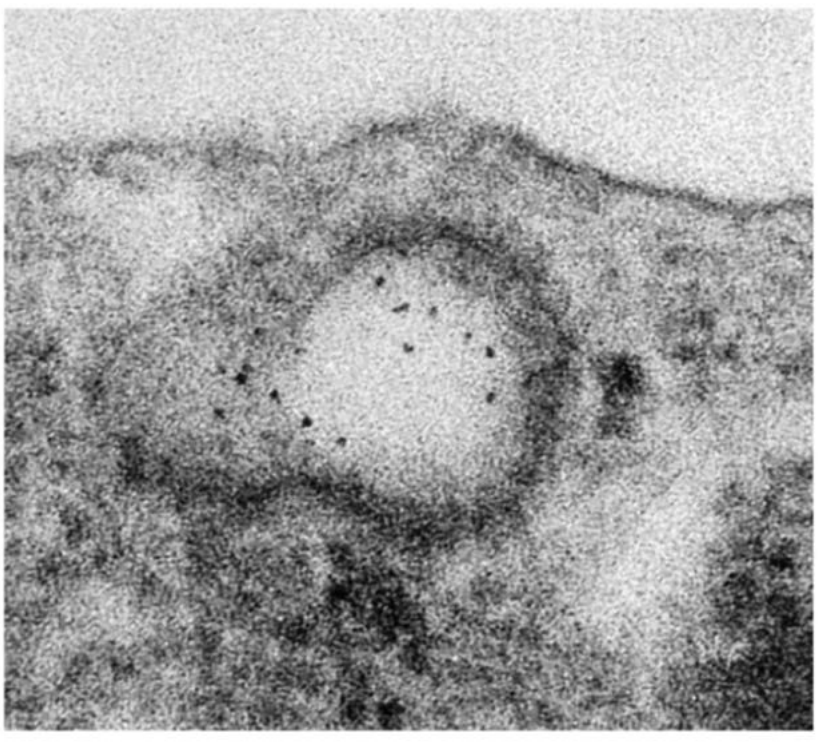
- **Lysosomal lipases and proteases degrade the LDL.**

- **Cholesterol then incorporates into cell membranes or is stored as cholesterol-esters of extrahepatocytes.**

LDL Receptor



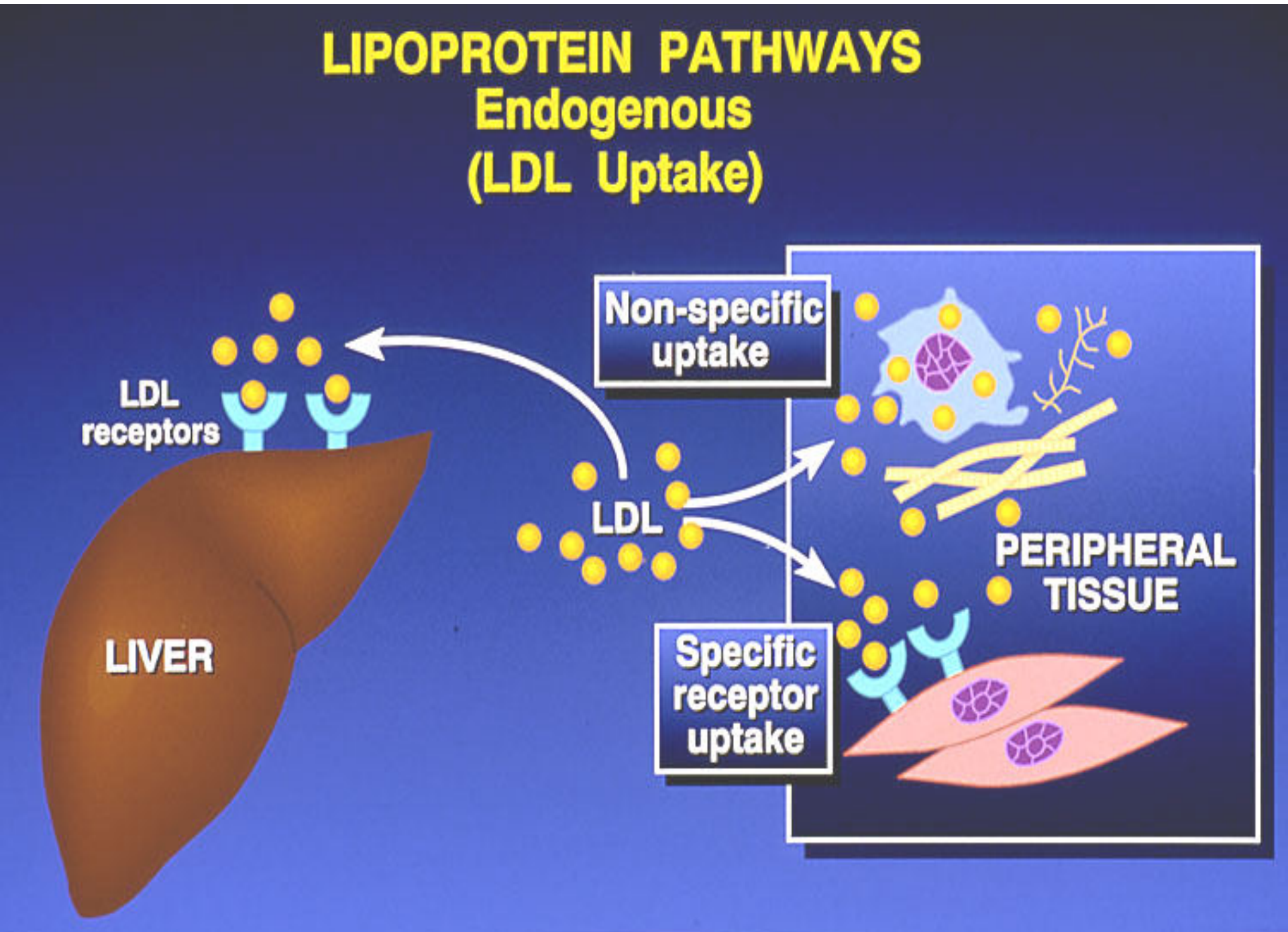
(A)



(B)

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LDL Cholesterol levels are positively related to risk of Cardiovascular Disease.

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- **LDL values within normal range is an indication of healthy status.**
- **But the high LDL levels are abnormal .**

- **The Cholesterol associated to this high levels of LDL molecules increases the risk of Atherosclerosis and CVD.**
- **Hence this LDL associated Cholesterol is termed as "bad Cholesterol"**

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Defect/Absence of LDL Receptors

Leads to Accumulation of LDL in Blood Circulation

Causing Hypercholesteremia and Atherosclerosis

- **Defect in LDL receptors** on tissues **impairs LDL metabolism**.
- **Decreases LDL internalization within the tissues.**
- Increases abnormal levels of LDL in blood (< 130 mg%).

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- **Increased LDL levels** in blood circulation **due to defect in LDL receptors** is termed as **Type II a Hyperlipoproteinemia**.

- The major form of **Lipid associated** with **LDL is Cholesterol .**
- Hence increased LDL levels is characterized by Hypercholesterolemia.
- The Cholesterol associated with **elevated levels of LDL (more than its normal range) is termed as bad Cholesterol**,
- Since it **increases the risk of Atherosclerosis and its complications .**

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- Persons lacking the LDL receptor suffer from **Familial Hypercholesteremia**
- Due to result of a **mutation in a single autosomal gene**
- Total plasma cholesterol and LDL levels are elevated.

– **Cholesterol Levels of:**

– **Healthy person = < 200 mg/dl**

– **Heterozygous individuals = 300 mg/dl**

– **Homozygous individuals = 680 mg/dl**

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High LDL levels can lead to Cardiovascular Disease

Most Homozygous individuals die of cardiovascular disease in childhood

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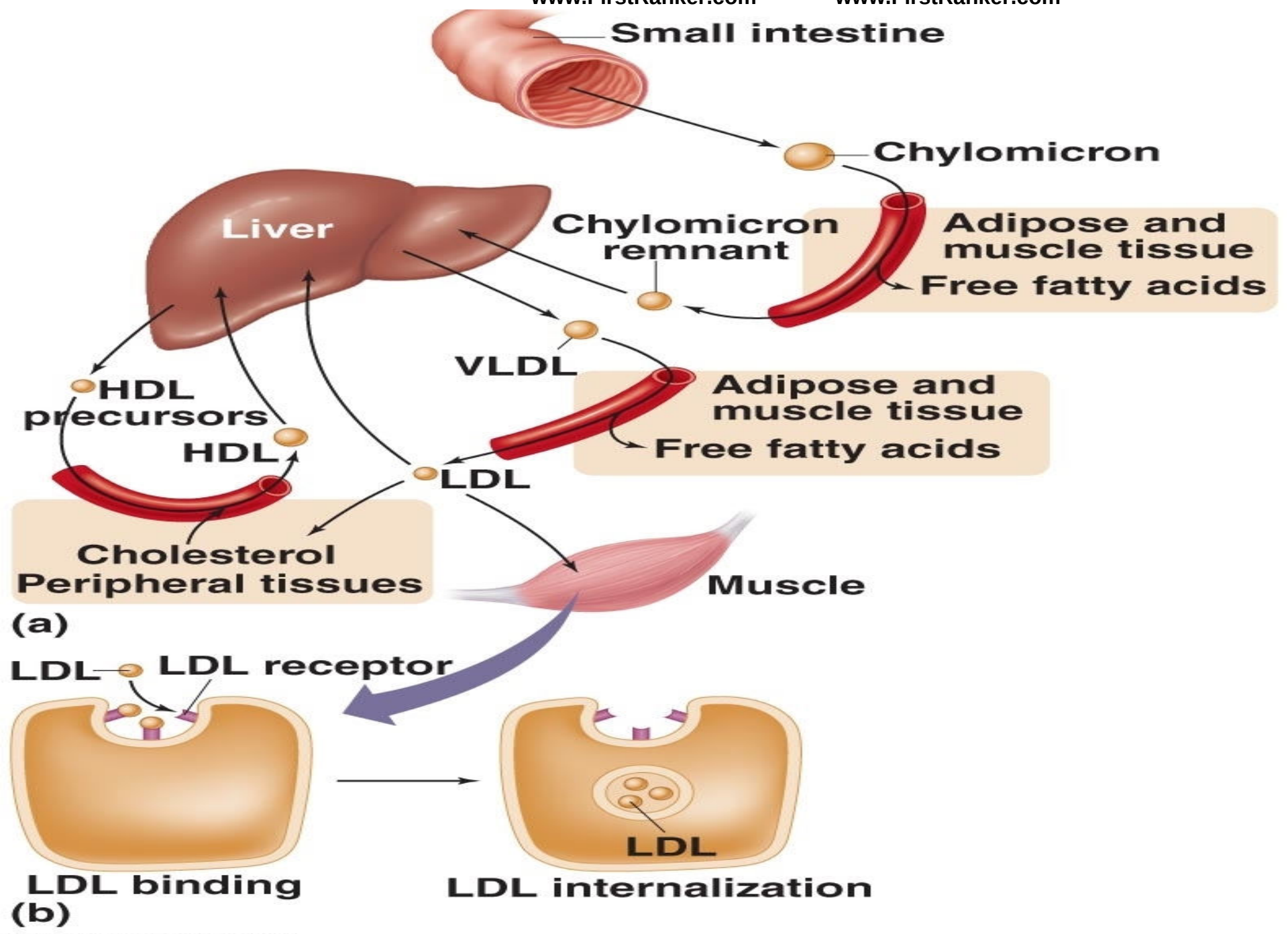
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- LDL can be oxidized to form oxidized LDL
- Oxidized LDL is taken up by immune cells called macrophages.
- Macrophages become engorged to form foam cells.

- Foam cells become trapped in the walls of blood vessels and contribute to the formation of atherosclerotic plaques.
- Causes narrowing of the arteries which can lead to MI/heart attacks.

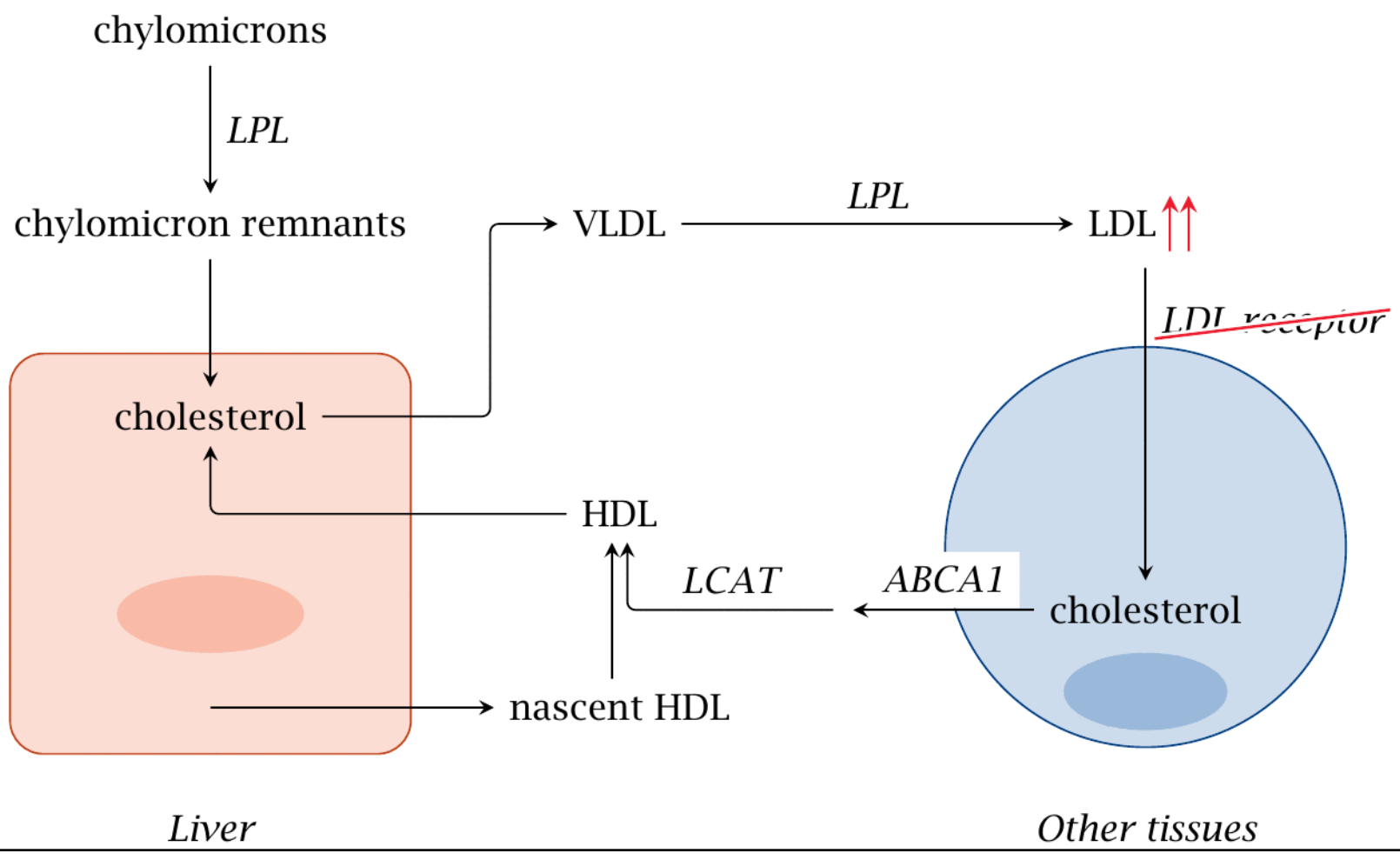
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Familial hypercholesterolemia is due to a gene defect in the LDL receptor



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Role Of HDL Reverse Transport Of Cholesterol

- HDL is a **high density Lipoprotein.**

- **Nascent HDL** is biosynthesized in Liver.

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- **HDL is the Lipoprotein, with highest density.**
- Since it is associated with 40-50% of Apoproteins.
- The Apoproteins of HDL are Apo A I, Apo A II, Apo C I,C II, Apo D and Apo E.

- **HDL serves as a reservoir of Apoprotein during its circulation.**
- HDL gives it Apo CII and Apo E to circulating nascent Chylomicrons and VLDL .

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- **Nascent HDL** of **discoid shaped** (Empty Bag) **biosynthesized in Liver**
- It is **released in the blood circulation for scavenging action.**

The HDL has Scavenging Action

It serves as a Scavenger For Unwanted Body Lipids

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- The Enzyme **Lecithin Cholesterol Acyl Transferase** (LCAT) is **associated with HDL metabolism.**

- **Apo A I,A IV and CI stimulates the LCAT activity of HDL.**

- LCAT by its activity help in **esterification of free Cholesterol to Esterified Cholesterol/Cholesterol Ester.**

- HDL by its scavenging action collects the extra non functional Cholesterol lying in blood vessels and peripheral tissues.

- **HDL esterifies Choleserol by its LCAT activity and to HDL bag.**

- **The nascent HDL bags changes to spherical shape .**

- HDL is more associated with Phospholipids and Cholesterol.

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- The receptors for HDL are present on Liver cells.

- **HDL transports the excess, unused Lipids** from extra hepatic tissues back to Liver for its metabolism and excretion.

- **The role of HDL is opposite to LDL.**

- **HDL transports Cholesterol From extra hepatic tissues back to Liver.**

- Thus the role of HDL is termed as **reverse transport of Cholesterol.**

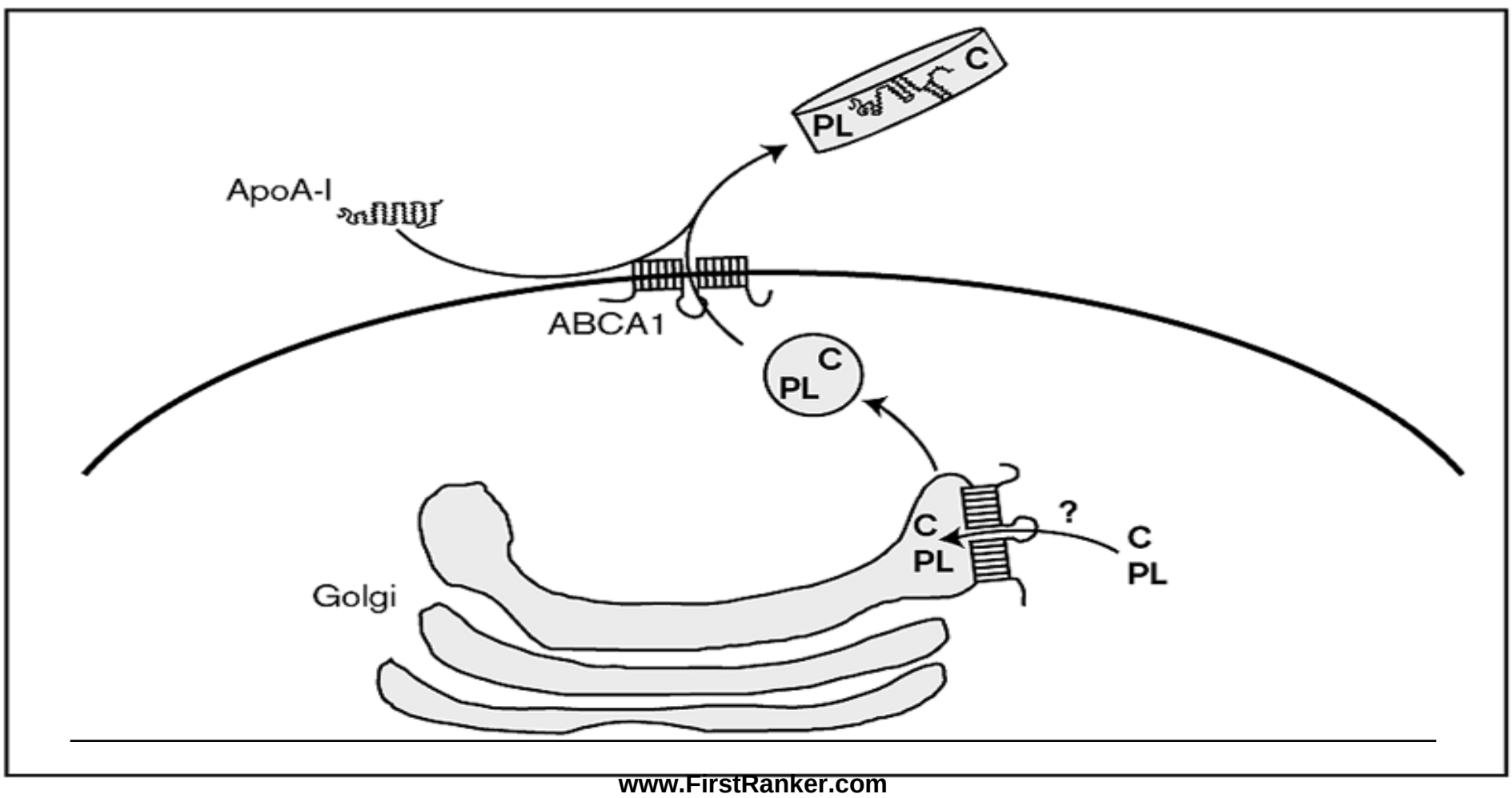
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- **Normal serum HDL levels** are **30-60 mg%.**

- The efficient activity of HDL is good to the body
- As it prevents risk of Atherosclerosis and their complications.

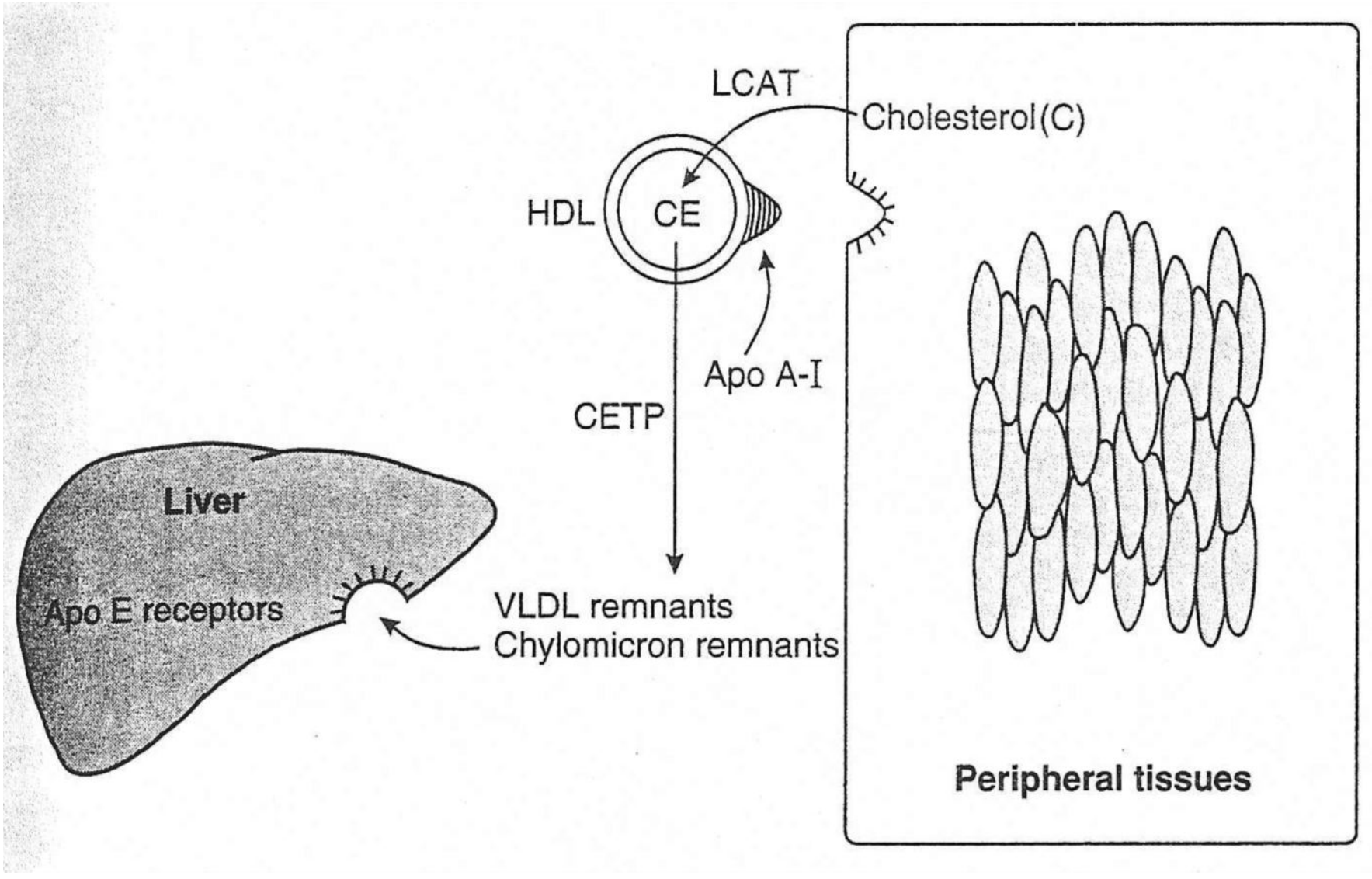
Reverse Cholesterol Transport (RCT)



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High Density Lipoproteins (HDL – Good)



- **CETP by its activity modifies HDL 3 to HDL 2.**
- **HDL2 is then get internalized in Hepatocytes for its final use**.
- Cholesterol Ester carried by HDL to hepatocytes **is degraded to Bile acids and Bile salts and get excreted out.**

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Fate of HDL

HDL 2 binds SR-B1 receptor on Hepatocytes

↓

Transfers Cholesterol &
Cholesterol ester to cell

↓

Depleted HDL dissociates
& re-enters circulation

- HDL can bind to specific **hepatic receptors SR-B1**

- But primary HDL clearance occurs through uptake by **scavenger receptor SR-B1.**

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- **SR-B1** can be upregulated in cells when Cholesterol levels are low in hepatic cells.

- **SR-B1** is down regulated when cholesterol levels are high in cells.

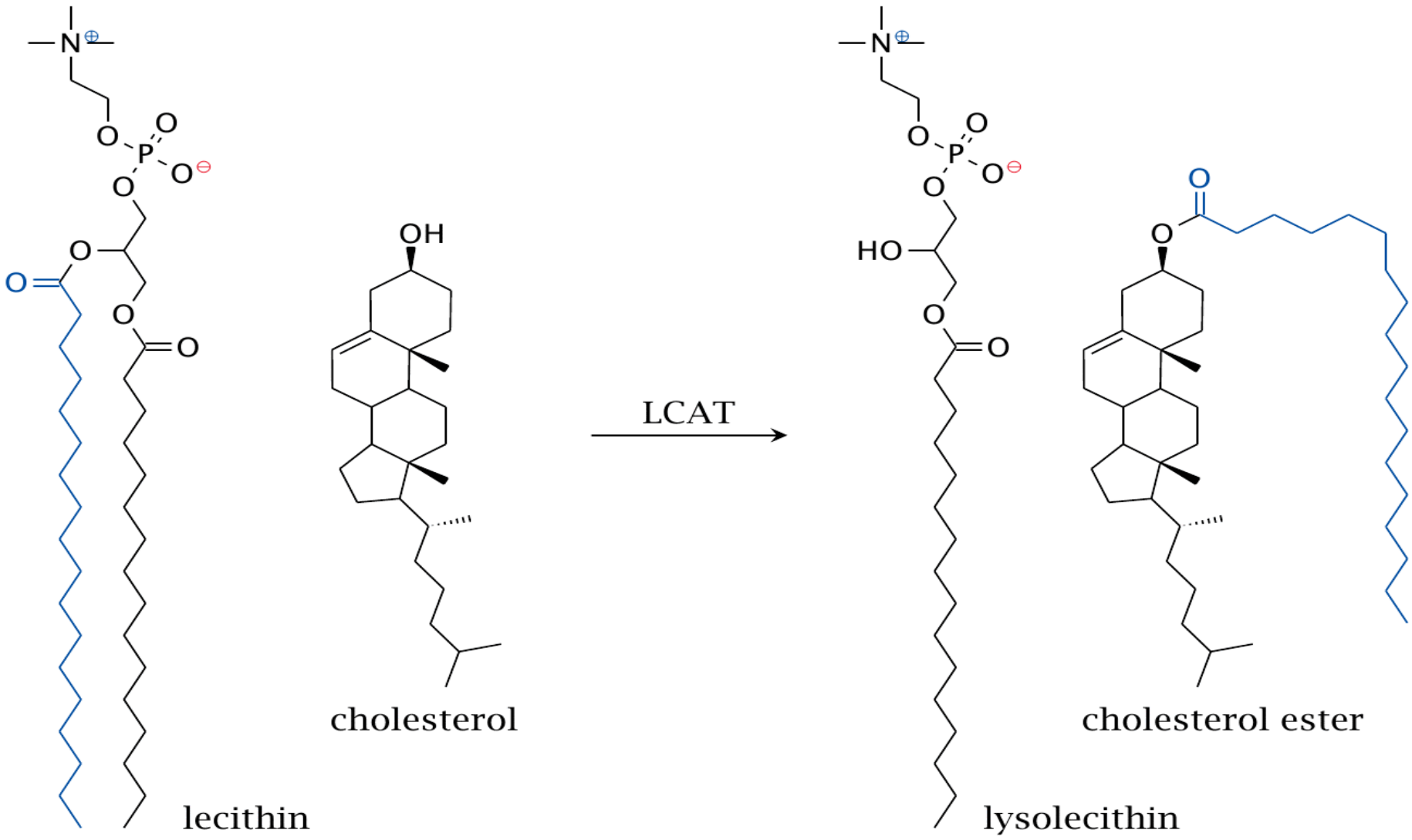
- **Defect in low HDL synthesis in Liver** lowers the HDL activity and **increases the risk of Atherosclerosis.**

- **Defect in HDL receptors** on Liver may abnormally increase the HDL levels in blood circulation and also increases the risk of Atherosclerosis.

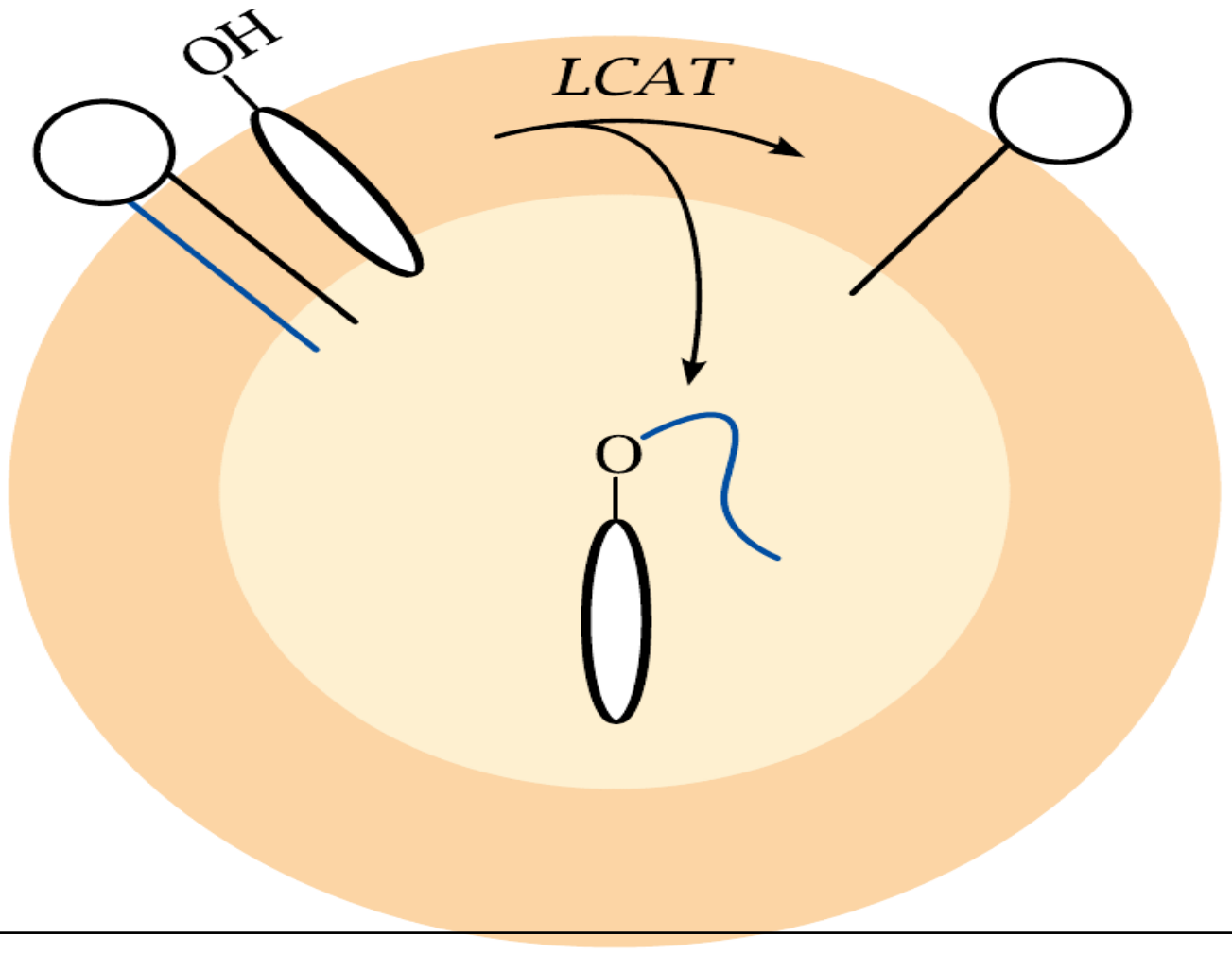
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The Lecithin-Cholesterol Acyltransferase (LCAT) reaction



Cholesterol esters can be stored inside lipoprotein particles

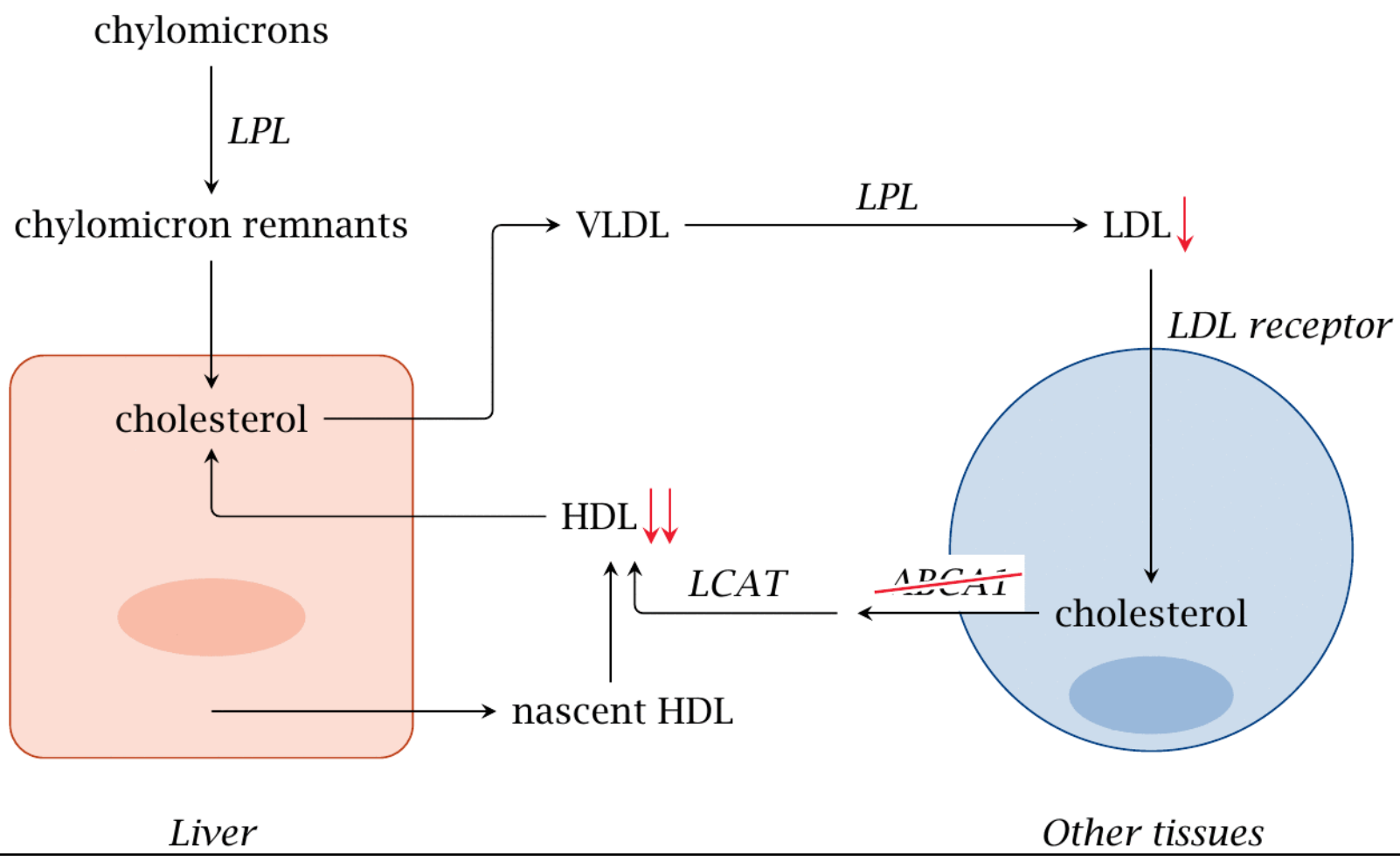


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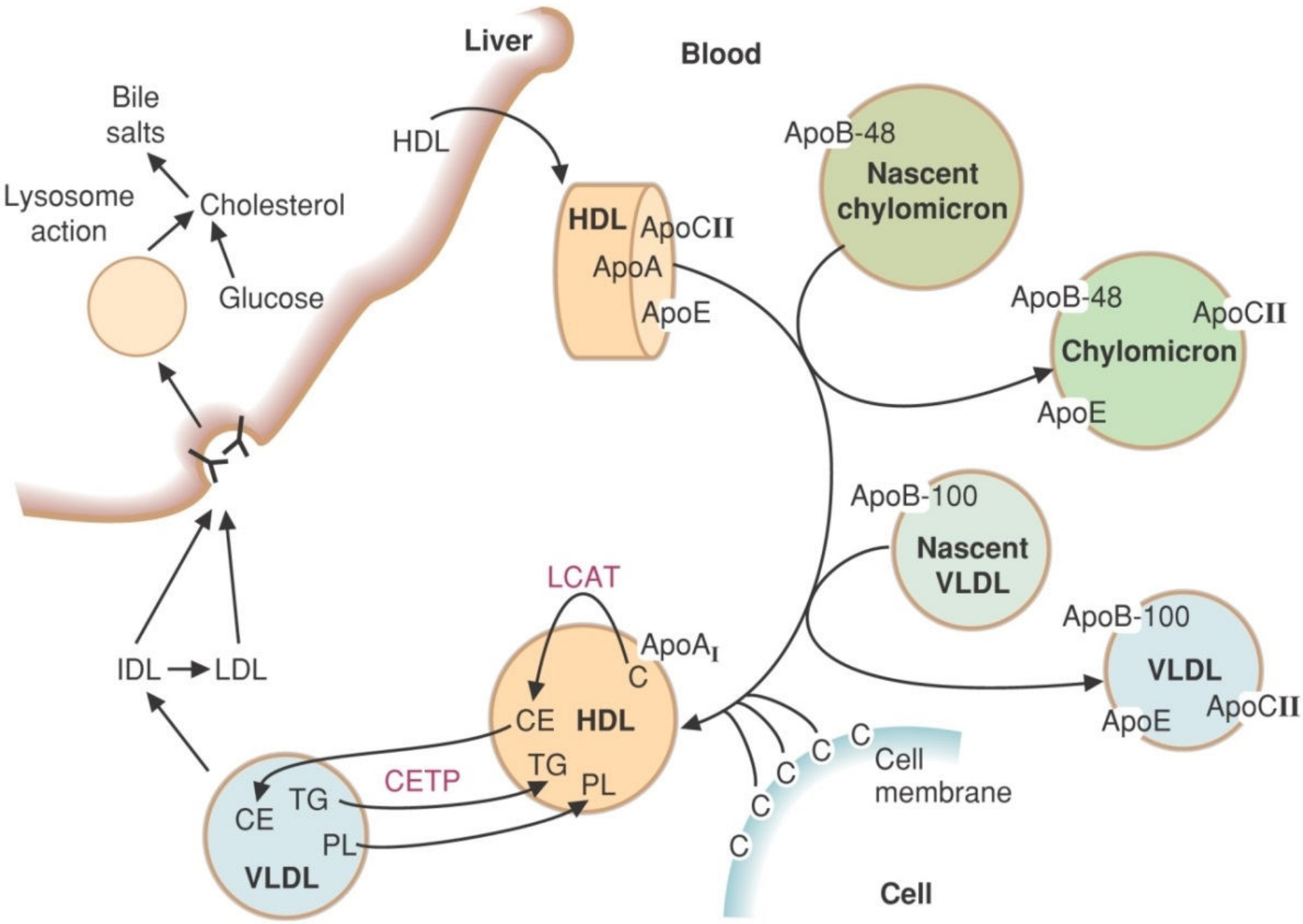
HDL Interactions with Other Particles

Tangier Disease: Disruption of Cholesterol Transfer to HDL

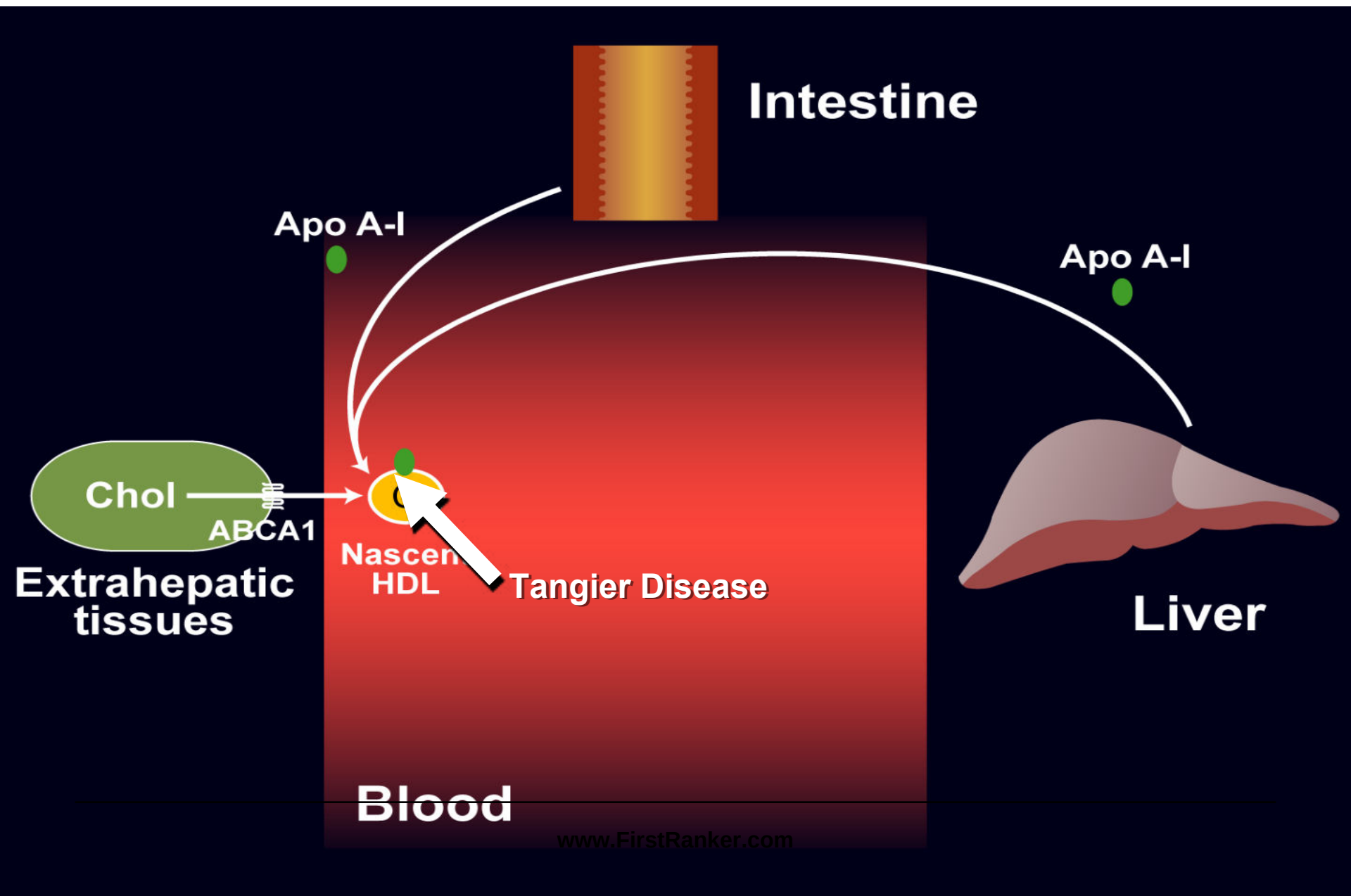


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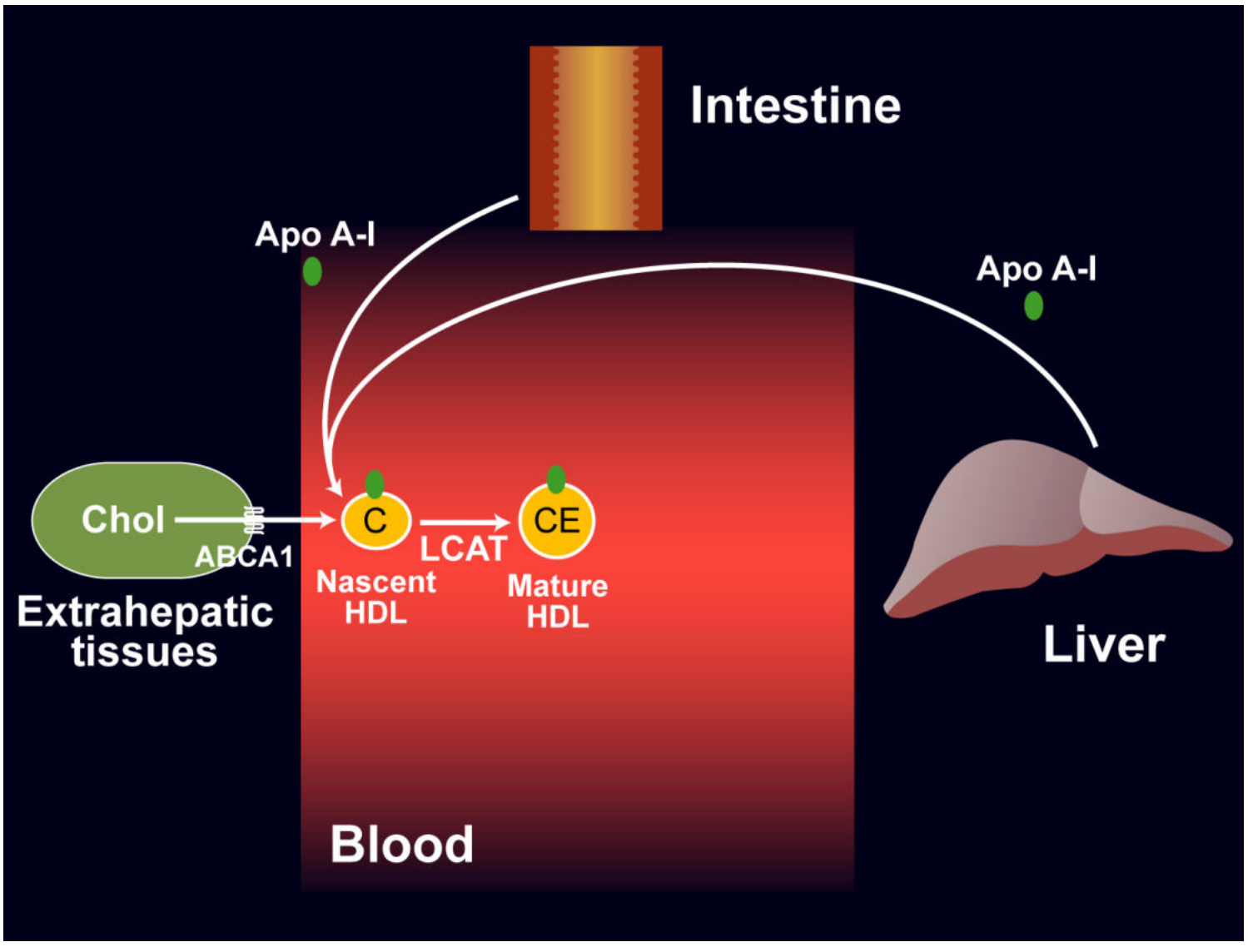


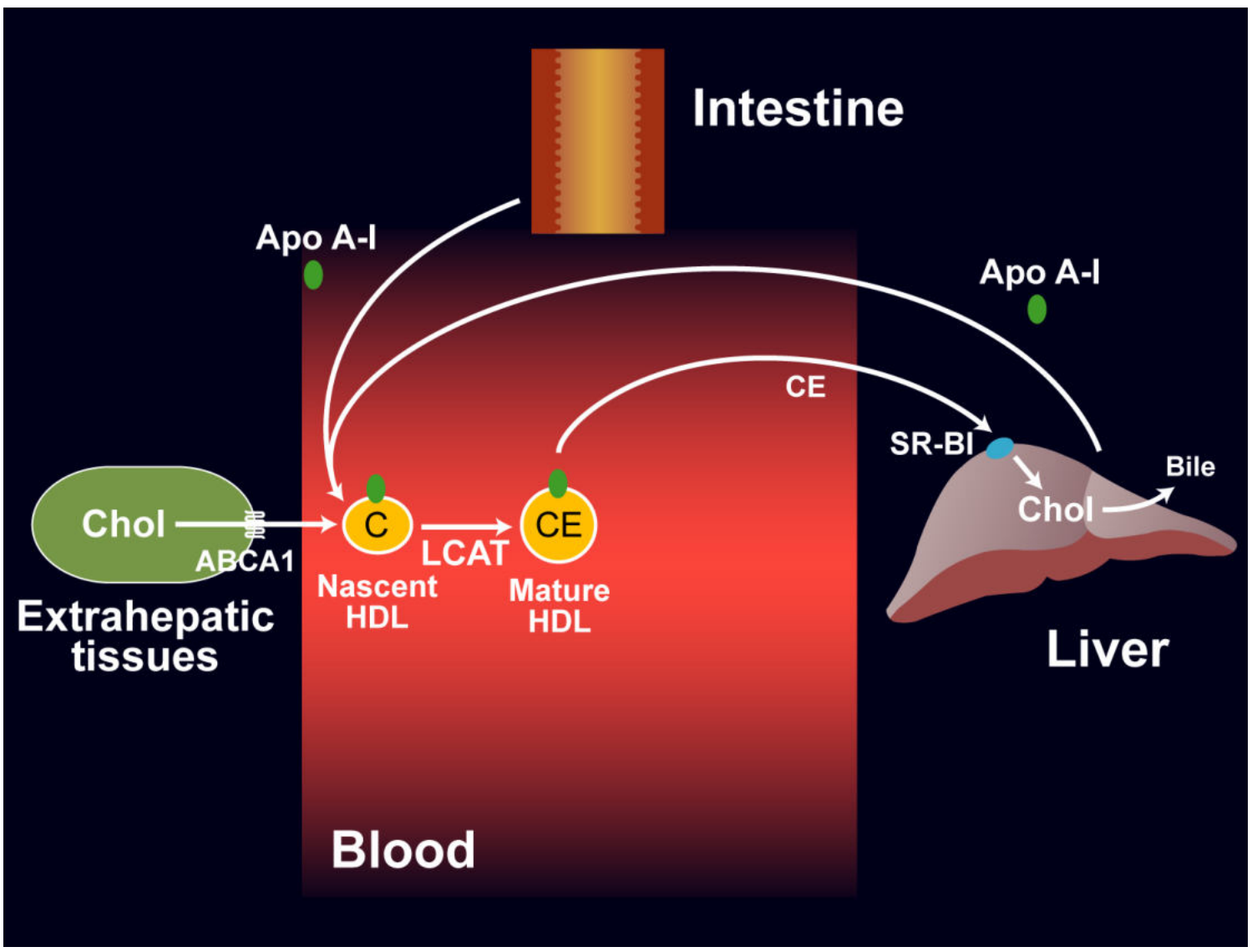
HDL and Reverse Cholesterol Transport



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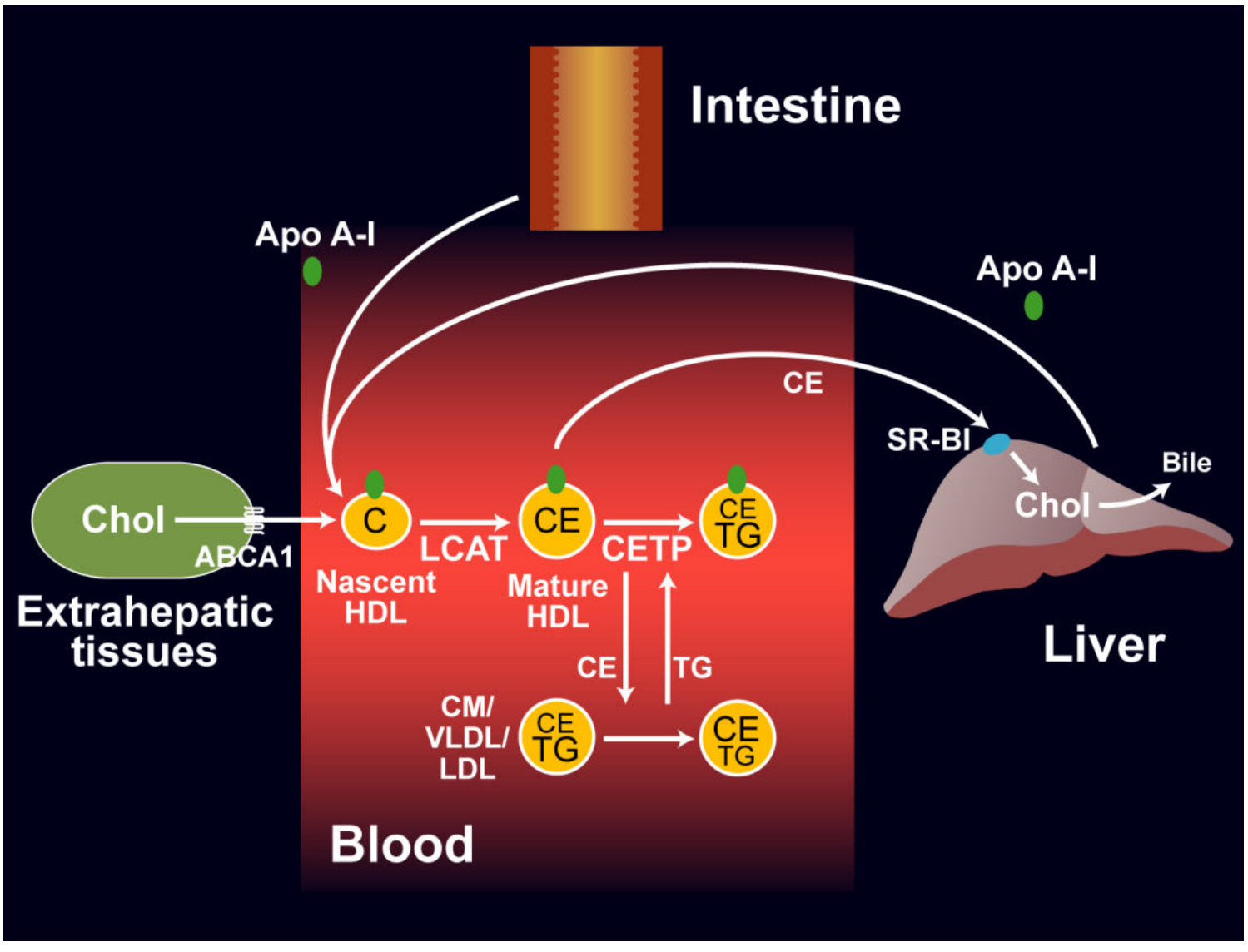
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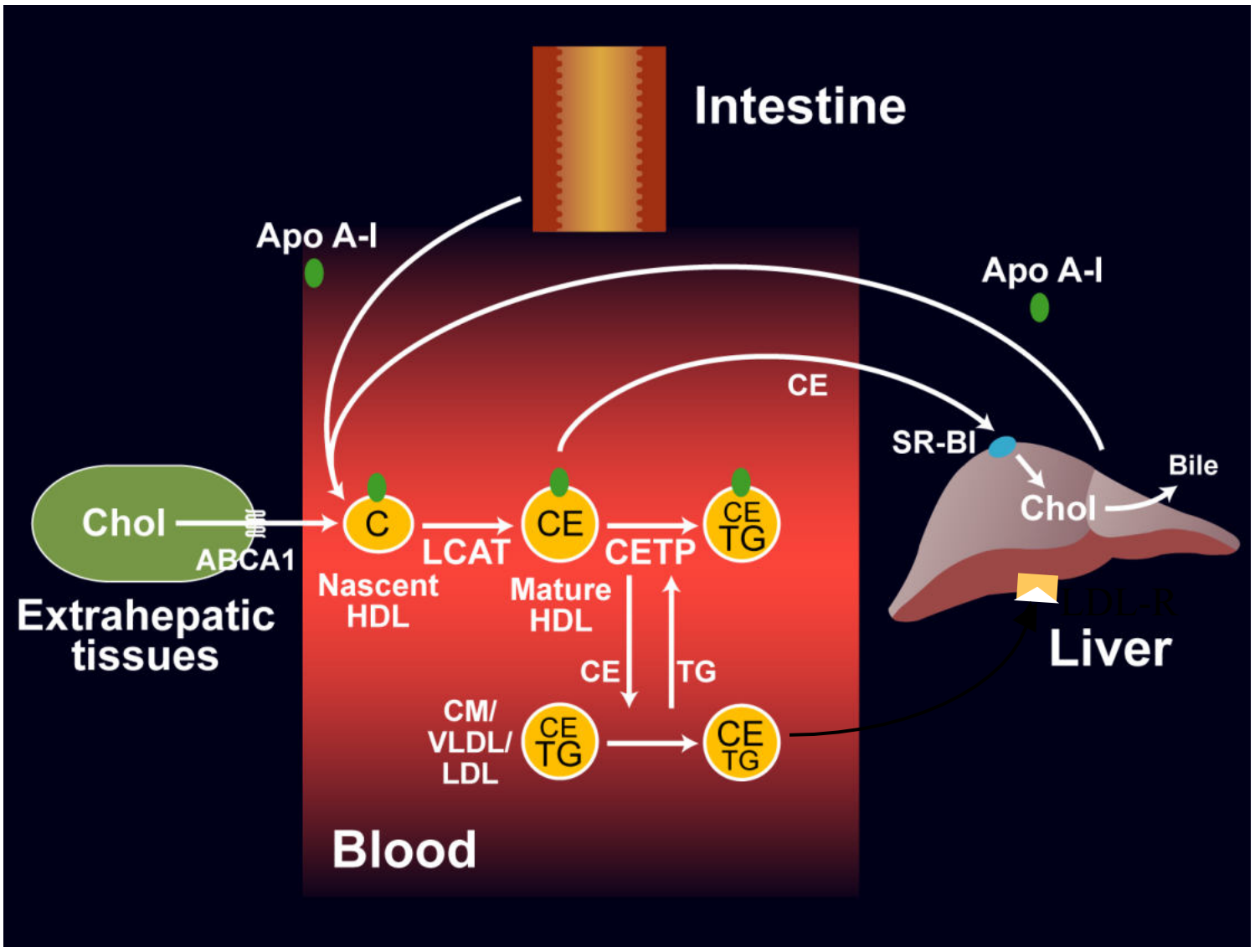




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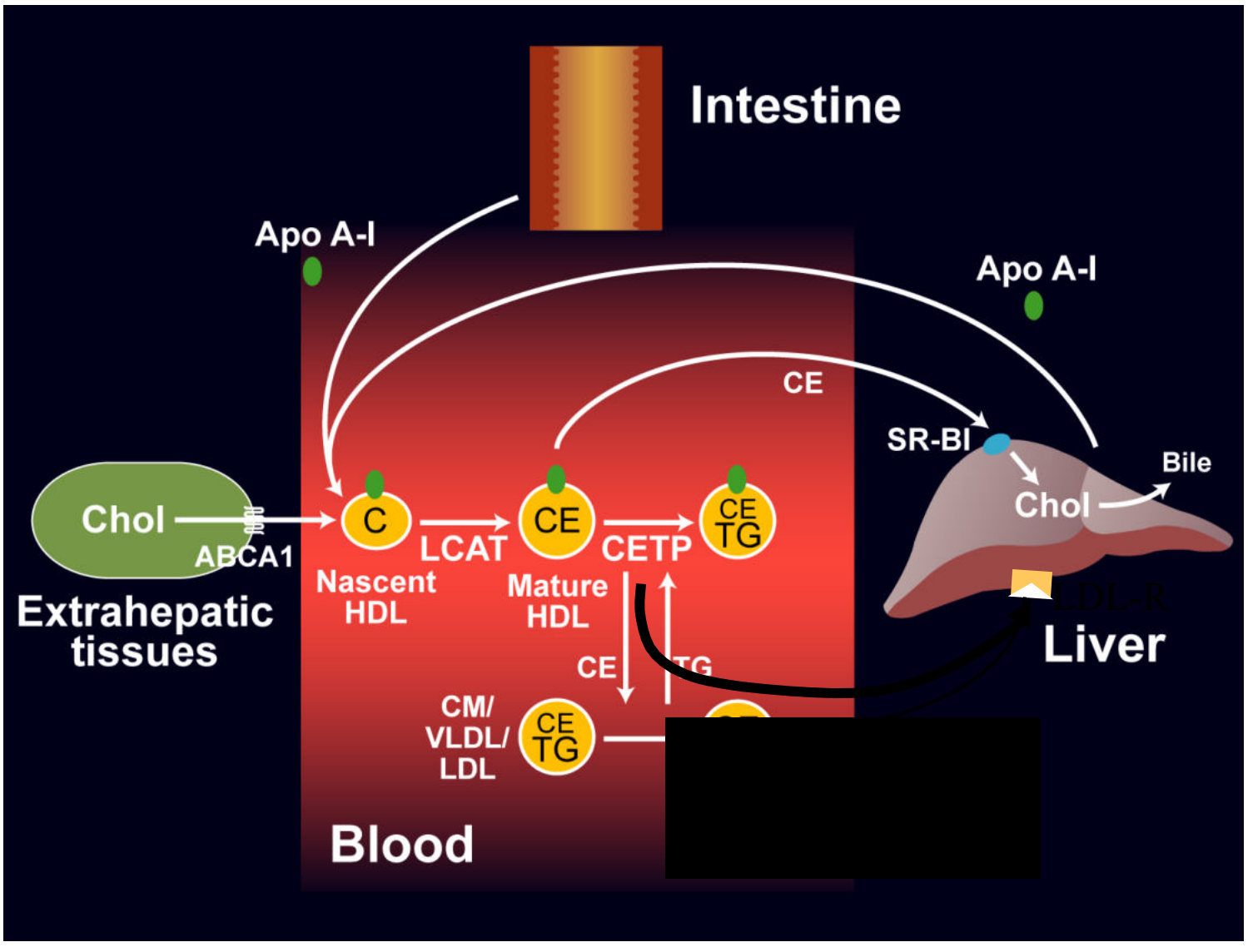
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LDL/HDL Ratio and Cardiovascular Disease

- **LDL/HDL ratios are used as a diagnostic tool for signs of Cardiovascular disease**
- **A good LDL/HDL ratio is 3.5**

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–LDL above normal range =

"Bad Cholesterol"

–HDL within normal range =

"Good Cholesterol"

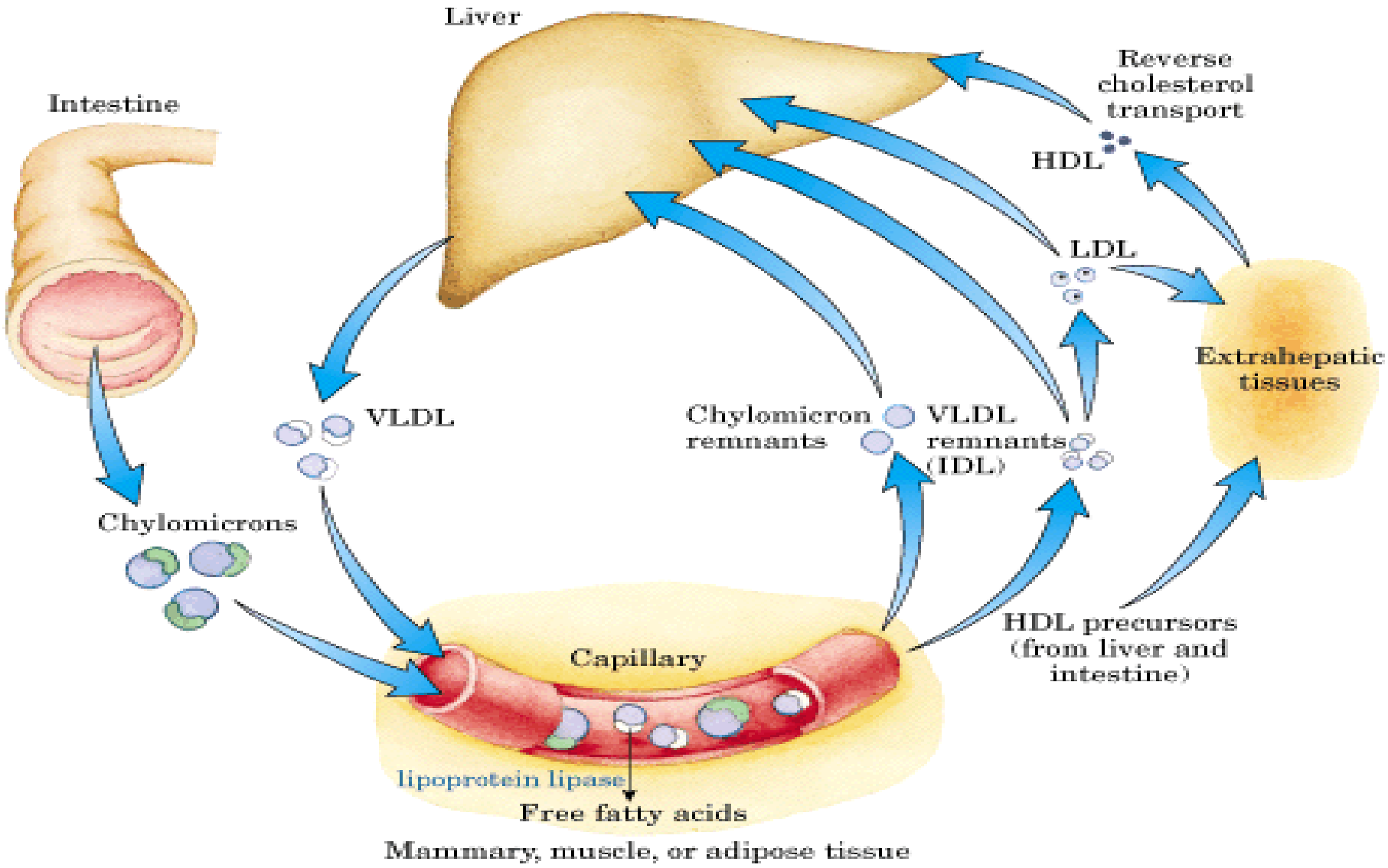
-HDL above normal range =

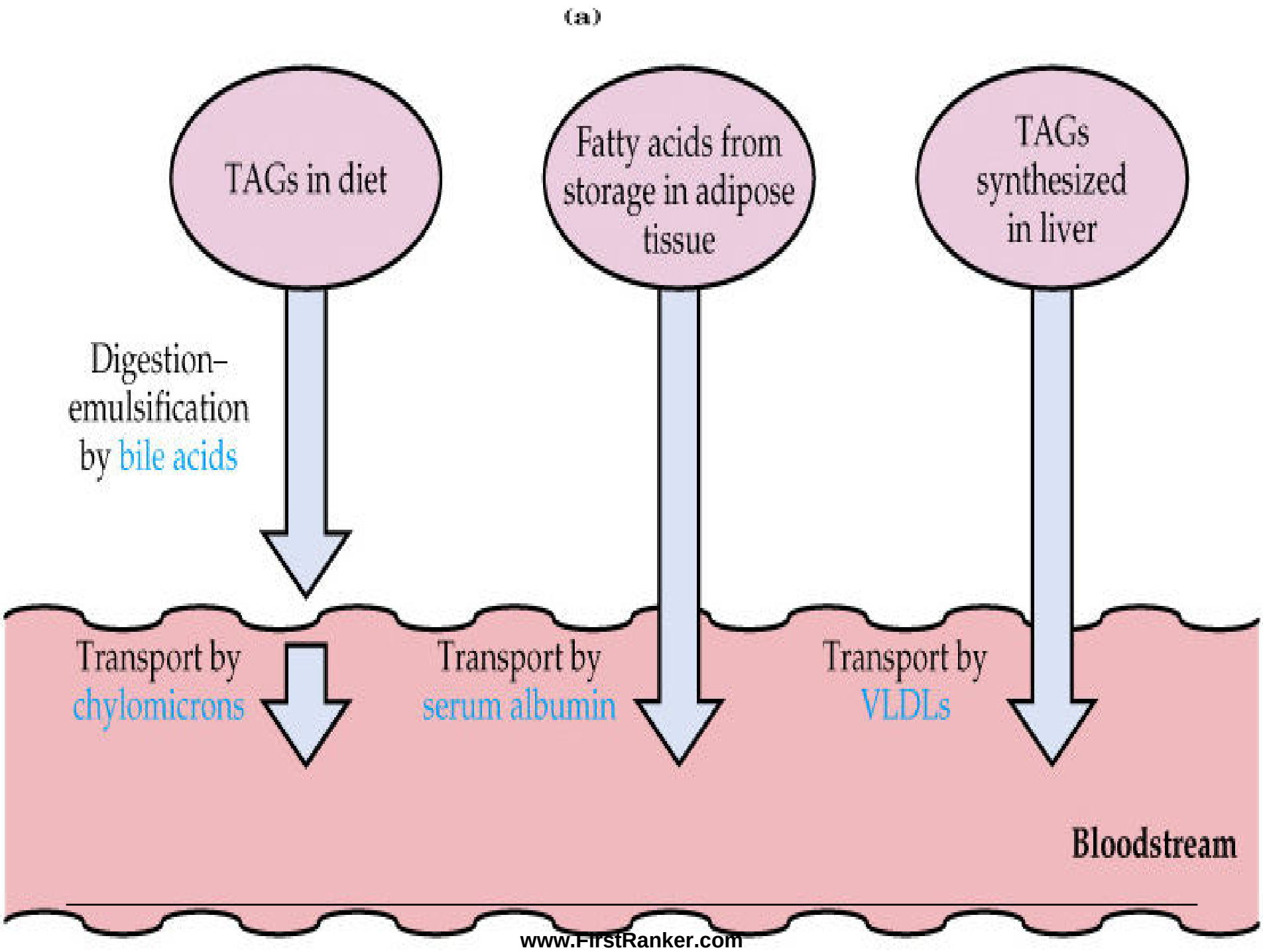
"Bad Cholesterol"

- **Protective role of HDL is not very clear.**
  - **An esterase that breaks down oxidized lipids is associated with HDL.**
  - **It is possible (but not proven) that this enzyme helps to destroy oxidized LDL**

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Lipoproteins Facilitate Lipid Transport





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Normal Lipoprotein Metabolism

Normal LP Metabolism

- **Maintains Normal levels of Lipoproteins in the blood circulation by:**
  - **Normal Formation of LP** by specific tissues
  - **Normal Transformation and Transport of LP** in blood
  - **Normal Uptake of LP by** specific tissues

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- **Normal Lipoprotein Metabolism Reduces the risk of:**
  - –Atherosclerosis
  - –Myocardial Infarction
  - –Stroke

Lipoprotein Population Distributions

- Serum Lipoprotein concentrations **differ between adult men and women**.
- Primarily as a result of **differences in sex hormone levels.**

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- Women having, on average, higher HDL cholesterol levels and lower total Cholesterol and TAG levels than men.

- The difference in total cholesterol, however, disappears in **post menopause** as **Estrogen decreases and use of Cholesterol is reduced.**

Lipid Associated Disorders

OR

Lipid Related Clinical Problems

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- DysLipoproteinemias/Dyslipidemias

(Hypo and Hyperlipoproteinemias)

– Fatty Liver

–Atherosclerosis

–Coronary Heart Diseases

Causes of Lipid Associated Disorders

- Diseases associated with abnormal lipid concentrations can be caused:
  - –Nutritional Imbalances
  - –Environmental Factors
  - –Lifestyle Patterns
  - –Genetic abnormalities
  - –Develop secondarily, as a consequence of other diseases.

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Disorders Of Lipoproteins
Dyslipoproteinemias/ Dyslipidemias

Hyperlipoproteinemias
And
Hypolipoproteinemias

Abnormal LP Metabolism

- **Abnormal Synthesis** of LP by specific tissues
- **Abnormal Transport** of LP in blood
- **Abnormal Uptake** by specific tissues
- **Leads to abnormal levels of Lipoproteins in the blood circulation**

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- Thus conditions and factors which **affects the Lipoprotein synthesis, transport and uptake**

- May lead to **Lipoprotein disorders/Dyslipidemias.**

Dyslipidemias

- Dyslipidemias are due to Defect in Lipoprotein metabolism

- Include **both the excess and deficiency of Lipoproteins**.

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- **Dyslipidemia** can manifest as the **elevation of plasma Cholesterol, Triacylglycerol, or both**.
- It can also be manifested by:
  - The **elevation** of **LDL Cholesterol**
  - The **abnormal decrease/increase** of **HDL Cholesterol** in the blood.

Causes Of Dyslipidemias/ DysLipoproteinemias

- Dyslipedimias states are generally caused by impaired Lipoprotein :
  - **Biosynthesis (Increased)**
  - **Transformation and Transport (Improper)**
  - **Uptake and Utilization (Decreased)**

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Dyslipidemias/Dyslipoproteinemias

- Dyslipidemias can be subdivided into two major categories

1. **Hyperlipoproteinemias**
   - Hypercholesterolemia
   - Hypertriglyceridemia
   - Combined Hyperlipoproteinemia
2. **Hypolipoproteinemias**

Types Of Lipoprotein Disorders

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Hyperlipoproteinemias

- Hyperlipoproteinemia are **abnormal conditions**

- With **increased levels of circulating Lipoproteins** in **the blood**.

Causes of Hyperlipoproteinemia

- **Increased formation of Lipoprotein**
- **Reduced clearance of LP from circulation**
  - **Factors Causing These**
    - Excessive dietary intake of Carbs and Lipids
    - Biochemical defects in LP metabolism
    - Deficient Protein to form Apo proteins
    - Defect in Enzymes and Protein Associated to LP
    - Defect in Receptors for LP
    - Use of drugs that perturb LP formation or catabolism

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Types of Hyperlipoproteinemias

Fredrickson Classification of Hyperlipoproteinemia

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Type I **Hyperlipoproteinemia**	**Lipoprotein Lipase Deficiency** **Increased Chylomicrons and VLDL** **Hypertriglyceridemia**
Type II a **Hyperlipoproteinemia**	**Defect in LDL Receptors** **Increased LDL levels in blood** **Hyperbetalipoproteinemia** **Hypercholesterolemia**
Type II b **Hyperlipoproteinemia**	**Increased production of Apo B** **Increased production of VLDL and impaired LDL catabolism Increased VLDL and IDL**
Type III **Familial Dysbeta Lipoproteinemias**	**Defect in ApoE** **Broad Beta Disease** **Increased IDL**
Type IV **Hyper-pre-β-Lipoproteinemia**	**Impaired VLDL metabo** Increased VLDL Due to acquired conditi ❑ **Obesity** ❑ **Alcoholism** ❑ **Diabetes mellitus**

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Type V

Combined Hyperlipoproteinemia

Increased VLDL and Chylomicrons

Due to acquired conditions viz

- ❑ Obesity
- ❑ Alcoholism
- ❑ Diabetes mellitus

Fredrickson Classification of the Hyperlipidemias

Phenotype	Lipoprotein(s) elevated	Serum cholesterol concentration	Serum triglyceride concentration	Relative frequency, %
I	Chylomicrons	Normal to ↑	↑↑↑↑	<1
IIa	LDL	↑↑	Normal	10
IIb	LDL and VLDL	↑↑	↑↑	40
III	IDL	↑↑	↑↑↑	<1
IV	VLDL	Normal to ↑	↑↑	45
V	VLDL and chylomicrons	↑ to ↑↑	↑↑↑↑	5

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Conditions Of Hyperlipoproteinemias

- **Increased endogenous/exogenous availability** of Lipids
- **Increased/Defective Apoprotein synthesis**
- **Decreased Lipoprotein Lipase activity**
- **Defective receptors on specific tissues**

Deficiency Of Lipoprotein Lipase Leads To

Familial Type I Hyperlipoproteinemia

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- **Defect in Lipoprotein Lipase** activity
- **Does not clear the circulating Chylomicrons and VLDL**;
- **Increases the levels of circulating Chylomicrons and VLDL**
- Associated **Hypertriglyceridemia**
- This is termed as **Familial Type I Hyperlipoproteinemia.**

Type I Hyperlipoproteinemias

- **Shows a dramatic accumulation (≥1000 mg/dl) of Chylomicrons and VLDL in plasma**

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- Usually associated with acute abdomen due to acute pancreatitis
- ↑ plasma TAG even in the fasted state

Type III Hyperlipoproteinemia

- Familial dysbetalipoproteinemia
- Due to Apo E deficiency
- Associated with Hypercholesterolemia & premature Atherosclerosis

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Hypolipoproteinemias

Hypolipoproteinemias

- Hypolipoproteinemias are abnormal conditions
- With **decreased levels of circulating Lipoproteins in the blood.**

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Conditions Of Hypolipoproteinemias

- **Decreased synthesis of Lipoproteins**
- **Deficiency of Lipotropic factors** required for Lipoprotein biosynthesis.

Types Of Hypolipoproteinemias

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Familial Hypobetalipoproteinemia

- **Impairment in the synthesis of Apo B**
- Characterized with **low LDL levels.**

Abeta Lipoproteinemia

- Rare disorder
- **No synthesis of Apo B (Total Absence)**
- **Absence of LDL** (Beta Lipoprotein) in blood circulation
- **Defect in TAG-transfer protein**
- **Accumulation of TAG in liver**

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Familial Alpha Lipoprotein Deficiency

Tangiers Disease

- **Absence of HDL (Alpha Lipoprotein) in blood**
- **Affects severely Reverse transport of Cholesterol**
- Hypercholesterolemia
- Increased risk of Atherosclerosis and its Complications.

Classification Of Dyslipidemias

Based On Number Of Gene Involvement

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Primary Hyperlipoproteinemia

- **Monogenic defect**
- **Polygenic Defect**

Monogenic Disorders

- **Familial Hypercholesterolemia**
  - Homozygous or Heterozygous
  - Defect: inactive LDL receptor
- **Familial Lipoprotein Lipase deficiency**
  - Defect: inactive lipoprotein lipase
- **Familial combined Hyperlipidemia**
  - Defect: Unknown

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Polygenic/Multifactorial

- These are commonly encountered
  - ❖Hypercholesterolemia
  - ❖Hypertriglyceridemia

Secondary Hyperlipidemias

- –Alcoholism
- –Diabetes mellitus
- –Uremia
- –Drugs; β blockers, oral contraceptives, thiazide diuretics
- –Diseases: Hypothyroidism, Nephrotic syndrome, Obstructive liver disease

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Combined Hyperlipoproteinemia

- Presence of elevated levels **of both serum Total Cholesterol and Triacylglycerols.**
- Genetic form of this condition
  - Familial Combined Hyperlipoproteinemia (FCH)
  - **Type V Hyperlipoproteinemia**
    - An accumulation of Cholesterol-rich VLDL and Chylomicron remnants as a result of defective catabolism of those particles

Diagnosis And Therapeutic Strategy Of Dyslipidemias

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A. Identify patients at risk

1. Routine screening of Serum Lipid profile
2. Assessment of contributing risk factors

B. Non-Pharmacologic therapy

1. Diet modification
2. Lifestyle modification

C. Pharmacologic therapy

- Lipids and lipoproteins are important indicators of CHD risk,

- This is the major reason for their measurement in research, as well as in clinical practice.

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Estimation Of Lipid Profile

- Serum Triacylglycerol
- Serum Total Cholesterol
- Serum VLDL
- Serum LDL Cholesterol
- Serum HDL Cholesterol

Hypertriglyceridemia

- **Serum Triacylglycerol**
  - Borderline = 150-200 mg/ dl
  - High 200-500 mg/dl
  - Very High > 500 mg/dl
- **Familial Hypertriglyceridemia**
  - Genetic
- **Secondary Hypertriglyceridemia**
  - Hormonal imbalances
  - Imbalance between synthesis and clearance of VLDL

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Hypertriglyceridemia

- Generally caused by deficiency of LPL or LPL cofactor.
- LPL hydrolyzes TAG in Chylomicrons and VLDL
- Deficiency of LPL prevents processing and clearing of Lipoproteins.
- Elevated even with fasting condition.

Hypercholesterolemia

- **Familial Hypercholesterolemia (FH)**
  - –Homozygous rare 1/million
    - Total cholesterol 800-1000 mg/dl
    - Heart attack as early as teenage years
  - –Heterozygous cholesterols 300-600 mg/dl
    - Heart attacks 20-50 years

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Hypercholesterolemia

- **Familial hypercholesterolemia (FH)**
  - Primarily LDL elevations
  - Synthesis is normal but decrease or lack LDL receptors
  - Therefore LDL builds-up in serum
  - Since cells cannot acquire from LDL increase internal synthesis

Lipid Profile and Lipoprotein Analyses

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LDL Methods

- **Friedewald Calculation**
  - VLDL is estimated as TAG/5

LDL = Total Cholesterol – HDL – TAG/5

Lipoprotein Assay Methods

- **Separate Lipoprotein Fractions By:**

- Electrophoresis – Agarose or Polyacrylamide
- Chromatographic
- Precipitation
- Ultracentrifugation
- Immunochemical

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Serum Triglycerides

Normal

- Less than 150 mg/dL

Borderline High

- 150-199 mg/dL

High

- 200-499 mg/dL

Very High

- 500+ mg/dL

Serum Total Cholesterol

Normal

- Less than 200 mg/dL

Borderline High

- 200-239 mg/dL

High

- 240 mg/dL or higher

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HDL Cholesterol

Optimal:

- 60+ mg/dL for both males and females

At Risk for Heart Disease:

- Women: less than 50 mg/dL
- Men: less than 40 mg/dL

LDL Cholesterol

Optimal

- Less than 100 mg/dL

Near or above Optimal

- 100-129 mg/dL

Borderline High

- 130-159 mg/dL

High

- 160-189 mg/dL

Very High

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- 190+ mg/dL

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Consequences Of Dyslipoprotein Metabolism

- Fatty Liver
- Atherosclerosis and its Complications

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Role Of Liver In Lipid Metabolism

- **Liver is the Biochemical Factory of Human Body.**
- Liver plays an **important role in Lipid metabolism.**
- Major **pathways of Lipid metabolism are efficiently carried out in Liver.**

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Lipid Metabolism
At Liver
In Well Fed Condition

- Liver in well fed condition efficiently carries out various metabolic pathways of Lipid Metabolism.
  - **De Novo biosynthesis of Fatty acids**
  - **Triacylglycerol Biosynthesis**
  - **Cholesterol Biosynthesis**
  - **Phospholipid Biosynthesis**
  - **Glycolipid Biosynthesis**
  - **VLDL Biosynthesis**

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Lipid Metabolism
At Liver
In Emergency Condition

- **Liver in emergency condition** carries following metabolic pathways of Lipid metabolism efficiently:
  - **Beta Oxidation of Fatty acids**
  - **Ketogenesis**
  - **Bile Acid and Bile Salt** Formation

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Fatty Liver

- Though **Liver is the predominant site for Lipid biosynthesis.**

- **Liver is not the storage organ for Lipids.**

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- Normally **3-5% of Lipids are present in Hepatocytes.**

- **Endogenously biosynthesized Lipids in Liver are**

- Mobilized out in the **form of VLDL molecule.**

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- **Efficient formation of VLDL in Liver**
- **Does not allow the excess of Lipids to remain in Liver tissue.**

Fatty Liver/ Fatty Liver Disease/ Hepatosteatosis

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What Is Fatty Liver?

- **Fatty Liver** is **an abnormal condition**

- Where there is **more than 5% of Lipids retained in Hepatocytes.**

What Is Fatty Liver Disease?

- **Fatty Liver disease** (**FLD**), is a **reversible condition of Liver**
- Wherein **large vacuoles of Lipids accumulate in Liver cells**
- Via the process of **Steatosis** (Abnormal retention of Lipids within a cell)

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What Is Steatohepatitis ?

- Progressive inflammation of the Liver (Hepatitis),
- Due to abnormal accumulation of Lipids(Steatosis) **is termed as Hepatosteatosis/Steatohepatitis**

.

Causes Of Fatty Liver

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Clinical Conditions Leading To Fatty Liver

OR

Risks For Developing Fatty Liver

- **Defect in Hepatic**
  - –Biosynthesis of Lipids
  - –No Mobilization of Endogenously biosynthesized Lipids in Liver
- **Accumulates Lipids in Liver**

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- **Increased biosynthesis of Lipids** than the mobilization capacity ,**due to increased Carbohydrates.**

- **Decreased mobilization of Lipids from Liver** cells **due to decreased VLDL formation.**

- Deficiency of **Lipotropic factors affects**
- The **VLDL formation** and **mobilization of Lipids out** of Hepatocytes.

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Conditions Leading To Fatty Liver

- **Metabolic Syndrome**
  - **Obesity**
  - **Hypertension**
  - **Dyslipidemias**
  - **Diabetes mellitus**
- **Alcoholism**
- **Malnutrition**

(Deficiency of Lipotropic Factors)

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- **Wilsons Disease**
- **Hepatitis A**
- **Hepatitis C**
- **Hepatotoxic Drugs** : MTX, VA, Acetaminophen, TC, Tamoxifen, Nefidepine, Amiodarone, CCl_4 etc

Lipotropic Factors and Their Role

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Adequate Presence of Lipotropic factor

Prevents Retention of Lipids in Liver

There by preventing Fatty Liver.

- **Lipotropic Factors** are chemical **substances which helps in formation of Phospholipids**.

- This in turn helps in **proper formation and mobilization of VLDL out from Liver.**

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Names Of Lipotropic Factors

- Lipotropic Factors are chemicals involved in biosynthesis of Phospholipids:
  - **Choline**
  - **Betaine forms Choline**
  - **Inositol**

Amino Acids As Lipotropic Agents

- **Glycine**
- **Serine**
- **Methionine**

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Vitamins As Lipotropic Factors

- Vitamin B 12
- Folic Acid

Types Of Fatty Liver

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4 Types Of Fatty Liver

- Alcoholic Fatty Liver
- Non Alcoholic Fatty Liver Disease (NAFLD)
- Non Alcoholic Steatohepatitis (NASH)
- Acute Fatty Liver of Pregnancy

Consequences Of Fatty Liver

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- Fatty liver is a **reversible condition** and **usually goes away on its own.**

- Generally Fatty liver **often has no symptoms** and

- **Does not cause any permanent damage.**

Consequences Of Fatty Liver

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- **Constant accumulation** of **abnormal excess amount of Lipids in Hepatocytes**
- **Affects the normal Liver functions**
- **Leads to Parenchymal damage to Liver Tissues**
- **Causes Liver Cirrhosis.**

- Excess of Lipids deposition in Hepatocytes
- **Interferes the biochemical functions**
- Brings inflammation of Liver **(Hepatitis)**
- **Changes the cytological features**
- Damages the cell components
- Causes Liver **Fibrosis**
- Leads to Liver **Cirrhosis**
- Liver **Carcinoma**

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Natural History of Fatty Liver Disease

Fatty liver

↓

Steatohepatitis

↓

Steatohepatitis + Fibrosis (First Stage of Scar)

↓

Steatohepatitis + Cirrhosis

↓

Cryptogenic Cirrhosis

When there is repeated damage to the Liver

Permanent scarring of Hepatocytes takes place

This is called Liver Cirrhosis

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Diagnostic Features OF Fatty Liver Disease

Laboratory Abnormalities In Fatty Liver Disease

- 2 - 4 fold ↑ ALT & AST
- AST: ALT Ratio < 1
- ALP slight ↑ in 1/3
- Dyslipidemia - ↑ TAG
- FBG and PPBG ↑
- BUN & Creatinine - N
- Normal Albumin. PT
- Low ANA + < 1 in 320
- ↑ Serum Ferritin
- ↑ Iron saturation
- AST: ALT Ratio > 1 if Cirrhosis sets in

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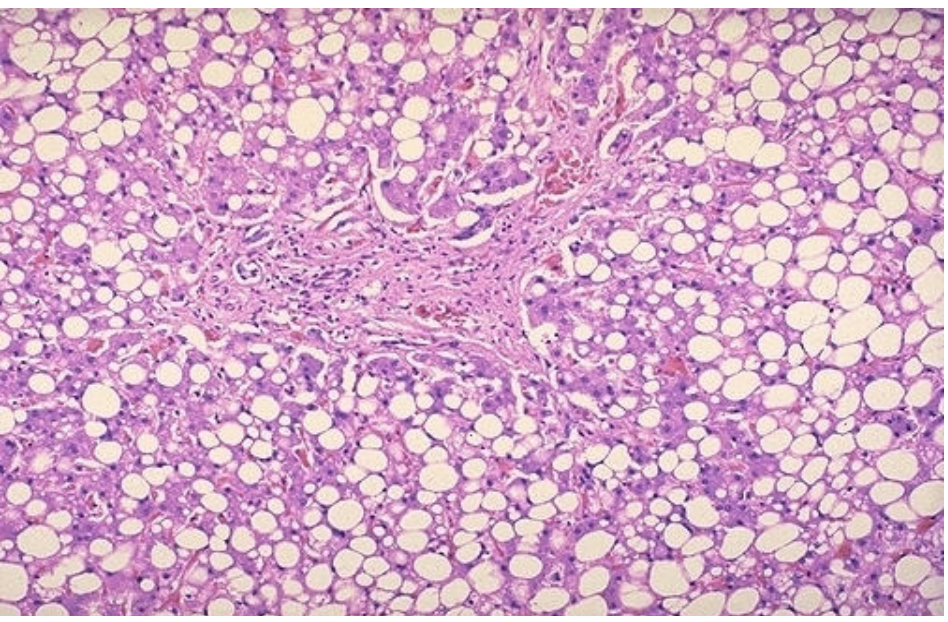
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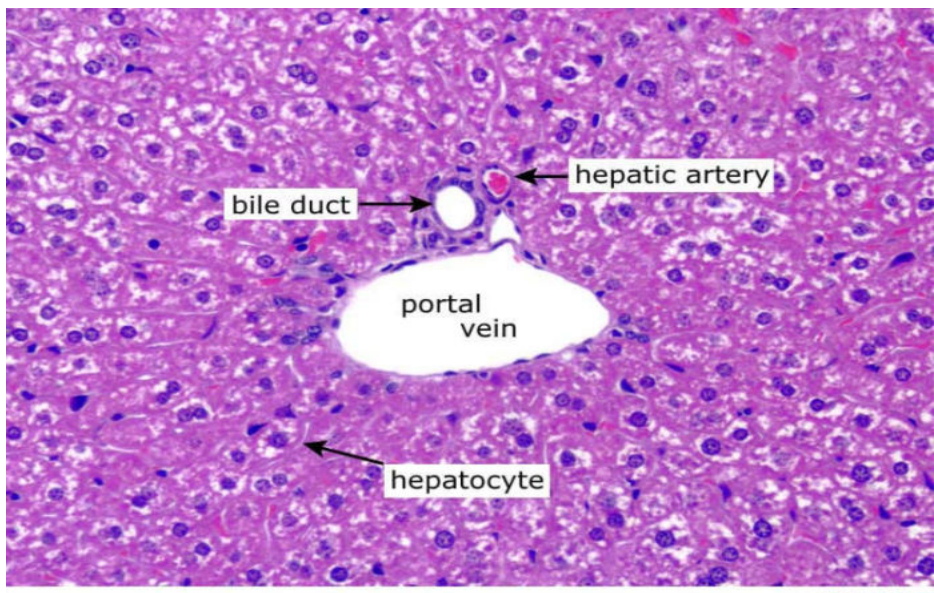
Fatty liver

Normal liver









Atherosclerosis Diseased Arteries

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Features Of Normal Arterial Wall

- The **lumen of healthy arterial wall** is lined by:
  - **–Confluent layer of Endothelial cells**

Features of Normal Endothelium Controls Important function Of Arterial wall

- Normal **healthy arterial endothelium,**
  - **Repels cells** and **inhibits blood clotting.**
  - **Healthy arteries are soft and Elastic.**

- Normal Endothelium- **Regulates tissue and organ blood flow.**
  - The ability of blood vessels to dilate- **vasodilatation**
  - The ability of blood vessels to constrict- **vasoconstriction**

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Arteriosclerosis

What Is Arteriosclerosis?

- **Arteriosclerosis** is **non-specific term** used to describe **hardening and thickening of the wall of arterioles**.

OR

- **Arteriosclerosis** is a general term describing any **hardening** (and loss of elasticity) **of medium or large arteries.**

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What Is Atherosclerosis?

- The term **Atherosclerosis**, comes from the **Greek words**
  - **Atheros-** meaning “gruel” or “paste”
  - **Sclerosis-** meaning “hardness”.

Atherosclerosis
is a form of
Arteriosclerosis

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Terms For Atherosclerosis

- There are many terms associated to Atherosclerosis including:
  - ❖**Atheroma**
  - ❖ **Fibrous Plaques**
  - ❖ **Fibro Fatty Lesions**
  - ❖**Atherosclerotic Plaques**

- Atherosclerosis are abnormal

Diseased/defective arteries.

- **Arteries becomes hard and non elastic**
- **Arteries are less or non Functional**
- **Arteries obstruct the normal blood flow to cells/tissues/organs.**

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Atherosclerosis is
Hardening of Blood Vessels
due to formation of
Fibro Inflammatory Fatty Lesions/Plaques

- **Atherosclerotic Plaque Results From Accumulation of :**
  - **Lipids**
  - **Connective tissue**
  - **Inflammatory cells**
  - **Smooth Muscle cells**
- **In the intima of blood vessels.**

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Causes Of Atherosclerosis

Risk Factors For Atherosclerosis

- Risk factors which accelerate the progression of Atherosclerosis and endothelial dysfunction are:
  - **Dyslipidemias/Dyslipoproteinemias**
  - **Hypercholesterolemia**
  - **Other Cardiovascular risk factors**

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Unchangeable Risk factors of Atherosclerosis

- **Age**
- **Genetic Alterations**
- **Male gender**
  - Men are at grater risk than are premenopausal women, because of the protective effects of natural Estrogens.
- **Family history of premature coronary heart disease**
  - Several genetically determined alterations in lipoprotein and cholesterol metabolism have been identified.

Changeable Risk Factors Of Atherosclerosis

- Hyperlipidemias:
  - The presence of Hyperlipidemia is the strongest risk factor for atherosclerosis in persons younger than 45 years of age.
  - Both primary and secondary hyperlipidemia increase the risk.

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Dietary Habits

- Eating a Balanced Diet
- Excess of Refined Sugars
- Excess of Saturated fatty acids
- Use of Trans Fatty acids

Dyslipidemias

- **Elevated LDL and Triacylglycerol – directly associated with increase risk**
- **Increased Serum HDL levels**
- **Increased LDL and decreased HDL**

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- **Smoking:** dose related
- Diabetes mellitus
- Metabolic Syndrome
- Increasing age and male sex
- Physical inactivity
- Stressful life style
- Homocysteine is toxic to endothelial cells
- C-Reactive Protein

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- **A Stressful life style:**
- **Hormonal Imbalances**
- **Oxidative Stress**

- **Improvement of diet and drugs** may regulate the levels of blood Lipoproteins and Lipids which **may reduce the risk of Atherosclerosis and CVDs.**

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❖Hypertension

❖High blood pressure produces **mechanical stress on the vessel endothelium.**

❖It is a **major risk factor for atherosclerosis in all age groups** and may be as important or more important than hypercholesterolemia after the age of 45 years.

❖**Blood Pressure >160 mmHg increase the risk for MI**

- **Regulation of Hypertension may reduce the risk of Atherosclerosis.**

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Less Well Established Risk Factors

- There are a number of other less well-established risk factors for atherosclerosis, including:
  - **High Serum Homocysteine Levels**
    - Homocysteine is derived from the metabolism of dietary Methionine
    - Homocysteine inhibits elements of the anticoagulant cascade and is associated with endothelial damage.
  - **Elevated serum C-Reactive Protein**
    - It may increase the likelihood of thrombus formation;
    - Inflammation marker
  - **Infectious agents**
    - The presence of some organisms (*Chlamydia pneumoniae, herpesvirus hominis, cytomegalovirus*) in atheromatous lesions has been demonstrated by immunocytochemistry,
    - The organisms may play a role in atherosclerotic development by initiating and enhancing the inflammatory response.

Reduction Of Atherosclerosis Risk

The risk of atherosclerotic event can be decreased by:

- Normal Carbohydrate diet
- Regular Exercise
- Smoking cessation
- Control of high pressure
- Drugs Statins, Ezetimibe,
- Intake of Antioxidants

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Common Arteries Atherosclerozied

- **Aorta** and its branches
- The **Coronary arteries**
- **Large vessels** that supply the **Brain**

3 Stages of Atherosclerosis:

1.Initiation and Formation Stage

2.Adaptation Stage

3.Clinical Stage

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Pathogenesis Of Atherosclerosis

- Pathogenesis of Atherosclerosis includes:
  - **Genetic Factors**
  - **Environmental Factors**

The Development of Atherosclerosis

- The key event is – **damage to the endothelium.**
- The damaged Endothelium becomes **more permeable to Lipoproteins.**
- Lipoproteins **move** below the **endothelial layer** (to intima).

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- **Damaged Endothelium loses its cell-repellent quality.**
  - **Inflammatory cells move into the vascular wall.**
  - Further **Endothelial injury occurs** by **attachment of leukocyte** (lymphocyte and monocyte) and **Platelet adherence**
  - **Smooth muscle cell emigration and proliferation**

- **Activated macrophages** releases **free radicals that oxidizes LDL.**

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❖Lipid Engulfment by Macrophages

- ❖**Oxidized LDL engulfed by Macrophages** to form **Foam cells**
- ❖Subsequent **development of an atherosclerotic plaque with lipid core**

Effects Of Oxidized LDL

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• Oxidized LDL is Toxic to the Endothelium:

- Causing Endothelial loss
- Exposure of the subendothelial tissue to blood components
- Chemotactic effect on lymphocytes and Monocytes
- Chemotactic effect on smooth muscle cells from the arterial media
- Stimulates production of MG-CSF, Cytokines, adhesion molecules in the endothelium;
- Inhibits endothelium derived releasing factor (EDRF), favoring vasospasm;
- Stimulates specific immune system (production of antibodies against oxidized LDL).

- **Activated Macrophages also ingest oxidized LDL** to **become foam cells,**
- Which are present in all stages of atherosclerotic plaque formation.
- **Lipids released from necrotic foam cells accumulate** to form the **lipid core of unstable plaques/Fatty streaks.**

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- Endothelial disruption leads :
  - **Platelet adhesion** and **aggregation**
  - **Fibrin deposition**

- **Platelets and activated macrophages release various factors that are thought to promote growth factors**

- This modulate the proliferation of smooth muscle cells and **deposition of extracellular matrix in the lesions: Elastin, Collagen, Proteoglycans.**

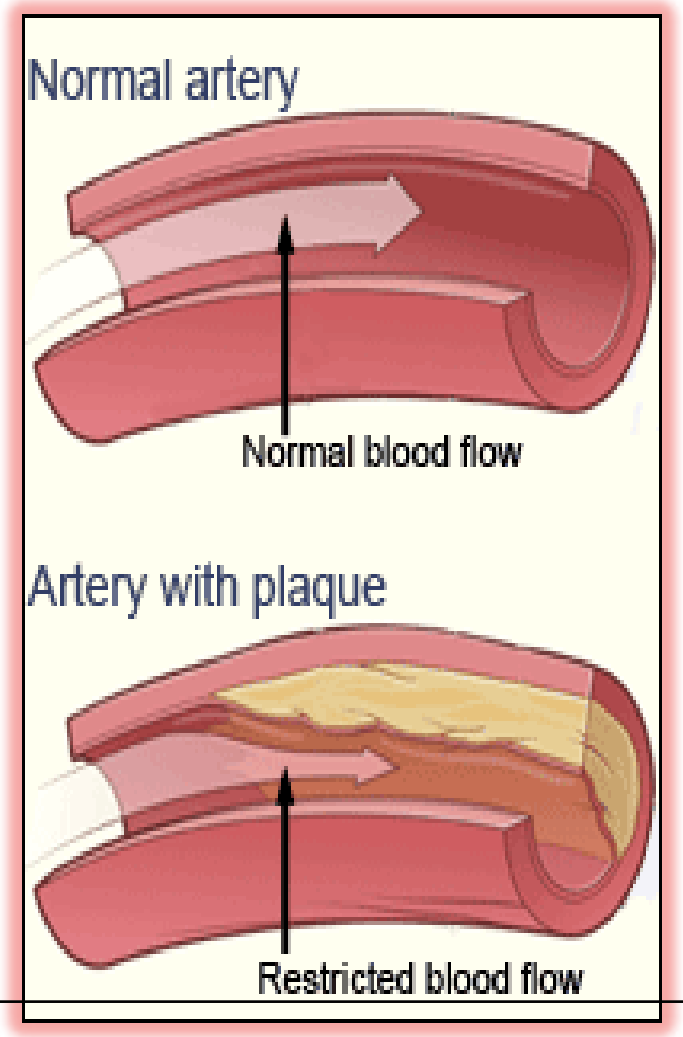
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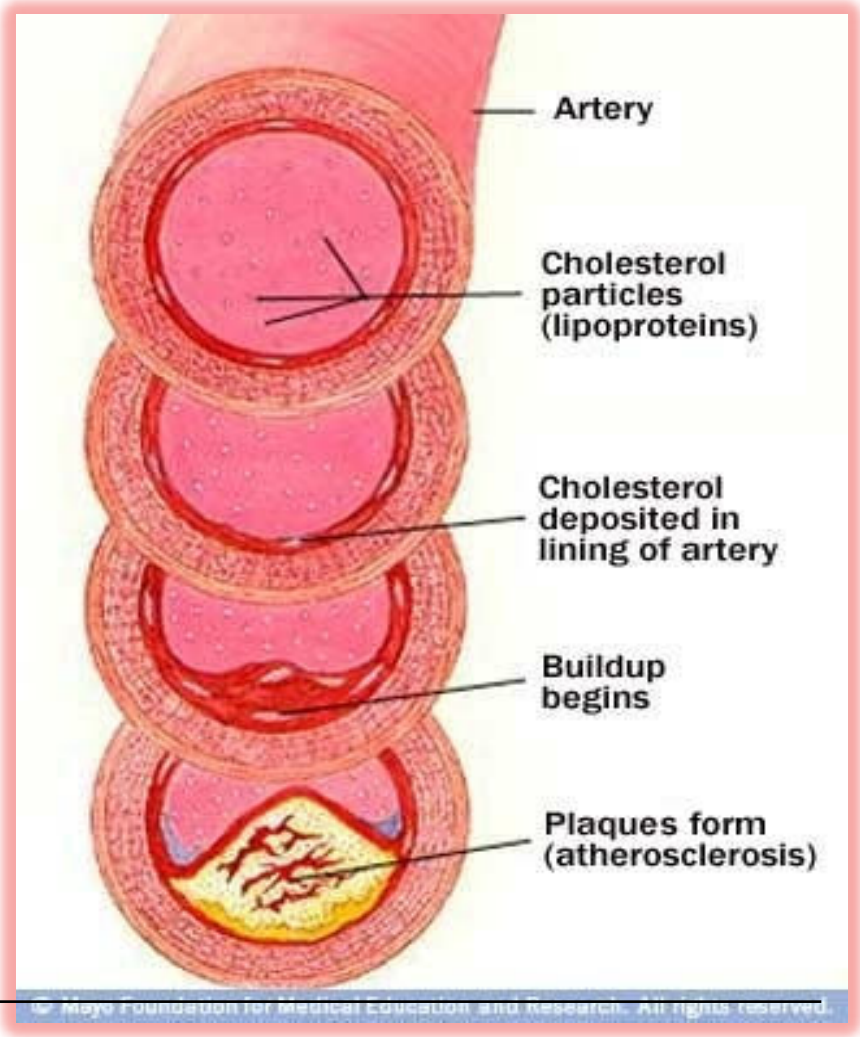
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- Thus **Connective tissue synthesis** and **Calcium fixation** determinates stiffness of blood vessels.

- Which causes further **ulceration of Atheromatous plaque.**

Arteriosclerosis





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Summary Of Pathogenesis Of Atherosclerosis

- **Accumulation of Lipids in vessel wall**
- Source: Plasma Lipoproteins
- Most important: Low-density lipoproteins LDL
- **LDL transported inside macrophages to vessel walls**
- **Damage to Endothelium**
- **Adhesion of Macrophages**
- **Inflammation at the site**
- **Fatty Streaks**
- **Foam cells**
- **Small Thrombi**
- **Calcification**
- **Plaque formation**
- **Ulceration**
- **Stiffening and Hardening of blood vessels**

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Lesions Associated with Atherosclerosis

- **The lesions** associated **with Atherosclerosis** are of **three types**:
  - **The Fatty streak**
  - **The Fibrous Atheromatous plaque**
  - **Complicated Lesion**
- The **latter two** are **responsible for the clinically significant manifestations** of the disease.

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- The **more advanced complicated lesions** are characterized by:
  - **–Hemorrhage**
  - **–Ulceration**
  - **–Scar tissue deposits**

- As a result of all pathogenic mechanism
- **Atherosclerosis** can be defined as **vicious inflammatory process**.

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Modern Theory of Atherosclerosis

- **Multifactor Theory:**

–**Structural and functional injury of vascular endothelium**

–The role of lipoproteins **in initiation and progression of lesions;**

–Response to **injury of immune cells and smooth muscle cells**

–The **role of growth factors and cytokines in inflammation**

–The **role of repeated thrombosis in lesions progression.**

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Consequences Of Atherosclerosis

OR

Effects/Complications Of Atherosclerosis

- Atherosclerosis is a **chronic process**
- Atherosclerosis **affects almost all people with variable severity.**

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- Atherosclerosis **develop over several decades.**

- If Congenital in origin It **may starts as early as infancy** and **childhood,**

- **Progress very slowly during life.**

- **Atherosclerosis** contributes to **more mortality** and

- **More serious morbidity** than any other disorder in the western world.

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- **Atherosclerosis affects** the **intimal lining of endothelium of**

- **Large and Medium-sized elastic and muscular arteries of body.**

- **Atherosclerotic plaque formation**
- **Narrows the diameter of blood vessel lumen.**

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- **Atherosclerosis leads** to the **narrowing or complete blockage of arteries /Occlusion by:**
  - **Endothelial Dysfunction**
  - **Lipid deposition**
  - **Inflammatory reaction in the vascular wall**
  - **Ulcerative Lesions**

Atherosclerosis BringgsAlterations Of Arteries :

- **Aneurysm**-Excessive localized swelling of blood vessel
- **Stenosis**-Abnormal narrowing of vessel
- **Occlusion**-Closing of blood vessel
- **Thrombosis**-Local clotting of blood
- **Embolism** -blockage of vessel by lodging of blood clot/fat globule
- **Fissure**-Small tear with bleeding
- **Ulceration**-Removal of top layer
- **Calcification-** Accumulation of Calcium Salts

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- **Atherosclerosis , can and does, occur in almost any artery in the body.**
- **Atherosclerosis of coronary arteries is very crucial**
- **This blocks, the blood circulation to Heart**
- **Which fails the cardiac muscle to sustain.**

- **Thus Atherosclerosis leads to disease of cardiovascular system affecting blood vessel wall.**
- **Causing Ischemic Heart Disease which** is the **leading cause of death in developed countries.**

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Biochemical Alterations In Atherosclerosis

Biochemical Basis Of Atherosclerosis

- **Low Blood supply** to Cells/Tissues
- **Low Nutrient and Oxygen Supply** to cells
- **Low Metabolism in cells**
- **Low Oxidative Phosphorylation**
- **Low ATP production** in cells
- **Low Cellular Activity**
- **Cellular/Tissue/Organ Dysfunction**
- **Irreversible Damage of cells/tissues/organ/system**

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Diagnosis Of Atherosclerosis

- Checking Lipid Profile/Lipoproteins
- B.P
- ECG
- Angiography
- EEG
- Color Doppler
- MRI

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Management Of Atherosclerosis

- Reducing the risk factors
- Correcting the underlying causes
- Angioplasty
- Other Surgeries

Complications of Atherosclerosis

- 1. **Acute Occlusion:**

  Thrombosis

  Occlusion

  Ischemia, Infarction
- 2. **Chronic Stenosis:**

  Chronic ischemia

  Atrophy

  Eg. Renal atrophy in renal artery stenosis, ischemic atrophy of skin in DM

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- 3. **Aneurysm Formation:**

  Extension to media

  Aneurysm

  Aneurysmal rupture eg. Abdominal aortic aneurysm
- 4. **Embolism:**

  Of atherosclerotic plaque or of thrombi

- **Thrombosis** is the most important complication of Atherosclerosis.
- It is caused by slowing and turbulence of blood flow in the region of the plaque and ulceration of the plaque.

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PHYSIOPATHOLOGICAL CONSEQUENCES OF THE PLAQUE

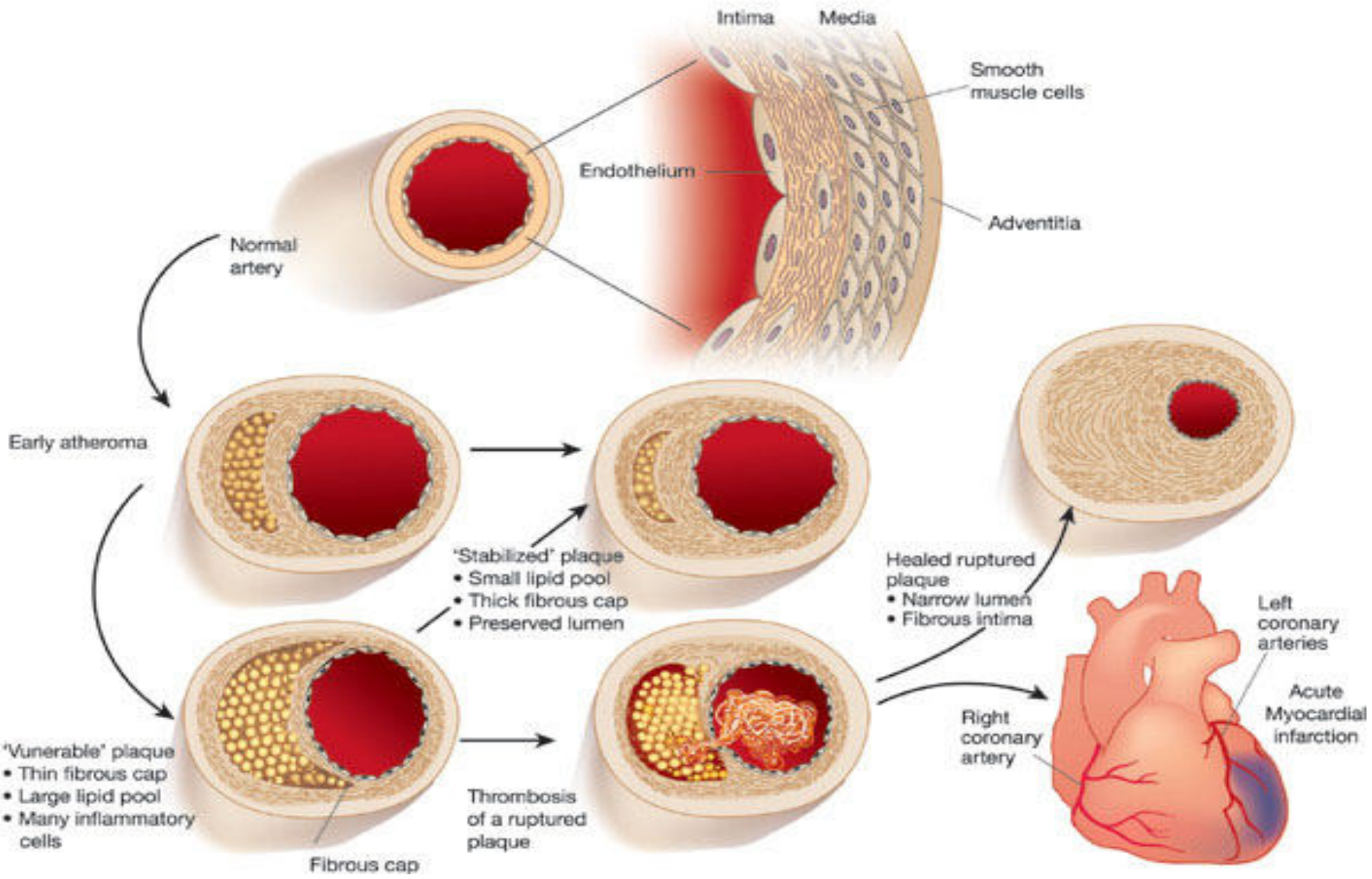
- Coronary Artery Disease (CAD) : Angina, MI
- Cerebro Vascular Disease (CVD)
- Peripheral Artery Disease (PAD)
- Ischemic Stroke (Brain infarct)
- Secondary Erectile Disorder (ED)
- Chronic Renal Ischemia (Renal failure)

- **Atherosclerosis commonly leads to:**
  - **Myocardial infarction**
  - **Stroke**
  - **Gangrene of extremities**

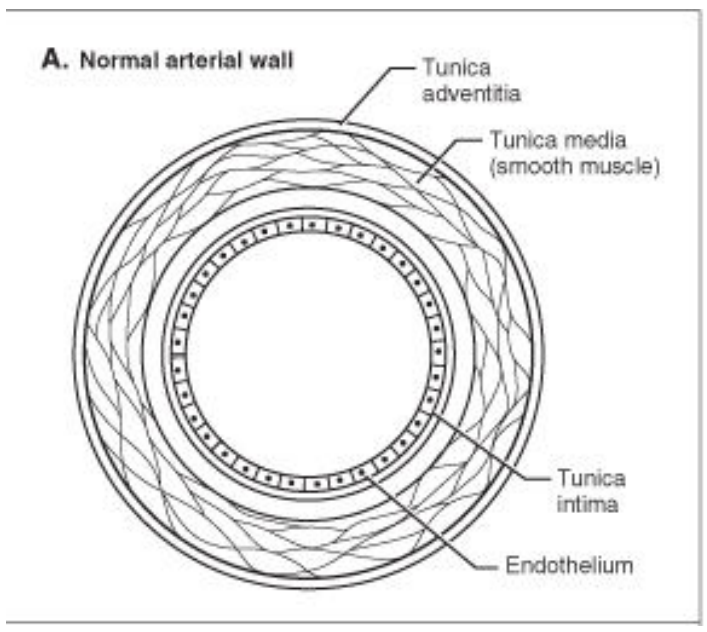
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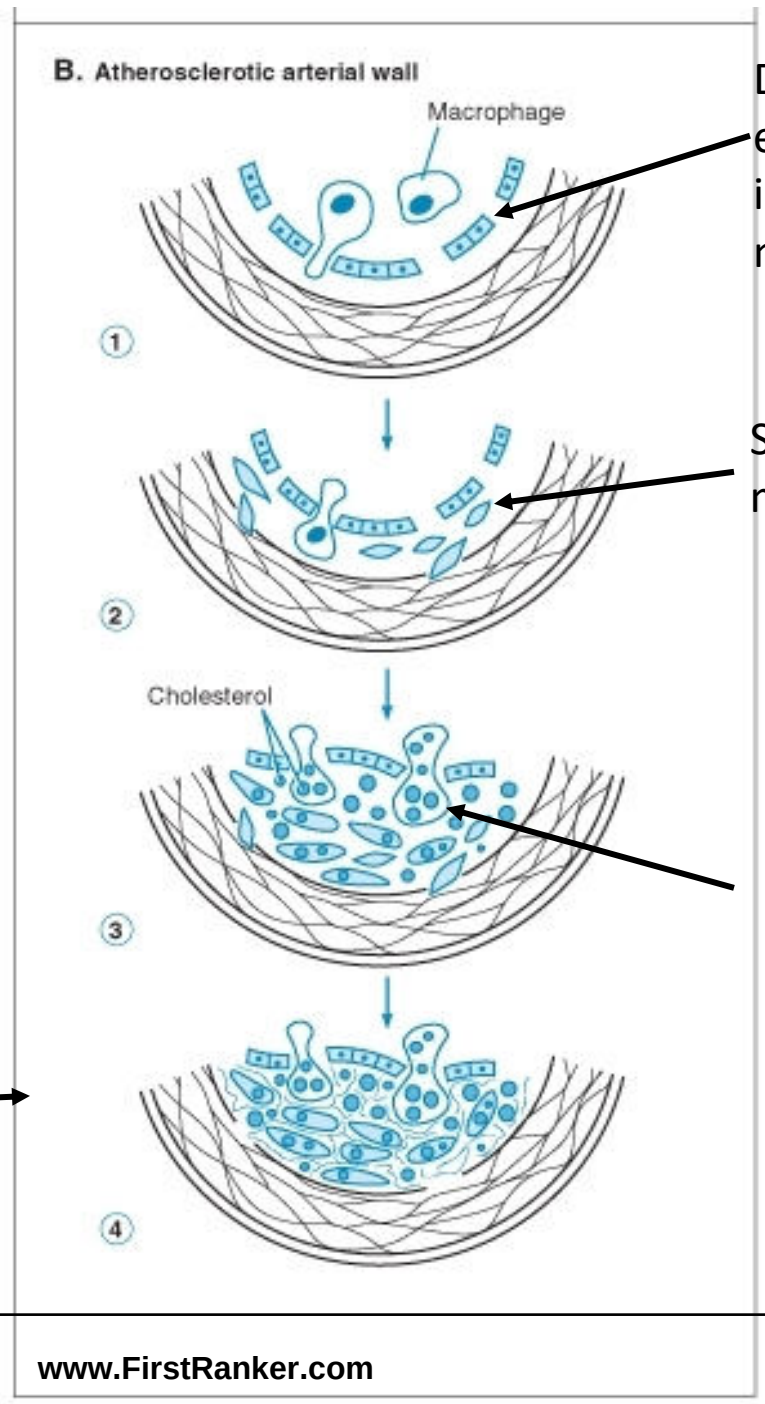
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The Process of Atherogenesis



Progression of CHD





Damage to endothelium and invasion of macrophages

Smooth muscle migration

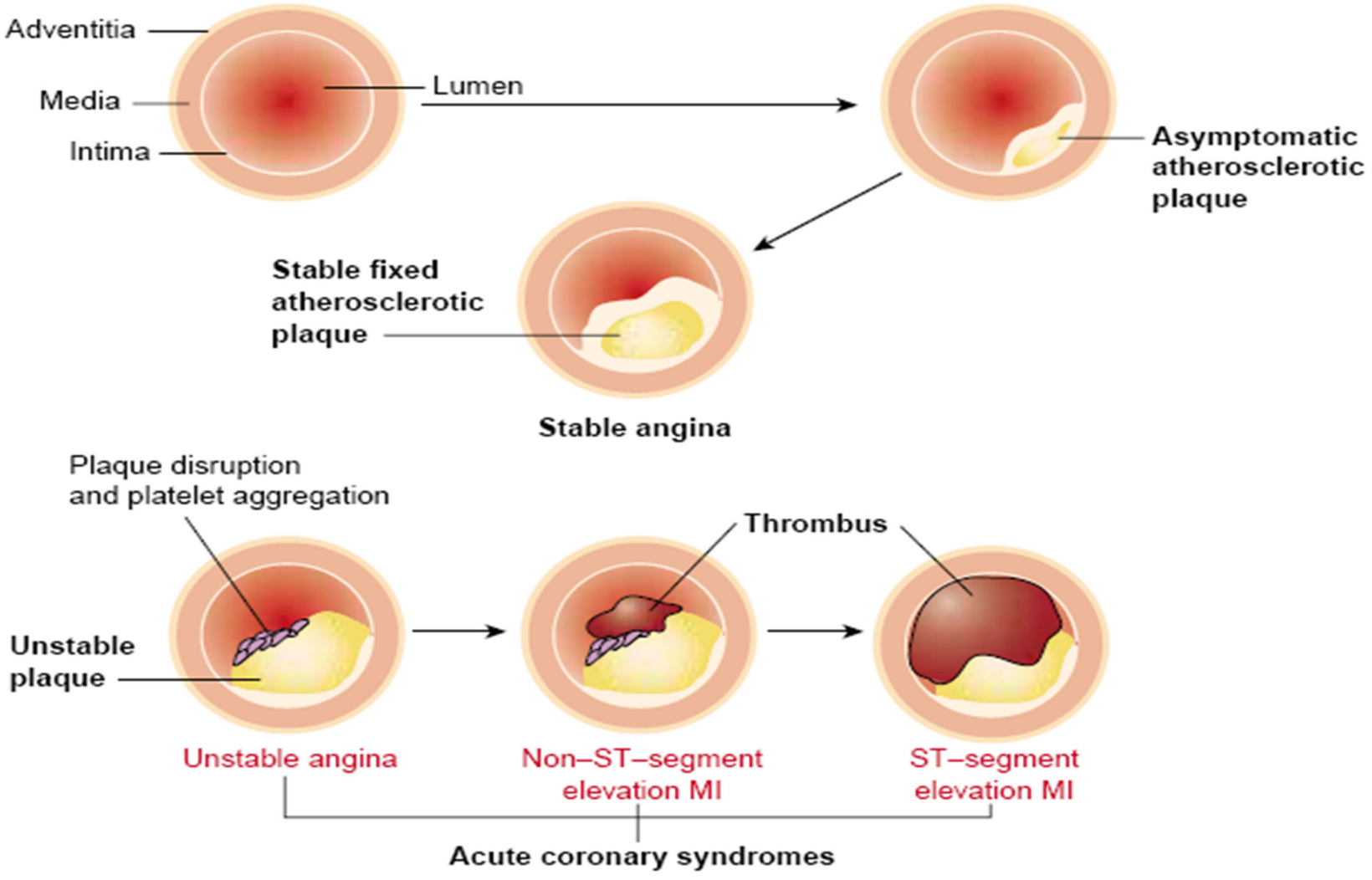
Cholesterol accumulates around macrophage and muscle cells

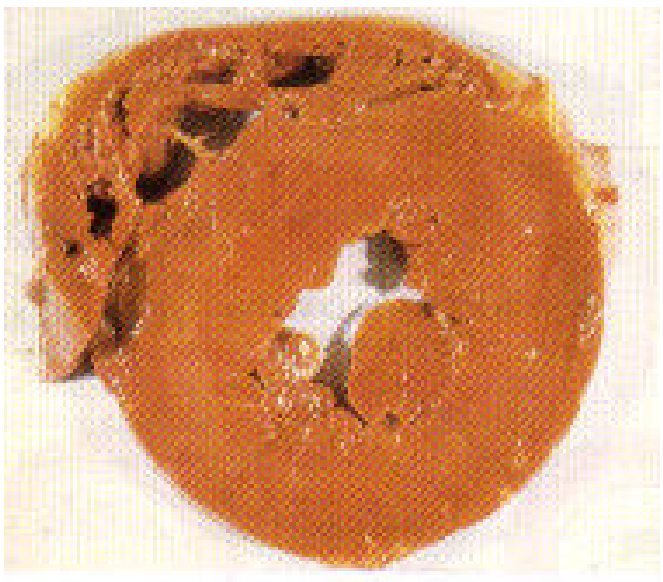
Collagen and elastic fibers form a matrix around the cholesterol, macrophages and muscle cells

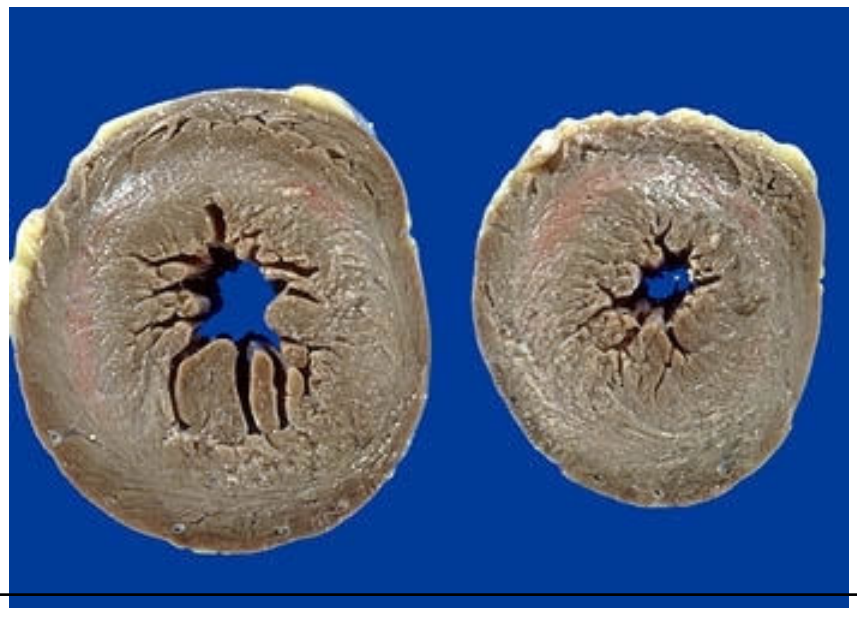
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Pathogenesis of Coronary Heart Disease (CHD)



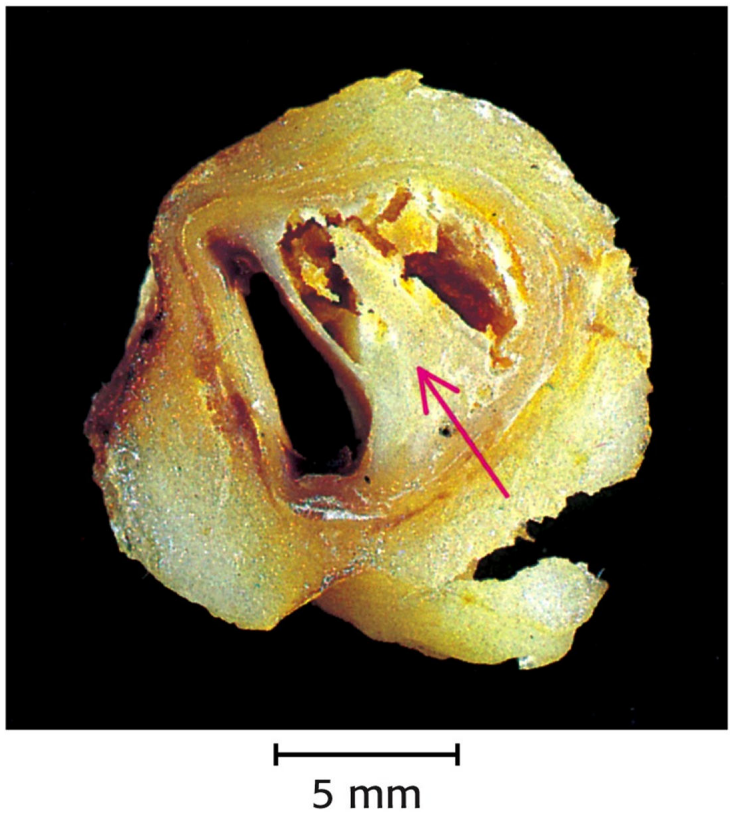




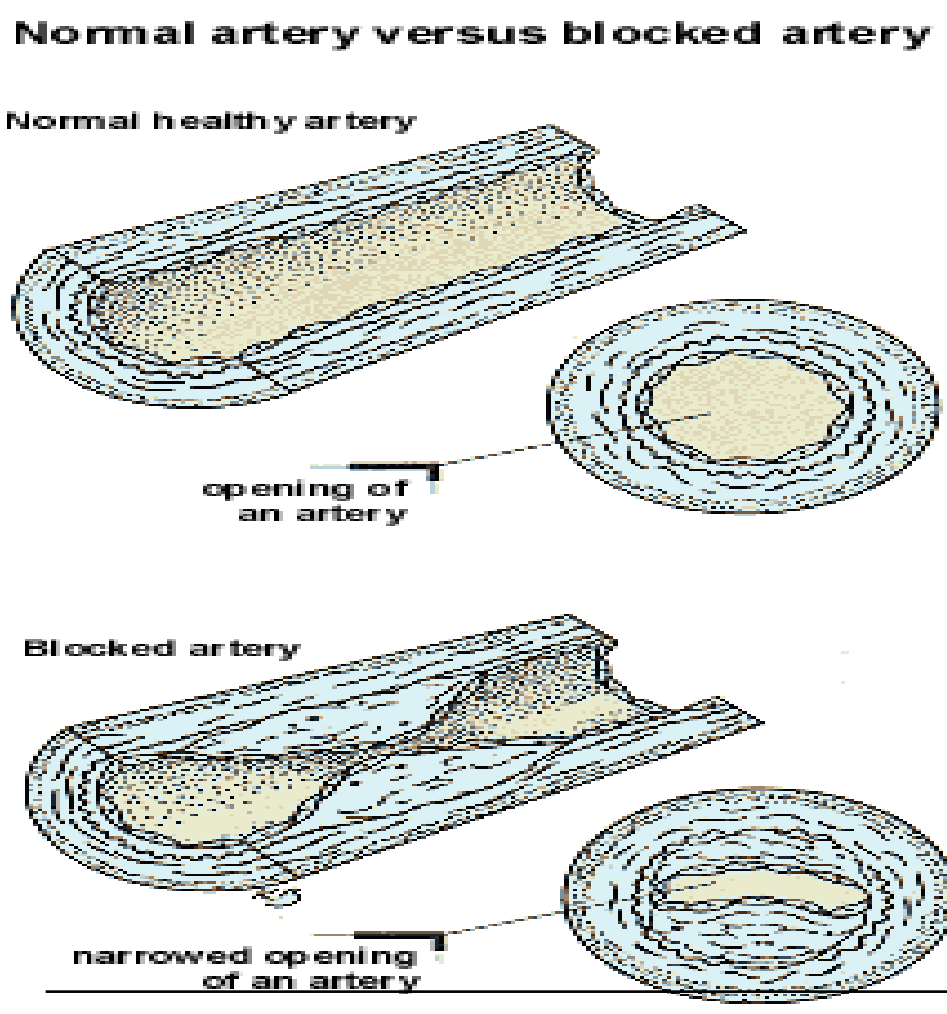
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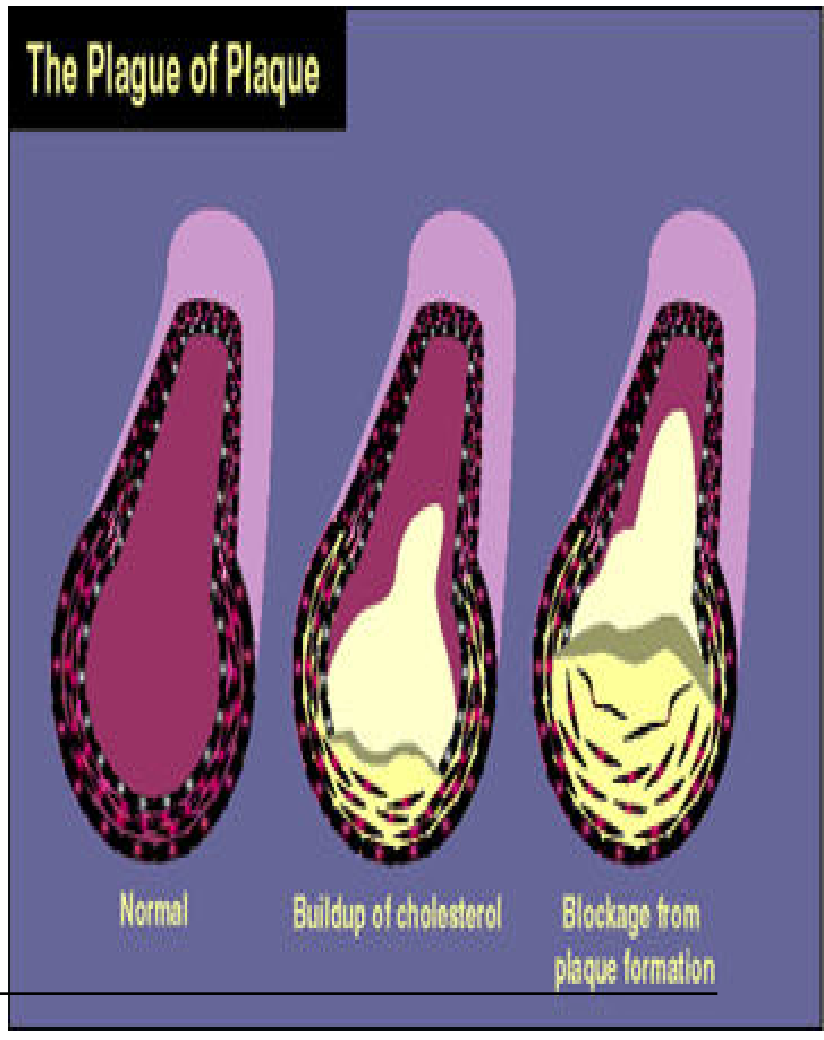
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Plaque Build up in Artery



Overview of the Artery

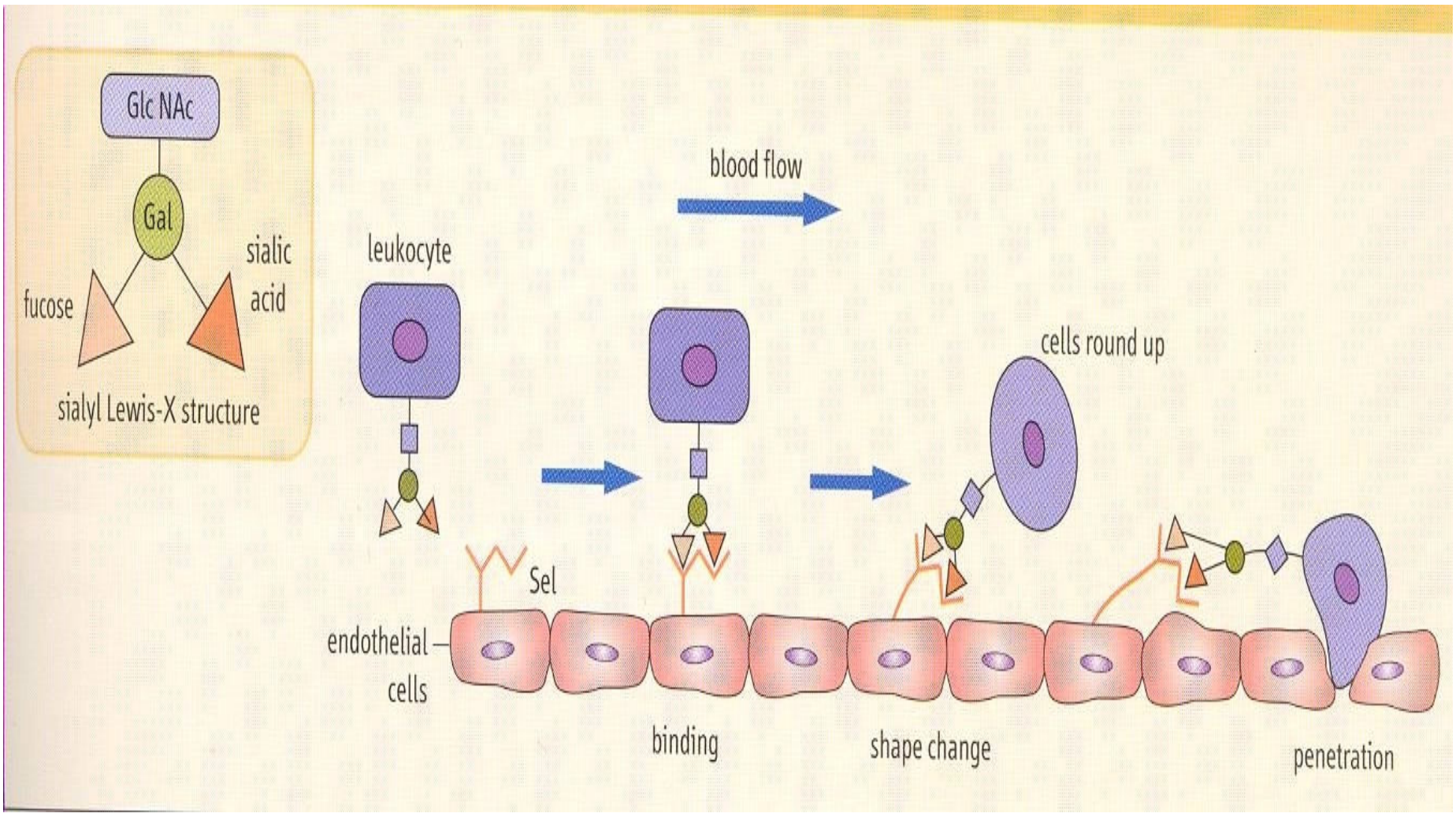




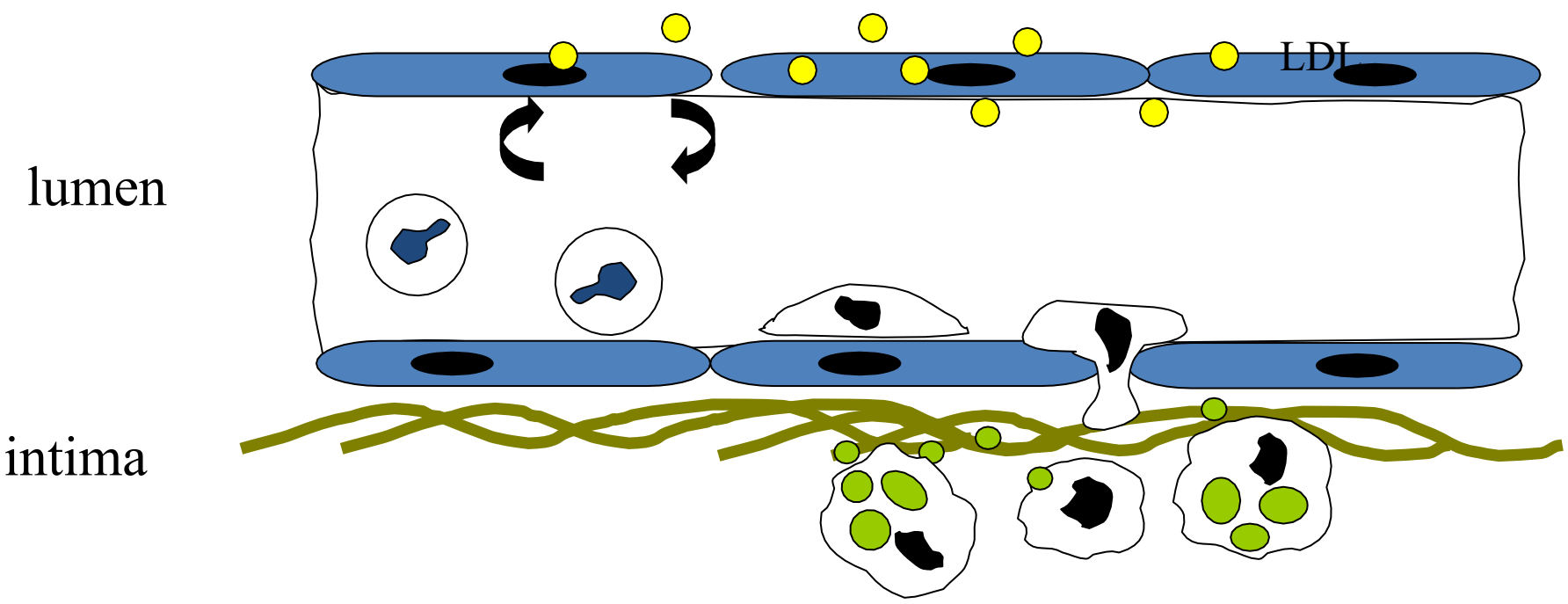
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The Development of Atherosclerosis



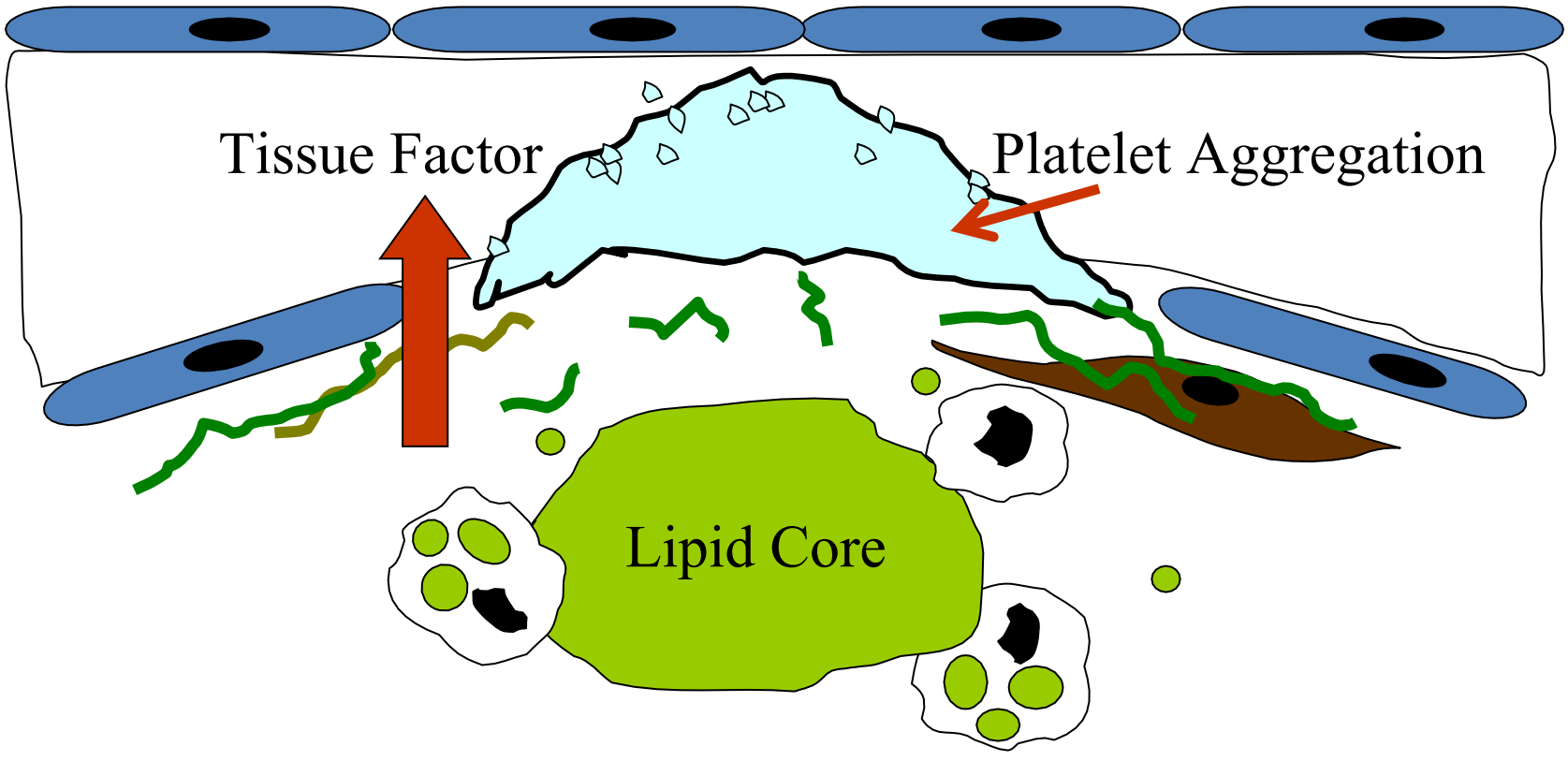
Monocyte Recruitment



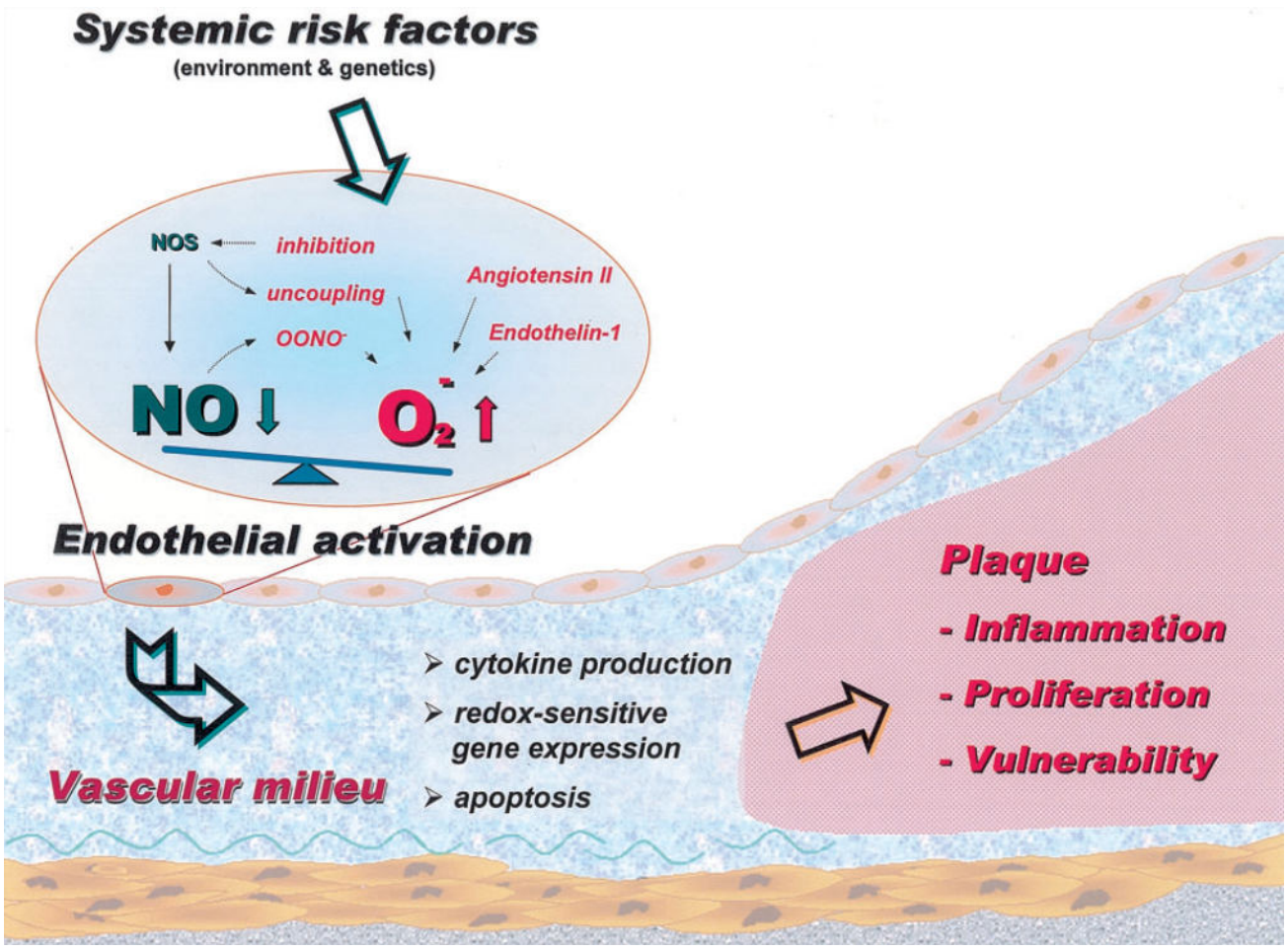
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Plaque Rupture and Thrombosis



NO Inactivation Due to Oxidative Stress

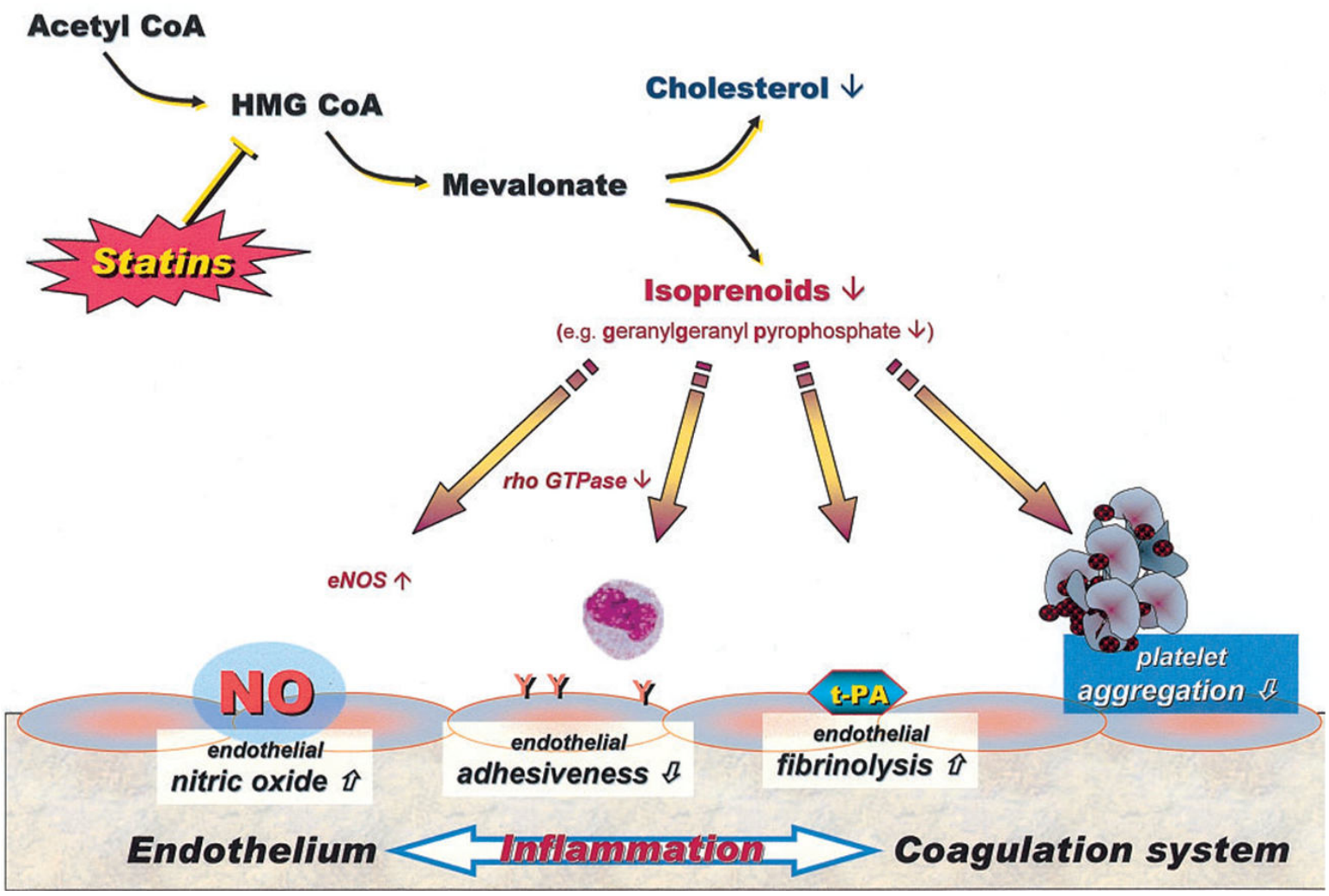


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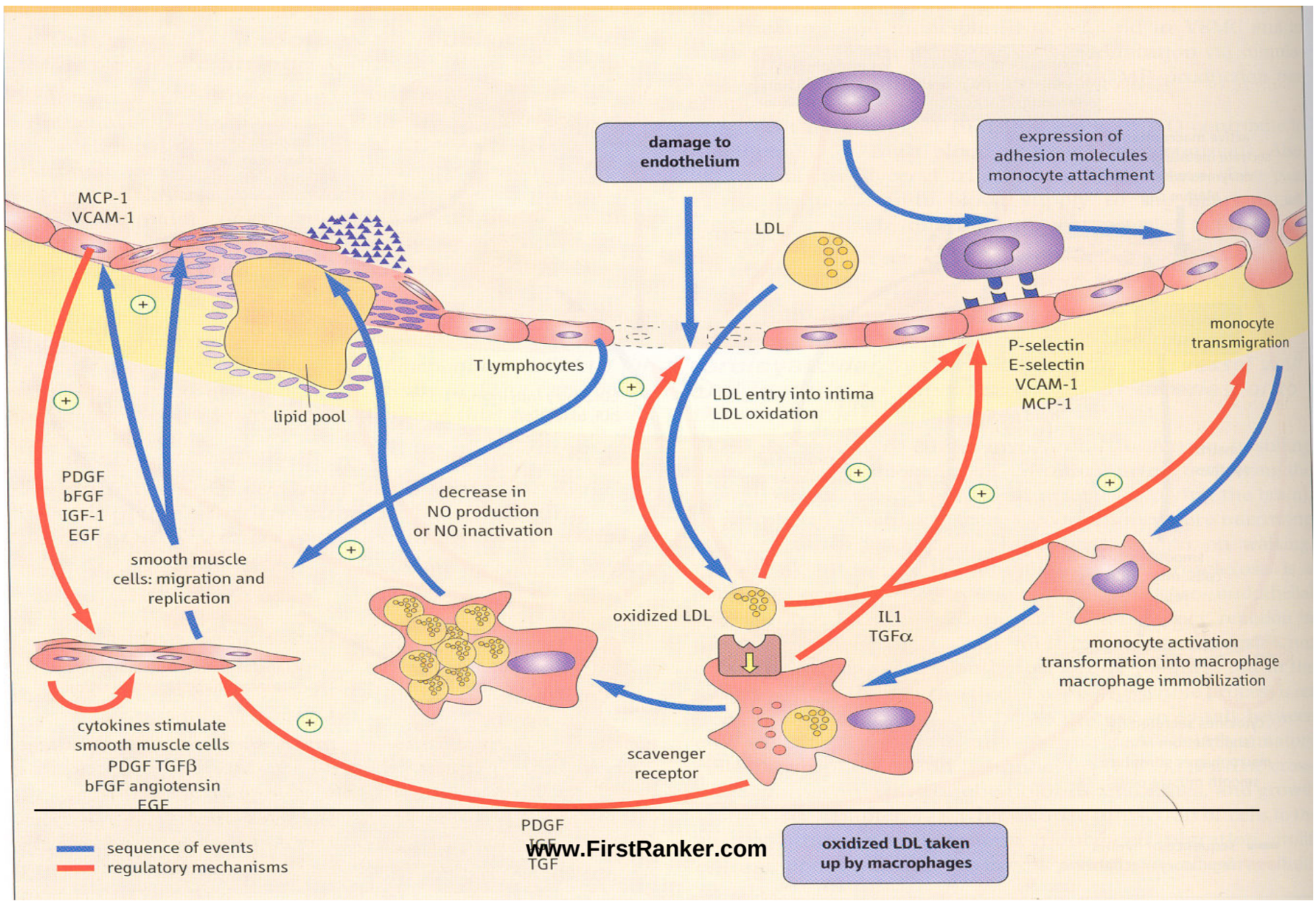
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Pleiotropic effects of statins



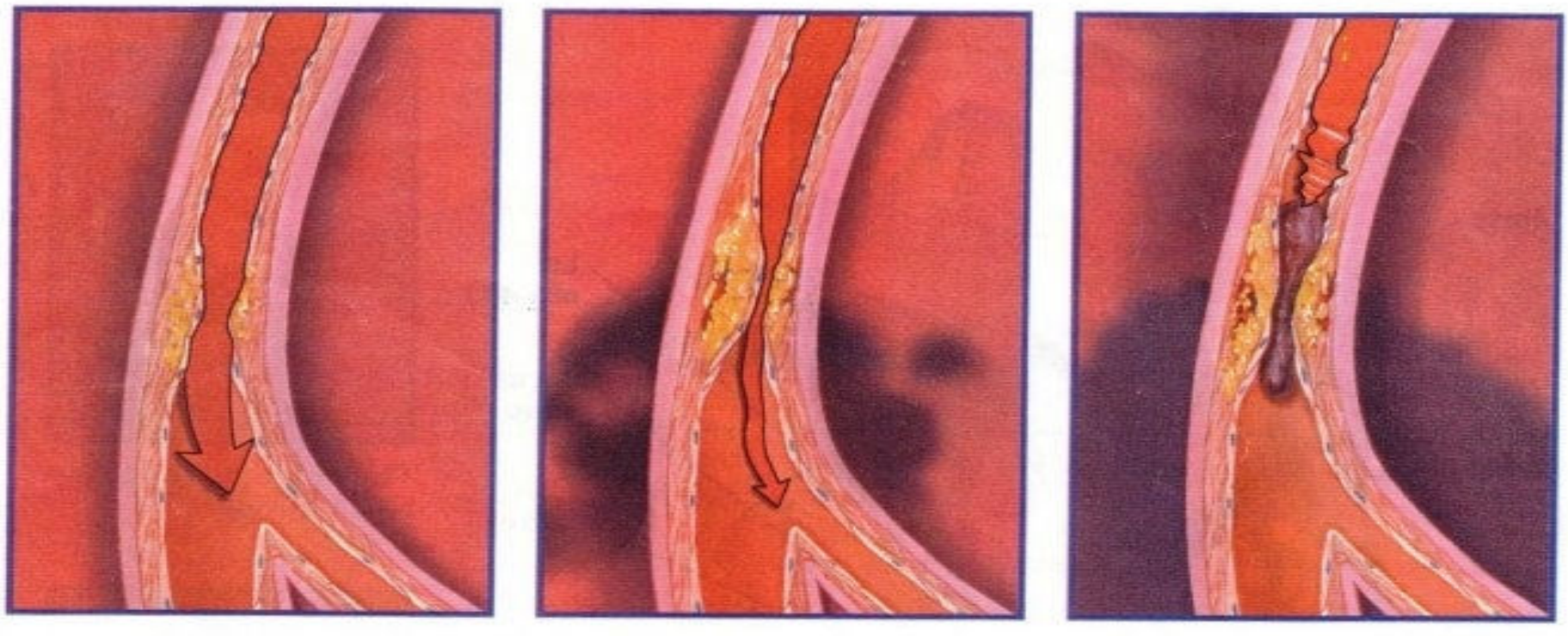
Schächinger V., Zeiher A.M.: Nephrol Dial Transplant (2002): 2055

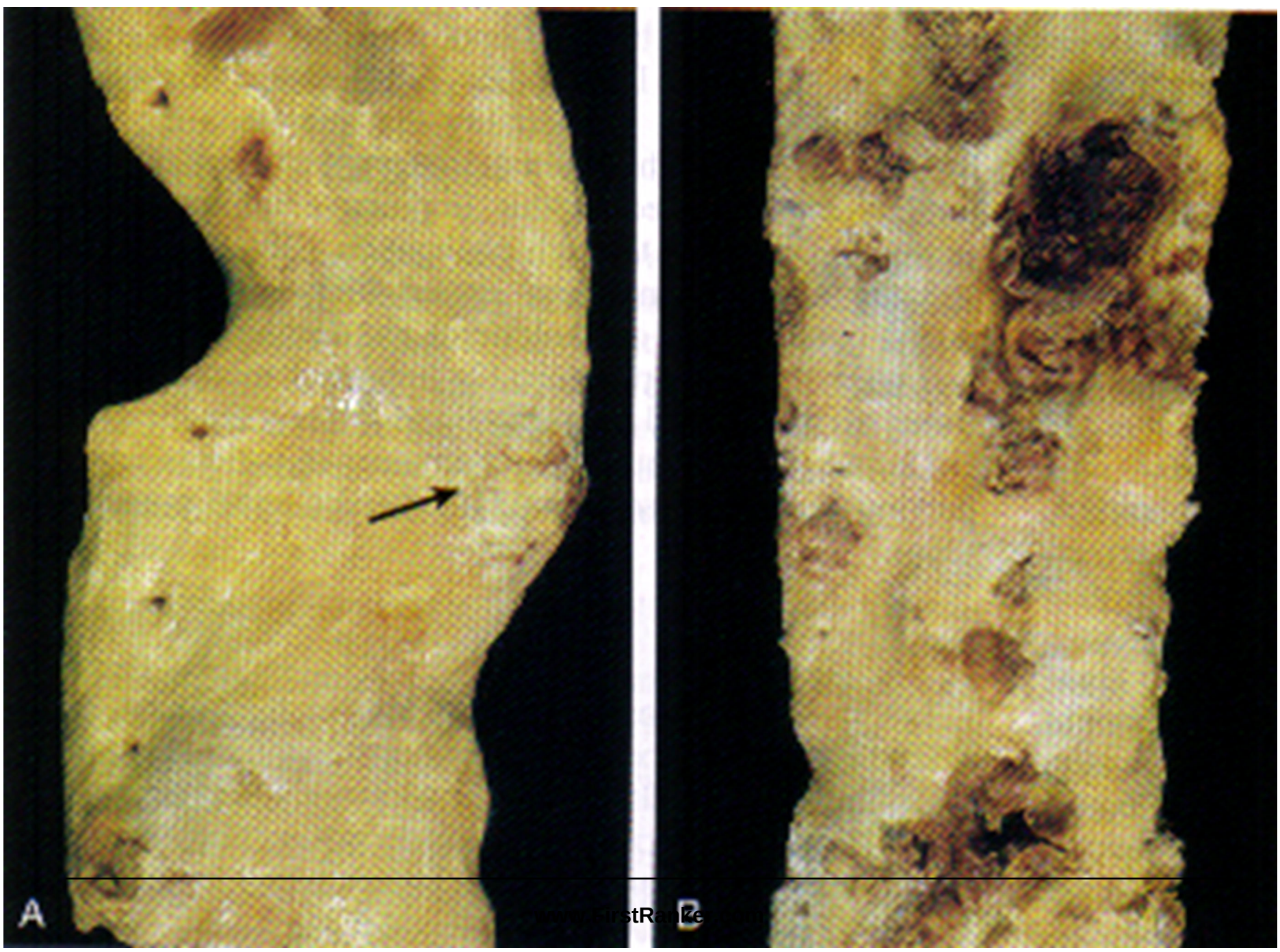
The Process of Atherogenesis – an overview



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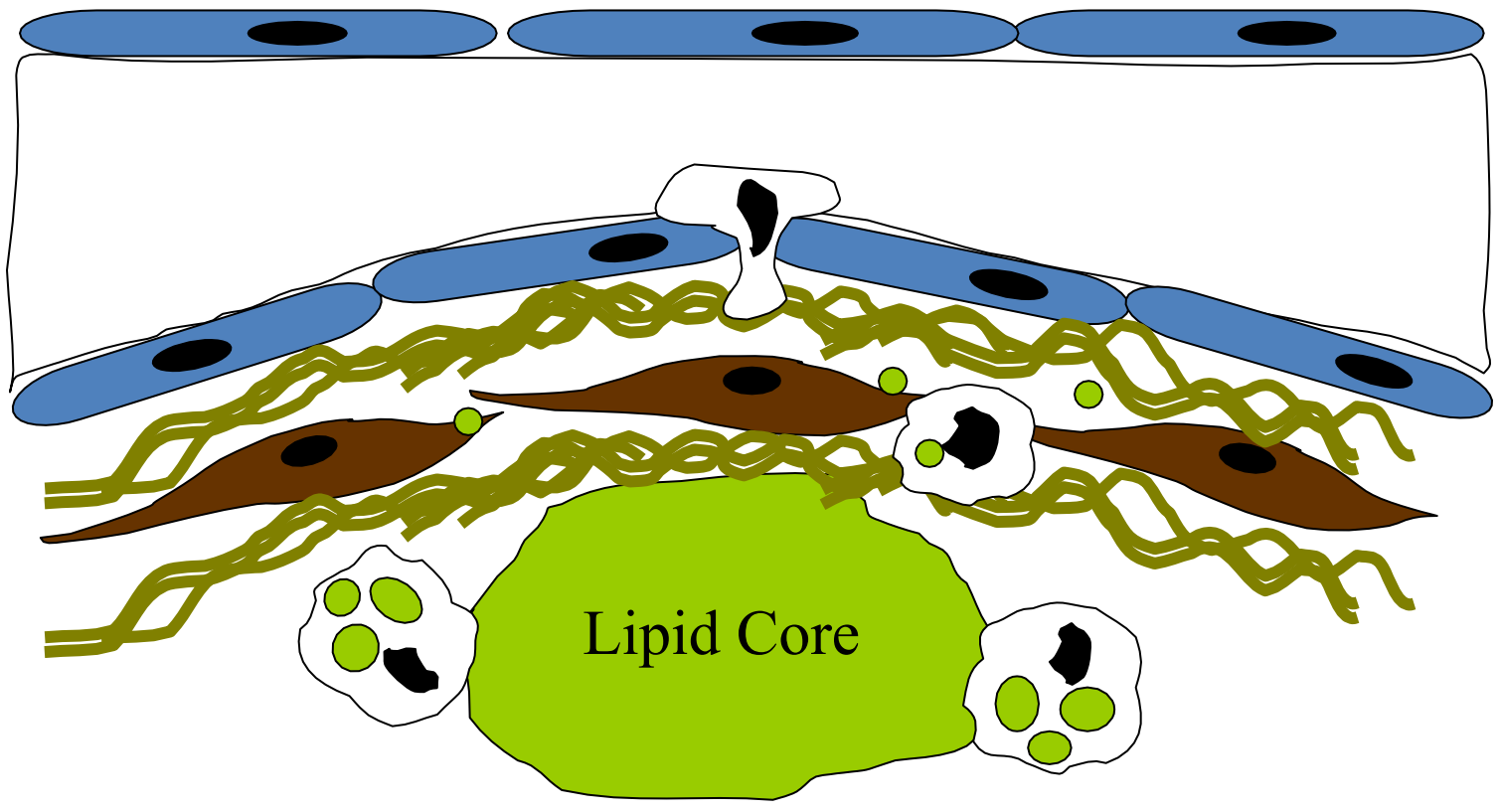


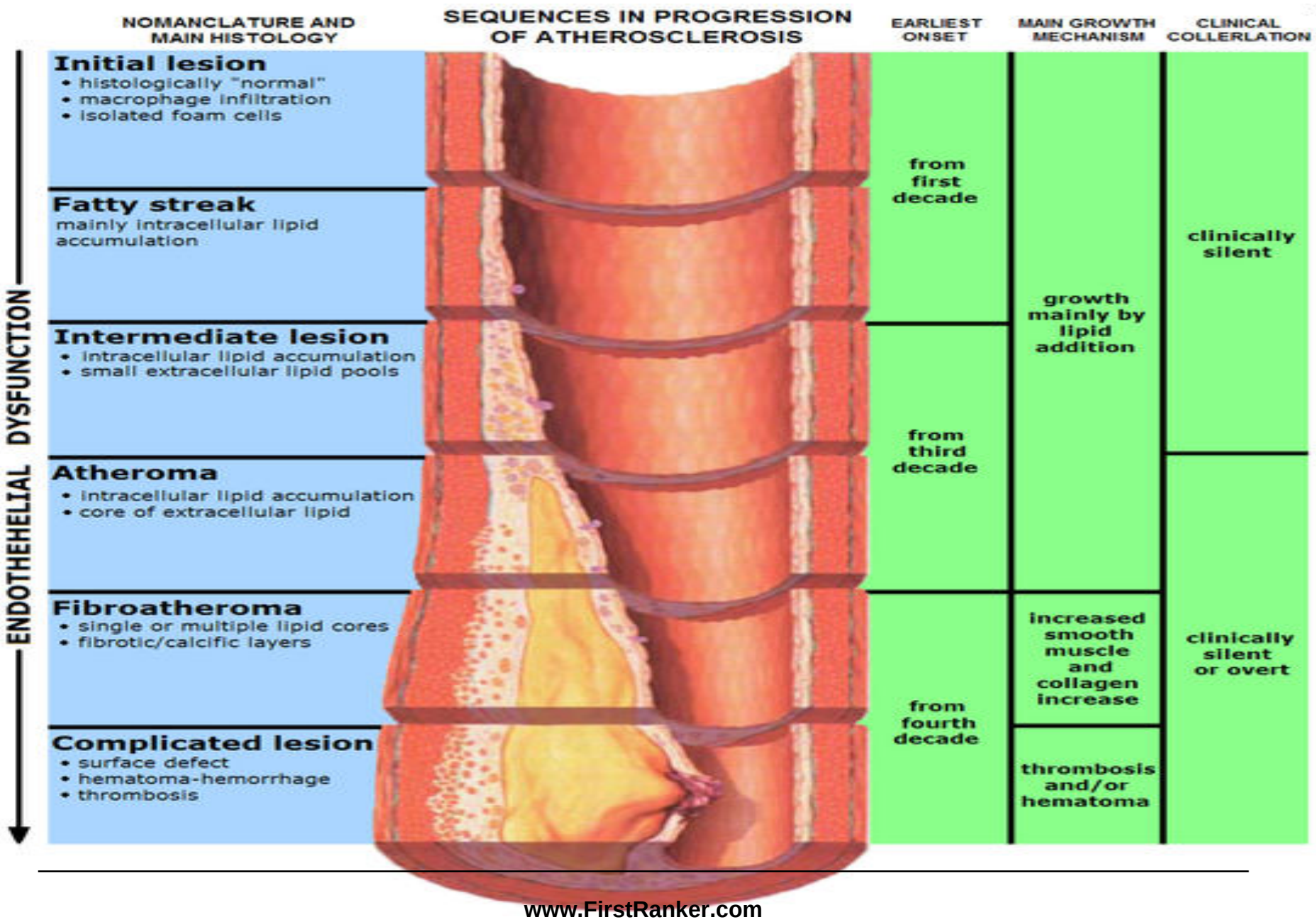


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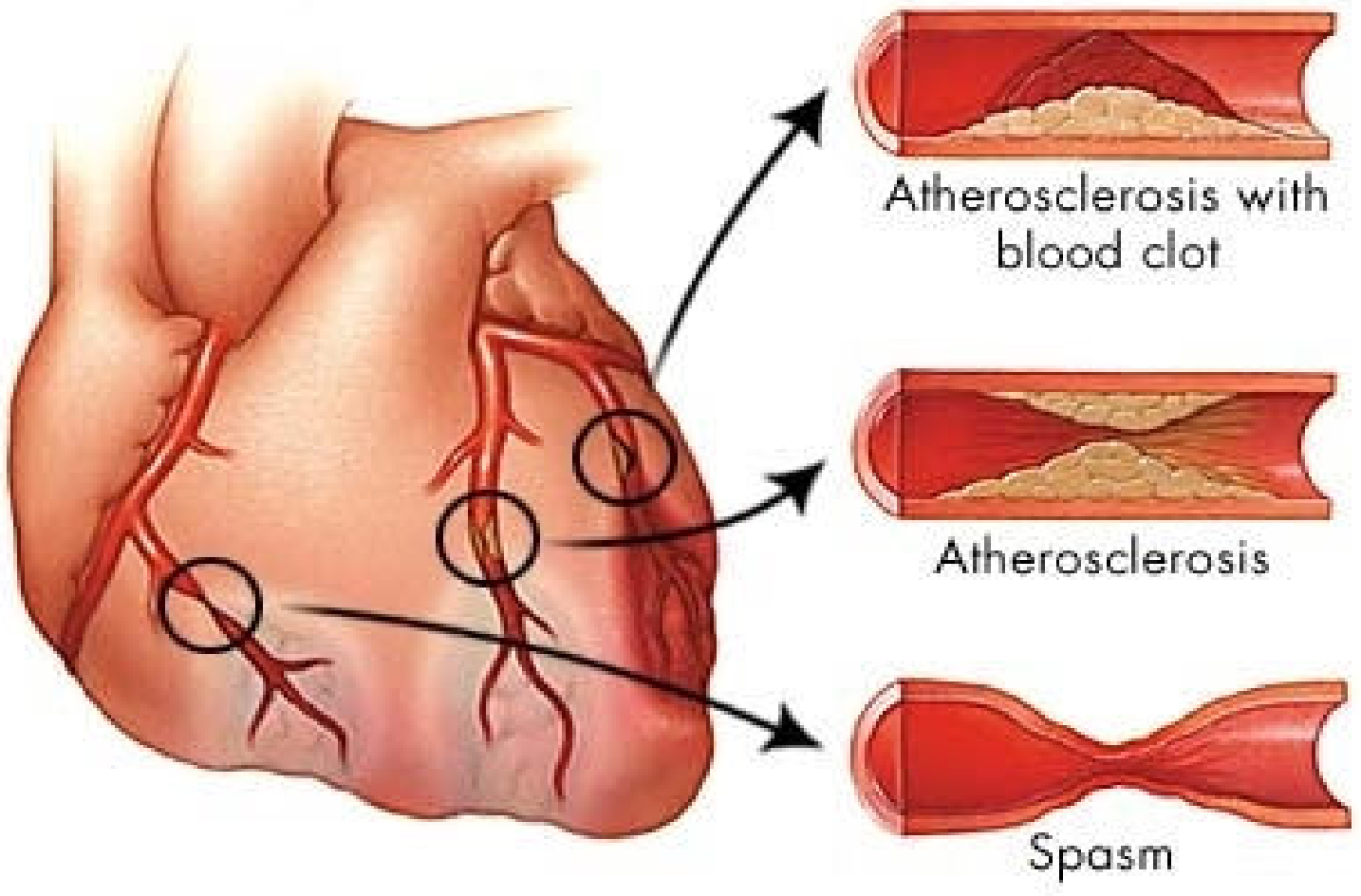
Formation of Atherosclerotic Plaques

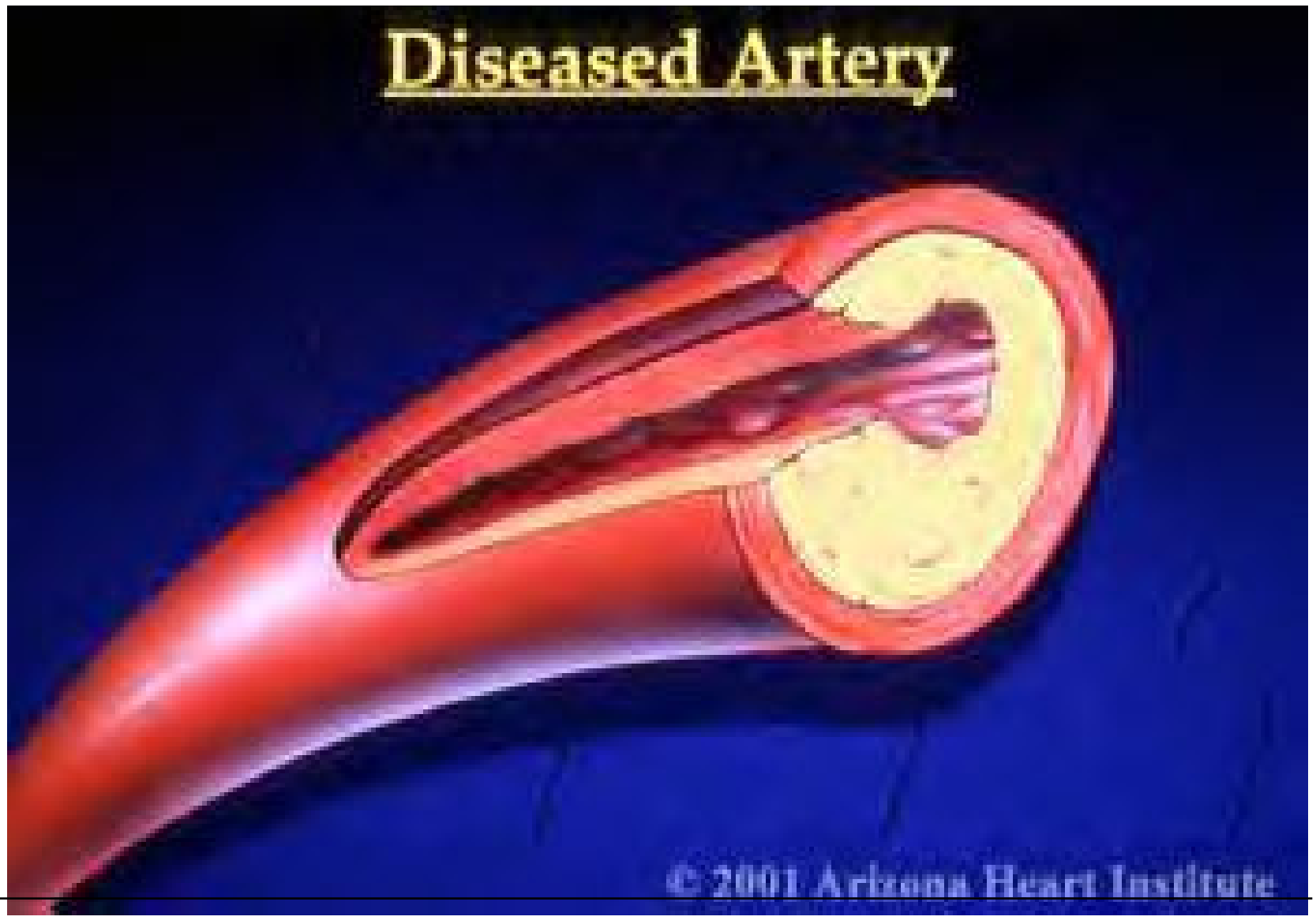




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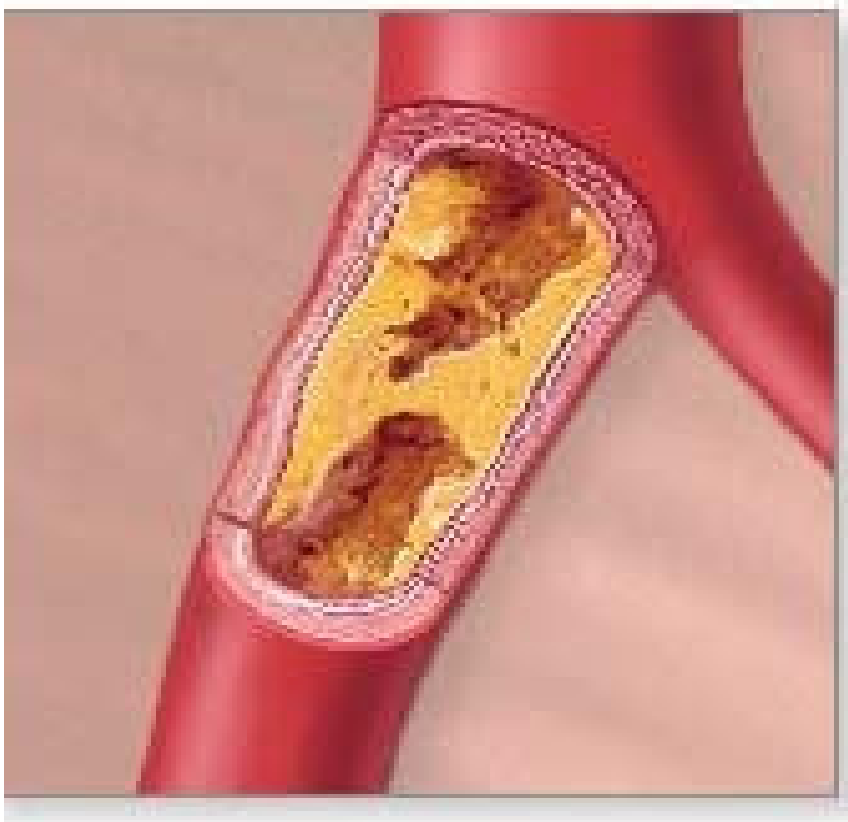
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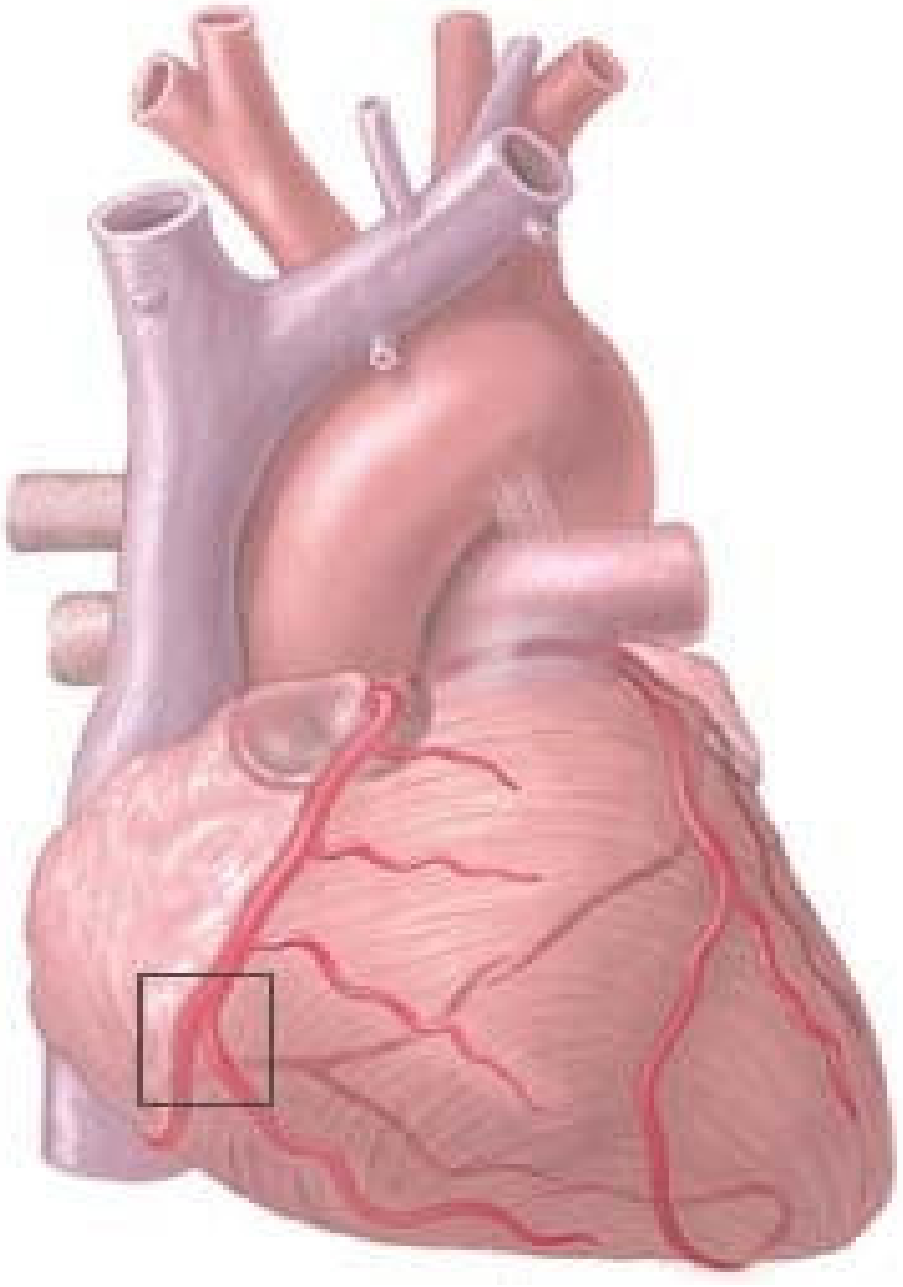


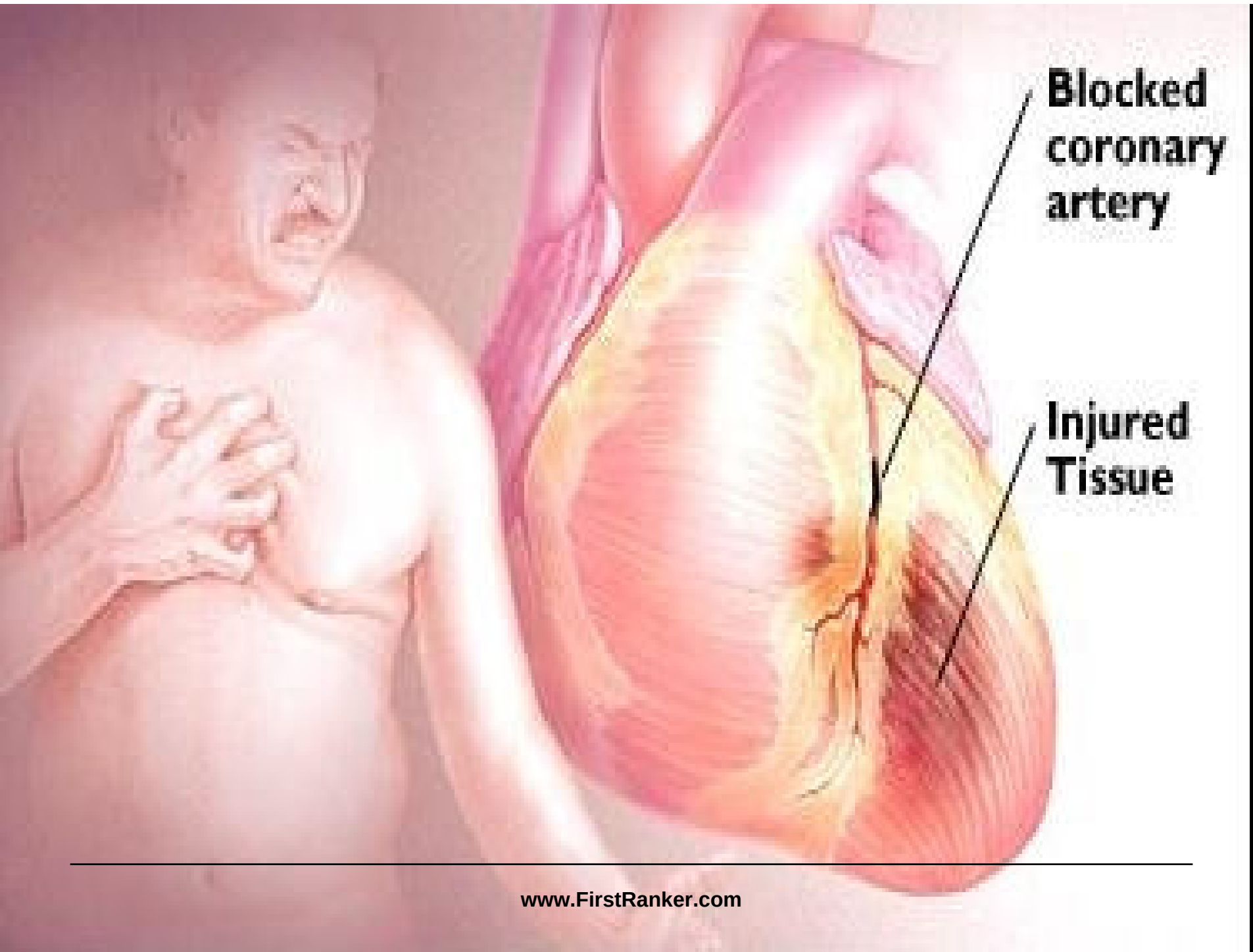
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Blockage in right coronary artery





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Cardio Vascular Disorders (CVD)

Coronary Artery Disease (CAD)

OR

Coronary Heart Disease(CHD)

OR

Ischemic Heart Disease(IHD)

Coronary Heart Disease

- The term **Coronary Heart Disease** (CHD) describes Heart disease caused by ***impaired coronary blood flow***.
- In most cases, it is **caused by Atherosclerosis of coronary arteries** which supply Myocardium.

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Clinical Manifestations

- The **clinical manifestations of Atherosclerosis depend on:**
  - **The vessels involved**
  - **The extent of vessel obstruction**

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- **Atherosclerotic Lesions produce their effects through:**
  - **Narrowing of the blood vessel** and production of Ischemia;
  - **Sudden vessel obstruction** caused by Plaque hemorrhage or rupture;
  - **Thrombosis and formation of emboli** resulting from damage to the vessel endothelium;

Coronary Artery Diseases Can cause:

- Angina/Chest Pain
- Myocardial Infarction /Heart attack
- Cardiac dysrhythmias
- Conduction defects
- Heart failure
- Sudden death

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Myocardial Infarction

Myocardial Infarction

- MI is an **irreversible damage** to Myocardium(Heart tissue)

- Acute myocardial infarction (AMI), **also known as a heart attack**

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- **AMI** is caused due to associated **Atherosclerotic disease of the coronary arteries.**

Risk Factors OF MI

Uncontrollable

- Sex
- Hereditary
- Race
- Age

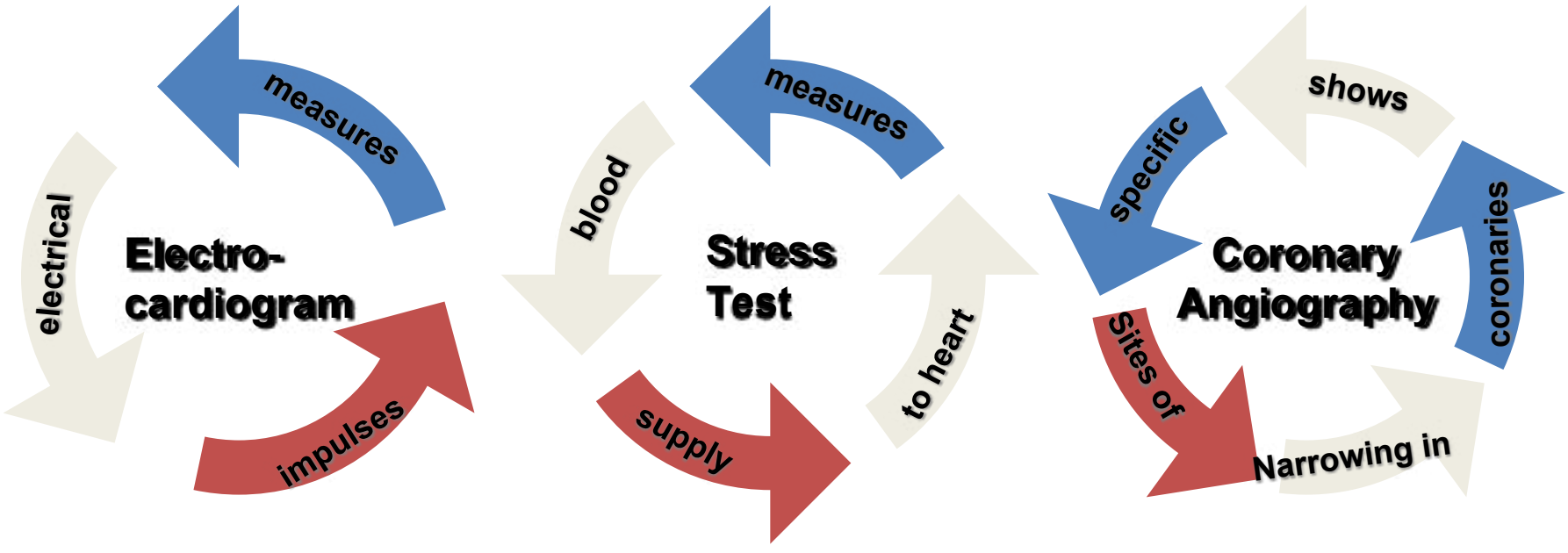
Controllable

- High blood pressure
- High blood cholesterol
- Smoking
- Physical activity
- Obesity
- Diabetes
- Stress and Anger

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Screening and Diagnosis



Diagnosis Of MI

1. Pain

- **Severe and Crushing,**
- **Constricting, Suffocating.**
- **Usually is Sub Sternal,** radiating to the left arm, neck, or jaw
- **Gastrointestinal Complaints**
  - **–Sensation of Epigastric distress**
  - **–Nausea and Vomiting**

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ECG

- **Elevation of the ST segment** usually indicates acute myocardial injury.

- When the **ST segment is elevated without associated Q waves**, it is called a ***Non–Q-wave Infarction***.

Diagnostic Biochemical Markers Of MI Enzymes and Proteins

- **Lipid Profile**
- **CK –MB**
- **AST**
- **LDH 1 and LDH2**
- **Trop T and Trop I**
- **Myoglobin**
- **Homocysteine**
- **hs CRP**
- **LP-PLA2**

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- ***Creatine kinase* (CK),** formerly called *creatinine phosphokinase,* is an intracellular enzyme found in muscle cells. Muscles, including cardiac muscle, use ATP as their energy source.
- Creatine Phosphate, which serves as a storage form of energy in muscle, uses CK to convert ADP to ATP.
- **CK exceeds normal range within 4 to 8 hours** of myocardial injury and declines to normal within 2 to 3 days.
- There are three isoenzymes of CK, with the MB isoenzyme (CK-MB) being highly specific for injury to myocardial tissue.

- ***Myoglobin*** is an **Oxygen-Storing Protein**, that is normally present in cardiac and skeletal muscle.
- It is a small molecule that is released quickly from infarcted myocardial tissue and becomes **elevated within 1 hour after myocardial cell death,** with peak levels reached within 4 to 8 hours.
- It **rapidly eliminates through urine** (low molecular weight).
- Because myoglobin is present in both cardiac and skeletal muscle, it is **not cardiac specific**.

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- T*he* ***Troponin complex*** **consists** of three subunits
  - ***T*roponin C**
  - **Troponin I**
  - **Troponin T**
- These subunits are released during myocardial infarction.
- Cardiac muscle forms of both troponin T and troponin I are used in diagnosis of myocardial infarction.

- **Troponin I (and Troponin T) rises more slowly than myoglobin**
- This may be useful for diagnosis of infarction, even up to 3 to 4 days after the event.
- It is thought that cardiac Troponin assays are more capable of detecting episodes of myocardial infarction **in which cell damage is below that detected by CK-MB level.**

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Effects of Acute Myocardial Infarction (AMI)

- The principal biochemical consequence of AMI is
- The **conversion from aerobic to anaerobic metabolism**
- With **inadequate production of energy(ATP)** to sustain normal Myocardial function.
- The **ischemic area ceases to function** within a matter of minutes, and
- **Irreversible Myocardial cell damage occurs after 20 to 40 minutes of severe ischemia**.

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Treatment

- **Reperfusion**
- **(Re-establishment of blood flow)**
- **Thrombolytic therapy**
  - **–Streptokinase/ Urokinase**
- **Revascularization procedures**

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– **Early Reperfusion** (within 15 to 20 minutes) after onset of ischemia can **prevent necrosis.**

– **Reperfusion after a longer interval** can salvage some of the myocardial cells that would have died because of longer periods of ischemia.

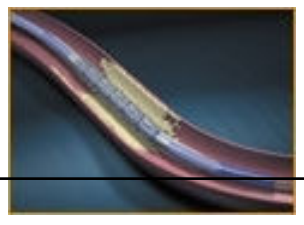
Treatment 1) Stenting

• **A Stent (narrow expandable tube**) is introduced into a blood vessel on a **balloon catheter** and advanced into the blocked area of the artery

• The **balloon is then inflated** and causes the stent to expand until it fits the inner wall of the vessel, conforming to contours as needed

• The balloon is then deflated and drawn back

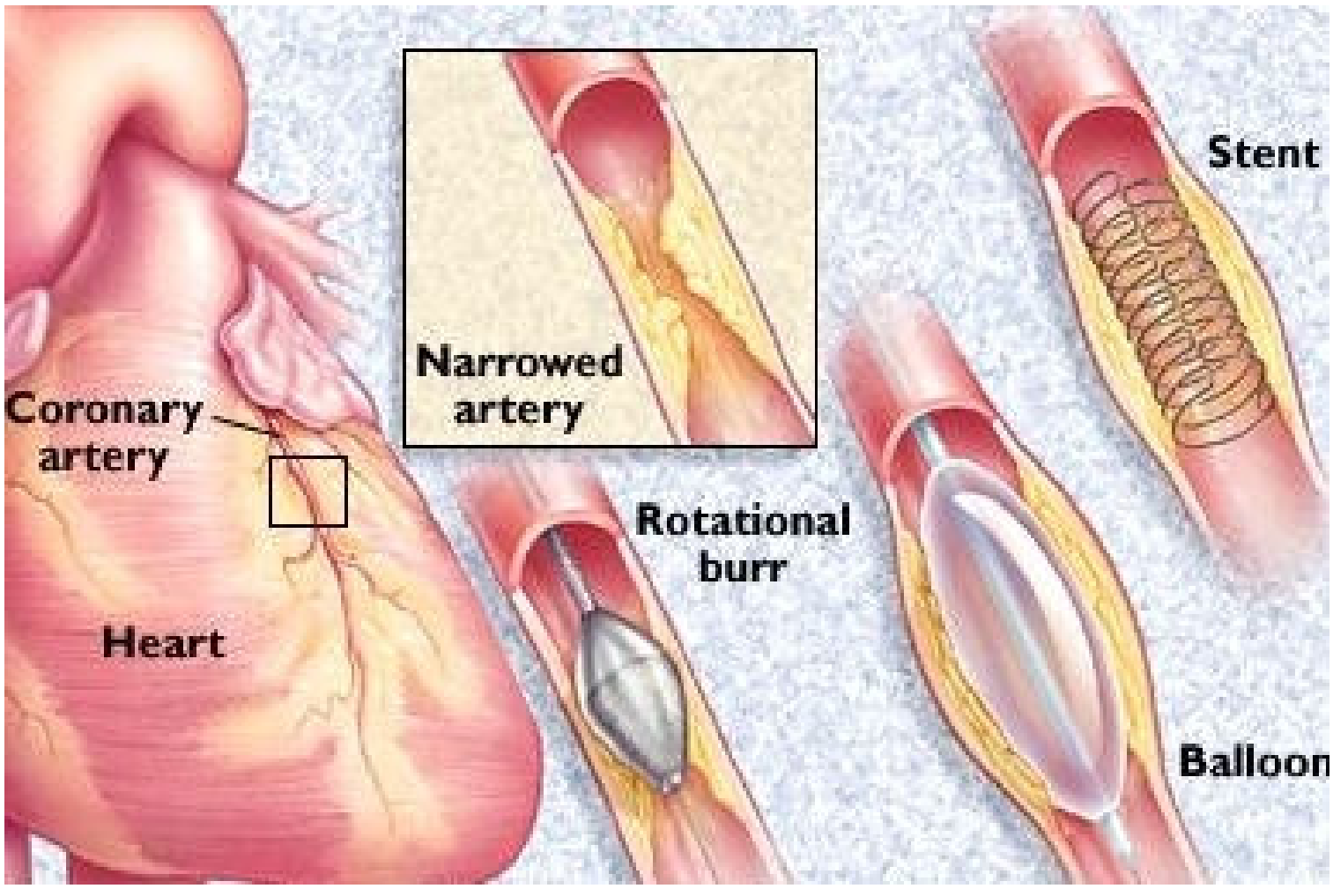
•The stent stays in place permanently, holding the vessel open and improving the flow of blood.





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Treatment 2) Angioplasty

- **Balloon catheter** is passed through the guiding catheter to the area near the narrowing. A guide wire inside the balloon catheter is then advanced through the artery until the tip is beyond the narrowing.
- The angioplasty catheter is moved over the guide wire until the balloon is within the narrowed segment.
- Balloon is inflated, compressing the plaque against the artery wall
- Once plaque has been compressed and the artery has been sufficiently opened, the balloon catheter will be deflated and removed.



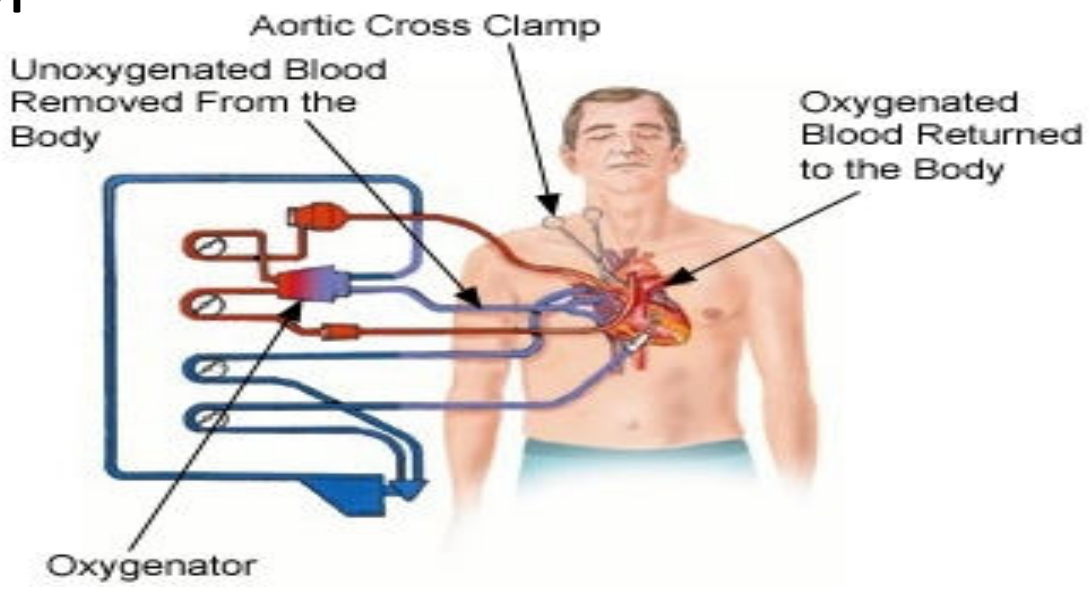
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Treatment

3) Bypass surgery

- healthy blood vessel is removed from leg, arm or chest
- blood vessel is used to create new blood flow path in your heart
- the “bypass graft” enables blood to reach your heart by flowing around (bypassing) the blocked portion of the diseased artery. The increased blood flow reduces angina and the risk of heart attack.



Peripheral Arterial Disease (PAD)

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Peripheral Arterial Disease (PAD)

- **PAD** refers to the **obstruction of large arteries** in lower extremities of leg
- It possess, **inflammatory processes** leading to **stenosis, an embolism, or thrombus** formation.

Risk of PAD

- Risk of PAD also increases in individuals who are:
  - **Over the age of 50**
  - **Male Obese**
  - **With a family history of vascular disease, heart attack, or stroke.**

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Symptoms OF PAD

- About **20% of patients with mild PAD may be asymptomatic;**
  - **Symptoms of PAD include:**
    - **Pain, weakness, numbness, or cramping in muscles** due to decreased blood flow
    - **Sores, wounds, or ulcers that heal** slowly or not at all
    - **Noticeable change in color** (blueness or paleness) or **temperature** (coolness) when compared to the other limb
    - **Diminished hair and nail growth** on affected limb and digits.

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Prevention Of Dyslipidemias And Its Consequences And Complications

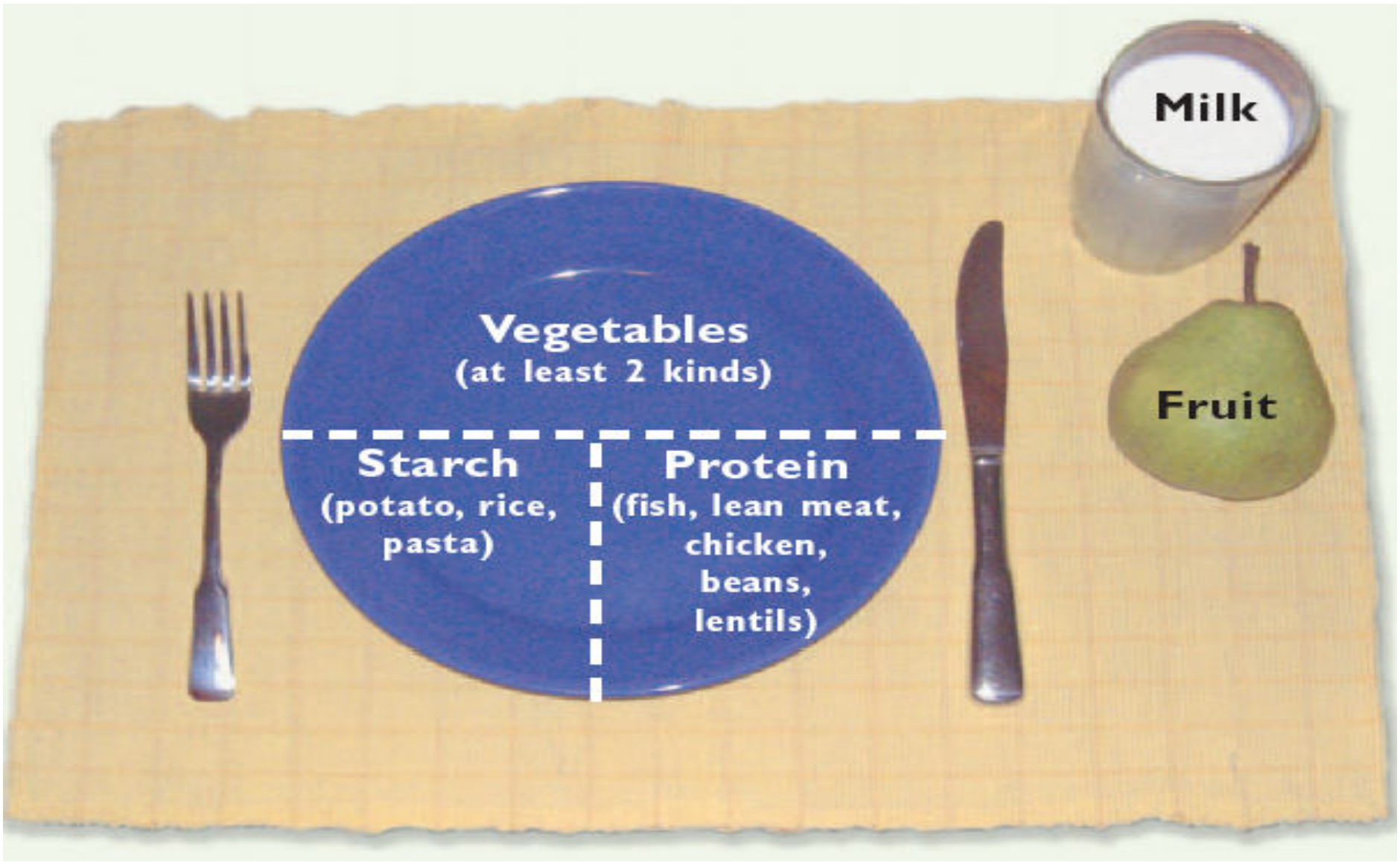
Prevention

- Get regular medical checkups
- Eat a Heart-Balanced healthy diet
- Control your blood pressure
- Check your Blood Cholesterol
- Don’t smoke and drink Alcohol
- Exercise regularly
- Maintain a healthy weight
- Manage stress

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THE HEALTHY PLATE



FOODS THAT LOWER LDL CHOLESTEROL

1. Oats
2. Barley and Whole grains
3. Beans
4. Eggplant and okra
5. Nuts
6. Vegetable oils (canola, sunflower, safflower)
7. Apples, grapes, strawberries, citrus fruits
8. Soy
9. Fatty Fish
10. Fiber supplements

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- Eat meat sparingly
- Add Fish to your diet
- Go for Nuts
- Eat Fruits and Vegetables
- Increase Complex Carbohydrates and fiber
- Opt for low-Fat dairy products
- Cut down on Saturated fat in cooking
- Avoid Palm and Coconut oils (Rich in SFAs)
- Avoid Trans Fats
- Reduce Dietary Cholesterol
- Reduce Salt intake
- Watch the Snacks

Blood Cholesterol levels increase by eating these products



- **Refined Sugars**
- **Beef**
- **Poultry**
- **Fish**
- **Milk**
- **Eggs**
- **Cheese**
- **Yogurt**

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EXERCISE

- ***Aerobic exercise (jogging, swimming, brisk walking, bicycling, etc)***

STRESS REDUCTION STEPS

- **Be Spiritual**
- **Balance All Actions**
- **Make and Follow Right protocols**
- **Be Planned and Organized**
- **Manage works based on priority**
- **Involve In work which you are chosen for**
- **Be Obedient and Have Patience**
- **Be Happy with what get**
- **Not expect too much in life**
- **Repent, Accept But Do Not Repeat**
- **Ventilate And Communicate**

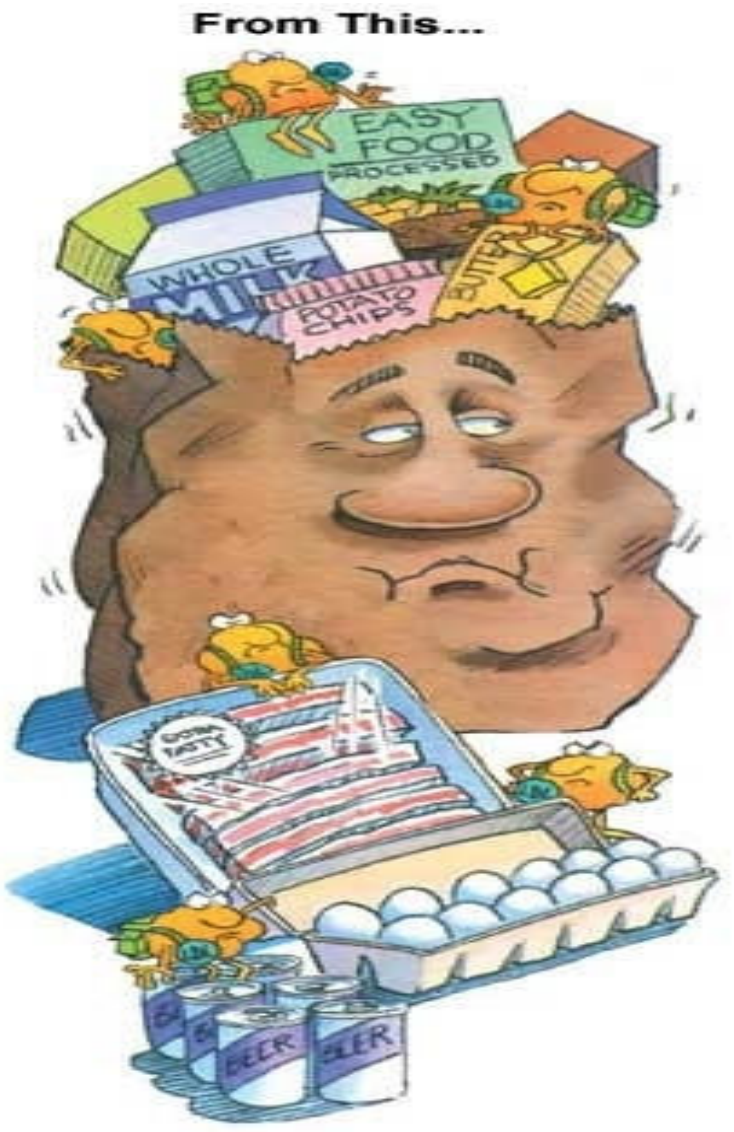
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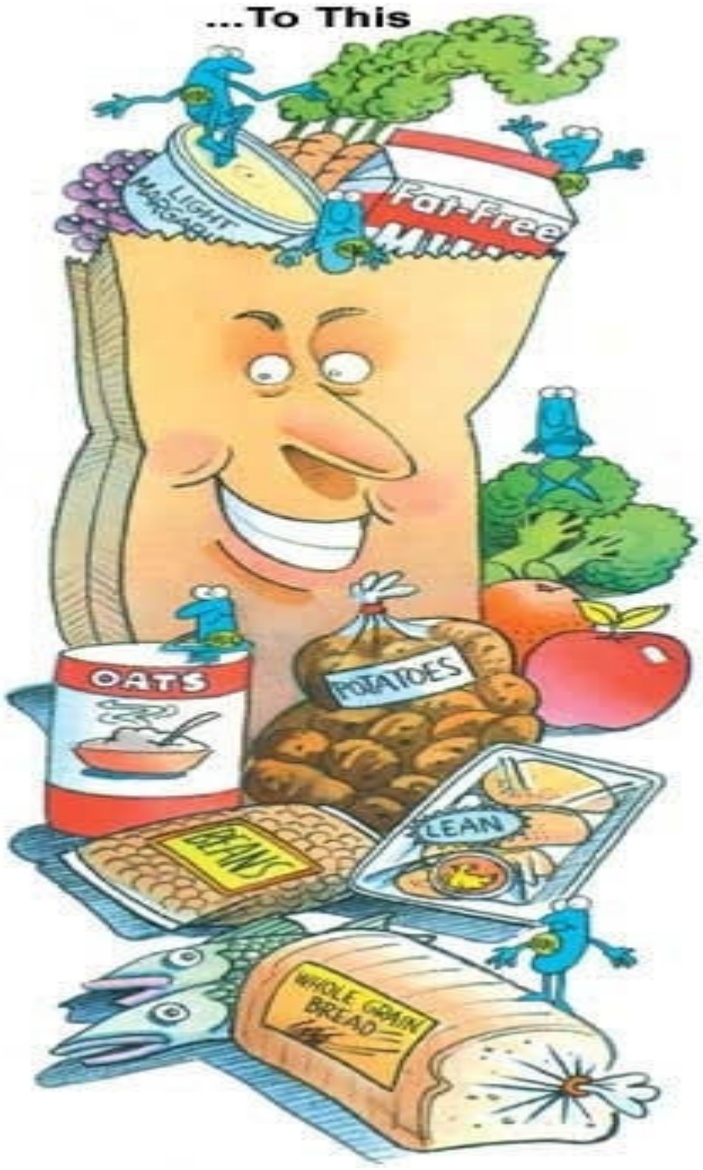
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Summary To Prevent

- **Eat right**
- **Watch your weight** -even a modest drop in weight can make a difference
- **Be Active** - start a program of light exercise for at least 30-45 minutes every day
- **Lower your stress levels**. Practice stress reduction techniques
- **Stop smoking and drinking alcohol**
- **Be Spiritual**





Avoid
Unhealthy eating

Promote
Healthy eating

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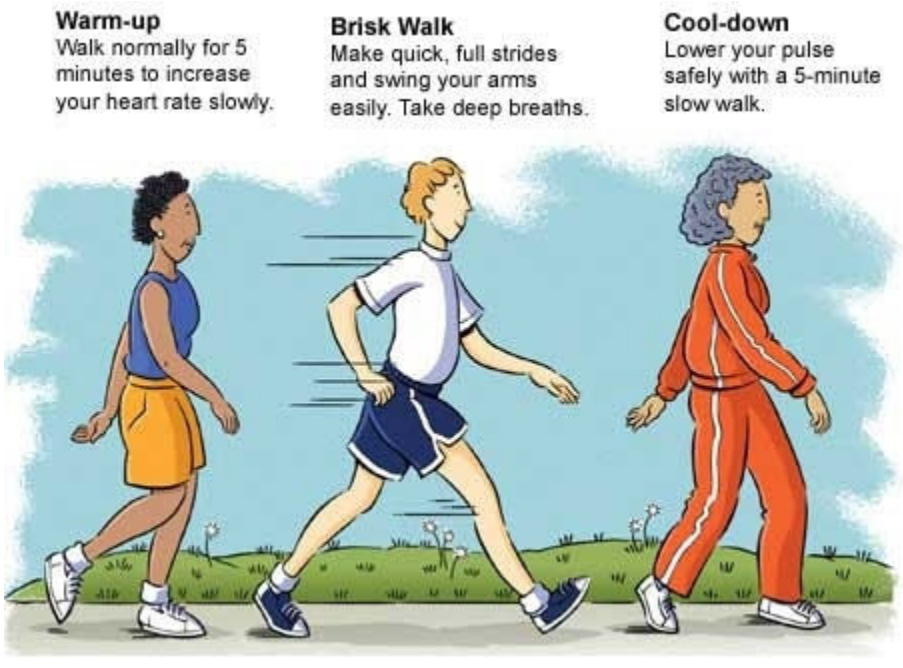
Relaxation



Visit your doctor regularly



Check your weight



Exercise regularly



Balance intake with output

Inborn Errors Of Lipid Metabolism

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Inborn Error Of Lipid Metabolism	Enzyme Deficient/ Defect	Abnormal Accumulation Of
Sudden Infant Death Syndrome (SIDS)	**Acyl CoA Dehydrogenase**	Acyl CoAs
Refsums Disease	**α-Phytanic Acid Oxidase**	Phytanic Acid
Zellwegers Syndrome	**Peroxisomal β Oxidation**	VLCFAs in Peroxisomes

Inborn Error Lipid Storage Disorders	Enzyme Defect	Abnormal Accumulation Of
Niemann Picks Disease	**Sphingomyelinase**	Sphingomyelin in Liver and Spleen
Tay Sachs Disease	**Hexoseaminidase Defect**	**Gangliosides in Tissues**
Gaucher's Disease	**Beta Glucosidase**	**Glucosides in Tissues**

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Inborn Error	Enzyme Defect	Abnormal Accumulation Of
Krabbe's Disease	**Beta Galactosidase**	Galactocerebroside
Farbers Disease	**Ceramidase**	Ceramides

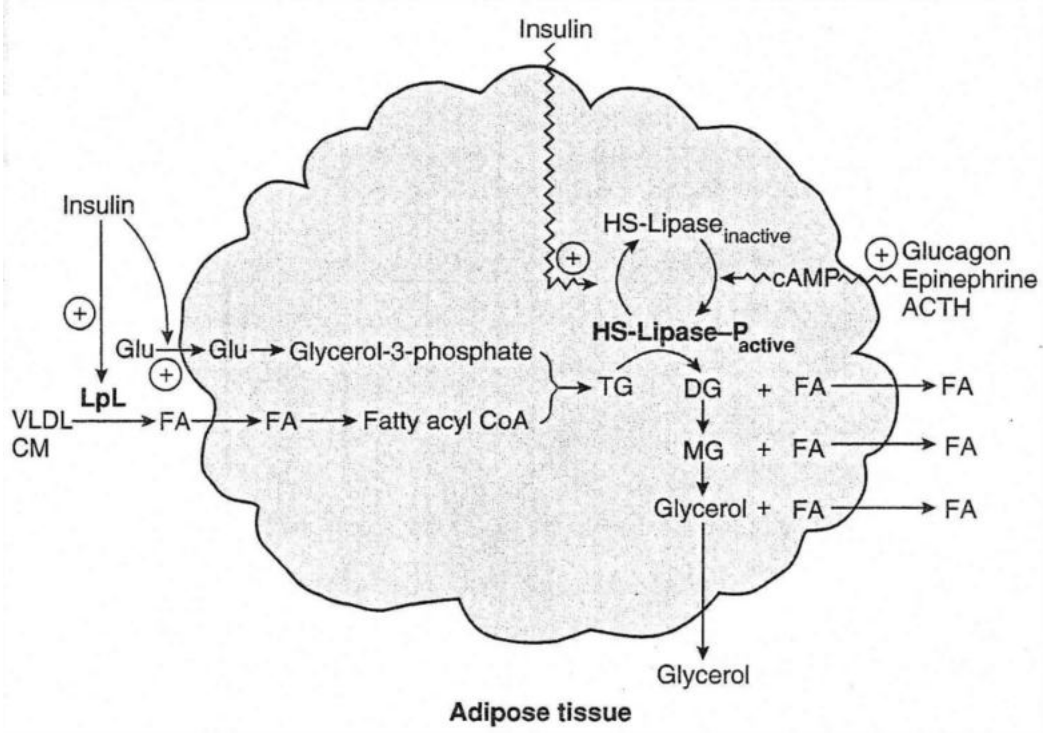
Disease	Defective Enzyme[a]	Accumulated Intermediate
GM_1 gangliosidosis	1 β-Galactosidase	GM_1 ganglioside
Tay–Sachs disease	2 β-*N*-Acetylhexosaminidase A	GM_2 (Tay–Sachs) ganglioside
Fabry's disease	3 α-Galactosidase A	Trihexosylceramide
Gaucher's disease	4 β-Glucosidase	Glucosylceramide
Niemann–Pick disease	5 Sphingomyelinase	Sphingomyelin
Farber's lipogranulomatosis	6 Ceramidase	Ceramide
Globoid cell leukodystrophy (Krabbe's disease)	7 β-Galactosidase	Galactosylceramide
Metachromatic leukodystrophy	8 Arylsulfatase A	3-Sulfogalactosyl-ceramide
Sandhoff disease	9 *N*-Acetylhexosaminidases A and B	GM_1 ganglioside and globoside

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Role Of Insulin In Lipid Metabolism

- **Insulin**
- **Stimulates LPL**
  - increased uptake of FA from Chylomicrons and VLDL
- **Stimulates Glycolysis**
  - increased glycerol phosphate synthesis
  - increases esterification
- **Induces HSL-phosphatase**
  - inactivates HSL
  - Inhibits Lipolysis
- **Net effect: TG storage**



- **Lack of Insulin**

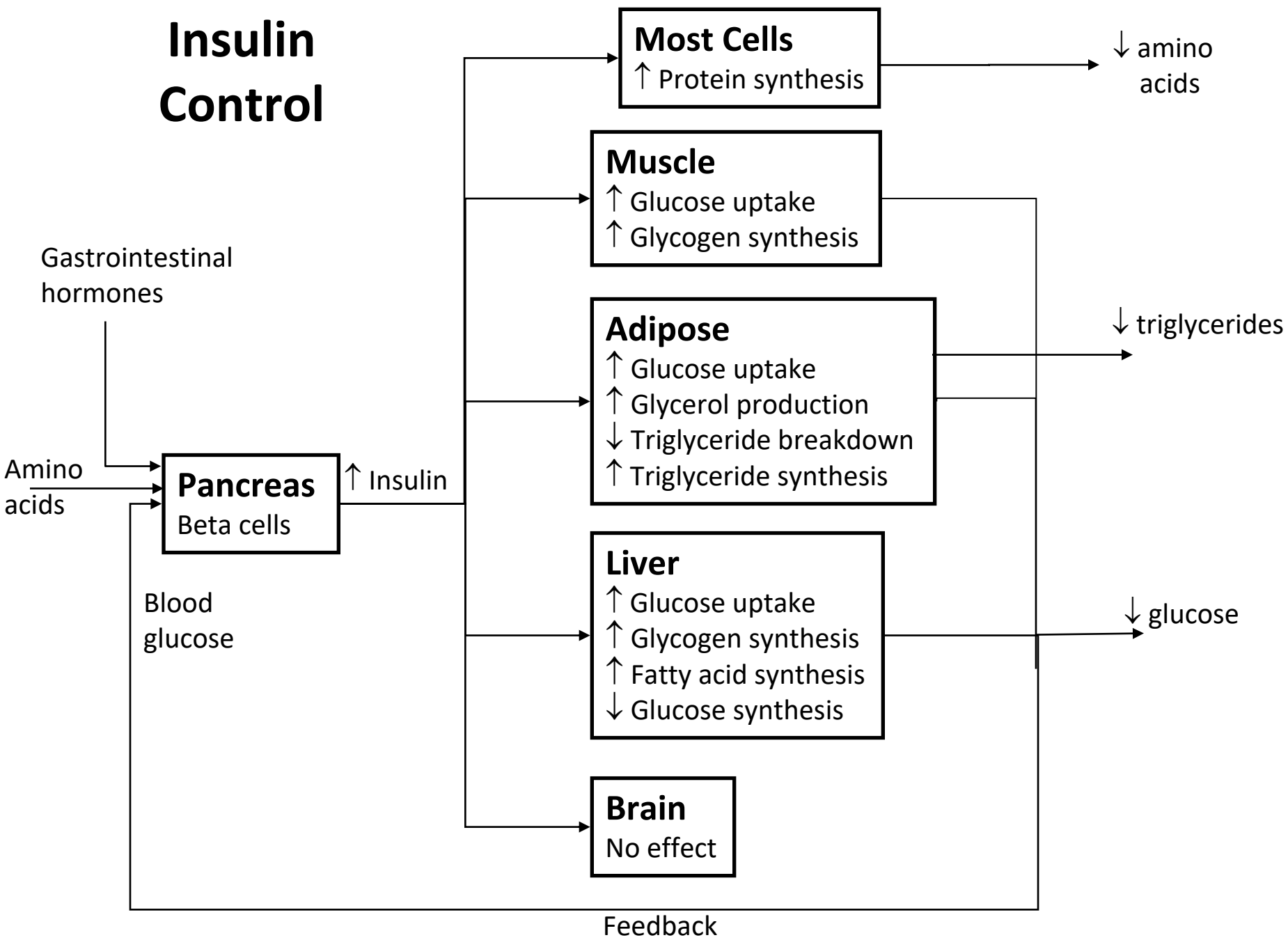
–Free Fatty acids build up in blood

–Can lead to excess Acetoacetic acid production and buildup of acetone (acidosis, which can lead to blindness and coma)

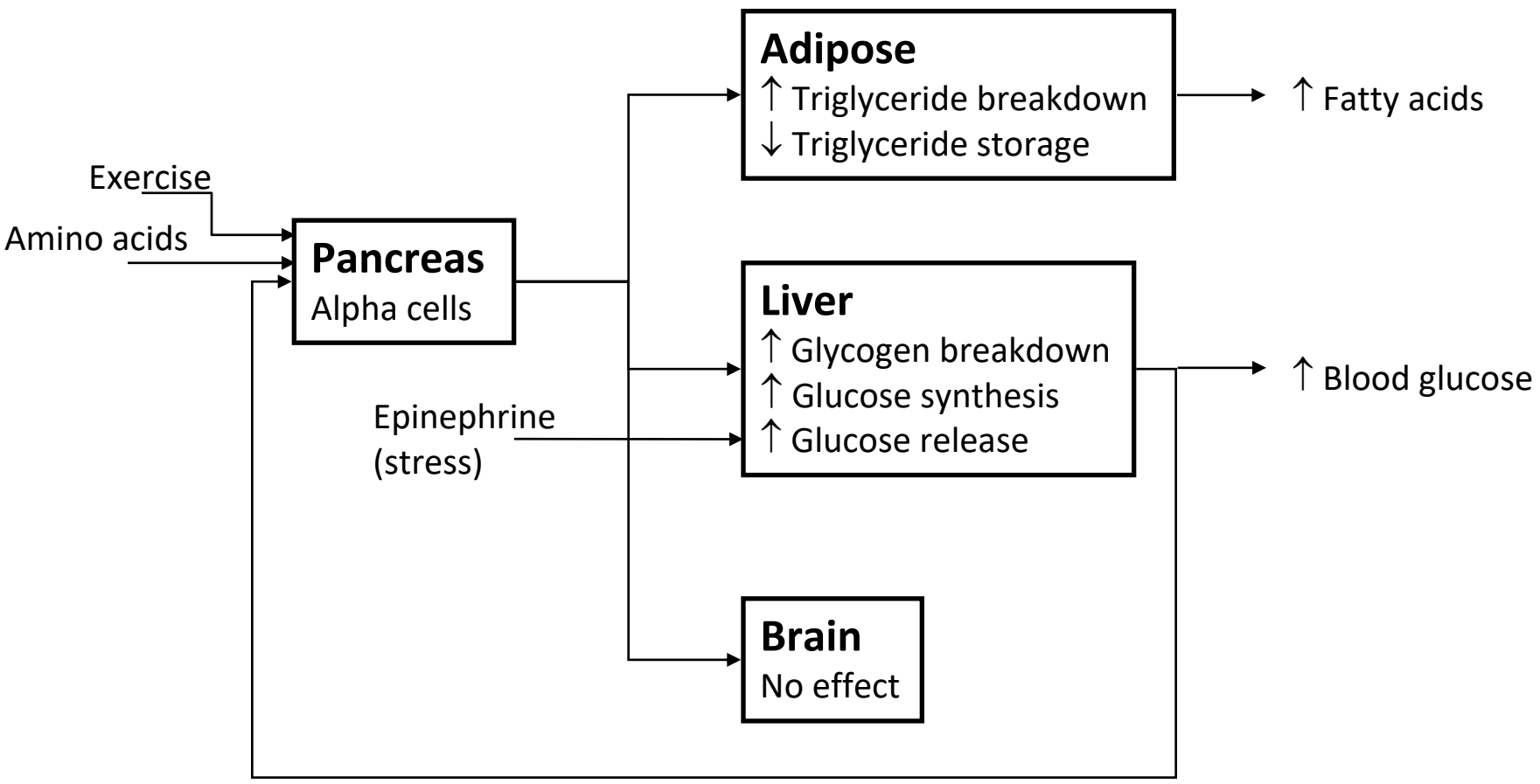
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Insulin Control

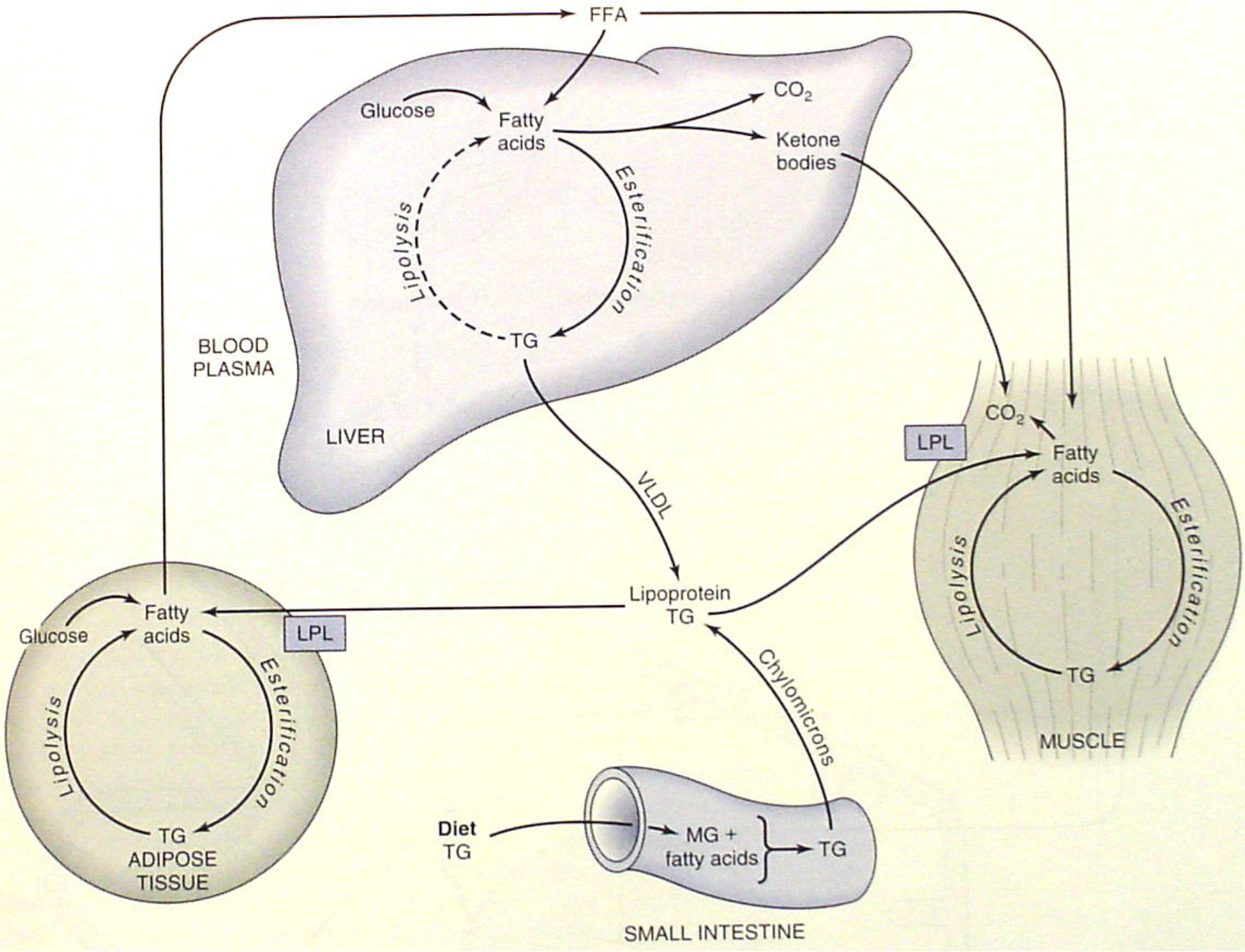


Glucagon Control



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Types Of Lipases

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S. No	Type Of Lipase	Location Action Upon
1	Lingual Lipase	**Mouth** Dietary TAG (Insignificant Action)
2	Gastric Lipase	**Stomach** Dietary TAG (Insignificant Action)
3	Pancreatic Lipase	**Small Intestine** Dietary TAG (Significant Action)

S. No	Type Of Lipase	Location Action
4	Lipoprotein Lipase	**Endothelial Lining** Of Blood Vessels Lipoprotein TAG
5	Hormone Sensitive Lipase	**Adiposecytes** Hydrolyzes Stored TAG
6	Hepatic Lipase	Liver TAG
7	~~Phopshpholipase A2~~	~~Small Intestine~~ Phospholipids

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Questions

Q.1. Describe in details the **digestion & absorption of dietary** form of lipids & add a note on Steatorrhoea

OR

Q.1.What are **different forms of dietary lipids**? How the **dietary lipids** are **digested & absorbed in G.I.T** ?

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Q.2. What are the different modes of oxidation of fatty acids in the body? Give **β-oxidation of even chain fatty acid.**

OR

Q.2. Define β -oxidation of fatty acid. Explain the **oxidation of Palmitate and calculate** its energetics./Fate of fatty acids in human body?

OR

Q.2. Explain **β -oxidation of odd chain fatty acids.**

Q.3. **What is Lipogenesis**? Describe in details the **De-novo synthesis of fatty acid.**

OR

Q.3. Explain the **Extra mitochondrial synthesis of Palmitate.**

Q.4. What is **ketoacidosis? Give fate & formation ketone bodies**.

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- **Short Notes**

- **Transport & storage of lipids** / Role lipoproteins.
- **Emulsification & its significance** / Role of Bile salts in digestion & absorption of lipid.
- Lipolysis **/ Role of Hormone Sensitive Lipase**/Adipose tissue metabolism.

- Clearing factor / **Lipoprotein lipase.**
- **Multi-enzyme complex** of Fatty acid biosynthesis / **Fatty acid synthesis complex.**
- Microsomal synthesis of fatty acid.
- **Fatty liver /Lipotropic factors.**

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- **Cholesterol-outline of Biosynthesis**.
- **Hypercholesterolemia** – causes & consequences
- Atherosclerosis
- Myocardial Infarction
- Enumerate the Inborn errors related to lipid metabolism.
- Transport & Excretion of Cholesterol/ Reverse transport of cholesterol.

- Fate & formation of Acetyl–CoA
- Fate of Propionyl-CoA
- Role of Carnitine in Lipid metabolism
- Role of Liver in Lipid metabolism.
- TAG metabolism.

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- Ketonemia & Ketonuria
- Represent the schematic structure of lipoprotein.
- Role of Citrate in lipid metabolism.
- Role of Carnitine in lipid metabolism.
- Hormonal Influence in Lipid Metabolism

- Catabolism of Cholesterol.
- CETP activity
- HDL2 and HDL 3
- Zellweger & Refsum’s disease.
- Mixed Micelle
- Four types of Lipoproteins & their role
- Hyperlipoproteinemias
- Hypolipoproteinemia's
- Different types of Lipases & their action.

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