

Organization of cells

- Eukaryotic cells contain well defined cellular organelles such as:
 - Nucleus
 - Mitochondria
 - Endoplasmic reticulum
 - Golgi apparatus
 - Peroxisomes
 - lysosomes

MITOCHONDRIA

- In electron micrographs of cells, mitochondria appears as – rods, spheres or filamentous bodies.
- Size: $0.5\mu\text{m}$ - $1\mu\text{m}$ in diameter
up to $7\mu\text{m}$ in length.

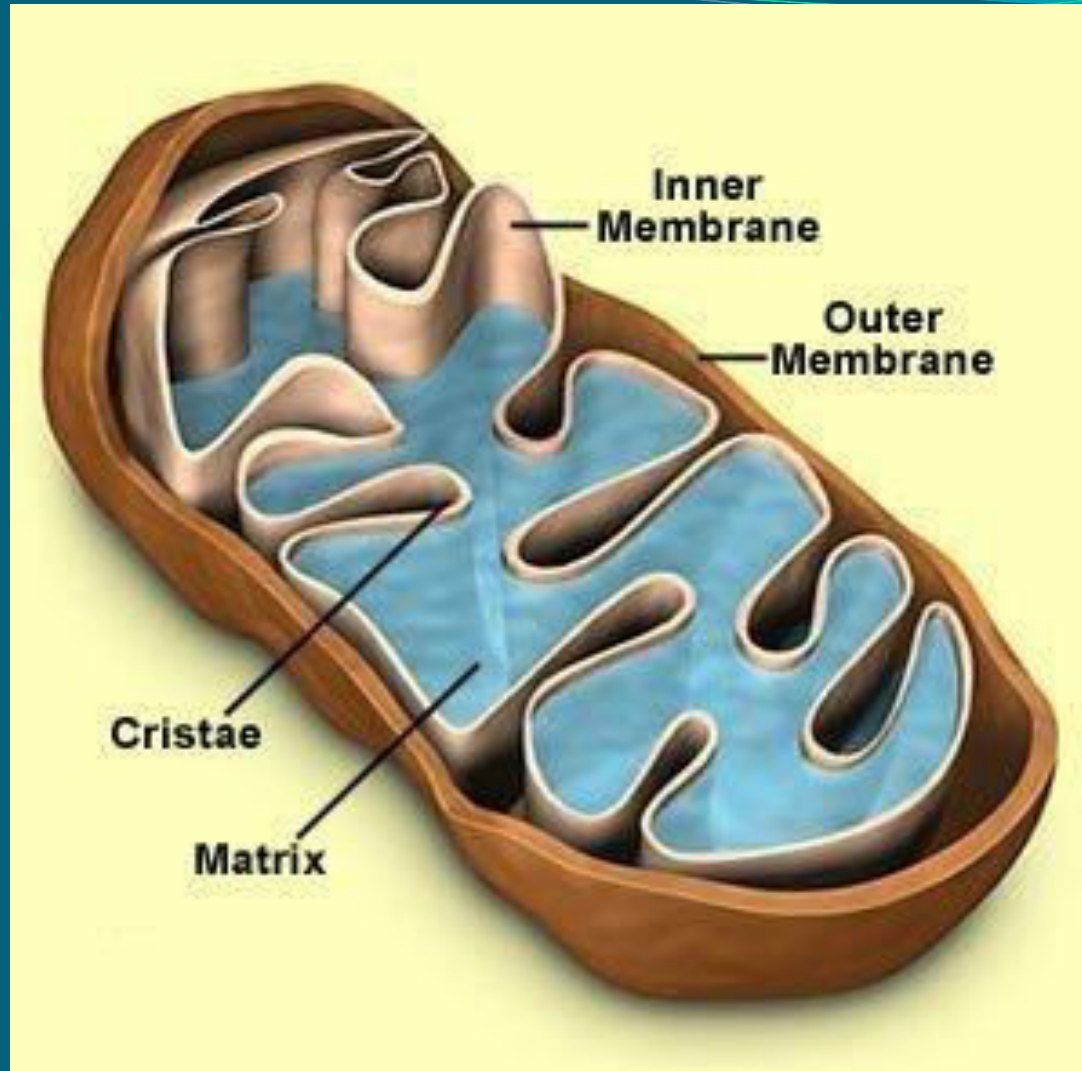
FEATURES

- Mitochondria has got an inner membrane and an outer membrane. The space between these two is called intermembranous space.
- Inner membrane convolutes into cristae and this increases its surface area.
- Both the membranes have different appearance and biochemical functions:

Biomedical importance

Inner membrane:

- It surrounds the matrix.
- It contains components of electron transport system.
- It is impermeable to most ions including H, Na, ATP, GTP, CTP etc and to large molecules.
- For the transport special carriers are present e.g. adenine nucleotide carrier(ATP –ADP transport).
- Complex II i.e. Succinate dehydrogenase .
- Complex V i.e. ATP synthase complex.



Outer membrane:

It is permeable to most ions and molecules which can move from the cytosol to intermembranous space.

Matrix:

- It is enclosed by the inner mitochondrial membrane.
- Contains enzymes of citric acid cycle.

- Enzymes of β -oxidation of fatty acids.
- Enzymes of amino acids oxidation.
- Some enzymes of urea and heme synthesis.
- NAD
- FAD
- ADP, Pi.
- Mitochondrial DNA.
- Mitochondrial cytochrome P₄₅₀ system- it causes:

- a. Hydroxylation of cholesterol to steroid hormones (placenta, adrenal cortex, ovaries and testes)
- b. Bile acid synthesis (liver)
- c. Vitamin D formation(kidney).

- Mitochondria plays a key role in aging-
Cytochrome c component of ETC plays a main role in cell death and apoptosis.
- Mitochondria have a role in its own replication- they contain copies of circular DNA called mitochondrial DNA, this DNA have information for 13 mitochondrial proteins and some RNAs. This is DNA inherited from mothers.

- Most mitochondrial proteins are derived from genes in nuclear DNA.
- Mutation rate in mt DNA is 10 times more.
- Mitochondrial Diseases:
 - i. Fatal infantile mitochondrial myopathy and renal dysfunction
 - ii. MELAS(mitochondrial encephalopathy, lactic acidosis and stroke).

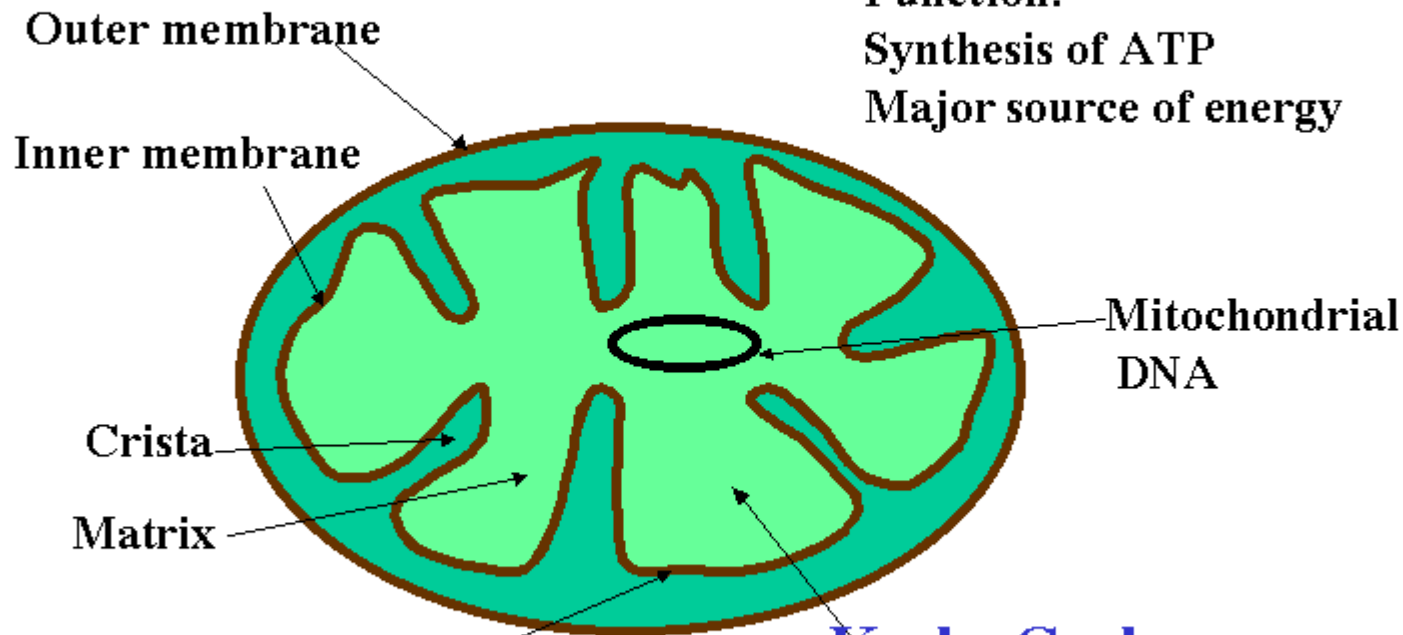
- i. Lebers hereditary optic neuropathy
- ii. Myoclonic epilepsy
- iii. Ragged red fiber disease.

- Also implicated in:

Alzheimer's disease, Parkinson's , Cardiomyopathies and diabetes.

Mitochondria

Function:
Synthesis of ATP
Major source of energy



Electron transport chain

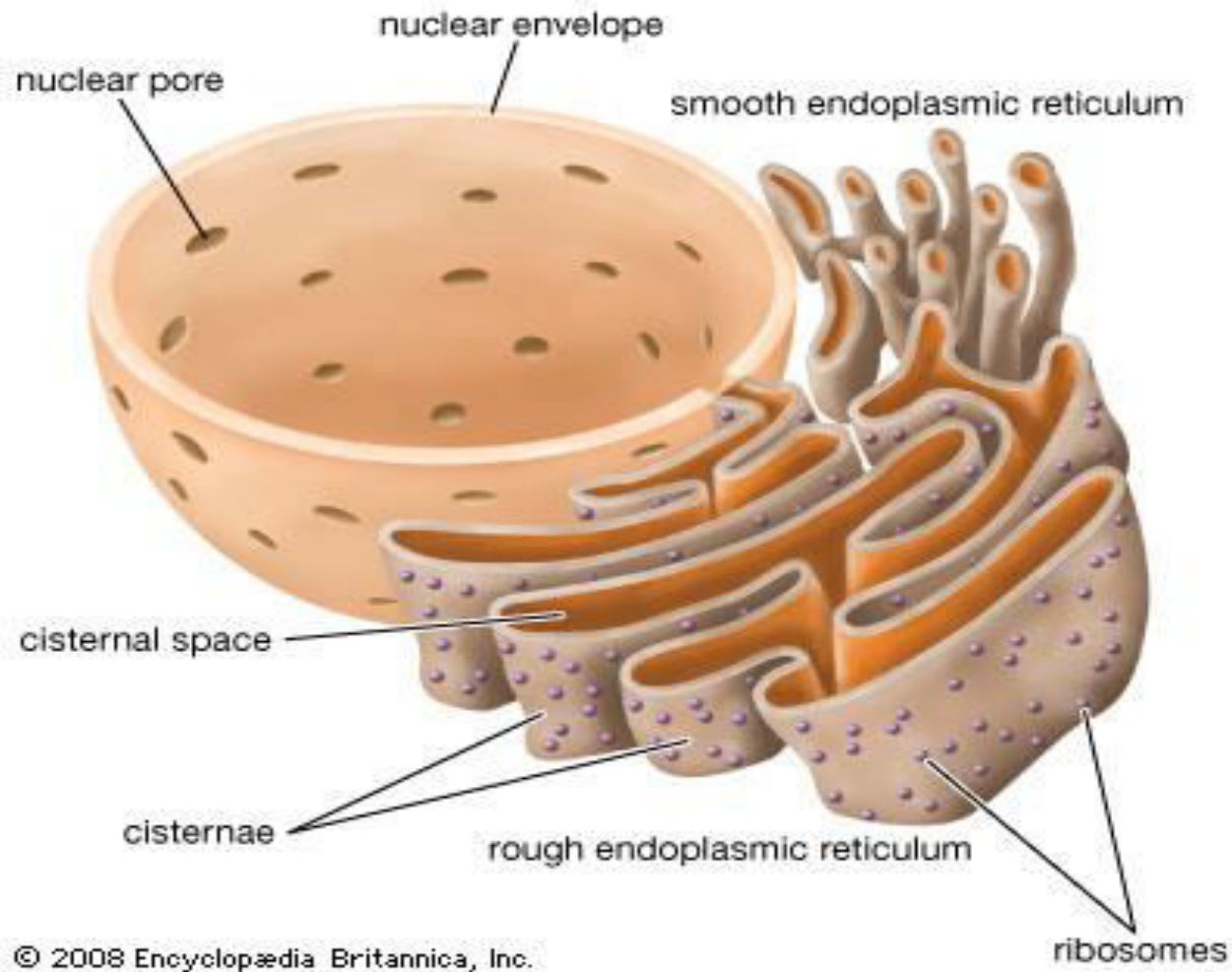
Krebs Cycle



ENDOPLASMIC RETICULUM

- Cytoplasm of eukaryotic cells contain a network of interconnecting membranes. This extensive structure is called endoplasmic reticulum.
- It consists of membranes with smooth appearance in some areas and rough appearance in some areas-
Smooth endoplasmic reticulum and rough endoplasmic reticulum.

Endoplasmic reticulum



Biomedical importance

Rough Endoplasmic Reticulum

- These membranes enclose a lumen.
- In this lumen newly synthesized proteins are modified.
- Rough appearance is due to the presence of ribosomes attached on its cytosolic side(outer side).
- These ribosomes are involved in the biosynthesis of proteins.

- These proteins are either incorporated into the membranes or into the organelles.
- Special proteins are present that are called CHAPERONES. These proteins play a role in proper folding of proteins.
- Protein glycosylation also occurs in ER i.e. the carbohydrates are attached to the newly synthesized proteins.

Smooth Endoplasmic Reticulum

- Smooth endoplasmic reticulum is involved in lipid synthesis.
- Cholesterol synthesis
- Steroid hormones synthesis.
- Detoxification of endogenous and exogenous substances.
- The enzyme system involved in detoxification is called Microsomal Cytochrome P₄₅₀ monooxygenase system(xenobiotic metabolism).

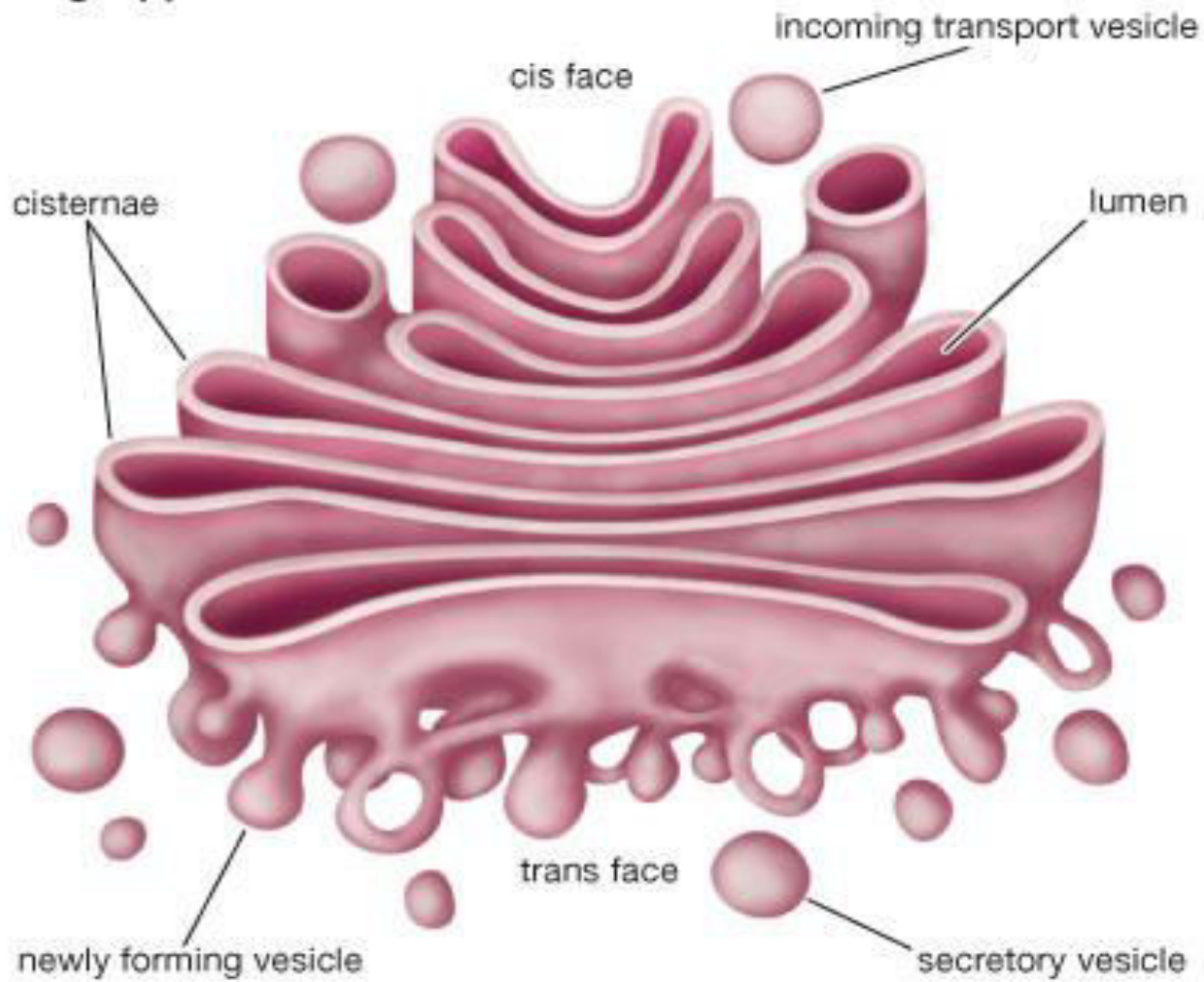
- ER along with Golgi apparatus is involved in the synthesis of other organelles –lysosomes & Peroxisomes.
- Elongation of fatty acids e.g. Palmitic acid 16 C-
Stearic acid 18 C.
- Desaturation of fatty acids.
- Omega oxidation of fatty acids.



GOLGI APPARATUS

- Golgi complex is a network of flattened smooth membranous sacs- cisternae and vesicles.
- These are responsible for the secretion of proteins from the cells(hormones, plasma proteins, and digestive enzymes).
- It works in combination with ER.

Golgi apparatus

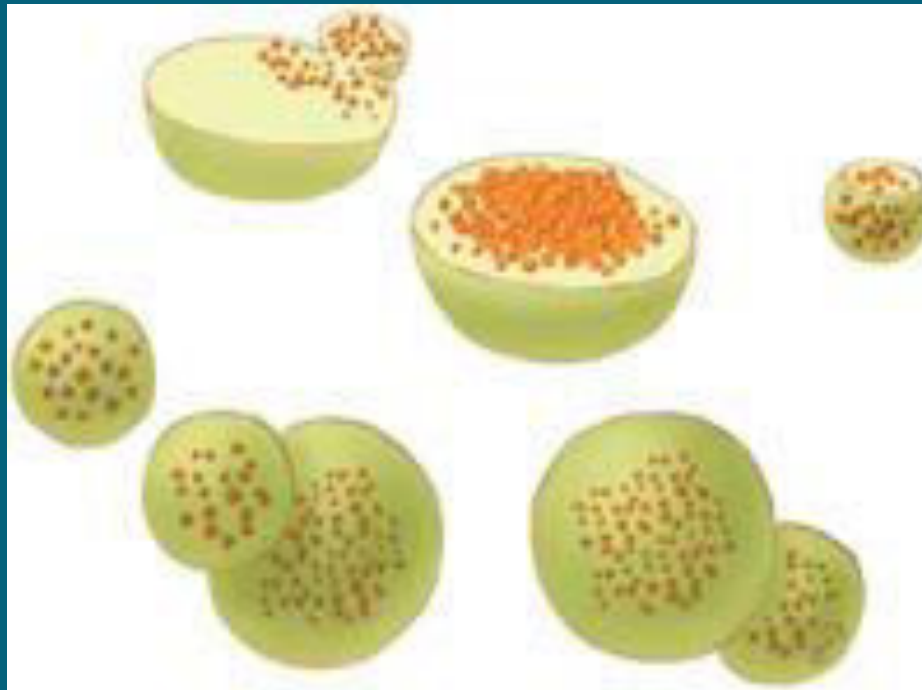


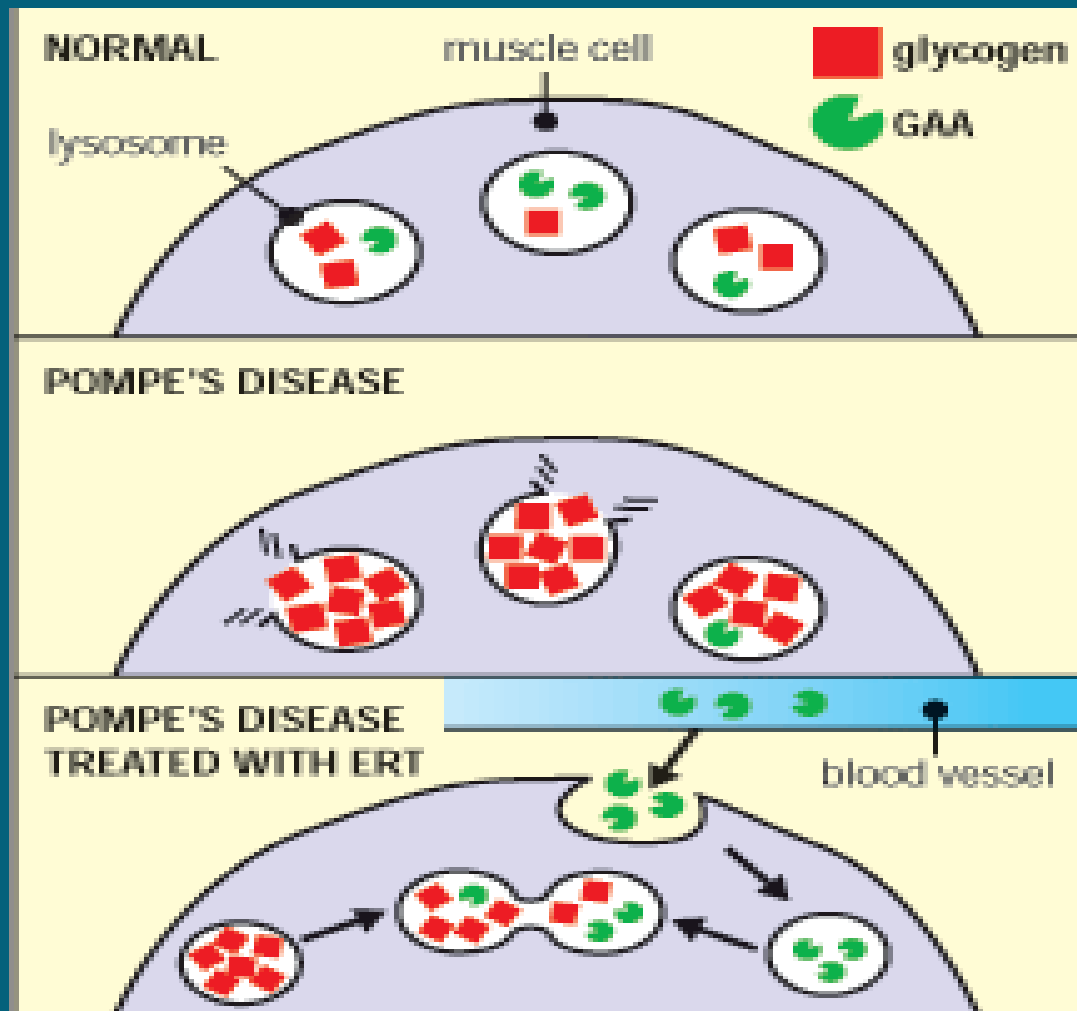
- Enzymes in golgi complex transfer carbohydrate units to proteins to form of glycoporoteins, this determines the ultimate destination of proteins.
- Golgi is the major site for the synthesis of new membrane, lysosomes and peroxisomes.
- It plays two major roles in the membrane synthesis:

- i. It is involved in the processing of oligosaccharide chains of the membranes (all parts of the GA participates).
- ii. It is involved in the sorting of various proteins prior to their delivery(Trans Golgi network).

LYSOSOMES

- These are responsible for the intracellular digestion of both intra and extracellular substances.
- They have a single limiting membrane.
- They have an acidic pH- 5
- They have a group of enzymes called Hydrolases.





Biomedical importance

- The enzyme content varies in different tissues according to the requirement of tissues or the metabolic activity of the tissue.
- Lysosomal membrane is impermeable and specific translocators are required.
- Vesicles containing external material fuses with lysosomes, form primary vesicles and then secondary vesicles or digestive vacuoles.
- Lysosomes are also involved in autophagy.

- Products of lysosomal digestion are released and reutilised.
- Indigestible material accumulates in the vesicles called residual bodies and their material is removed by exocytosis.
- Some residual bodies in non dividing cells contain a high amount of a pigmented substance called Lipofuscin.
- Also called age pigment or wear –tear pigment.

- In some genetic disease individual lysosomal enzymes are missing and this lead to the accumulation of that particular substance.
- Such lysosomes gets enlarged and they interfere the normal function of the cell.
- Such diseases are called lysosomal storage diseases
- Most impt is I-cell disease.

PEROXISOMES

- Called Peroxisomes because of their ability to produce or utilize H_2O_2 .
- They are small, oval or spherical in shape.
- They have a fine network of tubules in their matrix.
- About 50 enzymes have been identified.
- The number of enzymes fluctuates according to the function of the cells.

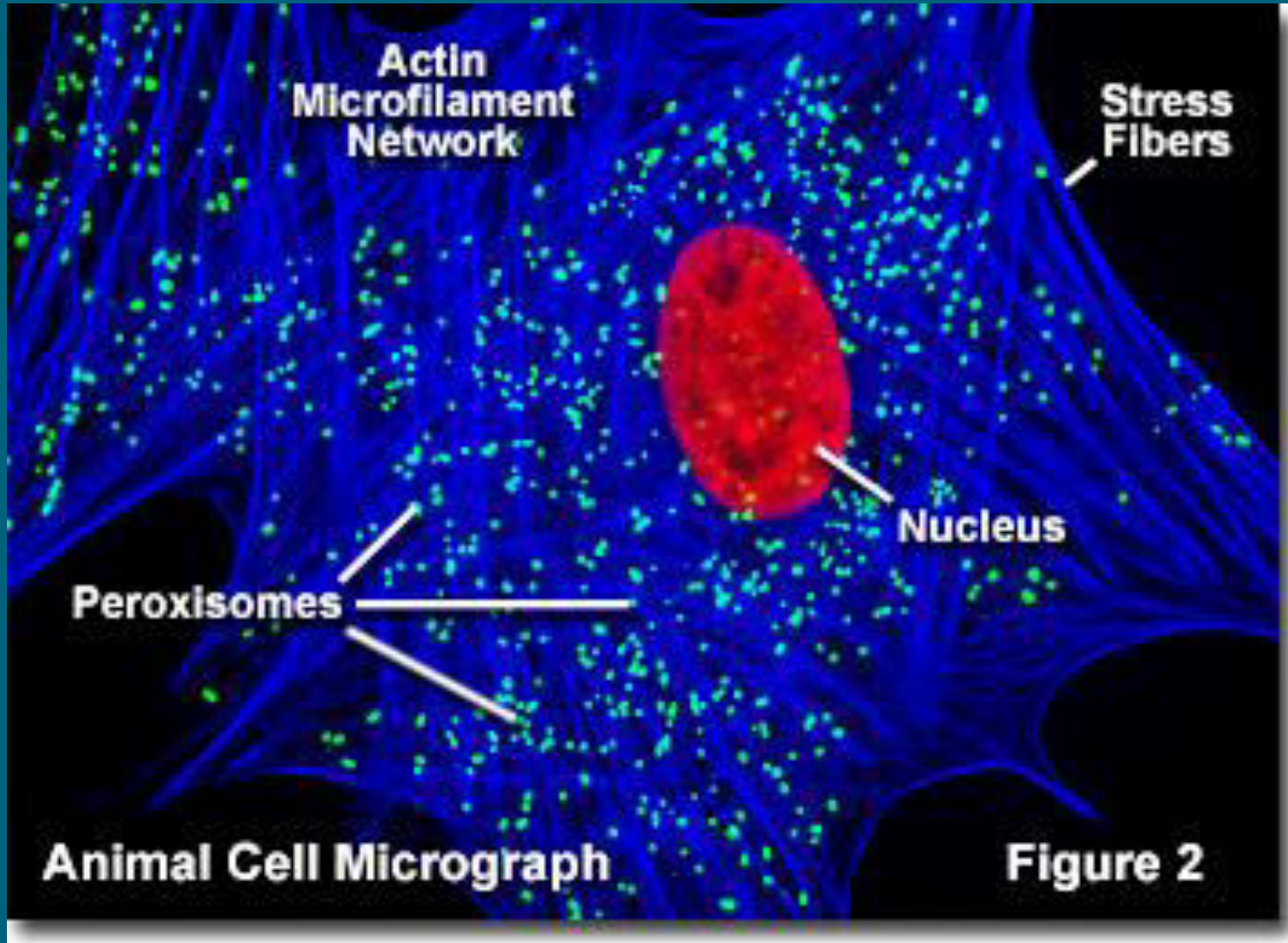
Biomedical importance

- Xenobiotics leads to the proliferation of Peroxisomes in the liver.
- Have an important role in the breakdown of lipids, particularly long chain fatty acids.
- Synthesis of glycerolipids.
- Synthesis of glycerol ether lipids.
- Synthesis of isoprenoids.
- Synthesis of bile.

- Oxidation of D- amino acids.
- Oxidation of Uric acid to allantoin (animals)
- Oxidation of Hydroxy acids which leads to the formation of H_2O_2 .
- Contain catalase enzyme, which causes the breakdown of H_2O_2 .

- Diseases associated:

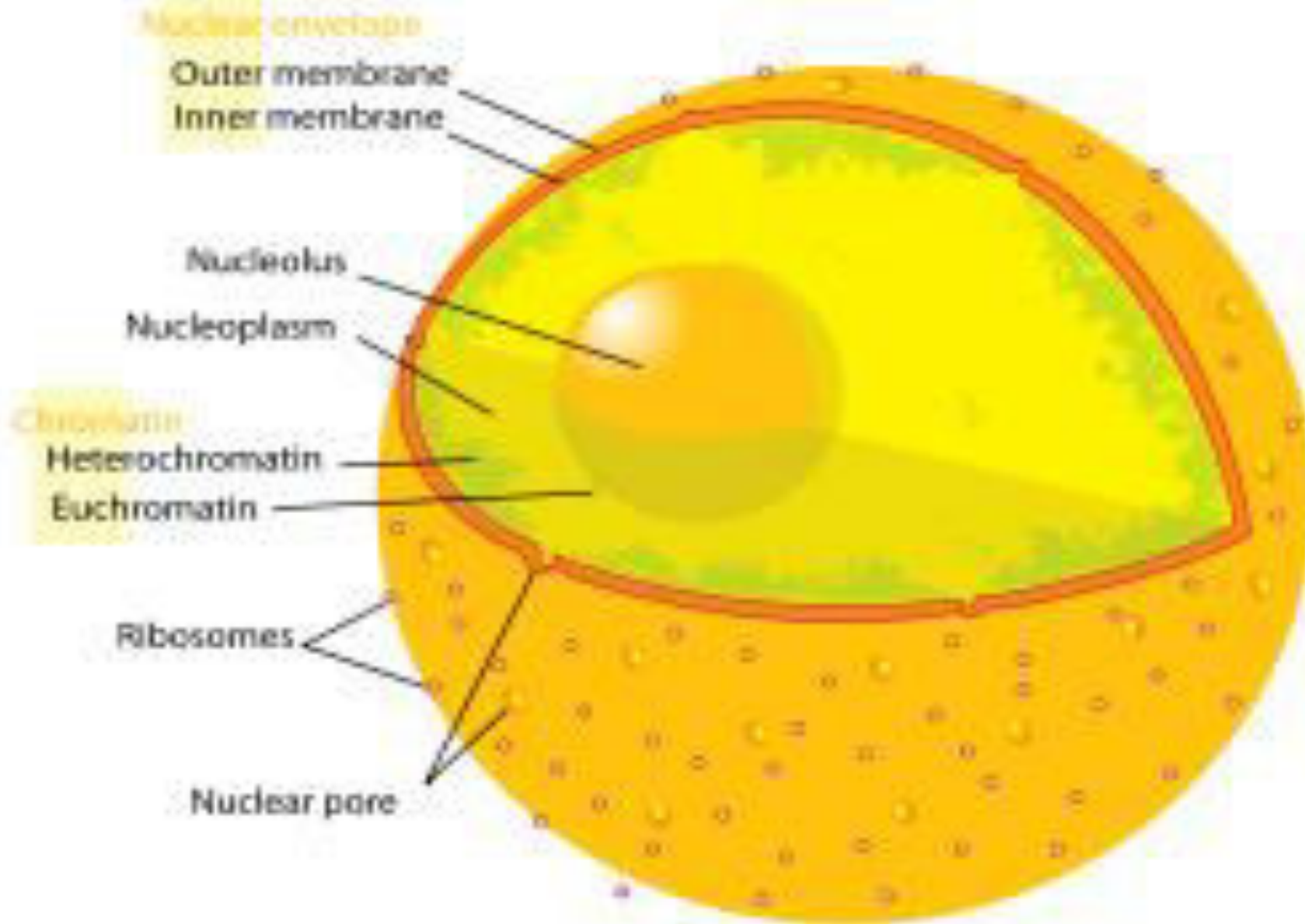
Most important disease is Zellweger Syndrome. There is absence of functional peroxisomes. This leads to the accumulation of long chain fatty acids in the brain, decreased formation of plasmalogens, and defects of bile acid formation.



NUCLEUS

- The nucleus is the largest cellular organelle in animals. In mammalian cells, the average diameter of the nucleus is approximately 6 micrometers (μm), which occupies about 10% of the total cell volume. The viscous liquid within it is called nucleoplasm, and is similar in composition to the cytosol found outside the nucleus. It appears as a dense, roughly spherical organelle.

- Eukaryotic cells contain a nucleus.
- It has got two membranes- nuclear envelope.
- Outer membrane is continuous with the membrane of endoplasmic reticulum.
- Nuclear envelope has numerous pores. That permit controlled movement of particles and molecules between the nuclear matrix and cytoplasm.



The Cell Nucleus

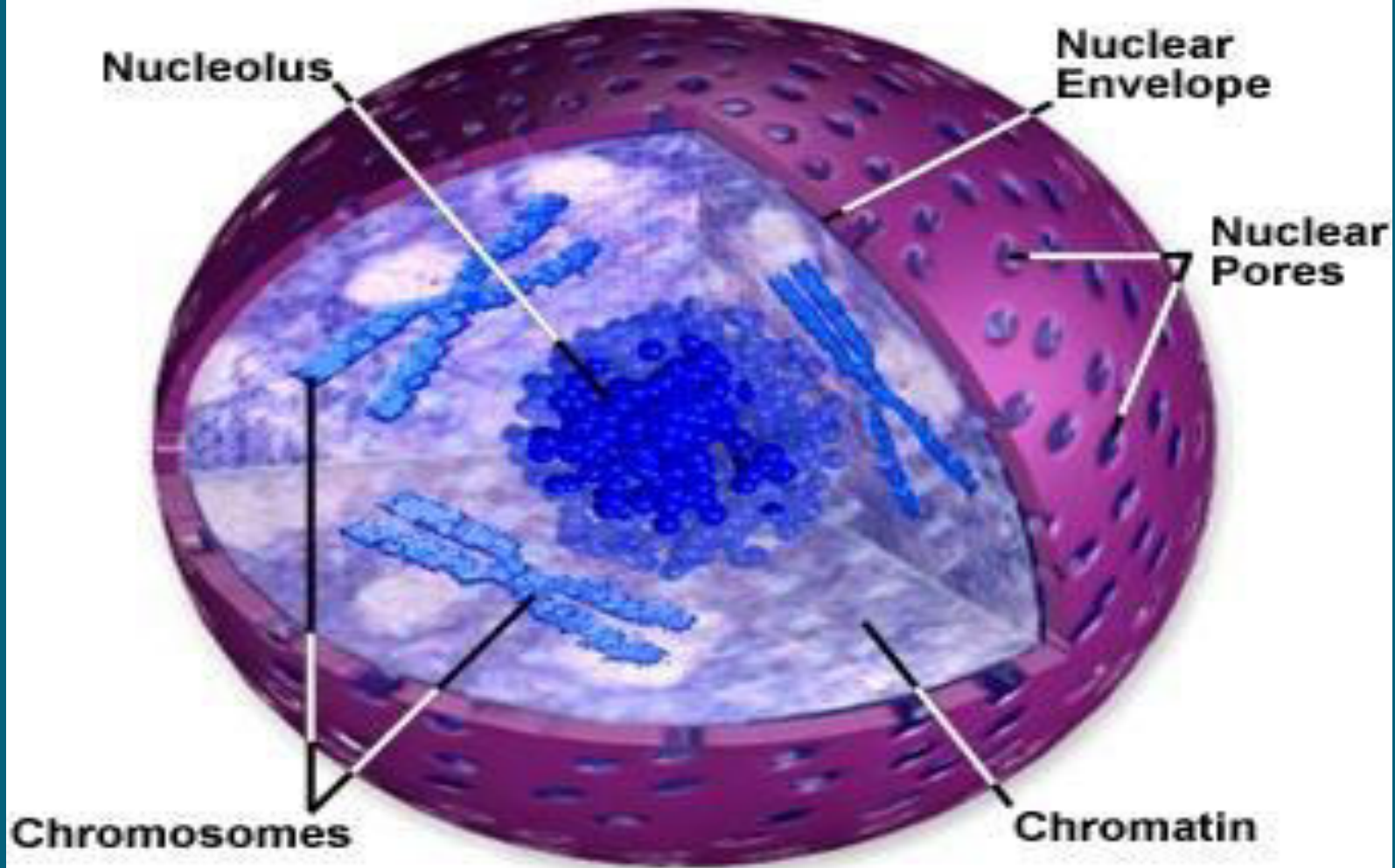


Figure 1

- Most proteins, ribosomal subunits, and some RNAs are transported through the pore complexes in a process mediated by a family of transport factors known as karyopherins. Those karyopherins that mediate movement into the nucleus are also called importins, while those that mediate movement out of the nucleus are called exportins.
- The space between the membranes is called the Perinuclear space and is continuous with the RER lumen.
- the nuclear lamina, a meshwork within the nucleus that adds mechanical support, much like the cytoskeleton supports the cell as a whole.

- Nucleus has got a major sub compartment- **nucleolus**.
- **Deoxyribonucleic acid (DNA)** is located in the nucleus. It is the repository of genetic information.
- Present as DNA- protein complex – **Chromatin**, which is organized into chromosomes.
- A typical human cell contains 46 chromosomes.
- To pack it effectively it requires interaction with a large number of proteins. These are called histones.
- They order the DNA into basic structural unit called Nucleosomes. Nucleosomes are further arranged into more complex structures called chromosomes

- CHROMATIN:
- It is the substance of chromosomes and each chromosome represents the DNA in a condensed form. It is the combination of DNA and proteins. These proteins are called histones.
- There are five classes of histones- H₁, H₂A, H₂B, H₃, H₄. These proteins are positively charged and they interact with negatively charged DNA.
- Two molecules each of H₂A, H₂B, H₃ and H₄ form the structural core of the nucleosome. Around this core the segment of DNA is wound nearly twice. Neighboring nucleosomes are joined by linker DNA. H₁ is associated with linker DNA

Biomedical importance

- Nucleus contains the biochemical processes involved in the **Replication of DNA** before mitosis.
- Involved in the **DNA repair**.
- **Transcription of DNA** – RNA synthesis.
- **Translation of DNA**- Protein synthesis.
- NUCLEOLUS- involved in the processing of rRNA and ribosomal units
- After being produced in the nucleolus, ribosomes are exported to the cytoplasm where they translate mRNA.

- Antibodies to certain types of chromatin organization, particularly nucleosomes, have been associated with a number of autoimmune diseases, such as systemic lupus erythematosus, multiple sclerosis. These are known as anti-nuclear antibodies (ANA).

Gene expression

- Gene expression first involves transcription, in which DNA is used as a template to produce RNA. In the case of genes encoding proteins, that RNA produced from this process is messenger RNA (mRNA), which then needs to be translated by ribosomes to form a protein. As ribosomes are located outside the nucleus, mRNA produced needs to be exported.

- Polynucleated cells contain multiple nuclei.
- In humans, skeletal muscle cells, called myocytes, become polynucleated during development; the resulting arrangement of nuclei near the periphery of the cells allows maximal intracellular space for myofibrils.
- Multinucleated cells can also be abnormal in humans; for example, cells arising from the fusion of monocytes and macrophages, known as giant multinucleated cells, sometimes accompany inflammation and are also implicated in tumor formation.

- Since the nucleus is the site of transcription, it also contains a variety of proteins which either directly mediate transcription or are involved in regulating the process. These proteins include helicases that unwind the double-stranded DNA molecule to facilitate access to it.

- RNA polymerases that synthesize the growing RNA molecule, topoisomerases that change the amount of supercoiling in DNA, helping it wind and unwind, as well as a large variety of transcription factors that regulate expression.

Processing of pre-mRNA

- Newly synthesized mRNA molecules are known as primary transcripts or pre-mRNA. They must undergo post-transcriptional modification in the nucleus before being exported to the cytoplasm.

- mRNA that appears in the nucleus without these modifications is degraded rather than used for protein translation.
- The three main modifications are 5' Capping, 3' Polyadenylation, and RNA splicing.

Nuclear transport

- Macromolecules, such as RNA and proteins, are actively transported across the nuclear membrane in a process called the Ran-GTP nuclear transport cycle.

- The entry and exit of large molecules from the nucleus is tightly controlled by the nuclear pore complexes. Although small molecules can enter the nucleus without regulation, macromolecules such as RNA and proteins require association karyopherins called importins to enter the nucleus and exportins to exit.

- Cargo proteins that must be translocated from the cytoplasm to the nucleus contain short amino acid sequences known as nuclear localization signals which are bound by importins, while those transported from the nucleus to the cytoplasm carry nuclear export signals bound by exportins.

- **Assembly and disassembly**
- During its lifetime a nucleus may be broken down, either in the process of cell division or as a consequence of apoptosis, a regulated form of cell death. During these events, the structural components of the nucleus—the envelope and lamina—are systematically degraded.

- **Anucleated and polynucleated cells**
- Although most cells have a single nucleus, some eukaryotic cell types have no nucleus, and others have many nuclei. This can be a normal process, as in the maturation of mammalian red blood cells, or a result of faulty cell division.

- Anucleated cells contain no nucleus and are therefore incapable of dividing to produce daughter cells. The best-known anucleated cell is the mammalian red blood cell, or erythrocyte, which also lacks other organelles such as mitochondria and serves primarily as a transport vessel to ferry oxygen from the lungs to the body's tissues.

- There are two types of chromatin – Euchromatin and Heterochromatin.
- Euchromatin is the less compact DNA form, and contains genes that are frequently expressed by the cell. The other type, heterochromatin, is the more compact form, and contains DNA that are infrequently transcribed.