Department of Biochemistry

Learning Objectives

- One Carbon Metabolism
- Catabolism of the Carbon Skeletons of amino acids and related disorders:

. Alanine, glycine, serine, cysteine, tryptophan, and threonine degraded to pyruvate

. Tryptophan, lysine, phenylalanine, tyrosine, leucine, isoleucine, and threonine degraded to Acetyl-CoA

Enzyme co-factors involved in aa catabolism

Involves one of the three co-factors: Biotin, Tetrahydrofolate (THF) and S-adenosylmethione (SAM)

- These cofactors transfer one-carbon groups in different oxidation states
- Biotin transfers carbon in its most oxidized state CO_2, it require for catabolism and utilization of branched chain aa

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- Tetrahydrofolate transfers one-carbon groups in intermediate oxidation states and as methyl groups
- S-adenosylmethionine transfers methyl groups, the most reduced state of carbon

Tetrahydrobiopterin (BH_4, THB) is a cofactor of the degradation of phenylalanine

One-Carbon Metabolism

- One-carbon (1C) metabolism, mediated by the folate cofactor, supports biosynthesis of purines and pyrimidines, aa homeostasis (glycine, serine and methionine)

- Folate (Vit B9), precursor for formation of THF by dihydrofolate reductase

- THF is active form that carries 1-carbon groups such as formyl, methenyl, methylene and methyl, act as cofactor, imp for nucleic acid and amino acid synthesis

Table 14.4. One-carbon compounds

Group	Structure	Carried by
Formyl	–CHO	N^5–formyl–THFA and N^{10}–formyl–THFA
Formimino	–CH=NH	N^5–formimino–THFA
Methenyl	=CH–	N^5,N^{10}–methenyl–THFA
Hydroxymethyl	$–CH_2OH$	N^{10}–hydroxymethyl THFA
Methylene	$–CH_2–$	N^5,N^{10}–methylene–THFA
Methyl	$–CH_3$	N^5–methyl–THFA and methyl cobalamin

Table 14.4: DM Vasudevan's Textbook of Biochemistry for Medical Students 6th edition

Folate mediated one carbon metabolism

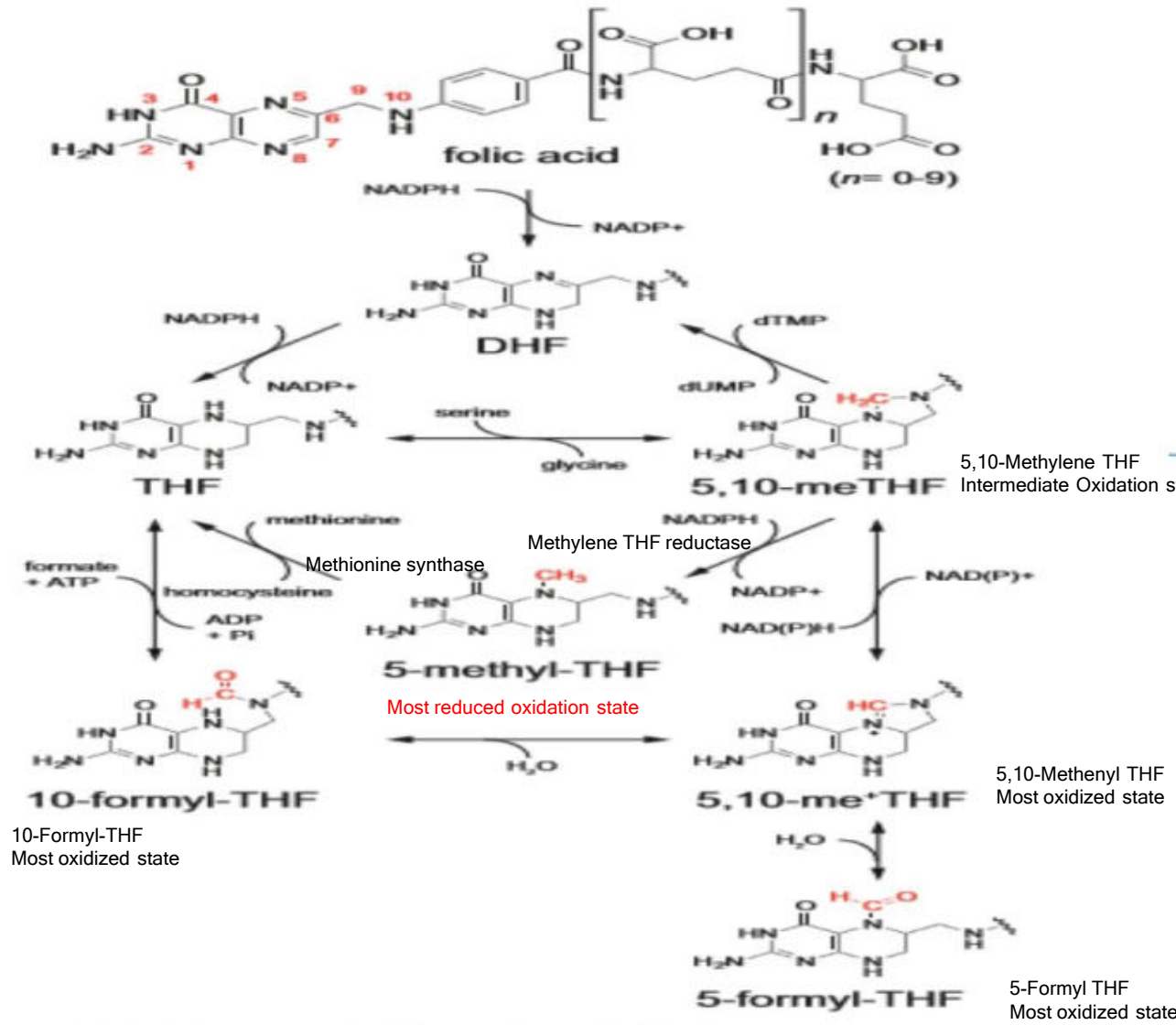

Figure 1. Chemical Transformations of Folates
Folic acid is reduced to THF, which can then accept a 1C unit and undergo a series of oxidative/ reductive transformations. DHF, dihydrofolate; THF, tetrahydrofolate; 5,10-meTHF, 5,10-methylene-THF; 5,10-me+THF, 5,10-methenyl-THF. Gregory S. Ducker and Joshua D Rabinowitz 2017

Folate trap

- Conversion of 5,10-methylen-THF into 5-methyl-THF, by MTHFR (methyl tetrahydrofolate reductase), is irreversible

- Use of 5-methyl-THF and to maintain folate cycle consists in vit-B12-dependent remethylation of homocysteine to methionine (regenerating THF)

- Methyl group transfer is dependent on 5-methyl-THF and availability of vit-B12

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- In vit B12 deficiency, in spite of sufficient availability of folates (and 5-methyl-THF), deficiency of active THF arises, this situation is called a ‘folate trap’

- Because concentration of 5-methyl-THF continues to rise due to it being prevented from releasing methyl groups, a ‘metabolic dead-end situation’ develops, which leads to blockage of methylation cycle.

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- Co-factors for C1-transfers decrease and replication as well as cell division rate are reduced

- Hence, decreasing activity of methionine synthase under vitamin-B12 deficiency with secondary disorders affecting folate metabolism and insufficient de-novo synthesis of purines and pyrimidines

- Deficiency in active folic acids first affects quickly dividing and highly proliferating haematopoiesis cells in bone marrow and lead to pancytopenia

Folic acid deficiency

- It may result from limited diets, when food is cooked at high temperatures for long periods, which destroys the vitamin

- Intestinal diseases (celiac disease), are characterized by folic acid deficiency caused by malabsorption

- Inability to absorb folate is rare. Folate deficiency is usually in newborns and produces symptoms of megaloblastic anemia

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- Besides the anemia, mental and other CNS symptoms are in patients with folate deficiency, and all respond to continuous therapy although permanent damage appears to be caused by delayed or inadequate treatment

Catabolism of the Carbon Skeletons of aa and related disorders

Introduction

Carbon skeletons are generally conserved as:

- Carbohydrate, via gluconeogenesis,
- Fatty acid via fatty acid synthesis pathways.

These pathways converge to form seven intermediate products:

- oxaloacetate, α-ketoglutarate, pyruvate, fumarate, succinyl coenzyme A (CoA) , acetyl CoA, and acetoacetate

Cont--

These products directly enter the pathways of intermediary metabolism:

- Resulting either in the synthesis of glucose or lipid or in the production of energy through their oxidation to CO_2 and water by the citric acid cycle

Catabolic pathways of six aa to Pyruvate

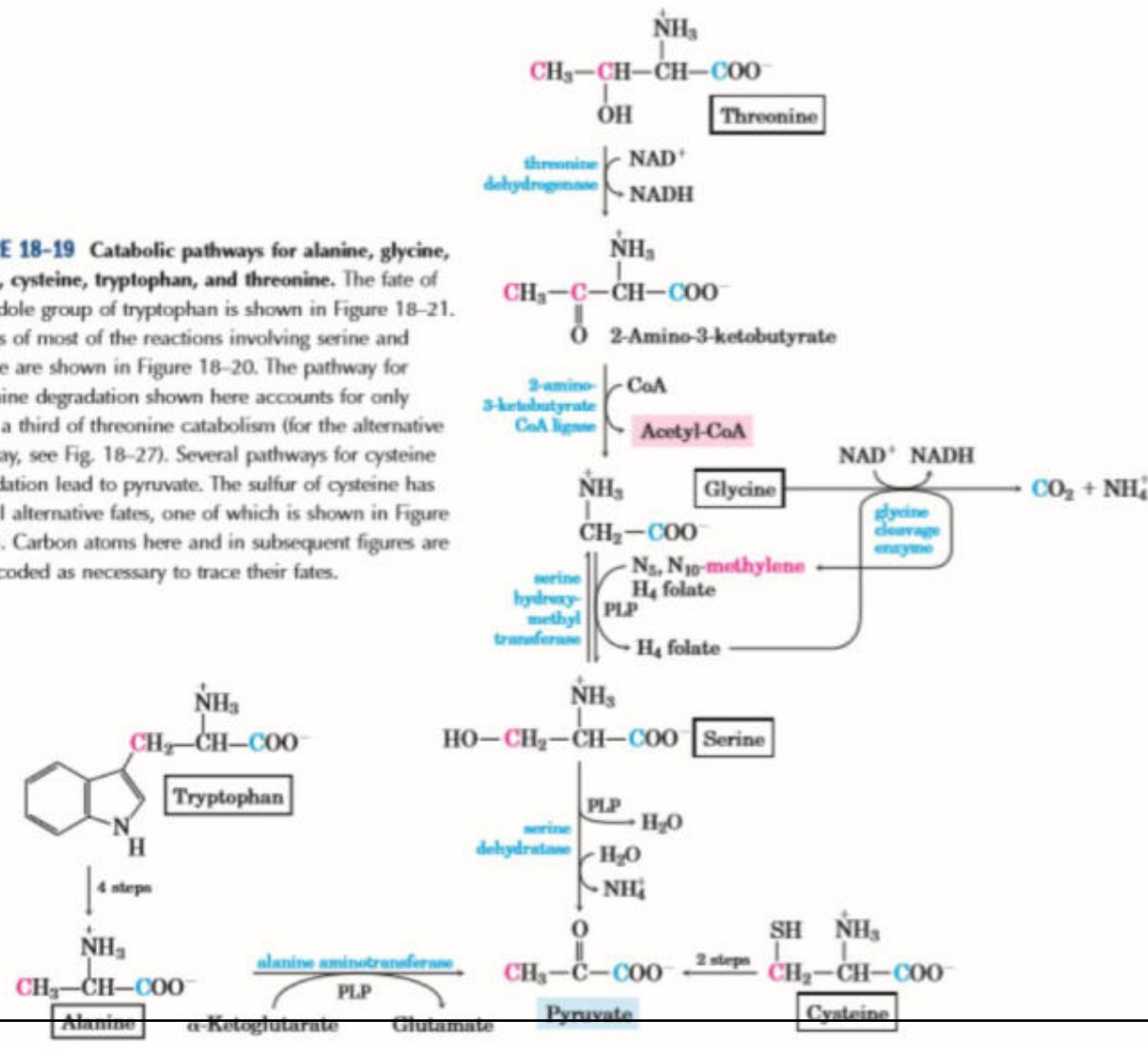

FIGURE 18–19 Catabolic pathways for alanine, glycine, serine, cysteine, tryptophan, and threonine. The fate of the indole group of tryptophan is shown in Figure 18–21. Details of most of the reactions involving serine and glycine are shown in Figure 18–20. The pathway for threonine degradation shown here accounts for only about a third of threonine catabolism (for the alternative pathway, see Fig. 18–27). Several pathways for cysteine degradation lead to pyruvate. The sulfur of cysteine has several alternative fates, one of which is shown in Figure 22–15. Carbon atoms here and in subsequent figures are color-coded as necessary to trace their fates.

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Glycine cleavage system is multienzyme complex: It consists of four proteins:

1. PLP-dependent glycine decarboxylase (P-protein)

2. Lipoamide-containing aminomethyl carrier (H-protein), which carries aminomethyl group remaining after glycine decarboxylation

3. N5,N10-methylene-THF synthesizing enzyme aminomethyltransferase (AMT) (T-protein), which accepts a methylene group from aminomethyl carrier, amino group is released as ammonia

4. NAD_+-dependent, FAD-requiring dihydrolipoyl dehydrogenase (L-protein), a protein shared by and known as E3 in pyruvate dehydrogenase complex

Disorder related to glycine

Non-ketotic hyperglycinemia (NKH)

- Humans with serious defects in glycine cleavage system activity due to absence of one of the components of glycine cleavage system

- The condition is characterized by elevated serum levels of glycine, leading to mental retardation and death in very early childhood

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- In one of the glycine degradation pathway, glycine is converted into glyoxylate by D-amino acid oxidase

- Glycine is the precursor of glyoxalate, which can be transaminated back to glycine or oxidized to oxalate by lactate dehydrogenase

- Excessive production of oxalate forms the insoluble calcium oxalate salt, lead to kidney stones.

Two pathways catabolize cysteine

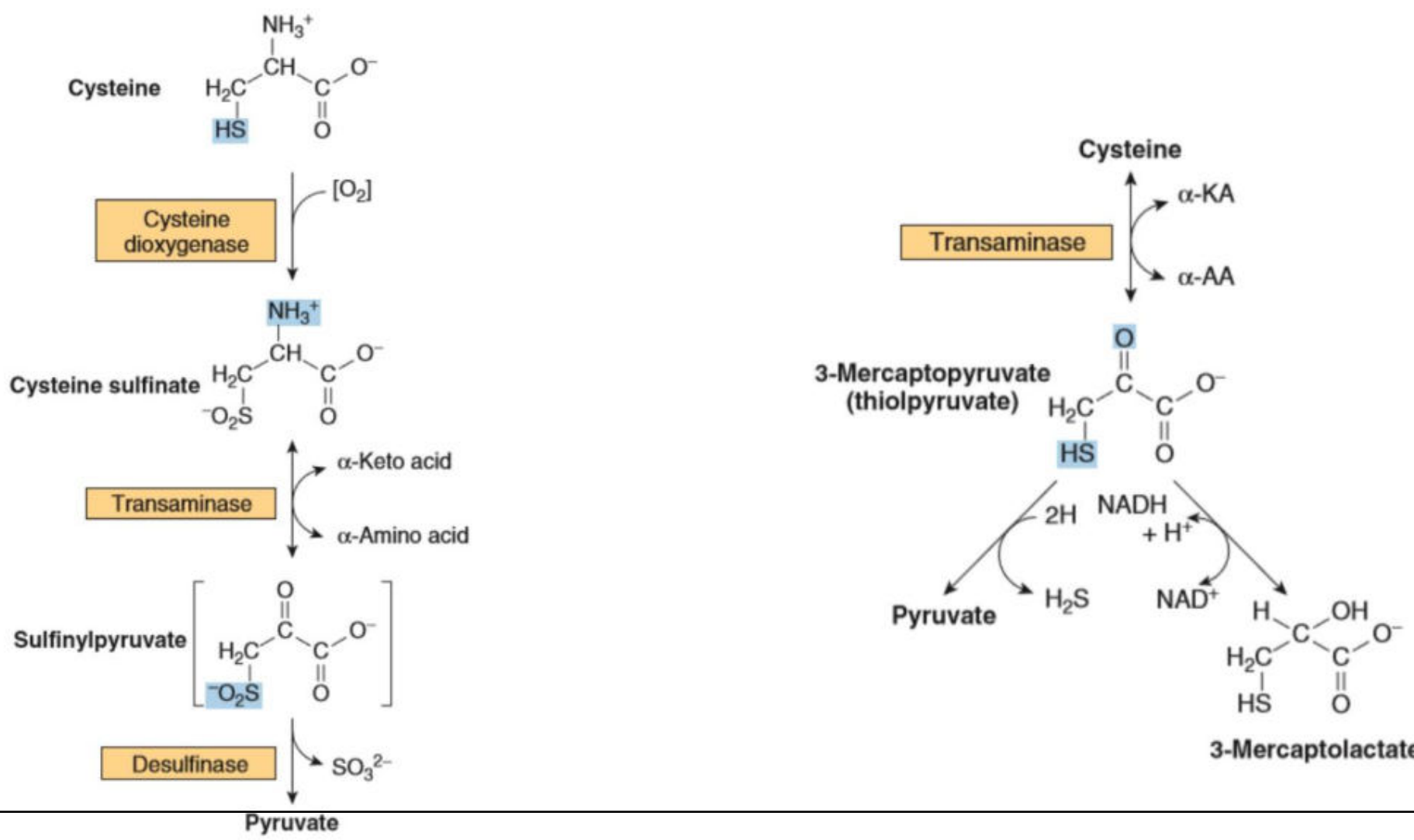

Fig 29.9: Harper's Illustrated Biochemistry 30th Edition

Disorders related to Cysteine

- Cystinuria is caused by mutations in SLC3A1 and SLC7A9 genes.
- These defects prevent reabsorption of basic positively charged aa (Cysteine, lysine, ornithine and arginine)
- Under normal condition, these proteins allow certain aa including cysteine to be reabsorbed into blood from filtered fluid that will become urine
- Mutations in either of these genes disrupt the ability of this transporter protein exist in kidney tubules to reabsorb these aa, allowing them to excretion of these aa in urin

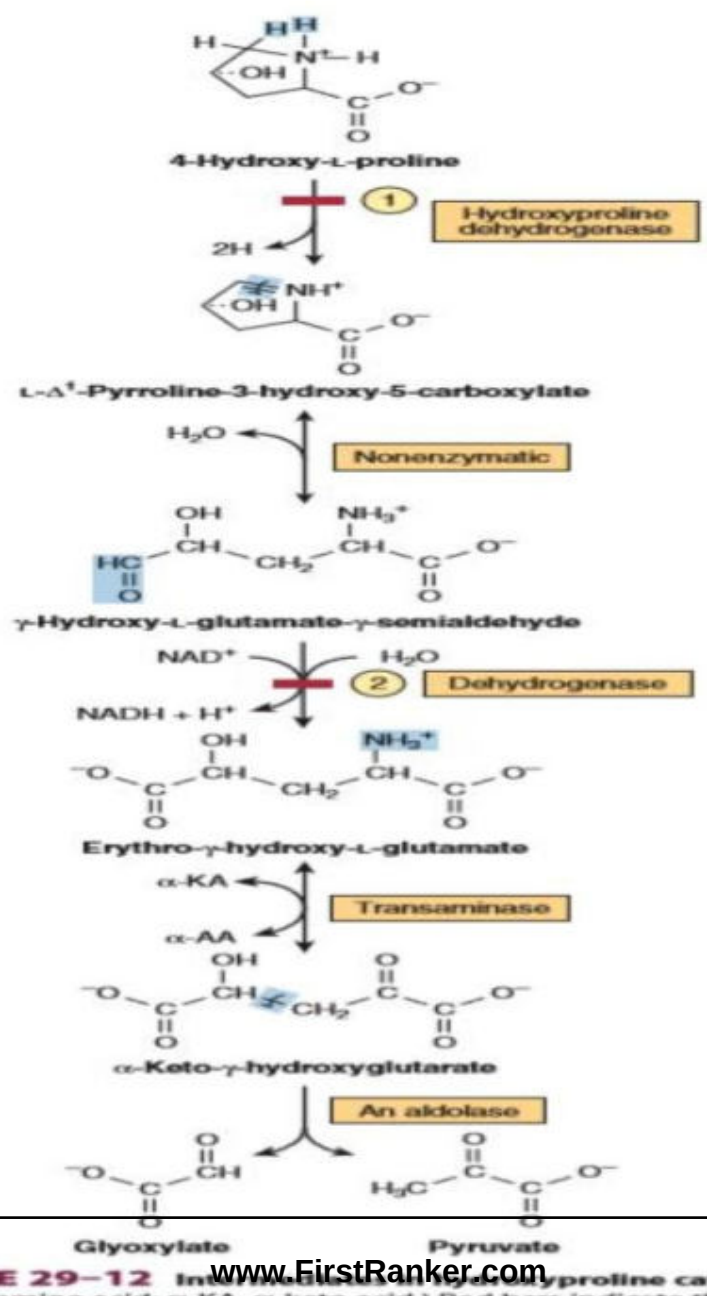

FIGURE 29–12 Intermediates in hydroxyproline catabolism. (α-AA, α-amino acid; α-KA, α-keto acid.) Red bars indicate the sites of the inherited metabolic defects in ① hyperhydroxyprolinemia and ② type II hyperprolinemia.

Disorders related to Hydroxyporoline

- A defect in 4-hydroxyproline dehydrogenase results in hyperhydroxyprolinemia, an excess of free hydroxyproline in the plasma and urine, it may be associated with mental retardation

- A defect in glutamate-γ-semialdehyde dehydrogenase/ 1-pyrroline-3-hydroxyl-5-carboxylate dehydrogenase results in type II hyperprolinemia which is accompanied by excretion of Δ1-pyrroline-3-hydroxy-5-carboxylate

- Type II hyperprolinemia is a rare form of disorder may appear benign at time but often involves seizures, convulsions and intellectual disability.

Catabolism of Tryptophan to α-Ketoadipate

FIGURE 29–16 Reactions and intermediates in the catabolism of tryptophan (PLP, pyridoxal phosphate.) Fig 29.16. Harper's Illustrated Biochemistry 30th Edition

Disorder related to Tryptophan

Hartnup disease: In catabolism of Typ, kynureninase requires PLP (active form of vit B6), acts on 3-L hydroxylkynurenine

- Defect in kynureninase limits tryptophan availability for niacin biosynthesis, cause reduced synthesis of NAD^+ and $NADP^+$ leads to pellagra-like signs and symptoms.
- Due to lack of PLP, Kynureninase reaction blocked and 3-L hydroxylkynurenine is diverted and form xanthurenate catalyzed by Kynurenine transferases

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- Elevated levels of xanthurenate shows vit B6 deficiency
- Hartnup disease reflects impaired intestinal and renal transport of tryptophan and other neutral aa
- Indole derivatives of unabsorbed tryptophan formed by intestinal bacteria are excreted

Catabolic pathways of seven aa to Acetyl-CoA

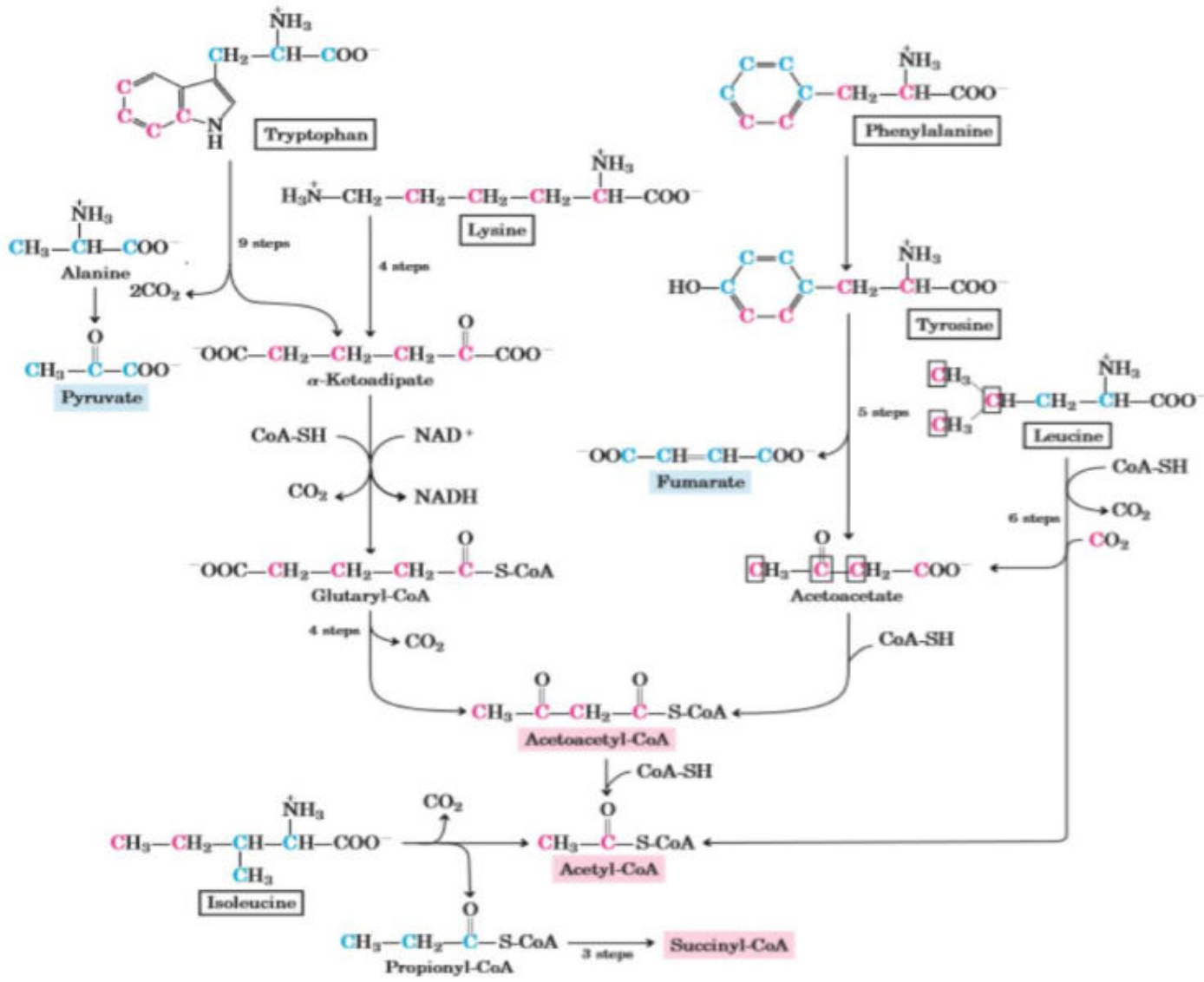

FIGURE 18–21 Catabolic pathways for tryptophan, lysine, phenylalanine, tyrosine, leucine, and isoleucine. These amino acids donate some of their carbons (red) to acetyl-CoA. Tryptophan, phenylalanine, tyrosine, and isoleucine also contribute carbons (blue) to pyruvate or citric acid cycle intermediates. The phenylalanine pathway is described in more detail in Figure 18–23. The fate of nitrogen atoms is not traced in this scheme; [illegible] α-ketoglutarate to form glutamate.

Threonine yield some acetyl CoA also

Fig18.21: Lehninger Principles of Biochemistry by David L Nelson

Disorder related to Lysine

- Genetic defect in saccharopine dehydrogenase that catalyzes lysine into saccharopine results in hyperlysinemia and hyperlysinuria (elevated levels of lysine in the blood and urine, respectively) along with mental and physical retardation.

Group Discussion

- Subtopics of previous class discussed in groups.

Thank you