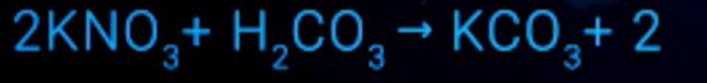
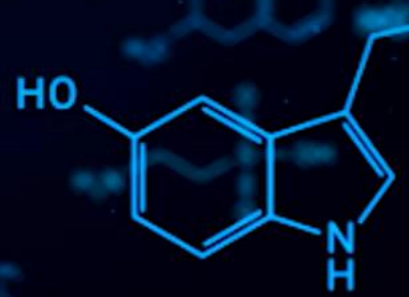
# Carbon Skeletons of Amino Acids

Prof. Nafez Abu Tarboush



# OVERVIEW

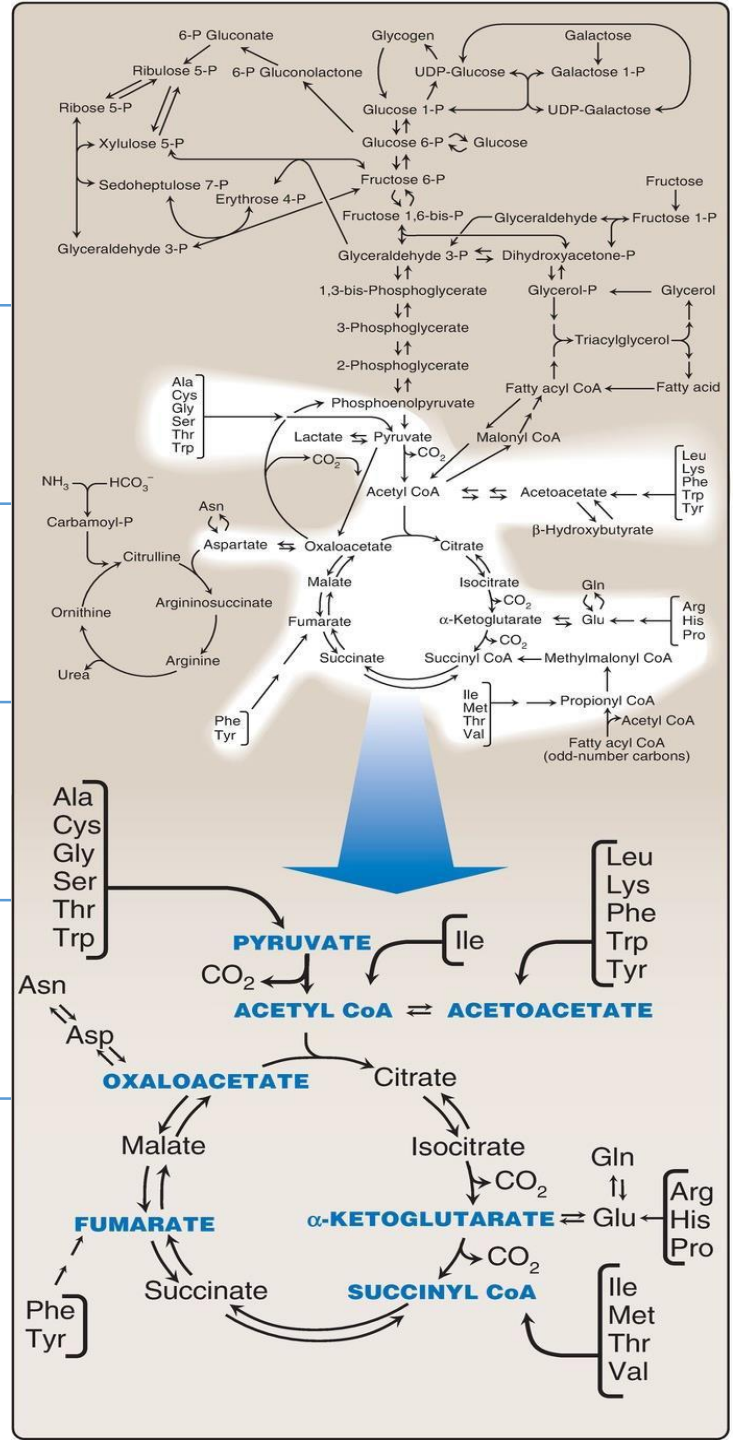
Removal of the α-amino group → Catabolism of α-keto acids (carbon skeletons)

Seven intermediate products: pyruvate, oxaloacetate, α-ketoglutarate, fumarate, succinyl-CoA, acetyl-CoA, & acetoacetate

Resulting either in the synthesis of glucose, ketone bodies, or lipids or in the production of energy (TCA)

Nonessential amino acids can be synthesized in sufficient amounts

Genetic defects in the pathways of amino acid metabolism can cause serious disease



# GLUCOGENIC AND KETOGENIC AMINO ACIDS

Glucogenic: substrates for gluconeogenesis (pyruvate and TCA intermediates)

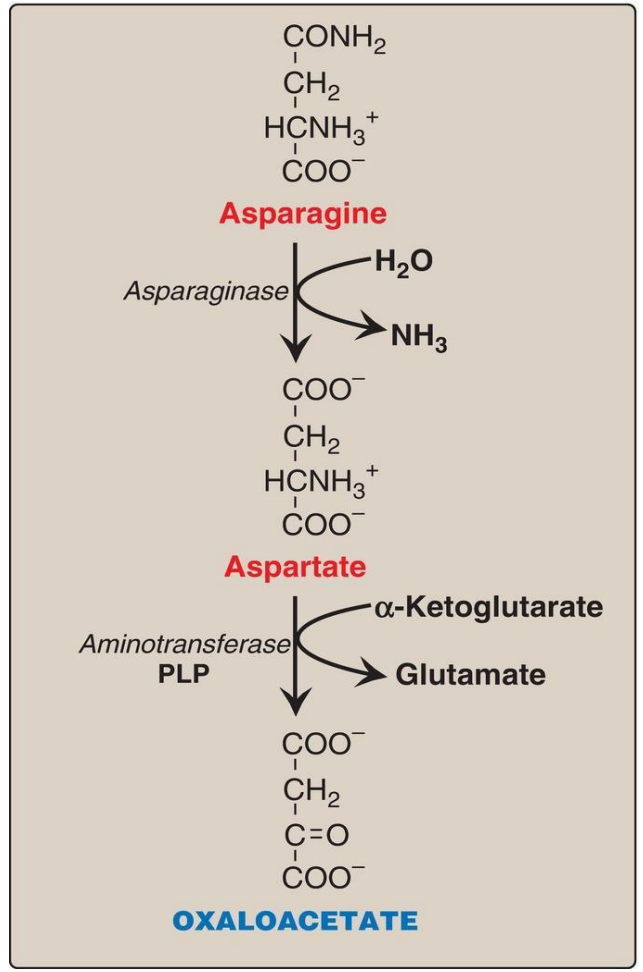
Ketogenic: acetoacetate or its precursors (acetyl CoA or acetoacetyl CoA)

Both

| | Glucogenic | Glucogenic and Ketogenic | Ketogenic |
|---|---|---|---|
| Nonessential | Alanine<br>Arginine<br>Asparagine<br>Aspartate<br>Cysteine<br>Glutamate<br>Glutamine<br>Glycine<br>Proline<br>Serine | Tyrosine | |
| Essential | Histidine<br>Methionine<br>Threonine<br>Valine | Isoleucine<br>Phenyl-alanine<br>Tryptophan | Leucine<br>Lysine |

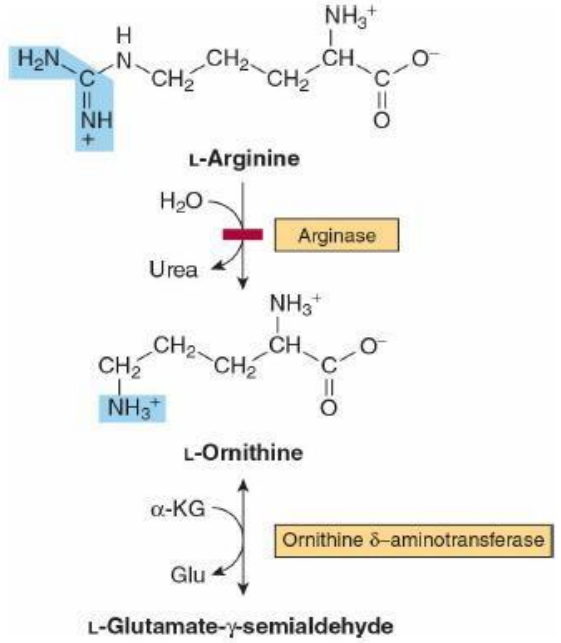
# Catabolism to OxaloAcetate

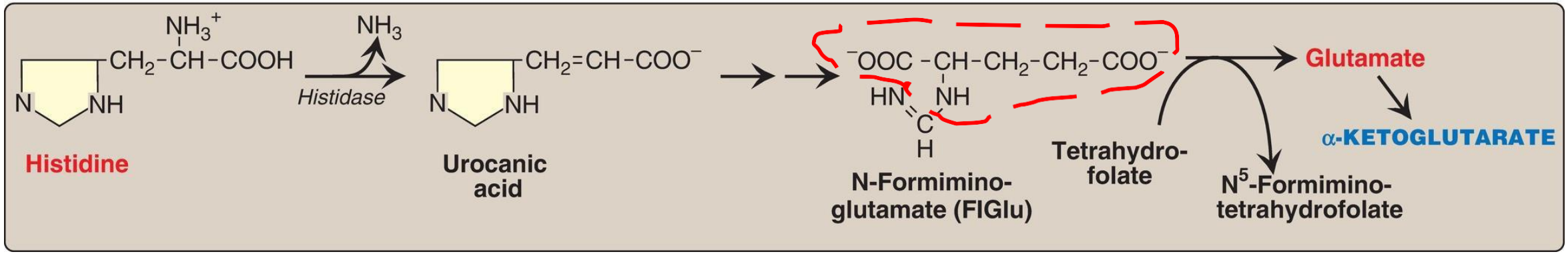
- Asparagine and aspartate
- Asparaginase systemically to treat leukemia!



# Catabolism to α-KetoGluterate (via Glu) - QHRP

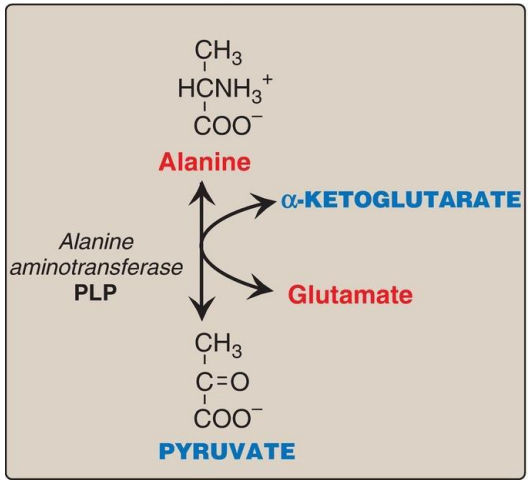
- Glutamine: glutaminase and GDH
- Proline: oxidized to Glu
- Arginine: arginase
- Histidine:
  - Folic acid deficiency
  - Impaired histidase: histidinemia and urocanic aciduria

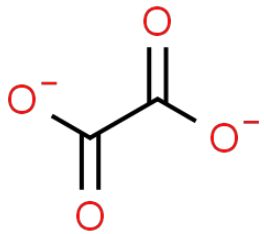


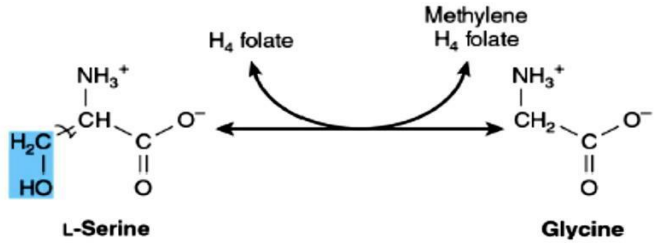



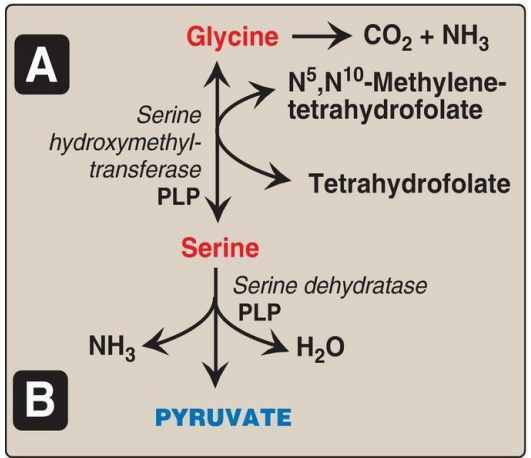
# Catabolism to pyruvate – (GSCAT$^2$)

- Alanine: ALT
- Tryptophan catabolism produces alanine
- Serine: glycine or pyruvate
- Glycine:
  - Reverse or $CO_2$ and $NH_3$ (glycine cleavage system)
  - Transaminated to glyoxylate → oxidized to oxalate or transaminated back to glycine
  - Deficiency of transaminase causes oxalate stones



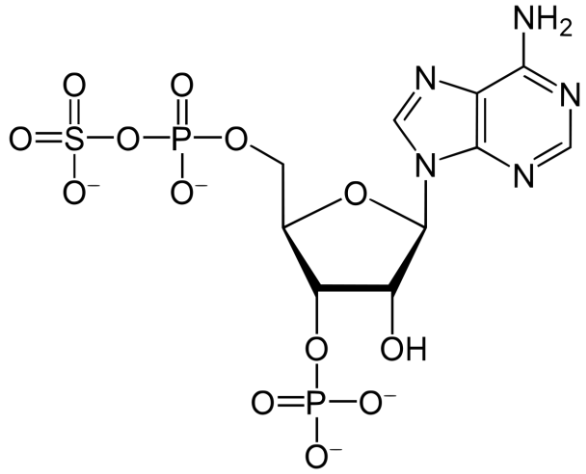



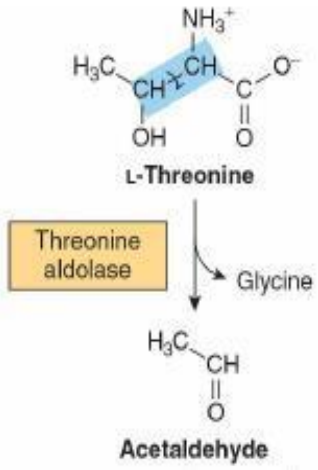


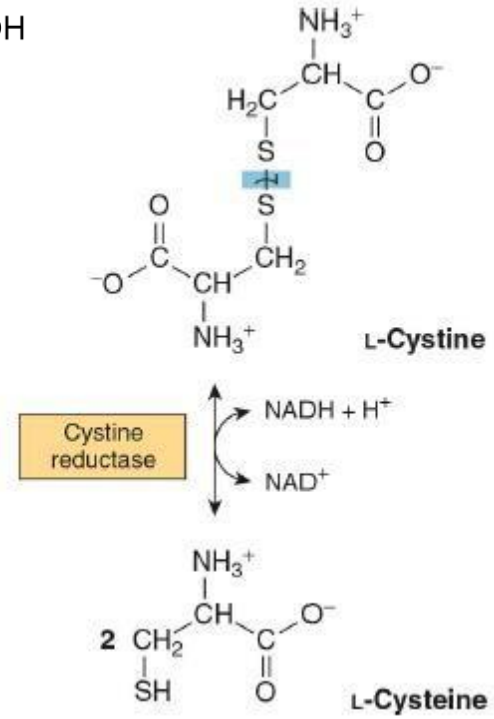



# Catabolism to pyruvate – (GSCAT$^2$)

- Cysteine: desulfurization to yield pyruvate (desulfinase)
  - Sulfate released can be used to synthesize 3’- phosphoadenosine-5’-phosphosulfate (PAPS), an activated sulfate donor
  - Oxidized to its disulfide derivative, Cystine
- Threonine: minor pathway in humans

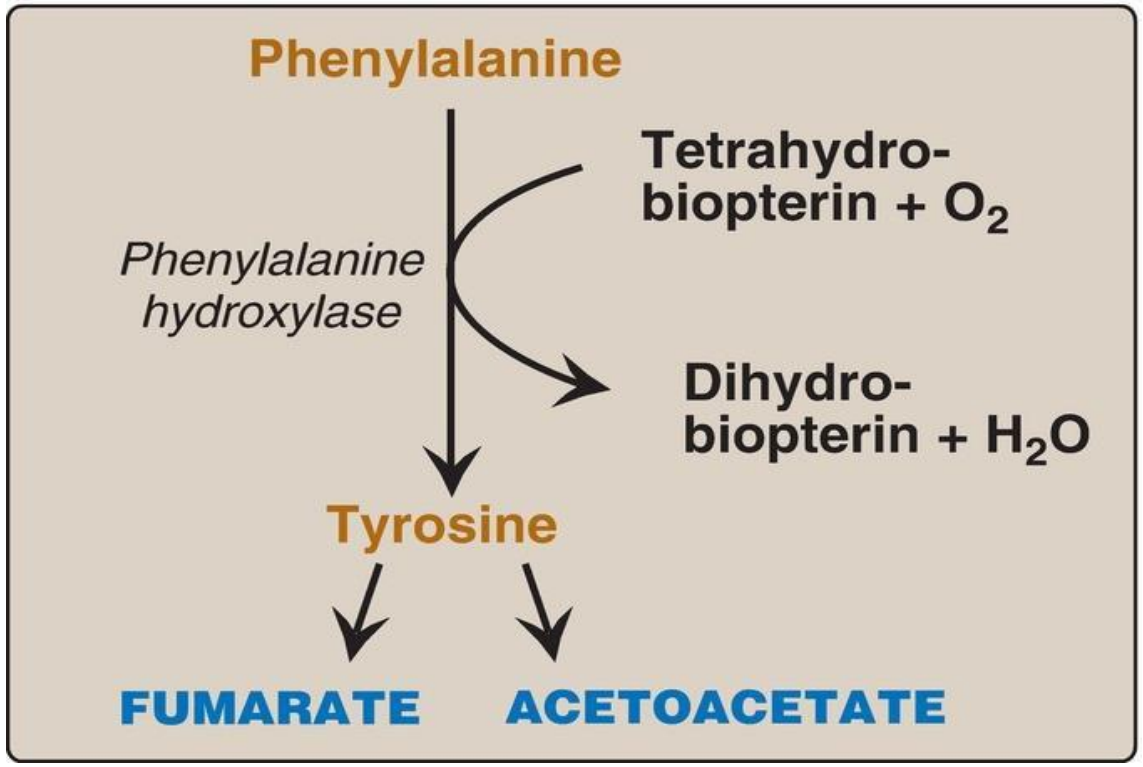




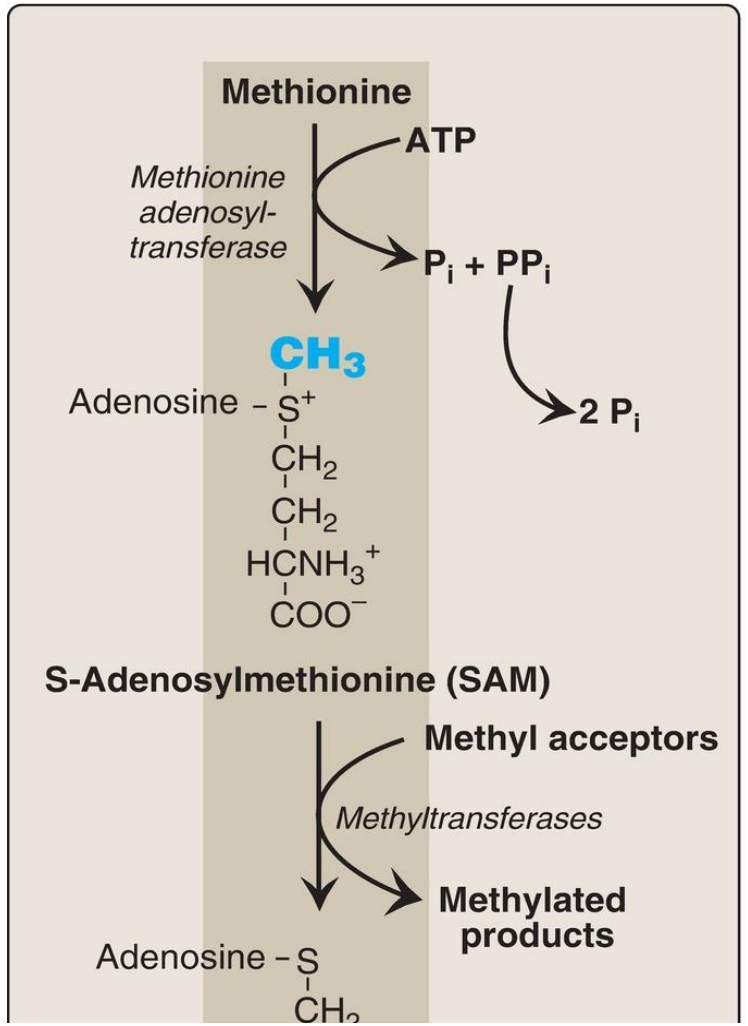
# Catabolism to fumarate

- Phenylalanine and tyrosine
  - Irreversible reaction
  - Phenylalanine hydroxylase (PAH)
  - Tetrahydrobiopterin
  - Fumarate and acetoacetate
- Inherited deficiencies: phenylketonuria (PKU), tyrosinemia, alkaptonuria as well as the condition of albinism



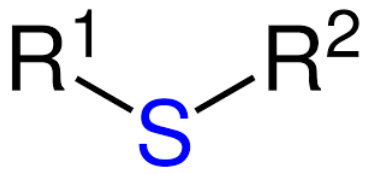
# Catabolism to succinyl CoA: Methionine

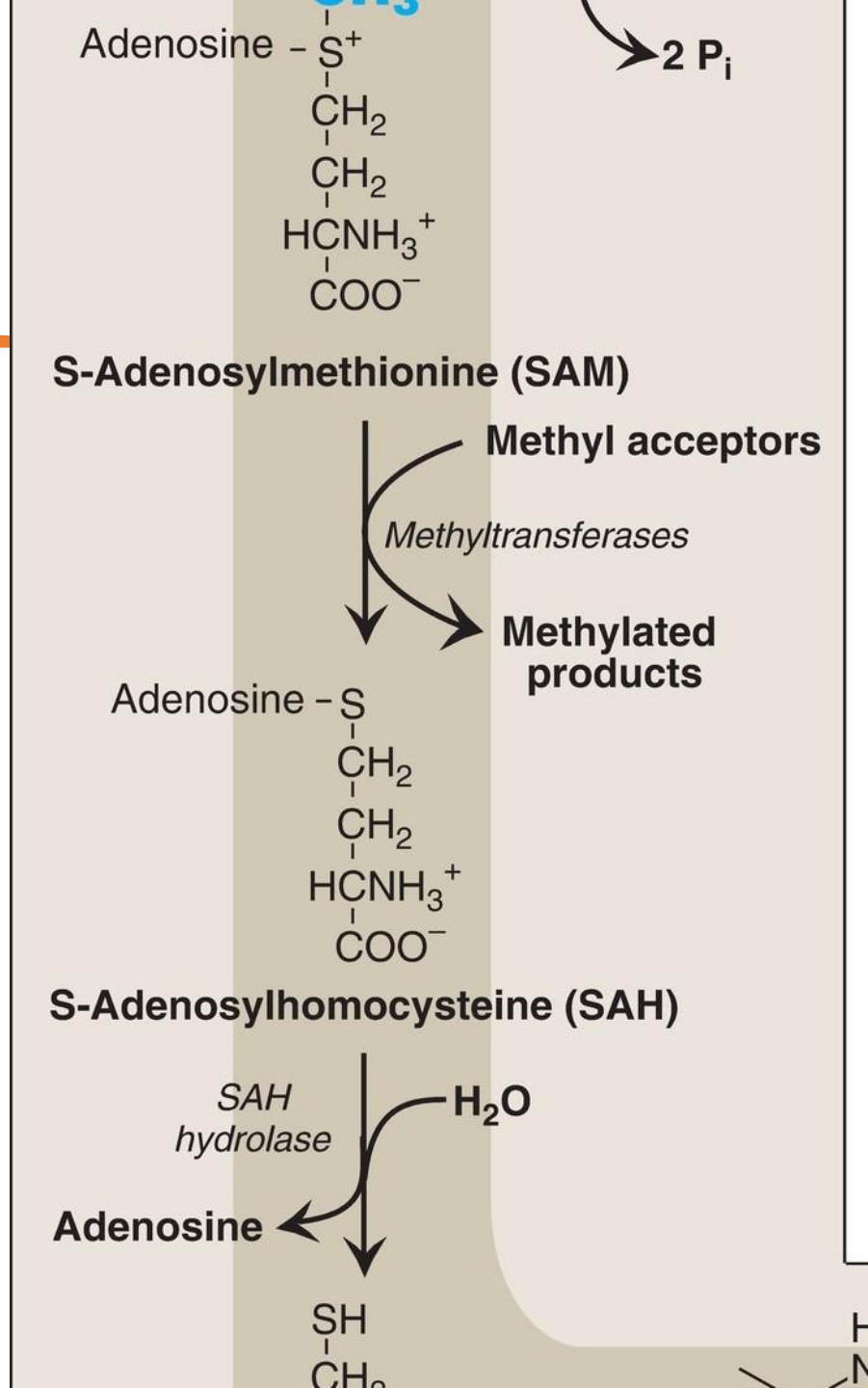
- S-adenosylmethionine (SAM)
- The major methyl group donor in one-carbon metabolism
- Source for homocysteine (Hcy)
- Atherosclerotic vascular disease and thrombosis
- SAM synthesis: Met condenses with ATP
- A high-energy compound that is unusual (no P)
- Hydrolysis of all three phosphate bonds



# Catabolism to succinyl CoA: Methionin

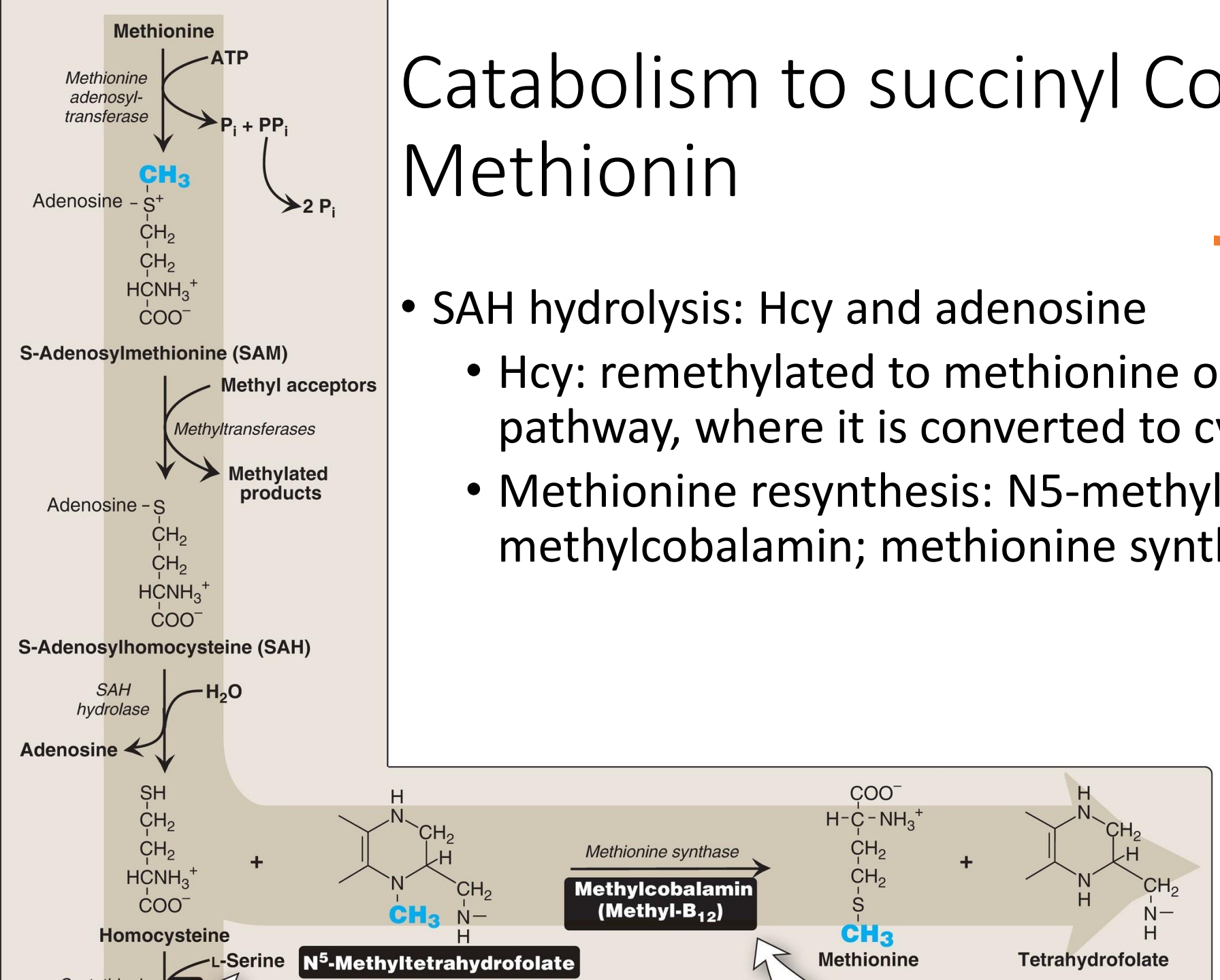
- Activated methyl group:
  - Can be transferred by methyltransferases
  - Nitrogen or oxygen atoms and sometimes to carbon atoms
  - The reaction product, S-adenosylhomocysteine (SAH), analogous to methionine (thioether)
  - Methyl transfer essentially irreversible



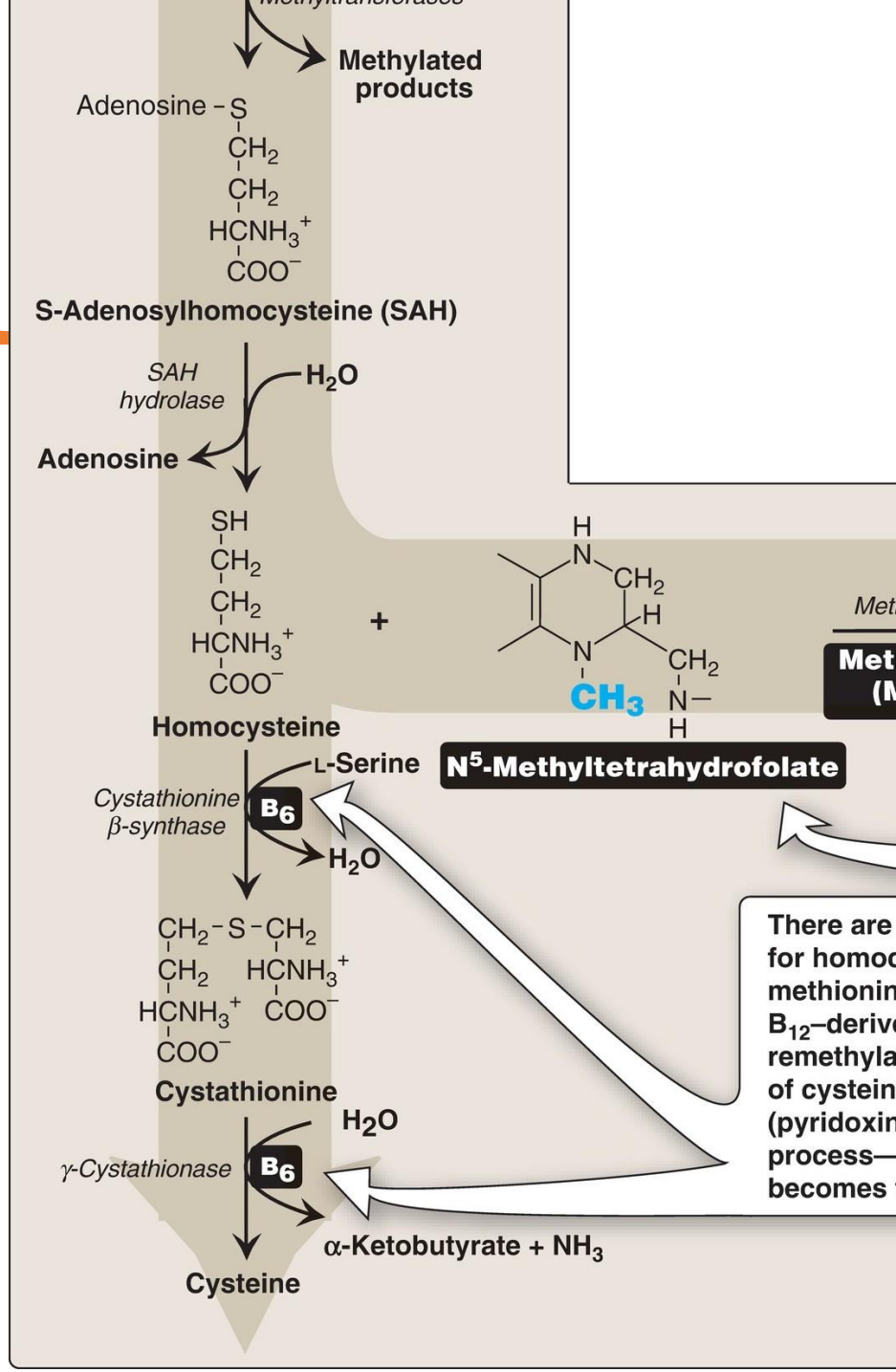
# Catabolism to succinyl CoA: Methionin

- SAH hydrolysis: Hcy and adenosine
  - Hcy: remethylated to methionine or transsulfuration pathway, where it is converted to cysteine
  - Methionine resynthesis: N5-methyl-THF; methylcobalamin; methionine synthase



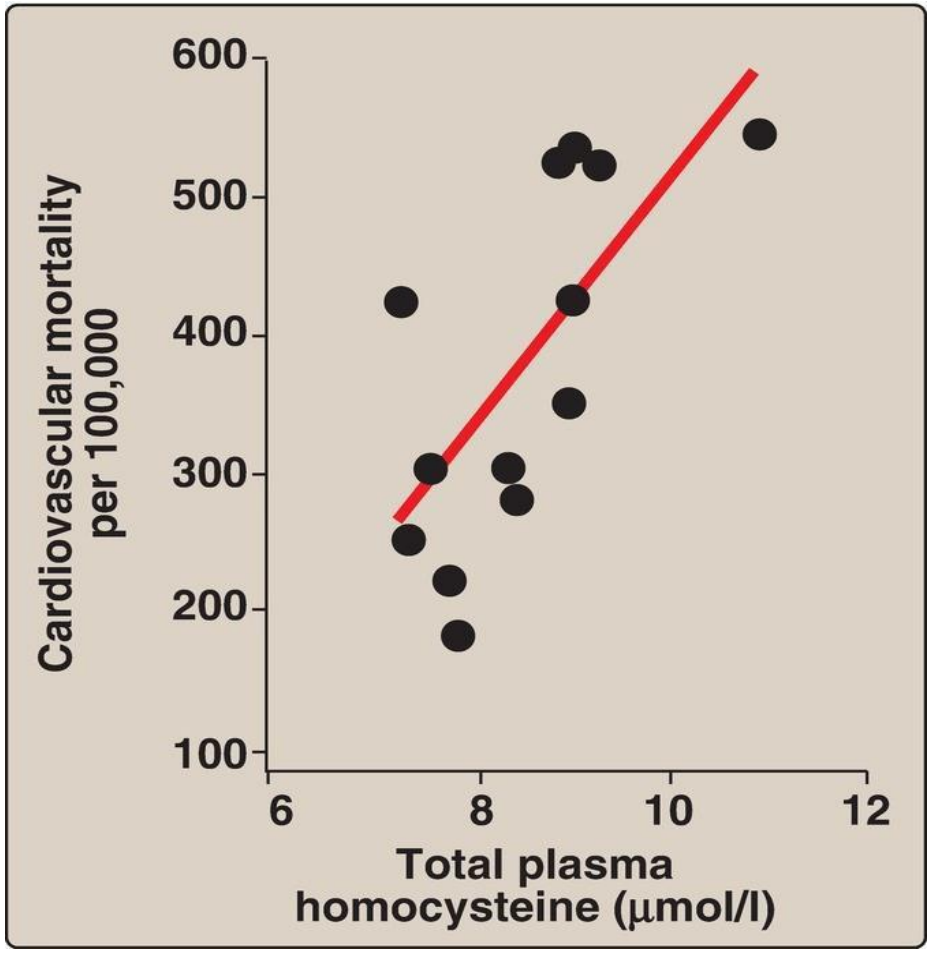
# Catabolism to succinyl CoA: Methionin

- SAH hydrolysis: Hcy and adenosine
  - Cysteine synthesis: condensation; Ser; cystathionine (α-ketobutyrate and cysteine); B6; oxidatively decarboxylated to form propionyl CoA. Propionyl CoA is converted to succinyl CoA
  - Cysteine is conditionally essential

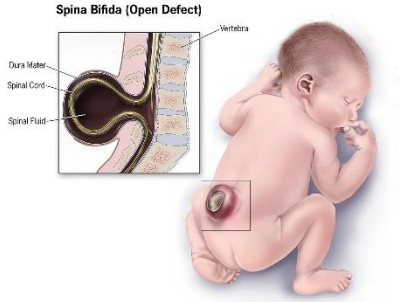


# Relationship of homocysteine to vascular disease

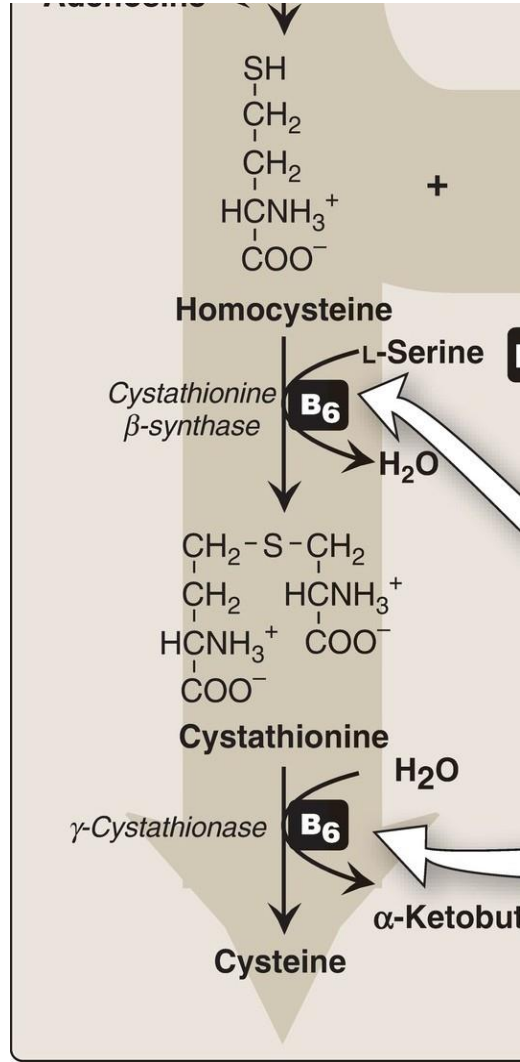
- Promotes oxidative damage, inflammation, and endothelial dysfunction
- Independent risk factor: CVD, stroke
- Mild elevations (hyper-homocysteinemia): ~7% of the population
- Inversely related to plasma levels of folate, B12, B6
- Supplementation therapy
- Whether Hcy is a cause or a marker of such damage



# Relationship of homocysteine to vascular disease

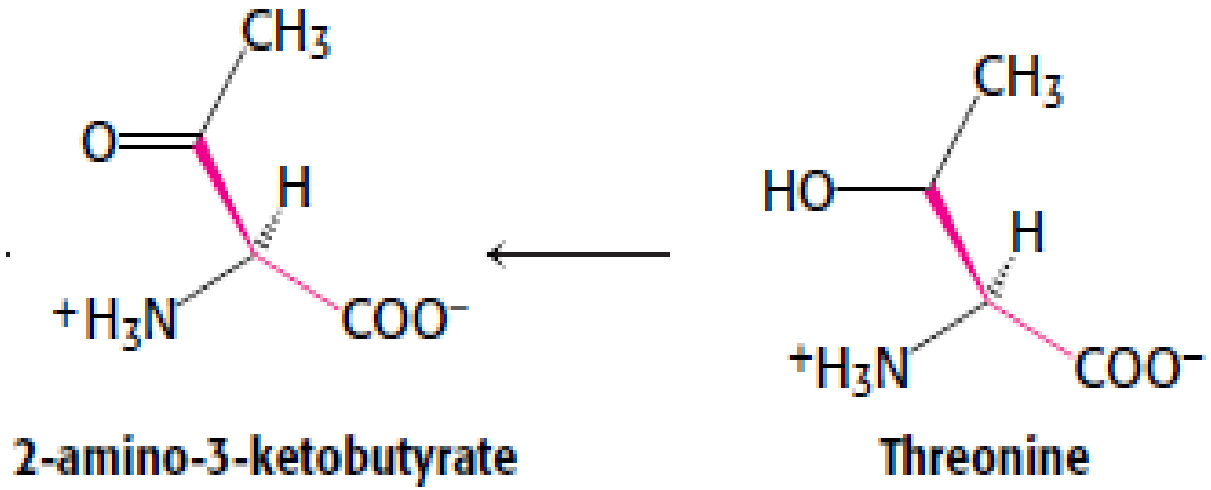


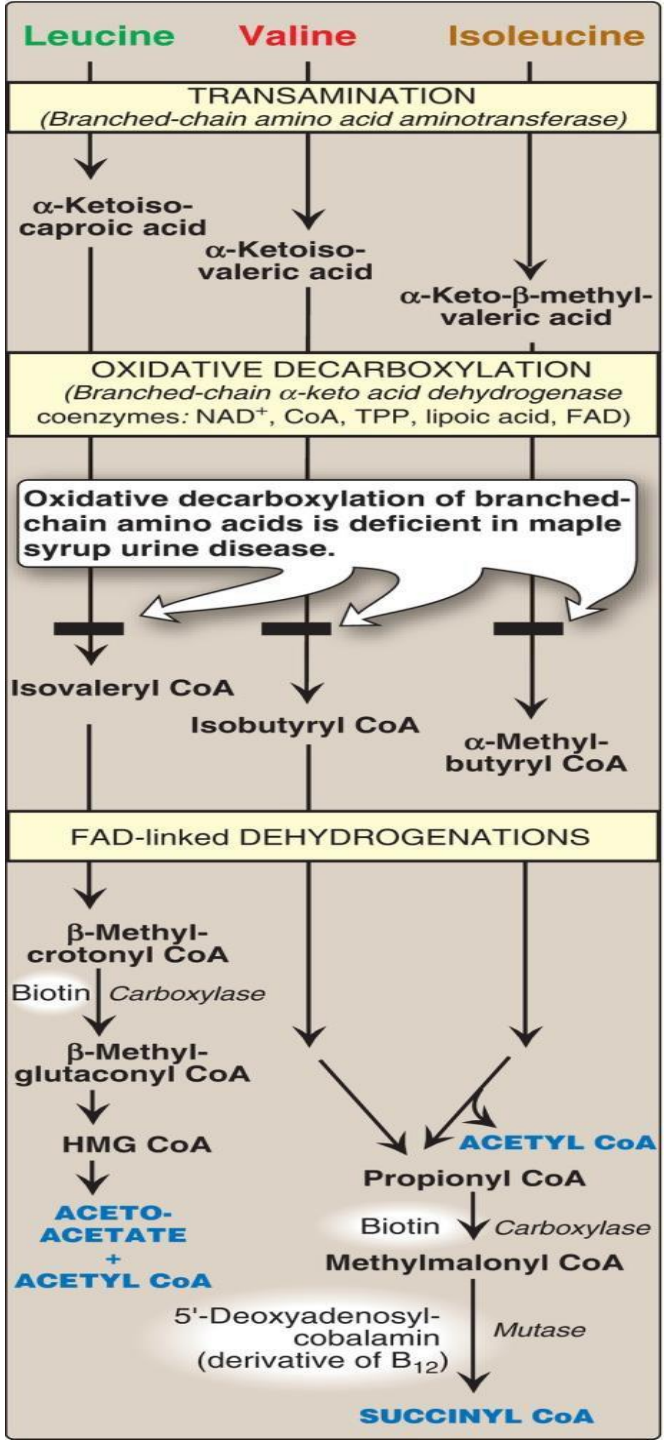

- Deficiencies in cystathionine β-synthase (transsulfuration):
  - Rare
  - Severe hyperhomocysteinemia (>100 µmol/L)
  - Classic homocystinuria
- Deficiencies in the remethylation reaction: rise in Hcy
- Elevated homocysteine and decreased folic acid: associated with increased incidence of neural tube defects (improper closure as in spina bifida) in the fetus
  - Periconceptual supplementation with folate reduces such defects



# Other amino acids that form succinyl CoA

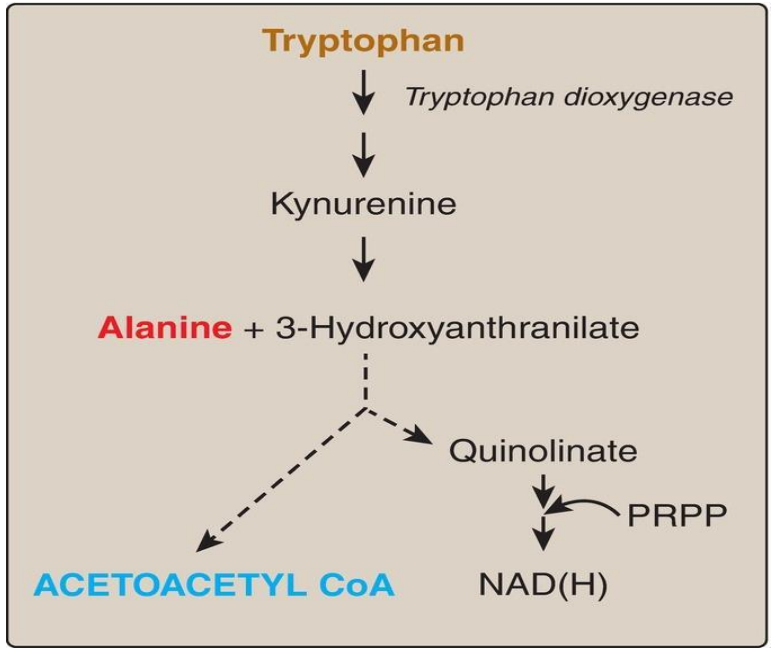
- Valine, isoleucine, and threonine
- Valine and isoleucine: BCAA
- Threonine: α-ketobutyrate → propionyl CoA → succinyl CoA

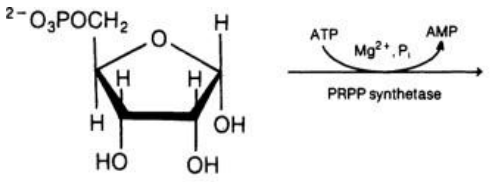


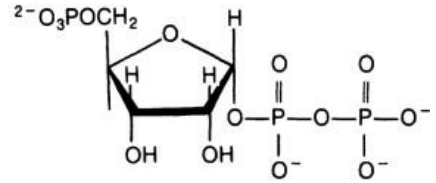
# Catabolism to acetyl CoA or acetoacetyl CoA

- Tryptophan, leucine, isoleucine, and lysine form acetyl CoA or acetoacetyl CoA directly, without pyruvate serving as an intermediate
- Phenylalanine and tyrosine also give rise to acetoacetate
- Tryptophan: alanine and acetoacetyl CoA
  - Quinolinate is used in the synthesis of NAD



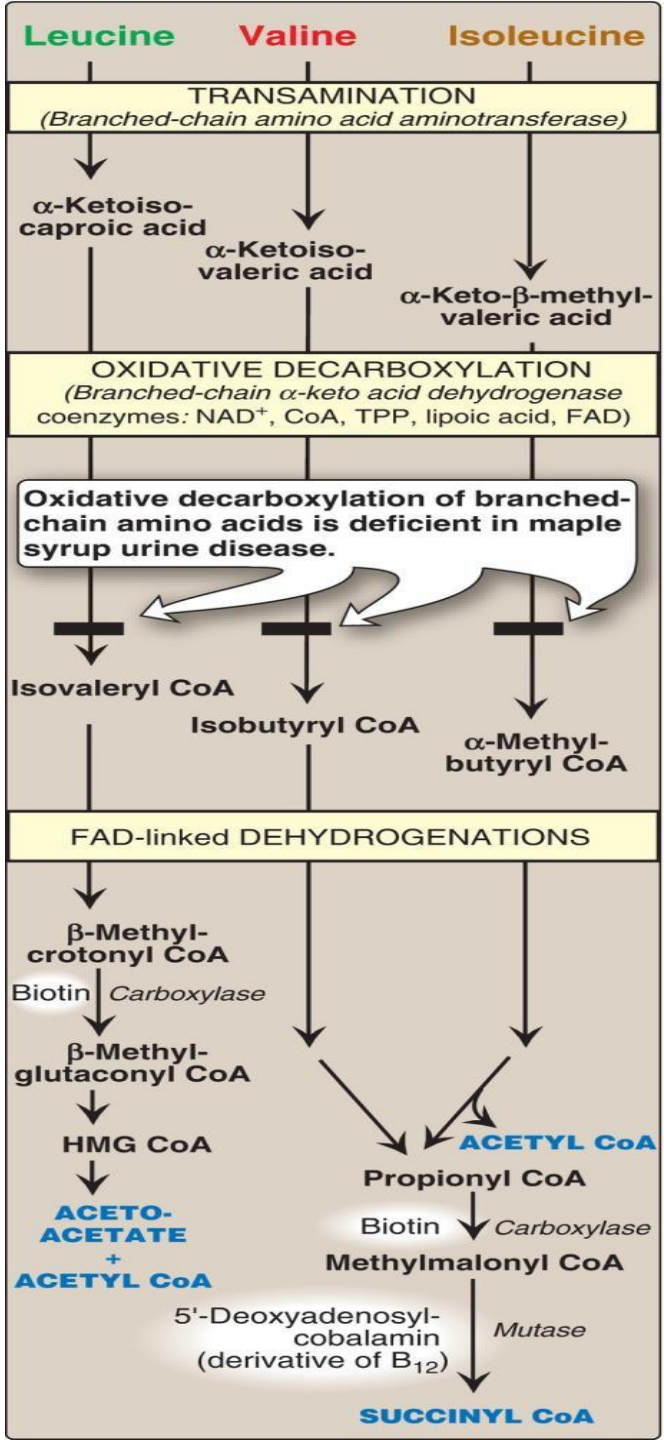

Ribose 5-phosphate



PRPP

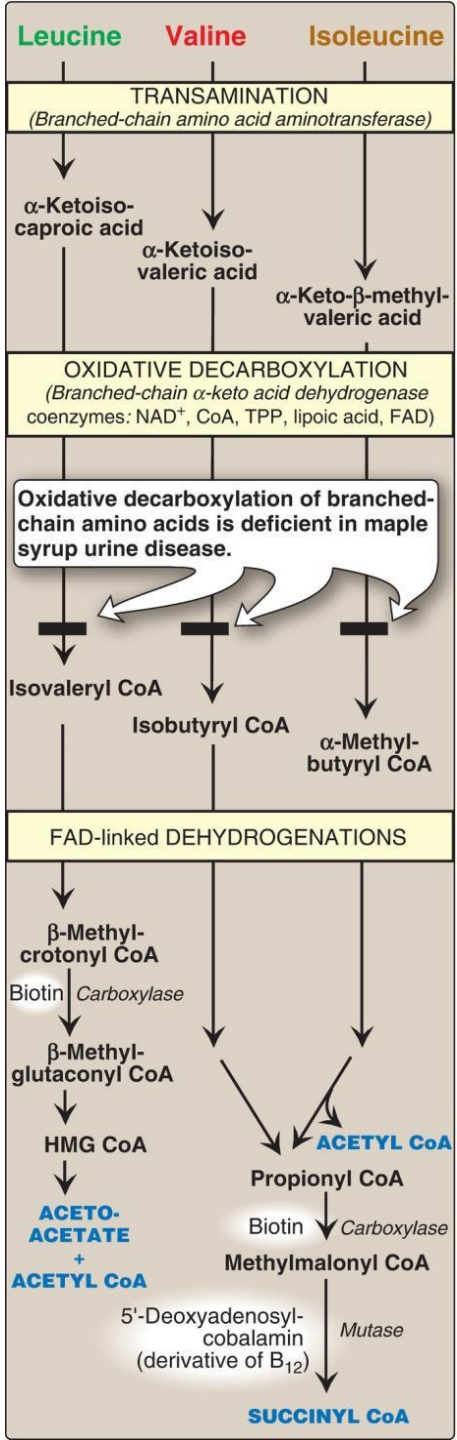
# Catabolism to acetyl CoA or acetoacetyl CoA

- Leucine: exclusively ketogenic
- Isoleucine: both ketogenic and glucogenic
- Lysine:
  - Exclusively ketogenic
  - Neither of its amino groups undergoes transamination



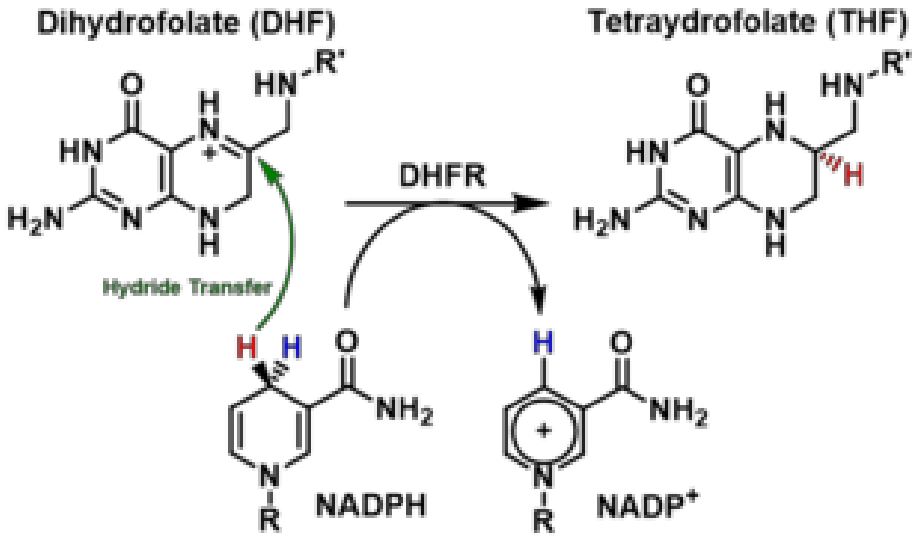
# Branched-chain amino acid degradation

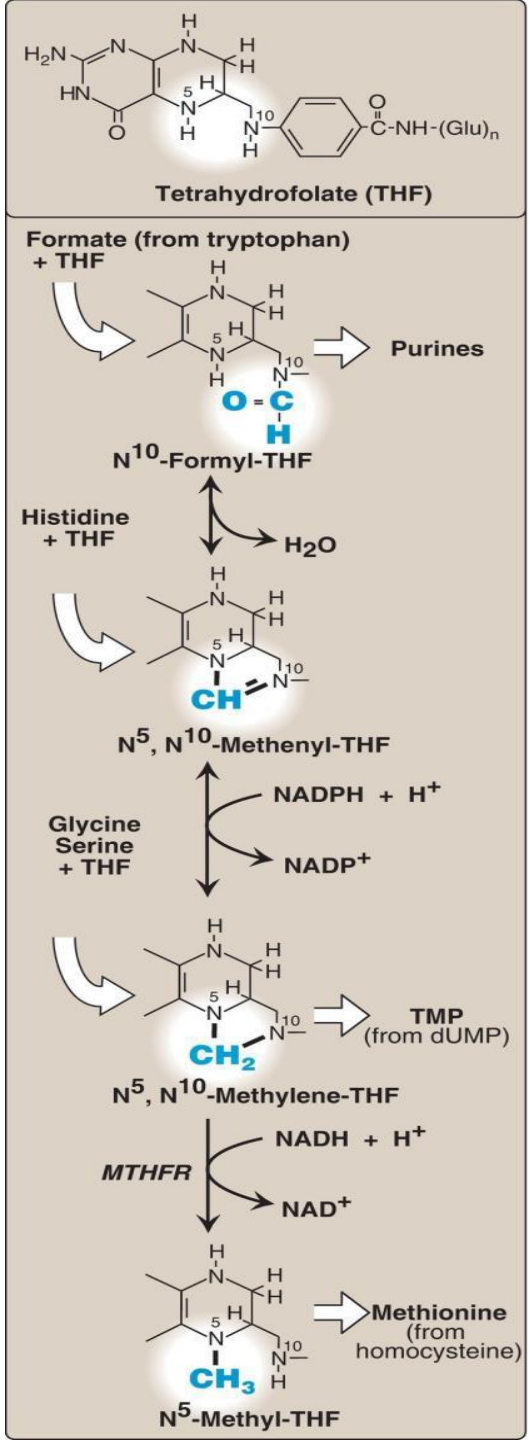
- BCAA are essential
- Particularly muscles
- Transamination (B6) branched-chain amino acid aminotransferase → Oxidative decarboxylation branched-chain α-keto acid dehydrogenase (BCKD) complex; E3 component is identical
- Produces unsaturated acyl CoA derivatives and $FADH_2$
- BCAA catabolism also results in glutamine and alanine being synthesized and sent out into the blood from muscle

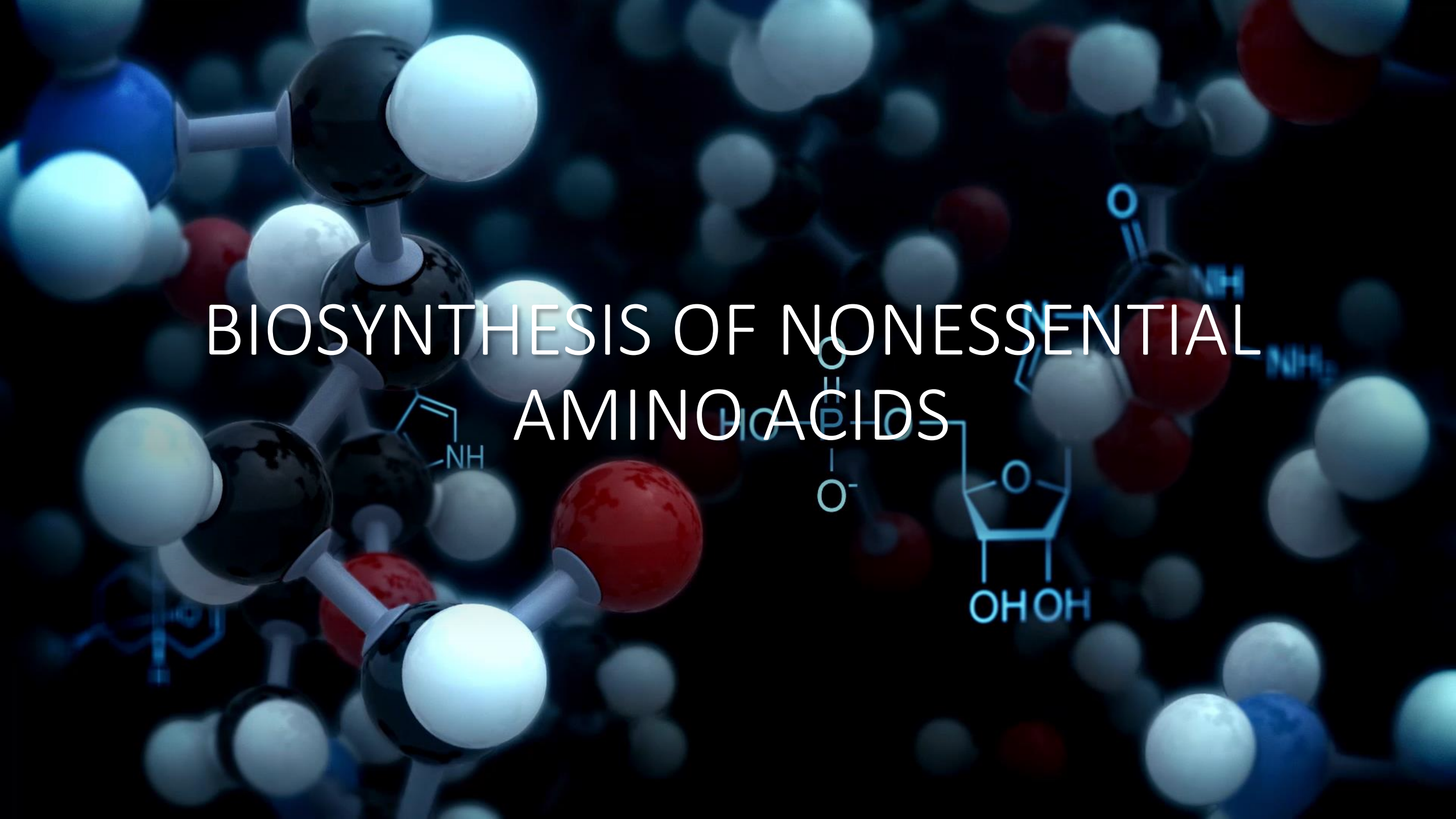


# Folic acid and one-carbon metabolism

- Addition of single-carbon groups: formyl, methenyl, methylene, and methyl
- Carrier compounds such as THF and SAM
- THF, dihydrofolate reductase, (NADPH) (N5 or N10 or both)
- Folate deficiency presents as a megaloblastic anemia



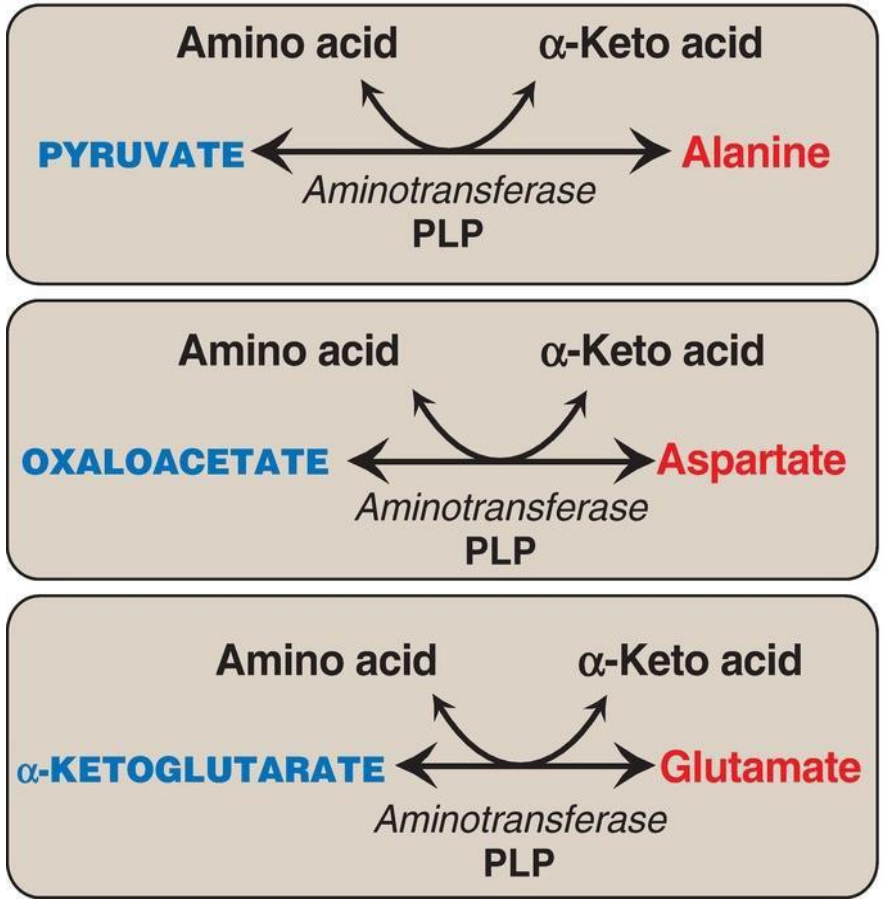





# BIOSYNTHESIS OF NONESSENTIAL AMINO ACIDS

# A. Synthesis from α-keto acids

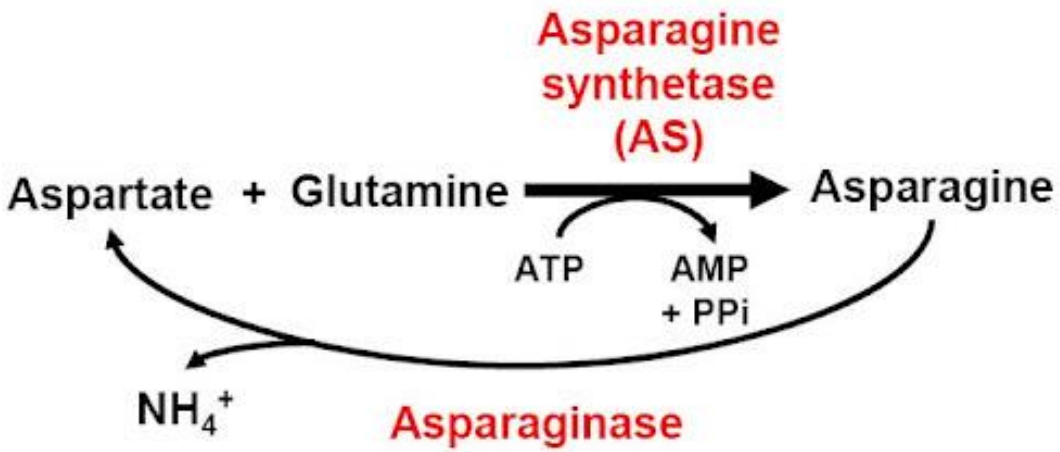
- Alanine, aspartate, and glutamate
- Transamination reactions
- Glutamate is unusual

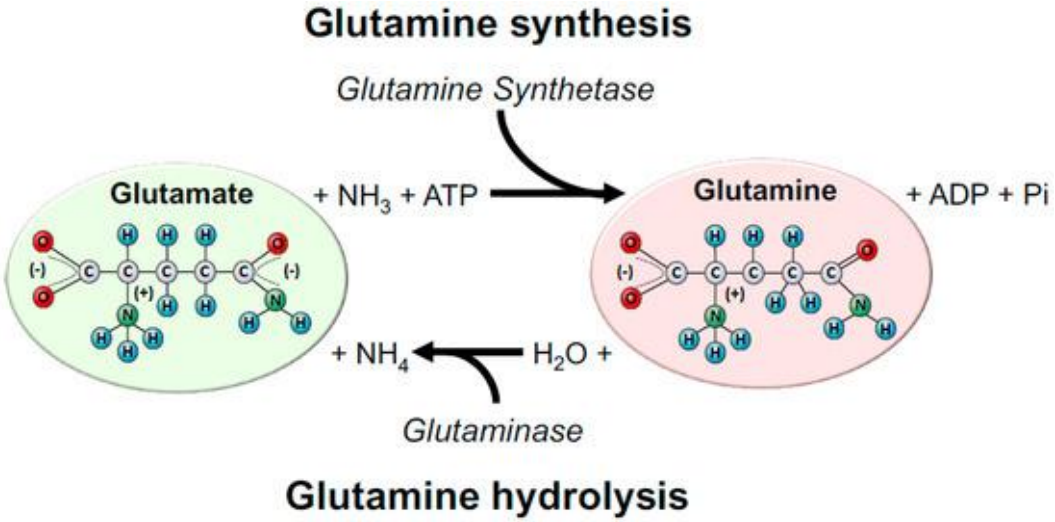


# B. Synthesis by amidation

- Glutamine: glutamine synthetase; ATP, source?

- Asparagine: asparagine synthetase; glutamine; ATP, source?

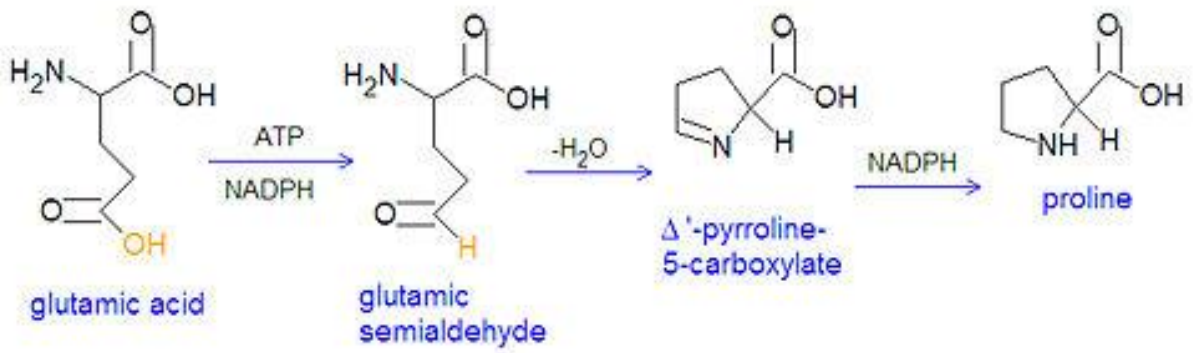


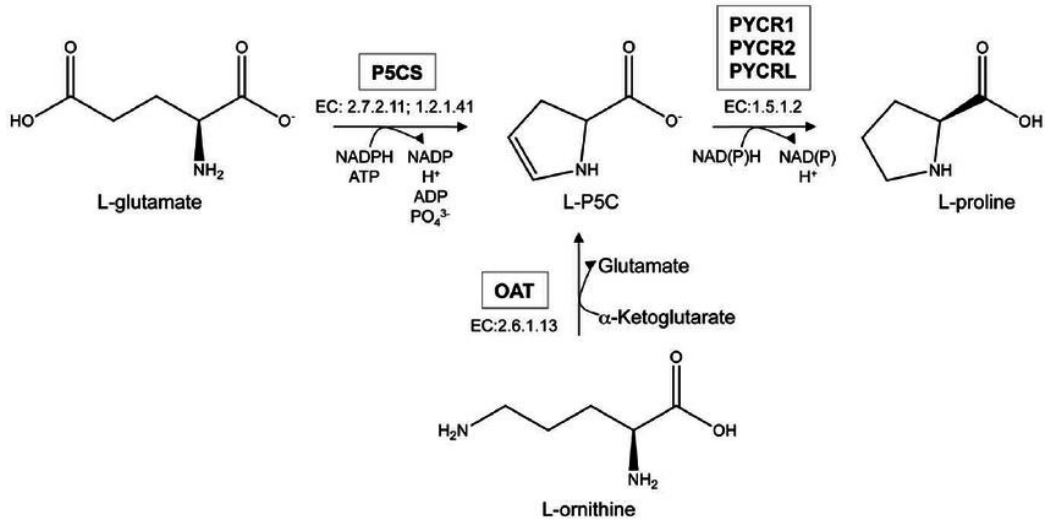



# C. Proline

- Glutamate via glutamate semialdehyde is converted to proline by cyclization and reduction reactions

- The semialdehyde can also be transaminated to ornithine

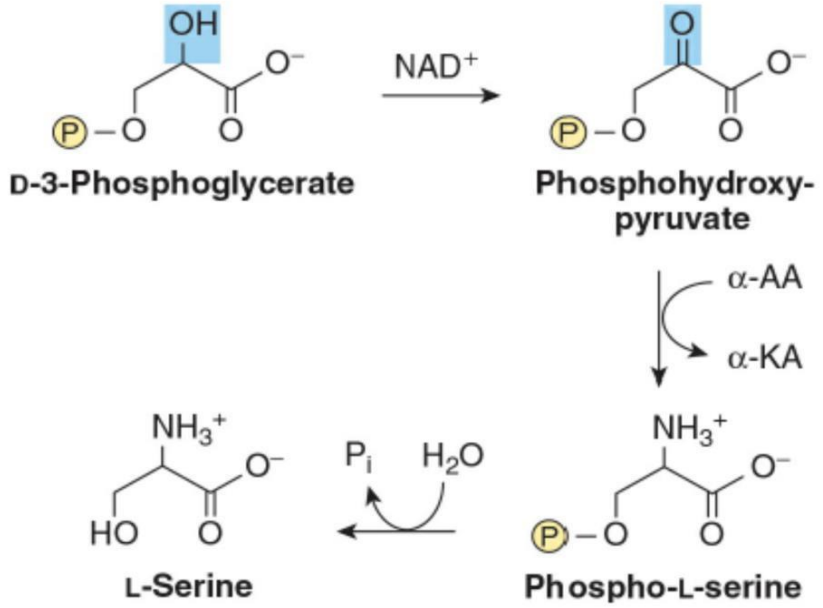


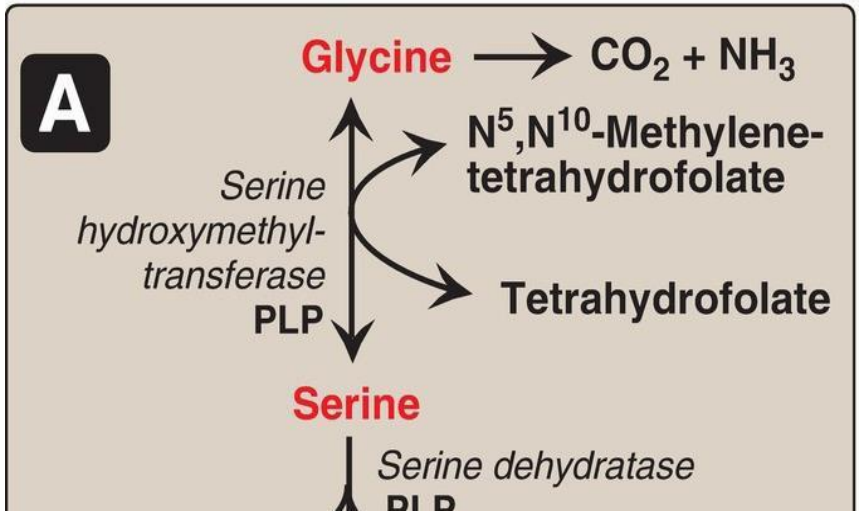



# D. Ser, Gly, and Cys: The pathways of synthesis are interconnected

- Serine - 1:
  - 3-phosphoglycerate → 3-phosphopyruvate → 3-phosphoserine → Serine
  - Oxidation; transamination; hydrolysis

- Serine – 2:
  - From Gly; serine hydroxymethyltransferase using THF as the one-carbon donor

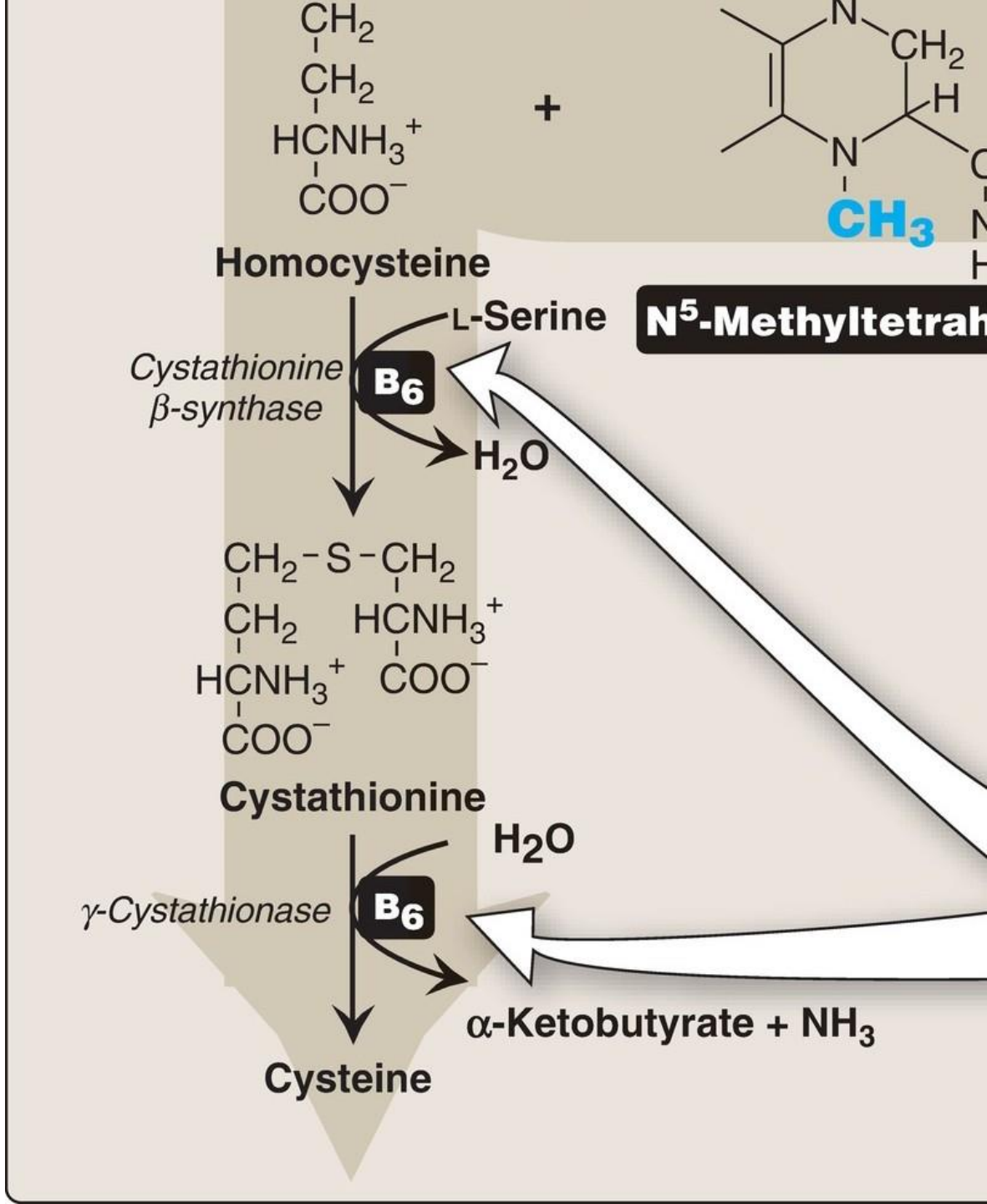


# D. Ser, Gly, and Cys: The pathways of synthesis are interconnected

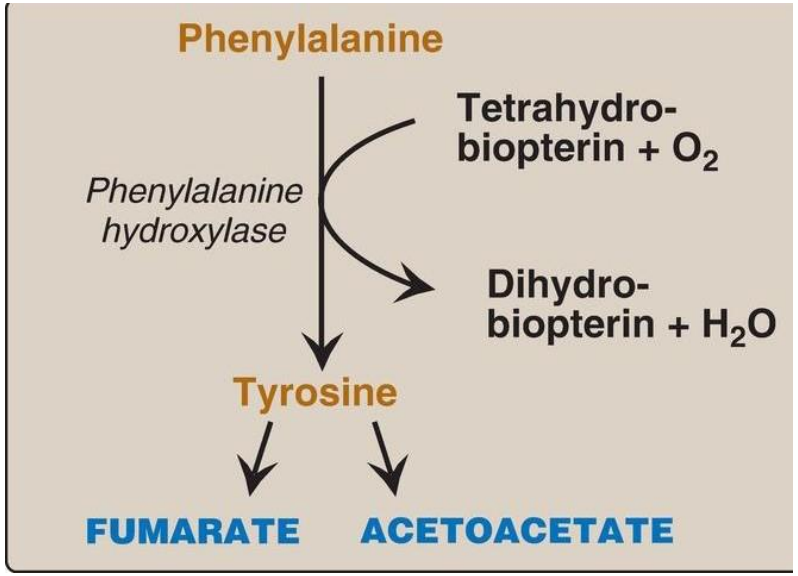
- Glycine:
  - From serine by removal of a hydroxymethyl group, also by serine hydroxymethyltransferase
  - THF is the one-carbon acceptor

- Cysteine:
  - Hcy combines with serine, forming cystathionine
  - Hydrolysis to α-ketobutyrate and cysteine



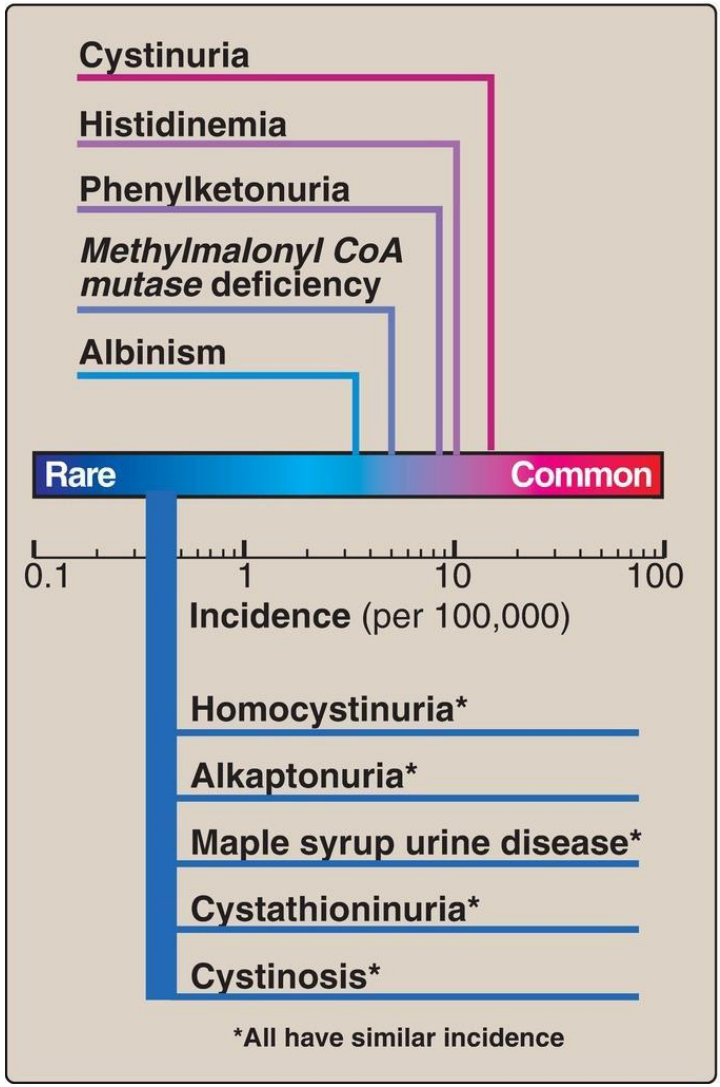
# E. Tyrosine

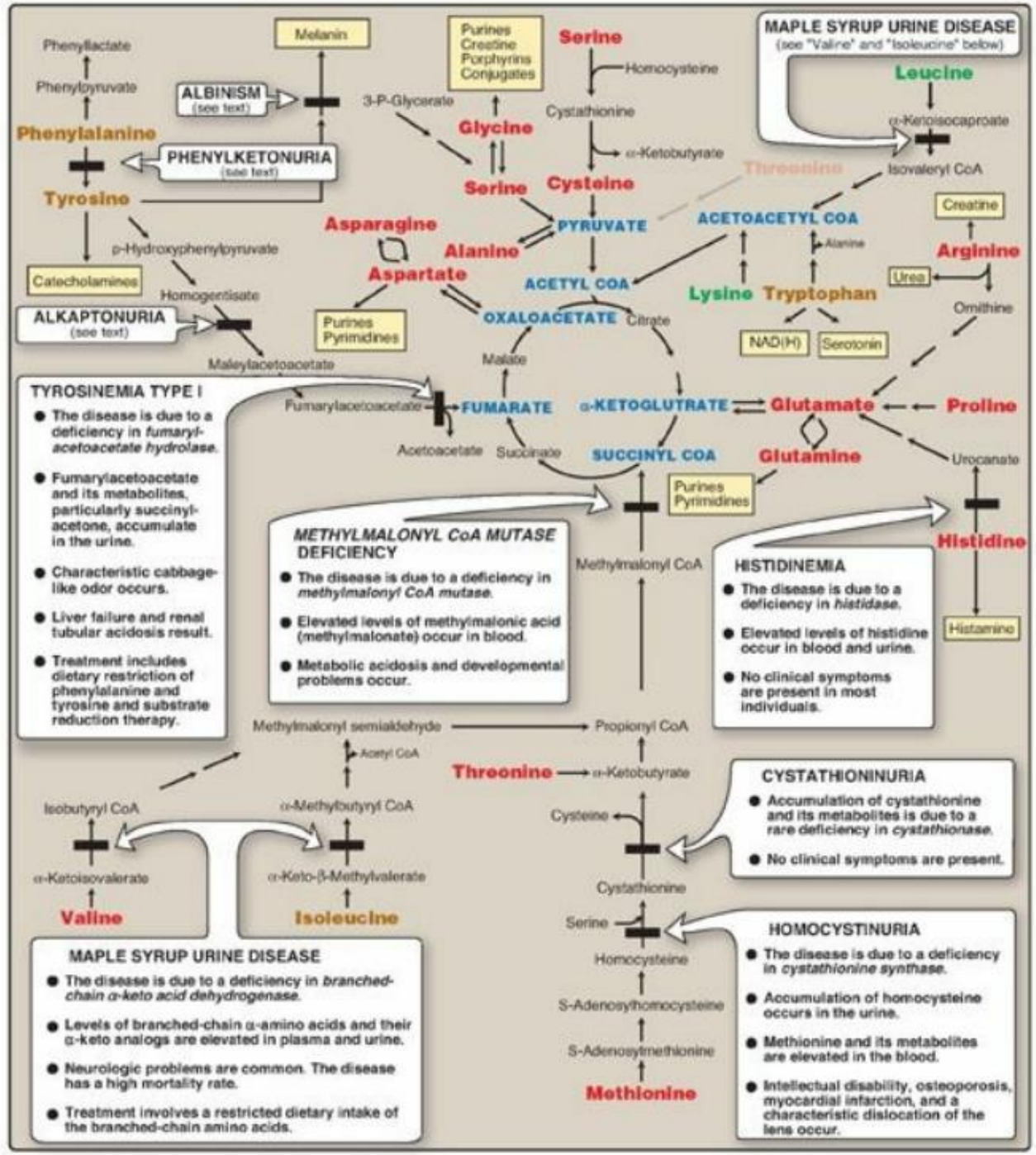
- Tyrosine is formed from phenylalanine by PAH
- Requires molecular oxygen and the coenzyme tetrahydrobiopterin ($BH_4$), which is synthesized from guanosine triphosphate (GTP)
- One atom of molecular oxygen becomes the hydroxyl group of tyrosine, and the other atom is reduced to water
- $BH_4$ is oxidized to dihydrobiopterin ($BH_2$). $BH_4$ is regenerated from $BH_2$ by NADH-requiring dihydropteridine reductase
- Tyrosine, like cysteine, is conditionally essential



# AMINO ACID METABOLISM DISORDERS

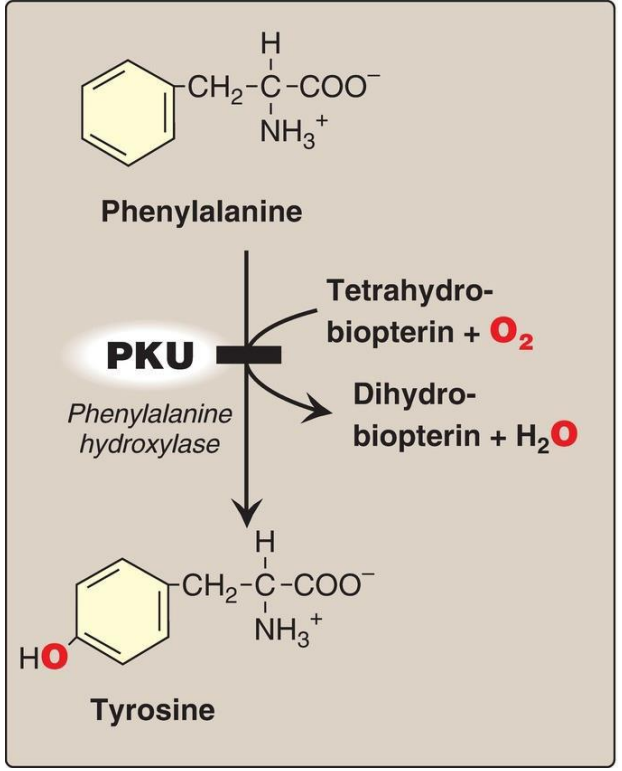
- Single gene disorders (inborn errors of metabolism)
- Variable activity of the enzymes
- Without treatment → intellectual disability or other developmental abnormalities
- >50 of these disorders have been described (most are rare , <1 per 250,000)
- Collectively, however, they constitute a very significant portion of pediatric genetic diseases

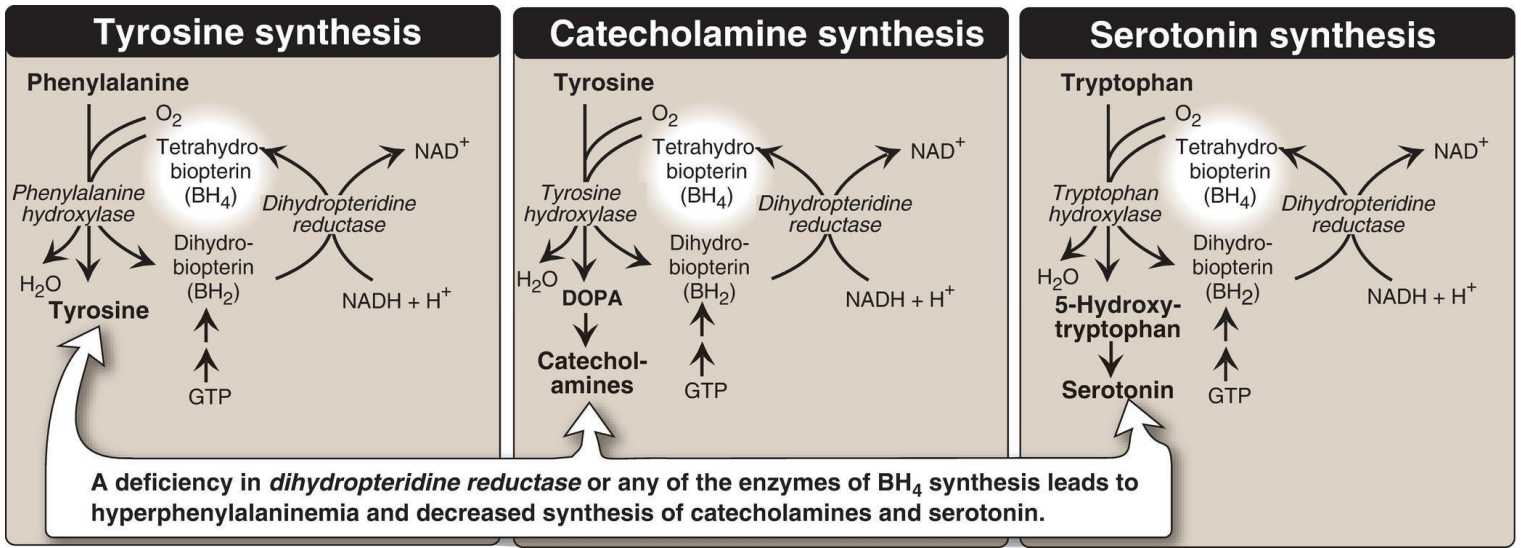



Phenyllactate
Phenylpyruvate
Phenylalanine
Tyrosine
ALBINISM
(see text)
Melanin
PHENYLKETONURIA
(see text)
Catecholamines
p-Hydroxyphenylpyruvate
Homogentisate
ALKAPTONURIA
(see text)
Maleylacetoacetate
Fumarylacetoacetate
FUMARATE
Acetoacetate
TYROSINEMIA TYPE I
● The disease is due to a deficiency in fumaryl-acetoacetate hydrolase.
● Fumarylacetoacetate and its metabolites, particularly succinyl-acetone, accumulate in the urine.
● Characteristic cabbage-like odor occurs.
● Liver failure and renal tubular acidosis result.
● Treatment includes dietary restriction of phenylalanine and tyrosine and substrate reduction therapy.
3-P-Glycerate
Glycine
Serine
Purines
Creatine
Porphyrins
Conjugates
Serine
Homocysteine
Cystathionine
α-Ketobutyrate
Cysteine
PYRUVATE
Asparagine
Alanine
Aspartate
Purines
Pyrimidines
ACETYL COA
OXALOACETATE
Citrate
Malate
α-KETOGLUTRATE
SUCCINYL COA
Succinate
METHYLMALONYL CoA MUTASE DEFICIENCY
● The disease is due to a deficiency in methylmalonyl CoA mutase.
● Elevated levels of methylmalonic acid (methylmalonate) occur in blood.
● Metabolic acidosis and developmental problems occur.
Methylmalonyl CoA
Methylmalonyl semialdehyde
Acetyl CoA
Propionyl CoA
Threonine
α-Ketobutyrate
Isobutyryl CoA
α-Methylbutyryl CoA
α-Ketoisovalerate
α-Keto-β-Methylvalerate
Valine
Isoleucine
MAPLE SYRUP URINE DISEASE
● The disease is due to a deficiency in branched-chain α-keto acid dehydrogenase.
● Levels of branched-chain α-amino acids and their α-keto analogs are elevated in plasma and urine.
● Neurologic problems are common. The disease has a high mortality rate.
● Treatment involves a restricted dietary intake of the branched-chain amino acids.
MAPLE SYRUP URINE DISEASE
(see "Valine" and "Isoleucine" below)
Leucine
α-Ketoisocaproate
Isovaleryl CoA
Threonine
ACETOACETYL COA
Alanine
Lysine
Tryptophan
NAD(H)
Serotonin
Creatine
Arginine
Urea
Ornithine
Proline
Glutamate
Glutamine
Urocanate
Histidine
Histamine
Purines
Pyrimidines
HISTIDINEMIA
● The disease is due to a deficiency in histidase.
● Elevated levels of histidine occur in blood and urine.
● No clinical symptoms are present in most individuals.
CYSTATHIONINURIA
● Accumulation of cystathionine and its metabolites is due to a rare deficiency in cystathionase.
● No clinical symptoms are present.
Cysteine
Cystathionine
Serine
Homocysteine
S-Adenosylhomocysteine
S-Adenosylmethionine
Methionine
HOMOCYSTINURIA
● The disease is due to a deficiency in cystathionine synthase.
● Accumulation of homocysteine occurs in the urine.
● Methionine and its metabolites are elevated in the blood.
● Intellectual disability, osteoporosis, myocardial infarction, and a characteristic dislocation of the lens occur.

# A. Phenylketonuria

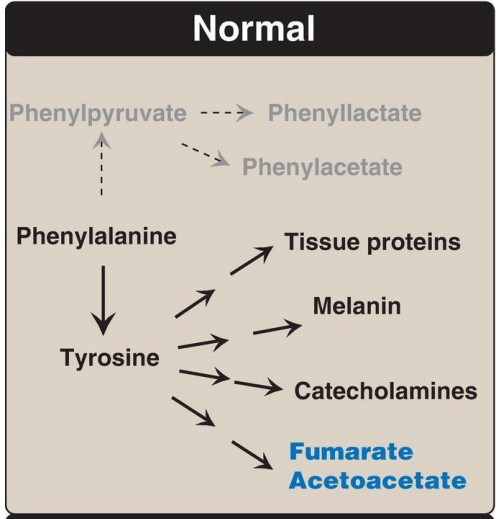
- The most common clinically encountered inborn error of amino acid metabolism (incidence 1:15,000)
- Deficiency of PAH and hyperphenylalaninemia (10 folds; plasma, urine, tissues), Tyrosine is deficient
- Management!
- Other causes of Hyperphenylalaninemia (indirect) and management!

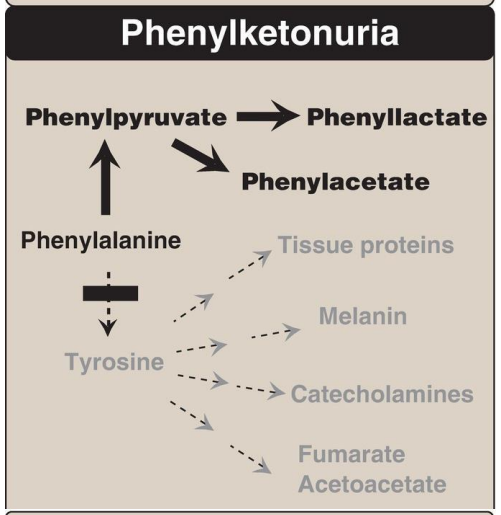


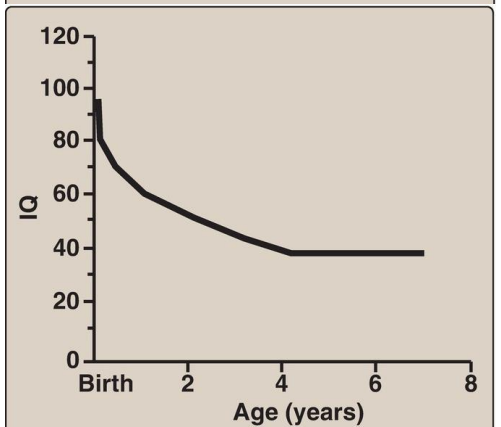



# A. Phenylketonuria

- Name of the disease?
  - Elevated levels of phenylketones
  - Phenylpyruvate (a phenylketone), phenylacetate, and phenyllactate, which are not normally produced in significant amounts
  - These metabolites give urine a characteristic musty ("mousy") odor
- CNS effects:
  - Severe intellectual disability, developmental delay, microcephaly, and seizures
  - Symptoms of intellectual disability by age 1 year and
  - Rarely achieves an intelligence quotient (IQ) >50

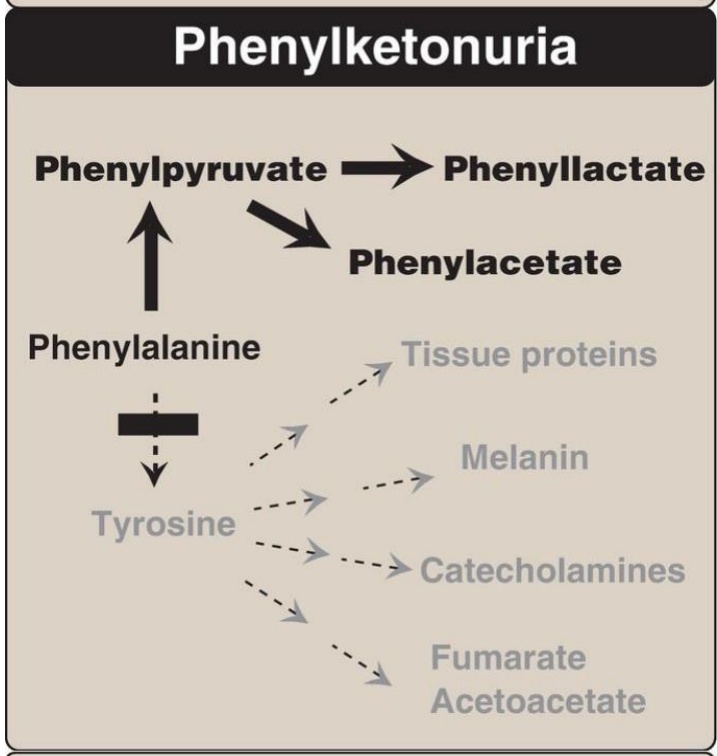


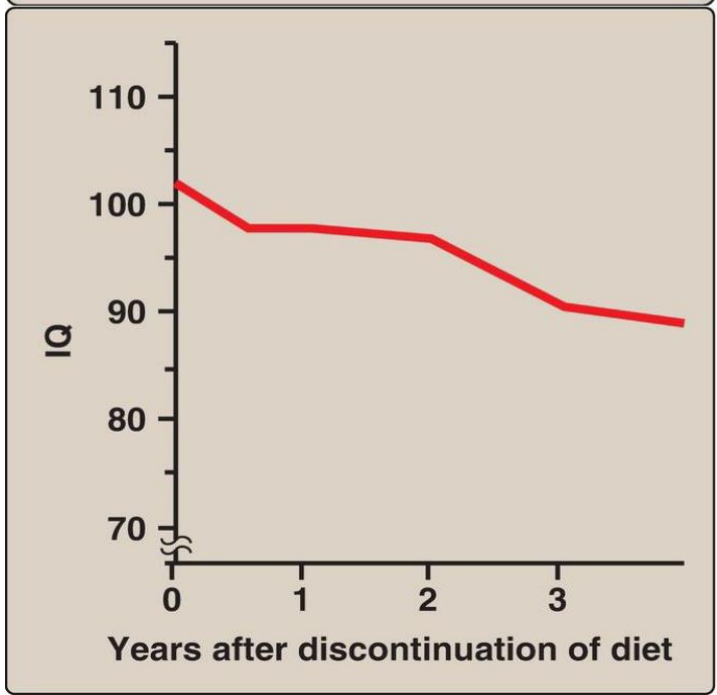



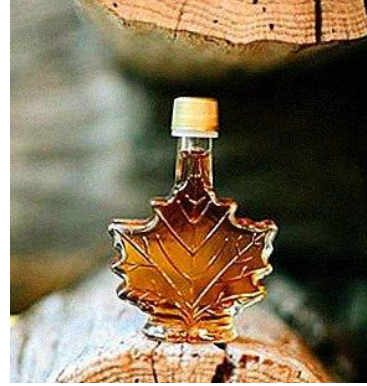
# A. Phenylketonuria

- Hypopigmentation
  - (fair hair, light skin color, and blue eyes)
  - The hydroxylation of tyrosine by copper-requiring tyrosinase, is decreased
- Newborn screening and diagnosis (24-48h)
- Management! Aspartame
- Maternal phenylketonuria syndrome:
  - Teratogenic (microcephaly and congenital heart abnormalities)
  - Prior to conception



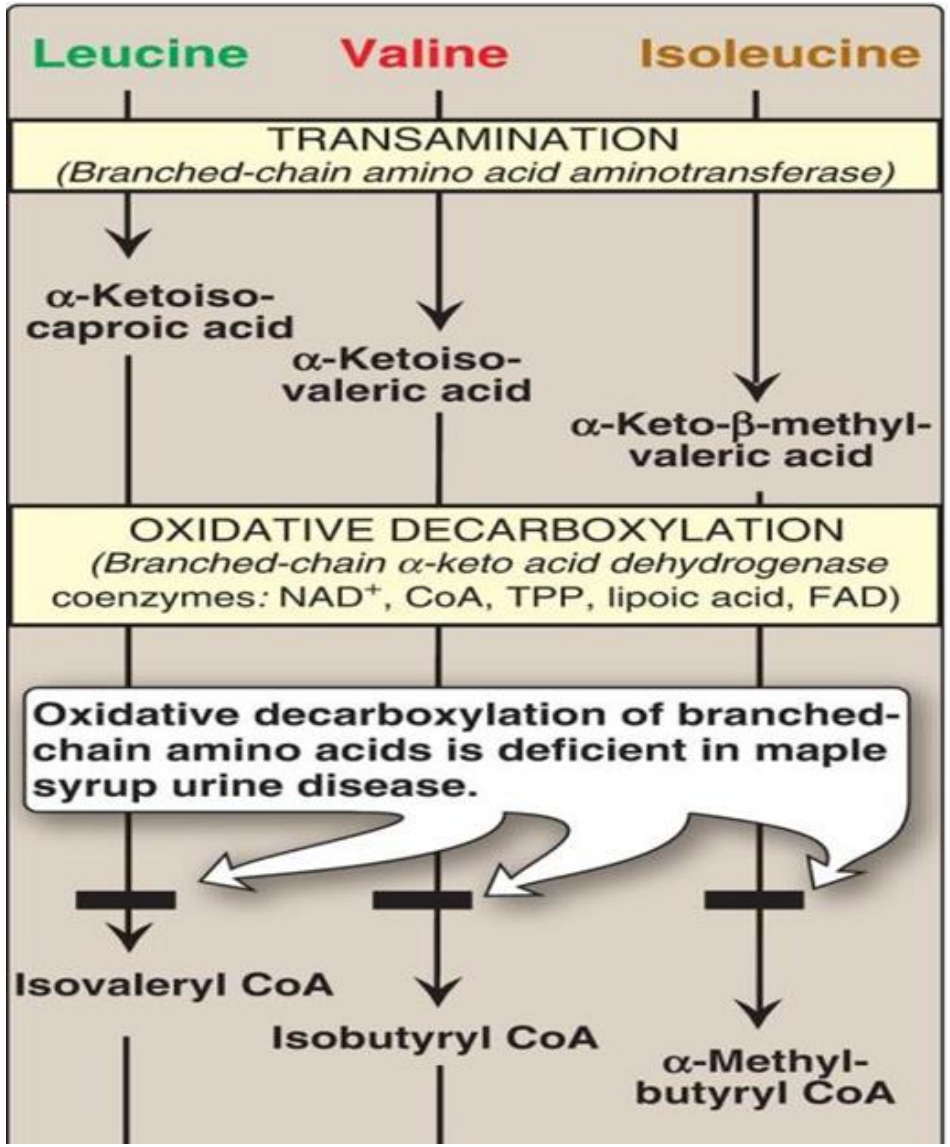
# B. Maple syrup urine disease

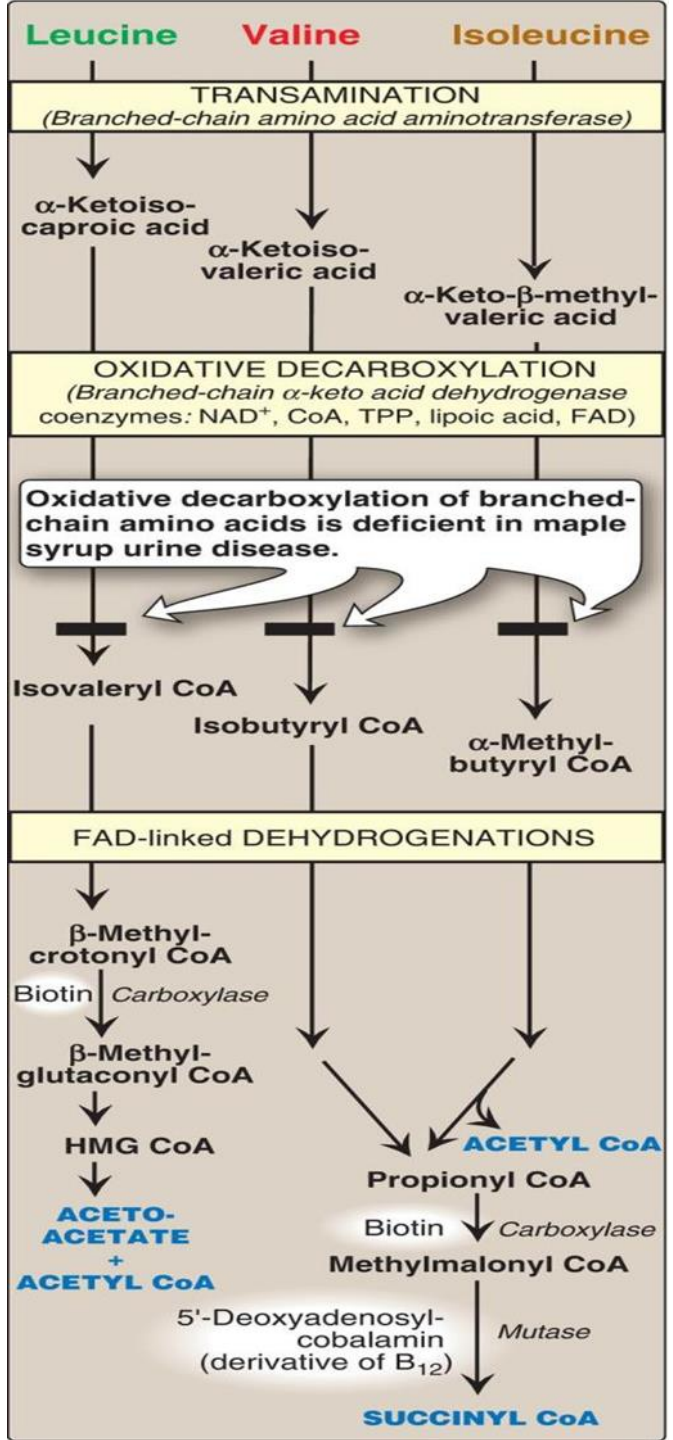


- Autosomal recessive
- Deficiency in BCKD
- BCAA and their corresponding α-keto acids accumulate causing CNS effects
- Feeding problems, vomiting, ketoacidosis, changes in muscle tone, neurologic problems
- Characteristic maple syrup–like urine odor (Ile)

- If untreated, the disease is fatal
- If treatment is delayed, intellectual disability results
- Screening and diagnosis

# B. Maple syrup urine disease



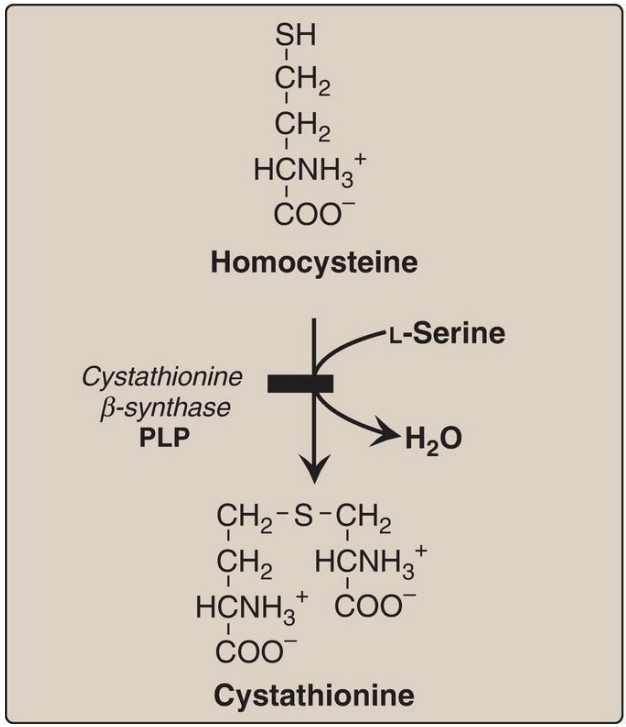
# C. Albinism

- A group of conditions in which a defect in tyrosine metabolism results in a deficiency in the production of melanin
- Partial or full absence of pigment from the skin, hair, and eyes
- Albinism appears in different forms, and it may be inherited as: autosomal recessive (primary mode), autosomal dominant, or X-linked

- Total absence of pigment (tyrosinase-negative oculocutaneous albinism, type 1 albinism), results from an absent or defective copper-requiring tyrosinase
- Hypopigmentation, vision defects, photophobia, increased risk for skin cancer

# D. Homocystinuria

- A group of disorders, autosomal-recessive, high urinary levels of Hcy, high plasma levels of Hcy and methionine, and low plasma levels of cysteine
- Most common cause: cystathionine β-synthase
- Homozygous patients exhibit increased risk for developing thrombi (the major cause of early death)
- Management: restriction of methionine and supplementation with vitamin B12 and folate
- Some patients are responsive to oral administration of pyridoxine (milder form)
- Deficiencies in methylcobalamin or MTHF reductase [MTHFR]; also result in elevated Hcy



# E. Alkaptonuria and Tyrosinemia Type 1

- A rare organic aciduria: a deficiency in homogentisic acid oxidase (accumulation of HA)
- Symptoms: homogentisic aciduria (oxidized to a dark pigment), early onset of arthritis in the large joints, and deposition of black pigment (ochronosis) in cartilage and collagenous tissue
- Management!

- Deficiencies in fumarylacetoacetate hydrolase, result in tyrosinemia type I and a characteristic cabbage-like odor to urine