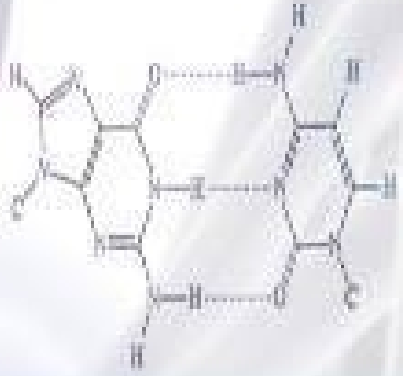
Medical Committee
The University of Jordan

SLIDE SHEET

SLIDE : 29

DR.NAME: Dr. Nafeth

Biochemistry



Majida Al-Foqaraa'

carbon skeleton
Amino Acid metabolism

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Important coenzymes

- **Pyridoxal phosphate** (PLP, B_6), transamination and certain **carbon skeleton catabolism**
- **Tetrahydrofolate** (FH_4), folic acid**, one-carbon transfer** regardless of the oxidation state, degradation & synthesis pathways
- **Tetrahydrobiopterin** (BH_4), required for **ring hydroxylation** reactions (e.g., phenylalanine to tyrosine), utilize molecular O_2

Synthesis of amino acids

- 11 non-essential, 9 essential
- Usually, non-essential are used for synthesis of nitrogen compounds
- 9/11 can be produced from glucose plus a source of nitrogen
- 2/11 (tyrosine & cysteine [S only]), require essential aa for synthesis
- 10/11 (glucose derived); carbon skeletons are derived from intermediates of glycolysis & TCA cycle

Essential Amino Acid Mnemonic

Private Tim Hall => PVT TIM HALL

P.V.T.

- P = Phenylalanine
- V - Valine
- T - Threonine

T.I.M.

- T - Tryptophan
- I - Isoleucine
- M - Methionine

H.A.L.L.

- H - Histidine
- A - Arginine*
- L - Leucine
- L - Lysine

* Only essential during (+)Nitrogen Balance

Synthesis of amino acids

- 4/10 (serine, glycine, cysteine, & alanine) are produced from intermediates of glycolysis
- 6/10 are produced from TCA cycle intermediates
- 4/6 (glutamate, glutamine, proline, & arginine) have α-Ketoglutarate as the precursor
- 2/6 (aspartate & asparagine) have oxaloacetate as the precursor

Degradation of amino acids

- Generally, pathways are distinct from biosynthetic ones
- Almost every amino acid will have a degradative pathway that can generate NADH
- The fate of the carbons depends on the physiologic state of the individual (fed vs. fasting)

Degradation of amino acids

- Liver is the only tissue that has all synthetic & degradative pathways

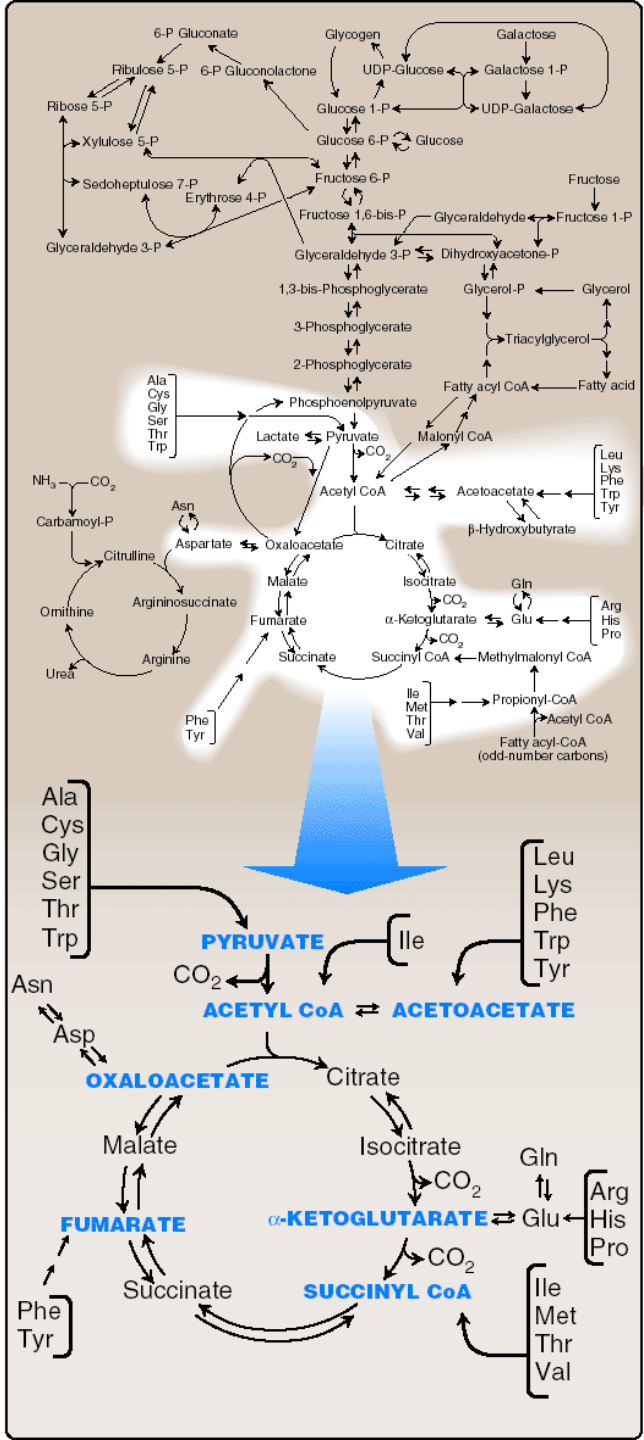
- Carbons are degraded & converted to
  - ✓ CO_2
  - ✓ Glucose (puruvate & TCA intermediates –(α-SCoA-F-O)
  - ✓ ketone bodies precursors (acetoacetate & acetyl CoA)
- Degradation classify amino acids to glucogenic, ketogenic, or both

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

Degradation of amino acids

- Carbon skeletons converge to form seven intermediate products:
  - ✓ **Oxaloacetate**
  - ✓ **α-ketoglutarate**
  - ✓ **Pyruvate**
  - ✓ **Fumarate**
  - ✓ **Succinyl CoA**
  - ✓ **Acetyl CoA**
  - ✓ **Acetoacetate**

- These products result either in:
  - ✓ **Synthesis of glucose**
  - ✓ **Synthesis of lipid**
  - ✓ **Production of energy (CO_2 & H_2O) by TCA cycle**

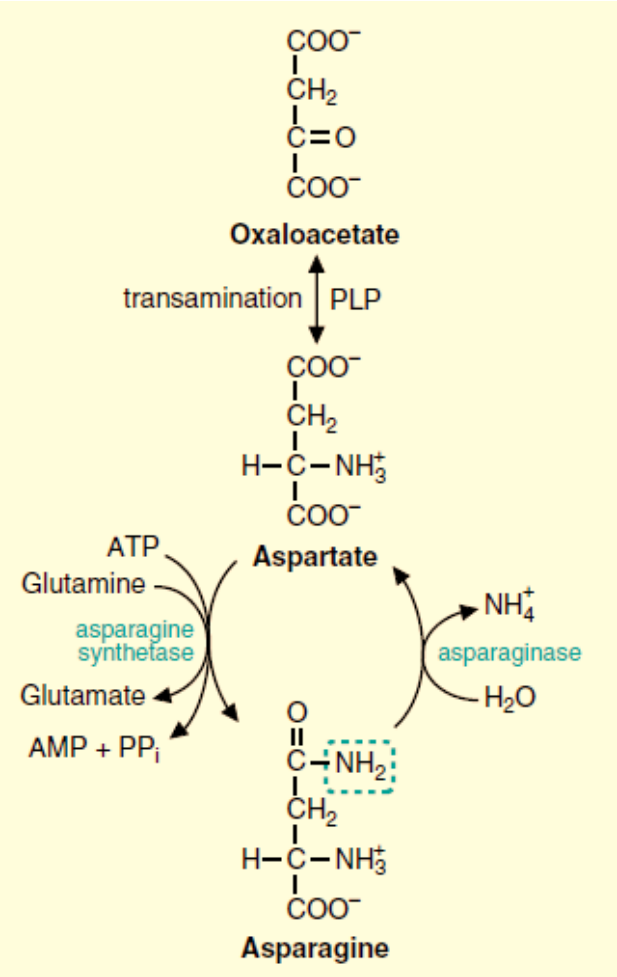


A. Amino Acids that form Oxaloacetate

- **1. Aspartate**
  - AST (reversible)

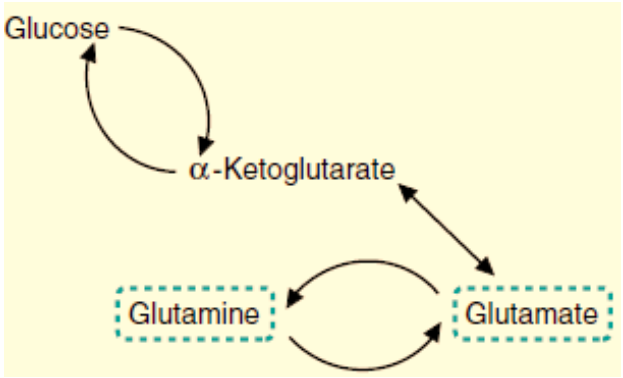
- **2. Asparagine**
  - Glutamine provides the nitrogen; different from glutamine
  - Degraded by asparginase; similar to glutaminase

✖ Asparagine is essential amino acid for some rapidly dividing leukemic cells (Asparaginase can be administered systemically to treat leukemic patients)

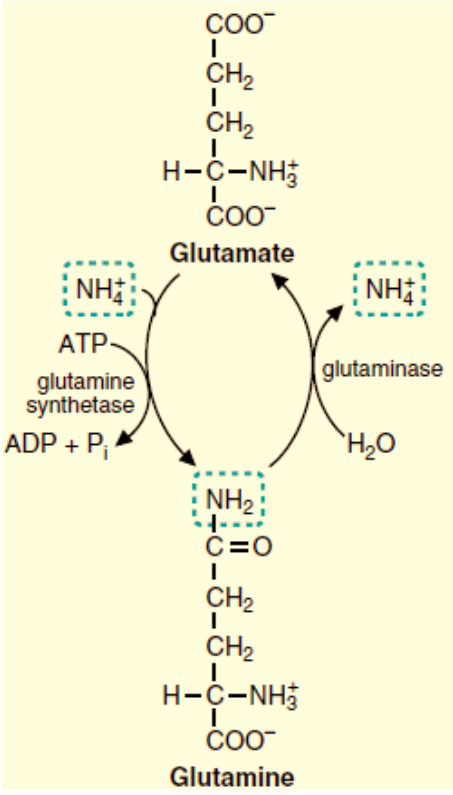


B. α-Ketoglutarate related

- **1. GLUTAMATE**
  - Transamination or Glutamate DH
  - Used for the synthesis of **Glutathione**; an important antioxidant

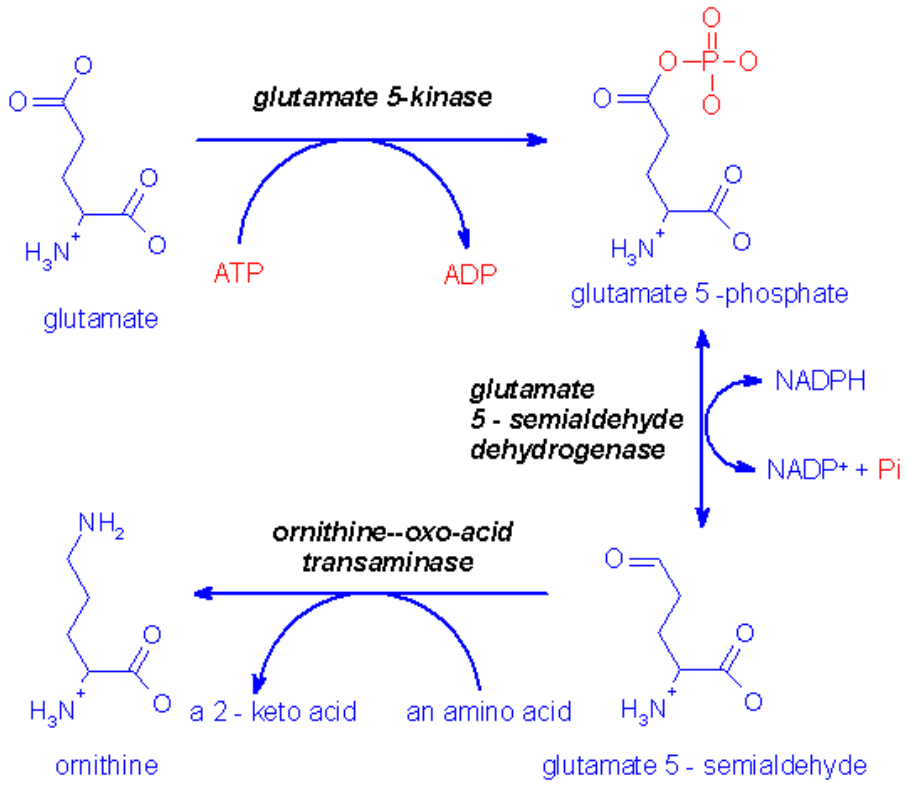


- **2. GLUTAMINE**
  - Glutamine synthetase
  - 3 human enzymes fixes free ammonia (glutamate DH & CPSI)
  - Reconverted to glutamate by a different enzyme, glutaminase



B. α-Ketoglutarate related

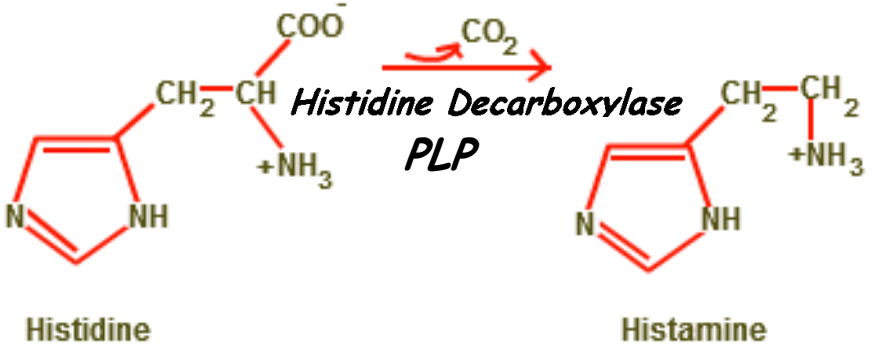
- **3. ARGININE**
  - Cleaved by arginase to form urea & ornithine
  - If ornithine is in excess, it will be transaminated to glutamate



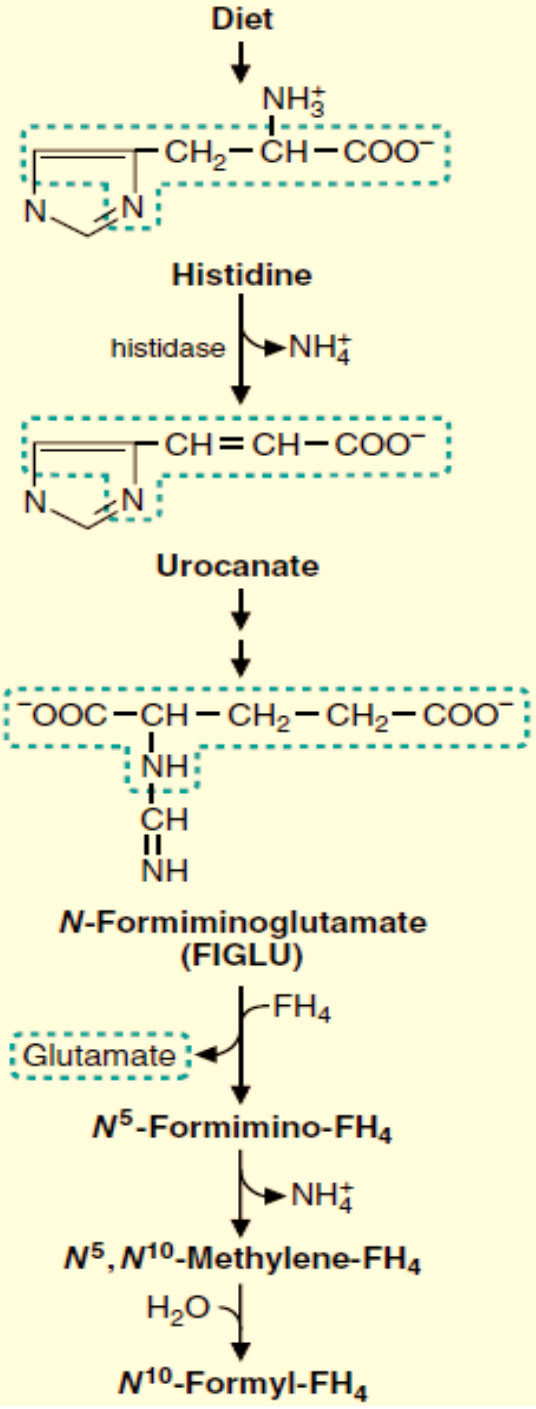
Ornithine synthesis from glutamate

B. α-Ketoglutarate related

- **4. HISTIDINE**
  - Essential, however, 5 carbons come from glutamate
  - In a series of steps, histidine is converted to N-Formiminoglutamate (FIGLU). The subsequent reactions transfer one carbon of FIGLU to the FH_4 pool and release NH_4^+ & glutamate
  - The FIGlu excretion test has been used in diagnosing a deficiency of folic acid

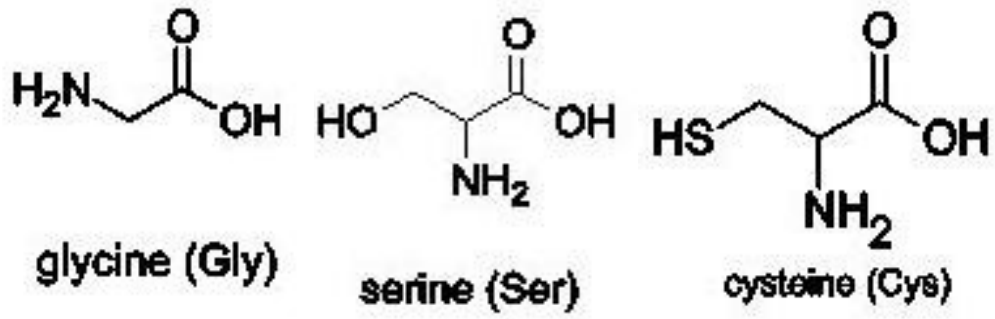


Histidine Histamine

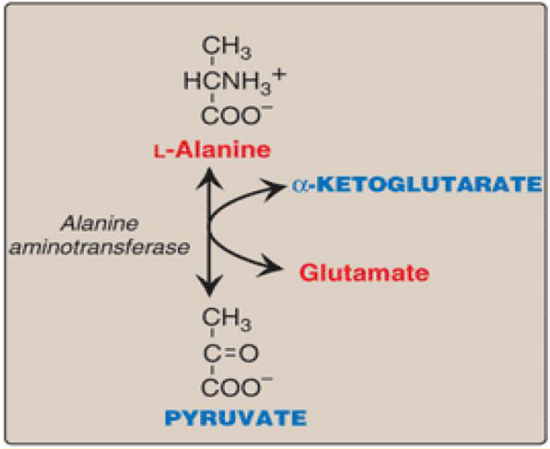


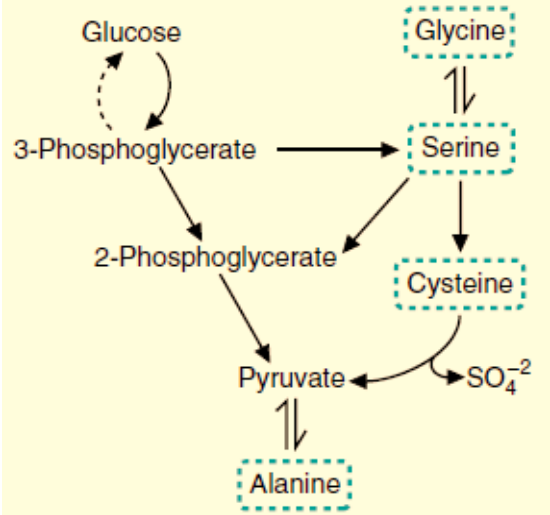
C. Pyruvate related

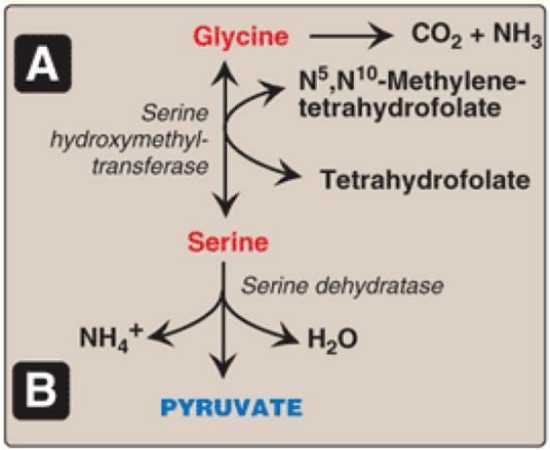
- **1. Alanine: transamination (ALT)**
- **2. Serine:**
  - Produces glycine & cysteine
  - Degraded to form pyruvate



- **3. Glycine:**
  - Synthesized mainly from serine (reversible)
  - Requires FH_4 & PLP
  - Energy can be generated directly through glycine cleavage enzyme (dehydrogenase) to produce CO_2, NH_3, & C to FH_4

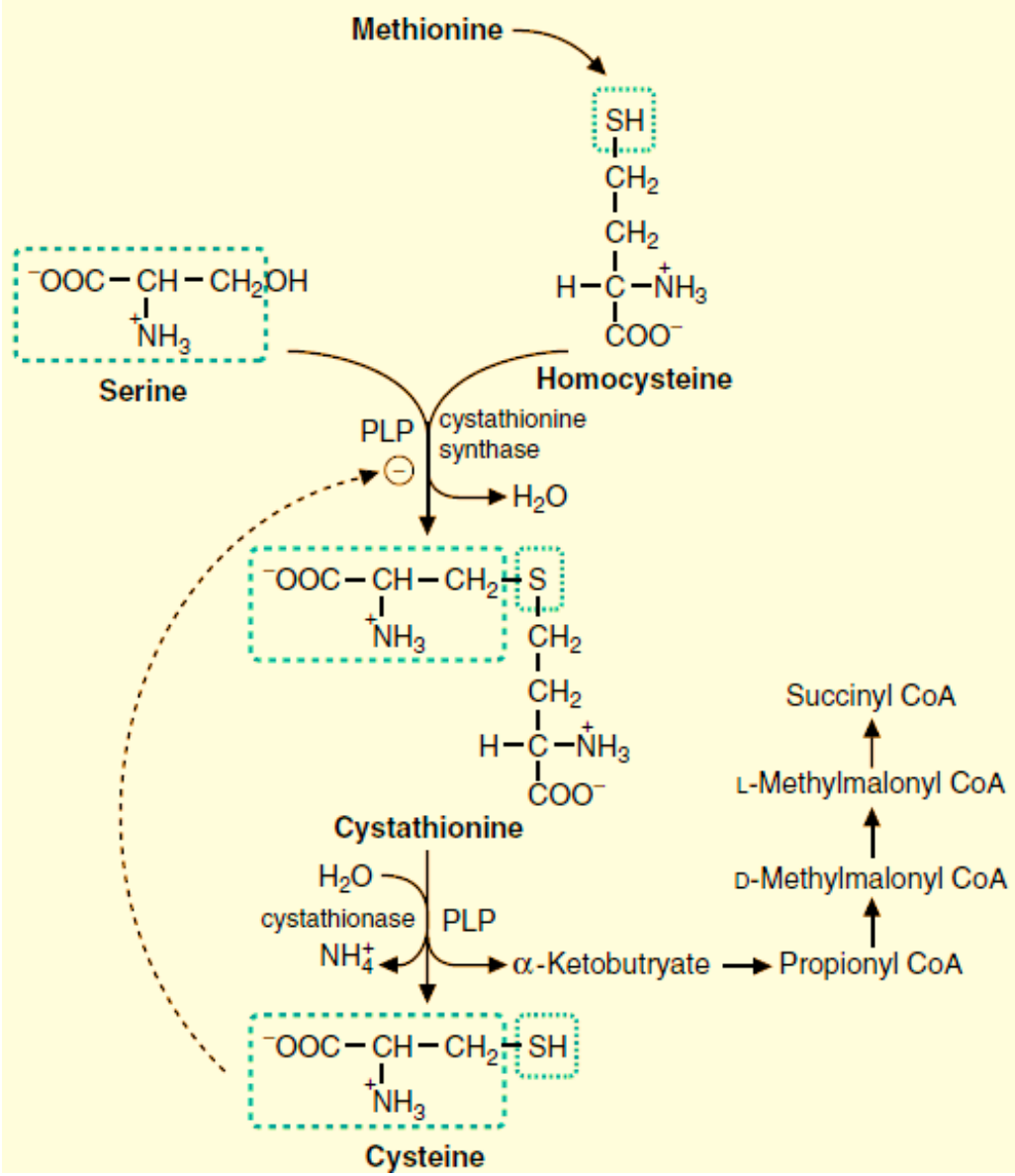






C. Pyruvate related

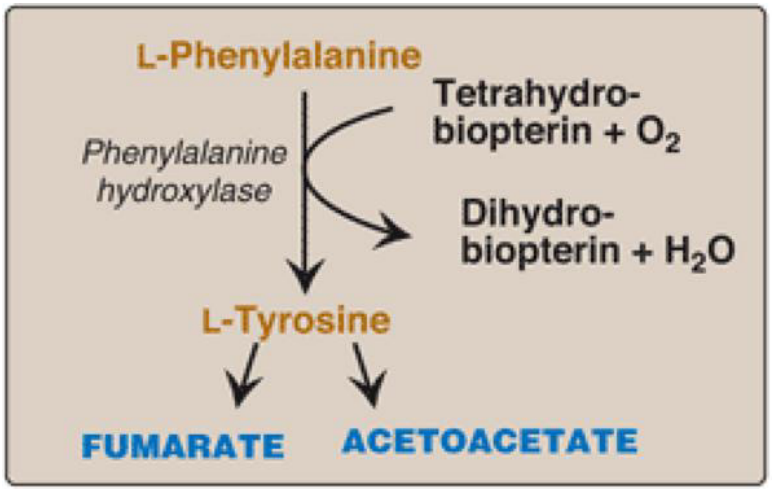
- **4. Cysteine**:
- C&N from serine
- S from methionine
- Feedback inhibition through cysteine
- <u>Cysteine essentiality is governed by methionine</u>
- <u>Excess cysteine in diet spares methionine</u>
- This is the only degradative route for homocysteine
- Requires PLP
- <u>liver desulfurase</u> produces hydrogen sulfide (H_2S) & pyruvate

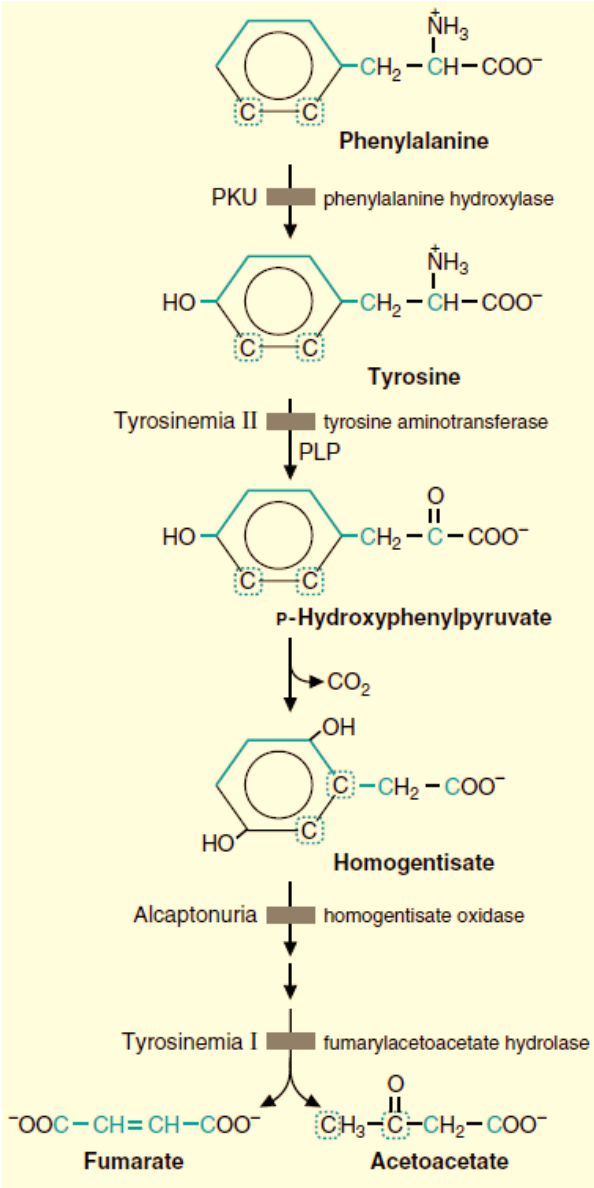


Vitamin B_6 or congenital enzyme deficiency result in homocystinemia, which is associated with CV disease

D. Fumarate related

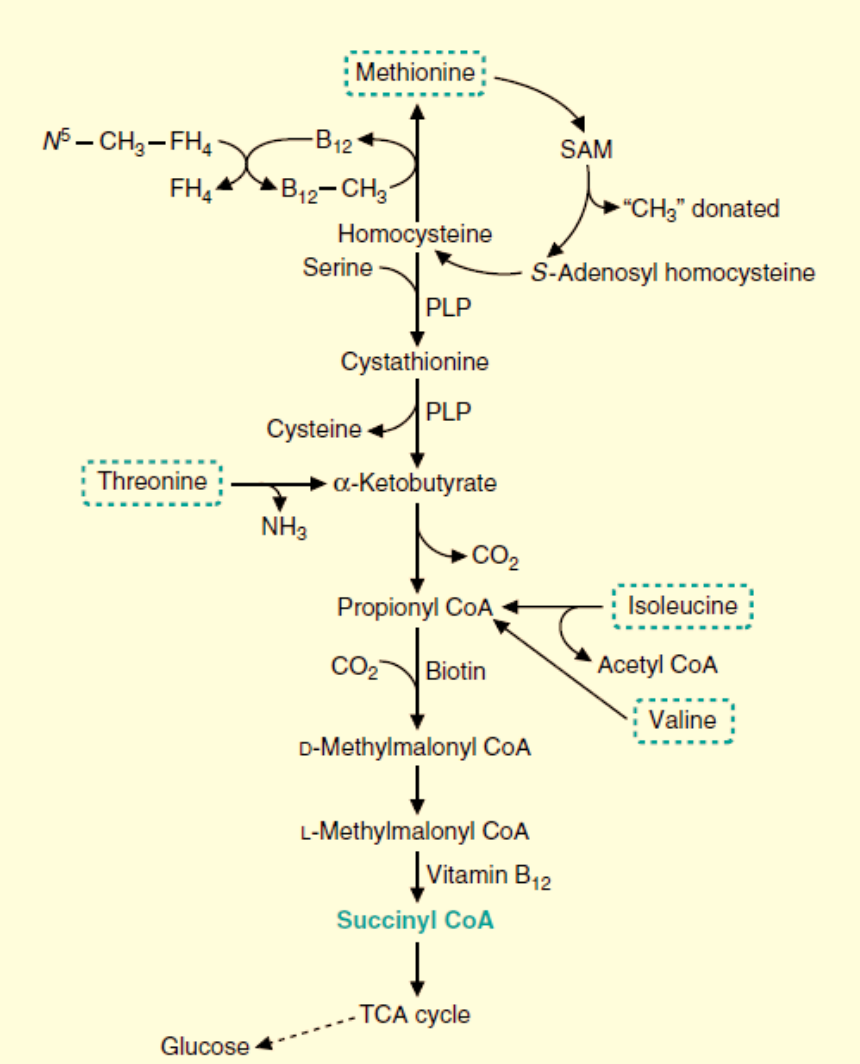
- **1. ASPARTATE**
  - Urea cycle
  - Fumarate to malate; anaplerotic or oxidative purposes
- **2. PHENYLALANINE & TYROSINE**
  - Tyrosine, hydroxylated or diet, is oxidized to form acetoacetate and fumarate
  - Diseases

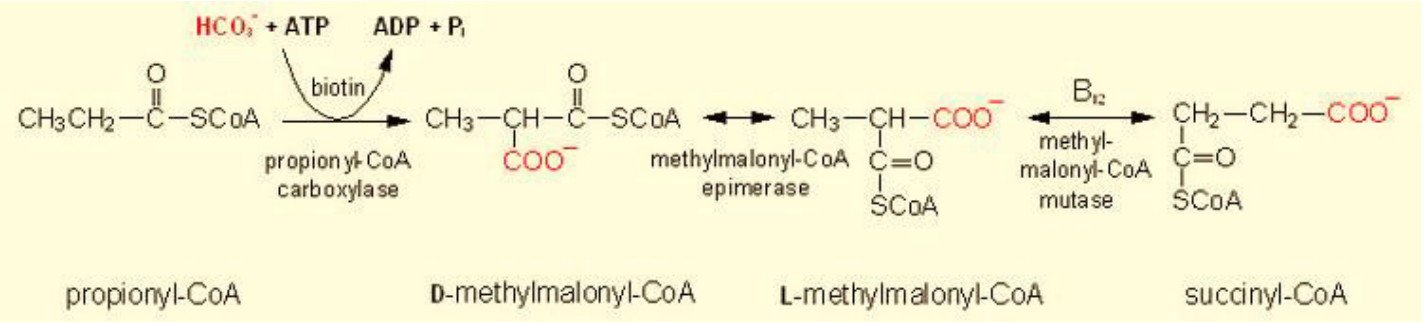




E. Amino Acids That Form Succinyl- CoA

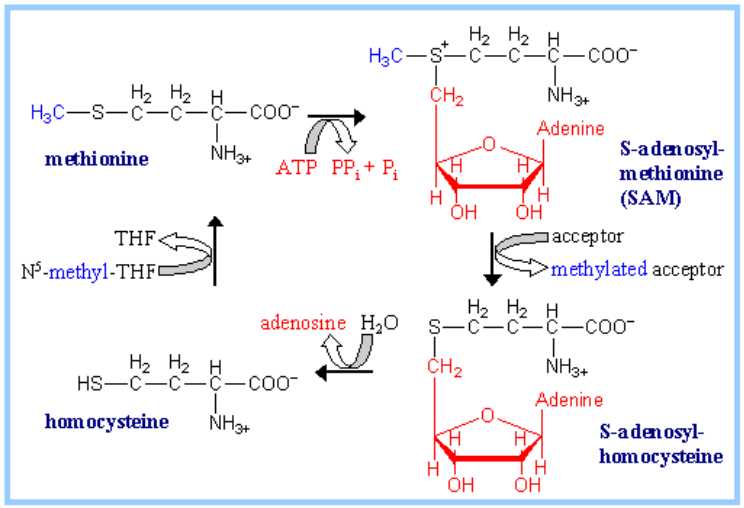
- **Met, Val, Ile, & Thr**
- Degraded to form **propionyl-CoA**
- Propionyl CoA is carboxylated (B_7) then converted to succinyl CoA (B_{12})

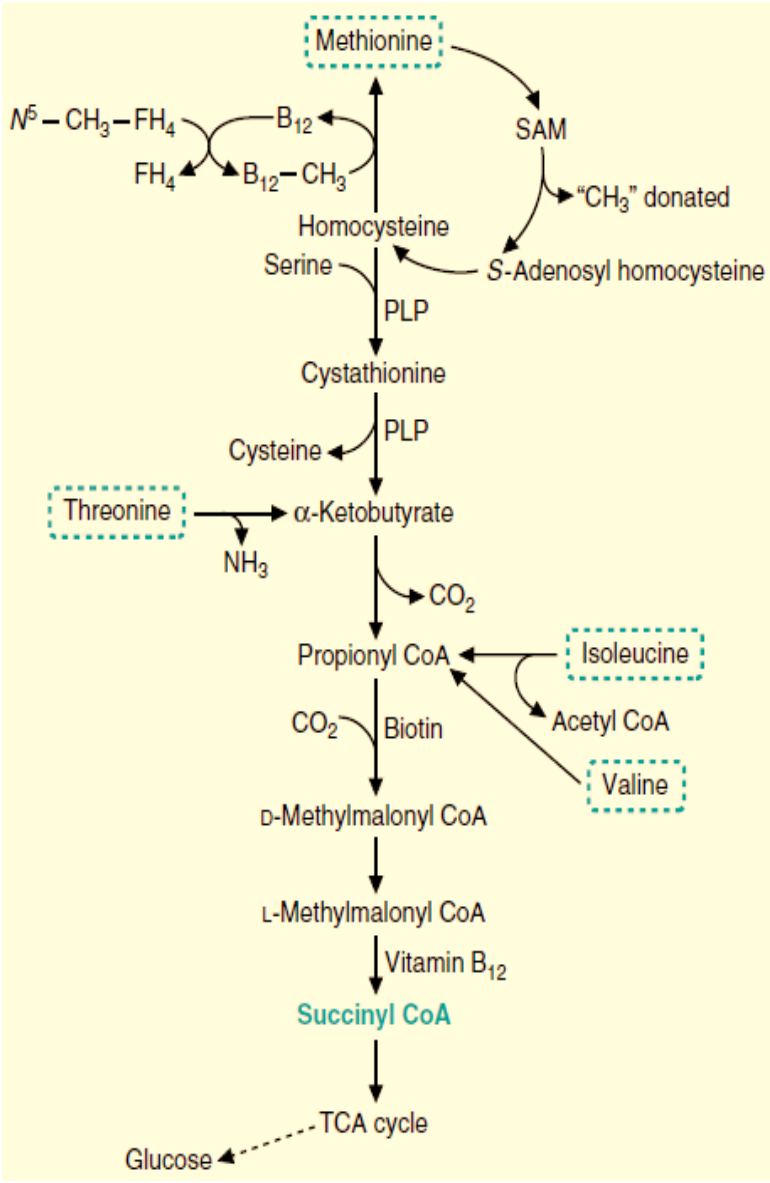




E. Amino Acids That Form Succinyl- CoA

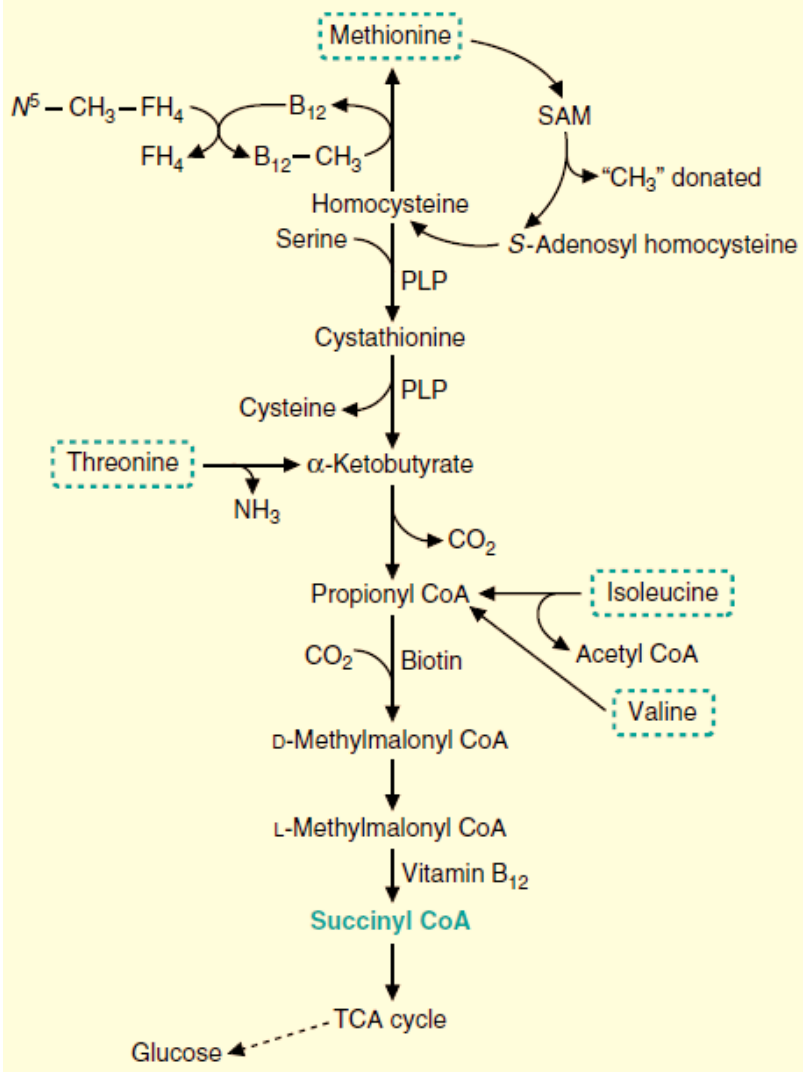
- **1. METHIONINE**
  - Methionine → SAM → S-adenosylhomocysteine (SAH)
  - SAH → homocysteine → cyseine (PLP)
  - Methionine can be regenerated from homocysteine (FH_4 & vitamin B_{12})
  - Homocystinemia is associated with CV disease





E. Amino Acids That Form Succinyl- CoA

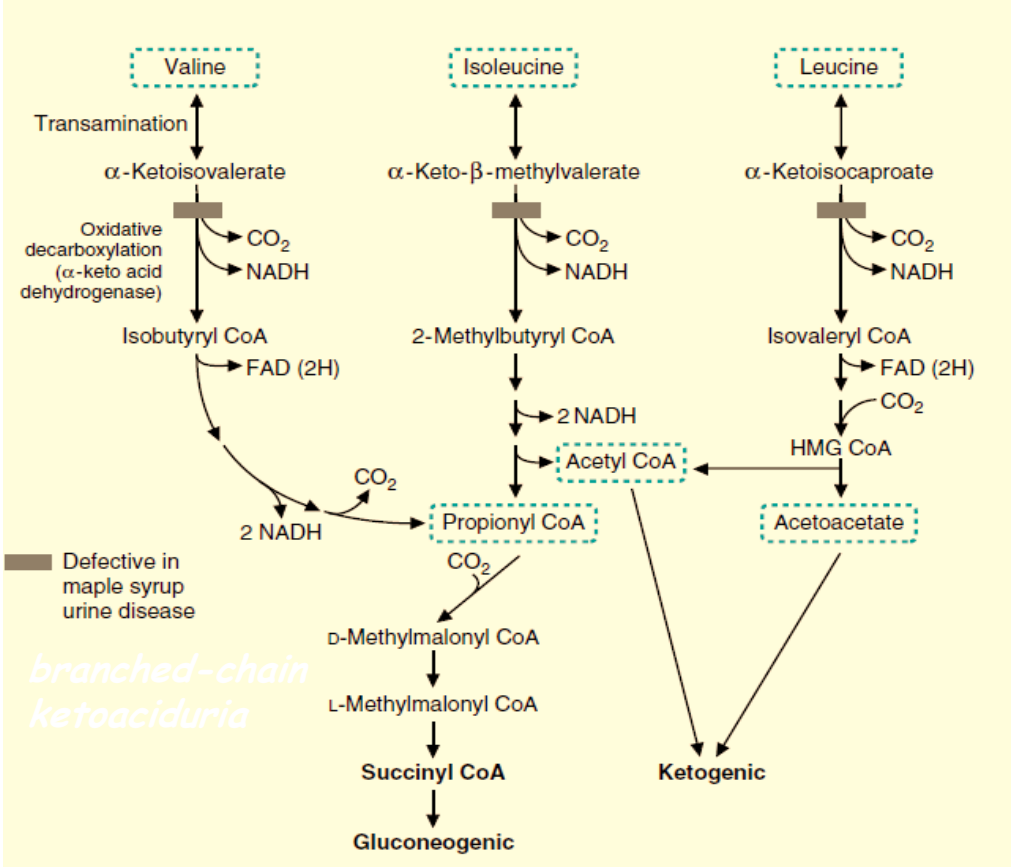
- **2. THREONINE**
  - Converted to pyruvate or to α-ketobutyrate
  - Degraded by threonine dehydratase (PLP) to ammonia and α-ketobutyrate, which subsequently undergoes oxidative decarboxylation to form propionyl CoA (succinyl CoA)



threonine --> alpha ketobutyrate + NH4+

E. Amino Acids That Form Succinyl- CoA

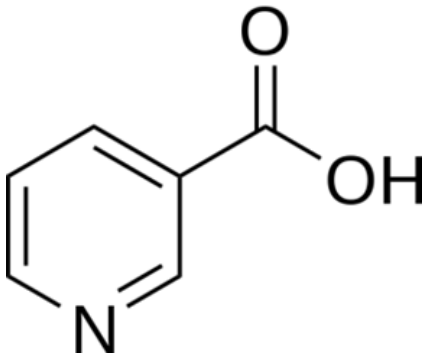
- **3. VALINE & ISOLEUCINE**
  - Branched-chain amino acids (V, I, L)
  - Almost <u>25% of the content of the average protein (energy)</u>
  - Highest degradation activity is in muscle (energy)

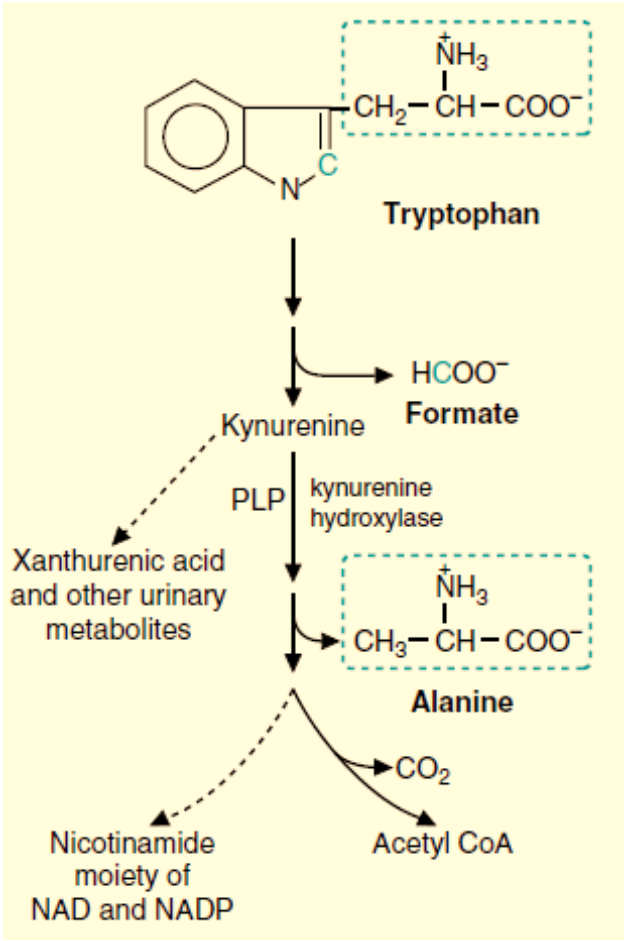


- A. Branched-chain α-amino acid aminotransferase, (PLP)
- B. Oxidative decarboxylation (α-keto acid dehydrogenase)
- Leucine, does not produce succinyl CoA (acetoacetate and acetyl CoA), strictly ketogenic

F. AMINO ACIDS THAT FORM ACETYL CoA & ACETOACETATE (ketogenic)

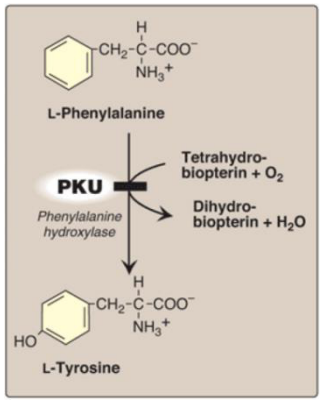
- Leu, Lys, Ile, Phe, Tyr, & Trp
- **1. Tryptophan**
  - Non-ring carbons oxidized to form alanine
  - Ring carbon oxidized to acetyl CoA
  - NAD^+ & $NADP^+$ can be produced from the ring structure of tryptophan (niacin requirements)

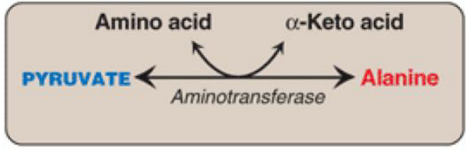


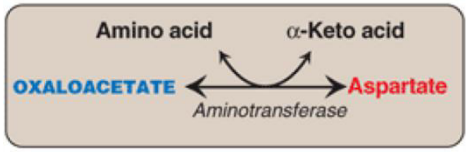


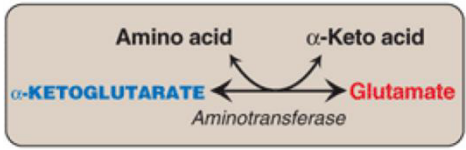
Biosynthesis of Nonessential Amino Acids

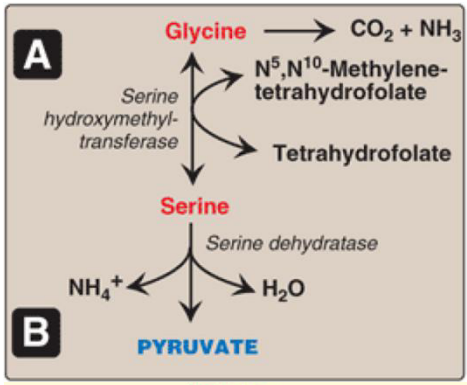
- Synthesized from intermediates of metabolism or, as in the case of tyrosine & cysteine
- A. Synthesis from α-keto acids: Alanine, aspartate, and glutamate
- B. Synthesis by amidation: Glutamine & Asparagine
- C. Proline: Glutamate converted to proline by cyclization & reduction rxns
- D. Serine, glycine, & cysteine:
  - **Serine: from glycine (serine hydroxymethyl transferase)**
  - **Glycine: from serine (serine hydroxymethyl transferase)**
  - **Cysteine: from homocysteine & serine**
- E. Tyrosine: from phenylalanine

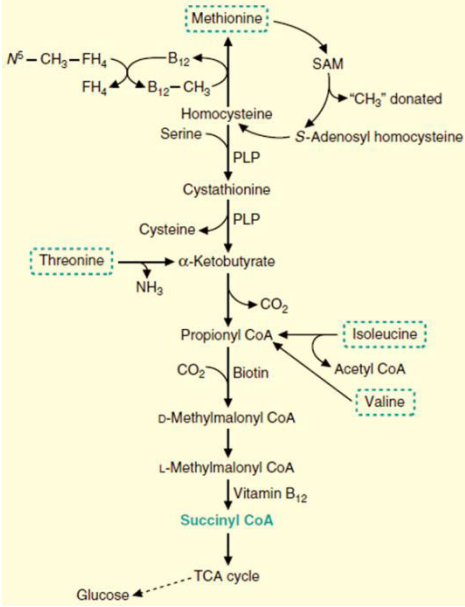










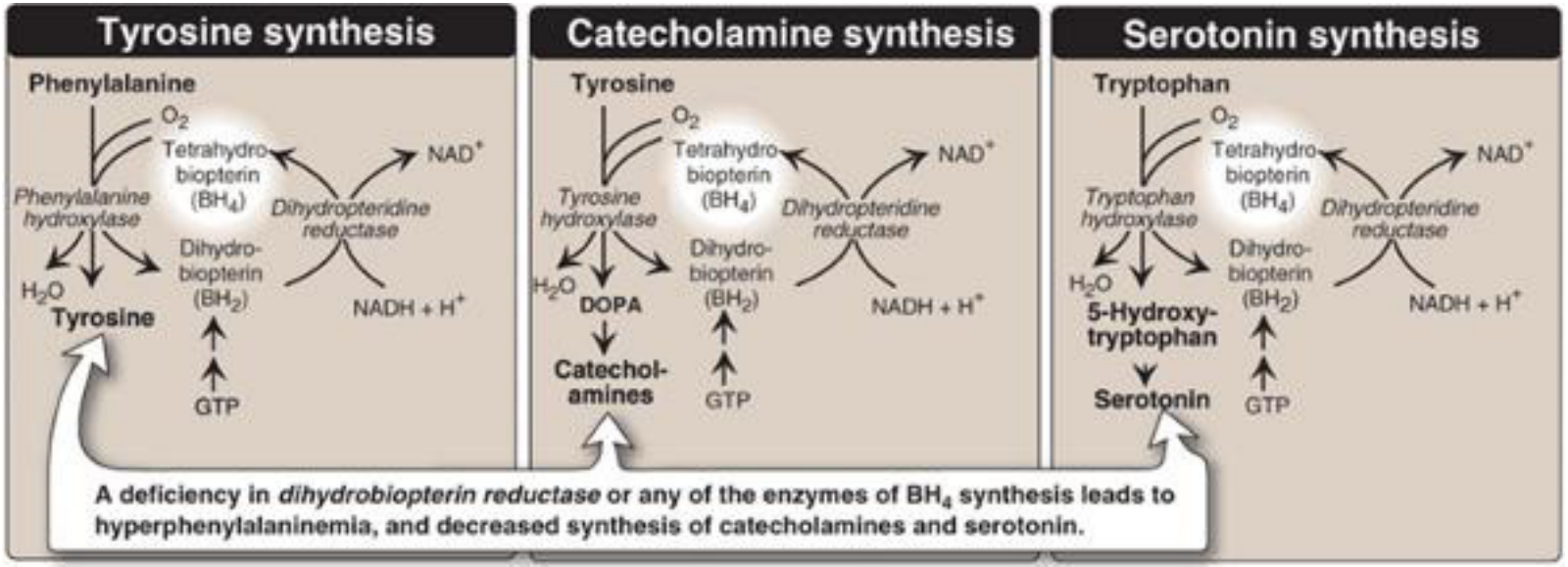


Metabolic Defects in Amino Acid Metabolism

- Commonly caused by mutant genes
- The inherited defects may be total or, mostly, partial deficiency in catalytic activity
- Without treatment, result in mental retardation or other developmental abnormalities
- More than 50 have been described, many are rare
- Phenylketonuria is relatively common

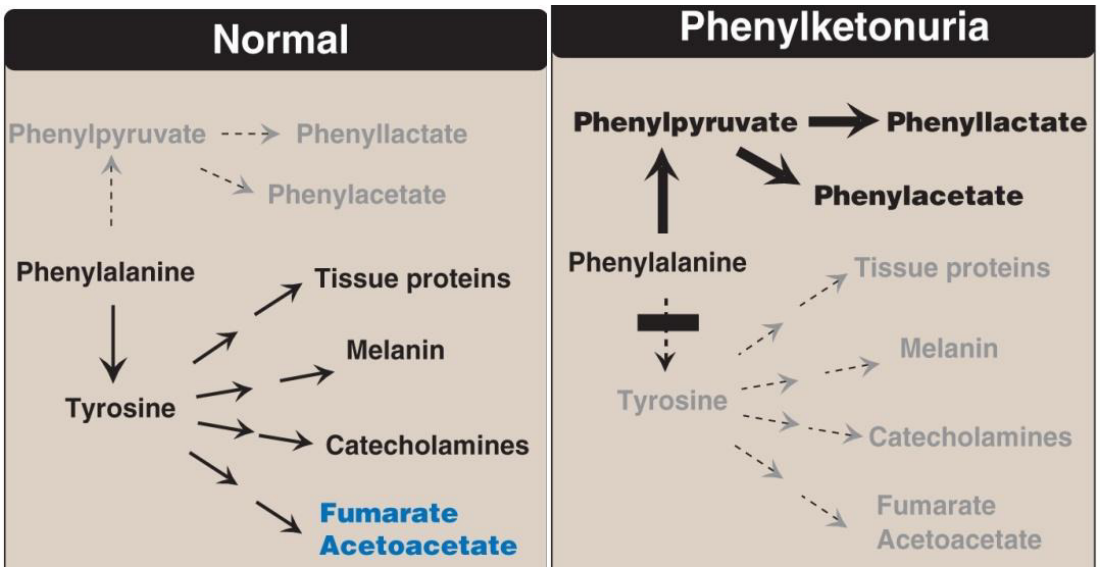
Phenylketonuria (PKU)

- Deficiency of phenylalanine hydroxylase, most common clinically encountered inborn error of amino acid metabolism
- Characterized by accumulation of phenylalanine and a deficiency of tyrosine
- Restricting dietary phenylalanine does not reverse the CNS effects (deficiencies in neurotransmitters)
- Replacement therapy improves the clinical outcome
- Maternal PKU syndrome



Phenylketonuria (PKU)

- **Characteristics of PKU:**
  - Elevated metabolites: musty (“mousey”) odor
  - CNS symptoms: Mental retardation, failure to walk or talk, seizures, …., and failure to grow



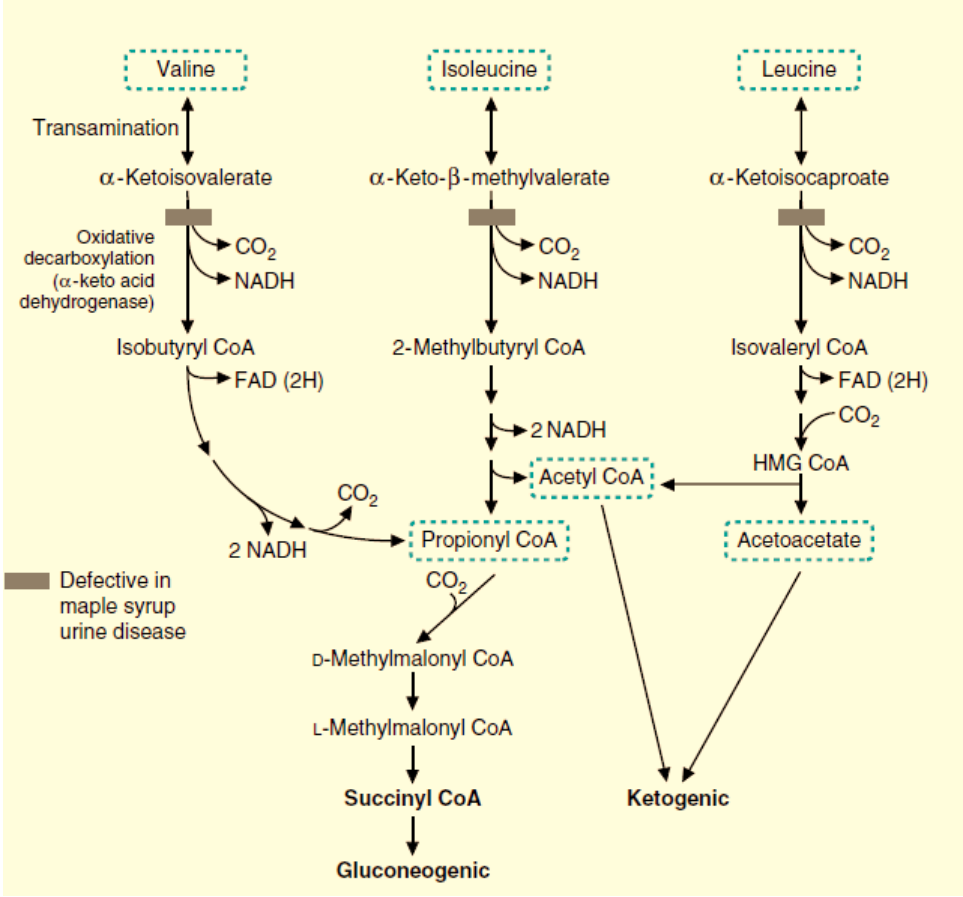
  - Untreated PKU typically shows symptoms of mental retardation by year 1 (neonatal screening, 24 to 48 hours of protein feeding)

  - Hypopigmentation: fair hair, light skin color, and blue eyes. The hydroxylation of tyrosine by tyrosinase, is the first step in the formation of the pigment melanin. It is competitively inhibited by the high levels of phenylalanine

Maple syrup urine disease

- Rare, autosomal recessive disorder
- Partial/complete deficiency (branched-chain α-keto acid dehydrogenase)

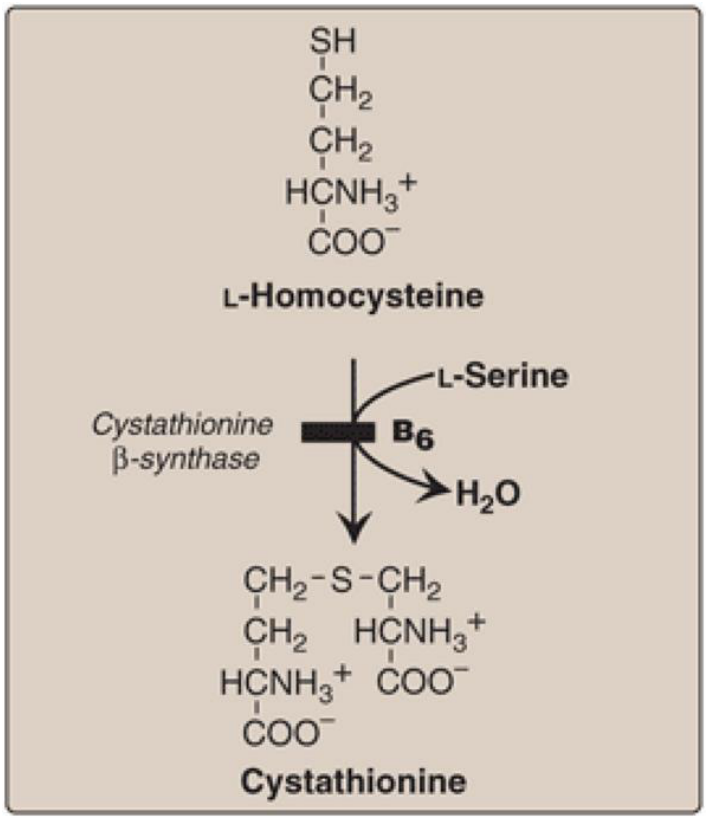
- Amino acids & their corresponding α-keto acids accumulate in the blood, causing a toxic effect that interferes with brain functions
- The disease is characterized a maple syrup odor of urine
- If untreated, leads to mental retardation, physical disabilities, & even death
- Treatment: synthetic formula - limited amounts of leucine, isoleucine, & valine — sufficient



Homocystinuria

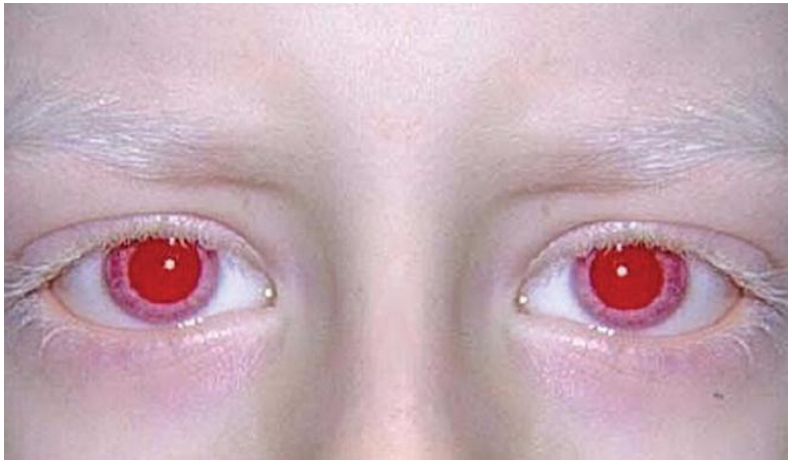
- A group of disorders involving defects in the metabolism of homocysteine
- Inherited as autosomal recessive illnesses
- Characterized by high plasma and urinary levels of homocysteine & methionine & low levels of cysteine

- The most common cause of homocystinuria is a defect in the enzyme cystathionine β-synthase, which converts homocysteine to cystathionine
- Patients can be responsive or nonresponsive to oral pyridoxine (B6)—a coenzyme of cystathionine β-synthase
- Responsive patients usually have a milder and later onset of clinical symptoms
- Treatment: restriction of methionine intake & supplementation with vitamins B6, B12, & folate



Albinism

- Refers to a group of conditions in which a defect in tyrosine metabolism results in a partial or full deficiency in the production of melanin
- Inherited by several modes: autosomal recessive, autosomal dominant, or X-linked
- Complete albinism - rare (the most severe form of the condition) results from a complete deficiency of tyrosinase activity, causing a total absence of pigment from the hair, eyes, and skin
- In addition: vision defects and photophobia and higher risk for skin cancer



Alkaptonuria

- A rare metabolic disease
- A deficiency in homogentisic acid oxidase → accumulation of homogentisic acid
- Three characteristic symptoms:
  - **Homogentisic aciduria**
  - **Large joint arthritis**
  - **Black pigmentation of cartilage & collagenous tissue**
- Patients asymptomatic until about age 40
- Diets low in protein— especially Phe & Tyr
- Although alkaptonuria is not life-threatening, the associated arthritis may be severely crippling