Lehninger

SIXTH EDITION

Principles of Biochemistry

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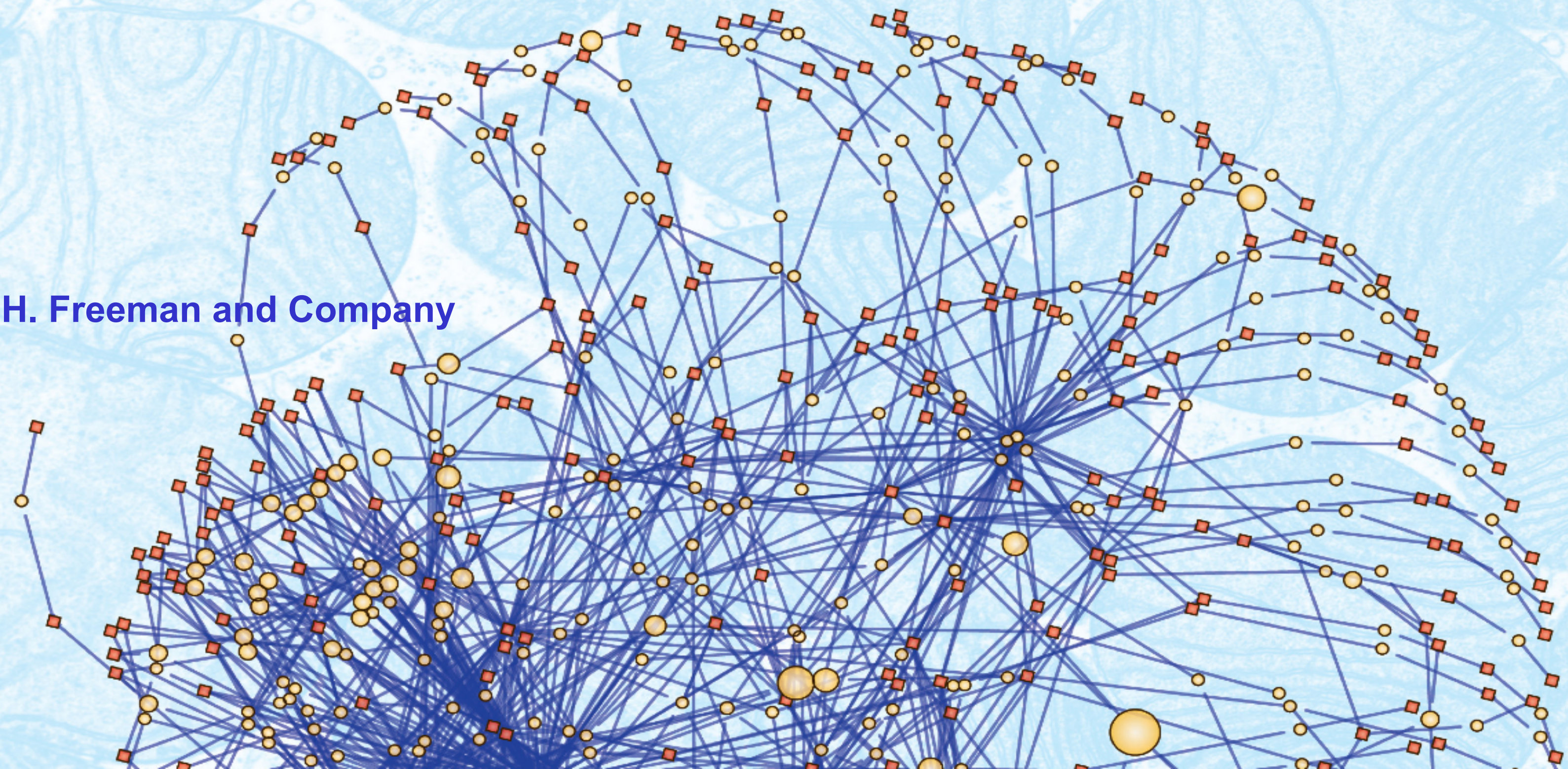
22| Biosynthesis of Amino Acids and Nucleotides



Week 16 Amino Acids and Nucleotides

22.1 Overview of Nitrogen Metabolism

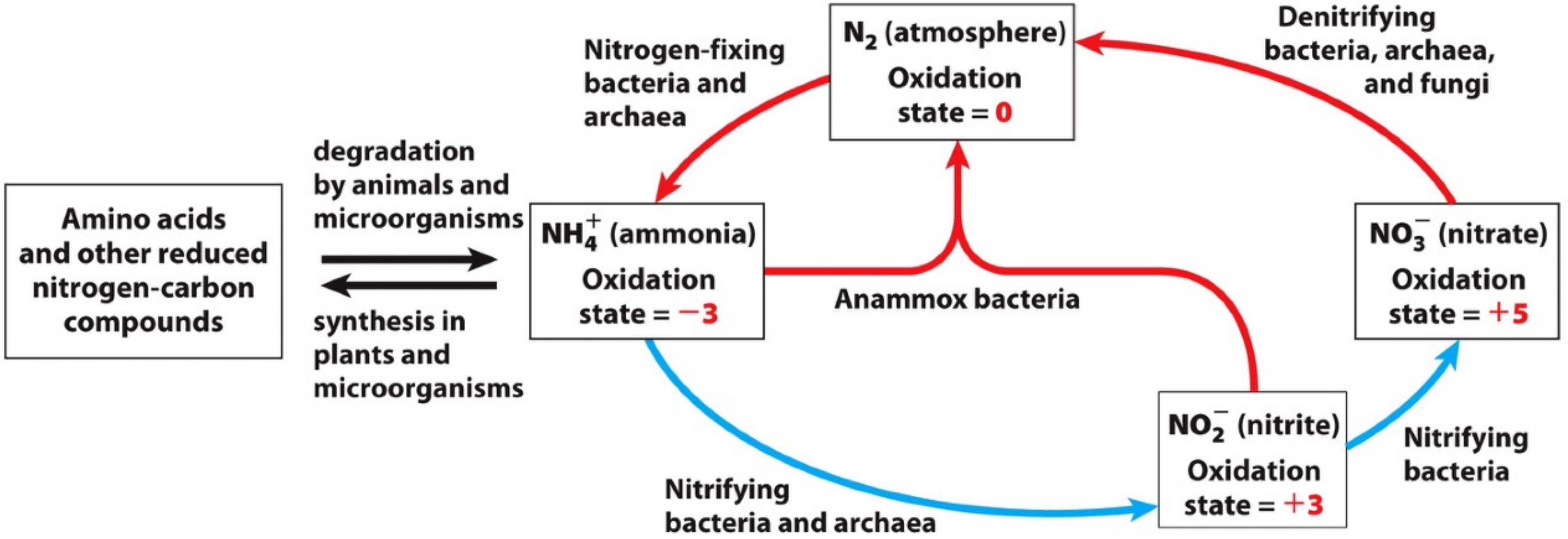
22.2 Biosynthesis of Amino Acids

22.3 Molecules Derived from Amino Acids

22.4 Biosynthesis and Degradation of Nucleotides

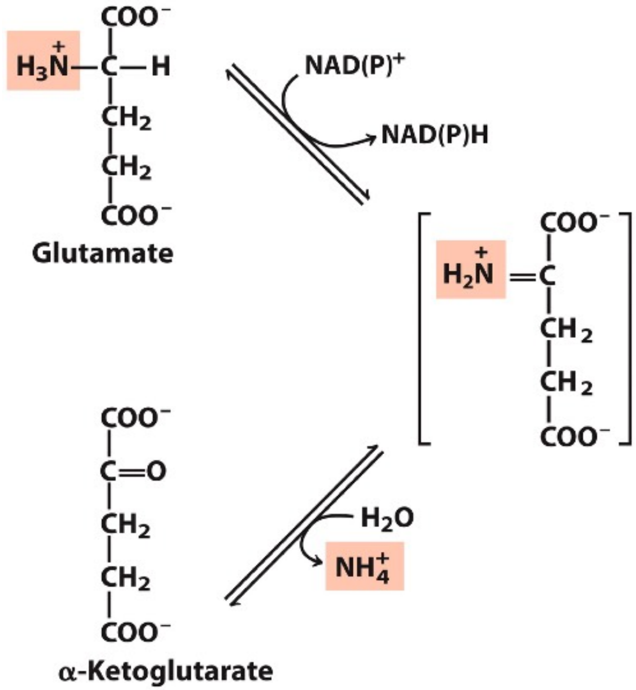
Nitrogen Cycle

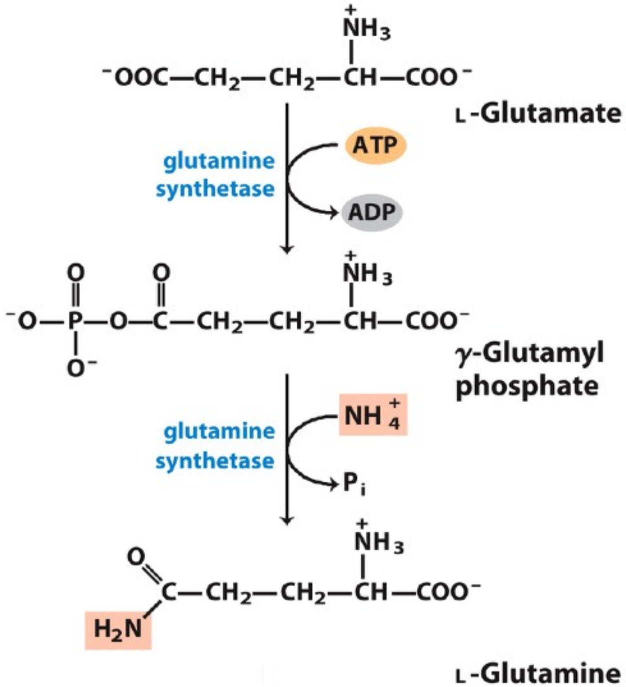
1. Fixation
   - Bacteria reduce atmospheric nitrogen (N_2) to ammonia (NH_3 or NH_4^+)
2. Nitrification
   - Bacteria oxidize ammonia to nitrite (NO_2^-) or nitrate (NO_3^-)
3. Assimilation
   - Plants and bacteria reduce nitrite + nitrate to ammonia for amino acid synthesis
4. Denitrification
   - Nitrate is reduced to N_2. NO_3^- is the ultimate electron acceptor instead of O_2



Ammonia is Incorporated through E and Q

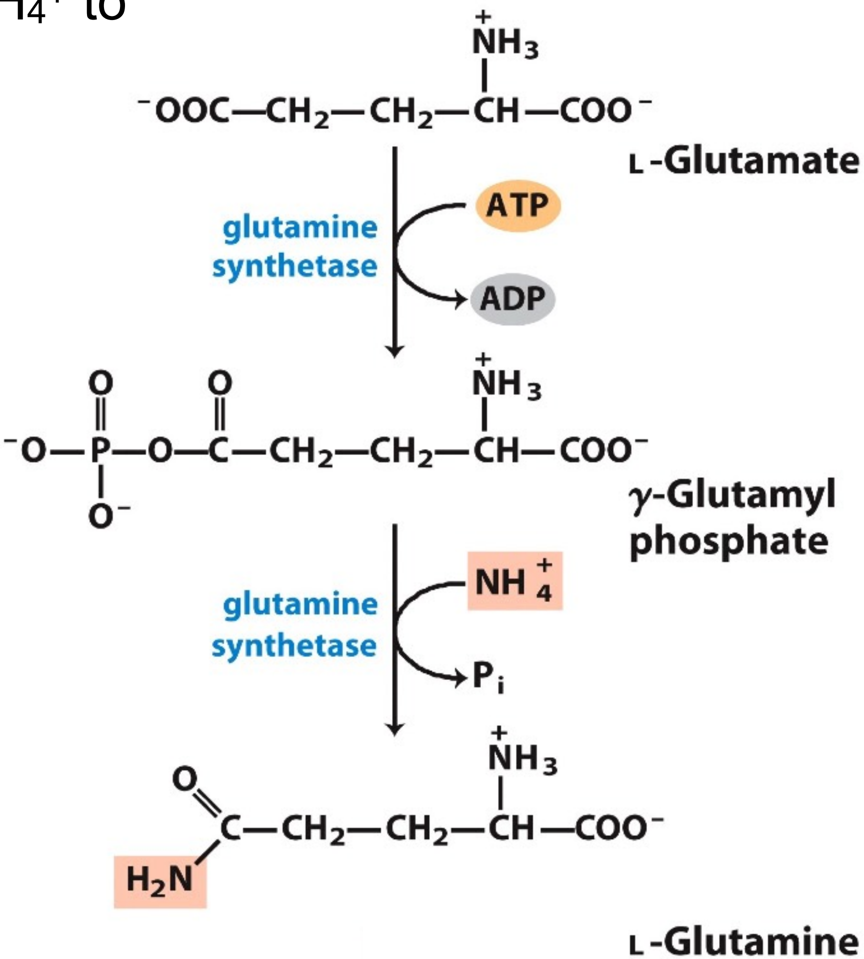
- Glutamate and glutamine are entry point of nitrogen assimilation into biomolecules such as amino acids
  - These two amino acids also play central roles in amino acid catabolism
    - Glutamate is a temporary storage of amino group
    - Glutamine is a nontoxic transport form of ammonia
  - Glutamate is synthesized by amination of α-ketoglutarate
  - Glutamine is synthesized by amination of glutamate





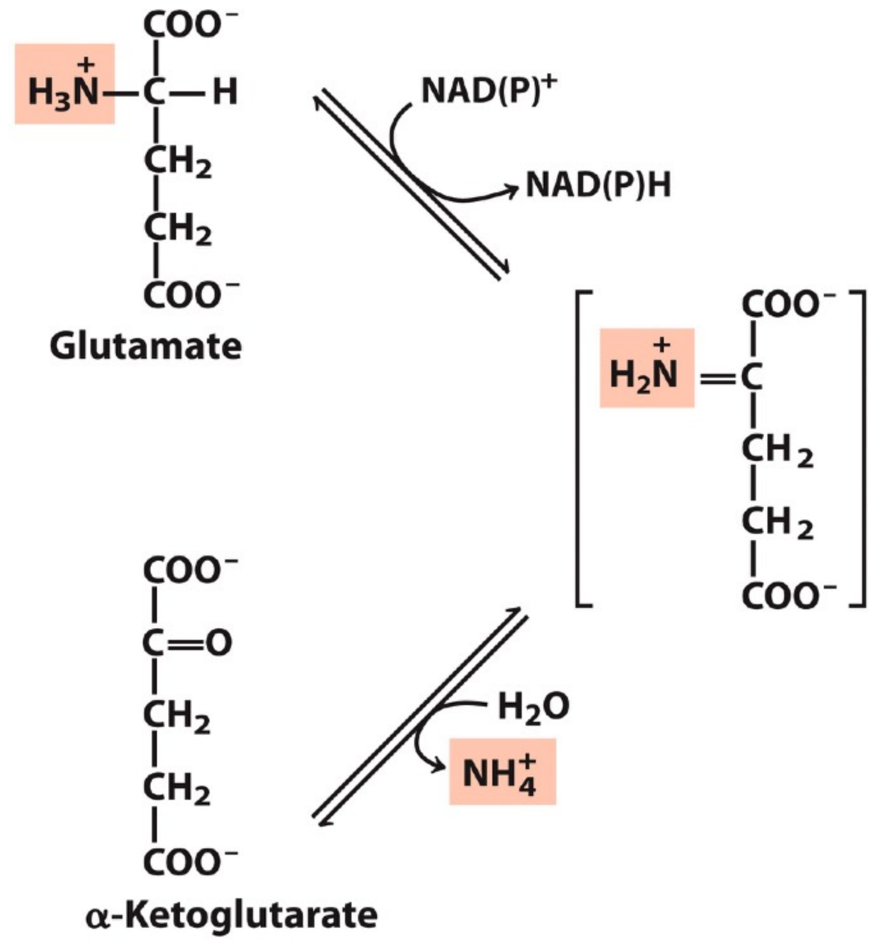
Biosynthesis of Glutamine

- Catalyzed by glutamine synthetase
  - Glu + NH_4^+ + ATP -> Gln + ADP + P_i
  - Also responsible for converting NH_4^+ to Gln
  - Found in all organisms



Biosynthesis of Glutamate

- Reductive amination catalyzed by glutamate synthase in plants and bacteria
  - α-ketoglutarate + glutamine + NADPH -> 2 glutamate + $NADP^+$
  - This enzyme is NOT present in animals
- Minor pathway catalyzed by glutamate dehydrogenase in all organisms
  - α-ketoglutarate + NH_4^+ + NADPH -> glutamate + $NADP^+$



Summary 22.1 Nitrogen Metabolism

- Molecular nitrogen that makes up 80% of atmosphere is unavailable to most living organisms until it is reduced to ammonia.
- Reduced nitrogen is first incorporated into amino acids and then into other biomolecules, including nucleotides.
- Key entry point is amino acid glutamate. Glutamate and glutamine (synthesis catalyzed by glutamine synthetase) are nitrogen donors in a wide range of biosynthetic reactions.

Week 16 Amino Acids and Nucleotides

22.1 Overview of Nitrogen Metabolism

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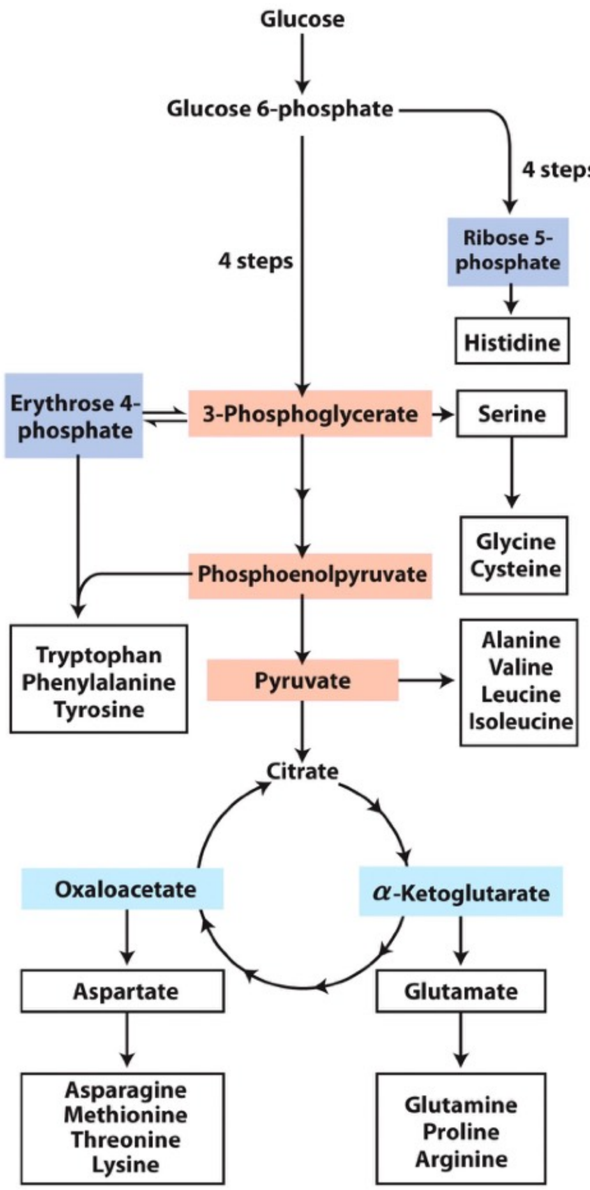
22.3 Molecules Derived from Amino Acids

22.4 Biosynthesis and Degradation of Nucleotides

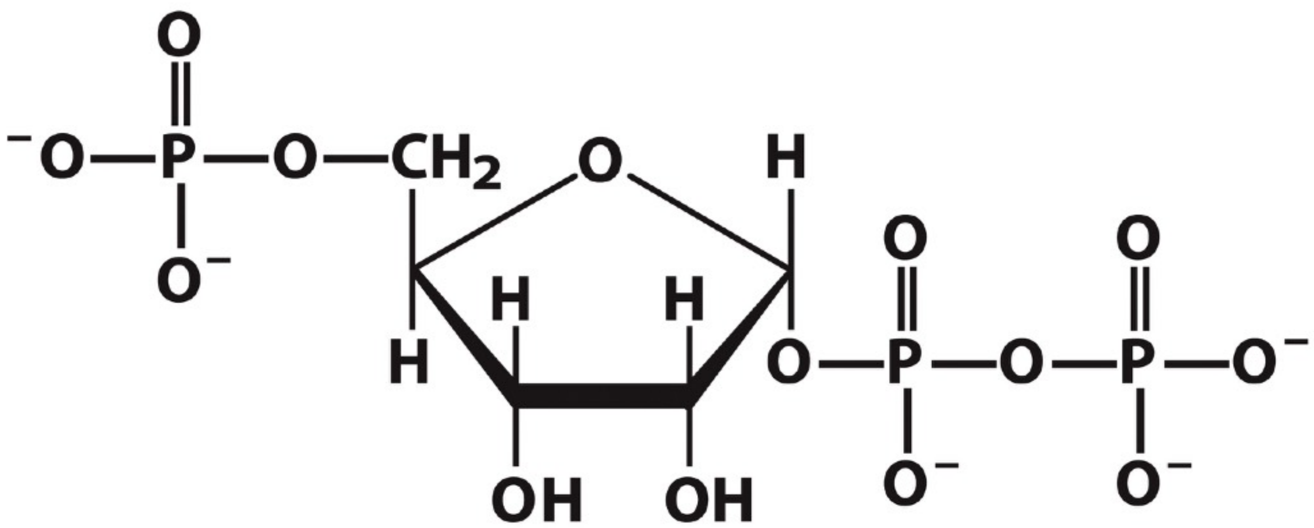
Amino Acids Derived from Intermediates

- All amino acids are derived from intermediates in three processes
  - Glycolysis
  - Citric acid cycle
  - Pentose phosphate pathway
- Source of N is glutamate or glutamine
- **Bacteria and plants can synthesize all 20. Mammals require some in diet**
- Compare with amino acid degradation
  - α-ketoglutarate <-> Glu, Gln, Pro, Arg
  - Oxaloacetate <-> Asp, Asn
  - Pyruvate <-> Ala



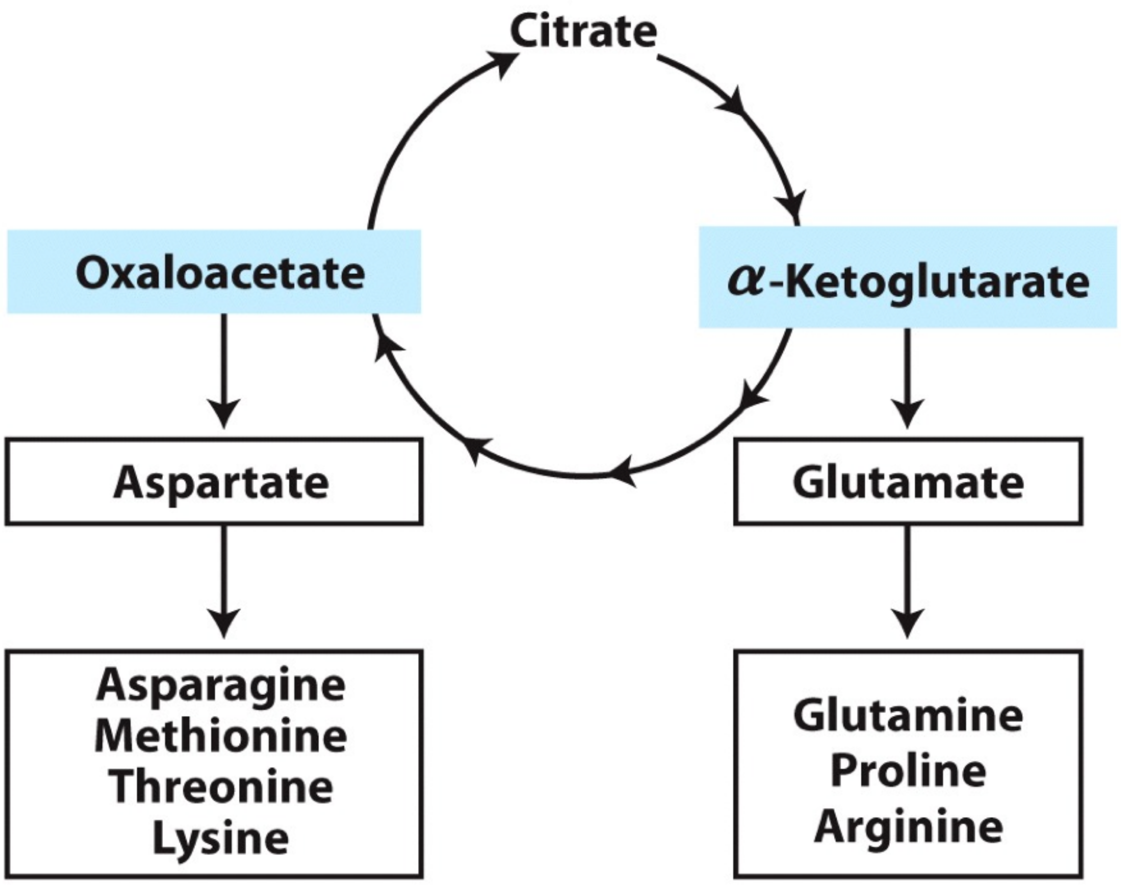
A Notable Intermediate PRPP

- 5-phosphoribosyl-1-pyrophosphate (PRPP)
- Synthesized from ribose 5-phosphate derived from pentose phosphate pathway
- Catalyzed by ribose phosphate pyrophosphokinase
  - Ribose 5-phosphate + ATP -> 5-phosphoribosyl-1-pyrophosphate + AMP



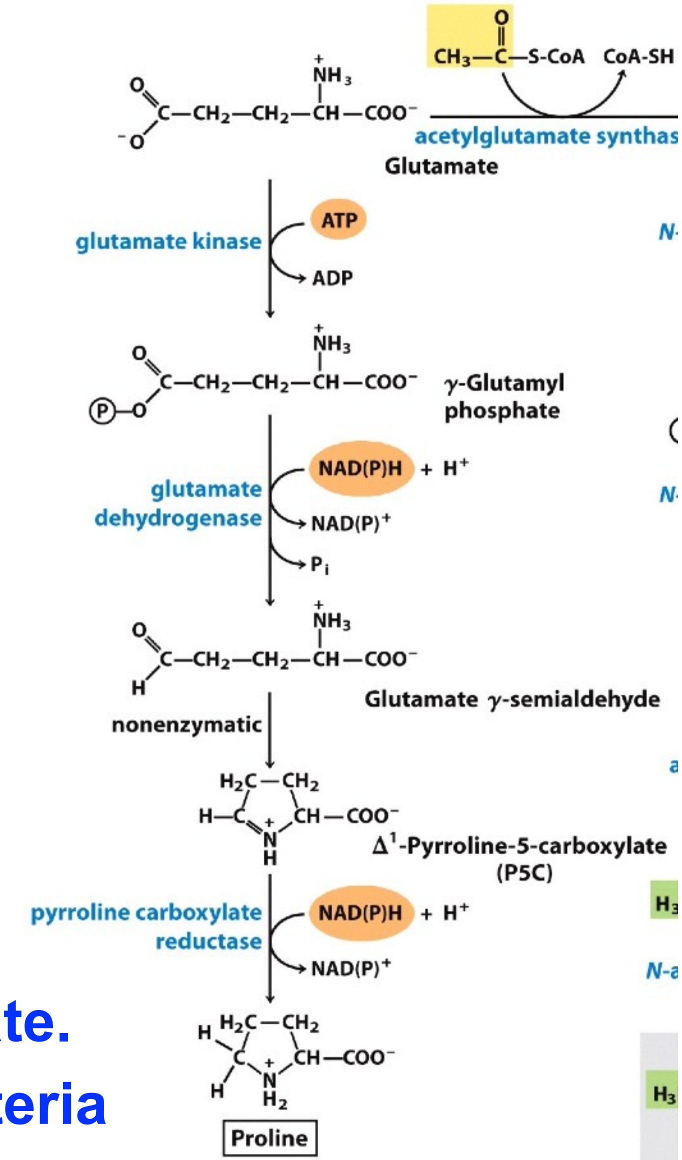
Group 1. α-Ketoglutarate

- Glutamate and glutamine are synthesized from α-ketoglutarate
- Human can synthesize proline and arginine



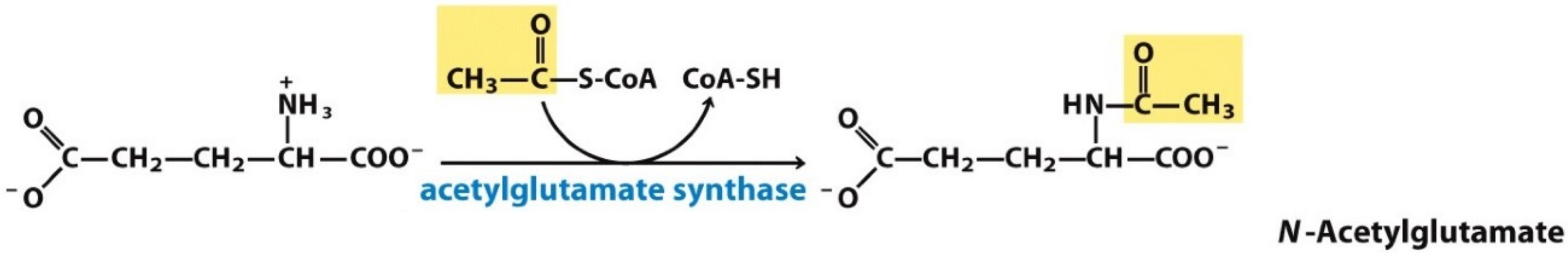
Pro is Cyclized Derivative of Glu

1. Glutamate -> acyl phosphate
   - ATP reacts with γ carboxyl group
   - Catalyzed by kinase
2. Acyl phosphate -> semialdehyde
   - NAD(P)H reduces acyl phosphate to semialdehyde
   - Catalyzed by dehydrogenase
3. Cyclization
   - Semialdehyde undergoes rapid spontaneous cyclization
4. Reduction
   - Double bond reduced to single bond
   - Catalyzed by reductase

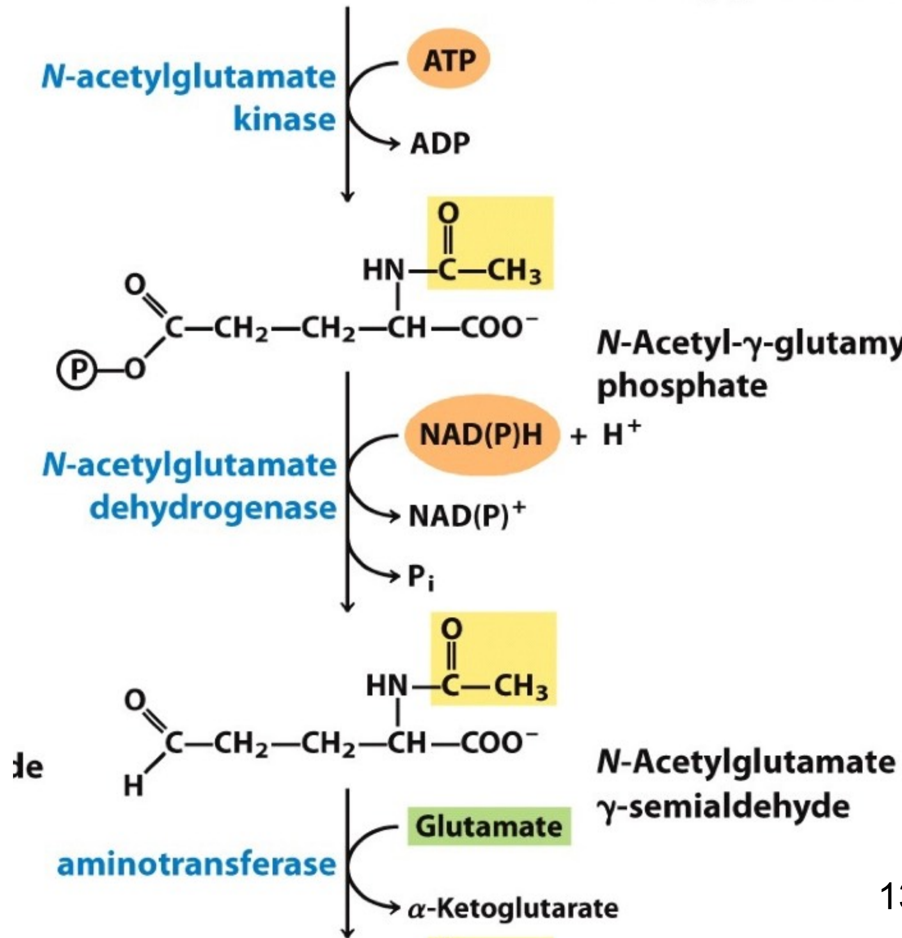


All C and N atoms come from glutamate.
Pathway operates in animals and bacteria

Arg from Glu via Urea Cycle. Part I

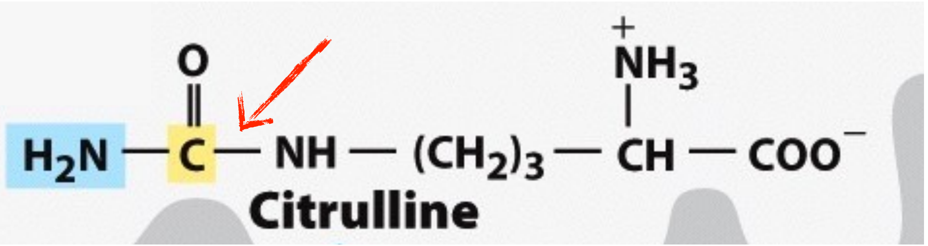


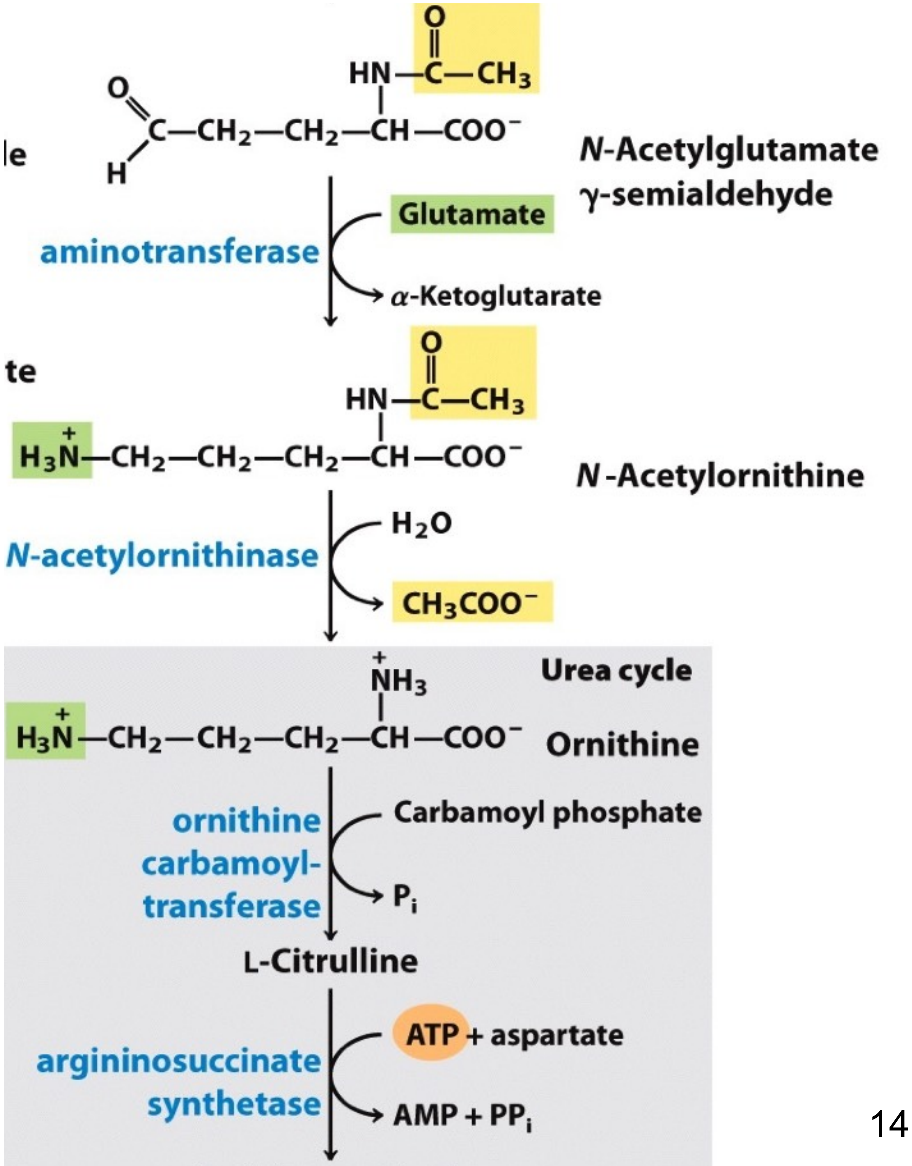
1. Glutamate -> N-acetylglutamate
   - Amino group is blocked by acetylation
2. Formation of acyl phosphate
   - Catalyzed by kinase
   - Consumes ATP
3. Formation of semialdehyde
   - Catalyzed by dehydrogenase
   - Consumes NAD(P)H
   - **Avoid spontaneous cyclization**



Arg from Glu via Urea Cycle. Part II

4. Formation of N-acetylornithine
   - Catalyzed by aminotransferase
   - Amino group donated by glutamate
5. Formation of ornithine
   - Acetyl group removed
6. Formation of citrulline
   - Catalyzed by carbamoyl transferase
   - 1st step in urea cycle
   - C from CO_2 and NH_2 from ammonia

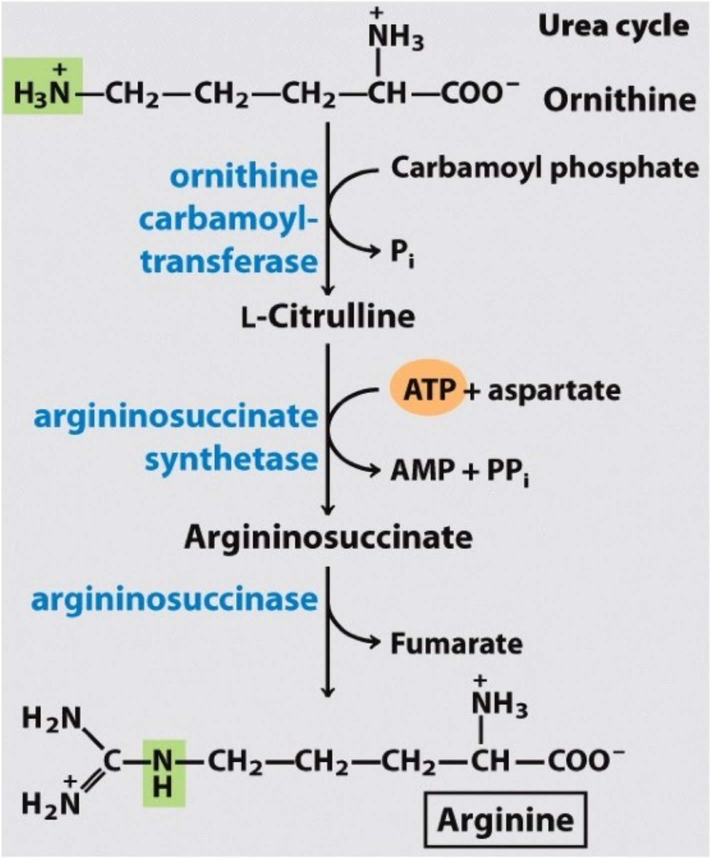


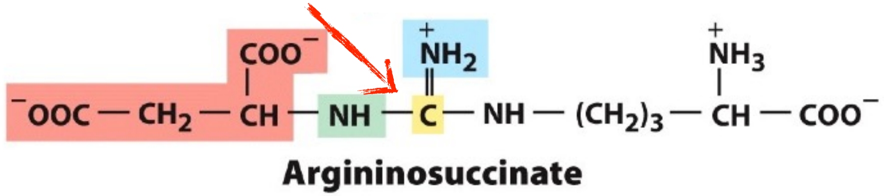


Arg from Glu via Urea Cycle. Part III

7. Formation of argininosuccinate
   - Catalyzed by synthetase
   - Amino group donated by aspartate
8. Formation of arginine
   - Catalyzed by argininosuccinase
   - Fumarate removed

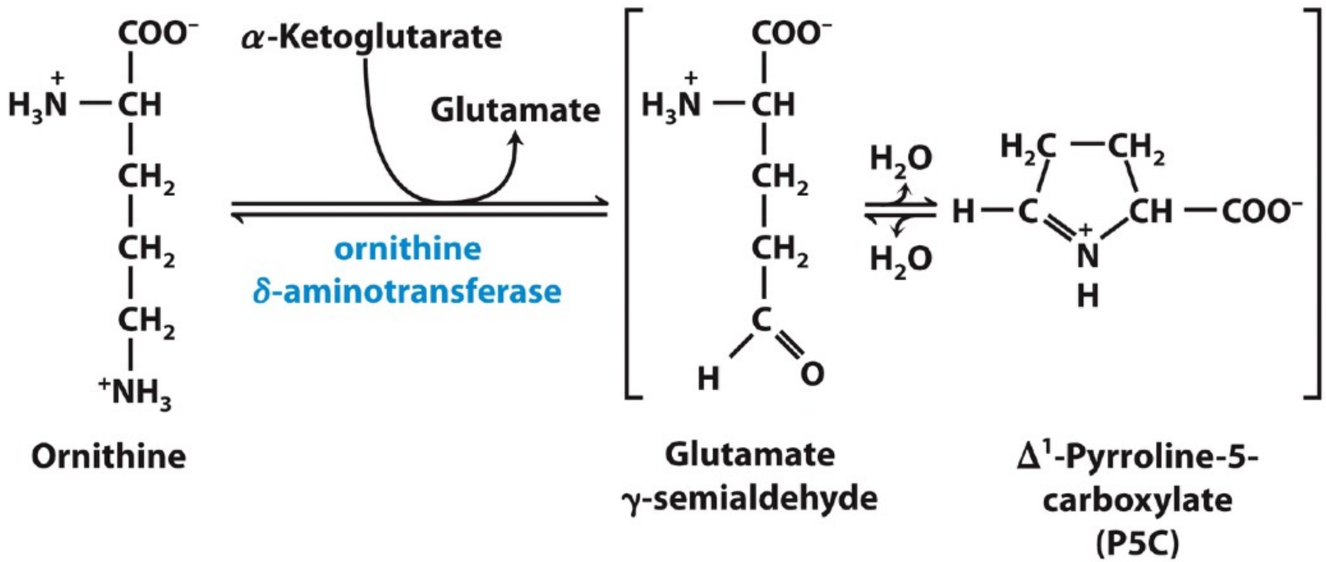
- **Source of arginine atoms**
   - 5 C and 1 N from glutamate
   - N from glutamate
   - C from CO_2. N from NH_4^+. N from Asp





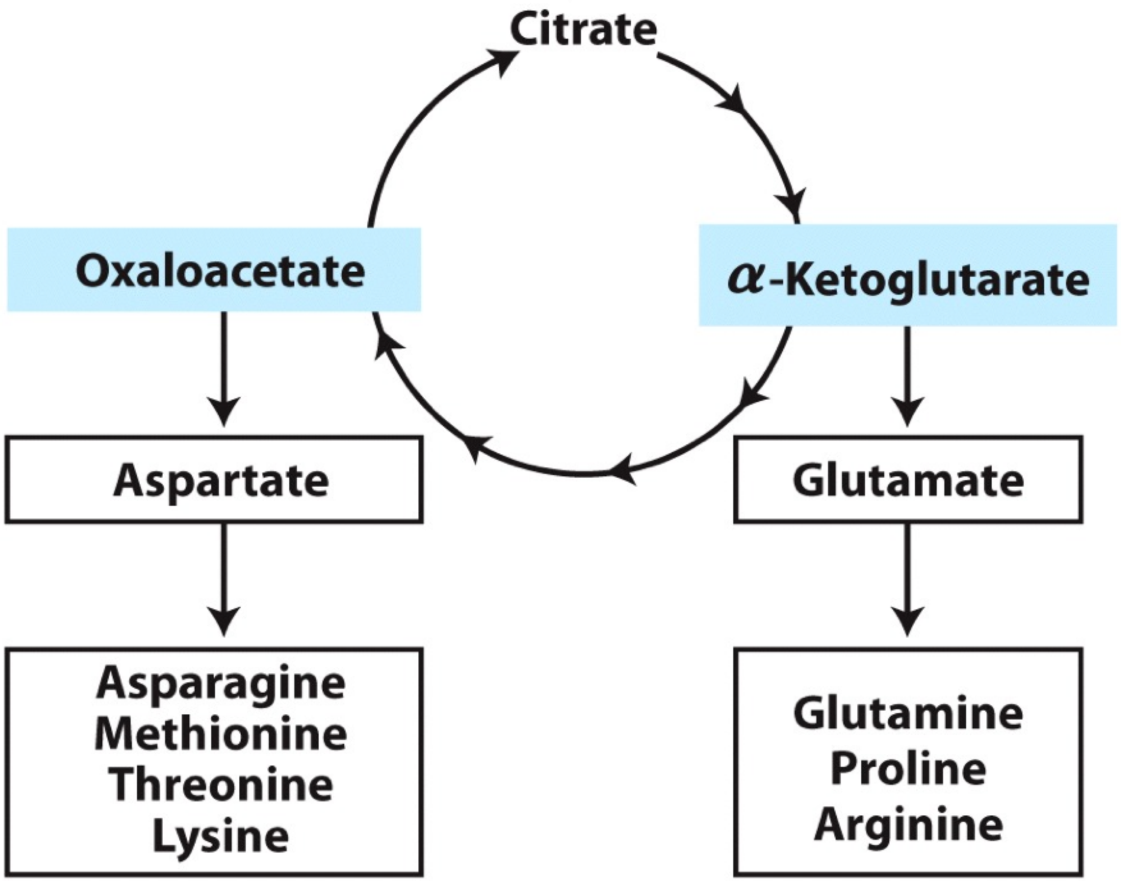
Interconnected Pro and Arg Biosynthesis

- Ornithine can be converted to glutamate γ-semialdehyde
  - Catalyzed by δ-aminotransferase
  - Ornithine is an intermediate in arginine biosynthesis
  - Glutamate γ-semialdehyde is an intermediate in proline biosynthesis
- Proline can be formed from arginine in dietary or tissue proteins
  - Arginine -> ornithine -> glutamate γ-semialdehyde
- When [arginine] is low, transamination favors ornithine formation
  - Glutamate γ-semialdehyde -> ornithine -> -> -> arginine



Group 2. Oxaloacetate

- Aspartate and asparagine are synthesized from Oxaloacetate
- Human cannot synthesize methionine, threonine and lysine
  - Met, Thr and Lys are essential amino acids

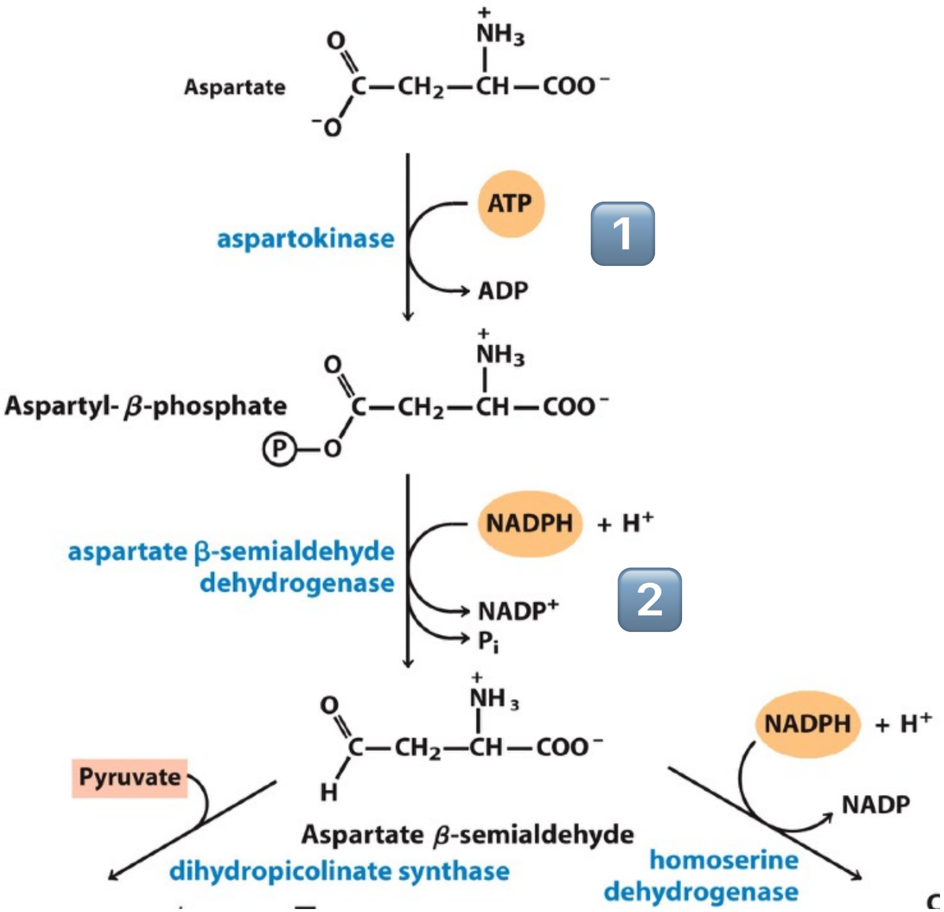


Met, Thr and Lys are Essential

- Human cannot synthesize methionine, threonine and lysine
- Shown here is bacterial biosynthetic pathways

1. Aspartate -> acyl phosphate
   - Catalyzed by kinase
2. Acyl phosphate -> semialdehyde
   - Catalyzed by dehydrogenase

- The above two steps are similar to the first two reactions in biosynthesis of proline and arginine
- **Aspartate β-semialdehyde is a branch point**
  - Threonine and methionine share the right pathway
  - Lysine follows the left pathway

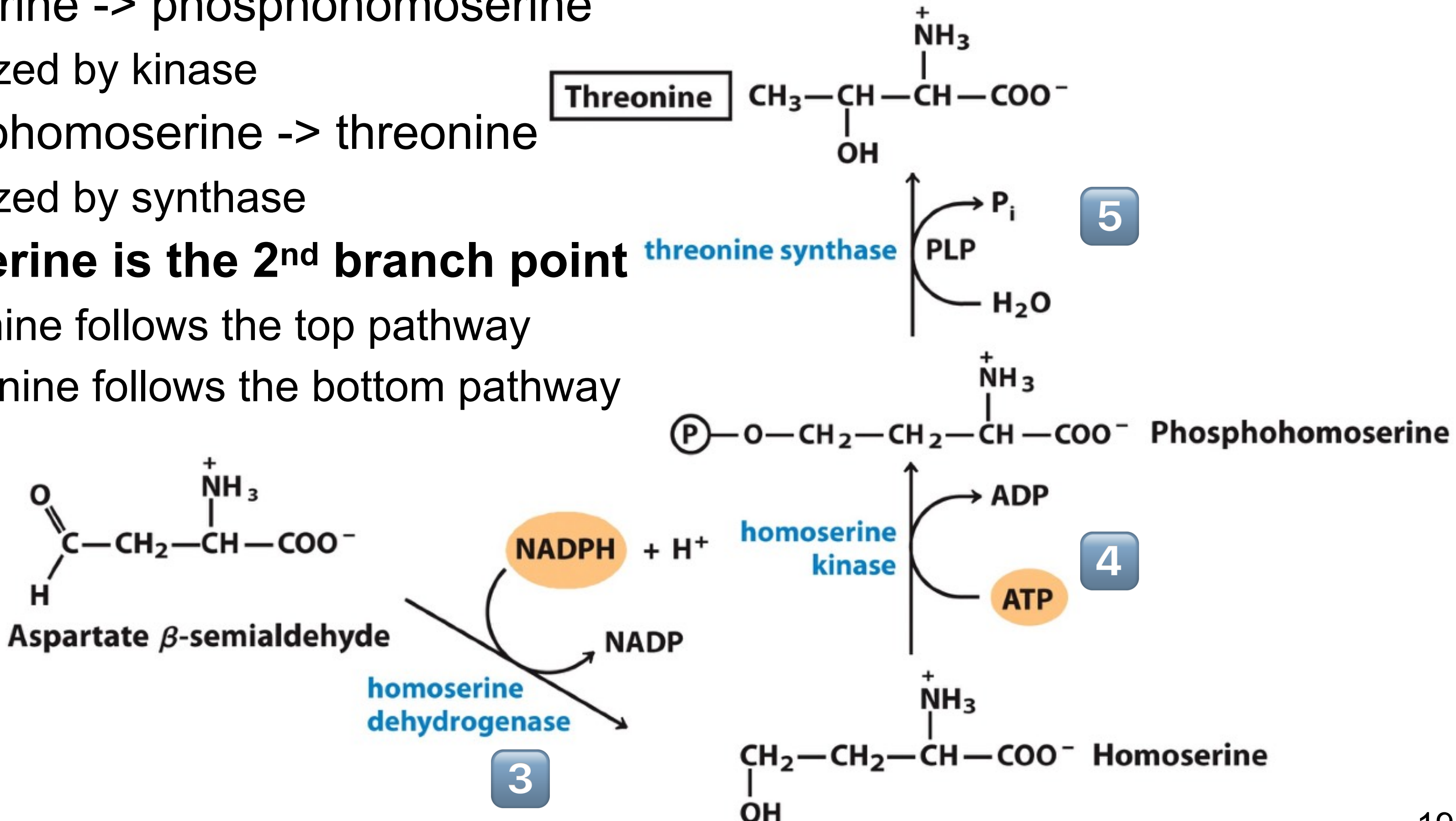


Biosynthesis of Threonine

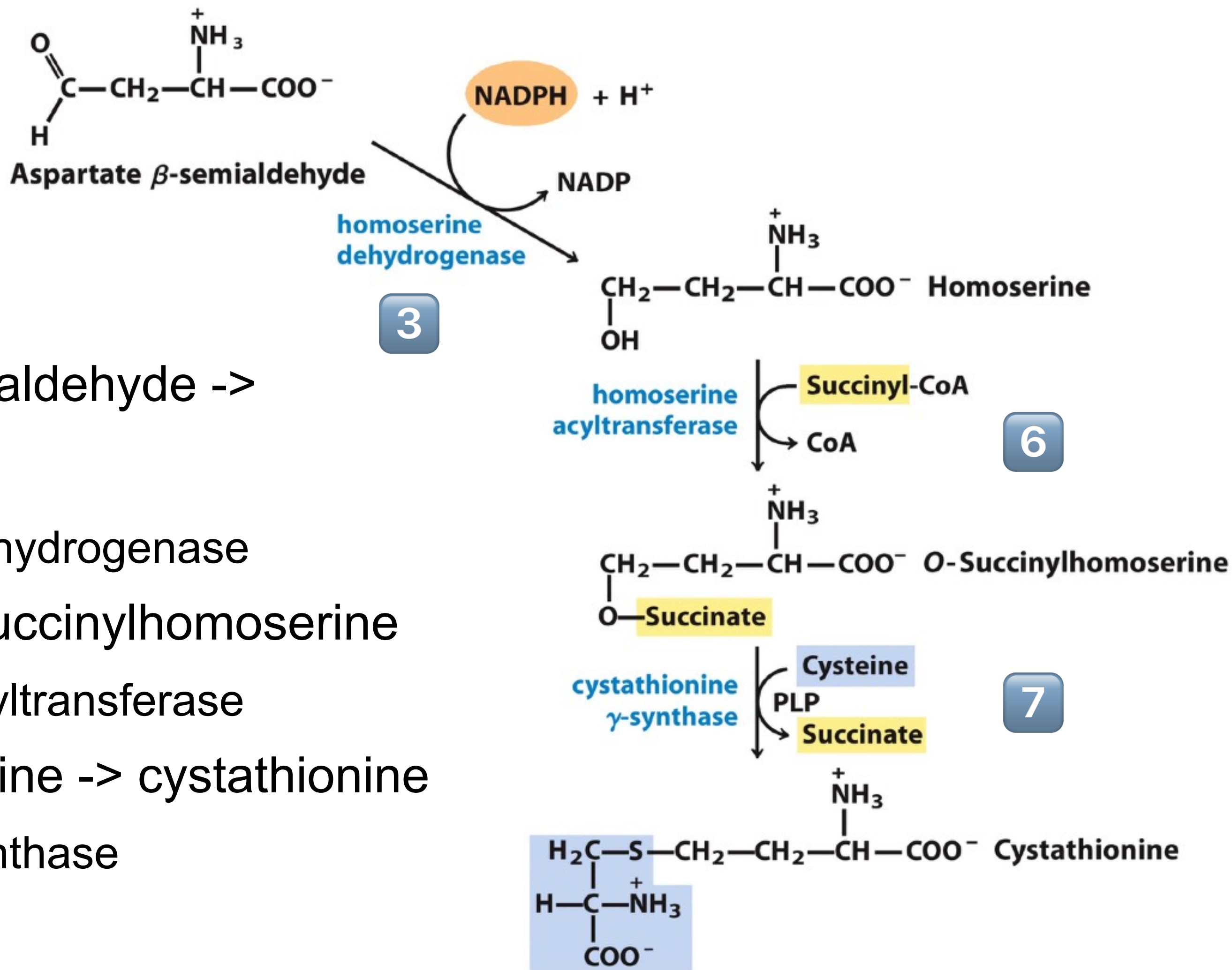
3. Aspartate β-semialdehyde -> homoserine
   - Catalyzed by dehydrogenase
4. Homoserine -> phosphohomoserine
   - Catalyzed by kinase
5. Phosphohomoserine -> threonine
   - Catalyzed by synthase

- **Homoserine is the 2nd branch point**
  - Threonine follows the top pathway
  - Methionine follows the bottom pathway

All C and N atoms come from aspartate



Biosynthesis of Methionine Part I

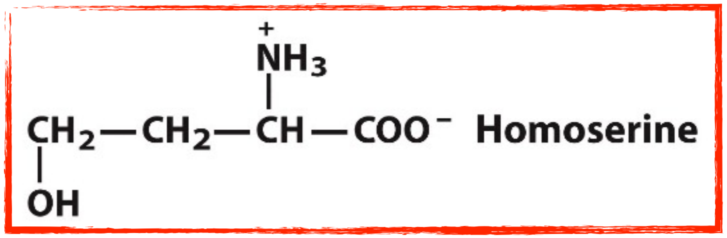


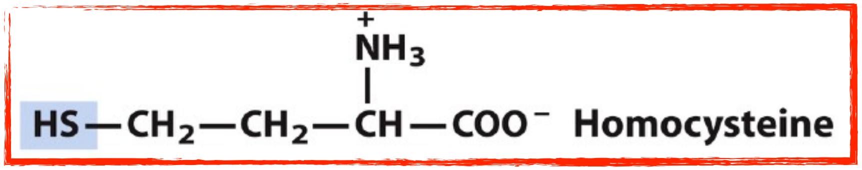
3. Aspartate β-semialdehyde -> homoserine
   - Catalyzed by dehydrogenase
6. Homoserine -> succinylhomoserine
   - Catalyzed by acyltransferase
7. Succinylhomoserine -> cystathionine
   - Catalyzed by synthase

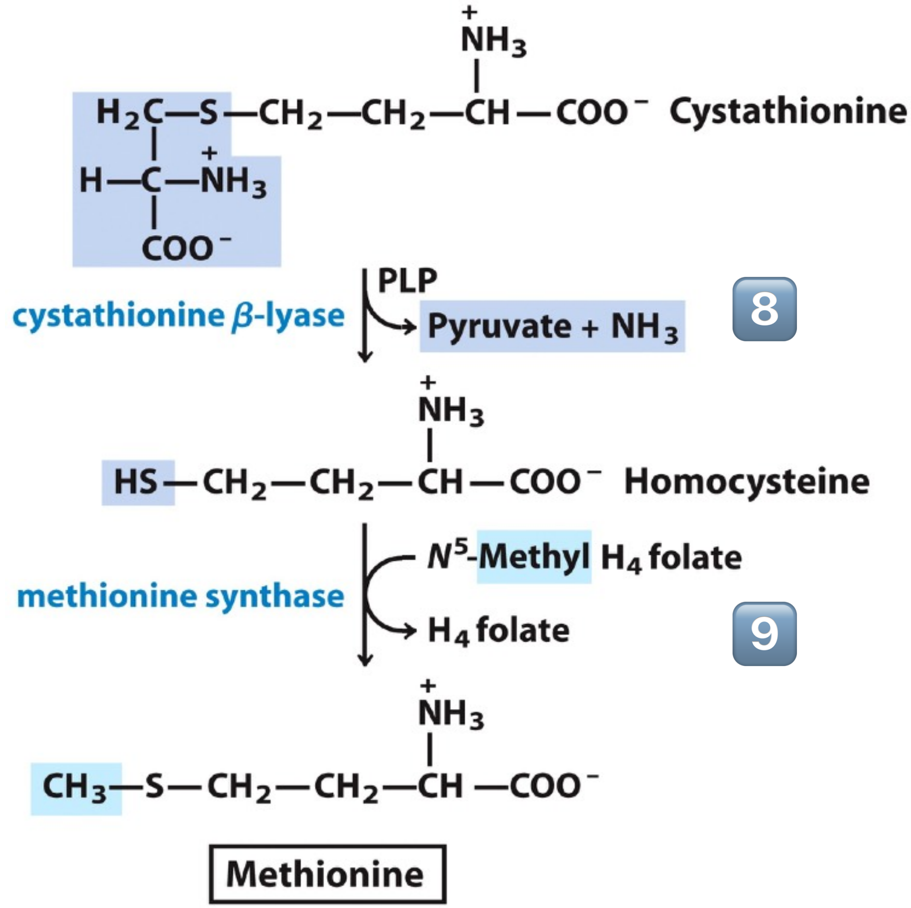
Biosynthesis of Methionine Part II

8. Cystathionine -> homocysteine
   - Catalyzed by lyase
9. Homocysteine -> methionine
   - Catalyzed by synthase

- **Compare following amino acids**
  - Serine vs. homoserine
  - Cysteine vs. homocysteine





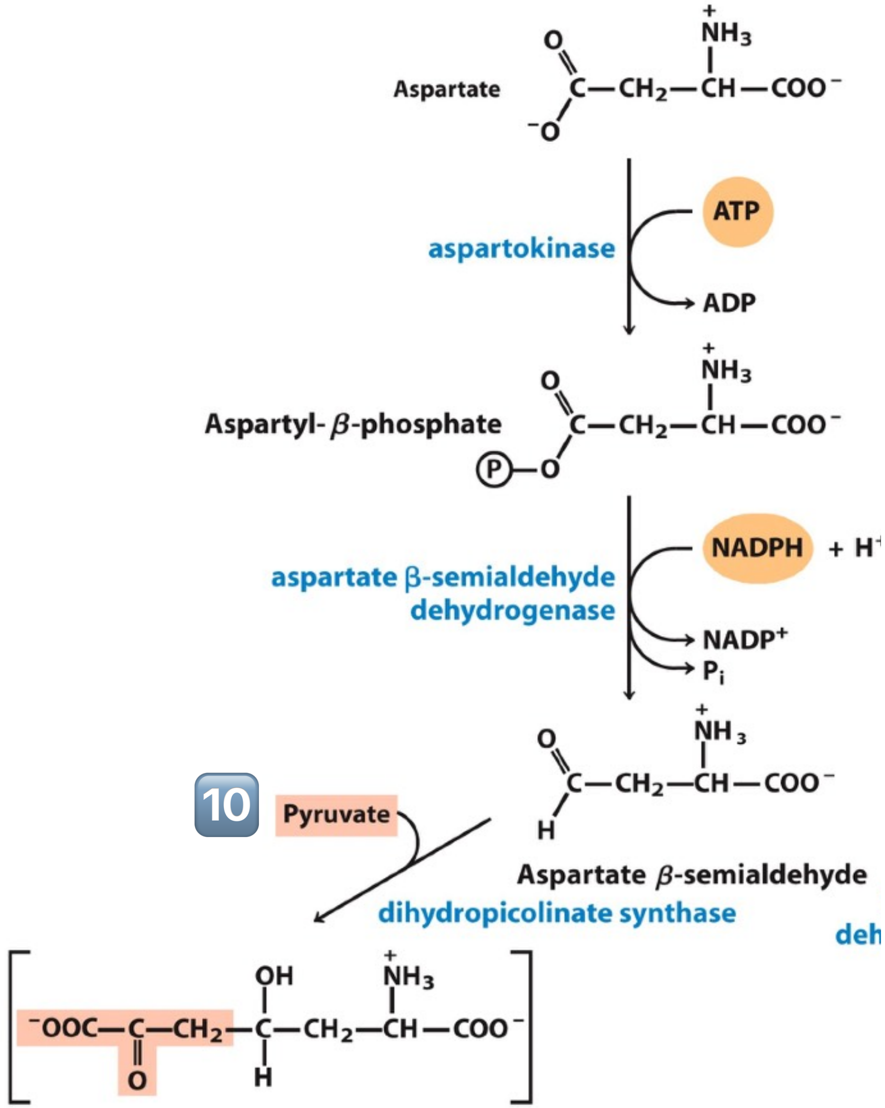


- **4 C and 1 N from aspartate**
- **S from cysteine**
- **Methyl group from cofactor**

Biosynthesis of Lysine Part I

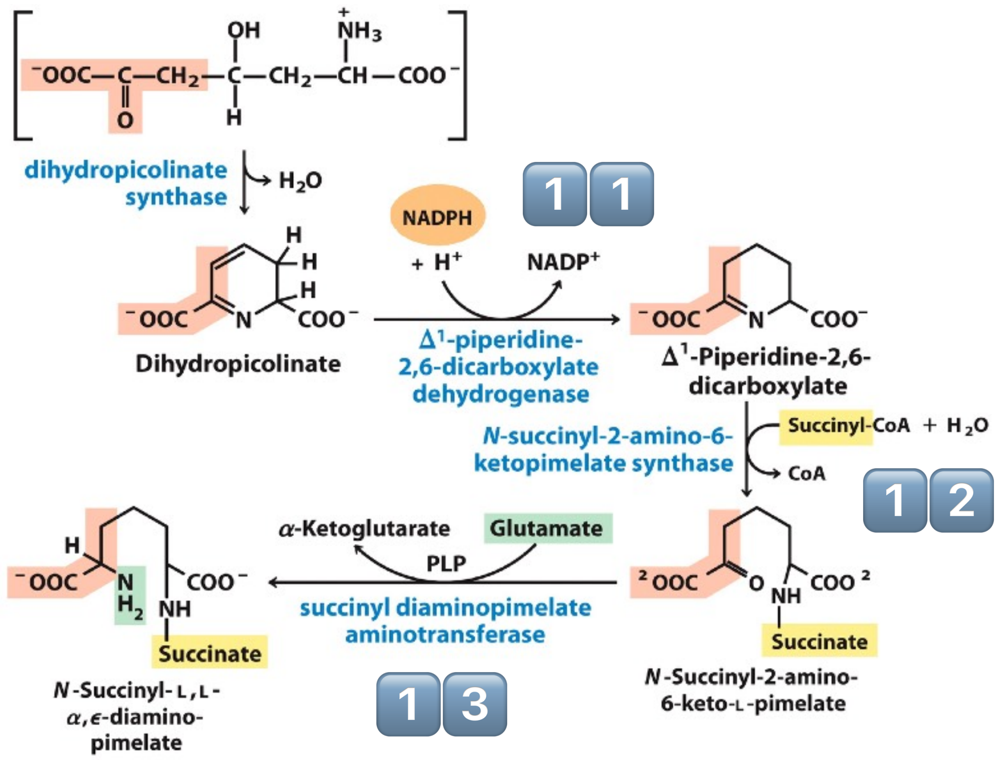
1. Aspartate -> acyl phosphate
   - Catalyzed by kinase
2. Acyl phosphate -> semialdehyde
   - Catalyzed by dehydrogenase
10. Semialdehyde -> dihydropicolinate
   - Catalyzed by synthase

- The first two steps are similar to the first two reactions in biosynthesis of proline and arginine
- **Aspartate β-semialdehyde is a branch point**
   - Threonine and methionine share the right pathway
   - **Lysine follows the left pathway**



Biosynthesis of Lysine Part II

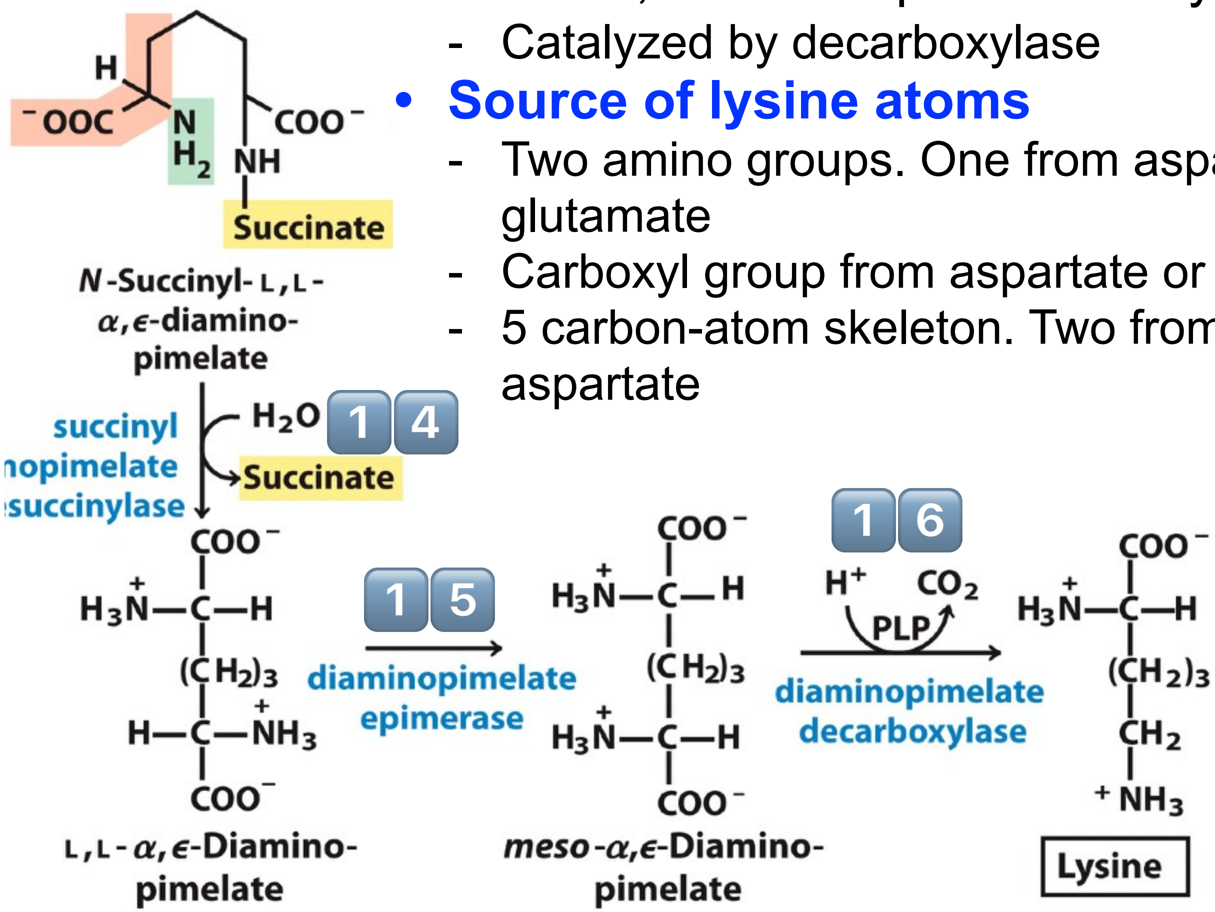
11. Dihydropicolinate -> piperidine dicarboxylate
    - Catalyzed by dehydrogenase
12. Piperidine dicarboxylate -> N-succinyl-2-amino-6-keto-pimelate
    - Catalyzed by synthase
13. N-succinyl-2-amino-6-keto-pimelate -> N-succinyl-α,ε-diamino-pimelate
    - Catalyzed by aminotransferase.



Biosynthesis of Lysine Part III

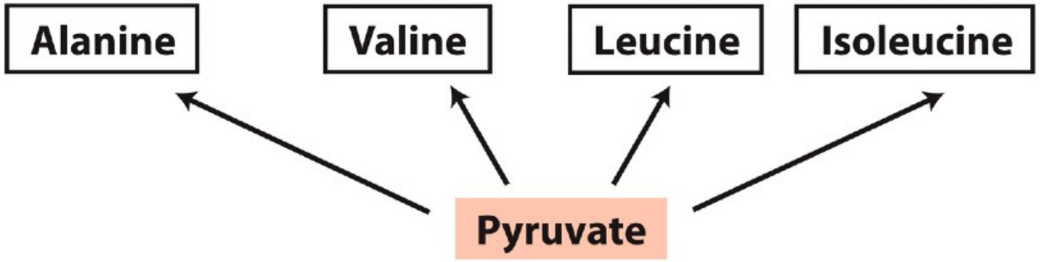
14. N-succinyl-α,ε-diamino-pimelate -> L,L-α,ε-diamino-pimelate
    - Catalyzed by desuccinylase
15. L,L-α,ε-diamino-pimelate -> meso-α,ε-diamino-pimelate
    - Catalyzed by epimerase
16. Meso-α,ε-diamino-pimelate -> lysine
    - Catalyzed by decarboxylase

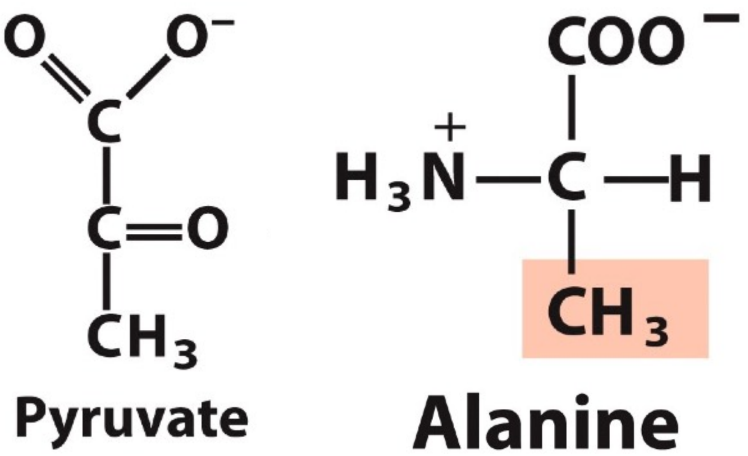
- **Source of lysine atoms**
  - Two amino groups. One from aspartate and the other from glutamate
  - Carboxyl group from aspartate or pyruvate
  - 5 carbon-atom skeleton. Two from pyruvate and three from aspartate



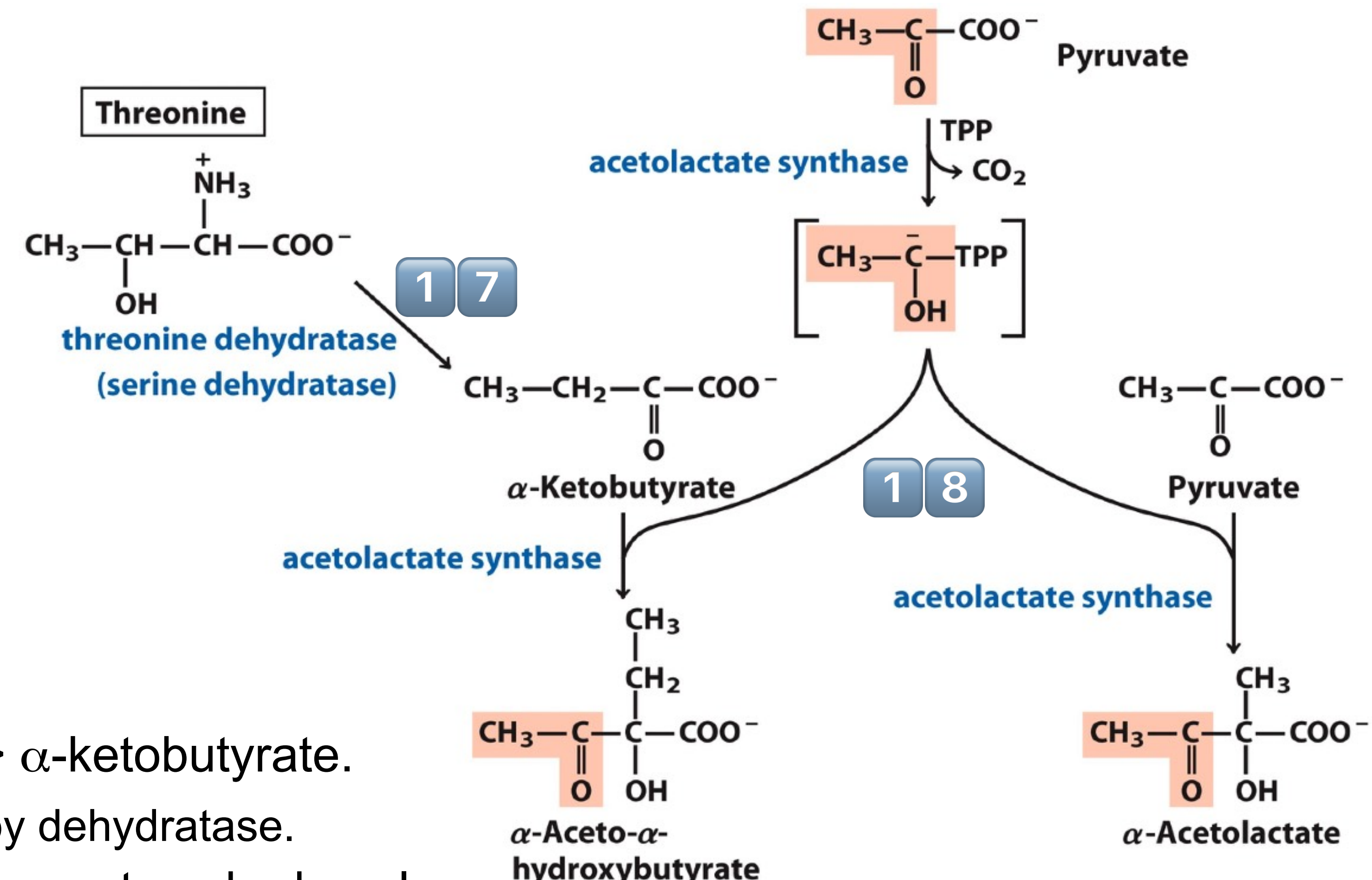
Group 3. Pyruvate

- Alanine is synthesized from pyruvate by transamination
- Human cannot synthesize isoleucine, valine and leucine
  - Ile, Val and Leu are also essential amino acids
- Shown here is bacterial biosynthetic pathways





Biosynthesis of Ile and Val Part I

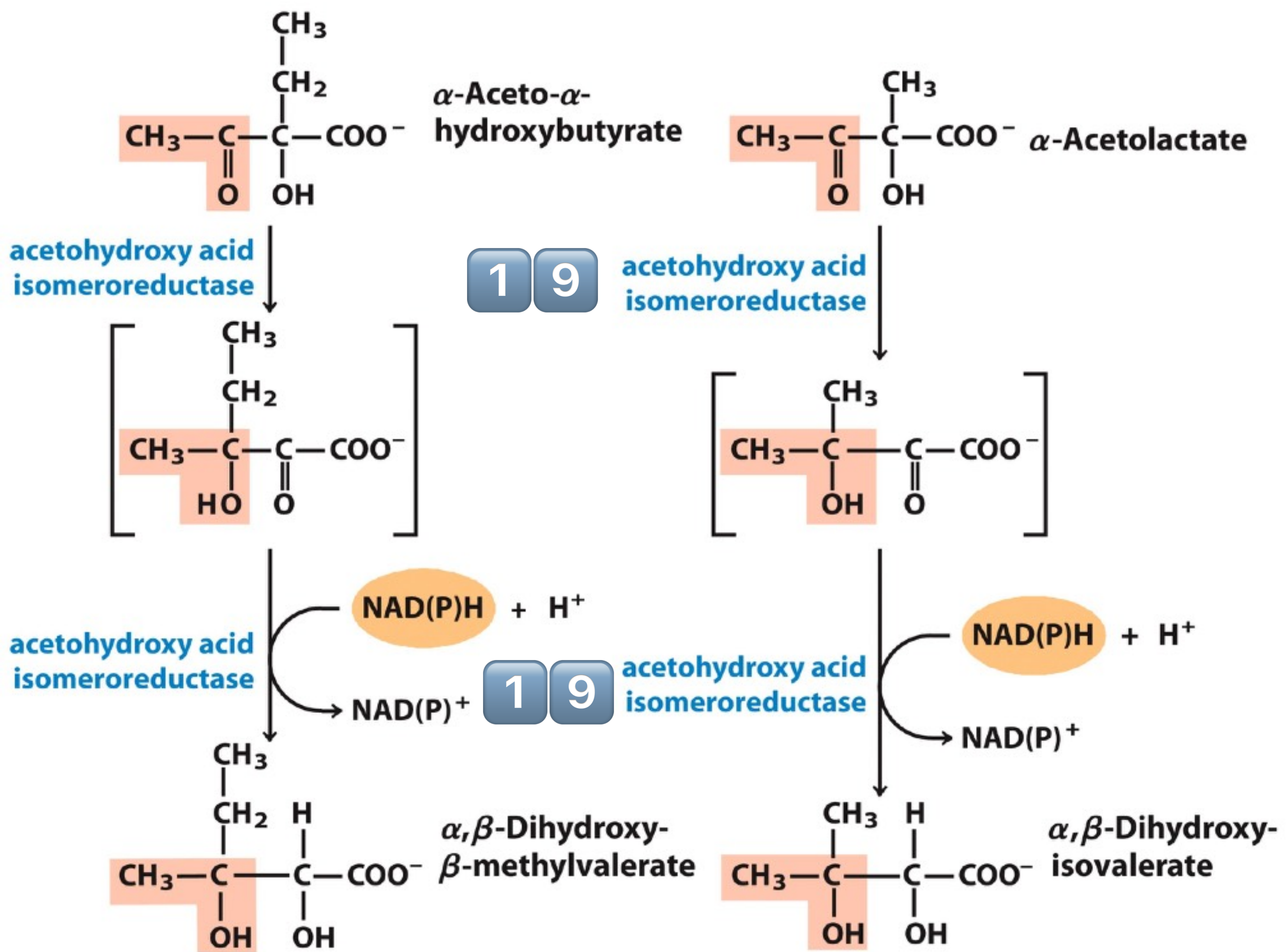


17. Threonine -> α-ketobutyrate.
    - Catalyzed by dehydratase.
18. Pyruvate -> α-aceto-α-hydroxyl acid.
    - Catalyzed by synthase.

Biosynthesis of Ile and Val Part II

19. α-aceto-α-hydroxyl acid -> α,β-dihydroxyl-β-methyl acid.

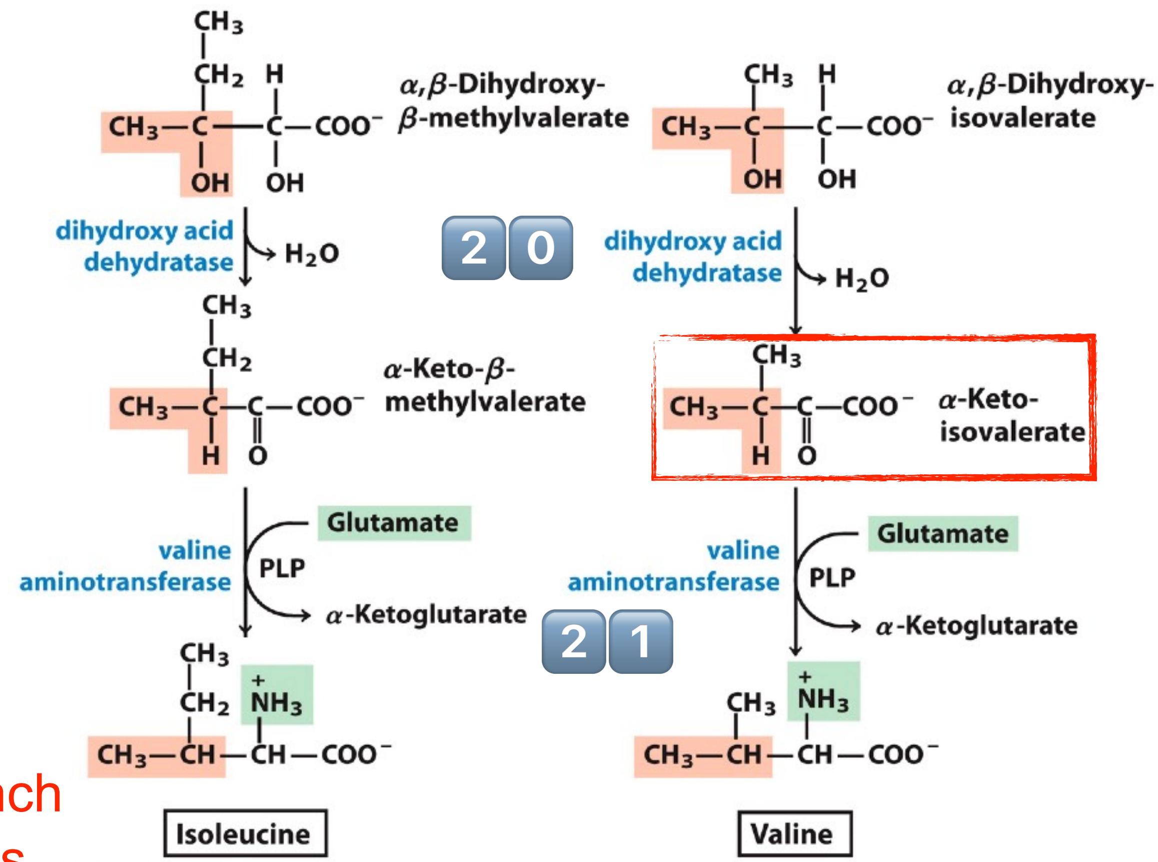
- Catalyzed by isomeroreductase.



Biosynthesis of Ile and Val Part III

20. α,β-dihydroxyl-β-methyl acid -> α-keto-β-methyl acid.
    - Catalyzed by dehydratase.
21. α-keto-β-methyl acid -> isoleucine or valine.
    - Catalyzed by aminotransferase.

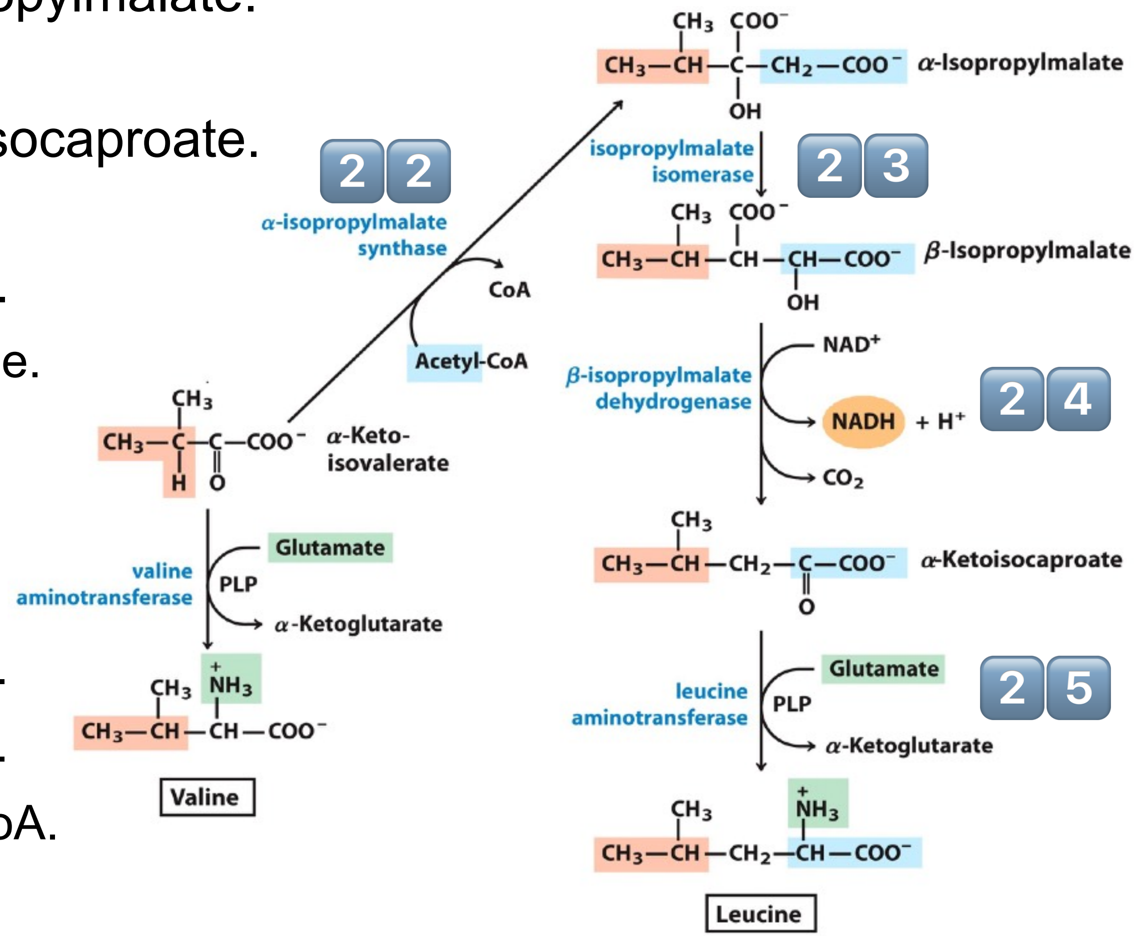
- **Source of isoleucine atoms.**
  - NH_2 from glutamate.
  - 2 carbon atoms from pyruvate.
  - 4 carbon atoms from threonine.
- **Source of valine atoms.**
  - NH_2 from glutamate.
  - 2 carbon atoms from pyruvate.
  - 3 carbon atoms from pyruvate.
- α-keto-isovalerate is a branch point to leucine biosynthesis.



Biosynthesis of Leu

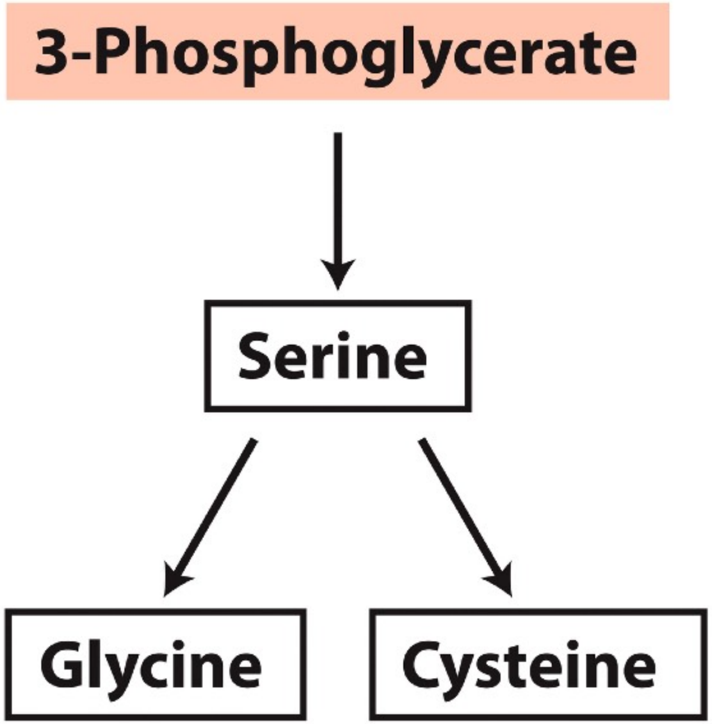
22. α-keto-isovalerate -> α-isopropylmalate.
    - Catalyzed by synthase.
23. α-isopropylmalate -> β-isopropylmalate.
    - Catalyzed by isomerase.
24. β-isopropylmalate -> α-ketoisocaproate.
    - Catalyzed by dehydrogenase.
25. α-ketoisocaproate -> leucine.
    - Catalyzed by aminotransferase.

- **Source of leucine atoms.**
  - NH_2 from glutamate.
  - 2 carbon atoms from pyruvate.
  - 2 carbon atoms from pyruvate.
  - 2 carbon atoms from acetyl-CoA.



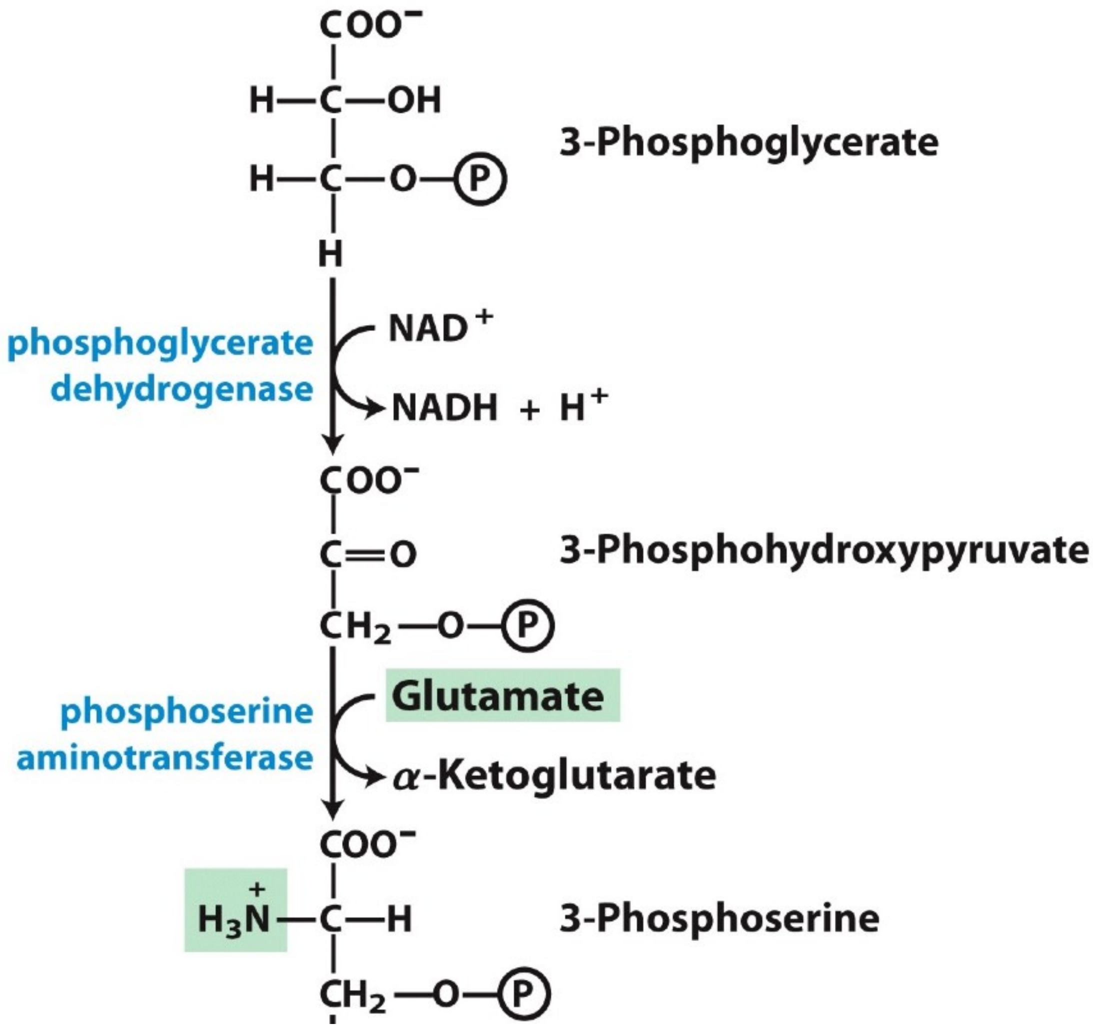
Group 4. 3-Phosphoglycerate

- Human can synthesize serine, glycine and cysteine.
  - Ser, Gly and Cys are NOT essential amino acids.
- Shown here is mammalian biosynthetic pathways.



Biosynthesis of Ser and Gly Part I

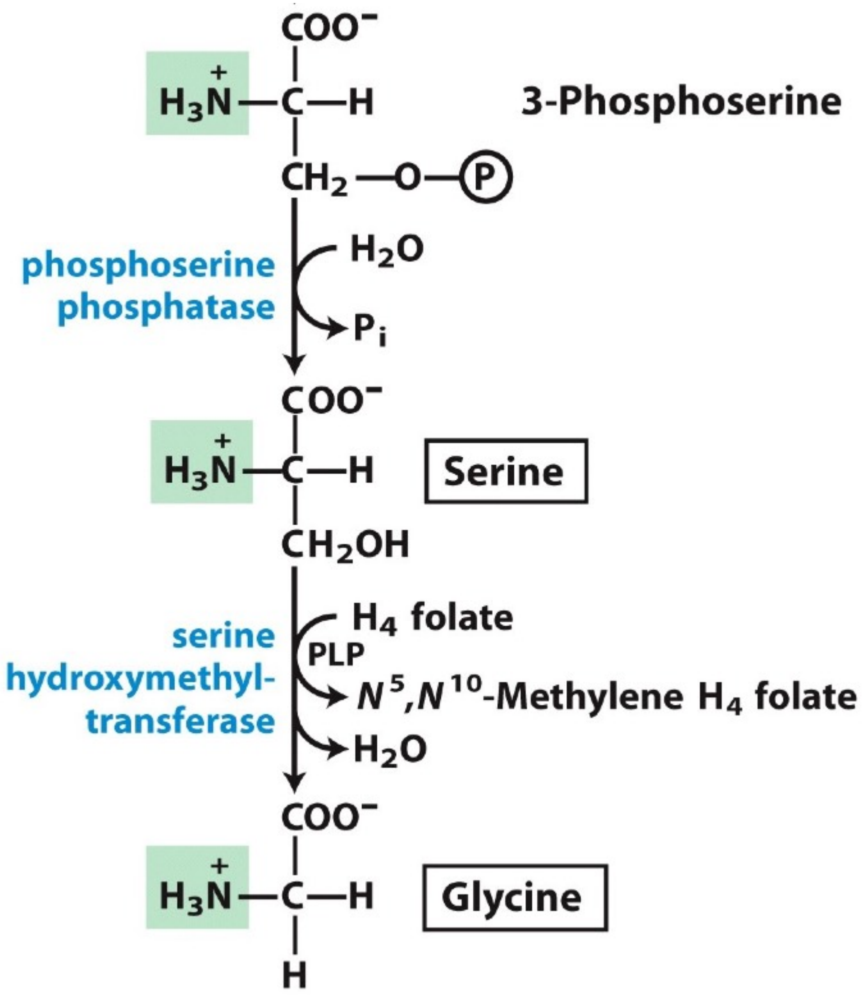
1. 3-phosphoglycerate -> 3-phosphohydroxypyruvate.
   - Catalyzed by dehydrogenase.
2. 3-phosphohydroxypyruvate -> 3-phosphoserine.
   - Catalyzed by aminotransferase.



Biosynthesis of Ser and Gly Part II

3. 3-phosphoserine -> serine.
   - Catalyzed by phosphatase.
4. Serine -> glycine.
   - Catalyzed by hydroxymethyl-transferase.

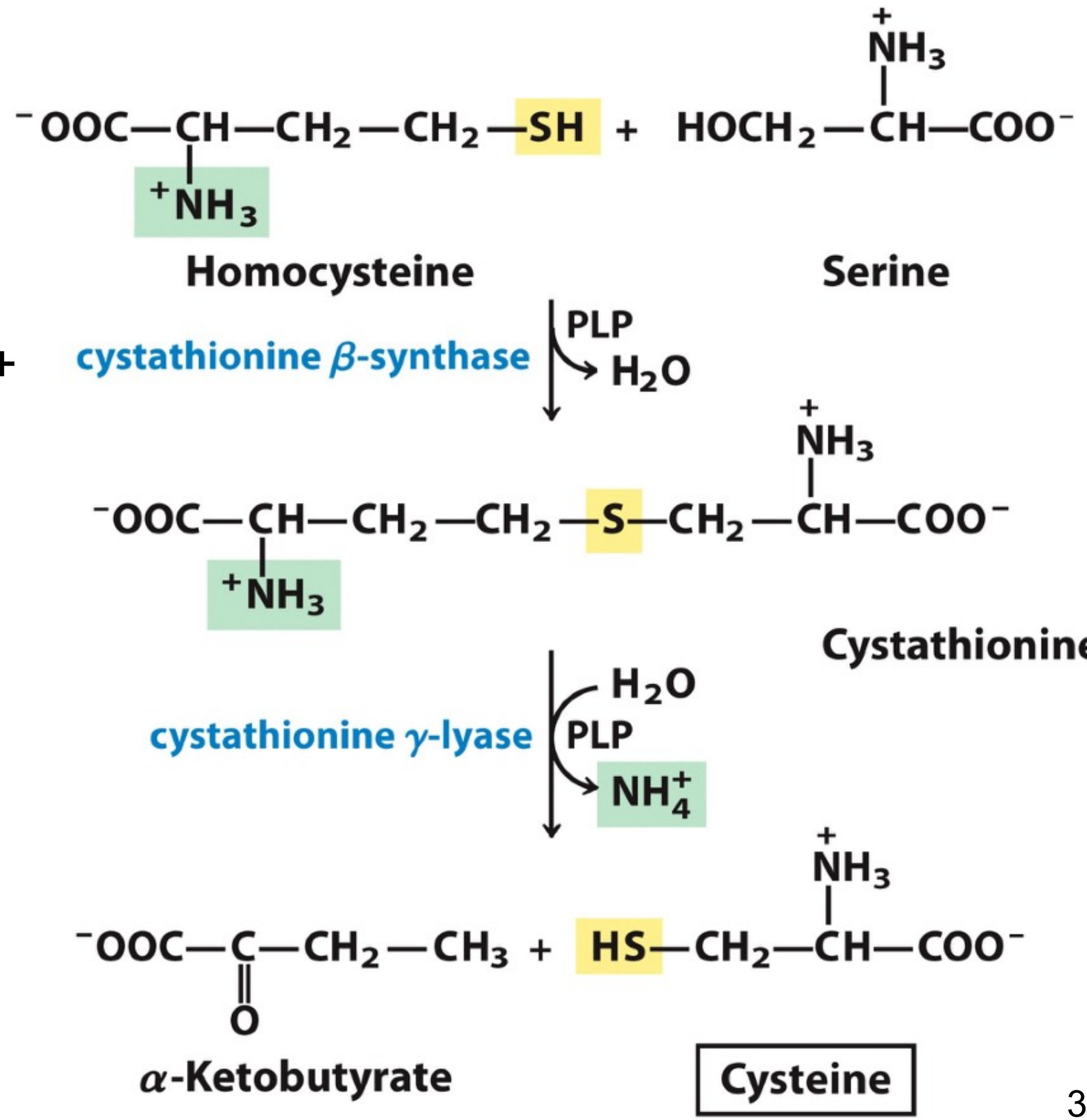
- **Source of serine atoms.**
  - NH_2 from glutamate.
  - 3 carbon atoms from 3-PG.
- **Source of glycine atoms.**
  - NH_2 from glutamate.
  - 2 carbon atoms from 3-PG.



Biosynthesis of Cys

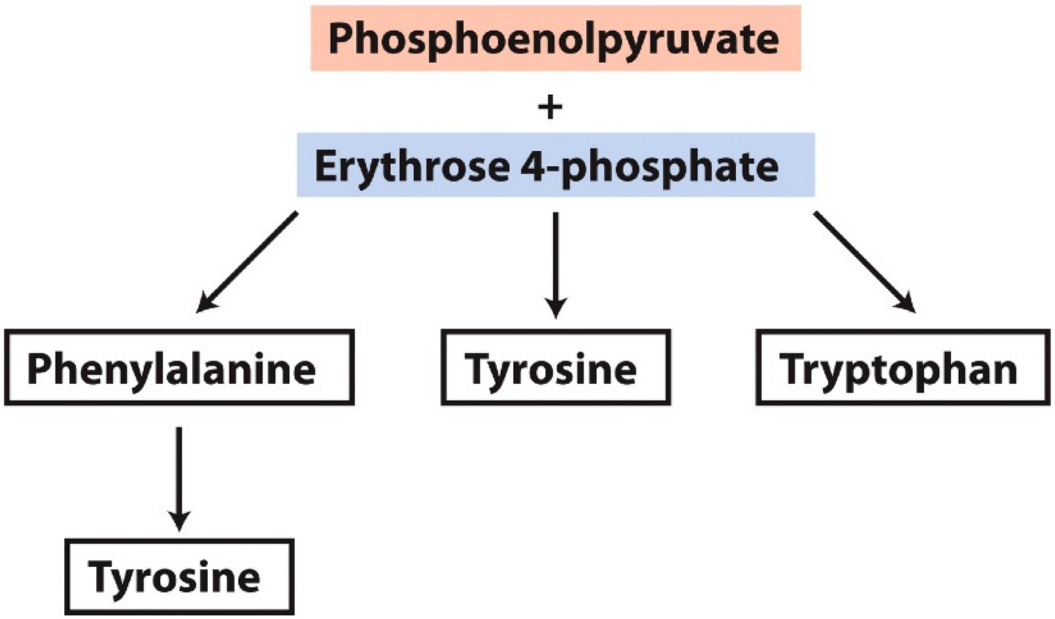
1. Homocysteine + serine -> cystathionine.
   - Catalyzed by synthase.
   - Homocysteine is formed from methionine.
2. Cystathionine -> ammonia + α-ketobutyrate + cysteine.
   - Catalyzed by lyase.

- **Source of cysteine atoms.**
  - NH_2 from serine.
  - 3 carbon atoms from serine.
  - S from methionine.



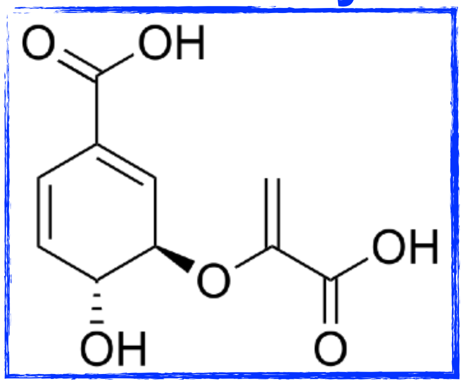
Group 5. PEP + Erythrose 4-Phosphate

- Human cannot synthesize phenylalanine and tryptophan.
  - Phe and Trp are essential amino acids.
- Human can synthesize tyrosine from phenylalanine.
  - Tyr is considered a conditionally essential amino acid.
- Shown here is bacterial biosynthetic pathways.

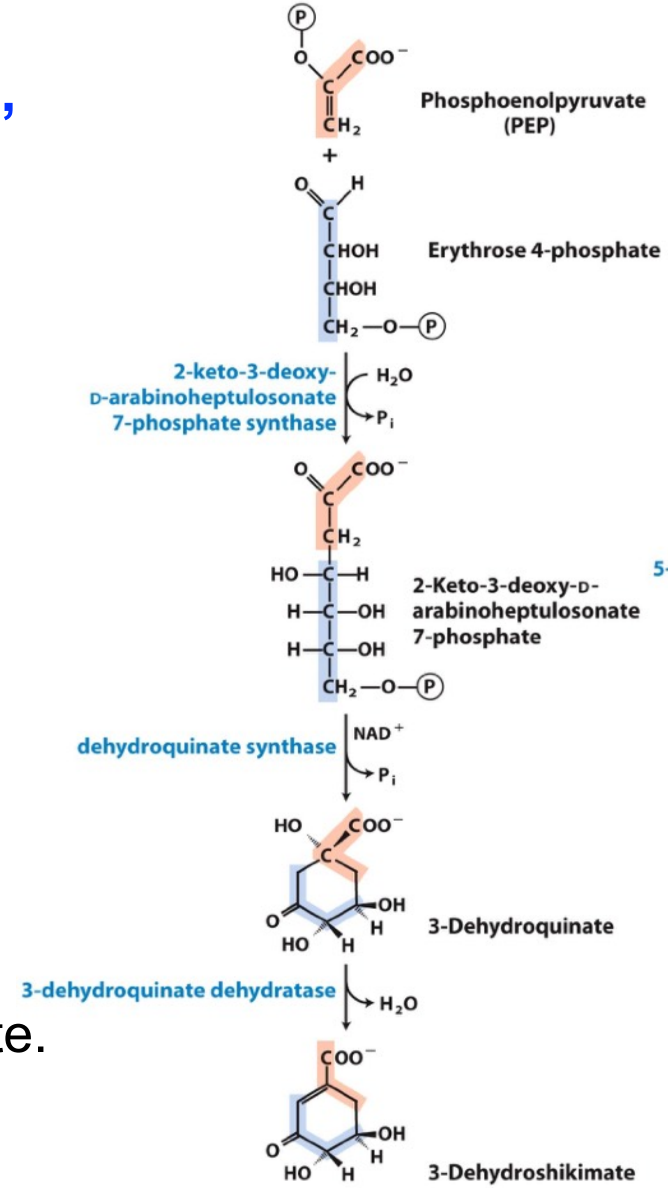


Biosynthesis of Chorismate Part I

Chorismate is a common intermediate in biosynthesis of Trp, Phe and Tyr.



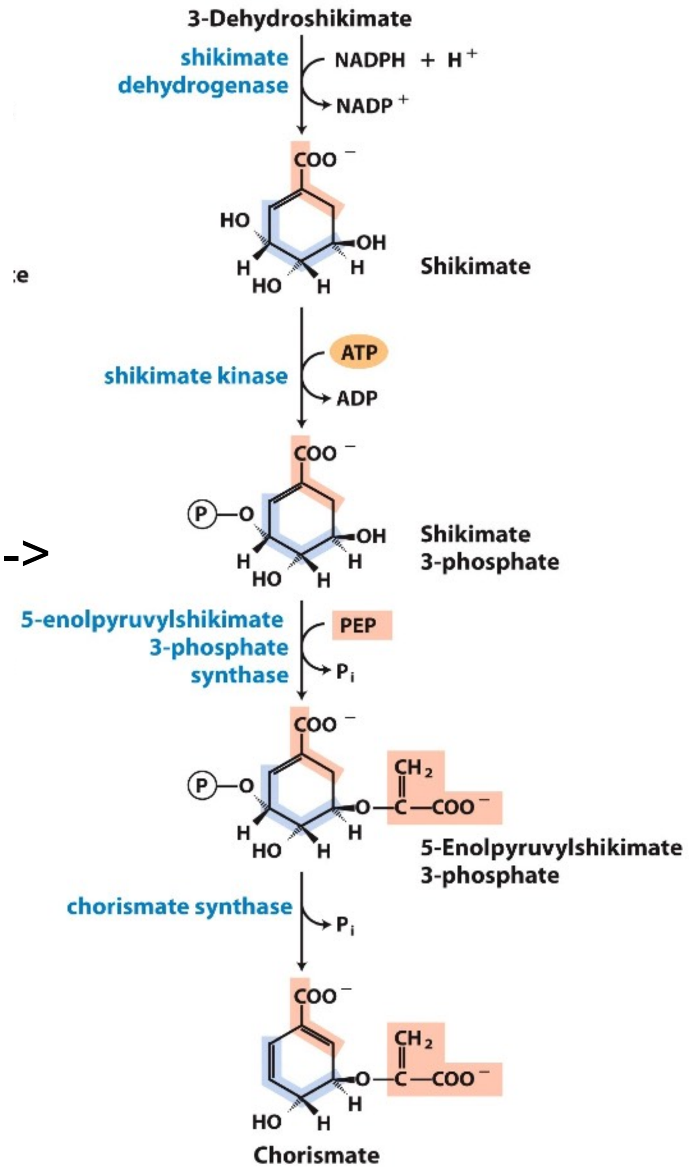
1. Phosphoenolpyruvate + erythrose 4-phosphate -> 7-carbon compound.
   - Catalyzed by synthase.
2. 7-carbon compound -> 3-dehydroquinate.
   - Catalyzed by synthase.
3. 3-dehydroquinate -> 3-dehydroshikimate.
   - Catalyzed by dehydratase.



Biosynthesis of Chorismate Part II

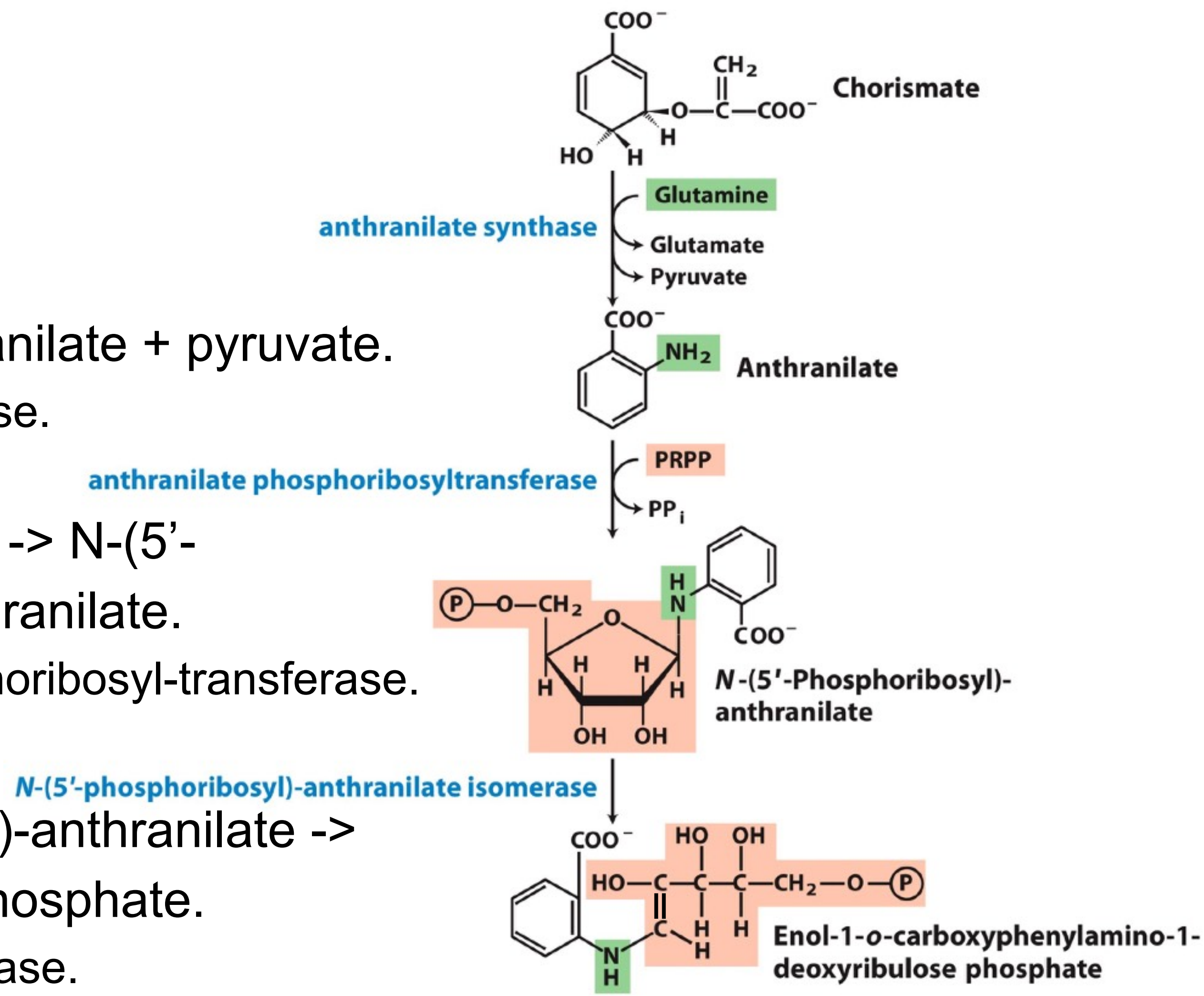
4. 3-dehydroshikimate -> shikimate.
   - Catalyzed by dehydrogenase.
5. Shikimate -> shikimate 3-phosphate.
   - Catalyzed by kinase.
6. Shikimate 3-phosphate + PEP -> 5-enolpyruvyl-shikimate 3-phosphate.
   - Catalyzed by synthase.
7. 5-enolpyruvyl-shikimate 3-phosphate -> chorismate.
   - Catalyzed by synthase.

- **Source of chorismate atoms.**
  - 4 carbon atoms from erythrose 4-P.
  - 3 carbon atoms from PEP.
  - 3 carbon atoms from PEP.

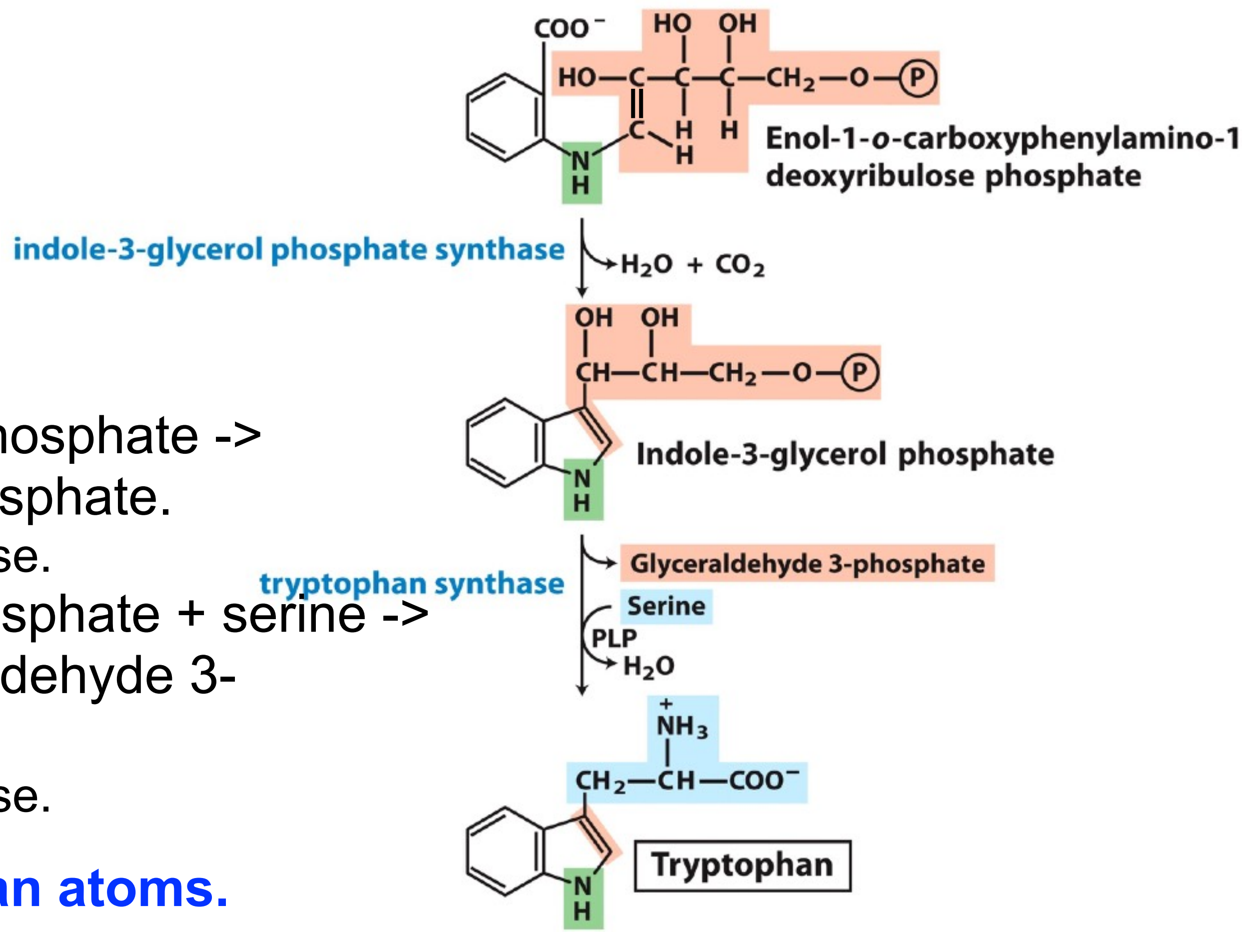


Biosynthesis of Tryptophan Part I

1. Chorismate -> anthranilate + pyruvate.
   - Catalyzed by synthase.
2. Anthranilate + PRPP -> N-(5'-phosphoribosyl)-anthranilate.
   - Catalyzed by phosphoribosyl-transferase.
3. N-(5'-phosphoribosyl)-anthranilate -> R-1-deoxyribulose phosphate.
   - Catalyzed by isomerase.



Biosynthesis of Tryptophan Part II



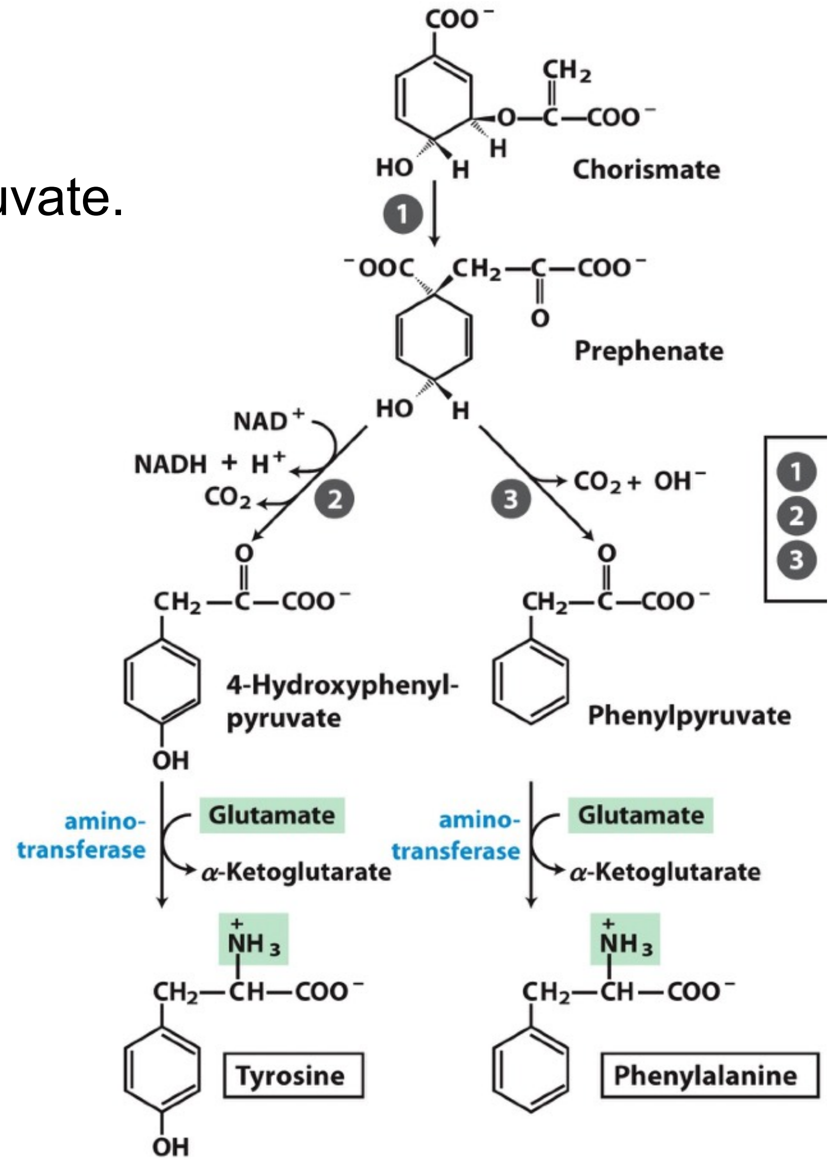
4. R-1-deoxyribulose phosphate -> indole-3-glycerol phosphate.
   - Catalyzed by synthase.
5. Indole-3-glycerol phosphate + serine -> tryptophan + glyceraldehyde 3-phosphate.
   - Catalyzed by synthase.

- **Source of tryptophan atoms.**
  - NH from glutamine.
  - 2 carbon atoms from PRPP.
  - 6 carbon atoms from chorismate.
  - 3 carbon atoms and α-amino group from serine.

Biosynthesis of Tyr and Phe

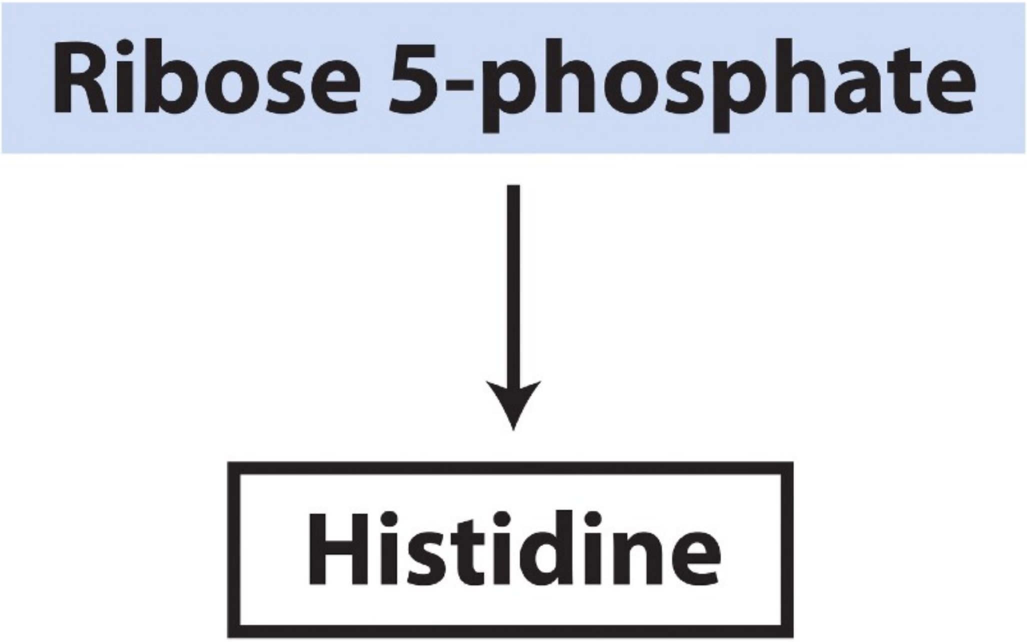
1. Chorismate -> prephenate.
   - Catalyzed by mutase.
2. Prephenate -> 4-hydroxylphenyl-pyruvate.
   - Catalyzed by dehydrogenase.
3. Prephenate -> phenyl-pyruvate.
   - Catalyzed by dehydratase.
4. Phenyl-pyruvate -> tyrosine or phenylalanine.
   - Catalyzed by aminotransferase.

- **Source of Tyr/Phe atoms.**
  - NH_2 from glutamate.
  - 9 carbon atoms from chorismate.

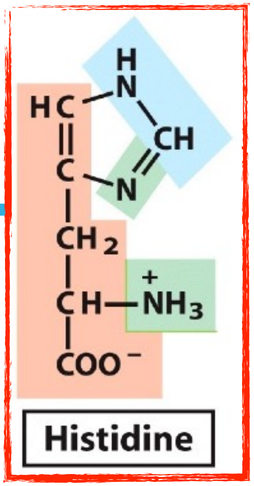


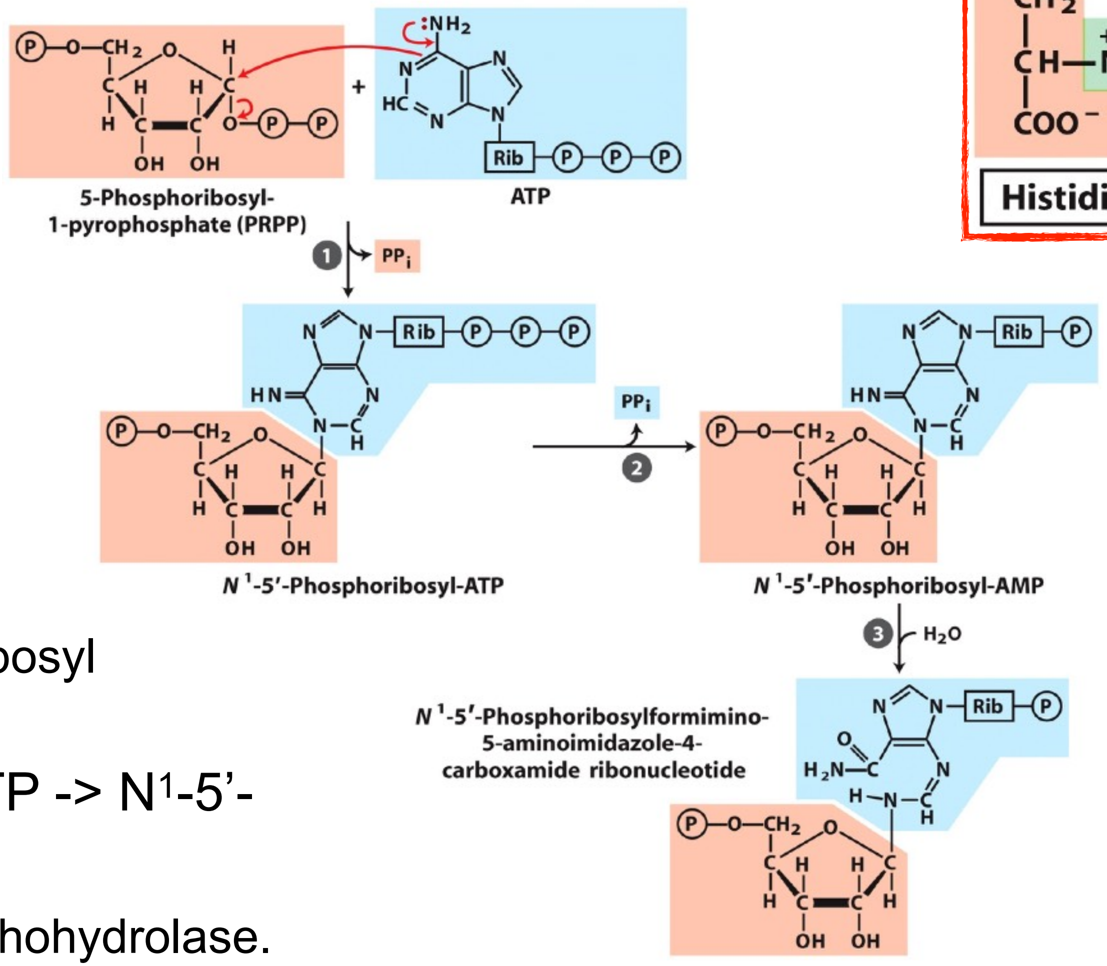
Group 6. Ribose 5-Phosphate

- Human cannot synthesize histidine.
  - His is an essential amino acid.
- Shown here is bacterial biosynthetic pathways.



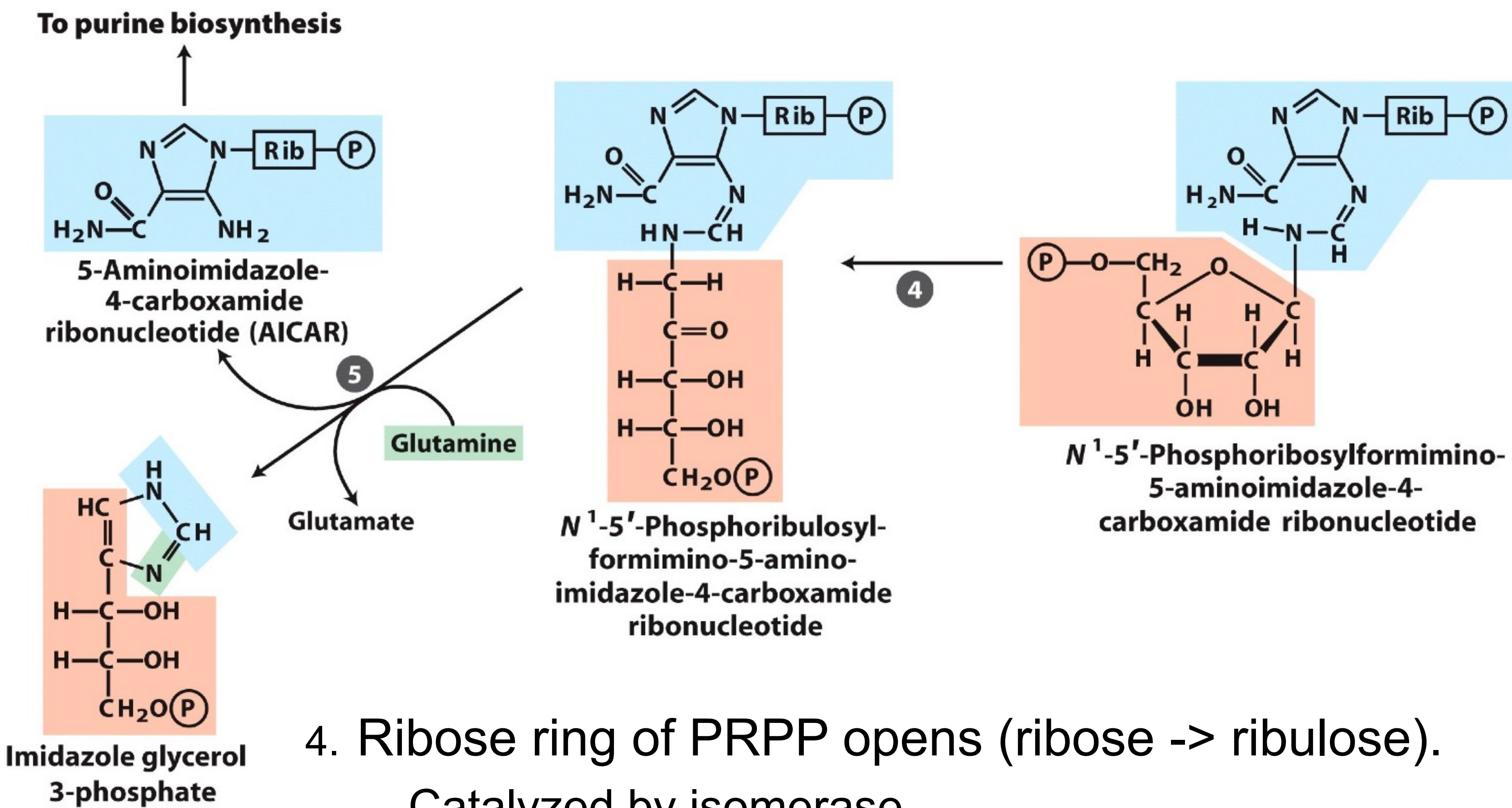
Biosynthesis of His Part I

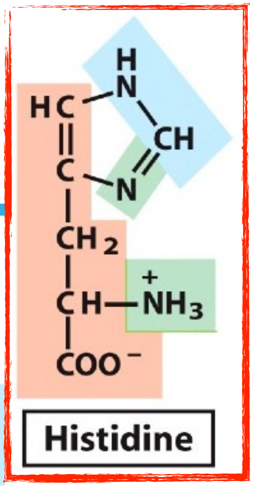




1. PRPP + ATP -> N^1-5'-phosphoribosyl-ATP.
   - Catalyzed by phosphoribosyl transferase.
2. N^1-5'-phosphoribosyl-ATP -> N^1-5'-phosphoribosyl-AMP.
   - Catalyzed by pyrophosphohydrolase.
3. 6-membered ring opens.
   - Catalyzed by cyclohydrolase.

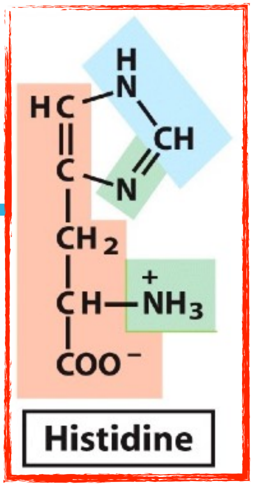
Biosynthesis of His Part II





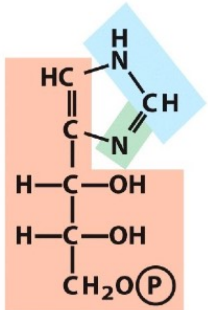
4. Ribose ring of PRPP opens (ribose -> ribulose).
   - Catalyzed by isomerase.
5. Formation of imidazole ring (imidazole glycerol 3-phosphate).
   - Catalyzed by amidotransferase.

Biosynthesis of His Part III

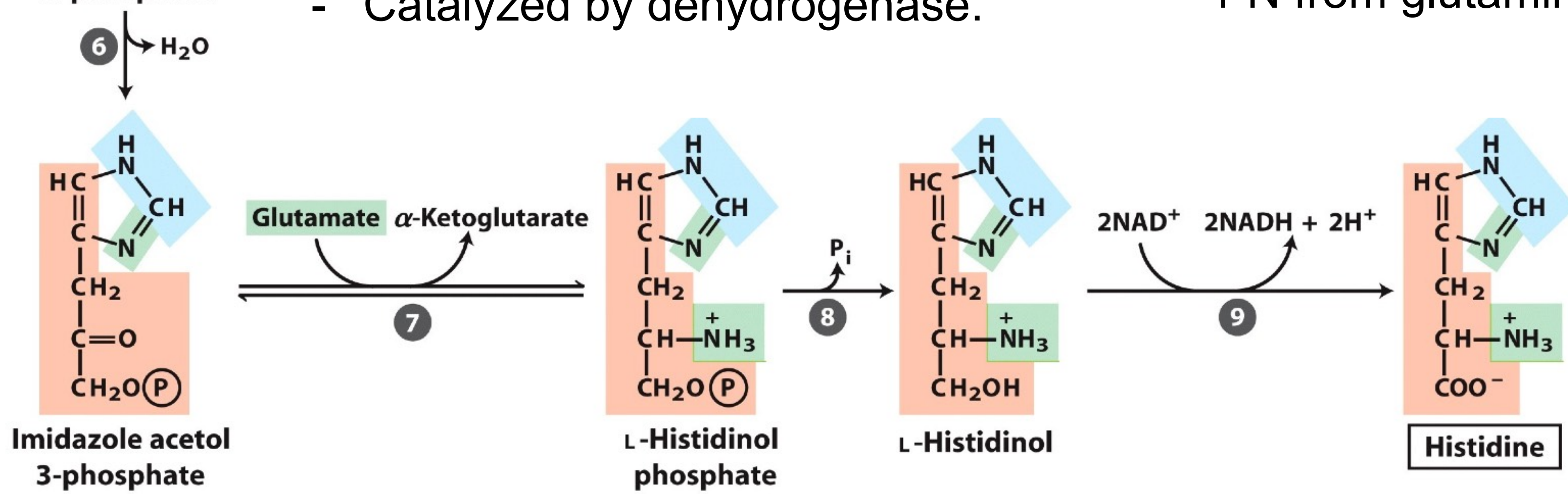


6. Imidazole glycerol 3-phosphate -> imidazole acetol 3-phosphate.
   - Catalyzed by dehydratase.
7. Imidazole acetol 3-phosphate -> histidinol phosphate.
   - Catalyzed by aminotransferase.
8. Histidinol phosphate -> histidinol.
   - Catalyzed by phosphatase.
9. Histidinol -> histidine.
   - Catalyzed by dehydrogenase.

- **Source of His atoms.**
  - NH_2 from glutamate.
  - 5 carbon atoms from PRPP.
  - 1 C and 1 N from ATP.
  - 1 N from glutamine.



Imidazole glycero 3-phosphate



Essential Amino Acids

- From oxaloacetate
  - Met, Thr and Lys
- From pyruvate
  - Val, Leu and Ile
- From PEP + E4P
  - Trp, Phe and Tyr
- From ribose 5-phosphate
  - His
- Nonessential amino acids.
  - Glu, Gln, Pro and Arg
  - Asp and Asn from oxaloacetate
  - Ala from pyruvate
  - Ser, Gly and Cys from 3-PG.

TABLE 22–1 Amino Acid Biosynthetic Families, Grouped by Metabolic Precursor

α-Ketoglutarate	**Pyruvate**
Glutamate	Alanine
Glutamine	Valine*
Proline	Leucine*
Arginine	Isoleucine*
3-Phosphoglycerate	**Phosphoenolpyruvate and erythrose 4-phosphate**
Serine	
Glycine	
Cysteine	Tryptophan*
Oxaloacetate	Phenylalanine*
Aspartate	Tyrosine†
Asparagine	**Ribose 5-phosphate**
Methionine*	Histidine*
Threonine*	
Lysine*	

Summary 22.2 Biosynthesis of Amino Acids

- Plants and bacteria synthesize all 20 common amino acids. Mammals can synthesize about half. The others are required in diet (essential amino acids).
- Nonessential amino acids
- α-ketoglutarate -> E, Q, P, R. Oxaloacetate -> D, N.
- Pyruvate -> A. 3-phosphoglycerate -> S, G, C
- Essential amino acids
- PEP + E4P -> W, Y, F. Oxaloacetate -> M, T, K.
- Pyruvate -> I, V, L. Ribose 5-phosphate -> H

Week 16 Amino Acids and Nucleotides

22.1 Overview of Nitrogen Metabolism

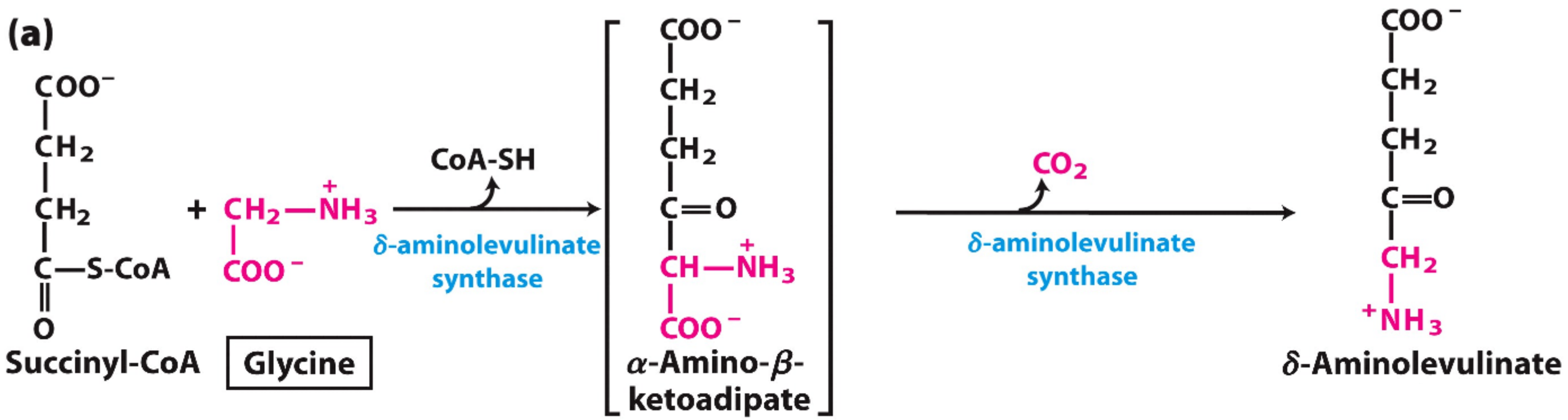
22.2 Biosynthesis of Amino Acids

22.3 Molecules Derived from Amino Acids

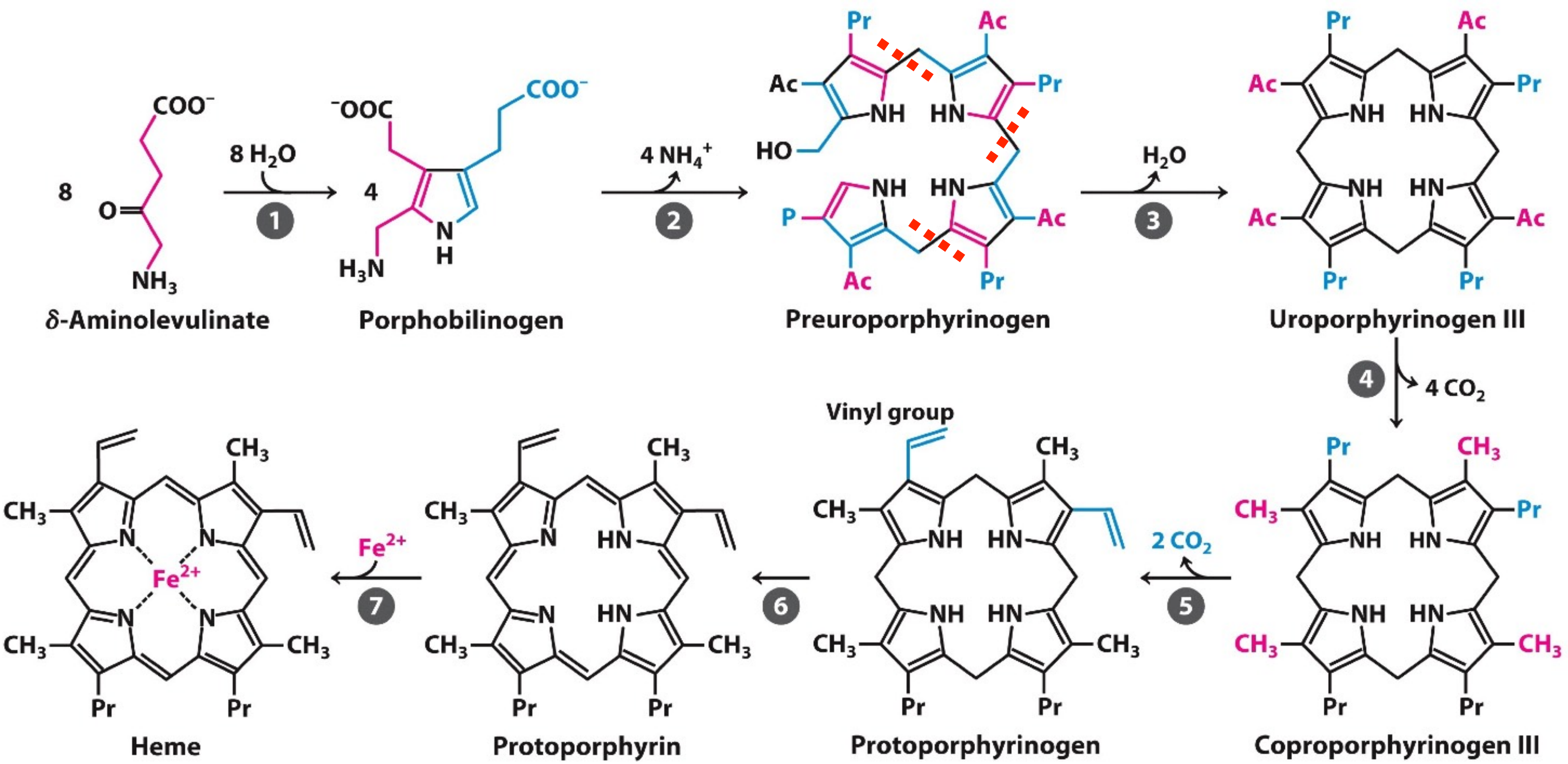
22.4 Biosynthesis and Degradation of Nucleotides

Glycine is a Precursor of Porphyrins

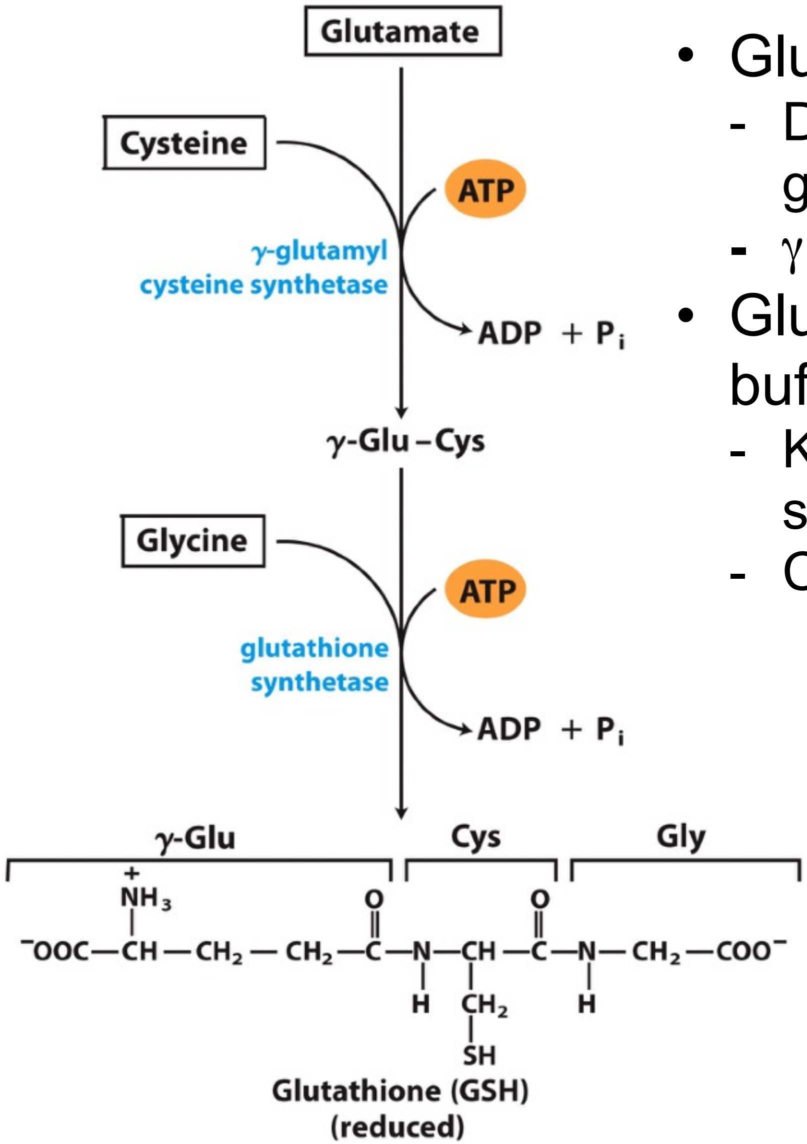
- Porphyrin nucleus is important in heme proteins.
  - Myoglobin, hemoglobin and cytochrome *c*.
- Succinyl-CoA + glycine -> δ-aminolevulinate.
- 2 δ-Aminolevulinate -> porphobilinogen.
- 4 Porphobilinogen -> porphyrin.



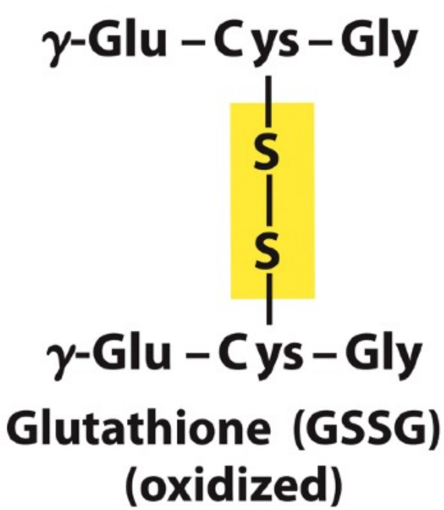
From δ-Aminolevulinate to Heme



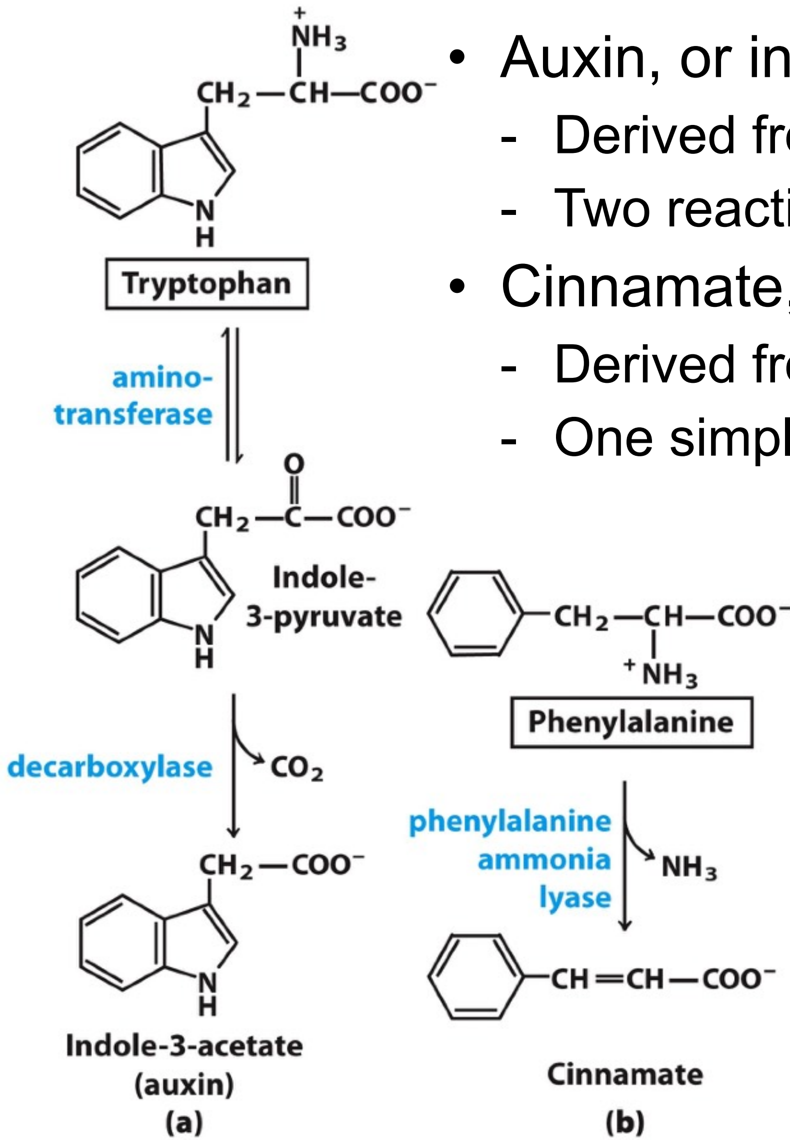
Glutathione (GSH) From E, C and G



- Glutathione is a tri-peptide.
  - Derived from glutamate, cysteine and glycine.
  - **γ-carboxyl group of glutamate.**
- Glutathione can be thought of as a redox buffer.
  - Keep proteins and metal ions at reduced state.
  - Can be oxidized to form a dimer (GSSG).



Aromatic Amino Acids -> Plant Substances



- Auxin, or indole-3-acetate, a plant growth hormone.
  - Derived from tryptophan.
  - Two reactions: transamination and decarboxylation.
- Cinnamate, flavor of cinnamon oil.
  - Derived from phenylalanine.
  - One simple reaction: removal of ammonia.

Summary 22.3 Amino Acid Derivatives

- Glycine is a precursor of porphyrins.
- Glutathione, formed from three amino acids, is an important cellular reducing agent.
- Aromatic amino acids give rise to many plant substances.

Week 16 Amino Acids and Nucleotides

22.1 Overview of Nitrogen Metabolism

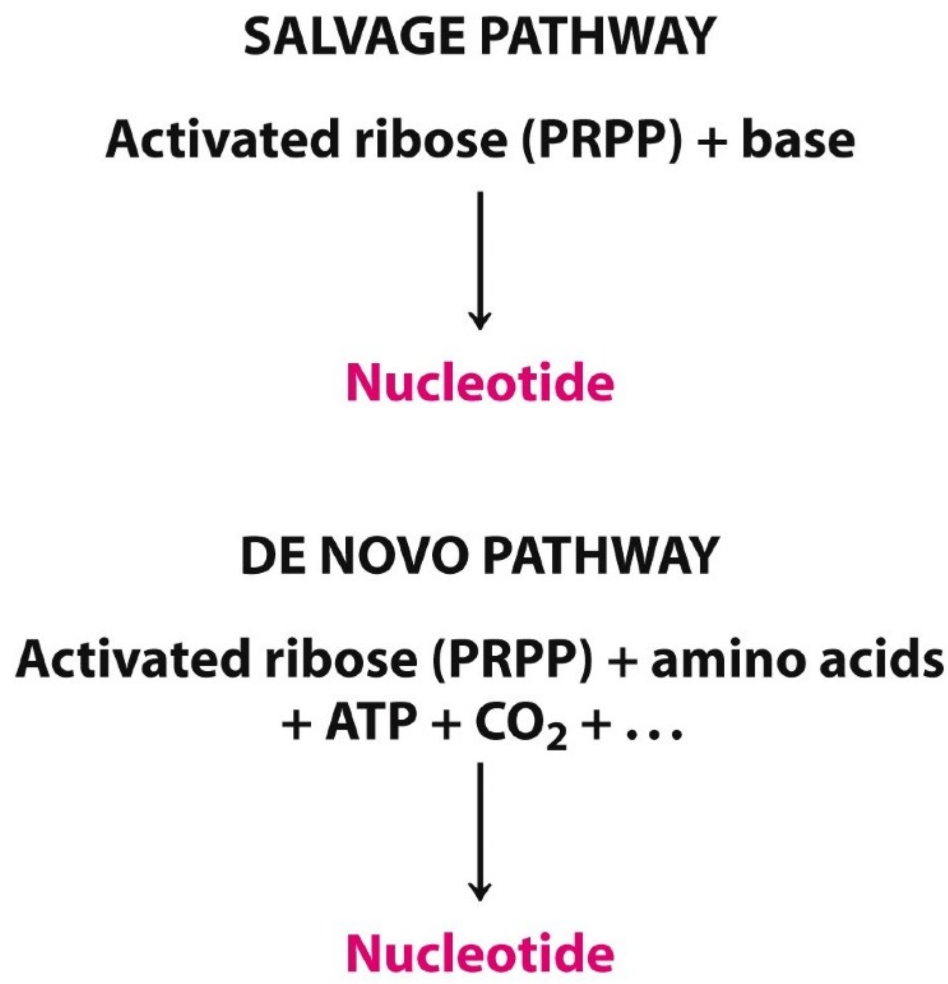
22.2 Biosynthesis of Amino Acids

22.3 Molecules Derived from Amino Acids

22.4 Biosynthesis and Degradation of Nucleotides

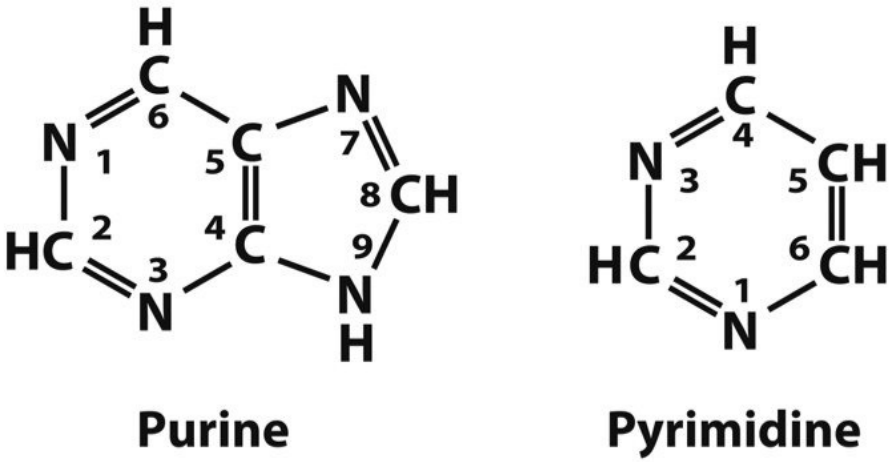
Biosynthesis of Nucleotides

- Two types of pathways lead to nucleotides.
  - De novo pathway.
  - Salvage pathway.
- De novo pathway.
  - Begin with metabolic precursors.
  - Amino acids, ribose 5-phosphate, CO_2 and NH_3.
- Salvage pathway.
  - Recycle free bases and nucleosides released from nucleic acid breakdown.



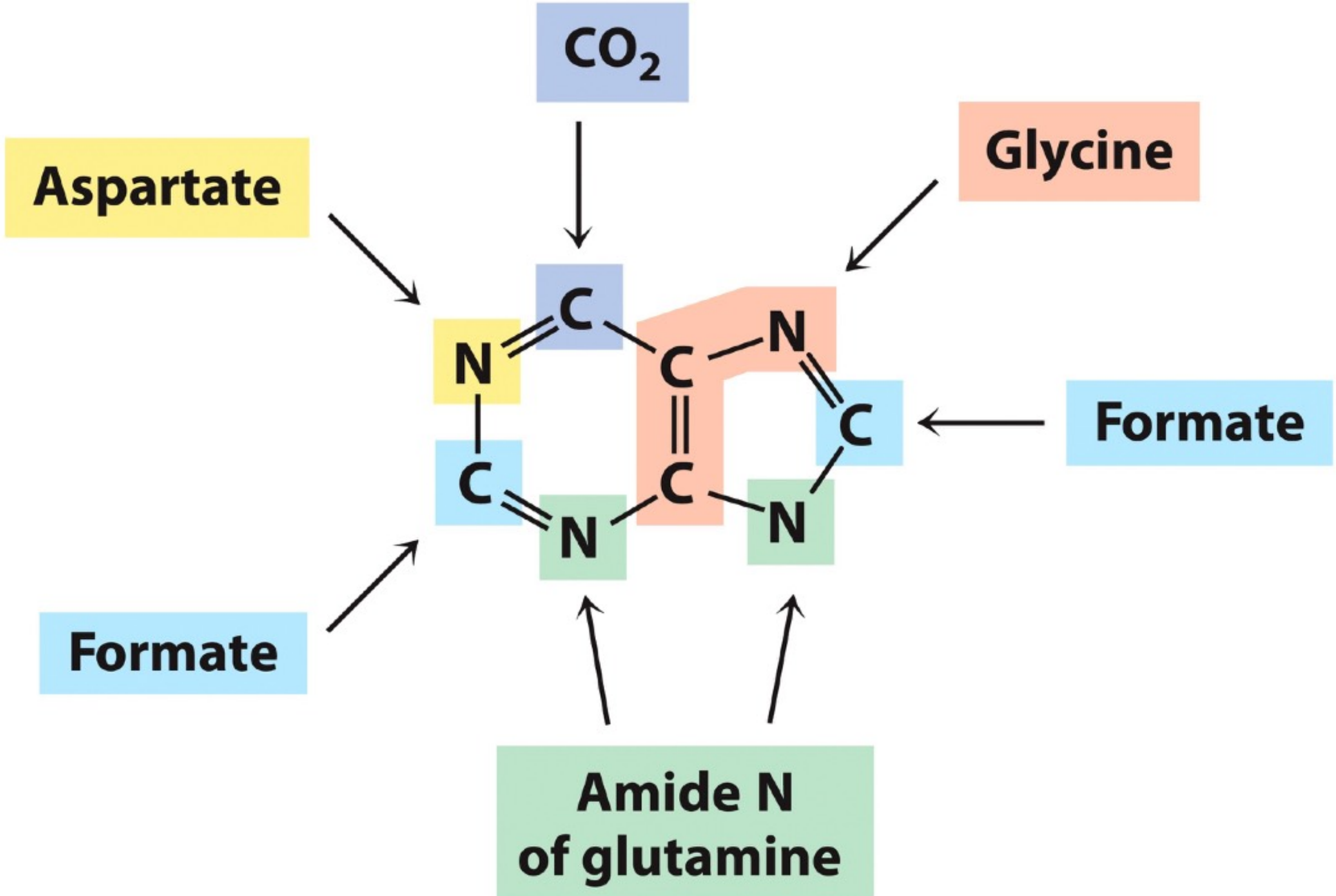
De Novo Biosynthesis

- Bases are synthesized while attached to ribose.
  - Free bases (GATCU) are NOT intermediates in biosynthetic pathways.
- **PRPP provides ribose sugar ring and monophosphate group.**
  - Different from Trp and His biosynthetic pathways.
  - Amino acids, ribose 5-phosphate, CO_2 and NH_3.
- An amino acid is an important precursor in each pathway.
  - Glycine for purines.
  - Aspartate for pyrimidines.
  - Glutamate is the most important source of amino groups.
    - Aspartate is also used in some reactions.



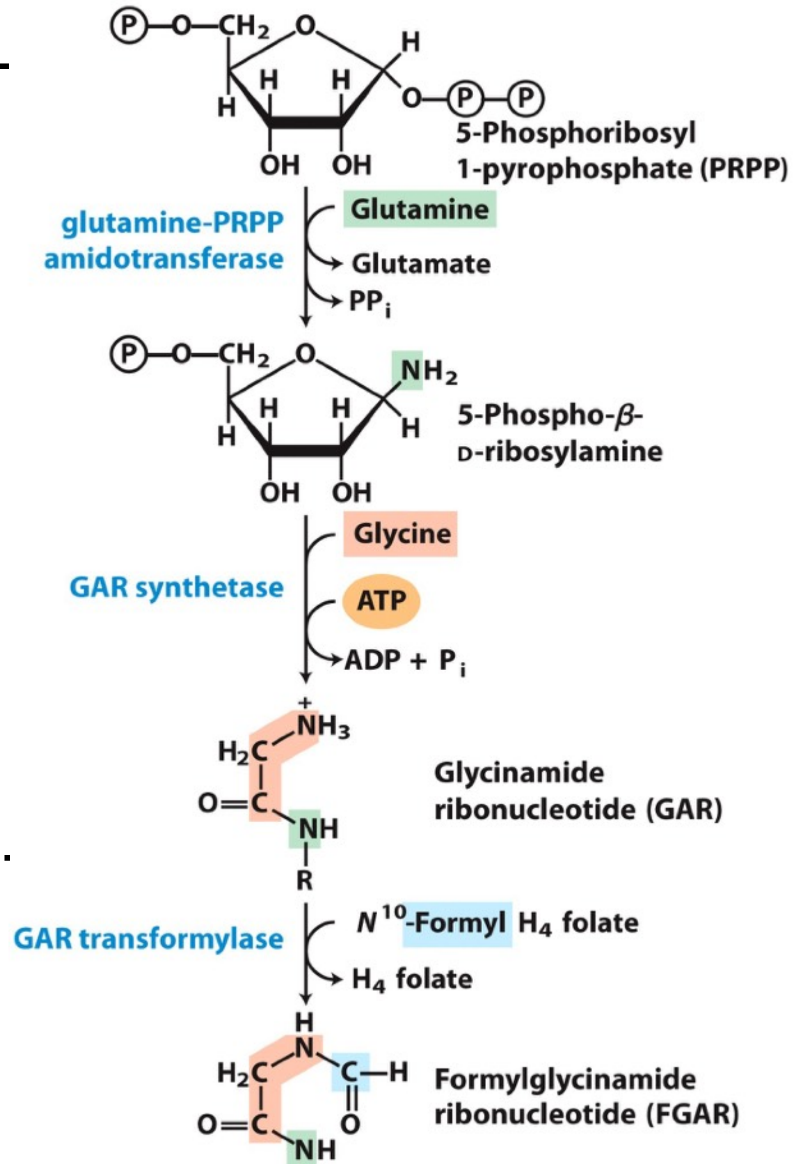
Origin of Ring Atoms of Purines

- Purine ring contains nine atoms.
- These nine atoms come from seven precursor molecules.



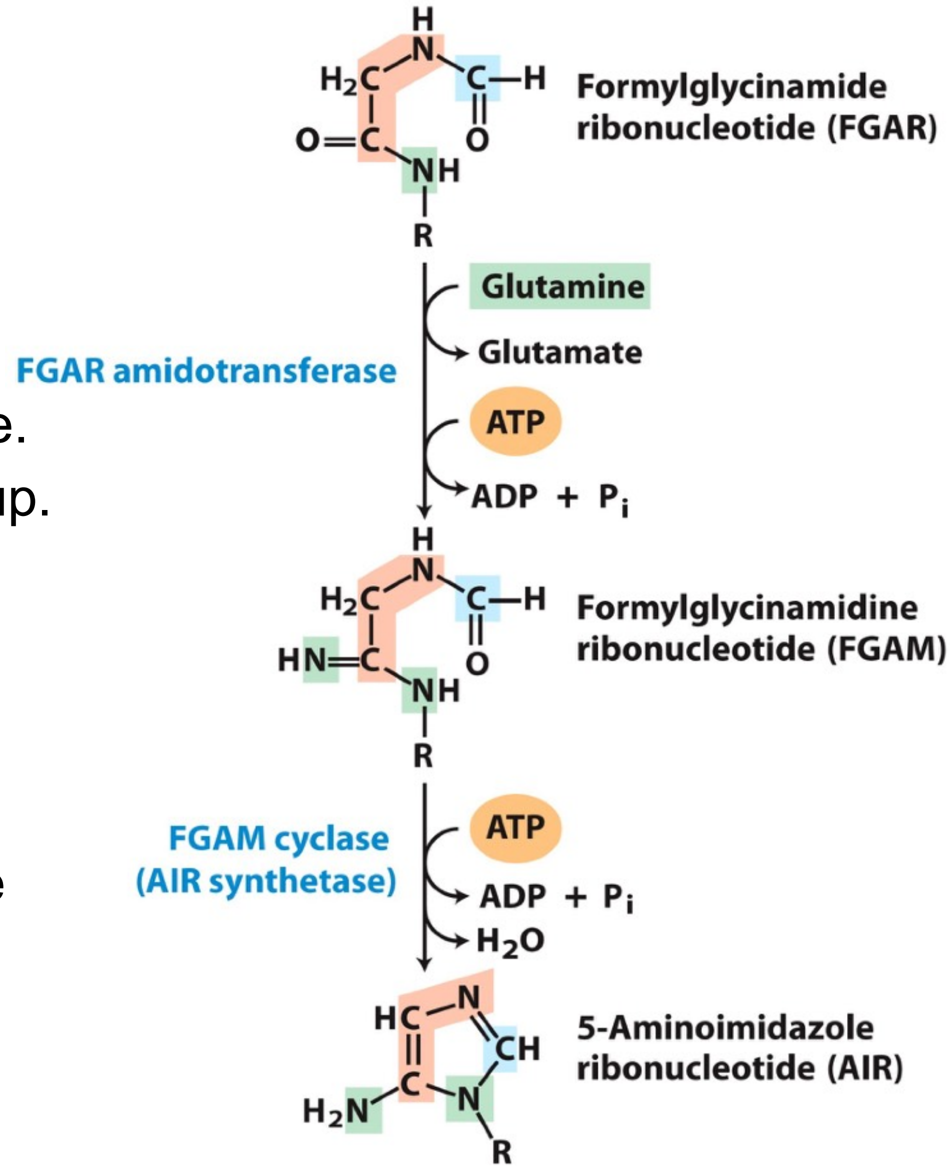
De Novo Purine Pathway Part I

1. PRPP + glutamine -> 5-phospho-β-ribosylamine.
   - Catalyzed by amidotransferase.
   - Glutamine donates amino group.
   - Amino group attached to C-1 of PRPP.
2. 5-phospho-β-ribosylamine + glycine -> glycinamide ribonucleotide.
   - Catalyzed by synthetase.
   - Addition of three atoms from glycine.
   - ATP consumed to activate glycine.
3. GAR -> formyl-glycinamide ribonucleotide.
   - Catalyzed by transformylase.
   - Glycine amino group formylated.



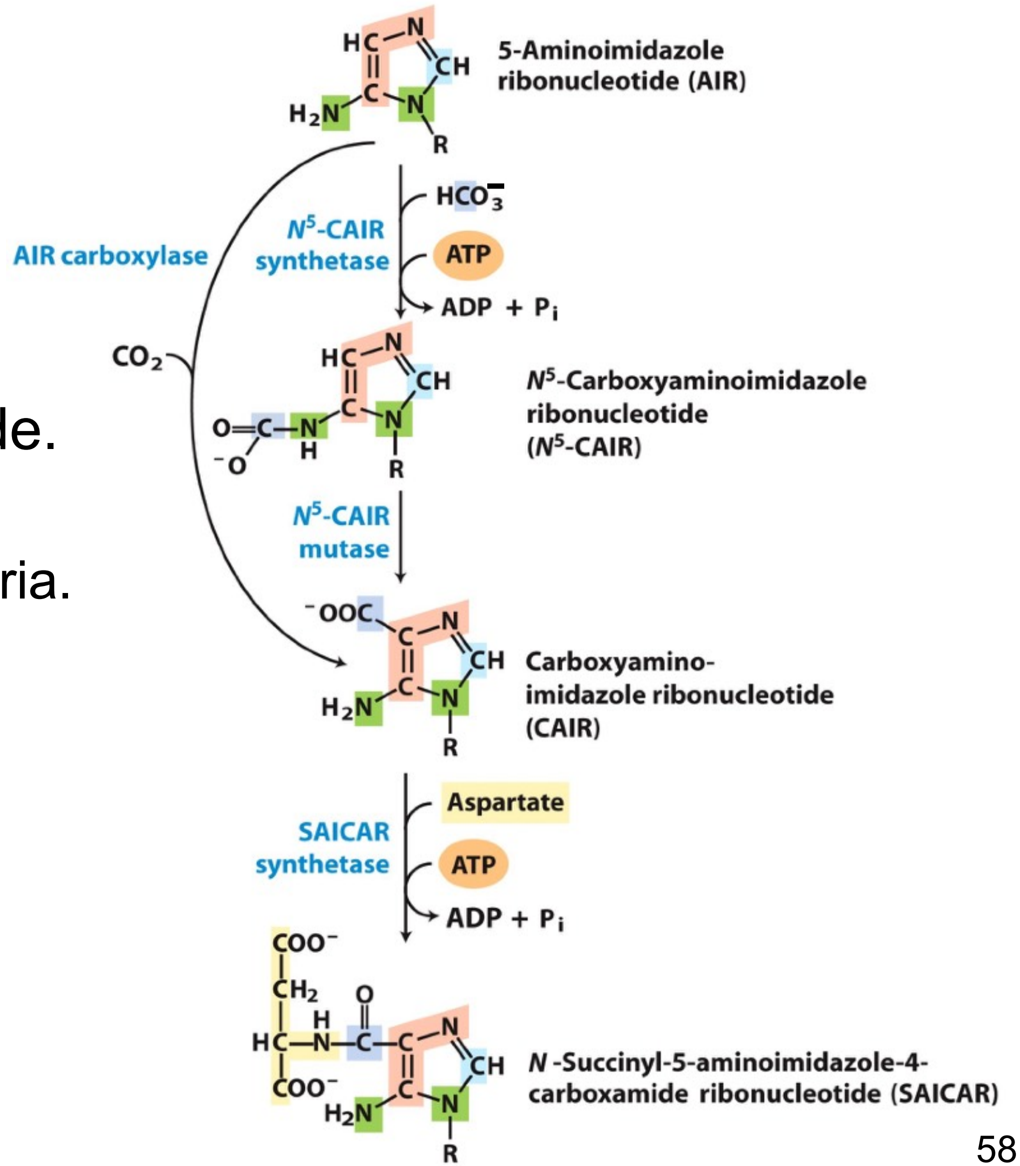
De Novo Purine Pathway Part II

4. FGAR + glutamine -> formyl-glycinamidine ribonucleotide.
   - Catalyzed by amidotransferase.
   - Glutamine donates amino group.
5. FGAM -> 5-aminoimidazole ribonucleotide.
   - Catalyzed by cyclase.
   - Dehydration reaction.
   - Yield five-membered imidazole ring.



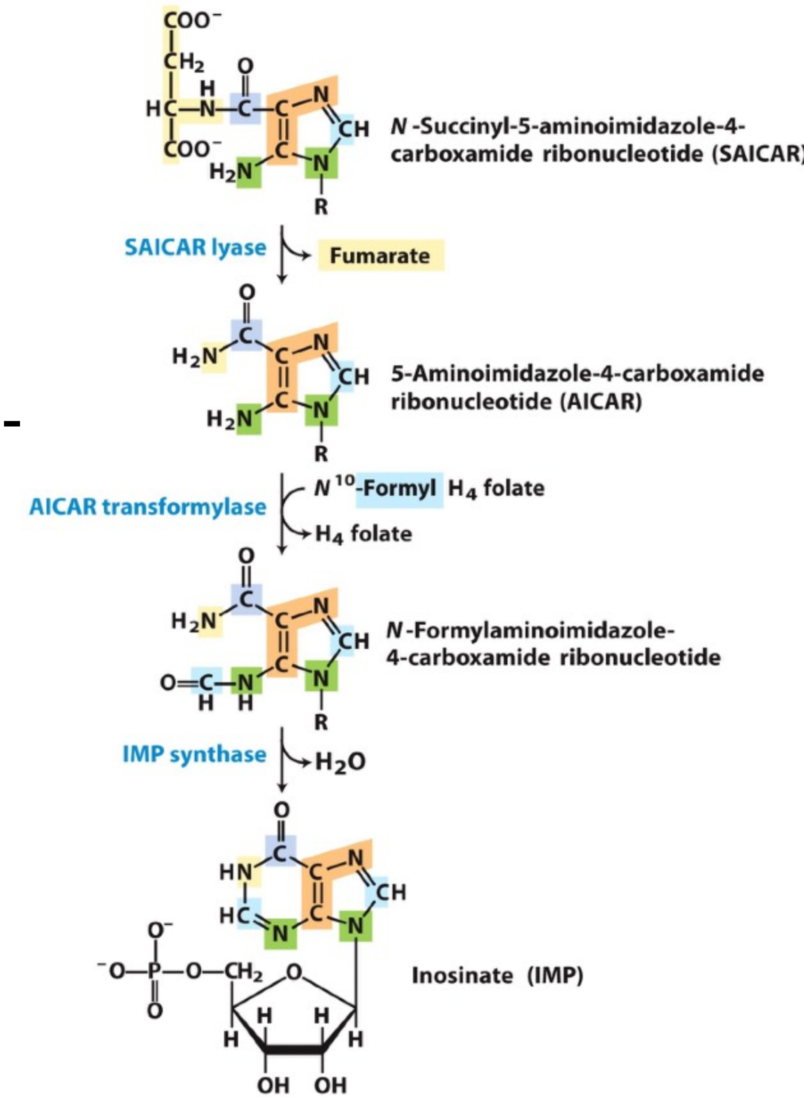
De Novo Purine Pathway Part III

6. AIR + CO_2 -> carboxy-aminoimidazole ribonucleotide.
   - Catalyzed by carboxylase.
   - Found in human but not bacteria.
8. CAIR + aspartate -> *N*-succinyl-5-aminoimidazole-4-carboxamide ribonucleotide.
   - Catalyzed by synthetase.
   - Formation of an amide bond.



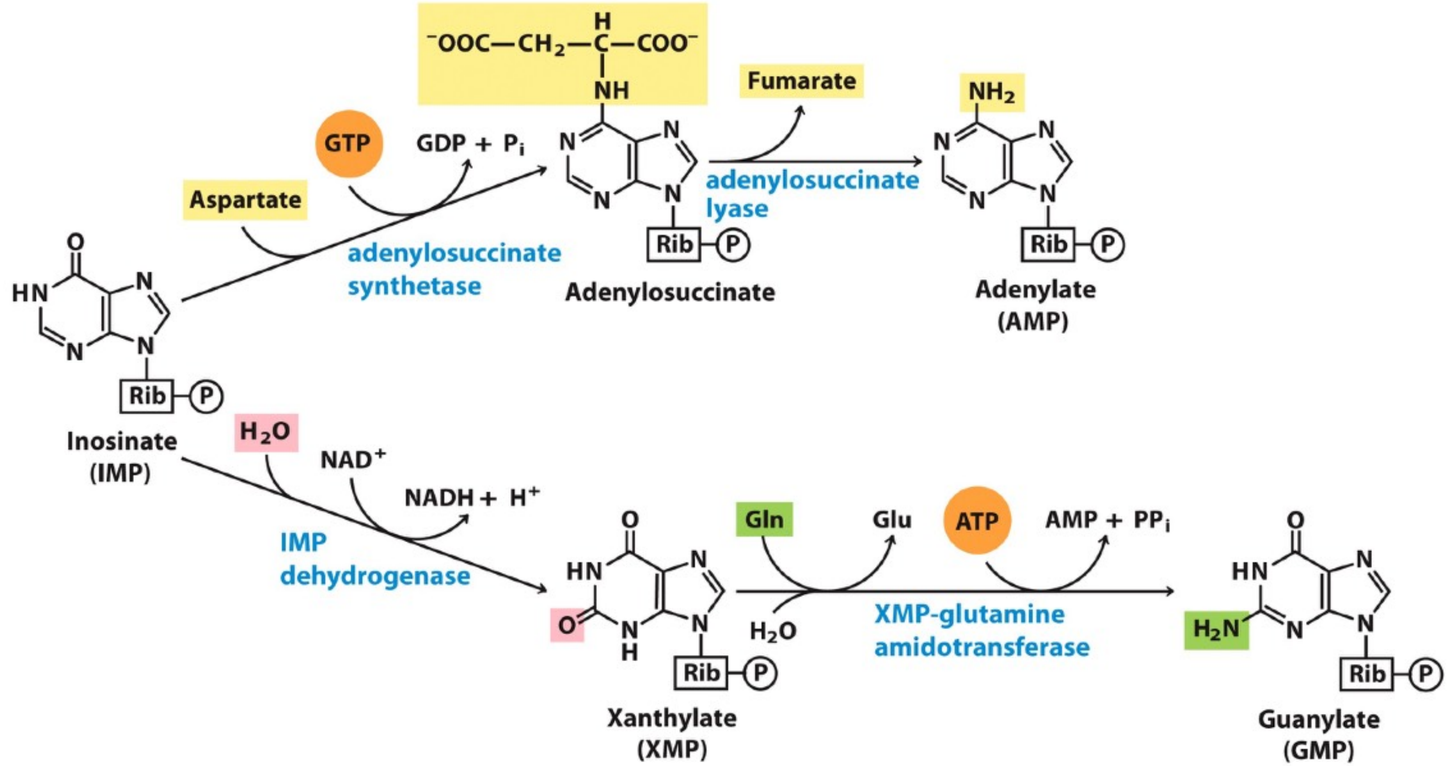
De Novo Purine Pathway Part IV

9. SAICAR -> 5-aminoimidazole-4-carboxamide ribonucleotide + fumarate.
   - Catalyzed by lyase.
   - Elimination of carbon skeleton of aspartate.
10. AICAR -> *N*-formyl-aminoimidazole-4-carboxamide ribonucleotide.
    - Catalyzed by transformylase.
    - Final carbon comes in as formyl group.
11. *N*-formyl-aminoimidazole-4-carboxamide ribonucleotide -> inosinate (IMP).
    - Catalyzed by synthase.
    - 2nd ring closure.
    - 1st intermediate with a complete purine ring is inosinate (IMP).



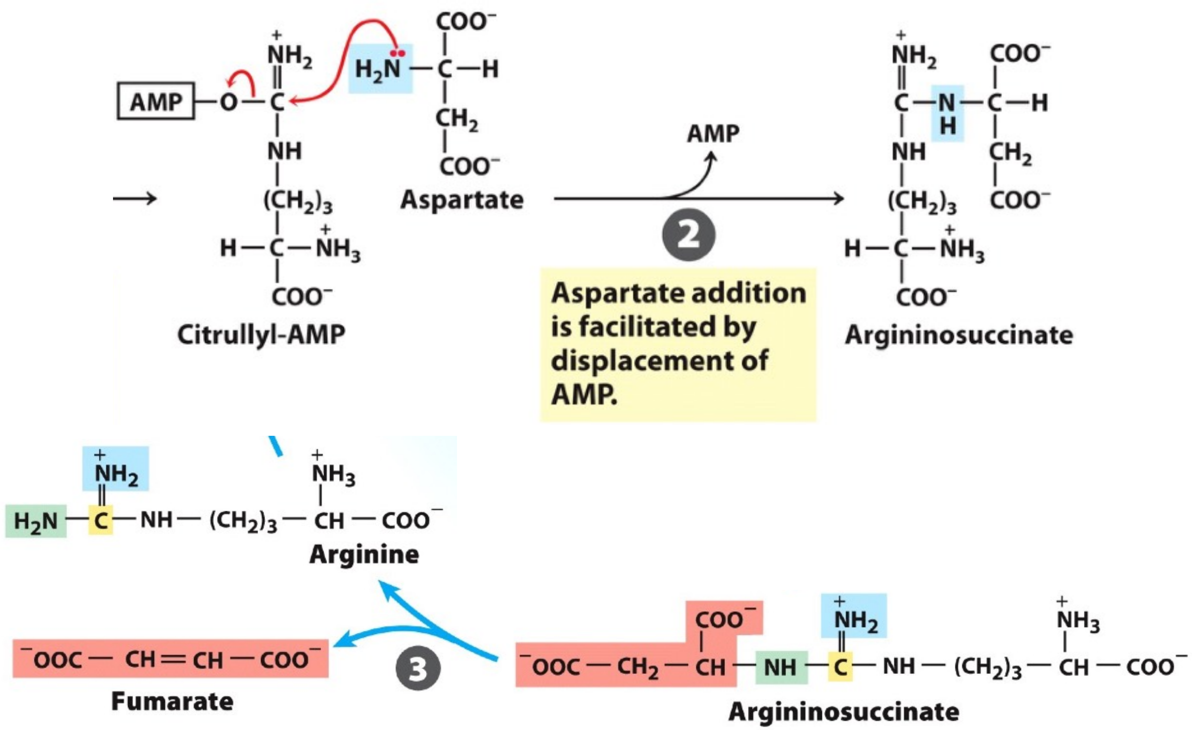
Synthesis of AMP and GMP From IMP

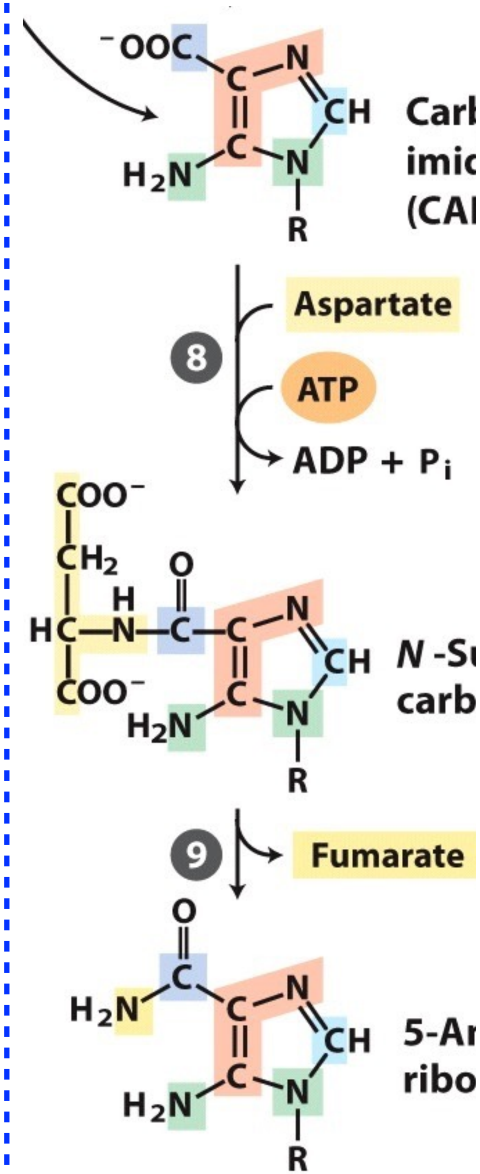
- Inosinate (IMP) -> adenylosuccinate -> adenylate (AMP).
  - Aspartate donates amino group.
- Inosinate (IMP) -> xanthylate (XMP) -> guanylate (GMP).
  - Glutamine donates amino group.



Aspartate Donates Amino Group

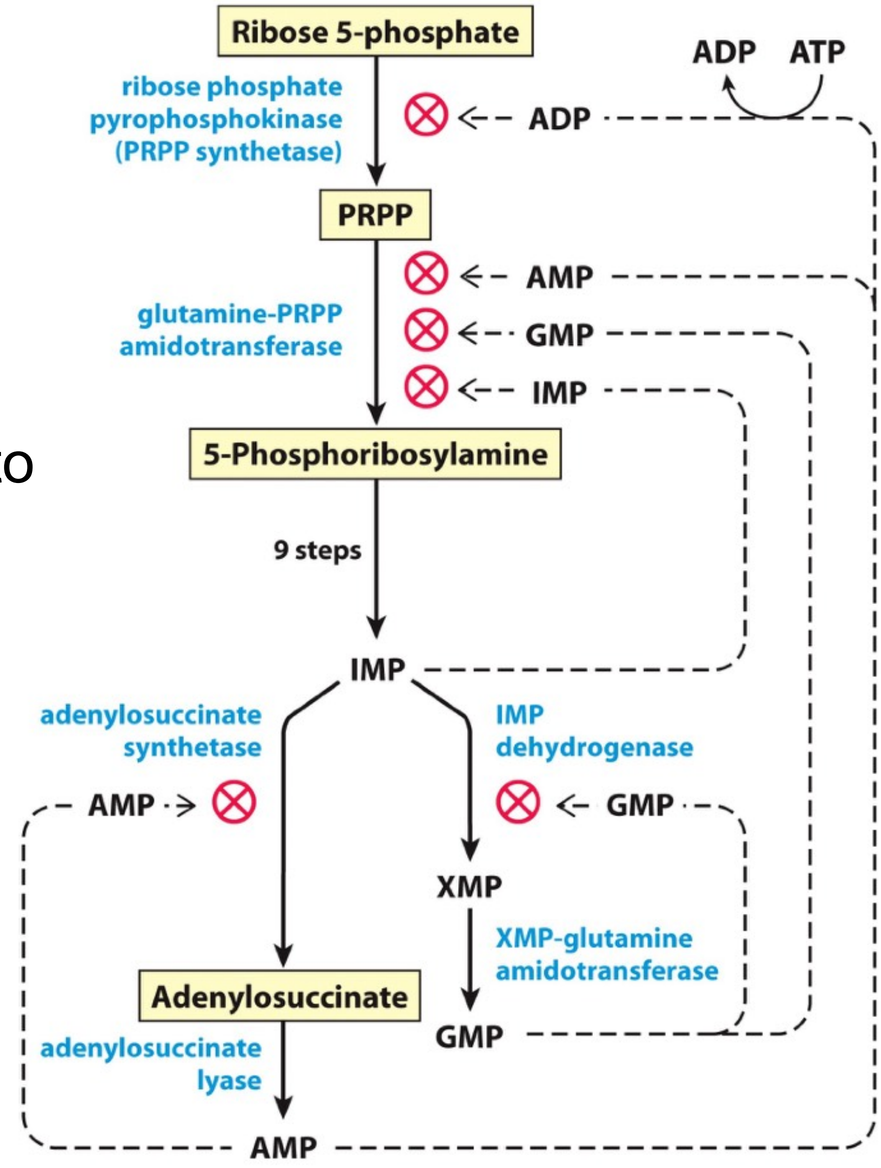
- Urea cycle.
  - Citrulline + aspartate -> argininosuccinate -> arginine + fumarate.
- De novo synthesis of purines.
  - CAIR + aspartate -> SAICAR -> AICAR + fumarate.





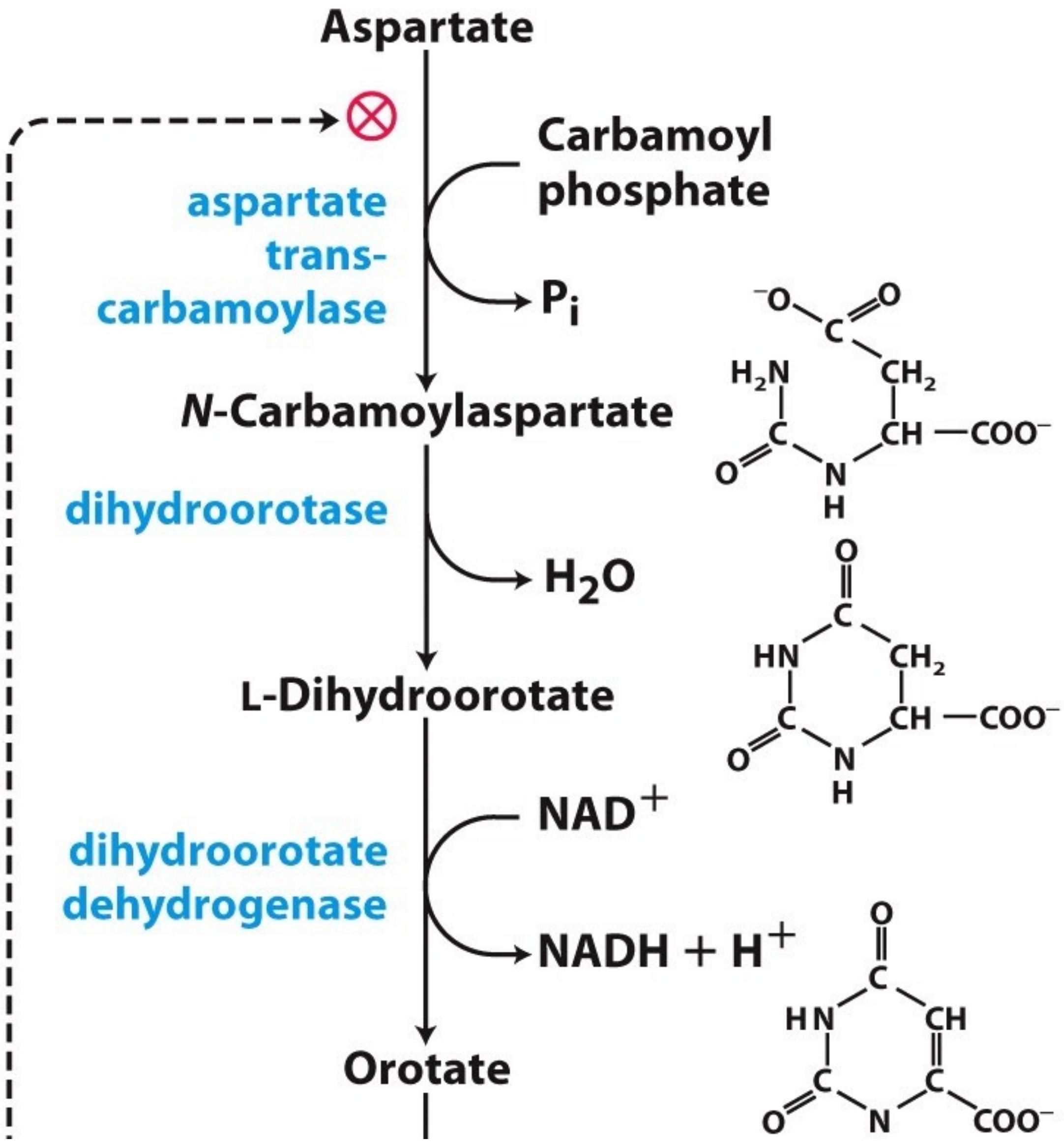
Regulation by Feedback Inhibition

- First reaction of purine biosynthesis.
  - Inhibited by end products AMP, GMP and IMP.
- Last reactions converting IMP to AMP and GMP.
  - AMP inhibits formation of adenylosuccinate.
  - GMP inhibits formation of XMP.
- Formation of precursor PRPP.
  - Consumes ATP.
  - Inhibited by ADP.



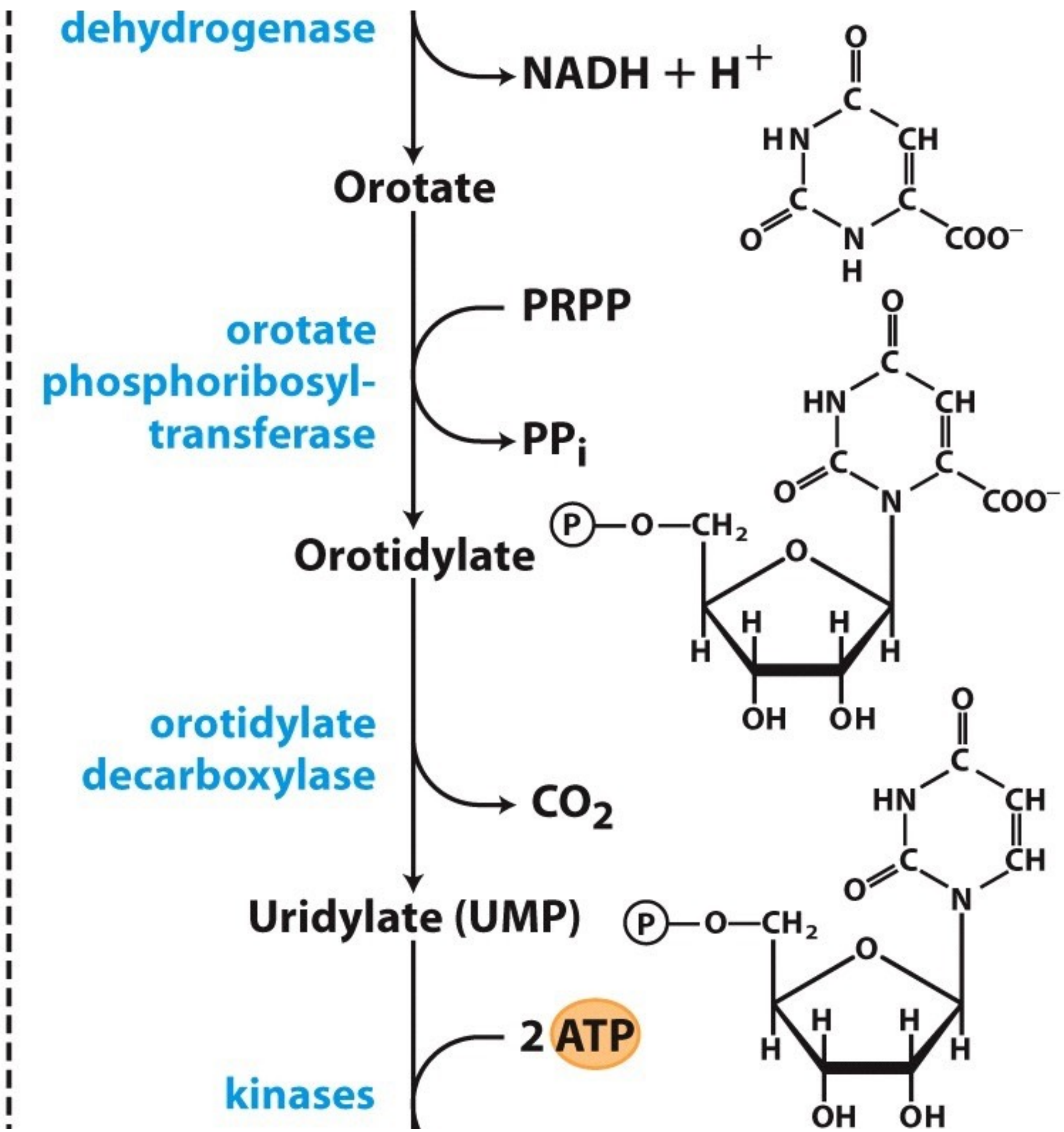
Pyrimidine Biosynthesis Part I

1. Aspartate + carbamoyl phosphate -> *N*-carbamoyl-aspartate.
   - Catalyzed by transcarbamoylase.
2. *N*-carbamoyl-aspartate -> dihydro-orotate.
   - Catalyzed by dihydroorotase.
3. Dihydro-orotate -> orotate.
   - Catalyzed by dehydrogenase.



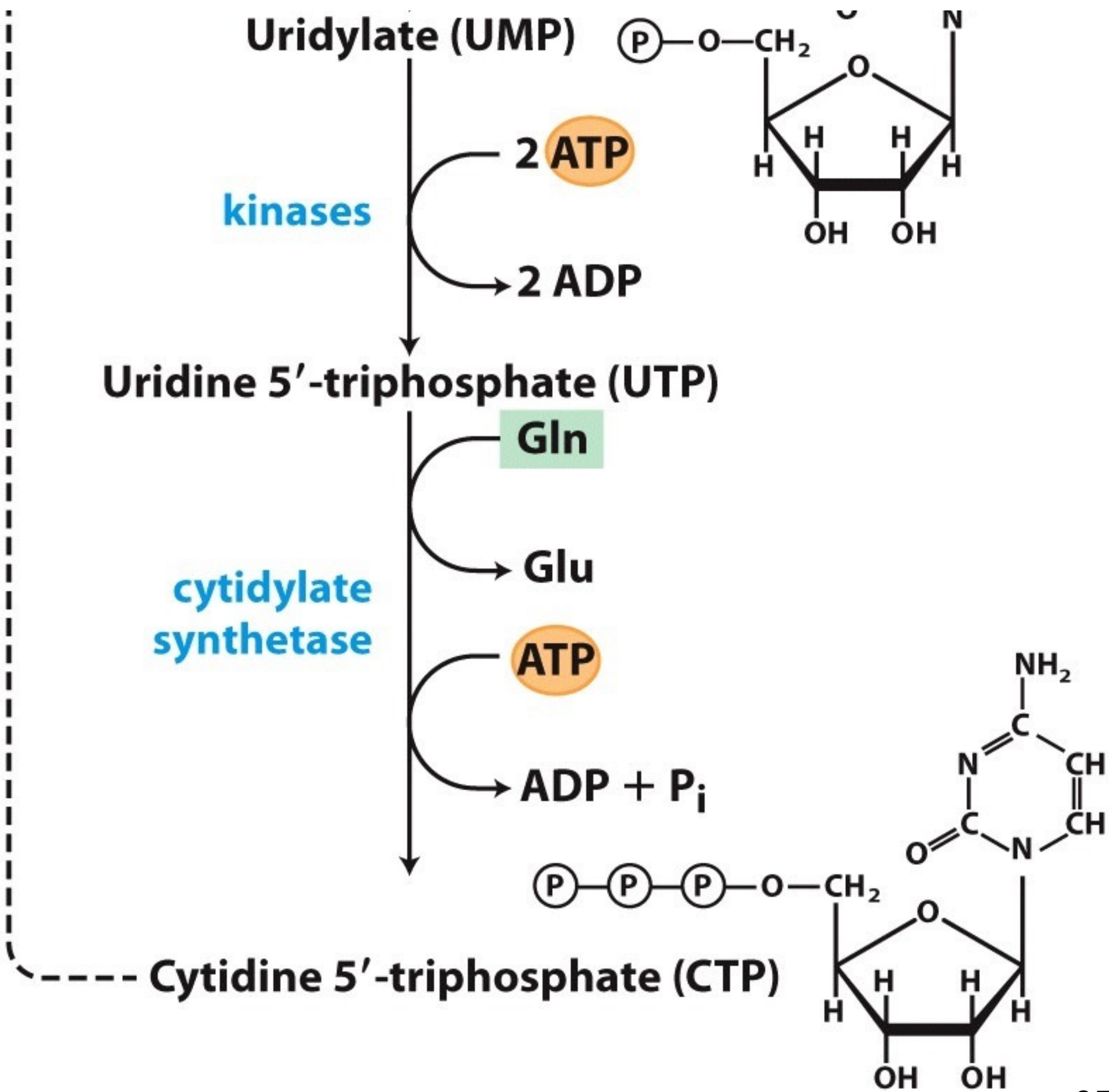
Pyrimidine Biosynthesis Part II

4. Orotate + PRPP -> orotidylate.
   - Catalyzed by transferase.
5. Orotidylate -> uridylate + CO_2.
   - Catalyzed by decarboxylase.



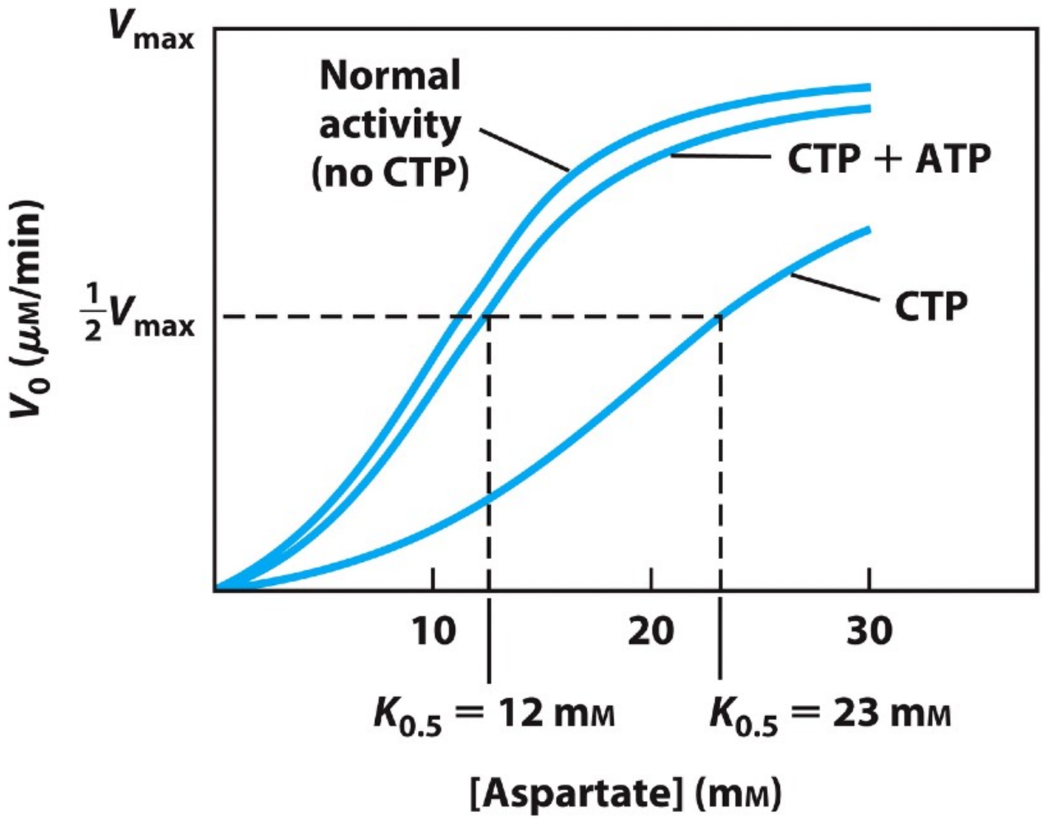
Pyrimidine Biosynthesis Part III

6. Uridylate (UMP) + 2 ATP -> UTP + 2 ADP.
   - Catalyzed by kinase.
7. UTP + glutamine -> CTP + glutamate.
   - Catalyzed by synthetase.

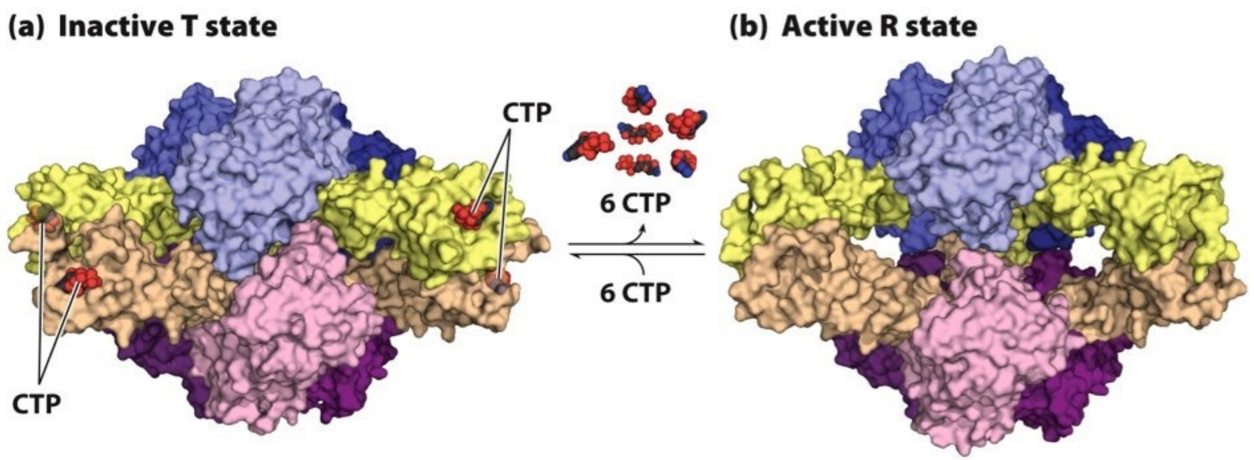


Regulation by Feedback Inhibition

- First reaction of pyrimidine biosynthesis.
  - Aspartate + carbamoyl phosphate -> *N*-carbamoyl-aspartate.
  - Catalyzed by aspartate transcarbamoylase (ATCase).
  - Inhibited by end product CTP.



Allosteric Behavior of ATCase



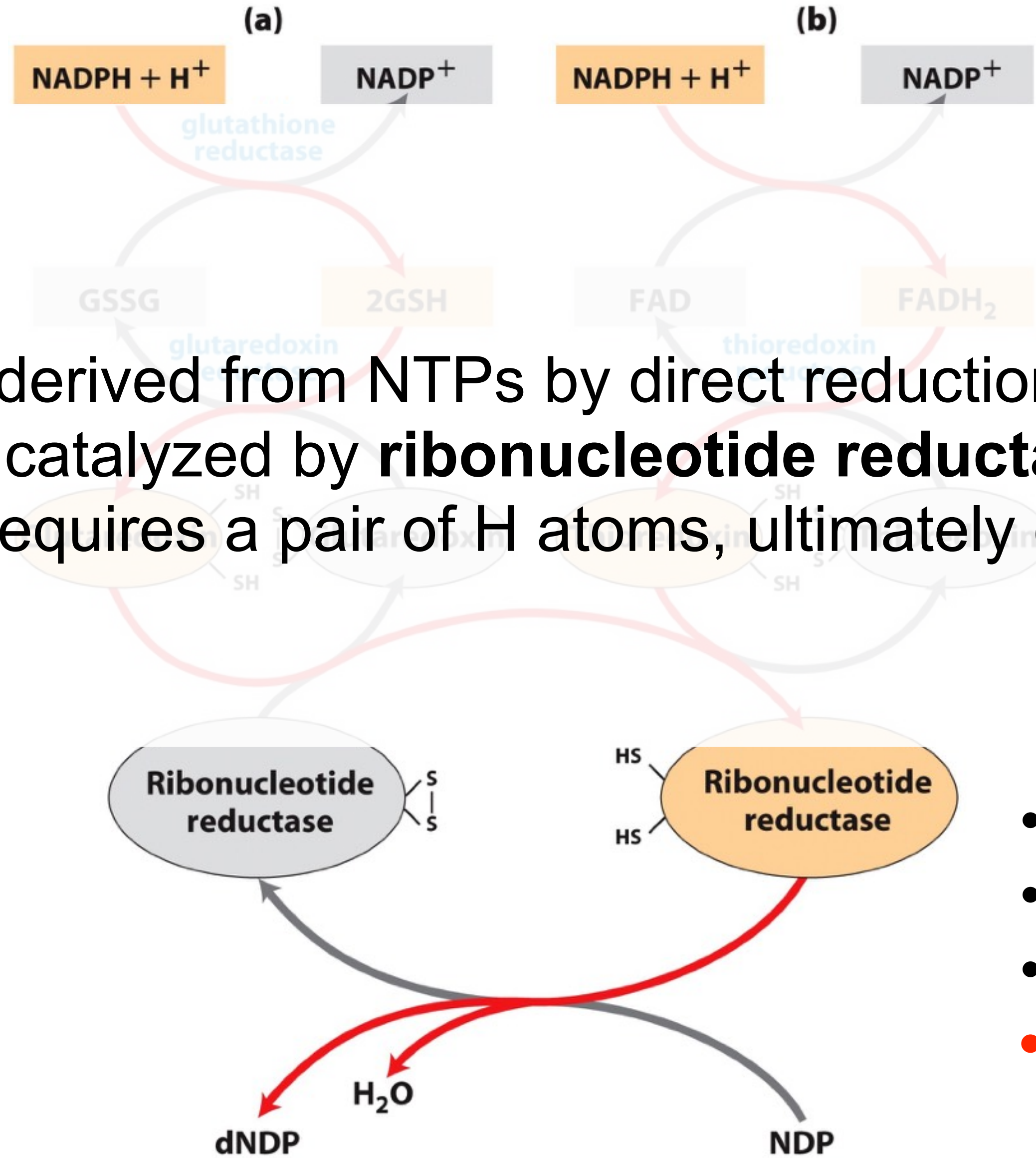
- Regulatory subunits have binding sites for CTP and ATP.
- CTP functions as a negative regulator.
  - CTP is one of end products of biosynthesis pathway.
  - When CTP is abundant, negative regulation limits ATCase activity.
- ATP functions as a positive regulator.
  - High concentrations of ATP indicates robust cellular metabolism.
  - Additional pyrimidine nucleotides needed to support RNA transcription.

NMP -> NDP -> NTP

- AMP is converted to ADP by phosphorylation.
  - Catalyzed by adenylate kinase.
  - ATP + AMP -> 2 ADP (reversible reaction).
- Other nucleoside monophosphates (NMPs) are converted to nucleoside diphosphates (NDPs).
  - Catalyzed by nucleoside monophosphate kinases.
  - ATP + NMP -> ADP + NDP (reversible reaction).
  - Intracellular conditions favor formation of NDP.
- ADP is converted to ATP in glycolysis or oxidative phosphorylation.
- Nucleoside diphosphates are converted to triphosphates.
  - Catalyzed by nucleoside diphosphate kinase.
  - NTP_D + NDP_A -> NDP_D + NTP_A (reversible reaction).
  - Donor (NTP_D) is almost always ATP because of its high intracellular concentration.

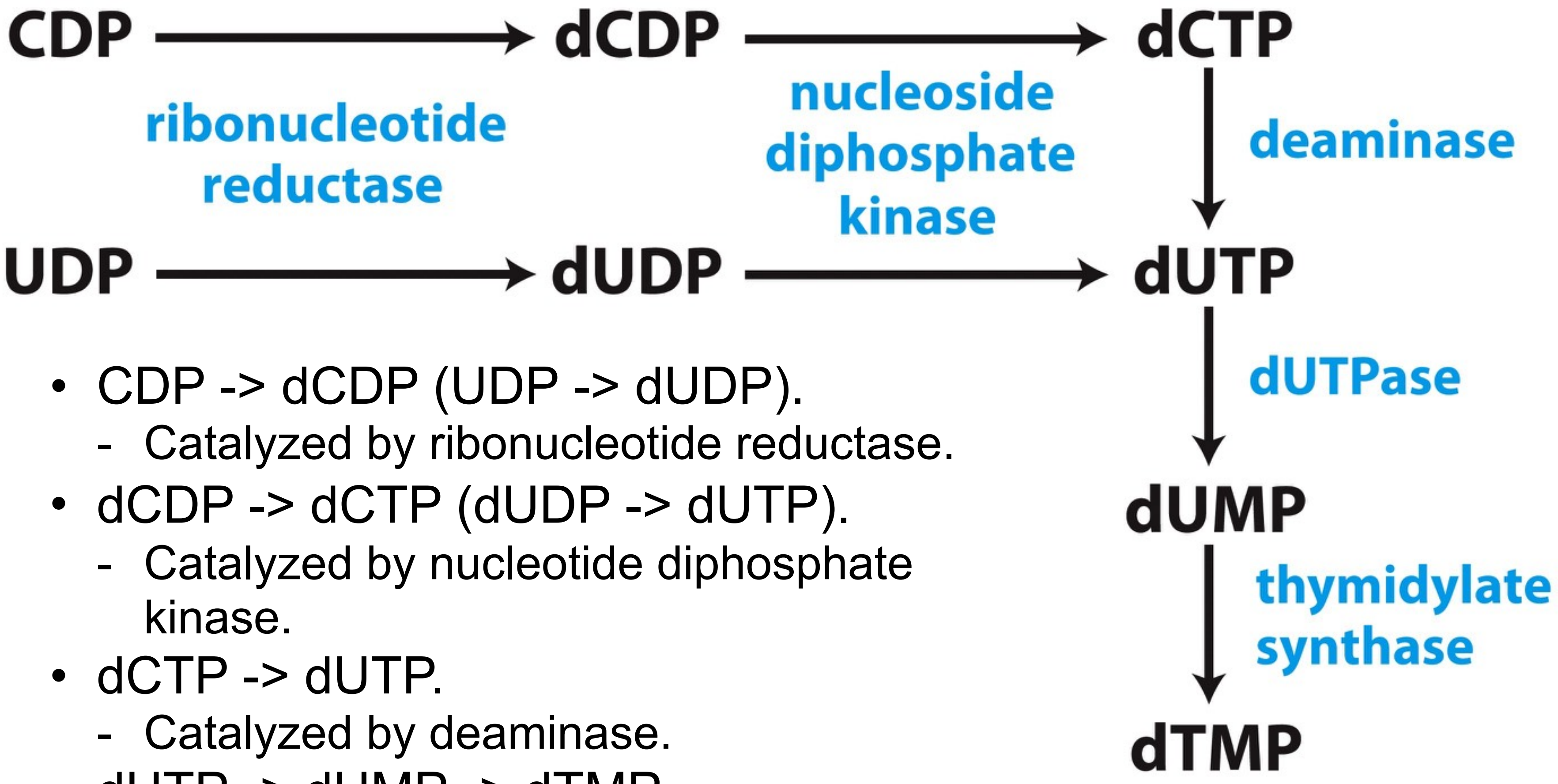
NTPs Are Precursors to dNTPs

- dNTPs are derived from NTPs by direct reduction at 2’-carbon.
- Reaction is catalyzed by **ribonucleotide reductase**.
- Reduction requires a pair of H atoms, ultimately donated by NADPH.



- ADP -> dADP
- GDP -> dGDP
- CDP -> dCDP
- **? -> dTDP**

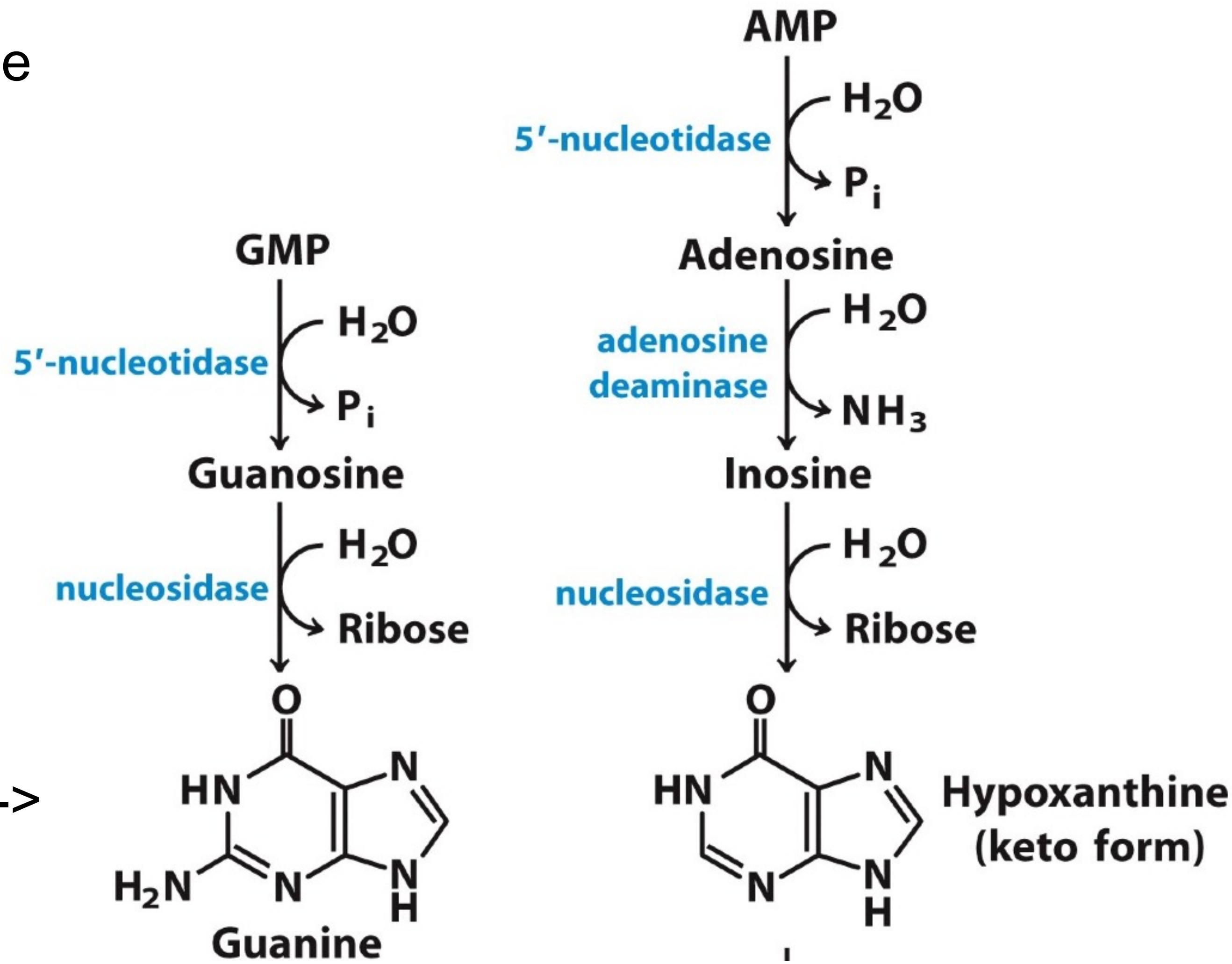
dTMP Derived From dCDP And dUMP



- CDP -> dCDP (UDP -> dUDP).
  - Catalyzed by ribonucleotide reductase.
- dCDP -> dCTP (dUDP -> dUTP).
  - Catalyzed by nucleotide diphosphate kinase.
- dCTP -> dUTP.
  - Catalyzed by deaminase.
- dUTP -> dUMP -> dTMP.
  - Catalyzed by dUTPase and thymidylate synthase.

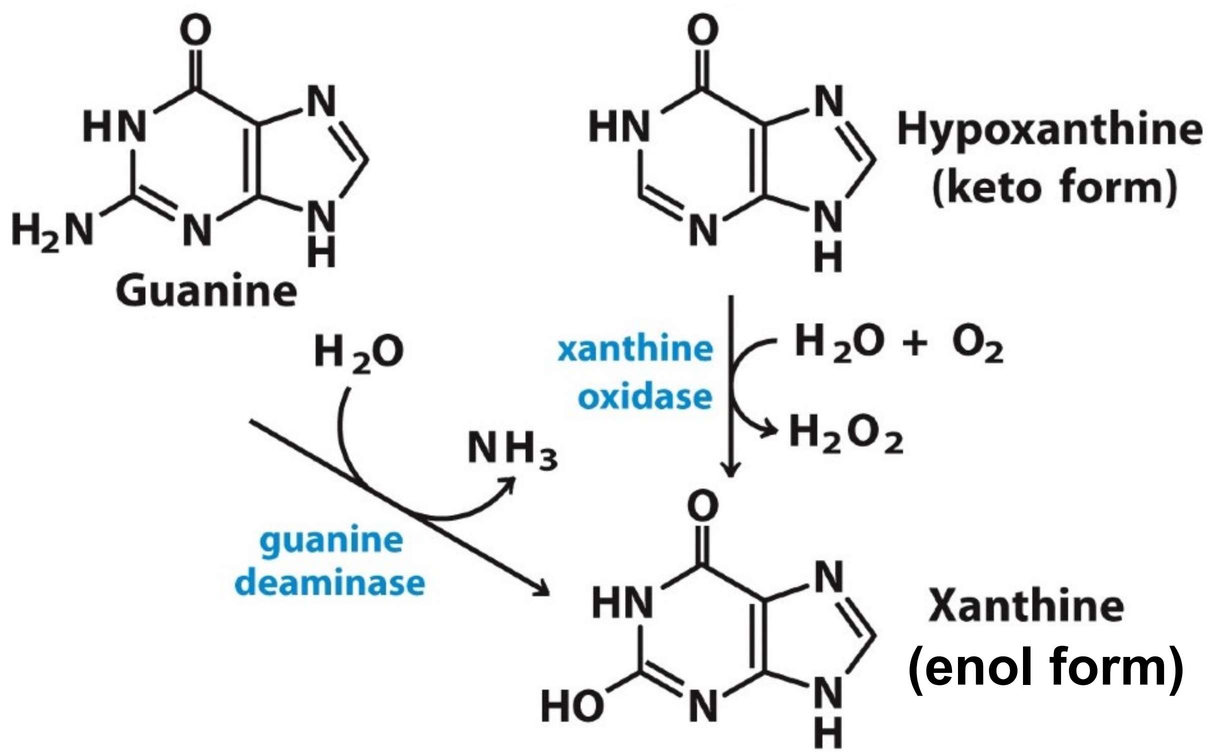
Degradation of Purines Part I

1. GMP -> guanosine (AMP -> adenosine).
   - Catalyzed by 5'-nucleotidase.
2. Adenosine -> inosine.
   - Catalyzed by deaminase.
3. Guanosine -> guanine (inosine -> hypoxanthine).
   - Catalyzed by nucleosidase.



Degradation of Purines Part II

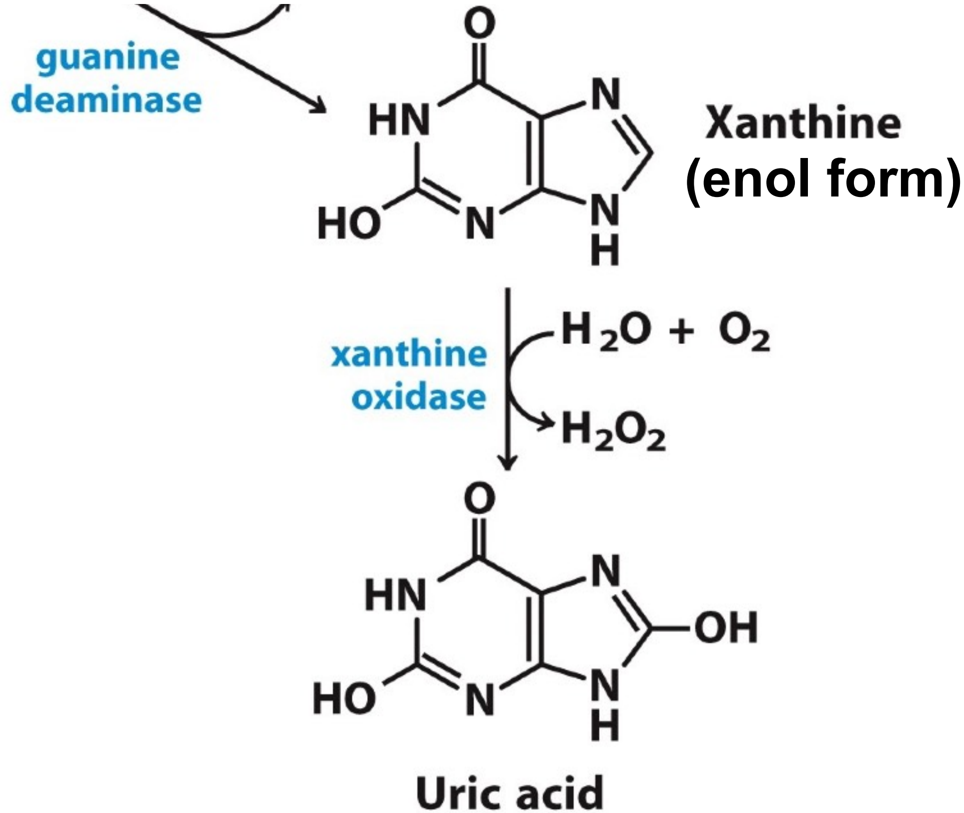
4. Guanine -> xanthine.
   - Catalyzed by deaminase.
5. Hypoxanthine -> xanthine.
   - Catalyzed by oxidase.



Degradation of Purines Part III

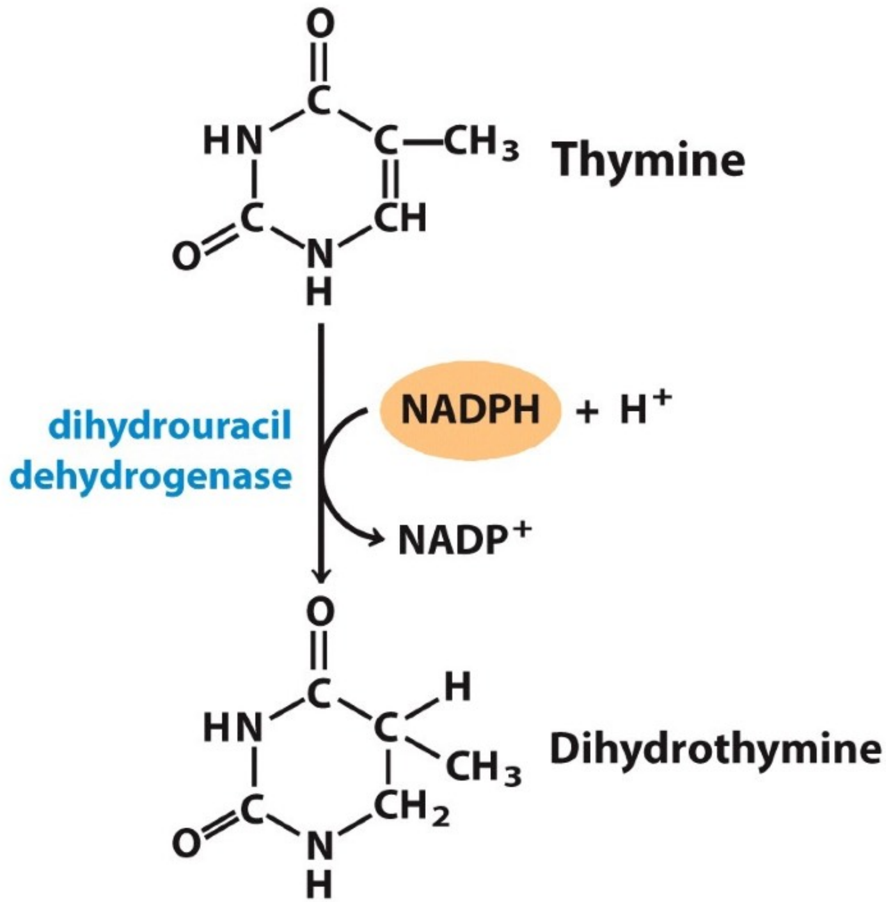
6. Xanthine -> uric acid.
   - Catalyzed by oxidase.

Uric acid is the excreted end product of purine catabolism in human.



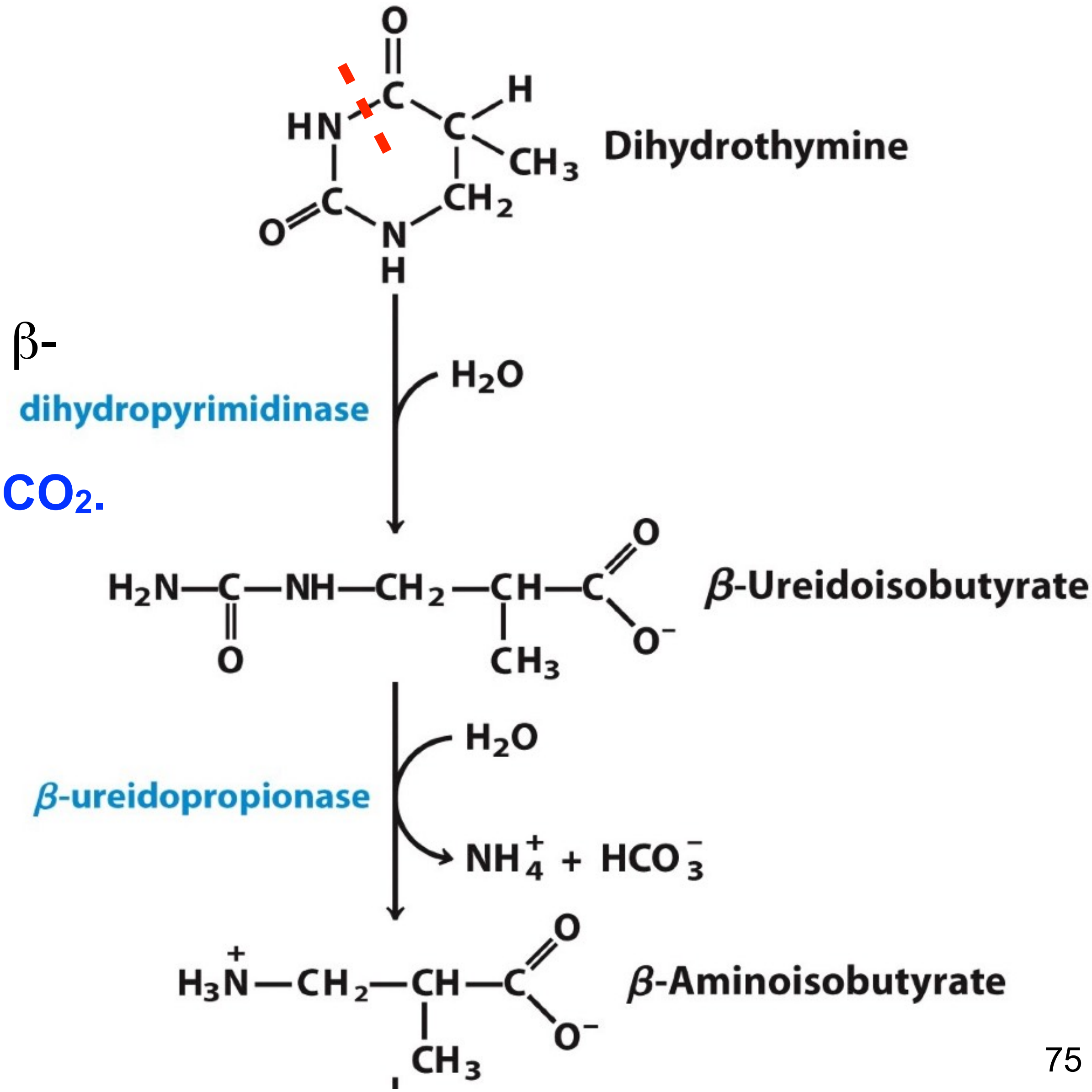
Degradation of Pyrimidines Part I

1. Thymine -> dihydrothymine.
   - Catalyzed by dehydrogenase.
   - Consumes NADPH.



Degradation of Pyrimidines Part II

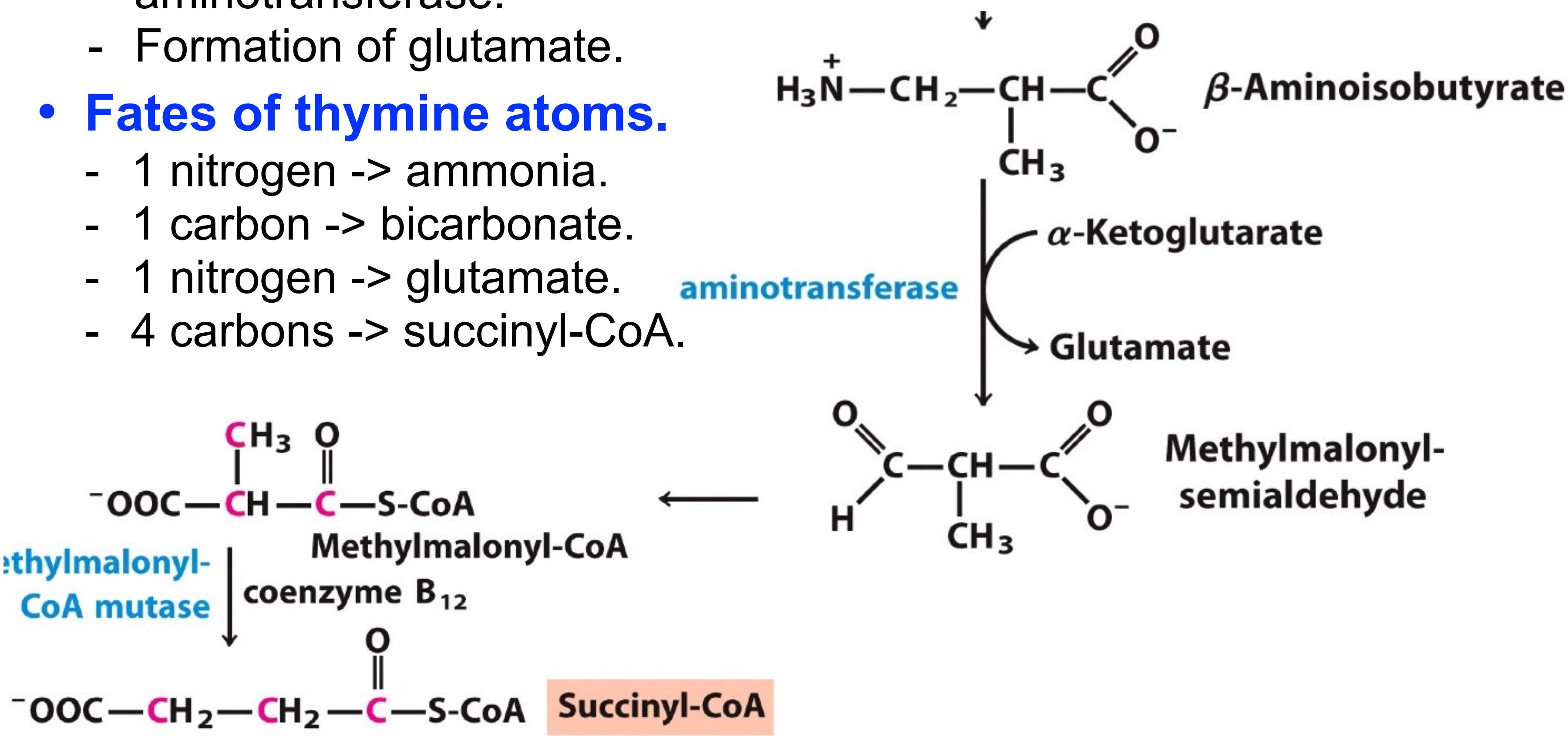
2. Dihydrothymine -> β-ureido-isobutyrate.
   - Catalyzed by dihydropyrimidinase.
3. β-ureido-isobutyrate -> β-amino-isobutyrate.
   - **Removal of NH_4^+ and CO_2.**



Degradation of Pyrimidines Part III

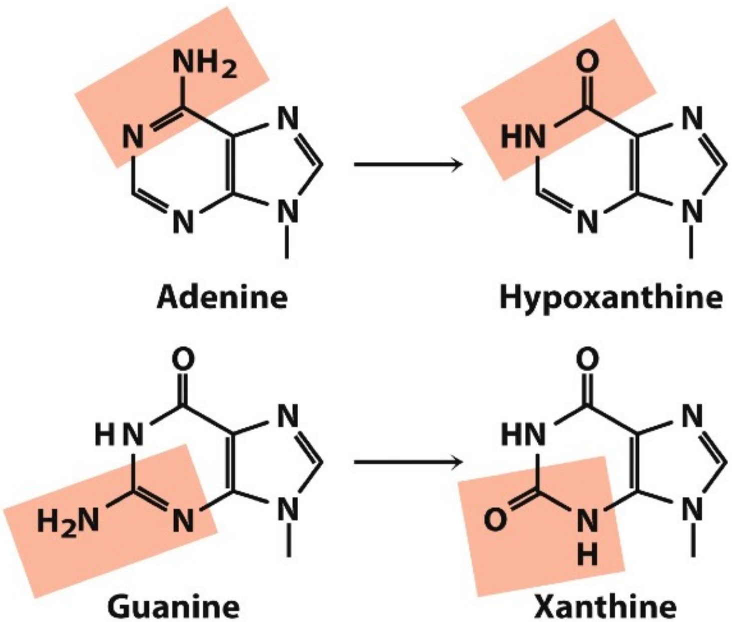
4. β-amino-isobutyrate -> methyl-malonyl-semialdehyde.
   - Catalyzed by aminotransferase.
   - Formation of glutamate.

- **Fates of thymine atoms.**
  - 1 nitrogen -> ammonia.
  - 1 carbon -> bicarbonate.
  - 1 nitrogen -> glutamate.
  - 4 carbons -> succinyl-CoA.



Salvage Pathways

- Free purine and pyrimidine bases are constantly released during metabolic degradation of nucleotides.
- Most purines are salvaged and reused to make nucleotides.
  - Adenine + PRPP -> AMP + PP_i.
  - Catalyzed by adenosine phosphoribosyltransferase.
  - Free guanine and hypoxanthine are salvaged in the same way by hypoxanthine-guanine phosphoribosyltransferase.



Summary 22.4 Purines And Pyrimidines

- Purine biosynthesis starts with PRPP. Amino acids glutamine, aspartate and glycine provide all the nitrogen atoms. Pyrimidines are synthesized from aspartate and carbamoyl phosphate.
- NMPs are converted to NTPs by enzymatic phosphorylation. rNTPs are converted to dNTPs by ribonucleotide reductase.
- Uric acid and urea are end products of purine and pyrimidine degradation. Free purines and pyrimidines can be salvaged and rebuilt into nucleotides.

Example Question

Glutamine, arginine, and proline:

A) do not have a common precursor.
B) may all be derived from a citric acid cycle intermediate.
C) may all be derived from an intermediate in fatty acid oxidation.
D) may all be derived from a glycolytic intermediate.
E) may all be derived from a urea cycle intermediate.

Example Question

An amino acid that is not synthesized from pyruvate is:

A) alanine.
B) leucine.
C) isoleucine.
D) lysine.
E) valine.

Example Question

Amino acid ________ is a precursor to synthesize plant hormone auxin (indole-3-acetate).

A) histidine.
B) tryptophan.
C) tyrosine.
D) phenylalanine.
E) proline.

Example Question

Which of the following molecules does not directly donate atoms in the biosynthesis of purine ring.

A) aspartate.
B) glycine.
C) glutamine.
D) alanine.
E) CO_2.

Example Question

Precursors for the biosynthesis of the pyrimidine ring system include:

A) carbamoyl phosphate and aspartate.
B) glutamate, NH_3, and CO_2.
C) glycine and succinyl-CoA.
D) glycine, glutamine, CO_2, and aspartate.
E) inosine and aspartate.

Example Question

The following reaction (from left to right) in lysine biosynthesis is catalyzed by a(n) __________.

A) carboxylase.
B) dehydrogenase.
C) kinase.
D) aminotransferase.
E) reductase.