Metabolism

فريق طوفان الأقصى

Modified N:

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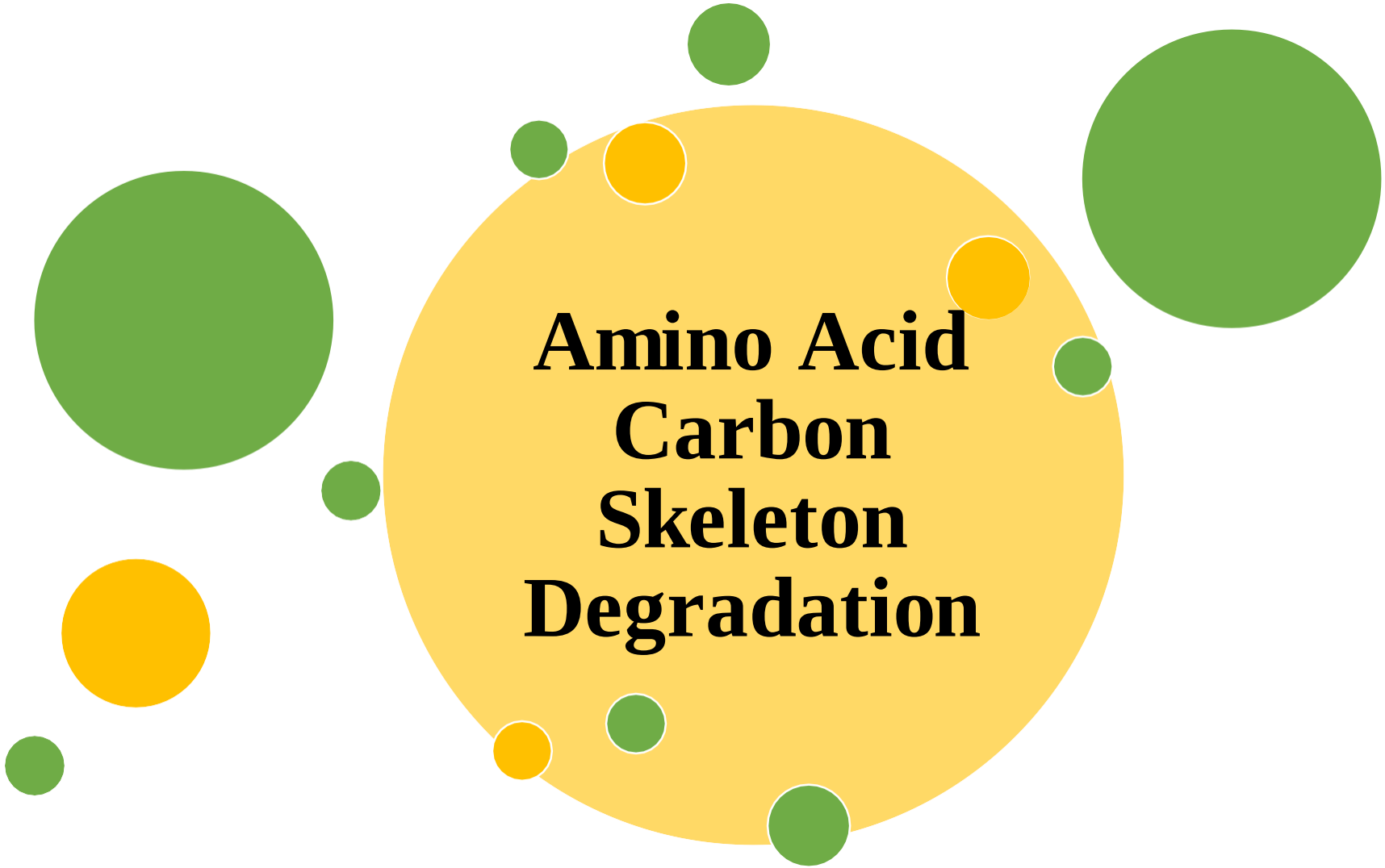

Amino Acid
Carbon
Skeleton
Degradation

- **Briefing:**
- In the last lecture we discussed the fate of the amine group in the amino acid, it was removed from the amino acid through transamination, then metabolized to urea through the urea cycle.
- In this lecture, we will discuss the fate of the remainder of the amino acid.

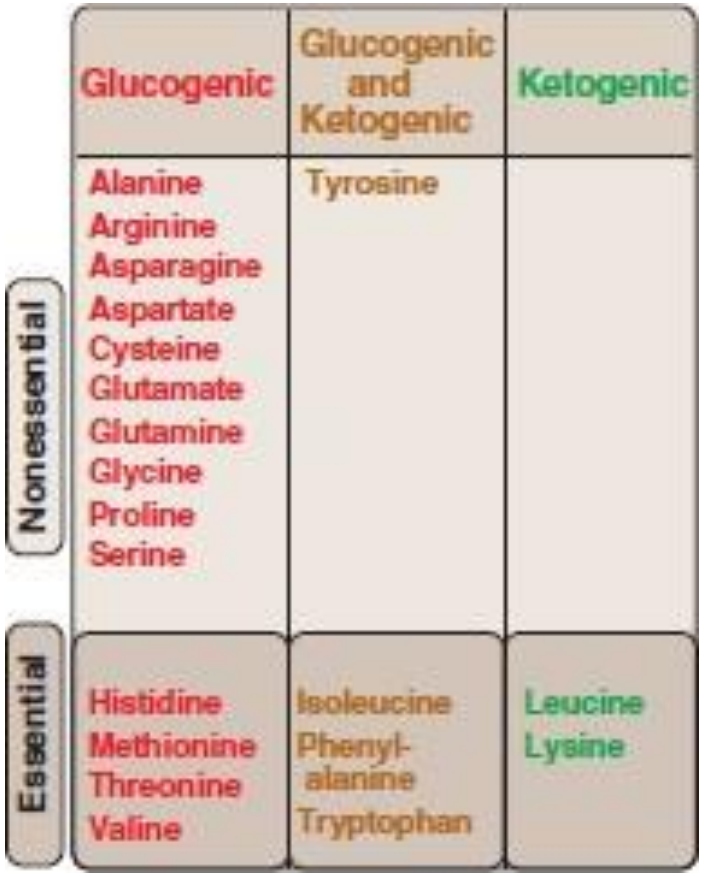
GLUCOGENIC AND KETOGENIC AMINO ACIDS

Seven intermediates are produced during AA catabolism (**oxaloacetate, pyruvate, *α*-ketoglutarate, fumarate, succinyl coenzyme A (CoA), acetyl CoA, and acetoacetate**).

Glucogenic amino acids catabolism yields pyruvate or one of the TCA cycle intermediates that can be used as substrates for gluconeogenesis in the liver and kidney.

Ketogenic amino acids catabolism yields either acetoacetate (a type of ketone bodies) or one of its precursors (acetyl CoA or acetoacetyl CoA). **(used in formation of ketone bodies)**

Other ketone bodies are 3-hydroxybutyrate and acetone



The complement in this slide:

Amino acids are metabolized into one of these 7 metabolites :
The first 5 are **gluconeogenic** (TCA cycle intermediates, or pyruvate) so they will lead to gluconeogenesis, and they are **1- oxaloacetate, 2- pyruvate , 3- α-ketoglutarate , 4- fumarate , 5- succinyl-CoA**.

The other two are **ketogenic** (ketone body producing) which are **6- acetyl-CoA , 7- acetoacetate**.

Amino acids could go through different pathways, but they might end up exclusively in one category.

For example, Leucine and lysine are exclusively metabolized to ketogenic metabolites.

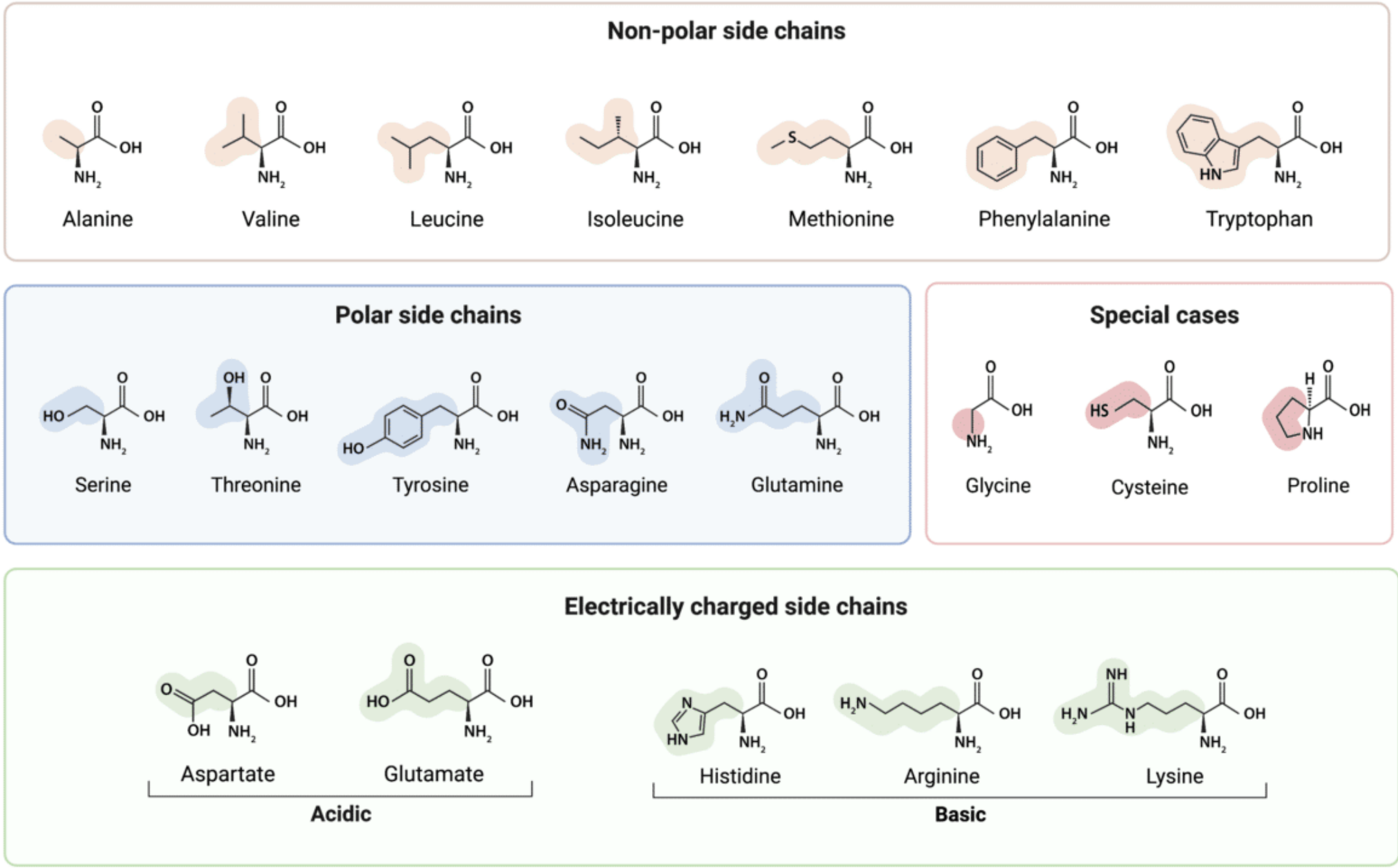
Aromatic AAs in addition to isoleucine might be metabolized to either ketogenic or gluconeogenic metabolites.

The rest of the AAs are exclusively gluconeogenic.

This table will sum it up

	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

You don't have to memorize them but while you are reading the next slides you can have a look at them to have better understanding

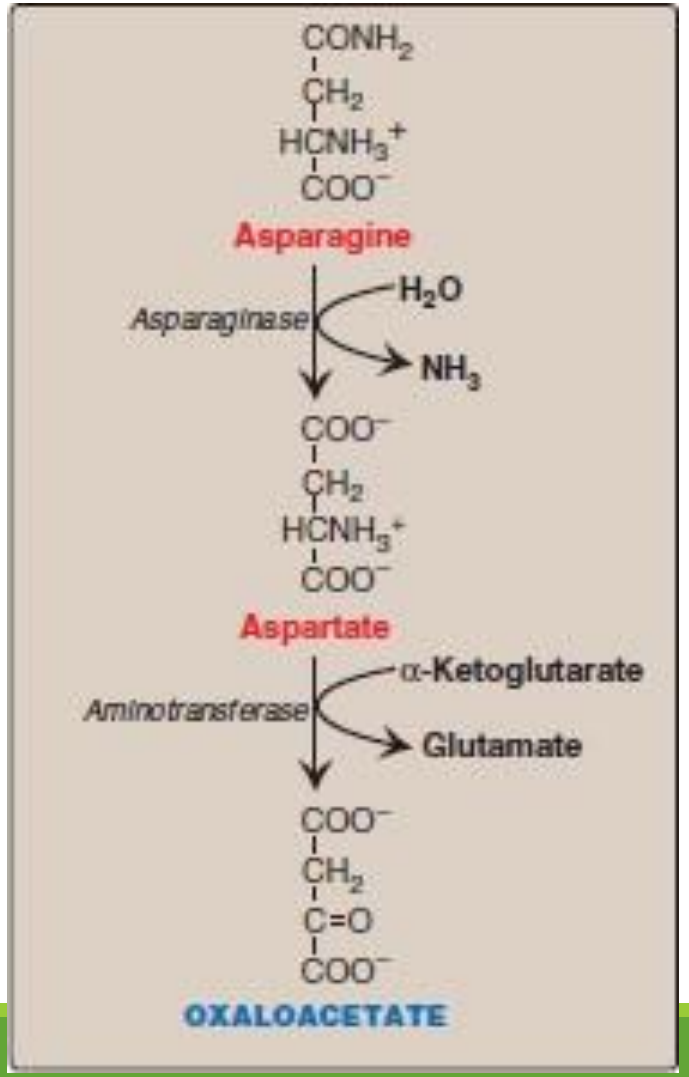


1. Amino acids that form oxaloacetate

- **NOTE:**
- Asparagine could be hydrolysed (remove the amine group) to Aspartate using ***Asparaginase*** enzyme.
- Like we said in the last lecture, Aspartate goes through transamination using AST, making oxaloacetate.
- Oxaloacetate is a gluconeogenic metabolite.

Hydrolysis

Transamination



2. Amino acids that form α-ketoglutarate via glutamate

NOTE: We will not go through details.

Glutamine **Proline** **Arginine** **Histidine**

3. Amino acids that form fumarate

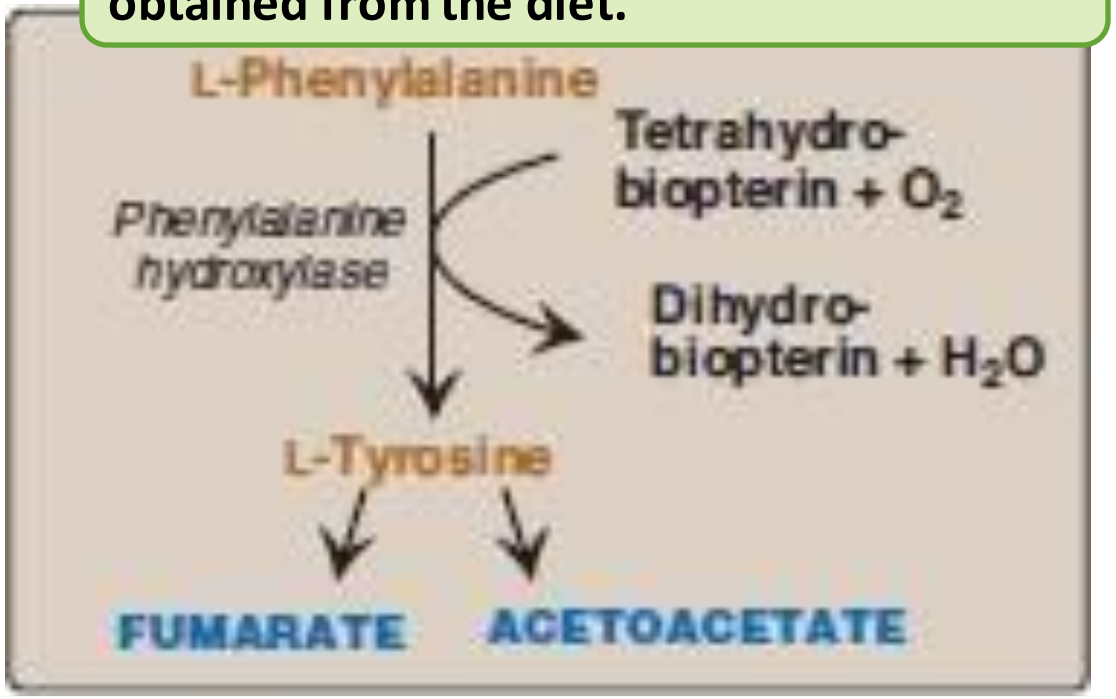
Phenylalanine and tyrosine(aromatic AAs):

Hydroxylation of phenylalanine produces tyrosine

Phenylalanine and tyrosine are both glucogenic and ketogenic.

Inherited deficiencies in the enzymes that metabolize Phe and Tyr lead to **phenylketonuria, alkaptonuria and albinism**

essential amino acid that has to be obtained from the diet.



The complement in this slide:

Amino acids that form α-ketoglutarate via glutamate

These amino acids are converted first to glutamate then deaminated to α-ketoglutarate (gluconeogenic).

1. Glutamine is transaminated using ***glutaminase*** like we said in the last lecture.
2. Proline and histidine have rings in their structure so their pathway includes opening their rings.
3. Arginine has nitrogen in its side chain so they have to be removed first.

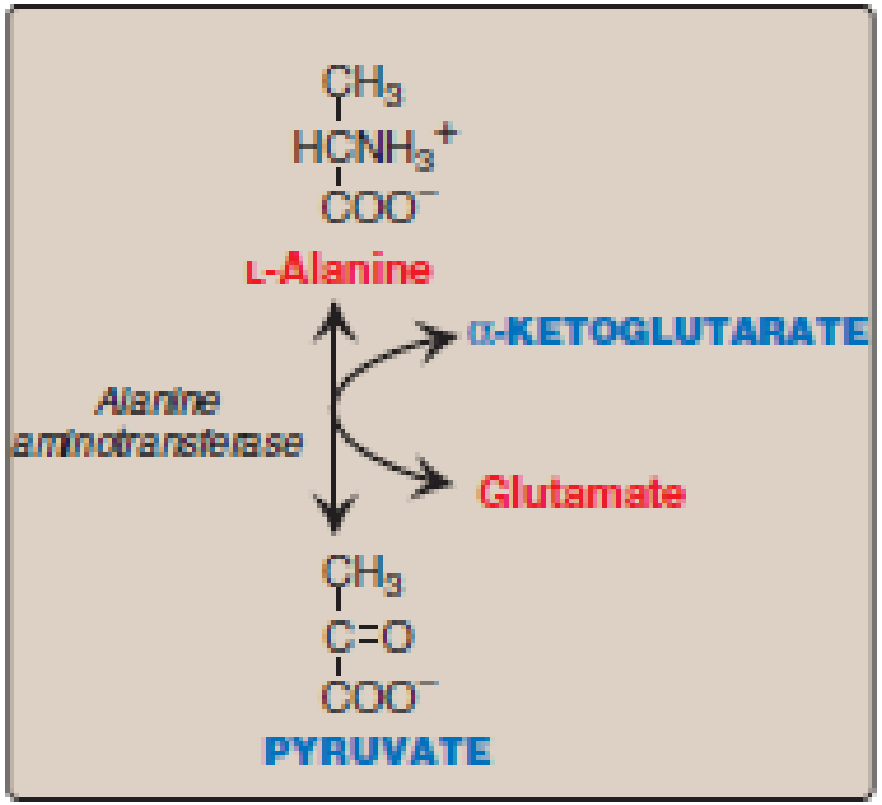
Amino acids that form <u>fumarate</u>

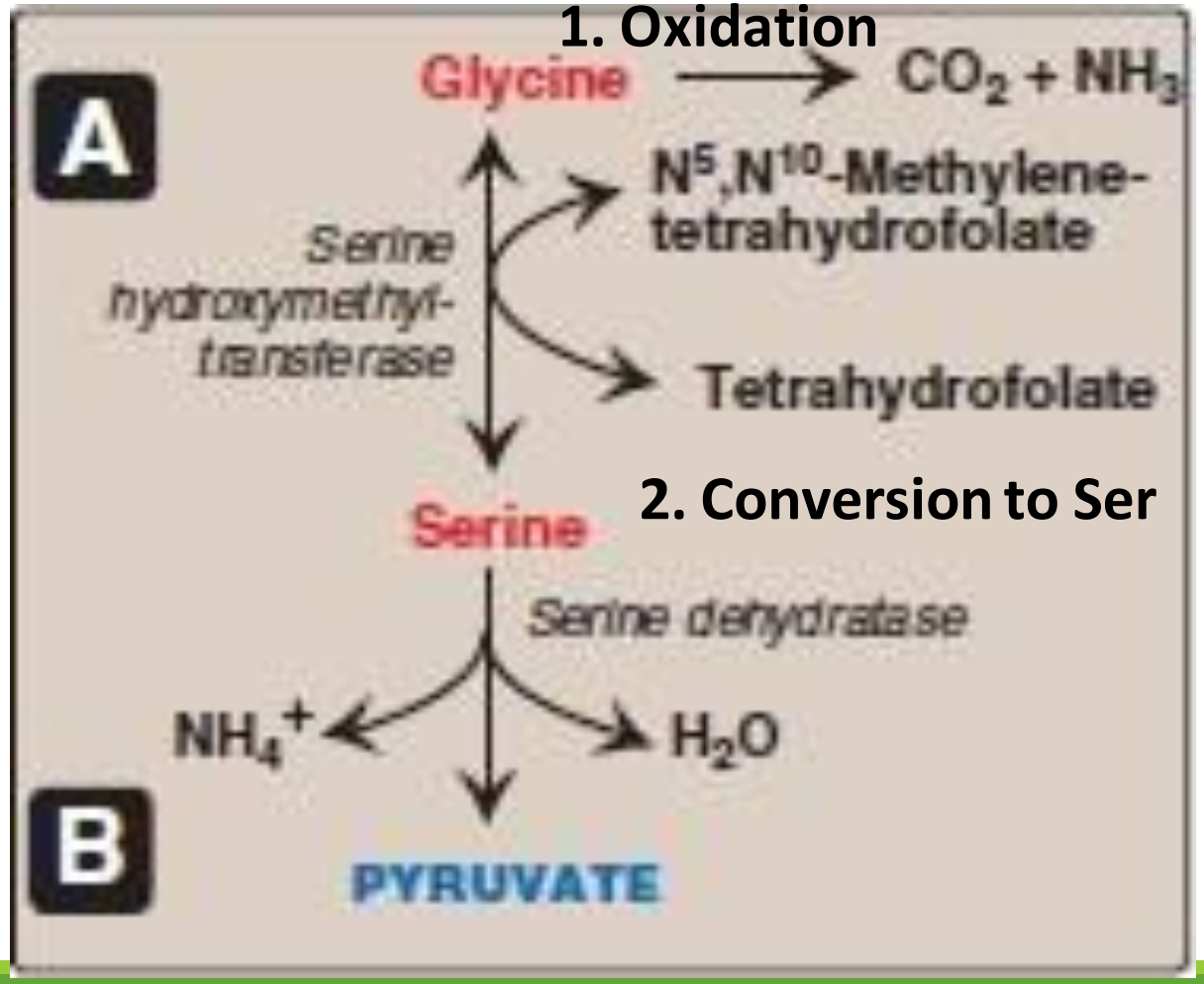
There are two AAs that can form fumarate and they are **Tyrosine and Phenylalanine**, and remember that tyrosine and phenylalanine are similar in structure except there are an extra hydroxyl group on tyrosine. So we can convert phenylalanine to tyrosine by hydroxyl action using ***phenylalanine hydroxylase***, this reaction needs a coenzyme called **Tetrahydrobiopterin** or **BH4**, that is oxidated to **dihydrobiopterin (BH2)** ,this coenzyme is recycled back to BH4 using an enzyme called ***dihydrobiopterin reductase***.
There are some diseases associated with this process: 1. A mutation causing ***phenylalanine hydroxylase*** deficiency causes phenylketonuria (PKU), 2.other problem in this metabolic pathway could cause different diseases like alkaptonuria(البول الاسود) or <u>albinism</u>.

Eventually, ,all the produced tyrosine is metabolized in two different pathways to make either **fumarate (gluconeogenic)**, or **acetoacetate (ketogenic)**.

4. Amino acids that form pyruvate

Alanine





The complement in this slide:

- Alanine is converted to **pyruvate** (gluconeogenic) through transamination using ***ALT*** mentioned in the last lecture.
- Glycine has a simple side chain (H) so it could be oxidized and directly degraded to CO2 and free NH3.
- Another pathway for Glycine is the formation of serine then pyruvate (by releasing an amine group and water using ***serine dehydrates*** enzyme).
- The conversion to serine is by **hydroxymethylation** (hydroxylation and methylation) using ***serine hydroxymethyl-transferase*** enzyme, this reaction is reversible, so we can go back to glycine.
- The methyl group given to the glycine was carried by compounds called **Single carbon unit carriers**, in this reaction we have tetrahydrofolate (active form of folic acid or vitamin B9) as the single carbon unit carrier in the form of mthylene-tetrahydrofolate, carried on N5 and N10.
- **Tetrahydrofolate as a single carbon unit carrier:** Tetrahydrofolate can carry single carbon units in different formats like **1. Formyl (C=O), 2. Formimino (C=N), 3. Methylene (C=), 4. Methyl(C—), 5. Methenyl,** unlike S-adenosyl methionine (also known as SAM, a metabolite of methionine which we will discuss later)that can only carry them as methyl groups only.

These formats are synthesized in an order ending with methyl-tetrahydrofolate.

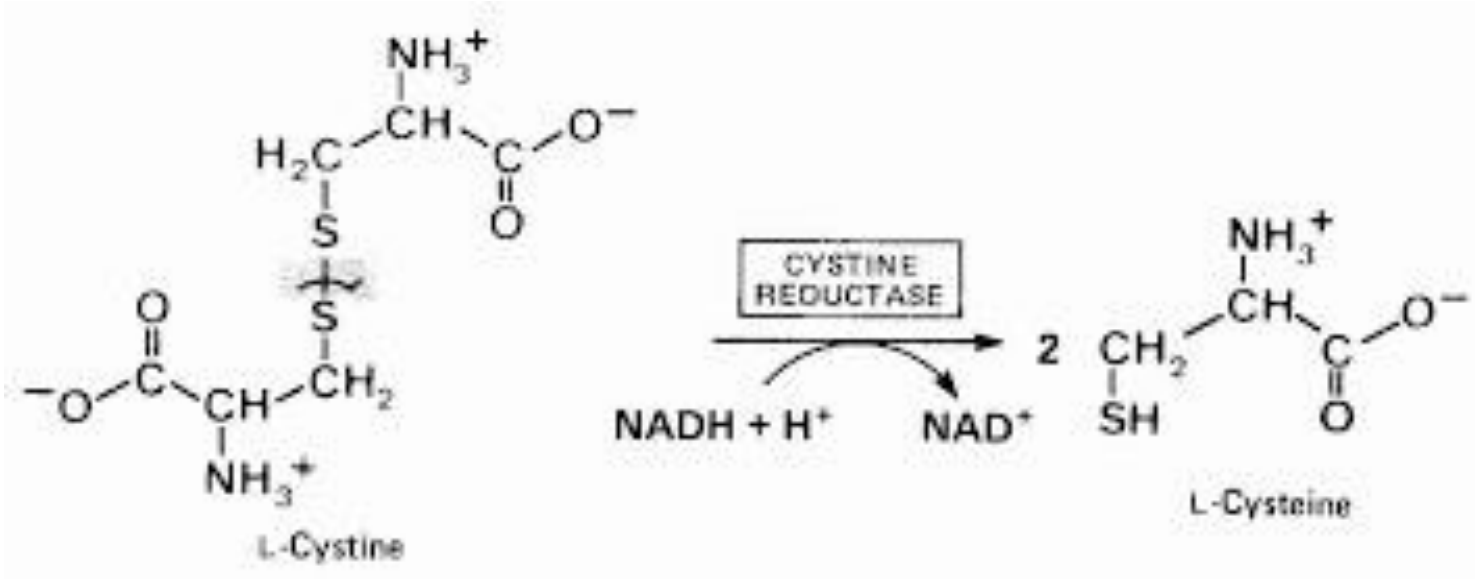
Single carbon units in the form of methylene and methenyl could be carried on both nitrogens (of the tetrahydrofolate) number N5 and N10 at the same, while the rest forms could only be carried on one of them.

4. Amino acids that form pyruvate

Cystine is reduced to cysteine

NADH + H+ act as a reductant.

Cysteine desulfuration yields pyruvate.



Threonine is converted to pyruvate or to α-ketobutyrate, which forms succinyl CoA.

The complement in this slide:

- Cysteine has a very similar structure to serine, it has a (SH) instead of (OH).
- Cysteine goes through desulfaration then deamination to make pyruvate (gluconeogenic), unless it's in the form of **Cystine** (sulfur bridge), it needs to be reduced using ***Cystine reductase***.
- Another AA that makes pyruvate is Threonine, it has a very similar structure to serine but with an extra carbon, so it can be degraded into pyruvate.

And because of its big structure, it can also go through another pathway, so it's converted to α-keto**butyrate**, then propyonyl-CoA then succinyl CoA (gluconeogenic).

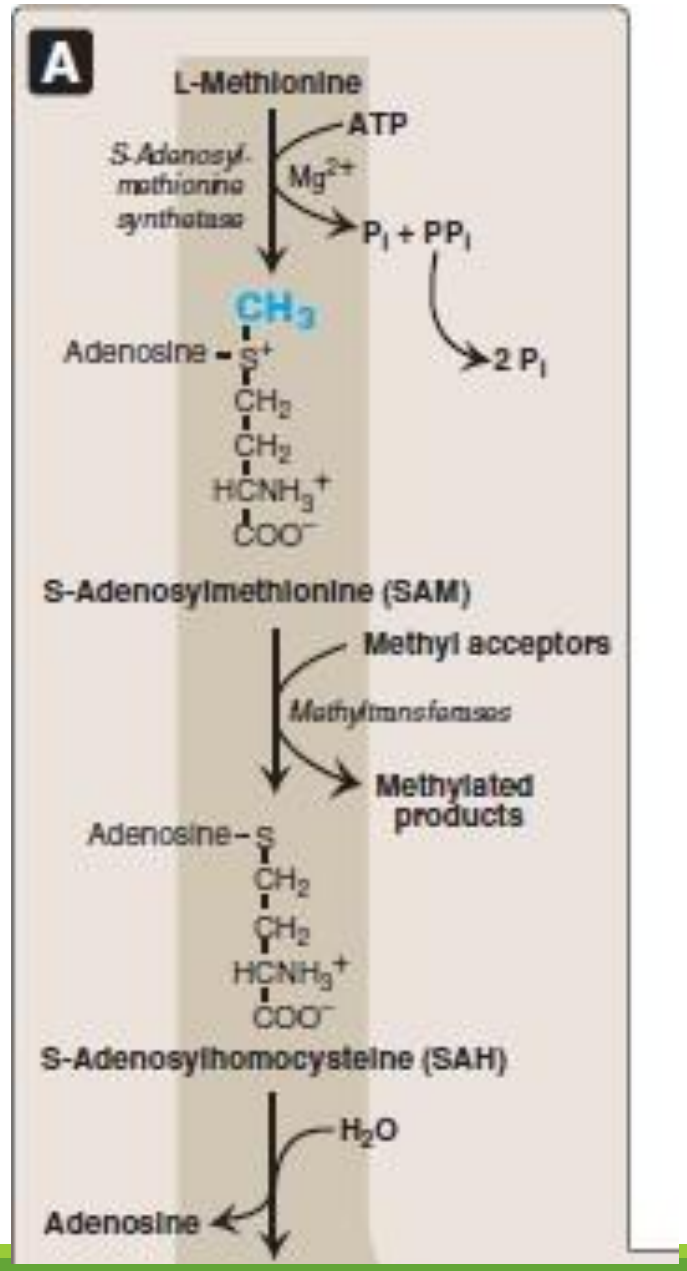
- There are a few amino acids that can produce multiple products falling into the same category, such as generating both pyruvate and intermediates in the (TCA) cycle. **Threonine is one of the examples.**

5. Amino acids that form succinyl CoA (a TCA cycle intermediate and glucogenic compound)

Valine and isoleucine are branched-chain amino acids **(they have branches in their hydrocarbon chains of the R group)**
They generate propionyl CoA that is converted to succinyl CoA by biotin- and vitamin B12–requiring reactions

Threonine is dehydrated to α-ketobutyrate, which is converted to propionyl CoA and then to succinyl CoA.
Thr can also be converted to pyruvate.

Methionine is converted to S-adenosyl methionine (SAM), the major methyl-group donor in one-carbon metabolism.



Methionine Metabolism

1.Synthesis of SAM (a high-energy compound that has no phosphate) requires energy (ATP)

2.Methyl group activation to be ready for transfer to acceptor molecules, such as norepinephrine in the synthesis of epinephrine.
Methyl group is transferred to O, N, or C atoms.
Methyl transfer is irreversible because of free energy loss.

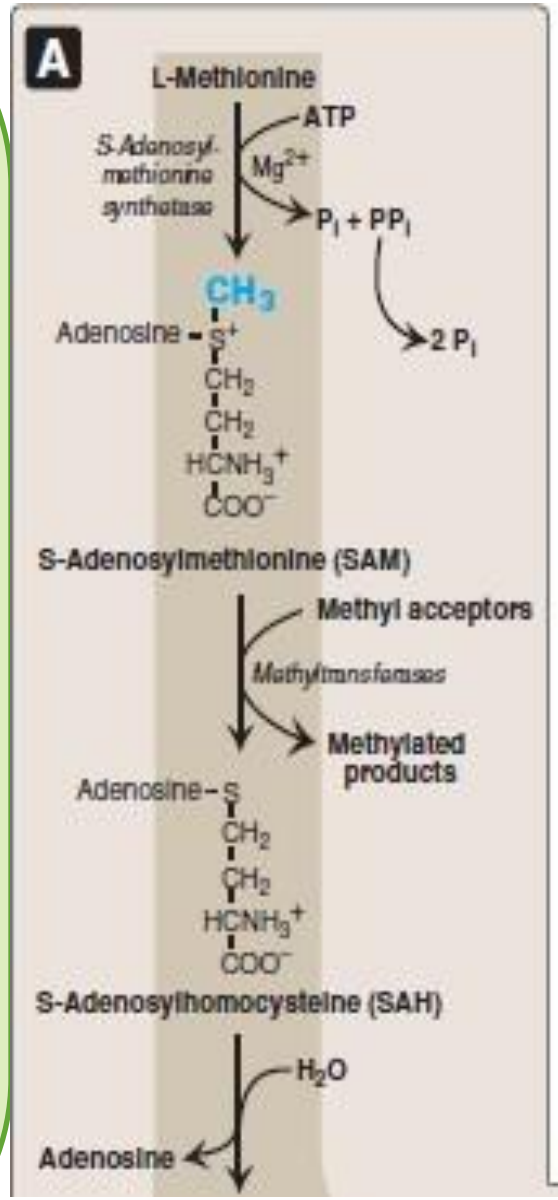
3. Hydrolysis of SAH to homocysteine and adenosine.

Homocysteine fates:

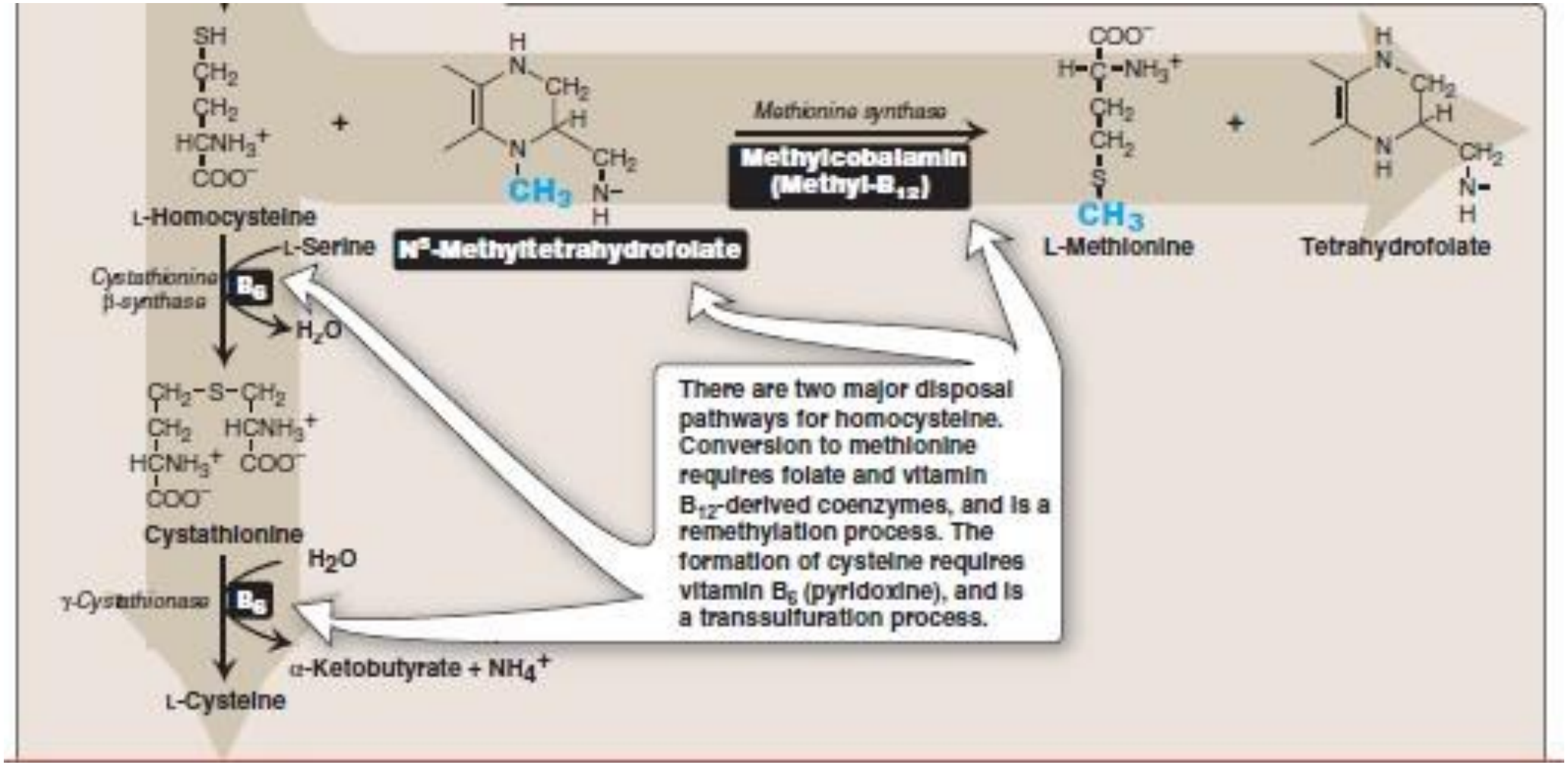
A. Remethylation if Met is deficient
B. Transulfuration pathway if Met is available to be converted to Cys

The complement in this slide:

- 1-Methionine has a sulfur between 2 carbons, so the metabolism starts by attaching adenosine (which is a nucleoside, nucleotide without phosphate) to the sulfur of the methionine to make S-adenosylmethionine (SAM)
- The enzyme in the first step is called S-adenosylmethionine synthetase so it need energy in the form of ATP.
- SAM: methyl doner in reactions as we said in "the 3-AAs that form fumarate" it is an intermediate in the metabolism and degradation of methionine
- Now the sulfur has 3 bonds so it has a positive charge (unstable for it) it gets rid of the methyl bound (the blue one)
- 2- SAM donates its methyl to a methyl acceptor forming methylated products by an enzyme called methyltransferase.
- 3-now notice that the rest of this AA (without the adenosine) has 2 carbons and S (very similar to the structure of cysteine except that cysteine has 1 Carbon) so we call it Homocysteine. With the adenosine we call it S-adenosylhomocysteine(SAH).
- 4- now we have to get rid of the adenosine and replace it with hydrogen making Homocysteine .



Synthesis of cysteine and methionine



The resulting α-ketobutyrate is oxidatively decarboxylated to form propionyl CoA that is then converted to succinyl CoA.

The complement in this slide:

- Homocysteine is an important molecule because it is a branching point in the pathway, it can either proceed into reproduction of Methionine or production of cysteine.

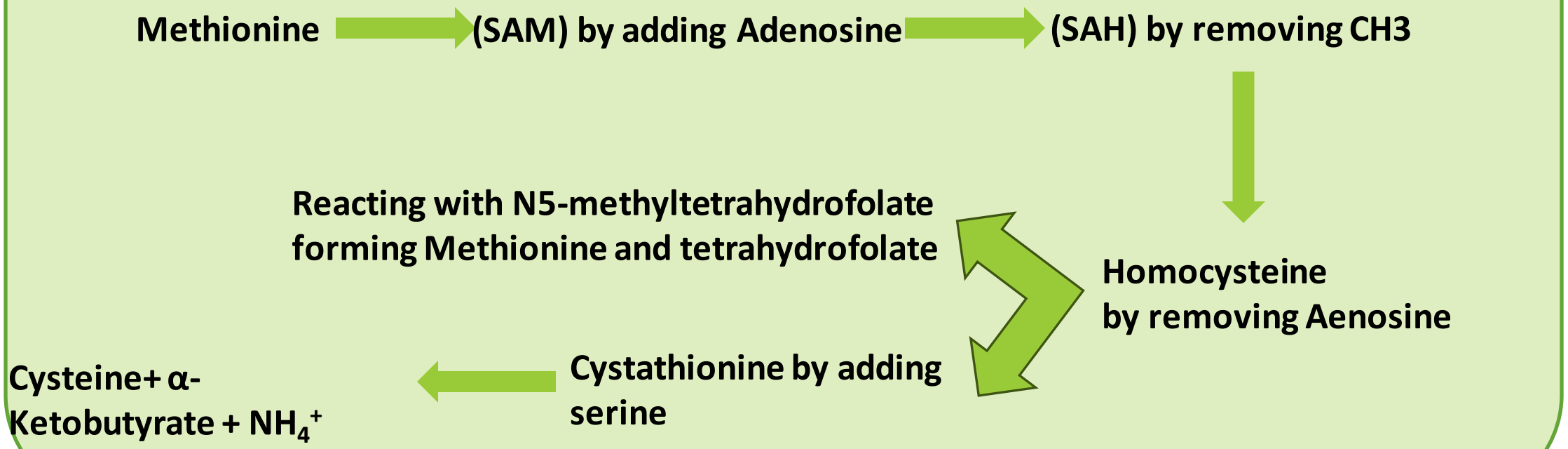
- In the first pathway(Homocysteine to methionine) I have to add a methyl group back, from where? N5-methyltetrahydrofolate (another form of folic acid), methionine synthase transfers the methyl group in the presence of B12.

- Good question now: Do I consider methionine as essential or non essential AA? essential 😊 think about it and you will know. The answer in the next slide

- In the second pathway (Homocysteine to cysteine) it is hard to remove one of the carbons so we attach serine (very similar to cysteine but it has OH group instead of SH) to Homocysteine by Cystathionine-β-synthase, this will lead to the releasing of OH in the form of H_2O, forming cystathionine, now I have cysteine in the left side(look at the picture) and it will be released by gamma cyatathionase as cysteine AA and the rest of the molecule can be converted to alpha-ketobutyrate-->propyonyl-CoA --> succinyl CoA.
- Amino group was released as NH_4^+ or ammonia(it can become NH_3)
- Note that first pathway needs vitamin B12,9 while the second pathway needs vitamin B6.

- Answer : it is essential because there is no pathway that has methionine as a product, and non of the reactions metabolizing methionine are reversible.

To sum up:



Clinical hint: Homocysteine and vascular disease

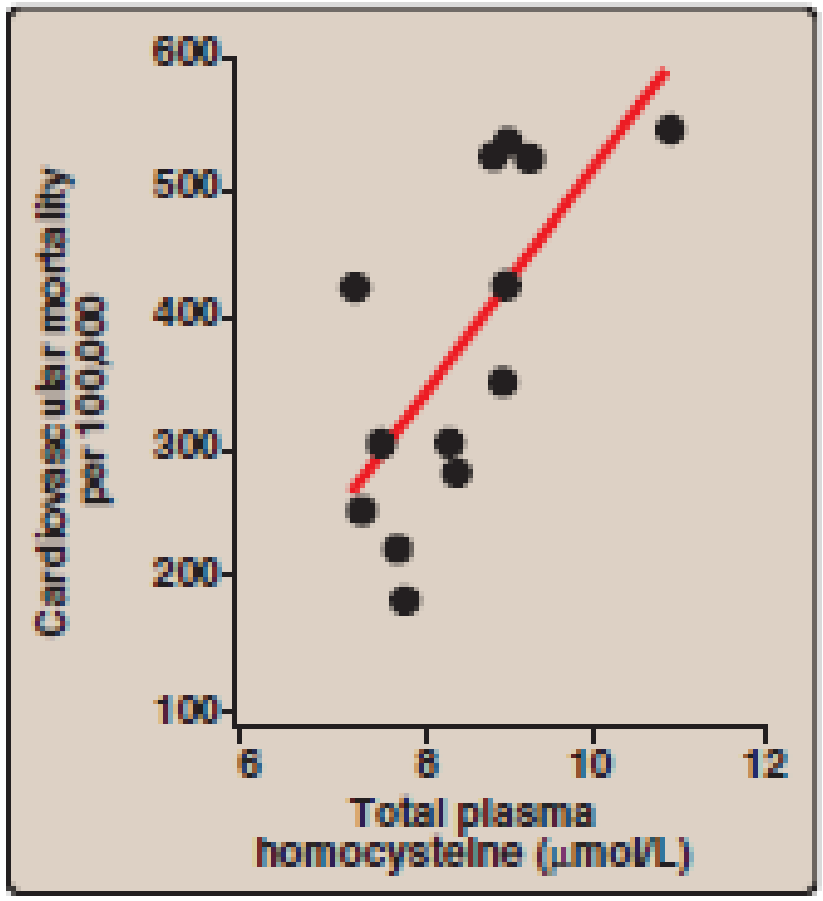
NOTE: **To treat the increasing levels of Homocysteine we can give patients vitamin B6B,12, B9, to enhance the pathways that metabolize homocysteine.**

High homocysteine promote oxidative damage, inflammation, and endothelial dysfunction, and increases risk for occlusive vascular disease

Homocysteine levels are inversely related to levels of folate, B12, and B6.

Elevated homocysteine or decreased folic acid levels during pregnancy increases the incidence of neural tube defects (improper closure, as in spina bifida) in the fetus.

For that, women planning to get pregnant, or in the first trimester of pregnancy are given vitamin B9, B12, B6 supplements.



6+7. Amino acids that form acetyl CoA or acetoacetyl CoA

Phe and Tyr produce acetoacetate(ketogenic) and fumarate (glucogenic) during their catabolism

Leucine is exclusively ketogenic (acetoacetate and acetyl CoA)

Isoleucine is both ketogenic and glucogenic (acetyl CoA, acetoacetyl CoA and succinyl CoA)

Lysine is an exclusively ketogenic (acetyl CoA and acetoacetyl CoA).

Tryptophan is both glucogenic and ketogenic (acetyl CoA and acetoacetyl CoA)

NOTE: Supplement of these AA to support 💪 , 🧠 ....

Branched chain amino-acids (Leu, Val, Ile)

- Essential amino acids
- Important for the synthesis of excitatory glutamate and inhibitory gamma-aminobutyric acid (GABA)
- In contrast to other amino acids, they are metabolized primarily by the peripheral tissues (particularly muscle), rather than by the liver. So, they have a role in the function of the muscle
- Are metabolized by a similar route of metabolism
- Transamination, oxidative decarboxylation, dehydrogenation and then end product formation

NOTE: Glutamate AA can also work as excitatory neurotransmitter, and we can synthesise inhibitory molecules from it like (GABA)

NOTE: Thier degradation start with transamination(from these AA to Alpha-Ketoglutarate), then the glutamate that is formed is going to be used for the synthesis of neurotransmitters, so not much oxidative deamination occurs but rather oxidative decarboxylation occurs(metabolism of the carboxyl group), then they are hydrogenated, and the products are used to synthesize different organic compounds in the human body.

The End

لا تنسوا الدعاء لأهلنا في غزة SP

V2: Slide 9

phenylalanine hydroxylase instead of phenylalanine hydrolase