PROTEIN METABOLISM: SPECIFIC WAYS OF AMINO ACIDS
CATABOLISM AND SYNTHESIS

- Alanine (A)
- Valine (V)
- Leucine (L)
- Isoleucine (I)
- Proline (P)
- Methionine (M)
- Phenylalanine (F)
- Tryptophan (W)
- Threonine (T)
- Cysteine (C)
- Asparagine (N)
- Glutamine (Q)
- Tyrosine (Y)

- Aspartic Acid (D)
- Glutamic Acid (E)
- Lysine (K)
- Arginine (R)
- Histidine (H)

Glycine (G)
Serine (S)
After removing of amino group the carbon skeletons of amino acids are transformed into metabolic intermediates that can be converted into glucose, fatty acids, ketone bodies or oxidized by the citric acid cycle.

The carbon skeletons of 20 fundamental amino acids are funneled into seven molecules:

- pyruvate,
- acetyl CoA,
- acetoacetyl CoA,
- α-ketoglutarate,
- succinyl CoA,
- fumarate,
- oxaloacetate.
Fates of carbon skeleton of amino acids

Glucose

- Asparagine
- Aspartate
- Pheny1alanine
- Tyrosine
- Isoleucine
- Methionine
- Threonine
- Valine

Pyruvate

- Alanine
- Cysteine
- Glycine
- Serine
- Threonine
- Tryptophan

- Isoleucine
- Leucine
- Tryptophan

Acetyl CoA

- Acetoacetyl CoA

Oxaloacetate

Fumarate

Succinyl CoA

α-Ketoglutarate

- Arginine
- Glutamate
- Glutamine
- Histidine
- Proline

Leucine
- Lysine
- Phenylalanine
- Tryptophan
- Tyrosine
Glucogenic vs ketogenic amino acids

- **Glucogenic** amino acids (are degraded to pyruvate or citric acid cycle intermediates) - can supply gluconeogenesis pathway

- **Ketogenic** amino acids (are degraded to acetyl CoA or acetoacetyl CoA) - can contribute to synthesis of fatty acids or ketone bodies

- Some amino acids are both glucogenic and ketogenic
Pyruvate as an Entry Point into Metabolism

Tryptophan → Alanine → Pyruvate

Glycine → Serine → Pyruvate

Cysteine → Pyruvate

Threonine → 2-amino-3-ketobutyrate

Pyruvate
Oxaloacetate as an Entry Point into Metabolism

Aspartate and asparagine are converted into oxaloacetate

\[
\text{aspartate} + \alpha\text{-ketoglutarate} \iff \text{oxaloacetate} + \text{glutamate}
\]

Asparagine is hydrolyzed to NH$_4^+$ and aspartate, which is then transaminated.
α-Ketoglutarate as an Entry Point into Metabolism

Proline  Arginine

Glutamine  Histidin

Glutamate  α-Ketoglutarate
Succinyl Coenzyme A is a point of entry for several nonpolar amino acids.
Methionine Degradation

*S-adenosylmethionine (SAM)* - a common methyl donor in the cell

*Homocysteine* promotes the development of vascular diseases and atherosclerosis
The Conversion of Branched-Chain Amino Acids

The degradative pathways of valine and isoleucine resemble that of leucine.

Isoleucine yields acetyl CoA and propionyl CoA.

Valine yields $CO_2$ and propionyl CoA.
Degradation of Aromatic Amino Acids

Acetoacetate, fumarate, and pyruvate — are common intermediates. Molecular oxygen is used to break an aromatic ring.

\[ \text{Phenylalanine} \xrightarrow{+\text{O}_2} \text{Homogentisate} \xrightarrow{\text{homogentisate oxidase}} \text{4-Fumarylacetoacetate} \]

\[ \xrightarrow{\text{PA hydroxylase tetrahydrobiopterin}} \text{Tyrosine} \]

\[ \xrightarrow{-\text{OOC}} \text{Acetoacetate} + \text{Fumarate} \]
Tryptophan degradation requires several oxygenases
**INBORN ERRORS OF AMINO ACIDS METABOLISM**

**Alcaptonuria** - inherited disorder of the tyrosine metabolism caused by the absence of **homogentisate oxidase**.

- **homogentisic acid** is accumulated and excreted in the urine
- turns a **black color** upon exposure to air

- **In children:**
  - urine in diaper may darken

- **In adults:**
  - darkening of the ear
  - dark spots on the sclera and cornea
  - arthritis
Maple syrup urine disease - the disorder of the oxidative decarboxylation of $\alpha$-ketoacids derived from valine, isoleucine, and leucine caused by the missing or defect of branched-chain dehydrogenase.

The levels of branched-chain amino acids and corresponding $\alpha$-ketoacids are markedly elevated in both blood and urine.

The urine has the odor of maple syrup

The early symptoms:
- lethargy
- ketoacidosis
- unrecognized disease leads to seizures, coma, and death
- mental and physical retardation
**Phenylketonuria** is caused by an absence or deficiency of *phenylalanine hydroxylase* or of its tetrahydrobiopterin cofactor.

Phenylalanine accumulates in all body fluids and converts to phenylpyruvate.

- Defect in myelination of nerves
- The brain weight is below normal.
- Mental and physical retardations.
- The life expectancy is drastically shortened.

**Diagnostic criteria:**
- Phenylalanine level in the blood
- FeCl₃ test
- DNA probes (prenatal)
Nitric oxide (\(\cdot\text{N}=\text{O}\)) is a gas which can diffuse rapidly into cells, and is a messenger that activates guanylyl cyclase (GMP synthesis).

NO relaxes blood vessels, lowers blood pressure, and is a neurotransmitter in the brain.

Nitroglycerin is converted to NO and dilates coronary arteries in treating angina pectoris.
Conversion of arginine to NO via nitric oxide synthase

Arginine $\rightarrow$ N-ω-Hydroxy-arginine $\rightarrow$ Citrulline + NO

$\text{H}_2\text{N} \searrow \text{NH} \nearrow \text{H} \searrow \text{N} \nearrow \text{COO}^- + \text{H}^+ + \text{O}_2 + \text{NADPH} \rightarrow \text{H}_2\text{N} \searrow \text{NH} \nearrow \text{H} \searrow \text{N} \nearrow \text{COO}^- + \text{HO} \searrow \text{N} \nearrow \text{H} \searrow \text{N} \nearrow \text{COO}^- + \text{O}_2 + \text{NADPH} \rightarrow \text{H}_2\text{N} \searrow \text{NH} \nearrow \text{H} \searrow \text{N} \nearrow \text{COO}^- + \cdot \text{NO} $
SPECIFIC WAYS OF AMINO ACID SYNTHESIS

- Plants and microorganisms can make all 20 amino acids

- Humans can make only 11 of the 20 amino acids ("nonessential" amino acids)

- Nonessential amino acids for mammals are usually derived from intermediates of glycolysis or the citric acid cycle

- The others are classed as "essential" amino acids and must be obtained in the diet
A deficiency of even one amino acid results in a negative nitrogen balance.

In this state, more protein is degraded than is synthesized.
The **nonessential amino acids** are synthesized by quite simple reactions. The pathways for the formation of the **essential amino acids** are quite complex.
The pathways for the biosynthesis of amino acids are diverse.

**Common feature:** carbon skeletons come from intermediates of
- glycolysis,
- pentose phosphate pathway,
- citric acid cycle.

All amino acids are grouped into families according to the intermediates that they are made from.
Oxaloacetate → Aspartate → Asparagine, Methionine, Threonine, Lysine, Isoleucine
Phosphoenolpyruvate + Erythrose 4-phosphate → Phenylalanine → Tyrosine → Tryptophan
$\alpha$-Ketoglutarate

Glutamate

- Glutamine
- Proline
- Arginine
3-Phosphoglycerate → Serine → Cysteine, Glycine

Ribose 5-phosphate → Histidine