Metabolism of Sulfur Containing Amino Acids
Methionine

\[ \text{S} - \text{CH}_3 \]
\[ \text{CH}_2 \]
\[ \text{CH}_2 \]
\[ \text{CHNH}_2 \]
\[ \text{COOH} \]

cysteine

\[ \text{CH}_2\text{SH} \]
\[ \text{CHNH}_2 \]
\[ \text{COOH} \]
Methionine

- Essential amino acid
- Non-polar amio acid
- Glucogenic amino acid

IMPORTANCE:
- As a constituent of protein, as well as the initiating amino acid in protein synthesis
- Source methyl groups for → Phosphotidyl choline, DNA, RNA, hormones via conversion of MET to S-adenosyl MET
- Source sulfur in Cysteine via trans-sulfuration pathway
First step: Activation of MET

$\rightarrow$ SAM (a high energy compound)

- Most Reactions with SAM are **Methyl transferases**
- Methyl transferred SAM $\rightarrow$ several compounds
S-adenosyl methionine, SAM

\[
\text{S-CH}_3 + \text{CH}_2 + \text{CH}_2 + \text{CHNH}_2 + \text{COOH} + \text{P} \sim \text{P} \sim \text{P} + \text{ATP} \rightarrow \text{S-CH}_3 \text{CH}_2 \text{CH}_2 \text{CHNH}_2 \text{COOH} + \text{PPi} + \text{Pi}
\]

Methionine  ATP  S-adenosyl methionine, SAM
SAM is the direct donor of methyl in body

\[ \text{SAM} \xrightarrow{\text{Methyl transferase}} \text{RH—CH}_3 \]

\[ \text{SAM} \rightarrow \text{SAM—adenosyl} \rightarrow \text{homocystein} \]
SAM is the methyl donor

- Phosphatidylethanolamine to phosphatidylcholine
- Guanidinoacetate to creatine
- Norepinephrine to epinephrine
- Inactivation of catecholamines by catechol-O-methyl transferase,
- Acetylserotonin to melatonin
- Methylation of cytosine residues in DNA
Regeneration of Met
(vitamins: folate+B₁₂)
SAM → Homocysteine (homoCYS)

• This represents a **branch point in MET** metabolism (direction depends on **physiological needs** of organism).

• If MET limited → **homoCYS** remethylated to MET

• If CYS needed and SAM adequate then **homoCYS** → **trans-sulfuration pathway**.
Regeneration of Met
(vitamins: folate+B₁₂)

Methionine synthase

Methionine

Homocysteine

Cystathionine synthase

Cystathionine

Cysteine

α-Ketobutyrate

on page
Vitamin B\textsubscript{12} Deficiency

- If vitamin B\textsubscript{12} is not available for the synthesis of methylcobalamin, then no acceptor is available for the methyl group of N\textsuperscript{5}-methyltetrahydrofolate and metabolic folates become trapped in the N\textsuperscript{5}-methyl form.
Cysteine

- Non-essential
- Glucogenic amino acid
- **Synthesis of Cysteine**: SH group from methionine is transferred to serine to form cysteine this is called trans-sulfuration reaction
Trans-Sulfuration Pathway

Both reactions use pyridoxal phosphate as a cofactor.
Cystine Formation

\[
\text{cysteine (SH)} + \text{cysteine (SH)} \rightleftharpoons \text{cysteine (S-S)}
\]

2H

\[
\text{cysteine (SH)} + \text{cysteine (SH)} \rightleftharpoons \text{cysteine (S-S)}
\]

2H
Keeping Correct Structure of Proteins

Cysteine residues in polypeptide chain form disulfide bridges to make stabilize structure of proteins e.g Insulin
Type I Homocystinuria

- **B6 responsive** - (responsive to vitamin therapy)
  - 50% Type I
  - doses B6 up to 1 g / day

- Remember defect in **cystathionine synthase**
- Enzyme that converts homoCYS → CYS (Step I)
- Pyridoxal phosphate is a cofactor
- B6 → pyridoxal phosphate
Regeneration of Met
(vitamins: folate+B_{12})
Type II Homocystinuria

- B6 unresponsive
- **Enzyme mutation** that does not involve cofactor binding site
- Therefore → dietary therapy
- THF → Why? Enhance alternate pathway
- keep MET ↓ (use plant protein like soybean/lentil which has half the MET of animal protein)
- CYS → conditionally essential because MET cannot be converted to CYS
- Start therapy early due to serious clinical symptoms
Hyperhomocysteinemia can result in:

- Vascular diseases, endothelial dysfunction, atherosclerosis, thrombophilia
- Skeletal anomalies
- Retardation of mental development
- Ectopic lens
- Alzheimer's disease
- Kidneys insufficiency
- Colorectal cancer
Trans-Sulfuration Pathway

Both use pyridoxal phosphate as a cofactor
Cystathioninuria

- Due to a defect in **cystathionase** (Step 2 CYS synthesis)
- **Less clinical abnormalities** than Type I
- Accumulation cystathionine *in blood/urine* (not detectable normally)
Cystinuria

- **Inheritance:** Autosomal recessive defect of intestinal absorption and proximal tubular reabsorption transport system
- **Symptoms:** All four amino acids appear in the urine.
Cystinosis

**Inheritance:** Autosomal recessive

**Defect:**
Deposition of cystine crystals in lysosomes
Accumulates in liver, bone marrow, spleen, WBC, cornea, kidney