M1 - Renal, Fall 2007

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### Medical relevance of the one-carbon pathways

- Mechanism of antibiotics
  - Sulfa drugs - antibacterial
  - Trimethoprim, pyrimethamin - antibacterial, antimalarial
- Pathologies
  - VitB₁₂ deficiency/pernicious anemia
  - dietary folate deficiency
  - sprue

(See also the Nucleic Acid lectures for anti-cancer chemotherapies)

### I. Tetrahydrofolate as a carrier of one-carbon units

#### A. Obtaining folate - an essential vitamin

1. Dietary sources (green veggies, fortified cereals, liver) provide folic acid. Cleaved by enzyme 'conjugase' to remove extra glutamate residues, absorbed, reduced to dihydrofolate, then to tetrahydrofolate by **Dihydrofolate Reductase** (DHFR). DHFR inhibitors are useful antibiotics if they affect other organisms but not humans.

   ![Folic Acid](image1)

   ![Dihydrofolate](image2)

   ![Tetrahydrofolate](image3)

   ![Chemical Reactions](image4)

   ![Chemical Reactions](image5)

2. Inhibitors of DHFR are used therapeutically: e.g. methotrexate (cancer chemotherapy). Tumors that resist methotrexate sometimes have amplified the DHFR gene to compensate for the inhibitor.
3. Compounds that inhibit bacterial folate biosynthesis can be excellent antibiotics. Example: sulfa drugs like sulfanilamide:

Para-aminobenzoic acid (PABA)

\[
\begin{align*}
&\text{NH}_2 - \text{C} - \text{O} - \text{OH} \\
&\text{NH}_2 - \text{O} - \text{NH}_2
\end{align*}
\]

B. Main entry of one-carbon units - $N^5$, $N^{10}$ methylene tetrahydrofolate

1) Serine conversion to glycine:

\[
\begin{align*}
\text{Serine} + \text{COO}^- & \rightarrow \text{Glycine} + \text{H}_2\text{O} \\
\text{NAD}^+ & \rightarrow \text{NADH} + \text{H}^+
\end{align*}
\]

2) Glycine conversion to $\text{CO}_2$ and $\text{NH}_4^{(+)}$:

\[
\begin{align*}
\text{Glycine} + \text{COO}^- & \rightarrow \text{NAD}^+ \rightarrow \text{NADH} + \text{H}^+ \\
\text{N}_5, \text{N}_8 \text{methylene tetrahydrofolate} & \rightarrow \text{N}_5, \text{N}_8 \text{methylene tetrahydrofolate}
\end{align*}
\]

C. Oxidation states of the one-carbon unit and inter-conversions (reversible reactions indicated by double-ended arrows)

\[
\begin{align*}
\text{N}_5 \text{ methyl tetrahydrofolate} & \rightarrow \text{Biosynthesis of methionine} \\
\text{N}_5 \text{ methionine} & \rightarrow \text{NAD}^+ \\
\text{Glycine} + \text{H} & \rightarrow \text{N}_5, \text{N}_8 \text{ methylene tetrahydrofolate} \\
\text{N}_5, \text{N}_8 \text{ methylene tetrahydrofolate} & \rightarrow \text{Biosynthesis of thymidylate} \\
\text{NADPH} + \text{H} & \rightarrow \text{N}_8, \text{N}_8 \text{ methyllene tetrahydrofolate} \\
\text{N}_8, \text{N}_8 \text{ methyllene tetrahydrofolate} & \rightarrow \text{H}_2\text{O} \\
\text{N}_7 \text{ formyl tetrahydrofolate} & \rightarrow \text{Biosynthesis of purines}
\end{align*}
\]
II. S-adenosylmethionine (‘SAM’, aka ‘AdoMet’) Overview:

\[
\begin{align*}
\text{Methionine} & \quad \text{S-Adenosyl Methionine} \\
\text{Homocysteine} & \quad \text{S-Adenosyl Homocysteine}
\end{align*}
\]
A. Biosynthesis of methionine
(see also the Amino Acid Metabolism handout)

\[
\begin{align*}
\text{homocysteine} & \quad \xrightarrow{\text{vitamin B}_{12}} \quad \text{methionine} \\
\text{N}^5\text{-methyl THF} & \quad \xrightarrow{} \quad \text{THF} \\
\end{align*}
\]

B. Re-utilization of folates:

\[
\begin{align*}
\text{Carbon donor (e.g. serine or glycine)} & \quad \xrightarrow{} \quad \text{N}^5, \text{N}^{10}\text{ methylene tetrahydrofolate} \\
\text{methionine} & \quad \xrightarrow{} \quad \text{homocysteine} \\
\text{N}^5\text{ methyl tetrahydrofolate} & \quad \xrightarrow{\text{NAD}^+} \quad \text{NADH} + \text{H}^+ \\
\end{align*}
\]

C. Synthesis of S-Adenosyl Methionine

\[
\begin{align*}
\text{methionine} & \quad \xrightarrow{\text{ATP PP + Pi}} \quad \text{S-adenosyl methionine} \\
\end{align*}
\]

D. Uses of SAM - biological methylator
Example: Conversion of norepinephrine to epinephrine:

Others: Conversion of phosphatidylethanolamine to phosphatidylcholine, methylation of mRNA and DNA

E. AdoMet cycle

III. Pathologies:
A. Folate deficiency is common. Symptom: megaloblastic anemia
   weakness, anemia, anorexia
   Appearance of large, immature erythrocytes ('megaloblasts') in the blood

B. several causes:
   - dietary deficiency common
   - alcoholism may compound folate deficiency
   - inability to absorb folates (e.g. tropical sprue and non-tropical or celiac sprue)

   Dietary folates are typically poly-glutamated (up to 6 γ-glutamyl residues)
   We can absorb only the mono-glutamyl form
   An enzyme 'conjugase' secreted by the brush border cells of the intestine
   hydrolytically removes the extra glu residues so we can absorb the folate
   Intestinal irritation can compromise production of conjugase

   - possibly secondary to B12 deficiency: pernicious anemia

   'Methyl trap' hypothesis and deficiency of vitamin B12:

   B12 deficiency can be caused by autoimmune response to 'Intrinsic Factor', a
   product of the gut that aids in the absorption of B12.