M1 - Renal, Fall 2007

Lyons, R.; Burney, R.

http://hdl.handle.net/2027.42/64946
Unless otherwise noted, the content of this course material is licensed under a Creative Commons Attribution – Share Alike 3.0 License.

Copyright 2007, Robert Lyons.

The following information is intended to inform and educate and is not a tool for self-diagnosis or a replacement for medical evaluation, advice, diagnosis or treatment by a healthcare professional. You should speak to your physician or make an appointment to be seen if you have questions or concerns about this information or your medical condition. You assume all responsibility for use and potential liability associated with any use of the material.

Material contains copyrighted content, used in accordance with U.S. law. Copyright holders of content included in this material should contact open.michigan@umich.edu with any questions, corrections, or clarifications regarding the use of content. The Regents of the University of Michigan do not license the use of third party content posted to this site unless such a license is specifically granted in connection with particular content objects. Users of content are responsible for their compliance with applicable law. Mention of specific products in this recording solely represents the opinion of the speaker and does not represent an endorsement by the University of Michigan.

Viewer discretion advised: Material may contain medical images that may be disturbing to some viewers.
Medical relevance of the one-carbon pathways

<table>
<thead>
<tr>
<th>Mechanism of antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfa drugs - antibacterial</td>
</tr>
<tr>
<td>Trimethoprim, pyrimethamin - antibacterial, antimalarial</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pathologies</th>
</tr>
</thead>
<tbody>
<tr>
<td>VitB\textsubscript{12} deficiency/pernicious anemia</td>
</tr>
<tr>
<td>dietary folate deficiency</td>
</tr>
<tr>
<td>sprue</td>
</tr>
</tbody>
</table>

(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.

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)](image)

![sulfanilamide](image)

**B. Main entry of one-carbon units - \(N^5, N^{10}\) methylene tetrahydrofolate**

1) Serine conversion to glycine:

![Serine conversion to glycine](image)

2) Glycine conversion to \(CO_2\) and \(NH_4^{(+)}\):

![Glycine conversion to \(CO_2\) and \(NH_4^{(+)}\)](image)

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

![Oxidation states of the one-carbon unit and inter-conversions](image)
II. S-adenosylmethionine ('SAM', aka 'AdoMet') Overview:

**Methionine**

\[
\text{CH}_3\text{SCH}_2\text{CH}_2\text{CH}_2\text{C}(-\text{COO})^+\quad \text{ATP} + \text{H}_2\text{O} \rightarrow \text{S-Adenosyl Methionine} \quad \text{PP}_i + \text{Pi}
\]

**Homocysteine**

\[
\text{HS}-\text{CH}_2\text{CH}_2\text{CH}_2\text{C}(-\text{COO})^+\quad \text{S-Adenosyl Homocysteine}
\]

**Biosynthetic Methylation reaction**

- Methyl acceptor
- Methylated acceptor

\[ \text{*see examples} \]
A. Biosynthesis of methionine
(see also the Amino Acid Metabolism handout)

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

B. Re-utilization of folates:

\[
\begin{align*}
\text{Tetrahydrofolate} & \quad \xrightarrow{\text{Carbon donor}} \quad N^9, N^{10} \text{ methylene tetrahydrofolate} \\
\text{methionine} & \quad \xrightarrow{} \quad \text{NAD}^+ \\
\text{homocysteine} & \quad \xrightarrow{} \quad \text{NADH} + H^+
\end{align*}
\]

C. Synthesis of S-Adenosyl Methionine

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

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

```
\[
\begin{align*}
\text{Norepinephrine} & \quad \text{SAM} \quad \text{SAH} \\
\text{Epinephrine} &
\end{align*}
\]
```

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

**E. AdoMet cycle**

```
\[
\begin{align*}
\text{Adenosine} & \quad \text{H}_2\text{O} \\
\text{NAD}^+ & \quad \text{NADH} \\
\text{N}^5-\text{methyl THF} & \quad \text{THF} \\
\text{Adenosine} & \quad \text{methionine} \\
\text{S-adenosyl homocysteine} & \quad \text{methyl group donated to biological substrate}
\end{align*}
\]
```

**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.