M1 - Renal, Fall 2007

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<http://hdl.handle.net/2027.42/64946>
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Viewer discretion advised: Material may contain medical images that may be disturbing to some viewers.
Folate (“One-Carbon”) Pathways

Click on any blue box to see details
(Start with the section with ‘Diet’ and follow the paths with red arrows)
Folic Acid is Synthesized By Bacteria

Dietary folate: folic acid (meats, green veggies) *requires* the intestinal enzyme ‘Conjugase’ for absorption.
Folic acid

Dihydrofolate

Tetrahydrofolate

\[ \text{NADPH} + \text{H}^+ \]

\[ \text{NADP}^+ \]
Inhibitors of DHFR are important therapeutics:
Methotrexate - chemotherapy
Trimethoprim - inhibits bacterial DHFR
Pyrimethamine - inhibits malarial DHFR
Tetrahydrofolate + serine → H₂O + glycine

\[\text{N}^6, \text{N}^5\text{ methylene tetrahydrofolate}\]
$N^\prime$-methyl tetrahydrofolate

$N^\prime$, $N^\circ$ methylene tetrahydrofolate

$N^\prime$, $N^\circ$ methylenyl tetrahydrofolate

$N^\prime$ formyl tetrahydrofolate

Biosynthesis of methionine

Biosynthesis of thymidylate

Biosynthesis of purines

$N^\prime$-methyl tetrahydrofolate

$N^\prime$ formyl tetrahydrofolate
Methionine Cycle
And Biological Methyl Groups

Methionine

\[
\text{CH}_3 - \text{S} - \text{CH}_2 - \text{CH}_2 - \text{CH}_3 - \text{COO}^(-)
\]

Methyl acceptor

S-Adenosyl Methionine

\[
\text{CH}_3 \text{S} - \text{C} - \text{CH}_2 - \text{CH}_2 - \text{CH}_3 - \text{COO}^(-)
\]

Methylated acceptor

NS methyl tetrahydrofolate

Homocysteine

\[
\text{X} - \text{CH}_3 - \text{CH}_2 - \text{CH}_2 - \text{CH}_3 - \text{COO}^(-)
\]

S-Adenosyl Homocysteine

\[
\text{CH}_3 \text{S} - \text{C} - \text{CH}_2 - \text{CH}_2 - \text{CH}_3 - \text{COO}^(-)
\]

Serine

\[
\text{X} - \text{CH}_2 - \text{COO}^(-)
\]

Cysteine

(remainder of homocysteine degraded for energy)
Homocysteine → $\text{N}^\text{6}-\text{methyl} \ THF$ → Vitamin $B_12$ → Methionine

- OOC$\text{C} \ \text{CH}_2 \ \text{CH}_2 \ \text{SH}$
- OOC$\text{C} \ \text{CH}_2 \ \text{CH}_2 \ \text{SCH}_3$
Carbon donor (e.g. serine or glycine)

Tetrahydrofolate

N^6, N^6 methylene tetrahydrofolate

NADH + H^+  

NAD^+  

methionine

homocysteine

N^6 methyl tetrahydrofolate
Other methyl acceptors:
DNA ("CpG Islands")
RNA
**Folate Deficiencies:** Symptom: megaloblastic anemia

Dietary deficiency:
Common especially in developing countries, lower socioeconomic classes
Folate deficiency secondary to bowel irritation:

- Conjugase is essential for adequate absorption of dietary folates

- Conjugase production may be compromised by bowel irritation:
  
  ‘Tropical Sprue’ - bowel irritation probably arising from bacterial origin, causes intestinal inflammation and malabsorption.

  ‘Celiac Sprue’ - similar outcome, but the original irritation is due to an allergic response, for example to gliadens (a component in gluten)
B12 is also critical in other reactions, ones for which the deficiency has serious neurological consequences.