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)

- Connects to Amino Acids
- Donation of one carbon (from Ser, Gly)
- THF
- DHF
- Folate

Methyl-THF
Methylene-THF
Formyl-THF
THF Cycle
Methionine Cycle

Connects to Nucleic Acids
Purine biosynthesis
Thymidylate synthetase
Folic Acid is Synthesized By Bacteria

Dietary folate: folic acid (meats, green veggies) *requires* the intestinal enzyme ‘Conjugase’ for absorption.
Inhibitors of DHFR are important therapeutics:
Methotrexate - chemotherapy
Trimethoprim - inhibits bacterial DHFR
Pyrimethamine - inhibits malarial DHFR
Tetrahydrofolate + serine $\rightarrow$ Tetrahydrofolate + glycine + N$^6$, N$^{10}$ methylene tetrahydrofolate

Tetrahydrofolate + glycine $\rightarrow$ Tetrahydrofolate + N$^6$, N$^{10}$ methylene tetrahydrofolate
\[ \text{N}^{\bullet} \text{ methyl tetrahydrofolate} \rightarrow \text{Biosynthesis of methionine} \]
\[ \text{Gly} \quad \text{Ser} \quad \rightarrow \text{N}^{\bullet}, \text{N}^{\bullet} \text{ methylene tetrahydrofolate} \rightarrow \text{Biosynthesis of thymidylate} \]
\[ \text{N}^{\bullet}, \text{N}^{\bullet} \text{ methenyl tetrahydrofolate} \]
\[ \text{H}_2\text{O} \rightarrow \text{N}^{14} \text{ formyl tetrahydrofolate} \rightarrow \text{Biosyntheses of purines} \]

\[ \begin{align*}
\text{N}^{\bullet} \text{ methyl tetrahydrofolate} & \\
\text{N}^{14} \text{ formyl tetrahydrofolate} &
\end{align*} \]
Methionine Cycle
And Biological Methyl Groups
Carbon donor (e.g. serine or glycine)

Tetrahydrofolate

N\textsuperscript{\textbeta}, N\textsuperscript{\textgamma} methylene tetrahydrofolate

methionine

homocysteine

N\textsuperscript{\textbeta} methyl tetrahydrofolate

NADH + H\textsuperscript{+}

NAD\textsuperscript{+}
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 gliaden (a component in gluten)
Folate Deficiency Secondary to B12 deficiency: the ‘methyl trap’ hypothesis

B12 is also critical in other reactions, ones for which the deficiency has serious neurological consequences.