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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)

Methyl-THF

Methylene-THF

THF Cycle

Methionine Cycle

THF

DHF

Folate

Folate

Connects to Nucleic Acids lectures

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 $\xrightleftharpoons[\text{H}_{2}\text{O}]{\text{NAD}^{+}}$ glycine $\text{N}^{\text{v}}, \text{N}^{\text{v}'}$ methylene tetrahydrofolate

Tetrahydrofolate + glycine $\xrightleftharpoons[\text{NADH}]{\text{NAD}^{+}}$ $\text{N}^{\text{v}}, \text{N}^{\text{v}'}$ methylene tetrahydrofolate
The diagram illustrates the pathways of biosynthesis involving tetrahydrofolate derivatives. Here are the key points:

1. **Biosynthesis of Methionine**:
   - The pathway starts with N'-methyl tetrahydrofolate and proceeds through NADPH + H⁺ to produce N⁰, N⁰-methylene tetrahydrofolate.
   - Gly and Ser are produced from this pathway.

2. **Biosynthesis of Thymidylate**:
   - N⁰, N⁰-methylenetetrahydrofolate undergoes a reaction with NAD⁺ to form N⁰-formyl tetrahydrofolate.
   - This pathway leads to the biosynthesis of thymidylate.

3. **Biosynthesis of Purines**:
   - N⁰-formyl tetrahydrofolate is involved in the biosynthesis of purines.

Additionally, the structures of N'-methyl tetrahydrofolate and N⁰-formyl tetrahydrofolate are shown to represent the chemical entities involved in these pathways.
Methionine Cycle
And Biological Methyl Groups
$\text{homocysteine} \rightarrow \text{N}^6\text{-methyl THF} \rightarrow \text{THF} \rightarrow \text{methionine}$
Carbon donor (e.g. serine or glycine)

Tetrahydrofolate

\[ \text{N}^6, \text{N}^5 \text{ methylene tetrahydrofolate} \]

methionine

\[ \text{N}^6 \text{ methyl tetrahydrofolate} \]

homocysteine

\[ \text{NAD}^+ + \text{H}^+ \]
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.