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

\[
\text{NADPH} + \text{H}^+ \quad \rightarrow \quad \text{NADP}^+ 
\]

Dihydrofolate

\[
\text{NADPH} + \text{H}^+ \quad \rightarrow \quad \text{NADP}^+ 
\]

Tetrahydrofolate
Inhibitors of DHFR are important therapeutics:  
Methotrexate - chemotherapy  
Trimethoprim - inhibits bacterial DHFR  
Pyrimethamine - inhibits malarial DHFR
Tetrahydrofolate + serine $\rightarrow$ glycine + Nε, N6′ methylene tetrahydrofolate

Tetrahydrofolate + glycine $\rightarrow$ Nε, N6′ methylene tetrahydrofolate

[Chemical structures and reactions diagram]
$N^\text{t}$-methyl tetrahydrofolate \xrightarrow{\text{Biosynthesis of methionine}} \ N^\text{t}, N^\text{t}$-methylene tetrahydrofolate \xrightarrow{\text{Biosynthesis of thymidylate}} \ N^\text{t}, N^\text{t}$-methyltetrahydrofolate \xrightarrow{\text{Biosynthesis of purines}} \ N^\text{t}$-formyl tetrahydrofolate

\begin{align*}
\text{Gly} & \quad \text{Ser} \\
\text{NAD}^+ & \xrightarrow{NADH + H^+} \text{NADP}^+ \\
\text{NADPH} + \text{H}^+ & \xrightarrow{H_2O} \text{NADP}^+
\end{align*}

$N^\text{t}$-methyl tetrahydrofolate

$N^\text{t}$-formyl tetrahydrofolate
Methionine Cycle
And Biological Methyl Groups
**Homocysteine**

\(-\text{OOC-C-CH}_2\text{CH}_2\text{SH}\)

\(\text{N}^6\text{-methyl THF}\)

\(\text{THF}\)

\(\text{vitamin B}_12\)

\(-\text{OOC-C-CH}_2\text{CH}_2\text{SCH}_3\)

**Methionine**
Tetrahydrofolate

Carbon donor (e.g. serine or glycine)

$N^\alpha, N^\beta$ methylene tetrahydrofolate

methionine

homocysteine

$N^\alpha$ methyl tetrahydrofolate

NADH + $H^+$

NAD$^+$
Other methyl acceptors:
- DNA ("CpG Islands")
- RNA

Chemical structures:
- Methionine
- S-Adenosyl methionine
- Norepinephrine
- Epinephrine
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.