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M1 Renal:
Folate Metabolism

Dr. Robert Lyons
Assistant Professor, Biological Chemistry
Director, DNA Sequencing Core

Web: http://seqcore.brcf.med.umich.edu/mcb500
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

Diet: THF, DHF

Folate

Connects to Nucleic Acids lectures

Purine biosynthesis

Thymidylate synthetase

Links to

Formyl-THF
Folic Acid is Synthesized By Bacteria

Para-aminobenzoic acid (PABA)

sulfanilamide

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

Dihydrofolate

Tetrahydrofolate
Inhibitors of DHFR are important therapeutics:
Methotrexate - chemotherapy
Trimethoprim - inhibits bacterial DHFR
Pyrimethamine - inhibits malarial DHFR
Gly, Ser → N5, N0 methylene tetrahydrofolate → Biosynthesis of thymidylate

N5, N0 methenyl tetrahydrofolate

N10 formyl tetrahydrofolate → Biosynthesis of purines

N5 methyl tetrahydrofolate → Biosynthesis of methionine

NADPH + H+ → NADP+ → NADH + H+ → NAD+
Methionine Cycle
And Biological Methyl Groups

Methionine

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

\[ \text{H} \]

\[ \text{NH}_3 \]

\[ (+) \]

\[ \text{ATP} + \text{H}_2\text{O} \]

\[ \text{PPi} + \text{Pi} \]

S-Adenosyl Methionine

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

\[ \text{H} \]

\[ \text{NH}_3 \]

\[ (+) \]

\[ \text{Adenine} \]

Homocysteine

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

\[ \text{H} \]

\[ \text{NH}_3 \]

\[ (+) \]

tetrahydrofolate

NS methyl tetrahydrofolate

S-Adenosyl Homocysteine

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

\[ \text{H} \]

\[ \text{NH}_3 \]

\[ (+) \]

\[ \text{Adenine} \]

Bio-synthetic Methylatation reaction

Methyl acceptor

Methylated acceptor

Serine

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

\[ \text{NH}_3 \]

\[ (+) \]

Cysteine

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

\[ \text{H} \]

\[ \text{NH}_3 \]

\[ (+) \]

(remainder of homocysteine degraded for energy)
homocysteine $\rightarrow$ N$^5$-methyl THF $\rightarrow$ THF $\rightarrow$ vitamin B$_{12}$ $\rightarrow$ methionine
Carbon donor (e.g. serine or glycine)

Tetrahydrofolate

N\textsuperscript{5}, N\textsuperscript{0} methylene tetrahydrofolate

methionine

homocysteine

N\textsuperscript{5} methyl tetrahydrofolate

NAD\textsuperscript{+}

NADH + H\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.
Additional Source Information

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