M1 - Renal, Fall 2007

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Viewer discretion advised: Material may contain medical images that may be disturbing to some viewers.
Formation of PRPP: Phosphoribose pyrophosphate

PRPP Use in Purine Biosynthesis:
The First Purine: Inosine Monophosphate
(folates are involved in this synthesis)

Conversion to Adenosine:

Conversion to Guanosine:
Nucleoside Monophosphate Kinases

AMP + ATP  \<--\>  2ADP  \hspace{1cm}  \text{(adenylate kinase)}

GMP + ATP  \<--\>  GDP + ADP  \hspace{1cm}  \text{(guanylate kinase)}

- similar enzymes specific for each nucleotide
- no specificity for ribonucleotide vs. deoxyribonucleotide
Ribonucleotide Reductase

Hydroxyurea inhibits this enzyme: chemotherapeutic use

\[
\text{HONH}^-\text{C}^-\text{NH}_2
\]
Regulation of Ribonucleotide Reductase
Nucleoside Diphosphate Kinase

\[ N_1 DP + N_2 TP \leftrightarrow N_1 TP + N_2 DP \]

\[ dN_1 DP + N_2 TP \leftrightarrow dN_1 TP + N_2 DP \]

- No specificity for base
- No specificity for ribo vs deoxy
Feed-forward regulation by PRPP
Feed-forward regulation by PRPP
Feed-forward regulation by PRPP

PRPP

IMP

GMP + ATP

AMP + GTP

GTP

ATP
Feed-forward regulation by PRPP
Degradation of the Purine Nucleosides:

Adenosine $\overset{\text{Adenosine deaminase (ADA)}}{\rightleftharpoons}$ Inosine $\overset{\text{purine nucleoside phosphorylase}}{\rightleftharpoons}$ Hypoxanthine

Guanosine $\overset{\text{purine nucleoside phosphorylase}}{\rightleftharpoons}$ Guanine $\overset{\text{Guanine deaminase}}{\rightleftharpoons}$ Xanthine

Xanthine $\overset{\text{xanthine oxidase}}{\rightarrow}$ Uric acid
“Salvage” Pathways for Purine Nucleotides

APRT - Adenine phosphoribosyl transferase - performs a similar function with adenine.
Adenosine Deaminase Deficiency:

Deoxyadenosine → dAMP → dADP → dATP

Adenosine deaminase (ADA)

2-deoxyribose

Deoxyinosine → Hypoxanthine

Guanine → Xanthine → Uric acid
Hyperuricemia can be caused by:

- Accelerated degradation of purines:
  - Accelerated synthesis of purines
  - Increased dietary intake of purines
- Impaired renal clearance of uric acid

Allopurinol inhibits xanthine oxidase and reduces blood uric acid levels:

Gout: deposition of urate crystals in joints, “tophi” in cooler periphery
The hands of a patient with a long history of gout, including high serum urate levels
Lesch-Nyhan Syndrome: Defective HGPRT

- hyperuricemia
- spasticity
- mental retardation
- self-mutilation behavior

A defect in APRT does NOT have similar consequences
Myoadenylate Deaminase ‘Fills’ the TCA Cycle in Muscle
Carbamoyl phosphate synthetase II - a cytoplasmic enzyme...

\[ 2\text{ATP} + \text{HCO}_3^- + \text{glutamine} + \text{H}_2\text{O} \rightarrow \text{NH}_2\text{C} = \text{O}\text{O}^2^- + \text{glutamate} + 2\text{ADP} + \text{P}_i \]

carbamoyl phosphate

...used for pyrimidine synthesis

\[
\begin{align*}
\text{carbamoyl phosphate} + \text{aspartate} & \rightarrow \text{ornithine} \\
\text{ornithine} + \text{P}^5\text{P} & \rightarrow \text{orotate}
\end{align*}
\]
Orotate is linked to PRPP to form Uridine monophosphate:
Newly-synthesized uridine monophosphate will be phosphorylated to UDP and UTP, as described for the purine nucleotides.

UTP can be converted to CTP by CTP Synthetase:
Some UDP is converted to dUDP via ribonucleotide reductase.

The Thymidylate Synthase Reaction:
Methotrexate Inhibits Dihydrofolate Reductase:

Dihydrofolate builds up, levels of THF become limiting, thymidylate synthase is unable to proceed. Follow it with a dose of Leucovorin, a.k.a. formyl-THF.
FdUMP Inhibits The Thymidylate Synthase Reaction:

5-fluorodeoxyuridine monophosphate (FdUMP)

\[ \text{thymidylate synthase} \]

\[ \text{dihydrofolate} \]

\[ \text{NAD}^+ \]

\[ \text{NADH} \]

\[ \text{methylenedonor} \]

\[ \text{DHFR} \]

\[ \text{THF} \]

\[ \text{deoxythymidine monophosphate} \]
Complicated Pathways for Pyrimididine Production:

This figure is primarily a study aid; you do not need to memorize it or reproduce it. The information here merely summarizes material from previous sections.
Pathologies of pyrimidine nucleotide biosynthesis:

Orotic acidurea due to OTC deficiency - please review your Urea Cycle notes.

Hereditary orotic acidurea - deficiency of the enzyme that convert orotate to OMP to UMP. Not common.
Pyrimidine degradation:

Cytidine deaminase converts cytidine to uridine

A phosphorylase removes the sugar

Degradation of the base proceeds (products are unimportant here)
Pyrimidines can be salvaged as well:

Enzyme: Pyrimidine nucleoside phosphorylases
Thymine + deoxyribose-1-phosphate $\rightarrow$ thymidine
(NOT thymidine monophosphate!)

Enzyme: Thymidine kinase - adds the monophosphate back
Thymidine + ATP $\rightarrow$ thymidine monophosphate

Herpes Simplex Virus carries its own tk gene
Certain drugs act via the pyrimidine salvage pathway:

![Chemical structures and reactions](image-url)
5-FU efficacy depends on rate of degradation vs activation

5-FU \rightarrow \text{FdUMP} + \text{methylene-THF} + \text{Thymidylate Synthase} \rightarrow \text{inactivation of TS}

Degradation
(via dihydropyrimidin dehydrogenase, DPD)

DPD inhibitors can potentiate 5FU activity
Capecitabine mode of action:

Cytosine arabinoside (araC) activation and inactivation: