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:

Inosine monophosphate + GTP → GDP + P_i + aspartate + fumarate → Adenosine monophosphate

Conversion to Guanosine:

Inosine monophosphate + NAD^+ → NADH + H^+ + AMP + P_i → Guanosine monophosphate
Nucleoside Monophosphate Kinases

\[ \text{AMP + ATP} \rightleftharpoons \text{2ADP} \quad \text{(adenylate kinase)} \]

\[ \text{GMP + ATP} \rightleftharpoons \text{GDP + ADP} \quad \text{(guanylate kinase)} \]

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

Hydroxyurea inhibits this enzyme: chemotherapeutic use

\[
\text{HONH}^\text{−} \text{C} \text{−NH}_2
\]
Regulation of Ribonucleotide Reductase

- CDP + ATP → dCDP → dCTP
- UDP + ATP → dUDP → dTTP
- GDP + ATP → dGDP → dGTP
- ADP + ATP → dADP → dATP
Nucleoside Diphosphate Kinase

\[ N_1DP + N_2TP \iff N_1TP + N_2DP \]

\[ dN_1DP + N_2TP \iff dN_1TP + N_2DP \]

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

Adenosine

\[ \text{Adenosine deaminase (ADA)} \rightarrow \text{Inosine} \]

Inosine

\[ \text{purine nucleoside phosphorylase} \rightarrow \text{Hypoxanthine} \]

Hypoxanthine

\[ \text{xanthine oxidase} \rightarrow \text{Xanthine} \]

Xanthine

\[ \text{xanthine oxidase} \rightarrow \text{Uric acid} \]
“Salvage” Pathways for Purine Nucleotides

APRT - Adenine phosphoribosyl transferase - performs a similar function with adenine.
Adenosine Deaminase Deficiency:
Hyperuricemia can be caused by:

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

Gout: deposition of urate crystals in joints, “tophi” in cooler periphery

Allopurinol inhibits xanthine oxidase and reduces blood uric acid levels:
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...

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

...used for pyrimidine synthesis

\[\text{carbamoyl phosphate} + \text{aspartate} \rightarrow \text{orotate}\]
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) inhibits the thymidylate synthase reaction, preventing the conversion of dihydrofolate to deoxythymidine monophosphate.

- Thymidylate synthase catalyzes the conversion of dihydrofolate to deoxythymidine monophosphate in the presence of N^5, N^10-methylene tetrahydrofolate and NADH.
- FdUMP binds to thymidylate synthase, blocking the reaction path.
Complicated Pathways for Pyrimidine Production:

\[
\begin{align*}
\text{dCTP} & \quad \text{CTP} \quad \text{UTP} \quad \text{dUTP} \quad \text{dTTP} \\
\text{dCDP} & \quad \text{CDP} \quad \text{UDP} \quad \text{dUDP} \quad \text{dTDP} \\
\text{UMP} & \quad \text{dUMP} \quad \text{dTMP} \\
\text{de novo synthesis} & \quad \text{OMP}
\end{align*}
\]

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 pyrimidinucleotide biosynthesis:

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

Hereditary orotic aciduria - 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:

\[
\text{Acyclovir} \xrightarrow{\text{HSV thymidine kinase}} \text{AcycloGMP}
\]

\[
\text{5-fluorouracil} + \text{deoxyribose-1-phosphate} \xrightarrow{\text{pyrimidine phosphorylase}} \text{fluorodeoxyuridine} \xrightarrow{\text{uridine kinase}} \text{fluorodeoxyuridine monophosphate (FdUMP)}
\]
5-FU efficacy depends on rate of degradation vs activation

5-FU $\rightarrow$ FdUMP $\rightarrow$ inactivation of TS

+ methylene-THF + Thymidylate Synthase

--> inactivation of TS

Degradation
(via dihydropyrimidine dehydrogenase, DPD)

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

Cytosine arabinoside (araC) activation and inactivation: