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 $\leftrightarrow$ 2ADP (adenylate kinase)

GMP + ATP $\leftrightarrow$ GDP + ADP (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

\[ N_1 \text{DP} + N_2 \text{TP} \leftrightarrow N_1 \text{TP} + N_2 \text{DP} \]

\[ \text{dN}_1 \text{DP} + N_2 \text{TP} \leftrightarrow \text{dN}_1 \text{TP} + N_2 \text{DP} \]

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

PRPP

\[ \text{IMP} \]

\[ \text{AMP} \quad \text{GTP} \]

\[ \text{GMP} \quad \text{ATP} \]

\[ \text{GTP} \quad \text{ATP} \]
Feed-forward regulation by PRPP

PRPP

IMP

GMP

GTP

ATP

AMP

GTP

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

1. Adenosine → Inosine
   - Adenosine deaminase (ADA)

2. Inosine → Hypoxanthine
   - Purine nucleoside phosphorylase

3. Hypoxanthine → Guanosine
   - Xanthine oxidase

4. Guanosine → Guanine
   - Purine nucleoside phosphorylase

5. Guanine → Xanthine
   - Guanine deaminase

6. Xanthine → Uric acid
   - Xanthine oxidase
“Salvage” Pathways for Purine Nucleotides

Hypoxanthine + PRPP $\xrightarrow{\text{Hypoxanthine-guanine phosphoribosyl transferase}}$ Inosine monophosphate + PP$_i$.

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

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...

\[
2\text{ATP} + HCO_3^- + \text{glutamine} + \text{H}_2\text{O} \rightarrow \text{NH}_2\text{C}=\text{O}P^2^- + \text{glutamate} + 2\text{ADP} + \text{P}_i
\]

...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) is converted by thymidylate synthase into deoxythymidine monophosphate. This process involves the transfer of a methylene group from tetrahydrofolate (THF) to the incoming deoxyuridine monophosphate (dUMP) in the presence of NADPH. The reaction is catalyzed by the enzyme thymidylate synthase (DHFR).
Complicated Pathways for Pyrimidine 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

[Chemical structure of cytidine and uridine with reaction arrow labeled cytidine deaminase]

A phosphorylase removes the sugar

[Chemical structure of thymine, deoxythymidine, and deoxyribose-1-phosphate with reaction arrow labeled pyrimidine phosphorylase]

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

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

Enzyme: Thymidine kinase - adds the monophosphate back
Thymidine + ATP --> 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.

\[
\begin{align*}
5\text{-FU} & \rightarrow \rightarrow \text{FdUMP} \\
& + \text{methylene-THF} + \text{Thymidylate Synthase} \\
& \rightarrow \text{inactivation of TS}
\end{align*}
\]

Degradation
(via dihydropyrimidine dehydrogenase, DPD)

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

Cytosine arabinoside (araC) activation and inactivation: