M1 - Renal, Fall 2007

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Nucleic Acid metabolism
Click on any blue rectangle to see details.

- **Purine Salvage**
  - IMP
  - Purine MP
  - NTP
  - dNTP
  - DNA
  - RNA
  - NH₄
  - Purine Degradation

- **Pyrimidine Salvage**
  - Carboxymoyl Phosphate
  - OMP
  - Pyrimidine MP
  - dNTP
  - NTP
  - DNA
  - RNA
  - (energy)
  - Pyrimidine Degradation

- **Purine Biosynthesis**
  - amino acids, folate
  - IMP

- **Pyrimidine Biosynthesis**
  - PRPP
  - OMP
  - Pyrimidine MP
  - dNTP
  - NTP
Formation of PRPP: Phosphoribose pyrophosphate

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

Conversion to Adenosine:

\[
\begin{array}{c}
\text{Inosine monophosphate} \\
\text{(GTP, aspartate, fumarate)} \\
\text{Adenosine monophosphate}
\end{array}
\]

Conversion to Guanosine:

\[
\begin{array}{c}
\text{Inosine monophosphate} \\
\text{(NAD\(^+\), NADH, ATP, glutamine, glutamic acid)} \\
\text{Guanosine monophosphate}
\end{array}
\]
Nucleoside Monophosphate Kinases

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

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

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

Hydroxyurea inhibits this enzyme: chemotherapeutic use

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

\[ \text{N}_1\text{DP} + \text{N}_2\text{TP} \leftrightarrow \text{N}_1\text{TP} + \text{N}_2\text{DP} \]

\[ \text{dN}_1\text{DP} + \text{N}_2\text{TP} \leftrightarrow \text{dN}_1\text{TP} + \text{N}_2\text{DP} \]

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

Adenosine $\xrightarrow{\text{H}_2\text{O}, \text{NH}_4^+} \xrightarrow{\text{Adenosine deaminase (ADA)}}$ Inosine $\xrightarrow{p_i, \text{ribose - 1 - P}}$ Hypoxanthine

Guanosine $\xrightarrow{p_i, \text{ribose - 1 - P}}$ Guanine $\xrightarrow{\text{Guanine deaminase}}$ Xanthine $\xrightarrow{\text{xanthine oxidase}}$ Uric acid

$\text{NH}_2$ $\text{NH}_2$ $\text{NH}_2$

$\text{N}$ $\text{N}$ $\text{N}$

$\text{H}_2\text{O}$ $\text{H}_2\text{O}$ $\text{H}_2\text{O}$

$\text{N}$ $\text{N}$ $\text{N}$

$\text{N}$ $\text{N}$ $\text{N}$
“Salvage” Pathways for Purine Nucleotides

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

Deoxyadenoosine → dAMP → dADP → dATP

Adenosine deaminase (ADA) → Deoxyinosine → 2-deoxyribose → 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...

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

carbamoyl phosphate

...used for pyrimidine synthesis

carbamoyl phosphate + aspartate → 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. The reaction involves the conversion of deoxythymidine monophosphate to thymidylate, catalyzed by thymidylate synthase. The inhibition occurs at the step where FdUMP competes with deoxythymidine monophosphate for the thymidylate synthase enzyme.
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

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 → 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

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

Cytosine arabinoside (araC) activation and inactivation: