M1 - Renal, Fall 2007

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Nucleic Acid metabolism

Click on any blue rectangle to see details.

- **Purine Salvage**
  - IMP
  - Purine Biosynthesis
  - PRPP
  - Carbamoyl Phosphate
  - Pyrimidine Biosynthesis
  - OMP
  - Pyrimidine MP
  - Ribonucleotide reductase
  - dNTP
  - NTP
  - DNA
  - RNA
  - Pyrimidine Degradation
  - (energy)
  - Uric Acid
  - NH₄
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

\[
\begin{align*}
\text{HONH}^- \text{C}^- \text{NH}_2
\end{align*}
\]
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
Feed-forward regulation by PRPP

- PRPP
- IMP
- GMP
- ATP
- GTP

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

Adenosine \xrightarrow{\text{H}_{2}\text{O}} \xrightarrow{\text{NH}_{4}^{+}} \xrightarrow{\text{Adenosine deaminase (ADA)}} \text{Inosine} \xrightarrow{\text{purine nucleoside phosphorylase}} \text{Hypoxanthine} \xrightarrow{\text{xanthine oxidase}} \text{Xanthine} \xrightarrow{\text{xanthine oxidase}} \text{Uric acid}

Guanosine \xrightarrow{\text{purine nucleoside phosphorylase}} \text{Guanine} \xrightarrow{\text{Guanine deaminase}} \text{Xanthine} \xrightarrow{\text{xanthine oxidase}} \text{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) → Deoxyinosine → 2-deoxyribose → 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…

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

Carbamoyl phosphate

…used for pyrimidine synthesis

![Pyrimidine synthesis](image-url)
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 (F-dUMP)

\[ \text{N}^5, \text{N}^{10} \text{methylene tetrahydrofolate} \rightarrow \text{dihydrofolate} \]

\[ \text{DHFR} \quad \text{NADH} \quad \text{NAD}^+ \]

\[ \text{THF} \]

\[ \text{methylene donor} \]
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 $\rightarrow$ 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

$+$ methylene-THF $+$ Thymidylate Synthase

$\rightarrow$ inactivation of TS

Degradation
(via dihydropyrimidine dehydrogenase, DPD)

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

Cytosine arabinoside (araC) activation and inactivation: