M1 - Renal, Fall 2007

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

Purine Salvage
- IMP
- Purine MP
- Purine Degradation
- Uric Acid

PRPP
- dNTP
- NTP
- Ribonucleotide reductase

Purine Biosynthesis

Carbamoyl Phosphate
- OMP
- Pyrimidine Biosynthesis
- Pyrimidine MP
- Pyrimidine Degradation
- (energy)

DNA
RNA
NTP
dNTP
Formation of PRPP: Phosphoribose pyrophosphate

\[
\begin{align*}
\text{ribose - 5 - phosphate} & \quad \text{ATP} \quad \text{AMP} \quad \text{phosphoribose - 1 pyrophosphate} \\
\end{align*}
\]

PRPP Use in Purine Biosynthesis:

\[
\begin{align*}
\text{phosphoribose - 1 pyrophosphate} & \quad \text{glutamine} \quad \text{glutamate} \quad \text{NH}_2 \\
\end{align*}
\]
The First Purine: Inosine Monophosphate
(folates are involved in this synthesis)

Conversion to Adenosine:

Conversion to Guanosine:
Nucleoside Monophosphate Kinases

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

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

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

Hydroxyurea inhibits this enzyme: chemotherapeutic use

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

[Diagram showing the conversion of CDP, UDP, GDP, and ADP to dCTP, dTTP, dGTP, and dATP with regulatory + and - symbols and ATP reactions]
Nucleoside Diphosphate Kinase

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

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

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

PRPP

↓

IMP

GMP

GTP

↓

ATP

AMP

GTP

↓

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

Adenosine → Inosine → Hypoxanthine

Adenosine deaminase (ADA)

Inosine → Hypoxanthine

Hypoxanthine → Xanthine

Putative nucleoside phosphorylase

Xanthine → Uric acid

Guanosine → Guanine

Guanine deaminase

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-deoxyxybose → 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...

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

carbamoyl phosphate

...used for pyrimidine synthesis

$$\text{NH}_2\text{C}^2- + \text{CH}_2\text{CO}\text{NH}_3^- \rightarrow \text{NH}_2\text{CH}_{2}\text{CO}\text{NH}_3^-$$

carbamoyl phosphate

aspartate

$$\text{H}_2\text{N}-\text{CH}\text{CO}\text{NH}_3^-$$

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)

\[ \text{thymidylate synthase} \quad \text{N}^5, \text{N}^{10} \text{methylene tetrahydrofolate} \quad \text{dihydrofolate} \]

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

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

Degradation (via dihydropyrimidine dehydrogenase, DPD)

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

Cytosine arabinoside (araC) activation and inactivation: