M1 - Renal, Fall 2007

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http://hdl.handle.net/2027.42/64946
Nucleic Acid metabolism

Click on any blue rectangle to see details.

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

- **Pyrimidine Salvage**
  - OMP
  - Pyrimidine MP
  - Pyrimidine Degradation
  - (energy)

- **PRPP**
  - Amino acids, folate

- **Carbamoyl Phosphate**
  - Pyrimidine Biosynthesis

- **Ribonucleotide reductase**
  - NTP
  - dNTP

- **DNA**
  - RNA
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

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

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

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

Hydroxyurea inhibits this enzyme: chemotherapeutic use

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

AMP

GTP

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

- Adenosine $\xrightarrow{\text{ADA}}$ Inosine $\xrightarrow{\text{purine nucleoside phosphorylase}}$ Hypoxanthine
  - $\text{NH}_2$ $\text{NH}_2$
  - $\text{H}_2\text{O}$ $\text{H}_2\text{O}$ $\text{NH}_4$
  - Adenosine deaminase (ADA)

- Guanosine $\xrightarrow{\text{purine nucleoside phosphorylase}}$ Guanine $\xrightarrow{\text{xanthine oxidase}}$ Uric acid
  - $\text{NH}_2$ $\text{NH}_2$
  - $\text{H}_2\text{O}$ $\text{H}_2\text{O}$ $\text{NH}_4$
  - Guanine deaminase

- Hypoxanthine $\xrightarrow{\text{xanthine oxidase}}$ Xanthine
“Salvage” Pathways for Purine Nucleotides

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

Deoxyadenosine → Adenosine deaminase (ADA) → Deoxyinosine → 2-deoxyribose → Hypoxanthine → Guanine → Xanthine → Uric acid

dAMP → dADP → dATP
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...

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

...used for pyrimidine synthesis

[Chemical structures and reactions are shown with labels for carbamoyl phosphate, aspartate, and 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)

\[ \text{thymidylate synthase} \]

\[ \text{deoxythymidine monophosphate} \]

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

\[ \text{dihydrofolate} \]

\[ \text{DHFR} \]

\[ \text{THF} \]

\[ \text{NAD}^+ \]

\[ \text{NADH} \]
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

\[
\text{Cytidine deaminase} \quad \xrightarrow{\text{cytidine deaminase}} \quad \text{Uridine}
\]

A phosphorylase removes the sugar

\[
\text{pyrimidine phosphorylase} \quad \xrightarrow{\text{pyrimidine phosphorylase}} \quad \text{thymine} + \text{deoxyribose-1-phosphate}
\]

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:

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

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

* Depicted is the metabolic pathway of 5-FU (5-fluorouracil) that leads to the formation of FdUMP (fluorodeoxyuridine monophosphate), which inhibits thymidylate synthase (TS) activity.

* 5-FU is converted to FdUMP via a series of enzymatic reactions:
  - 5-FU is phosphorylated by pyrimidine phosphorylase to form 5-fluorodeoxyuridine (FdUMP).
  - Thymidylate synthase then catalyzes the conversion of FdUMP to deoxythymidine monophosphate (dTMP), with the degradation product being dihydropyrimidine (DPD).

* DPD inhibitors can potentiate 5FU activity by inhibiting the degradation of FdUMP.
Capecitabine mode of action:

Cytosine arabinoside (araC) activation and inactivation: