2007-09

M1 - Renal, Fall 2007

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<http://hdl.handle.net/2027.42/64946>  
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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 Adenosine reaction diagram]

Inosine monophosphate + GTP → GDP + P_i + aspartate + fumarate → Adenosine monophosphate

Conversion to Guanosine:

![Conversion to Guanosine reaction diagram]

Inosine monophosphate + NAD^+ → NADH + H^+ + Xanthosine monophosphate
Xanthosine monophosphate + H_2O + ATP + AMP + P_i → Guanosine monophosphate + glu
Nucleoside Monophosphate Kinases

AMP + ATP  $\leftrightarrow$  2ADP  \hspace{1cm} \text{(adenylate kinase)}

GMP + ATP  $\leftrightarrow$  GDP + ADP  \hspace{1cm} \text{(guanylate kinase)}

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

Hydroxyurea inhibits this enzyme: chemotherapeutic use

\[
\begin{align*}
\text{O} \\
\text{HONH}^- \text{C}^- \text{NH}_2
\end{align*}
\]
Regulation of Ribonucleotide Reductase

- CDP + ATP → dCDP → dCTP
- UDP + ATP → dUDP → dTTP
- GDP + ATP → dGDP → dGTP
- ADP + ATP → dADP → dATP
Nucleoside Diphosphate Kinase

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

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

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

PRPP

↑

IMP

ATP

GMP

GTP

AMP

GTP

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

- **Adenosine**
  - $\text{H}_2\text{O} + \text{NH}_4^+$
  - Adenosine deaminase (ADA)

- **Inosine**
  - $\text{p}_i$
  - Ribose-1-P
  - Purine nucleoside phosphorylase

- **Hypoxanthine**
  - Xanthine oxidase

- **Guanosine**
  - $\text{p}_i$
  - Ribose-1-P
  - Purine nucleoside phosphorylase

- **Guanine**
  - $\text{H}_2\text{O}$
  - $\text{NH}_4^+$
  - Guanine deaminase

- **Xanthine**
  - Xanthine oxidase

- **Uric acid**
“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 → 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...

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

...used for pyrimidine synthesis

[Chemical reactions and structures showing the conversion from carbamoyl phosphate and aspartate to 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)

N<sup>5</sup>, N<sup>10</sup> methylene tetrahydrofolate

dihydrofolate

DHFR

NADH

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 \rightarrow \text{FdUMP} + \text{methylene-THF} + \text{Thymidylate Synthase} \\
\quad \rightarrow \text{inactivation of TS}

Degradation
(via dihydroptopyrimidine dehydrogenase, DPD)

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

Cytosine arabinoside (araC) activation and inactivation: