2007-09

M1 - Renal, Fall 2007

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<http://hdl.handle.net/2027.42/64946>
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Formation of PRPP: Phosphoribose pyrophosphate

\[
\text{ribose - 5 - phosphate} \xrightarrow{\text{ATP}} \text{AMP} \xrightarrow{\text{AMP}} \text{phosphoribose - 1 pyrophosphate}
\]

PRPP Use in Purine Biosynthesis:

\[
\text{phosphoribose - 1 pyrophosphate} \xrightarrow{\text{glutamine}} \text{glutamate} \xrightarrow{\text{H}_2\text{O}} \text{NH}_2
\]
The First Purine: Inosine Monophosphate
(folates are involved in this synthesis)

Conversion to Adenosine:

\[
\text{Inosine monophosphate} \rightarrow \text{GTP} \rightarrow \text{GDP + P}_i \rightarrow \text{Adenosine monophosphate}
\]

Conversion to Guanosine:

\[
\text{Inosine monophosphate} \rightarrow \text{NAD}^+ \rightarrow \text{NADH + H}^+ \rightarrow \text{Xanthosine monophosphate} \rightarrow \text{Guanosine monophosphate}
\]
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

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

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

$N_1\text{DP} + N_2\text{TP} \leftrightarrow N_1\text{TP} + N_2\text{DP}$

d$N_1\text{DP} + N_2\text{TP} \leftrightarrow dN_1\text{TP} + N_2\text{DP}$

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

PRPP

IMP

GMP

GTP

AMP

ATP

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

Adenosine → Inosine → Hypoxanthine → Xanthine → Uric acid

Adenosine deaminase (ADA) → Inosine

Putative nucleoside phosphorylase → Hypoxanthine

Guanosine → Guanine

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 → 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…

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

cARBAMOYL phosphate

…used for pyrimidine synthesis

cARBAMOYL phosphate + aspartate \rightarrow orotate
Orotate is linked to PRPP to form Uridine monophosphate:

\[
\text{orotate} \quad + \quad \text{phosphoribose - 1 pyrophosphate} \quad \rightarrow \quad \text{orotidine monophosphate} \quad \rightarrow \quad \text{uridine monophosphate}
\]
UTP can be converted to CTP by CTP Synthetase:

Newly-synthesized uridine monophosphate will be phosphorylated to UDP and UTP, as described for the purine nucleotides.
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 forming deoxythymidine monophosphate.
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 aciduria due to OTC deficiency - please review your Urea Cycle notes.

Hereditary orotic aciduria - 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

\[
\text{5-FU} \rightarrow \text{FdUMP} \rightarrow \text{inactivation of TS}
\]

Degradation
(via dihydropyrimidine dehydrogenase, DPD)

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

Cytosine arabinoside (araC) activation and inactivation: