M1 - Renal, Fall 2007

Lyons, R.; Burney, R.

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

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

PRPP Use in Purine Biosynthesis:

\[
\begin{align*}
\text{phosphoribose - 1 pyrophosphate} & \quad \xrightarrow{\text{glutamine, glutamate}} \quad \text{glutamate} \\
\text{H}_2\text{O} & \quad \xrightarrow{\text{AMP}} \quad \text{phosphoribose - 1 pyrophosphate} \\
\end{align*}
\]
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

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

CDP → dCDP → dCTP

UDP → dUDP → dTTP

GDP → dGDP → dGTP

ADP → dADP → dATP
Nucleoside Diphosphate Kinase

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

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

- 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

PRPP

IMP

ATP + GTP

GMP + AMP

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

- Adenosine
- Inosine
- Hypoxanthine
- Guanosine
- Guanine
- Xanthine
- 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 → Hypoxanthine

2-deoxyribose

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...

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

carbamoyl phosphate

...used for pyrimidine synthesis

\[
\begin{align*}
\text{NH}_2\text{C} = \text{O}\text{O}^{2-} & \quad + \\
\text{O}^-\text{C} - \text{CH}_2 & \quad \rightarrow \\
\text{NH}_3 & \quad \rightarrow \\
\text{O}^-\text{C} - \text{CH}_2 & \quad \rightarrow \\
\text{O}^-\text{C} - \text{N} & \quad \rightarrow \\
\text{O}^-\text{C} - \text{N} & \quad \rightarrow \\
\text{HN} & \quad \rightarrow \\
\text{O} & \quad \rightarrow
\end{align*}
\]

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:
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
(NO 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

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

Degradation (via dihydopyrimidine dehydrogenase, DPD)

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

Cytosine arabinoside (araC) activation and inactivation: