M1 - Renal, Fall 2007

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Formation of PRPP: Phosphoribose pyrophosphate

\[ \text{PRPP Use in Purine Biosynthesis:} \]

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The First Purine: Inosine Monophosphate
(folates are involved in this synthesis)

Conversion to Adenosine:

Conversion to Guanosine:
Nucleoside Monophosphate Kinases

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

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

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

Hydroxyurea inhibits this enzyme: chemotherapeutic use

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

\[ \text{N}_1\text{DP} + \text{N}_2\text{TP} \Leftrightarrow \text{N}_1\text{TP} + \text{N}_2\text{DP} \]

\[ \text{dN}_1\text{DP} + \text{N}_2\text{TP} \Leftrightarrow \text{dN}_1\text{TP} + \text{N}_2\text{DP} \]

- No specificity for base
- No specificity for ribo vs deoxy
Feed-forward regulation by PRPP
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Degradation of the Purine Nucleosides:

Adenosine $\xrightarrow{\text{H}_2\text{O}, +\text{NH}_4}^{\text{Adenosine deaminase (ADA)}}$ Inosine $\xrightarrow{\text{p}_i, \text{ribose-1-P}}$ Hypoxanthine

Inosine $\xrightarrow{\text{purine nucleoside phosphorylase}}$ Guanosine $\xrightarrow{\text{p}_i, \text{ribose-1-P}}$ Guanine $\xrightarrow{\text{Guanine deaminase}}$ Xanthine $\xrightarrow{\text{xanthine oxidase}}$ 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

Deoxyinosine → Guanine → Xanthine

Hypoxanthine → 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

\[
\begin{align*}
\text{carbamoyl phosphate} & \quad + \quad \text{aspartate} \\
\text{orotate} & \quad \rightarrow \quad \text{NH}_2\text{C} = \text{O} \text{C} = \text{NH} \quad \rightarrow \quad \text{NH}_2\text{C} = \text{O} \text{C} = \text{NH} \\
\end{align*}
\]
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)

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

\[ \text{dihydrofolate} \]

\[ \text{DHFR} \] 

\[ \text{NADH} \]

\[ \text{NAD}^+ \] 

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 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:

Acyclovir \[\rightarrow\] AcycloGMP

5-fluorouracil + deoxyribose-1-phosphate \[\rightarrow\] fluorodeoxyuridine \[\rightarrow\] fluorodeoxyuridine monophosphate (FdUMP)
5-FU efficacy depends on rate of degradation vs activation

\[
\begin{align*}
\text{5-FU} & \rightarrow \quad \text{FdUMP} \\
& + \text{methylene-THF} + \text{Thymidylate Synthase} \\
& \quad \rightarrow \text{inactivation of TS}
\end{align*}
\]

Degradation
(via dihydropyrimidine dehydrogenase, DPD)

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

Cytosine arabinoside (araC) activation and inactivation: