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M1 - Renal, Fall 2007

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Viewer discretion advised: Material may contain medical images that may be disturbing to some viewers.
Formation of PRPP: Phosphoribose pyrophosphate

![Diagram of ribose-5-phosphate and ATP forming phosphoribosylpyrophosphate]

PRPP Use in Purine Biosynthesis:

![Diagram of phosphoribosylpyrophosphate reacting with glutamine to form glutamate]

H₂O

NH₂
The First Purine: Inosine Monophosphate
(folates are involved in this synthesis)

Conversion to Adenosine:

Conversion to Guanosine:
Nucleoside Monophosphate Kinases

AMP + ATP $\rightleftharpoons$ 2ADP  (adenylate kinase)

GMP + ATP $\rightleftharpoons$ 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 + ATP → dCDP → dCTP

UDP + ATP → dUDP → dTTP

GDP + dGDP → dGTP

ADP + ATP → dATP
Nucleoside Diphosphatase Kinase

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

\[ dN_1\text{DP} + N_2\text{TP} \rightleftharpoons dN_1\text{TP} + N_2\text{DP} \]

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

PRPP
\[\downarrow\]
IMP
\[\downarrow\]
GMP
\[\downarrow\]
GTP
AMP
\[\downarrow\]
ATP
Feed-forward regulation by PRPP
Feed-forward regulation by PRPP
Feed-forward regulation by PRPP
Degradation of the Purine Nucleosides:

Adenosine $\xrightarrow{\text{H}_2\text{O}}$ Inosine $\xrightarrow{\text{NH}_4^+} \text{Hypoxanthine}$

$\xrightarrow{\text{Adenosine deaminase (ADA)}}$ $\xrightarrow{\text{purine nucleoside phosphorylase}}$ $\xrightarrow{xanthine oxidase}$

Guanosine $\xrightarrow{\text{purine nucleoside phosphorylase}}$ Guanine $\xrightarrow{xanthine oxidase}$ Uric acid

$\xrightarrow{\text{Guanine deaminase}}$
“Salvage” Pathways for Purine Nucleotides

<table>
<thead>
<tr>
<th>Hypoxanthine</th>
<th>PRPP</th>
<th>Hypoxanthine-guanine phosphoribosyl transferase</th>
<th>Inosine monophosphate</th>
</tr>
</thead>
<tbody>
<tr>
<td>HN</td>
<td>O</td>
<td>O</td>
<td>HN</td>
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APRT - Adenine phosphoribosyl transferase - performs a similar function with adenine.
Adenosine Deaminase Deficiency:

Deoxyadenosine → dAMP → dADP → dATP

Adenosine deaminase (ADA)

2-deoxyribose → Deoxyinosine

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...  

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

...used for pyrimidine synthesis

\[\text{carbamoyl phosphate} + \text{aspartate} \rightarrow \text{orotate}\]
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)

\[ \text{FdUMP} \rightarrow \text{thymidylate synthase} \rightarrow \text{deoxythymidine monophosphate} \]

N\textsubscript{5}, N\textsubscript{10} methylene tetrahydrofolate dihydrofolate

\[ \text{DHFR} \rightarrow \text{NADH} \rightarrow \text{NAD}^+ \]

methylenedonor

THF
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 $\rightarrow$ thymidine
(NOT thymidine monophosphate!)

Enzyme: Thymidine kinase - adds the monophosphate back
Thymidine + ATP $\rightarrow$ thymidine monophosphate

Herpes Simplex Virus carries its own tk gene
Certain drugs act via the pyrimidine salvage pathway:

Acyclovir $\xrightarrow{HSV\text{ thymidine kinase}}$ AcycloGMP

5-fluorouracil + deoxyribose-1-phosphate $\xrightarrow{\text{pyrimidine phosphorylase}}$ fluorodeoxyuridine $\xrightarrow{\text{uridine kinase}}$ fluorodeoxyuridine monophosphate (FdUMP)
5-FU efficacy depends on rate of degradation vs activation

5-FU \rightarrow \text{FDUMP} + \text{methylene-THF} + \text{Thymidylate Synthase} \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: