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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

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

Conversion to Adenosine:

\[
\begin{align*}
\text{Inosine monophosphate} & \quad \xrightarrow{\text{GTP}} \quad \text{GDP} + \text{P}_i \\
\text{aspartate} & \quad \xrightarrow{\text{fumarate}} \\
\text{Inosine monophosphate} & \quad \xrightarrow{\text{GTP}} \quad \text{Adenosine monophosphate}
\end{align*}
\]

Conversion to Guanosine:

\[
\begin{align*}
\text{Inosine monophosphate} & \quad \xrightarrow{\text{NAD}^+} \quad \text{NADH} + \text{H}^+ \\
\text{Inosine monophosphate} & \quad \xrightarrow{\text{ATP}} \quad \text{AMP} + \text{PP}_i \\
\text{Inosine monophosphate} & \quad \xrightarrow{\text{glu}} \\
\text{Inosine monophosphate} & \quad \xrightarrow{\text{glu}} \quad \text{Guanosine monophosphate}
\end{align*}
\]
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
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

GMP

GTP

AMP

ATP

GTP
Feed-forward regulation by PRPP
Feed-forward regulation by PRPP

PRPP

IMP

ATP +

GMP

AMP

GTP +

ATP

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

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

Inosine $\xrightarrow{\text{phosphorylase}} \text{Hypoxanthine}$

Hypoxanthine $\xrightarrow{\text{oxidase}} \text{Xanthine}$

Guanosine $\xrightarrow{\text{phosphorylase}} \text{Guanine}$

Xanthine $\xrightarrow{\text{oxidase}} \text{Uric acid}$
“Salvage” Pathways for Purine Nucleotides

APRT - Adenine phosphoribosyl transferase - performs a similar function with adenine.
Adenosine Deaminase Deficiency:

Deoxyadenosine → Adenosine deaminase (ADA) → Deoxynosine → Hypoxanthine

Deoxynosine → 2-deoxyribose

Hypoxanthine → Guanine → Xanthine → Uric acid

dAMP → dADP → dATP
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... 

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

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)

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

\[ \text{thymidylate synthase} \rightarrow \text{dihydrofolate} \]

\[ \text{dihydrofolate} \rightarrow \text{tetrahydrofolate} \]

\[ \text{tetrahydrofolate} \rightarrow \text{methylenetetrahydrofolate} \]

\[ \text{methylenetetrahydrofolate} \rightarrow \text{methylene donor} \]

\[ \text{methylene donor} \rightarrow \text{THF} \]

\[ \text{THF} \rightarrow \text{DHFR} \]

\[ \text{DHFR} \rightarrow \text{NADH} \]

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

![Chemical structures of cytidine and uridine](image)

A phosphorylase removes the sugar

![Chemical structures of thymine, deoxythymidine, and deoxyribose-1-phosphate](image)

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

5-fluorouracil $\xrightarrow{\text{pyrimidine phosphorylase}} $ fluorodeoxyuridine $\xrightarrow{\text{uridine kinase}} $ 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 dihydroxpyrimidine dehydrogenase, DPD)

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

Cytosine arabinoside (araC) activation and inactivation: