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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:

\[
\text{Inosine monophosphate} \xrightarrow{\text{aspartate, fumarate}} \text{GTP} \xrightarrow{\text{GDP + P}_i} \text{Adenosine monophosphate}
\]

Conversion to Guanosine:

\[
\text{Inosine monophosphate} \xrightarrow{\text{NAD}^+, \text{NADH} + \text{H}^+} \text{Xanthosine monophosphate} \xrightarrow{\text{glutamine}} \text{Guanosine monophosphate}
\]
Nucleoside Monophosphate Kinases

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

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

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

Hydroxyurea inhibits this enzyme: chemotherapeutic use

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

CDP + ATP → dCDP → dCTP

UDP + ATP → dUDP → dTTP

GDP → dGDP → dGTP

ADP → dADP → dATP
Nucleoside Diphosphate Kinase

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

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

• 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
ATP +

AMP
GTP +

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

Adenosine

\[ \text{Adenosine deaminase (ADA)} \]

Inosine

\[ \text{purine nucleoside phosphorylase} \]

Hypoxanthine

\[ \text{xanthine oxidase} \]

Guanosine

\[ \text{purine nucleoside phosphorylase} \]

Guanine

\[ \text{Guanine deaminase} \]

Xanthine

\[ \text{xanthine oxidase} \]

Uric acid
"Salvage" Pathways for Purine Nucleotides

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

Deoxyadenosine → Adenosine deaminase (ADA) → Deoxyinosine → 2-deoxyribose → Hypoxanthine

Deoxyadenosine → 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...**

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

...used for pyrimidine synthesis

![Chemical reaction and structures]

- **Carbamoyl phosphate**
- **Aspartate**
- **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 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:

[Diagram showing the conversion of Acyclovir to AcycloGMP and the conversion of 5-fluorouracil to fluorodeoxyuridine monophosphate (FdUMP).]
5-FU efficacy depends on rate of degradation vs activation

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

Degradation
(via dihydropyrimidine dehydrogenase, DPD)

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

Cytosine arabinoside (araC) activation and inactivation: