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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:

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

\[
\begin{align*}
\text{Ribonucleotide Reductase} \\
\text{Hydroxyurea inhibits this enzyme: chemotherapeutic use}
\end{align*}
\]

\[
\begin{align*}
\text{Ribonucleotide Reductase} \\
\text{Hydroxyurea inhibits this enzyme: chemotherapeutic use}
\end{align*}
\]
Regulation of Ribonucleotide Reductase
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

- **PRPP**
  - **IMP**
    - **GMP**
      - GTP
    - **AMP**
      - ATP
Feed-forward regulation by PRPP

PRPP → IMP → GMP, ATP, GTP → AMP, GTP, ATP
Feed-forward regulation by PRPP
Feed-forward regulation by PRPP
Degradation of the Purine Nucleosides:

1. Adenosine → Inosine
   - Adenosine deaminase (ADA)
   - Purine nucleoside phosphorylase
2. Inosine → Hypoxanthine
   - Xanthine oxidase
3. Guanosine
4. Guanine
   - Guanine deaminase
   - Xanthine oxidase
5. 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...

$$2\text{ATP} + \text{HCO}_3^- + \text{glutamine} + \text{H}_2\text{O} \rightarrow \text{NH}_2\text{C}\text{OPO}_4^{2-} + \text{glutamate} + 2\text{ADP} + \text{P}_i$$

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:
The Thymidylate Synthase Reaction:

Some UDP is converted to dUDP via ribonucleotide reductase.
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)

\[ \text{thymidylate synthase} \]

\[ \text{dihydrofolate} \]

DHFR

NADH

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 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:

[Chemical diagrams of Acyclovir, thymidine kinase, AcycloGMP, 5-fluorouracil, deoxyribose-1-phosphate, fluorodeoxyuridine, and fluorodeoxyuridine monophosphate (FdUMP)]
5-FU efficacy depends on rate of degradation vs activation

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

Degradation
(via dihydropyrimidine dehydrogenase, DPD)

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

Cytosine arabinoside (araC) activation and inactivation: