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M1 - Renal, Fall 2007

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Nucleic Acid metabolism

Click on any blue rectangle to see details.

- **Purine Salvage**
  - IMP
  - Purine MP
  - dNTP
  - NTP
  - Uric Acid
  - Purine Degradation

- **Pyrimidine Salvage**
  - OMP
  - Pyrimidine MP
  - dNTP
  - NTP
  - Pyrimidine Degradation

**Carbamoyl Phosphate**
- *Pyrimidine Biochemistry*
- *Purine Biochemistry*
- *Ribonucleotide reductase*
- *DNA*
- *RNA*
- *Energy*
Formation of PRPP: Phosphoribose pyrophosphate

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

Conversion to Adenosine:

Inosine monophosphate → Adenosine monophosphate
Inosine monophosphate → GDP + P_i
GTP → GDP + P_i
Aspartate → fumarate

Conversion to Guanosine:

Inosine monophosphate → Xanthosine monophosphate
Xanthosine monophosphate → Guanosine monophosphate
Inosine monophosphate → AMP + P_i
Glu → AMP + P_i
ATP → AMP + P_i
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

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

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

- No specificity for base
- No specificity for ribo vs deoxy
Feed-forward regulation by PRPP
Feed-forward regulation by PRPP
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Degradation of the Purine Nucleosides:
“Salvage” Pathways for Purine Nucleotides

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

Deoxyadenosine → Adenosine deaminase (ADA) → Deoxyinosine → Hypoxanthine

Deoxyinosine → 2-deoxyribose → 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...

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

carbamoyl phosphate

...used for pyrimidine synthesis

\[ \text{carbamoyl phosphate} + \text{aspartate} \rightarrow \text{orotate} \]
Orotate is linked to PRPP to form Uridine monophosphatate:
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:
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 $\rightarrow$ 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:

\[
\text{Acyclovir} \xrightarrow{\text{HSV thymidine kinase}} \text{AcycloGMP}
\]

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

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

Degradation
(via dihydropyrimidine dehydrogenase, DPD)

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

Cytosine arabinoside (araC) activation and inactivation: