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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
  - Purine Degradation
  - Uric Acid

- **Purine Biosynthesis**
  - amino acids, folate
  - PRPP
  - IMP
  - Purine MP
  - dNTP
  - NTP

- **Pyrimidine Biosynthesis**
  - Carbamoyl Phosphate
  - OMP
  - Pyrimidine MP
  - Ribonucleotide reductase
  - DNA
  - RNA
  - dNTP
  - NTP

- **Pyrimidine Salvage**
  - Pyrimidine Degradation
  - (energy)
Formation of PRPP: Phosphoribose pyrophosphate

\[
\begin{align*}
\text{ribose - 5 - phosphate} & \quad \xrightarrow{\text{ATP, AMP}} \quad \text{phosphoribose - 1 pyrophosphate} \\
\end{align*}
\]

PRPP Use in Purine Biosynthesis:

\[
\begin{align*}
\text{phosphoribose - 1 pyrophosphate} & \quad \xrightarrow{\text{glutamine, glutamate}} \quad \text{glutamine, glutamate} \\
\end{align*}
\]
The First Purine: Inosine Monophosphate
(folates are involved in this synthesis)

Conversion to Adenosine:

Conversion to Guanosine:
Nucleoside Monophosphate Kinases

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

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

- 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
Nucleoside Diphosphate Kinase

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

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

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

PRPP

IMP

ATP
GMP
GTP

GTP

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

1. Adenosine → Inosine → Hypoxanthine
   - Adenosine deaminase (ADA)

2. Inosine → Guanine
   - Purine nucleoside phosphorylase

3. Guanine → Xanthine
   - Guanine deaminase

4. Xanthine → Uric acid
   - Xanthine oxidase
“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)

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...

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

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) is converted by thymidylate synthase to deoxythymidine monophosphate.
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

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:

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

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

5-FU \rightarrow \text{Degradation (via dihydropyrimidine dehydrogenase, DPD)} \rightarrow FdUMP + \text{methylene-THF} + \text{Thymidylate Synthase} \rightarrow \text{inactivation of TS}

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

Cytosine arabinoside (araC) activation and inactivation: