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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**
  - PRPP
  - Amino acids, folate
  - dNTP
  - NTP

- **Pyrimidine Biosynthesis**
  - Carbamoyl Phosphate
  - OMP
  - Pyrimidine MP
  - Pyrimidine Degradation

- **Pyrimidine Salvage**
  - dNTP
  - NTP
  - DNA
  - RNA
  - (energy)

- **Ribonucleotide reductase**
Formation of PRPP: Phosphoribose pyrophosphate

\[
\text{ribose - 5 - phosphate} \quad \xrightarrow{\text{ATP, AMP}} \quad \text{phosphoribose - 1 pyrophosphate}
\]

PRPP Use in Purine Biosynthesis:

\[
\text{phosphoribose - 1 pyrophosphate} \quad \xrightarrow{\text{glutamine, glutamate}} \quad \text{glutamine} \quad \xrightarrow{\text{H}_2\text{O}} \quad \text{glutamate}
\]
The First Purine: Inosine Monophosphate
(folates are involved in this synthesis)

Conversion to Adenosine:

Inosine monophosphate → Adenosine monophosphate

Conversion to Guanosine:

Inosine monophosphate → Xanthosine monophosphate → Guanosine monophosphate
Nucleoside Monophosphate Kinases

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

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

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

Hydroxyurea inhibits this enzyme: chemotherapeutic use

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

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

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

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

PRPP

↓

IMP

↓

GTP

↓

AMP

↓

GTP

↓

ATP

↓

GTP

↓

ATP
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
  - $\text{NH}_2$
  - $\text{H}_2\text{O}$
  - $\text{NH}_4^+$
  - $\text{Adenosine deaminase (ADA)}$
  - $\text{ribose}$
  - $\rightarrow$
  - $\text{Inosine}$
  - $\text{ribose}$
  - $\rightarrow$
  - $\text{Hypoxanthine}$
  - $\text{purine nucleoside phosphorylase}$
  - $\text{p}_i$
  - $\text{ribose - 1 - p}$

- Guanosine
  - $\text{NH}_2$
  - $\text{H}_2\text{O}$
  - $\text{NH}_4^+$
  - $\text{purine nucleoside phosphorylase}$
  - $\text{p}_i$
  - $\text{ribose - 1 - p}$
  - $\rightarrow$
  - $\text{Guanine}$
  - $\text{Guanine deaminase}$
  - $\text{NH}_2$
  - $\text{H}_2\text{O}$
  - $\text{NH}_4^+$
  - $\rightarrow$
  - $\text{Xanthine}$
  - $\text{xanthine oxidase}$
  - $\rightarrow$
  - $\text{Uric acid}$
“Salvage” Pathways for Purine Nucleotides

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

![Chemical Reaction Diagram](image-url)
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...

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

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)

\[ \text{thymidylate synthase} \rightarrow \text{dihydrofolate} \rightarrow \text{deoxythymidine monophosphate} \]
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 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:

- Acyclovir
- AcycloGMP
- 5-fluorouracil
- deoxyribose-1-phosphate
- fluorodeoxyuridine
- fluorodeoxyuridine monophosphate (FdUMP)
5-FU efficacy depends on rate of degradation vs activation

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

Degradation
(via dihydropyrimidine dehydrogenase, DPD)

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

Cytosine arabinoside (araC) activation and inactivation: