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M1 - Renal, Fall 2007

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Amino Acid metabolism

- Amino acids
  - Glu, Gln, Asp, NH₃
  - Urea

TCA Cycle
- oxaloacetate
  - fumarate

Folate metabolism
- Methylene THF
  - Met Cycle

Nucleic Acid metabolism
- Purines
  - DNA
  - RNA
  - Pyrimidines
  - Uric Acid
  - (energy)
Nucleic Acid metabolism

Click on any blue rectangle to see details.

Purine Salvage

- amino acids, folate
  - IMP

Purine Biosynthesis

- PRPP
- Ribonucleotide reductase
- dNTP
- NTP

Purine MP

Purine Degradation

- Uric Acid
- NH₄

Pyrimidine Biosynthesis

- Carboxamoyl Phosphate
- OMP
- Pyrimidine MP

Pyrimidine Salvage

- DNA
- RNA
- dNTP
- NTP

Pyrimidine Degradation

(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:

Conversion to Guanosine:
Nucleoside Monophosphate Kinases

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

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

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

Hydroxyurea inhibits this enzyme: chemotherapeutic use

\[
\text{HONH}^-\text{C-NH}_2
\]
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

ATP

GMP

GTP

AMP

GTP

ATP
Feed-forward regulation by PRPP

[Diagram of biochemical pathways involving PRPP, IMP, GMP, AMP, GTP, and ATP]
Feed-forward regulation by PRPP
Feed-forward regulation by PRPP
Degradation of the Purine Nucleosides:

Adenosine → Inosine → Hypoxanthine → Xanthine → Uric acid

- Adenosine deaminase (ADA)
- Purine nucleoside phosphorylase
- Guanine deaminase
- Xanthine oxidase

Chemical structures and reactions depicted in the diagram.
“Salvage” Pathways for Purine Nucleotides

\[
\text{Hypoxanthine} + \text{PRPP} \rightarrow \text{Inosine monophosphate} + \text{PP}_i
\]

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

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...

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

...used for pyrimidine synthesis

![Chemical reaction diagram](attachment:image.png)
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)

thymidylate synthase

N5, N10-methylene tetrahydrofolate

dihydrofolate

methylene donor

THF

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  --> 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:

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

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

5-FU \rightarrow \text{FdUMP} \rightarrow \text{inactivation of TS}

Degradation
(via dihydroxyridine dehydrogenase, DPD)

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

Cytosine arabinoside (araC) activation and inactivation: