M1 - Renal, Fall 2007

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Nucleic Acid metabolism
Click on any blue rectangle to see details.

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

- **Purine Biosynthesis**
  - PRPP
  - amino acids, folate

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

- **Ribonucleotide reductase**
  - dNTP
  - DNA
  - RNA
  - NTP

(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

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

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

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

Hydroxyurea inhibits this enzyme: chemotherapeutic use

\[
O
\]

\[
HONH^- C - NH_2
\]
Regulation of Ribonucleotide Reductase
Nucleoside Diphosphate Kinase

\[ \text{N}_1\text{DP} + \text{N}_2\text{TP} \leftrightarrow \text{N}_1\text{TP} + \text{N}_2\text{DP} \]

\[ \text{dN}_1\text{DP} + \text{N}_2\text{TP} \leftrightarrow \text{dN}_1\text{TP} + \text{N}_2\text{DP} \]

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

PRPP

↓

IMP

GTP

↓

AMP

ATP

GTP

↓

GMP

↓

PRPP
Feed-forward regulation by PRPP
Feed-forward regulation by PRPP

PRPP → IMP

IMP → ATP, GTP

GMP → IMP

AMP → IMP

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

Adenosine $\rightarrow$ Inosine $\rightarrow$ Hypoxanthine $\rightarrow$ Xanthine $\rightarrow$ Uric acid

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

Chemical structures and reactions are shown for each step.
“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 → 2-deoxyribose → 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…

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

(carbamoyl phosphate)

…used for pyrimidine synthesis

(carbamoyl phosphate) + (aspartate) → (orotate)
Orotate is linked to PRPP to form Uridine monophosphate:

\[
\text{orotate} + \text{phosphoribose - 1 pyrophosphate} \rightarrow \text{orotidine monophosphate} \rightarrow \text{uridine monophosphate}
\]
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)

\[ \text{FdUMP} \]

5-fluorodeoxyuridine monophosphate

\[ \text{FdUMP} \]

5-fluorodeoxyuridine monophosphate

\[ \text{FdUMP} \]

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\[ \text{FdUMP} \]

5-fluorodeoxyuridine monophosphate

\[ \text{FdUMP} \]
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:

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

5-fluorouracil $\xrightarrow{\text{pyrimidine phosphorylase}}$ fluorodeoxyuridine $\xrightarrow{\text{uridine kinase}}$ fluorodeoxyuridine monophosphate (FdUMP)
5-FU efficacy depends on rate of degradation vs activation

![Chemical diagram showing the conversion of 5-FU to FdUMP and the inactivation of Thymidylate Synthase (TS) due to DPD inhibition.]

5-FU $\rightarrow$ FdUMP $\rightarrow$ inactivation of TS

Degradation
(via dihydropyrimidine dehydrogenase, DPD)

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

![Chemical structure of capecitabine and its transformation into fluorouracil]

Cytosine arabinoside (araC) activation and inactivation:

![Chemical structures of uridine arabinoside, cytosine arabinoside, and cytosine arabinoside monophosphate, with associated enzymes and transformations]