M1 - Renal, Fall 2007

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Amino Acid metabolism

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

Folate metabolism

- Methylene THF
  - Met Cyrcle

TCA Cycle

- oxaloacetate
  - fumarate

Nucleic Acid metabolism

- Purines
- DNA
- RNA
- Pyrimidines
- Uric Acid
- (energy)
Nucleic Acid metabolism
Click on any blue rectangle to see details.

- Amino acids, folate
- PRPP

Purine Salvage

IMP

Purine Biosynthesis

- Carbamoyl Phosphate
- Pyrimidine Biosynthesis

OMP

Pyrimidine MP

- Ribonucleotide reductase
- DNA
- RNA
- dNTP
- NTP

Purine MP

- dNTP
- NTP

Purine MP

- Ribonucleotide reductase

Purine Degradation

- Uric Acid
- NH₄

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

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

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

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

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

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

PRPP

↓

IMP

↓

GTP

ATP

AMP

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

Adenosine → Inosine → Hypoxanthine

Guanosine → Guanine → Xanthine → Uric acid
“Salvage” Pathways for Purine Nucleotides

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

Deoxyadenosine → dAMP → dADP → dATP

Insufficient Adenosine deaminase (ADA) leads to:

Deoxynosine → 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

\[ \text{carbamoyl phosphate} + \text{aspartate} \rightarrow \text{orotate} \]
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:
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

\[
\text{Cytidine} \xrightarrow{\text{cytidine deaminase}} \text{Uridine}
\]

A phosphorylase removes the sugar

\[
\text{Thymine} + \text{deoxyribose-1-phosphate} \xleftarrow{\text{pyrimidine phosphorylase}} \text{deoxycytidine}
\]

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 $\rightarrow$ AcycloGMP

$5'$-fluorouracil + deoxyribose-1-phosphate $\rightarrow$ fluorodeoxyuridine $\rightarrow$ fluorodeoxyuridine monophosphate (FdUMP)
5-FU efficacy depends on rate of degradation vs activation

5-FU → FdUMP
  + methylene-THF + Thymidylate Synthase
  --> inactivation of TS

Degradation
(via dihydropyrimidine dehydrogenase, DPD)

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

Cytosine arabinoside (araC) activation and inactivation: