M1 - Renal, Fall 2007

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Amino Acid metabolism

Amino acids

Glu, Gln, Asp, NH₃

Urea

Folate metabolism

Met Cycle

Methylene THF

Nucleic Acid metabolism

Purines

DNA

RNA

Pyrimidines

Uric Acid

(energy)
Nucleic Acid metabolism
Click on any blue rectangle to see details.
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  $\rightleftharpoons$  2ADP  \hspace{1cm} \text{(adenylate kinase)}

GMP + ATP  $\rightleftharpoons$  GDP + ADP  \hspace{1cm} \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

Diagram:
- CDP + ATP → dCDP → dCTP
- UDP + ATP → dUDP → dTTP
- GDP → dGDP → dGTP
- ADP → dADP → dATP

Notes:
- ATP: Activating
- (-): Inhibiting

Nucleoside Diphosphate Kinase

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

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

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

PRPP

IMP

GMP

GTP

ATP

AMP

GTP

ATP
Feed-forward regulation by PRPP
Feed-forward regulation by PRPP
Feed-forward regulation by PRPP
Degradation of the Purine Nucleosides:
“Salvage” Pathways for Purine Nucleotides

Hypoxanthine + PRPP → Inosine monophosphate

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

Deoxyadenosine → dAMP → dADP → dATP

Adenosine deaminase (ADA)

Deoxyadenosine → Deoxyinosine → 2-deoxyribose → Hypoxanthine

Deoxyinosine → Guanine

Hypoxanthine → Xanthine

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...

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

carbamoyl phosphate

...used for pyrimidine synthesis

[Chemical structures of carbamoyl phosphate synthetase II and its reaction products]
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

N<sup>5</sup>, N<sup>10</sup> methylene tetrahydrofolate
dihydrofolate

methylenedonor

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 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:

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

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

![Chemical diagram showing the conversion of 5-FU to FdUMP and the subsequent interactions with Thymidylate Synthase.]

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

Degradation (via dihydropyrimidine dehydrogenase, DPD)

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

Cytosine arabinoside (araC) activation and inactivation: