M1 - Renal, Fall 2007

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Viewer discretion advised: Material may contain medical images that may be disturbing to some viewers.
Nucleic Acid metabolism
Click on any blue rectangle to see details.

Purine Salvage
- IMP
- Purine Biosynthesis
- PRPP
- Carbamoyl Phosphate
- OMP
- Pyrimidine Biosynthesis
- Pyrimidine MP
- Pyrimidine Degradation
- (energy)
- Uric Acid

Purine MP
- dNTP
- NTP
- Ribonucleotide reductase
- DNA
- RNA

Pyrimidine MP
- dNTP
- NTP
- Ribonucleotide reductase

Amino acids, folate

Click on any blue rectangle to see details.
Formation of PRPP: Phosphoribose pyrophosphate

\[ \text{Ribose - 5 - phosphate} \xrightarrow{\text{ATP}} \text{AMP} \rightarrow \text{phosphoribose - 1 pyrophosphate} \]

PRPP Use in Purine Biosynthesis:

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

Conversion to Adenosine:

Conversion to Guanosine:
Nucleoside Monophosphate Kinases

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

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

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

Hydroxyurea inhibits this enzyme: chemotherapeutic use

\[
\text{HONH}^-\text{C}^-\text{NH}_2
\]
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
Feed-forward regulation by PRPP
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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
“Salvage” Pathways for Purine Nucleotides

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

Deoxyadenosine → dAMP → dADP → dATP

Deoxyadenosine → Adenosine deaminase (ADA) → Deoxyinosine → 2-deoxyribose → Hypoxanthine

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 pyrimidin synthesis

\[ \text{carbamoyl phosphate} + \text{aspartate} \rightarrow \text{orotate} \]
Orotate is linked to PRPP to form Uridine monophosphate:
UTP can be converted to CTP by CTP Synthetase:

Newly-synthesized uridine monophosphate will be phosphorylated to UDP and UTP, as described for the purine nucleotides.
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) inhibits the thymidylate synthase reaction, preventing the conversion of deoxyuridine monophosphate to deoxythymidine monophosphate. This inhibition is achieved through the formation of a covalent complex with the enzyme, blocking its active site.

Key enzymatic steps:
1. Thymidylate synthase catalyzes the conversion of deoxyuridine monophosphate to deoxythymidine monophosphate.
2. Methylenetetrahydrofolate serves as a methyl group donor for the reaction.
3. DHFR (dihydrofolate reductase) reduces dihydrofolate to tetrahydrofolate, providing the methyl donor.
4. NADH is used as the reductant in the DHFR reaction.

Chemical structures:
- 5-fluorodeoxyuridine monophosphate (FdUMP)
- Deoxythymidine monophosphate
- Methylenetetrahydrofolate
- Dihydrofolate
- Tetrahydrofolate (THF)

Reactions:
- FdUMP + DHFR + NADH → DHFR + THF + NADH
- THF + Methylenetetrahydrofolate → Dihydrofolate + Methylene tetrahydrofolate
- Dihydrofolate + FdUMP → Thymidylate synthase + FdUMP
- Thymidylate synthase + Methylenetetrahydrofolate + NADH → Deoxythymidine monophosphate + DHFR + NADH
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 convet 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

\[
\text{(deoxy)thymidine} \xrightarrow{\text{pyrimidine phosphorylase}} \text{thymine} + \text{deoxyribose-1-phosphate}
\]

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:

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

\[
\text{5-fluorouracil} + \text{pyrimidine phosphorylase} \quad \text{fluorodeoxyuridine} \xrightarrow{\text{uridine kinase}} \text{fluorodeoxyuridine monophosphate (FdUMP)}
\]

\[
\text{deoxyribose-1-phosphate}
\]
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: