M1 - Renal, Fall 2007

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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

$$\text{AMP} + \text{ATP} \leftrightarrow 2\text{ADP}$$ \hspace{1cm} \text{(adenylate kinase)}

$$\text{GMP} + \text{ATP} \leftrightarrow \text{GDP} + \text{ADP}$$ \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
Nucleoside Diphosphate Kinase

\[ \text{N}_1\text{DP} + \text{N}_2\text{TP} \quad \text{<-->} \quad \text{N}_1\text{TP} + \text{N}_2\text{DP} \]

\[ \text{dN}_1\text{DP} + \text{N}_2\text{TP} \quad \text{<-->} \quad \text{dN}_1\text{TP} + \text{N}_2\text{DP} \]

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

PRPP

IMP

GMP  ATP

GTP

AMP  GTP

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

- Adenosine
  - Deaminated by Adenosine deaminase (ADA) to form Inosine.
  - Inosine is phosphorylated by ribose-1-phosphate to form Hypoxanthine.

- Guanosine
  - Phosphorylated by ribose-1-phosphate to form Guanine.
  - Guanine is deaminated to form Xanthine.
  - Xanthine is oxidized to form Uric acid.
“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

[Diagram showing the metabolic pathway involving myoadenylate deaminase, Adenosine monophosphate, Inosine monophosphate, Fumarate, and TCA Cycle.]
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:
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) inhibits the thymidylate synthase reaction. The reaction involves the conversion of FdUMP to deoxythymidine monophosphate. The enzyme thymidylate synthase is inhibited by FdUMP, which is a competitive inhibitor. The reaction also involves the conversion of dihydrofolate to tetrahydrofolate (THF) by DHFR, with NADH and NAD+ as co-factors.
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

\[
\text{thymine} + \text{deoxyribose-1-phosphate}
\]

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** (G) can be phosphorylated by HSV thymidine kinase to form AcycloGMP.

- **5-fluorouracil** and **deoxyribose-1-phosphate** can be phosphorylated by pyrimidine phosphorylase to form fluorodeoxyuridine.

- Fluorodeoxyuridine can be phosphorylated by uridine kinase to form fluorodeoxyuridine monophosphate (FdUMP).
5-FU efficacy depends on rate of degradation vs activation

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

Degradation
(via dihydropyrimidine dehydrogenase, DPD)

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

Cytosine arabinoside (araC) activation and inactivation: