M1 - Renal, Fall 2007

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

- Amino acids, folate → PRPP
- Purine Biosynthesis
- Carbamoyl Phosphate → OMP
- Pyrimidine Biosynthesis
- Pyrimidine MP
- DNA → RNA
- Purine MP → dNTP
- Uric Acid
- Pyrimidine Degradation
- (energy)

PRPP → IMP → Purine MP → dNTP → NTP → DNA → RNA → dNTP → NTP → Pyrimidine MP → Pyrimidine Degradation
Formation of PRPP: Phosphoribose pyrophosphate

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

PRPP Use in Purine Biosynthesis:

\[ \text{Phosphoribose - 1 pyrophosphate} + \text{Glutamine} \rightarrow \text{Glutamate} \rightarrow \text{NH}_2 \]
The First Purine: Inosine Monophosphate
(folates are involved in this synthesis)

Conversion to Adenosine:

\[
\text{Inosine monophosphate} \xrightarrow{\text{aspartate, fumarate}} \text{GTP} \xrightarrow{\text{GDP + P}_i} \text{Adenosine monophosphate}
\]

Conversion to Guanosine:

\[
\text{Inosine monophosphate} \xrightarrow{\text{NAD}^+, \text{NADH + H}^+} \text{Xanthosine monophosphate} \xrightarrow{\text{H}_2\text{O, ATP}} \text{AMP + PP}_i \xrightarrow{\text{glu, glu}} \text{Guanosine monophosphate}
\]
Nucleoside Monophosphate Kinases

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

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

- 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

PRPP

\[ \rightarrow \]

IMP

\[ \rightarrow \]

GMP
\[ \rightarrow \]

GTP

\[ \rightarrow \]

ATP

\[ \rightarrow \]

AMP
\[ \rightarrow \]

GTP
\[ \rightarrow \]

ATP

\[ \rightarrow \]
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

Xanthine → Uric acid

Adenosine deaminase (ADA) → Purine nucleoside phosphorylase → Guanine deaminase
“Salvage” Pathways for Purine Nucleotides

Hypoxanthine + PRPP → Inosine monophosphate

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

[Chemical structures and reactions]

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)

\[ \text{thymidylate synthase} \]

\[ \text{methylene tetrahydrofolate} \]

\[ \text{dihydrofolate} \]

\[ \text{DHFR} \]

\[ \text{NADH} \]

\[ \text{NAD}^+ \]

\[ \text{methylenedonor} \]

(deoxythymidine monophosphate)
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 $\rightarrow$ thymidine
(NOT thymidine monophosphate!)

Enzyme: Thymidine kinase - adds the monophosphate back
Thymidine + ATP $\rightarrow$ thymidine monophosphate

Herpes Simplex Virus carries its own tk gene
Certain drugs act via the pyrimidine salvage pathway:

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

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

Degradation
(via dihydropyrimidine dehydrogenase, DPD)

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

Cytosine arabinoside (araC) activation and inactivation: