M1 - Renal, Fall 2007

Lyons, R.; Burney, R.

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Nucleic Acid metabolism

Click on any blue rectangle to see details.

**Amino Acids, Folate**

- IMP
- Purine MP
- Purine Biosynthesis
  - Ribonucleotide reductase
  - dNTP
  - NTP

**PRPP**

**Carbamoyl Phosphate**

- OMP
- Pyrimidine Biosynthesis
  - Ribonucleotide reductase
  - dNTP

**Pyrimidine MP**

**Pyrimidine Salvage**

**DNA**

**RNA**

**NTP**

**Uric Acid**

**Purine Degradation**

**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:

\[
\text{Inosine monophosphate} \xrightarrow{\text{aspartate, fumarate}} \text{GTP} \xrightarrow{\text{GDP, P_i}} \text{Adenosine monophosphate}
\]

Conversion to Guanosine:

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

AMP + ATP   <--->   2ADP    (adenylate kinase)

GMP + ATP   <--->   GDP + ADP   (guanylate kinase)

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

Hydroxyurea inhibits this enzyme: chemotherapeutic use

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

\[ N_1DP + N_2TP \iff N_1TP + N_2DP \]

\[ dN_1DP + N_2TP \iff dN_1TP + N_2DP \]

- No specificity for base
- No specificity for ribo vs deoxy
Feed-forward regulation by PRPP
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Degradation of the Purine Nucleosides:

Adenosine

\[ \text{H}_{2}\text{O} \rightarrow \text{NH}_{4}^{+} \]

Adenosine deaminase (ADA)

Inosine

\[ \text{p}_{i} \rightarrow \text{ribose} - 1 - \text{P} \]

Putine nucleoside phosphorylase

Hypoxanthine

Xanthine oxidase

Guanosine

\[ \text{p}_{i} \rightarrow \text{ribose} - 1 - \text{P} \]

Putine nucleoside phosphorylase

Guanine

Xanthine oxidase

Xanthine

Uric acid
“Salvage” Pathways for Purine Nucleotides

Hypoxanthine + PRPP \[\xrightarrow{\text{Hypoxanthine-guanine phosphoribosyl transferase}}\] Inosine monophosphate + PP\(_i\)

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

Deoxyadenosine $\xrightarrow{\text{Adenosine deaminase (ADA)}}$ Deoxyinosine $\xrightarrow{\text{2-deoxyribose}}$ Hypoxanthine

Deoxyadenosine $\xrightarrow{}$ dAMP $\xrightarrow{}$ dADP $\xrightarrow{}$ dATP

Hypoxanthine $\xrightarrow{}$ Guanine $\xrightarrow{}$ Xanthine $\xrightarrow{}$ 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

Allopurinol inhibits xanthine oxidase and reduces blood uric acid levels:

Gout: deposition of urate crystals in joints, “tophi” in cooler periphery
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

Fumarate

To TCA Cycle

Adenosine monophosphate

myoadenylate deaminase

H$_2$O → NH$_3$

Inosine monophosphate

GDP + Pi

Asp, GTP

ribose-5-P

ribose-5-P
Carbamoyl phosphate synthetase II - a *cytoplasmic* enzyme...

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

...used for pyrimidine 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:
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

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

5-FU $\rightarrow$ FdUMP
+ methylene-THF + Thymidylate Synthase
$\rightarrow$ inactivation of TS

Degradation
(via dihydropyrimidine dehydrogenase, DPD)

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

Cytosine arabinoside (araC) activation and inactivation: