2007-09

M1 - Renal, Fall 2007

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<http://hdl.handle.net/2027.42/64946>
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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 MP
    - Ribonucleotide reductase
      - dNTP
      - NTP
  - Purine Degradation
    - NH₄

- **PRPP**

- **Pyrimidine Biosynthesis**
  - OMP
    - Pyrimidine MP
      - Ribonucleotide reductase
        - dNTP
        - NTP
  - Pyrimidine Degradation
    - (energy)

- **Carbamoyl Phosphate**
- **DNA**
- **RNA**
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

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

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

- 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

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

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

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

PRPP

↓

IMP

↓

GMP

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 $\xrightarrow{\text{H}_2\text{O}}$ Inosine $\xrightarrow{\text{NH}_4^+}$ Hypoxanthine

Guanosine $\xrightarrow{\text{p}_i, \text{ribose - 1 - P}}$ Guanine $\xrightarrow{\text{H}_2\text{O}, \text{NH}_4^+}$ Xanthine

Xanthine $\xrightarrow{\text{xanthine oxidase}}$ Uric acid
“Salvage” Pathways for Purine Nucleotides

Hypoxanthine + Inosine monophosphate

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

Deoxyadenosine → dAMP → dADP → dATP

Adenosine deaminase (ADA) → Deoxynosine → 2-deoxyribose

Deoxynosine → Hypoxanthine → Guanine

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...

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

...used for pyrimidine synthesis

\[
\begin{align*}
\text{carbamoyl phosphate} & \quad + \quad \text{aspartate} \\
\text{orotate}
\end{align*}
\]
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 Thymidylate Synthase Reaction:

- 5-fluorodeoxyuridine monophosphate (FdUMP)
- Thymidylate synthase
- Deoxothymidine monophosphate
- 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 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 $\rightarrow$ 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:

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

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

\[
\begin{align*}
5\text{-FU} & \rightarrow \text{deoxythymidine-1-phosphate} & \text{Pyrimidine phosphorylase} \\
 & \rightarrow \text{fluorodeoxyuridine} & \text{Thymidine kinase} \\
 & \rightarrow \text{fluorodeoxyuridine monophosphate (FdUMP)} & \\
\end{align*}
\]

\[
5\text{-FU} \quad \rightarrow \quad \text{FdUMP} \\
+ \text{methylene-THF} + \text{Thymidylate Synthase} \\
\rightarrow \text{inactivation of TS}
\]

Degradation
(via dihydropyrimidine dehydrogenase, DPD)

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

Cytosine arabinoside (araC) activation and inactivation: