2007-09

M1 - Renal, Fall 2007

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<http://hdl.handle.net/2027.42/64946>
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Nucleic Acid metabolism
Click on any blue rectangle to see details.
Formation of PRPP: Phosphoribose pyrophosphate

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

PRPP Use in Purine Biosynthesis:

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

Conversion to Adenosine:

Conversion to Guanosine:
Nucleoside Monophosphate Kinases

AMP + ATP  $\leftrightarrow$  2ADP  (adenylate kinase)

GMP + ATP  $\leftrightarrow$  GDP + ADP  (guanylate kinase)

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

Hydroxyurea inhibits this enzyme: chemotherapeutic use

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

\[ \text{N}_1\text{DP} + \text{N}_2\text{TP} \rightleftharpoons \text{N}_1\text{TP} + \text{N}_2\text{DP} \]

\[ \text{dN}_1\text{DP} + \text{N}_2\text{TP} \rightleftharpoons \text{dN}_1\text{TP} + \text{N}_2\text{DP} \]

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

- Adenosine
  - $\text{NH}_2$
  - $\text{H}_2\text{O}$
  - $\text{NH}_4^+$
  - Adenosine deaminase (ADA)
  - Inosine
  - $\text{NH}_2$
  - Purine nucleoside phosphorylase
  - Hypoxanthine
    - $\text{NH}_4^+$
    - Xanthine oxidase
    - Guanosine
    - $\text{NH}_2$
    - Purine nucleoside phosphorylase
    - Guanine
    - $\text{NH}_2$
    - Guanine deaminase
    - Xanthine
      - $\text{NH}_4^+$
      - Xanthine oxidase
      - Uric acid
“Salvage” Pathways for Purine Nucleotides

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

Deoxyadenosine is converted to dAMP, then dADP, and finally dATP by Adenosine deaminase (ADA). The breakdown continues with the formation of deoxyinosine, 2-deoxyribose, deoxyinosine, hypoxanthine, guanine, xanthine, and uric acid.
Hyperuricemia can be caused by:

- 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...

\[ 2\text{ATP} + HCO_3^- + \text{glutamine} + H_2O \rightarrow \text{NH}_2\text{C} \overset{\text{O}}{\text{O}}\text{P}^{2-} + \text{glutamate} + 2\text{ADP} + P_i \]

carbamoyl phosphate

...used for pyrimidine synthesis

\[
\begin{align*}
\text{NH}_2\text{C} \overset{\text{O}}{\text{O}}\text{P}^{2-} + \text{NH}_3\text{C} \overset{\text{O}}{\text{CH}_2} \rightarrow \text{NH}_2\text{C} \overset{\text{O}}{\text{C}}\text{CH}_2 \rightarrow \text{HN} \text{C} \overset{\text{O}}{\text{C}}\text{CH}_2 \rightarrow \text{CO}_2
\end{align*}
\]
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-fluoro-2'-deoxyuridine monophosphate (FdUMP) is converted by thymidylate synthase to deoxythymidine monophosphate (dTMP) through a sequence of reactions involving methylene tetrahydrofolate (N<sup>5</sup>,N<sup>10</sup>-methylene tetrahydrofolate) and dihydrofolate (DHFR) catalyzed by NADH and 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  --> 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 \[\xrightarrow{HSV \text{ thymidine kinase}}\] AcycloGMP

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

5-FU $\rightarrow$ FdUMP
$\rightarrow$ inactivation of TS

Degradation
(via dihydropyrimidine dehydrogenase, DPD)

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

Cytosine arabinoside (araC) activation and inactivation: