2007-09

M1 - Renal, Fall 2007

Lyons, R.; Burney, R.

<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

- amino acids, folate → IMP → Purine MP
- IMP → dNTP → NTP
- NTP → Purine Degradation → NH₄

Purine Biosynthesis

- PRPP

Pyrimidine Biosynthesis

- Carbamoyl Phosphate → OMP
- Pyrimidine MP
- dNTP → NTP
- DNA → RNA
- dNTP

Pyrimidine Salvage

- 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:

Conversion to Guanosine:
Nucleoside Monophosphate Kinases

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

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

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

Hydroxyurea inhibits this enzyme: chemotherapeutic use

\[
O
\]

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

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

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

- 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
  \( \overset{\text{H}_2\text{O}}{\overset{\text{NH}_4^+}{\overset{\text{Adenosine deaminase (ADA)}}{\overset{\text{purine nucleoside phosphorylase}}{\text{Inosine}}}}} \)

- Guanosine
  \( \overset{\text{purine nucleoside phosphorylase}}{\overset{\text{Guanine deaminase}}{\overset{\text{Guanine}}{\overset{\text{xanthine oxidase}}{\text{Xanthine}}}}} \)

- Hypoxanthine
  \( \overset{\text{xanthine oxidase}}{\text{Uric acid}} \)
“Salvage” Pathways for Purine Nucleotides

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

Deoxyadenosine → Adenosine deaminase (ADA) → Deoxyinosine → 2-deoxyribose → Hypoxanthine → Guanine → Xanthine → Uric acid

dAMP → dADP → dATP
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...

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

...used for pyrimidine synthesis

\[
\text{carbamoyl phosphate} + \text{aspartate} \rightarrow \text{orotate}
\]
Orotate is linked to PRPP to form Uridine monophosphate:

Orotate + phosphoribose-1 pyrophosphate → orotidine monophosphate → 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-fluoro-2'-deoxyuridine monophosphate
(F-dUMP)

\[
\begin{align*}
\text{FdUMP} & \quad \text{thymidylate synthase} \quad \text{THF} \quad \text{DHFR} \\
\text{dUMP} & \quad \text{dihydrofolate} \quad \text{NADH} \quad \text{NAD}^+ \\
\end{align*}
\]

deoxothymidine monophosphate
Complicated Pathways for Pyrimididine 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

G

HSV thymidine kinase

AcycloGMP

5-fluorouracil

+ deoxyribose-1-phosphate

pyrimidine phosphorylase

fluorodeoxyuridine

uridine kinase

fluorodeoxyuridine monophosphate (FdUMP)
5-FU efficacy depends on rate of degradation vs activation

5-FU \rightarrow \text{Degradation (via dihydropyrimidine dehydrogenase, DPD)} \rightarrow \text{FdUMP} + \text{methylene-THF} + \text{Thymidylate Synthase} \rightarrow \text{inactivation of TS}

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

Cytosine arabinoside (araC) activation and inactivation: