2007-09

M1 - Renal, Fall 2007

Lyons, R.; Burney, R.

<http://hdl.handle.net/2027.42/64946>
http://hdl.handle.net/2027.42/64946
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

$$\text{AMP} + \text{ATP} \leftrightarrow 2\text{ADP}$$ \hspace{1cm} \text{(adenylate kinase)}

$$\text{GMP} + \text{ATP} \leftrightarrow \text{GDP} + \text{ADP}$$ \hspace{1cm} \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

\[ N_1 DP + N_2 TP \leftrightarrow N_1 TP + N_2 DP \]

\[ dN_1 DP + N_2 TP \leftrightarrow dN_1 TP + N_2 DP \]

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

\[ \text{PRPP} \rightarrow \text{IMP} \]

\[ \text{IMP} \rightarrow \text{GMP} \quad \text{ATP} \rightarrow \text{GTP} \]

\[ \text{IMP} \rightarrow \text{AMP} \quad \text{GTP} \rightarrow \text{ATP} \]
Feed-forward regulation by PRPP
Feed-forward regulation by PRPP
Feed-forward regulation by PRPP
Degradation of the Purine Nucleosides:

Adenosine $\xrightarrow{\text{H}_{2}\text{O}, \text{NH}_4^+} \xrightarrow{\text{ADA}}$ Inosine $\xrightarrow{\text{p}_i, \text{ribose - 1 - p}}$ Hypoxanthine $\xrightarrow{\text{xanthine oxidase}}$

Guanosine $\xrightarrow{\text{p}_i, \text{ribose - 1 - p}}$ Guanine $\xrightarrow{\text{Guanine deaminase}}$ Xanthine $\xrightarrow{\text{xanthine oxidase}}$ Uric acid
“Salvage” Pathways for Purine Nucleotides

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

Deoxyadenosine → dAMP → dADP → dATP

Adenosine deaminase (ADA) → 2-deoxyribose → Deoxyinosine → Hypoxanthine

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...

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

(carbamoyl phosphate)

...used for pyrimidine synthesis

\[ \text{carbamoyl phosphate} + \text{aspartate} \rightarrow \text{orotate} \]
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) → thymidylate synthase → dihydrofolate → NADH

methylenedonor → THF → NAD+ → DHFR
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  --> 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** → **AcycloGMP**

\[ 5\text{-fluorouracil} + \text{deoxyribose-1-phosphate} \rightarrow \text{fluorodeoxyuridine} \rightarrow \text{fluorodeoxyuridine monophosphate (FdUMP)} \]

- **HSV thymidine kinase**
- **Pyrimidine phosphorylase**
- **Uridine kinase**
5-FU efficacy depends on rate of degradation vs activation

5-FU → FdUMP
+ methylene-THF + Thymidylate Synthase

--> inactivation of TS

Degradation
(via dihydropyrimidine dehydrogenase, DPD)

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

Cytosine arabinoside (araC) activation and inactivation: