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M1 - Renal, Fall 2007

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Nucleic Acid metabolism

Click on any blue rectangle to see details.
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

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

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

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

Hydroxyurea inhibits this enzyme: chemotherapeutic use

\[
\text{O} \\
\text{HONH}^- \text{C} - \text{NH}_2
\]
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
    - GTP
  - AMP
    - ATP
  - GTP
  - ATP
Feed-forward regulation by PRPP
Feed-forward regulation by PRPP
Feed-forward regulation by PRPP
Degradation of the Purine Nucleosides:

- **Adenosine**
  - $\text{NH}_2$
  - $\text{NH}_2$
  - Ribose
  - $\xrightarrow{\text{H}_2\text{O}}$ Inosine
  - $\xrightarrow{\text{NH}_4^+}$ Adenosine deaminase (ADA)

- **Inosine**
  - Ribose
  - $\xrightarrow{p_i}$ Hypoxanthine
  - $\xrightarrow{\text{purine nucleoside phosphorylase}}$ Purine nucleoside phosphorylase

- **Hypoxanthine**
  - $\xrightarrow{xanthine oxidase}$ Xanthine
  - $\xrightarrow{\text{Guanine deaminase}}$ Guanine

- **Guanosine**
  - $\text{NH}_2$
  - $\text{NH}_2$
  - Ribose
  - $\xrightarrow{p_i}$ Guanine
  - $\xrightarrow{\text{purine nucleoside phosphorylase}}$ Purine nucleoside phosphorylase

- **Guanine**
  - $\xrightarrow{\text{Guanine deaminase}}$ Guanine
  - $\xrightarrow{xanthine oxidase}$ Uric acid
  - $\xrightarrow{\text{Uric acid oxidase}}$ 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

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
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
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) inhibits the thymidylate synthase reaction, which converts deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP) through a series of enzymatic reactions involving thymidylate synthase (THF), dihydrofolate reductase (DHFR), and methylene donor 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

\[
\text{Cytidine} \xrightarrow{\text{cytidine deaminase}} \text{Uridine}
\]

A phosphorylase removes the sugar

\[
\text{Uridine} \xrightarrow{\text{pyrimidine phosphorylase}} \text{Thymine} + \text{deoxyribose-1-phosphate}
\]

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:

\[
\text{HO} \quad \text{G} \quad \text{HSV thymidine kinase} \quad \text{HO} \quad \text{G}
\]

\[\text{Acyclovir} \rightarrow \text{AcycloGMP}\]

\[
\text{HN} \quad \text{N} \quad \text{F} \\
\text{O} \quad \text{N} \\
\text{H}
\]

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