M1 - Renal, Fall 2007

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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

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

\[ \text{GMP} + \text{ATP} \leftrightarrow \text{GDP} + \text{ADP} \]  (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

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

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

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

PRPP

IMP

ATP
GMP

GTP

GTP

AMP

ATP
Feed-forward regulation by PRPP
Feed-forward regulation by PRPP
Feed-forward regulation by PRPP
Degradation of the Purine Nucleosides:

Adenosine → Inosine → Hypoxanthine → Xanthine → Uric acid

Adenosine deaminase (ADA) catalyzes the reaction of adenosine to inosine, releasing ammonia and phosphate. Hypoxanthine is then converted to xanthine by xanthine oxidase. Finally, xanthine is oxidized to uric acid by the same enzyme.
“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) → Deoxyinosine → 2-deoxyribose → Deoxyribose → 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...

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

carbamoyl phosphate

...used for pyrimidine synthesis

\[
\begin{align*}
\text{NH}_2\text{C} = \text{O}\text{O}^\text{2-} &+ \text{aspartate} \\
\rightarrow &\text{orotate}
\end{align*}
\]
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 The Thymidylate Synthase Reaction:

5-fluorodeoxyuridine monophosphate (FdUMP) interacts with thymidylate synthase, inhibiting the formation of deoxythymidine monophosphate.
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

\[ \text{HSV thymidine kinase} \]

AcycloGMP

5-fluorouracil + deoxyribose-1-phosphate

\[ \text{pyrimidine phosphorylase} \]

fluorodeoxyuridine

\[ \text{uridine kinase} \]

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

5-FU $\rightarrow$ FdUMP
+ methylene-THF + Thymidylate Synthase
$\rightarrow$ inactivation of TS

Degradation
(via dihydropyrimidine dehydrogenase, DPD)

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

\[
\begin{align*}
\text{capecitabine} & \xrightarrow{\text{dealkylation}} \text{cytidine deaminase} \xrightarrow{\text{pyrimidine phosphorylase}} \text{fluorouracil}
\end{align*}
\]

Cytosine arabinoside (araC) activation and inactivation:

\[
\begin{align*}
\text{Uridine arabinoside (INACTIVE)} & \xrightarrow{\text{cytidine deaminase}} \text{Cytosine arabinoside (araC)} & \xrightarrow{\text{cytidine kinase}} & \text{Cytosine arabinoside monophosphate (ACTIVE)}
\end{align*}
\]