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:

Inosine monophosphate

\[ \text{GTP} \xrightarrow{\text{aspartate}} \text{GDP} + \text{P}_i \xrightarrow{\text{fumarate}} \text{Adenosine monophosphate} \]

Conversion to Guanosine:

Inosine monophosphate

\[ \text{NAD}^+ \xrightarrow{\text{NADH} + \text{H}^+} \text{Xanthosine monophosphate} \xrightarrow{\text{AMP} + \text{PP}_i} \text{Guanosine monophosphate} \]
Nucleoside Monophosphate Kinases

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

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

- Similar enzymes specific for each nucleotide
- No specificity for ribonucleotide vs. deoxyribonucleotide
Ribonucleotide Reductase

Hydroxyurea inhibits this enzyme: chemotherapeutic use

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

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

\[ \text{dN}_1\text{DP} + N_2\text{TP} \iff \text{dN}_1\text{TP} + N_2\text{DP} \]

- No specificity for base
- No specificity for ribo vs deoxy
Feed-forward regulation by PRPP
Feed-forward regulation by PRPP
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Degradation of the Purine Nucleosides:
“Salvage” Pathways for Purine Nucleotides

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

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

carbamoyl phosphate

...used for pyrimidine synthesis

[Chemical structures and reactions]

carbamoyl phosphate
aspartate
orotate
Orotate is linked to PRPP to form Uridine monophosphate:
UTP can be converted to CTP by CTP Synthetase:

Newly-synthesized uridine monophosphate will be phosphorylated to UDP and UTP, as described for the purine nucleotides.
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)

\[ \text{thymidylate synthase} \times \]

\[ \text{dihydrofolate} \]

\[ \text{methylene donor} \]

\[ \text{DHFR} \]

\[ \text{NADH} \]

\[ \text{NAD}^+ \]

\[ \text{methylene tetrahydrofolate} \]

\[ \text{(N}^5, \text{N}^{10} \text{) methylene} \]

\[ \text{deoxythymidine monophosphate} \]
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:

\[
\text{Acyclovir} \xrightarrow{HSV \text{ thymidine kinase}} \text{AcycloGMP}
\]

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

![Chemical structures](image)

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: