M1 - Renal, Fall 2007

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Viewer discretion advised: Material may contain medical images that may be disturbing to some viewers.
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

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

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

- 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

\[ \text{N}_1\text{DP} + \text{N}_2\text{TP} \leftrightarrow \text{N}_1\text{TP} + \text{N}_2\text{DP} \]

\[ \text{dN}_1\text{DP} + \text{N}_2\text{TP} \leftrightarrow \text{dN}_1\text{TP} + \text{N}_2\text{DP} \]

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

PRPP

IMP

ATP

GTP

GMP

AMP

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

Adenosine

\[ \text{H}_2\text{O} + \text{NH}_4^+ \rightarrow \text{Inosine} \]

Adenosine deaminase (ADA)

Inosine

\[ \text{p}_i + \text{ribose - 1 - P} \rightarrow \text{Hypoxanthine} \]

Putative nucleoside phosphorylase

Hypoxanthine

\[ \text{xanthine oxidase} \rightarrow \text{Xanthine} \]

Guanosine

\[ \text{Guanylic nucleoside phosphorylase} \rightarrow \text{Guanine} \]

Guanine

\[ \text{Guanylic deaminase} \rightarrow \text{Xanthine} \]

\[ \text{xanthine oxidase} \rightarrow \text{Uric acid} \]
"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…

\[ 2\text{ATP} + \text{HCO}_3^- + \text{glutamine} + \text{H}_2\text{O} \rightarrow \text{NH}_2C\text{O}O\text{P}^{2-} + \text{glutamate} + 2\text{ADP} + \text{P}_i \]

*carbamoyl phosphate*

…used for pyrimidine synthesis

*carbamoyl phosphate*  \[\text{aspartate}\]  \[\text{orotate}\]
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) inhibits the thymidylate synthase reaction, which converts N5, N10-methylene tetrahydrofolate to dihydrofolate. Dihydrofolate is then converted back to tetrahydrofolate (THF) by DHFR, which requires NADH as a cofactor. THF is a necessary donor for methylation reactions, including the conversion of dUMP to dTMP.
Complicated Pathways for Pyrimidine Production:

dCTP \[\rightarrow\] CTP \[\leftarrow\] UTP \[\rightarrow\] dUTP \[\rightarrow\] dTTP

dCDP \[\leftarrow\] CDP \[\rightarrow\] UDP \[\rightarrow\] dUDP \[\rightarrow\] dTDP

UMP \[\rightarrow\] dUMP \[\rightarrow\] dTMP

de novo synthesis \[\rightarrow\] OMP

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

\[
\text{Cytidine} \rightarrow \text{Uridine}
\]

A phosphorylase removes the sugar

\[
\text{(deoxy)thymidine} \rightarrow \text{pyrimidine phosphorylase} \rightarrow \text{thymine} + \text{deoxyribose-1-phosphate}
\]

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:

Acyclovir → AcycloGMP

5-fluorouracil + deoxyribose-1-phosphate → fluorodeoxyuridine → fluorodeoxyuridine monophosphate (FdUMP)
5-FU efficacy depends on rate of degradation vs activation

\[
\begin{align*}
5\text{-FU} & \rightarrow \quad \rightarrow \quad \text{FdUMP} \\
& + \text{methylene-THF} + \text{Thymidylate Synthase} \\
& \rightarrow \text{inactivation of TS}
\end{align*}
\]

Degradation
(via dihydropyrimidine dehydrogenase, DPD)

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

Cytosine arabinoside (araC) activation and inactivation: