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 → Adenosine monophosphate

Conversion to Guanosine:

Inosine monophosphate → Xanthosine monophosphate → Guanosine monophosphate
Nucleoside Monophosphate Kinases

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

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

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

Hydroxyurea inhibits this enzyme: chemotherapeutic use

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

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

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

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

PRPP

IMP

GMP

ATP

GTP

AMP

GTP

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

- Adenosine \( \xrightarrow{\text{H}_2\text{O}, +\text{NH}_4^+} \) Inosine \( \xrightarrow{\text{purine nucleoside phosphorylase}} \) Hypoxanthine
  - Hypoxanthine \( \xrightarrow{\text{xanthine oxidase}} \) Xanthine \( \xrightarrow{\text{xanthine oxidase}} \) Uric acid

- Guanosine \( \xrightarrow{\text{purine nucleoside phosphorylase}} \) Guanine
  - Guanine \( \xrightarrow{\text{guanine deaminase}} \) Hypoxanthine

Note: The reactions are not labeled as per the original image.
“Salvage” Pathways for Purine Nucleotides

Hypoxanthine + PRPP → Inosine monophosphate

Hypoxanthine-guanine phosphoribosyl transferase

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

Deoxyadenosine → dAMP → dADP → dATP

Adenosine deaminase (ADA) → Deoxyinosine → 2-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

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...

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

(carbamoyl phosphate)

...used for pyrimidine synthesis

(carbamoyl phosphate + aspartate → 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)

\[ \begin{align*} &\text{thymidylate synthase} \\
&\text{methylene donor} \\
&\text{THF} \\
&\text{DHFR} \quad \text{NADH} \\
&\text{methylene tetrahydrofolate} \end{align*} \]

\[ \begin{align*} &\text{dihydrofolate} \\
&\text{NAD}^+ \\
&\text{deoxythymidine monophosphate} \end{align*} \]
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
  - Reactions:
    - Acyclovir $\rightarrow$ AcycloGMP by HSV thymidine kinase.

- 5-fluorouracil + deoxyribose-1-phosphate
  - Reactions:
    - $5\text{-fluorouracil} + \text{pyrimidine phosphorylase} \rightarrow \text{fluorodeoxyuridine}$
    - $\text{fluorodeoxyuridine} \rightarrow \text{fluorodeoxyuridine monophosphate (FdUMP)}$
5-FU efficacy depends on rate of degradation vs activation

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

Degradation
(via dihydropyrimidine dehydrogenase, DPD)

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

Cytosine arabinoside (araC) activation and inactivation: