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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

\[
\begin{align*}
\text{Ribose-5-phosphate} & \quad \text{ATP} \quad \text{AMP} \quad \text{phosphoribose-1-phosphate} \\
\end{align*}
\]

PRPP Use in Purine Biosynthesis:

\[
\begin{align*}
\text{phosphoribose-1-phosphate} & \quad \text{glutamine} \quad \text{glutamate} \quad \text{OH} \quad \text{OH} \quad \text{NH}_2 \\
\end{align*}
\]
The First Purine: Inosine Monophosphate
(folates are involved in this synthesis)

Conversion to Adenosine:

Conversion to Guanosine:
Nucleoside Monophosphate Kinases

AMP + ATP $\rightleftharpoons$ 2ADP  (adenylate kinase)

GMP + ATP $\rightleftharpoons$ GDP + ADP  (guanylate kinase)

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

Hydroxyurea inhibits this enzyme: chemotherapeutic use

\[
\begin{align*}
\text{O} \\
\text{HONH}^- \text{C} \text{NH}_2
\end{align*}
\]
Regulation of Ribonucleotide Reductase

CDP + ATP → dCDP → dCTP

UDP + ATP → dUDP → dTTP

GDP → dGDP → dGTP

ADP → dADP → dATP
Nucleoside Diphosphate Kinase

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

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

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

[Diagram of metabolic pathways involving PRPP, IMP, GMP, ATP, GTP,AMP, and GTP, showing regulatory interactions.]
Degradation of the Purine Nucleosides:
“ Salvage ” Pathways for Purine Nucleotides

[Diagram showing the reaction of Hypoxanthine with PRPP to form Inosine monophosphate]
Adenosine Deaminase Deficiency:

Deoxyadenosine → dAMP → dADP → dATP

Adenosine deaminase (ADA) → 2-deoxyribose → Deoxyinosine → Hypoxanthine → Guanine → Xanthine → Uric acid
Gout: deposition of urate crystals in joints, “tophi” in cooler periphery

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:
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

H₂O \( \rightarrow \) NH₃

\[ \text{myoadenylate deaminase} \]

\( \text{ribose-5-P} \) \( \rightarrow \) \( \text{H₂O} \) \( \rightarrow \) \( \text{NH₃} \)

\( \text{Adenosine monophosphate} \)

\( \text{Fumarate} \)

To TCA Cycle

\( \text{Asp, GTP} \)

\( \text{GDP + Pi} \)

\( \text{Inosine monophosphate} \)
Carbamoyl phosphate synthetase II - a *cytoplasmic* enzyme...

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

carbamoyl phosphate

...used for pyrimidine synthesis

\[
\text{carbamoyl phosphate} + \text{aspartate} \rightarrow \text{orotate}
\]
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 thymidylate synthase, which converts deoxythymidine monophosphate to thymidylate. The reaction involves the conversion of methylene tetrahydrofolate to dihydrofolate, catalyzed by DHFR, with NADH as a cofactor.
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:

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

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

\[
5\text{-FU} \rightarrow \text{FdUMP} \rightarrow \text{inactivation of TS}
\]

\[
\text{Degradation (via dihydropyrimidine dehydrogenase, DPD)}
\]

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

Cytosine arabinoside (araC) activation and inactivation: