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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:

\[
\text{Inosine monophosphate} \rightarrow \text{GTP} \rightarrow \text{GDP + P}_i \rightarrow \text{Adenosine monophosphate}
\]

Conversion to Guanosine:

\[
\text{Inosine monophosphate} \rightarrow \text{NAD}^+ \rightarrow \text{NADH + H}^+ \rightarrow \text{Xanthosine monophosphate} \rightarrow \text{AMP + P}_i \rightarrow \text{Guanosine monophosphate}
\]
Nucleoside Monophosphate Kinases

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

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

- 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

\[ N_1DP + N_2TP \rightleftharpoons N_1TP + N_2DP \]

\[ dN_1DP + N_2TP \rightleftharpoons dN_1TP + N_2DP \]

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

PRPP → IMP

IMP → ATP, GTP
IMP → GMP, AMP

AMP → ATP
GMP → GTP
Feed-forward regulation by PRPP
Feed-forward regulation by PRPP
Feed-forward regulation by PRPP
Degradation of the Purine Nucleosides:

Adenosine $\xrightarrow{\text{H}_2\text{O} + \text{NH}_4^+} \text{Inosine} \xrightarrow{\text{purine nucleoside phosphorylase}} \text{Hypoxanthine}$

Guanosine $\xrightarrow{\text{purine nucleoside phosphorylase}} \text{Guanine} \xrightarrow{\text{Guanine deaminase}} \text{Xanthine} \xrightarrow{\text{xanthine oxidase}} \text{Uric acid}$
“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 → 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...

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

...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)

thymidylate synthase

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

dihydrofolate

\( \text{DHFR} \)

NADH

methylenedonor

\( \text{THF} \)

NAD+
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

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

Degradation
(via dihydropyrimidine dehydrogenase, DPD)

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

Cytosine arabinoside (araC) activation and inactivation: