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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

PRPP Use in Purine Biosynthesis:
The First Purine: Inosine Monophosphate
(folates are involved in this synthesis)

Conversion to Adenosine:

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

Conversion to Guanosine:

\[
\text{Inosine monophosphate} \xrightarrow{\text{NAD}^+, \text{NADH} + \text{H}^+} \text{Xanthosine monophosphate} \xrightarrow{\text{H}_2\text{O, ATP}} \text{AMP + PP}_i \xrightarrow{\text{glu, glu}} \text{Guanosine monophosphate}
\]
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
Regulation of Ribonucleotide Reductase

- CDP + ATP → dCDP → dCTP
- UDP + ATP → dUDP → dTTP
- GDP + ATP → dGDP → dGTP
- ADP + ATP → dADP → dATP
Nucleoside Diphosphate Kinase

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

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

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

PRPP

IMP

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

Adenosine → Inosine → Hypoxanthine

Guanosine → Guanine → Xanthine → Uric acid

Enzymes involved:
- Adenosine deaminase (ADA)
- Purine nucleoside phosphorylase
- Guanine deaminase
- Xanthine oxidase
“Salvage” Pathways for Purine Nucleotides

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

1. Deoxyadenosine
   - Chemical structure
   - Converted to deoxyinosine by adenosine deaminase (ADA)
   - Further converted to 2-deoxyribose
   - Deoxyinosine
   - Hypoxanthine
   - Guanine
   - Xanthine
   - Uric acid

2. Metabolism pathways:
   - dATP
   - dADP
   - dAMP
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...

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

Carbamoyl phosphate

...used for pyrimidine synthesis

\[
\text{carbamoyl phosphate} + \text{aspartate} \rightarrow \text{orotate}
\]
Orotate is linked to PRPP to form Uridine monophosphate:

\[
\text{orotate} + \text{phosphoribose-1 pyrophosphate} \rightarrow \text{ostridine monophosphate} \rightarrow \text{uridine monophosphate}
\]
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. The reaction involves the conversion of thymidine monophosphate to deoxythymidine monophosphate. The inhibitory effect of FdUMP accounts for its use as an anti-cancer drug.
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 \( \rightarrow \) 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 $\xrightarrow{HSV \text{ thymidine kinase}}$ AcycloGMP

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

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: