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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.
Nucleic Acid metabolism
Click on any blue rectangle to see details.

- **Purine Salvage**
  - IMP
  - Purine Biosynthesis
  - PRPP
  - Uric Acid
  - Purine MP
  - Ribonucleotide reductase
  - dNTP
  - NTP
  - Purine Degradation
  - NH₄

- **Pyrimidine Salvage**
  - Carbamoyl Phosphate
  - OMP
  - Pyrimidine Biosynthesis
  - Pyrimidine MP
  - Ribonucleotide reductase
  - dNTP
  - NTP
  - Pyrimidine Degradation
  - (energy)

- **DNA**
- **RNA**
Formation of PRPP: Phosphoribose pyrophosphate

\[
\begin{align*}
&\text{ribose - 5 - phosphate} & \xrightarrow{\text{ATP, AMP}} & \text{phosphoribose - 1 pyrophosphate} \\
&\text{ATP} & \rightarrow & \text{AMP}
\end{align*}
\]

PRPP Use in Purine Biosynthesis:

\[
\begin{align*}
&\text{phosphoribose - 1 pyrophosphate} \xrightarrow{\text{glutamine, glutamate}} \text{glutamine} \xrightarrow{\text{glutamate}} \text{glutamate}
\end{align*}
\]
The First Purine: Inosine Monophosphate
(folates are involved in this synthesis)

Conversion to Adenosine:

Conversion to Guanosine:
Nucleoside Monophosphate Kinases

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

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

• 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

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

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

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

PRPP

IMP

GMP

GTP

ATP

AMP

GTP

ATP
Feed-forward regulation by PRPP

- PRPP
- IMP
- GMP
  - ATP
  - GTP
- AMP
  - GTP
  - ATP
Feed-forward regulation by PRPP

PRPP

IMP

GMP → ATP +

AMP → GTP +

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

Adenosine $\rightarrow$ Inosine $\rightarrow$ Hypoxanthine

Guanosine $\rightarrow$ Guanine $\rightarrow$ Xanthine $\rightarrow$ 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

2-deoxyribose

Deoxyinosine → 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...

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

carbamoyl phosphate

...used for pyrimidine synthesis

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

Cytidine deaminase converts cytidine to uridine

\[
\text{Cytidine} \xrightarrow{\text{cytidine deaminase}} \text{Uridine}
\]

A phosphorylase removes the sugar

\[
\text{dThymidine} \xrightarrow{\text{pyrimidine phosphorylase}} \text{Thymine} + \text{deoxyribose-1-phosphate}
\]

Degradation of the base proceeds (products are unimportant here)
Pyrimidines can be salvaged as well:

Enzyme: Pyrimidine nucleoside phosphorylases  
Thymine + deoxyribose-1-phosphate → 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 → HSV thymidine kinase → AcycloGMP

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

Degradation
(via dihydropyrimidine dehydrogenase, DPD)

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

Cytosine arabinoside (araC) activation and inactivation: