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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.
Amino Acid metabolism

- Amino acids
  - Glu, Gln, Asp, NH₃
- Urea

Folate metabolism

- Methylene THF
- Met Cycle

TCA Cycle

- oxaloacetate
- fumarate

Nucleic Acid metabolism

- Purines
- DNA
- RNA
- Pyrimidines
- Uric Acid
- (energy)
Formation of PRPP: Phosphoribose pyrophosphate

\[
\text{ribose - 5 - phosphate} \xrightarrow{\text{ATP}} \text{AMP} \xrightarrow{} \text{phosphoribose - 1 pyrophosphate}
\]

PRPP Use in Purine Biosynthesis:

\[
\text{phosphoribose - 1 pyrophosphate} \xrightarrow{\text{glutamine, glutamate}} \text{NH}_2
\]
The First Purine: Inosine Monophosphate
(folates are involved in this synthesis)

Conversion to Adenosine:

Conversion to Guanosine:
Nucleoside Monophosphate Kinases

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

GMP + ATP  $\leftrightarrow$  GDP + ADP  (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
  ↓
  ATP
  ↓
GMP
  ↓
GTP
  GTP
  ↓
AMP
  ↓
ATP
Feed-forward regulation by PRPP
Feed-forward regulation by PRPP
Feed-forward regulation by PRPP
Degradation of the Purine Nucleosides:

Adenosine → Inosine → Hypoxanthine → Xanthine → Uric acid

Adenosine deaminase (ADA)

Putine nucleoside phosphorylase

Guanosine → Guanine → Xanthine

Guanine deaminase

Putine nucleoside phosphorylase
“Salvage” Pathways for Purine Nucleotides

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

Deoxyadenosine → DAMP → dADP → dATP

Deoxyadenosine → Adenosine deaminase (ADA) → Deoxyinosine → Hypoxanthine

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...

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

...used for pyrimidine synthesis

\[
\begin{align*}
\text{carbamoyl phosphate} & \quad \text{aspartate} \\
\text{octate} & \quad \text{orotate}
\end{align*}
\]
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.
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

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

5-fluorouracil + deoxyribose-1-phosphate

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

5-FU $\rightarrow$ FdUMP $\rightarrow$ inactivation of TS + methylene-THF + Thymidylate Synthase  
$\rightarrow$ inactivation of TS

Degradation (via dihydropyrimidine dehydrogenase, DPD)

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

Cytosine arabinoside (araC) activation and inactivation: