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

Purines

DNA

RNA

Pyrimidines

Uric Acid

(energy)

Nucleic Acid metabolism
Formation of PRPP: Phosphoribose pyrophosphate

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

Conversion to Adenosine:

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

Conversion to Guanosine:

\[
\text{Inosine monophosphate} \xrightarrow{\text{NAD}^+} \text{NADH + H}^+ \xrightarrow{\text{H}_2\text{O}} \text{AMP + PP}_i \xrightarrow{\text{glu}} \text{Guanosine monophosphate}
\]
Nucleoside Monophosphate Kinases

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

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

• 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

\[ N_1 \text{DP} + N_2 \text{TP} \ <--> \ N_1 \text{TP} + N_2 \text{DP} \]

\[ \text{d}N_1 \text{DP} + N_2 \text{TP} \ <--> \ dN_1 \text{TP} + N_2 \text{DP} \]

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

PRPP

IMP

GMP
ATP
GTP

AMP
GTP
ATP
Feed-forward regulation by PRPP

PRPP

↓
↓
↓

IMP

ATP

GTP

GMP

AMP

GTP

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

- Adenosine $\xrightarrow{\text{H}_2\text{O}, +\text{NH}_4^+} \text{Inosine}$ (Adenosine deaminase (ADA))
- Inosine $\xrightarrow{\text{p}_i, \text{ribose} - 1\cdot \text{P}} \text{Hypoxanthine}$ (purine nucleoside phosphorylase)
- Guanosine $\xrightarrow{\text{p}_i, \text{ribose} - 1\cdot \text{P}} \text{Guanine}$ (purine nucleoside phosphorylase)
- Guanine $\xrightarrow{\text{NH}_3^+, \text{H}_2\text{O}} \text{Xanthine}$ (Guanine deaminase)
- 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

Deoxyadenosine → Adenosine deaminase (ADA) → Deoxyinosine → 2-deoxyribose → Deoxyribose → 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...

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

carbamoyl phosphate

...used for pyrimidine synthesis

\[
\begin{align*}
\text{carbamoyl phosphate} & \quad \text{aspartate} \\
\text{NH}_2 & \quad \text{O} \\
\text{O} & \quad \text{C} \quad \text{CH}_2 \\
\text{O} & \quad \text{C} \quad \text{NH}_3 \\
\text{O} & \quad \text{O} \quad \text{O}_2 \\
\end{align*}
\]

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.
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

\[ \text{HSV thymidine kinase} \rightarrow \text{AcycloGMP} \]

5-fluorouracil + deoxyribose-1-phosphate

\[ \text{pyrimidine phosphorylase} \rightarrow \text{fluorodeoxyuridine} \]

\[ \text{uridine kinase} \rightarrow \text{fluorodeoxyuridine monophosphate (FdUMP)} \]
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: