M1 - Renal, Fall 2007

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Amino Acid metabolism

Amino acids

Glu, Gln, Asp, NH₃

Urea

oxaloacetate

fumarate

TCA Cycle

Folate metabolism

Methylene THF

Met Cycle

Nucleic Acid metabolism

Purines

RNA

Pyrimidines

Uric Acid

(energy)
Formation of PRPP: Phosphoribose pyrophosphate

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

Conversion to Adenosine:

Conversion to Guanosine:
Nucleoside Monophosphate Kinases

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

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

- similar enzymes specific for each nucleotide
- no specificity for ribonucleotide vs. deoxyribonucleotide
Ribonucleotide Reductase

Hydroxyurea inhibits this enzyme: chemotherapeutic use

\[
\text{O} \quad \text{HONH}^- \text{C} \text{NH}_2
\]
Regulation of Ribonucleotide Reductase

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

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

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

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

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

![Diagram showing the regulation of IMP, GMP, AMP, GTP, and ATP by PRPP]
Feed-forward regulation by PRPP

PRPP

IMP

GMP

ATP

AMP

GTP

ATP

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

- Adenosine (NH₂) → Inosine (NH₂) → Hypoxanthine (NH₄⁺)
- Adenosine deaminase (ADA) catalyzes the conversion of Adenosine to Inosine.
- Hypoxanthine is then converted to Guanine by xanthine oxidase.
- Guanine is deaminated to Xanthine by Guanine deaminase.
- Xanthine is oxidized to Uric acid by xanthine oxidase.
“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 → 2-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... 

\[ 2\text{ATP} + \text{HCO}_3^- + \text{glutamine} + H_2O \rightarrow \text{NH}_2\text{C} = \text{O}\text{O}^2^- + \text{glutamate} + 2\text{ADP} + \text{P}_i \]

carbamoyl phosphate

...used for pyrimidine synthesis

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

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

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

\[
\begin{align*}
5\text{-FU} & \rightarrow \quad \rightarrow \quad \text{FdUMP} \\
& \quad + \text{methylene-THF} + \text{Thymidylate Synthase} \\
& \quad \rightarrow \text{inactivation of TS}
\end{align*}
\]

Degradation
(via dihydropyrimidine dehydrogenase, DPD)

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

Cytosine arabinoside (araC) activation and inactivation:

Uridine arabinoside (INACTIVE) → Cytidine deaminase → Cytosine arabinoside (araC) → Cytidine kinase → Cytosine arabinoside monophosphate (ACTIVE)