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M1 - Renal, Fall 2007

Lyons, R.; Burney, R.

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Amino Acid metabolism

- Amino acids
  - Glu, Gln, Asp, NH$_3$
  - 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

PRPP Use in Purine Biosynthesis:
The First Purine: Inosine Monophosphate

(folates are involved in this synthesis)

Conversion to Adenosine:

### Inosine Monophosphate to Adenosine Monophosphate

\[ \text{GTP} \xrightarrow{\text{aspartate}} \text{GDP + } \text{Pi} \]

\[ \text{Inosine monophosphate} \]

\[ \text{Adenosine monophosphate} \]

Conversion to Guanosine:

### Inosine Monophosphate to Guanosine Monophosphate

\[ \text{NAD}^+ \xrightarrow{\text{NADH + H}^+} \]

\[ \text{Inosine monophosphate} \]

\[ \text{Xanthosine monophosphate} \]

\[ \text{Guanosine monophosphate} \]

### Pathway:

\[ \xrightarrow{\text{H}_2\text{O}} \text{AMP + Pi} \]

\[ \xrightarrow{\text{ATP}} \text{Glutamine (glu)} \]

\[ \xrightarrow{\text{glu}} \text{Guanosine monophosphate} \]
Nucleoside Monophosphate Kinases

AMP + ATP  $\leftrightarrow$  2ADP  \hspace{2cm} (adenylate kinase)

GMP + ATP  $\leftrightarrow$  GDP + ADP  \hspace{2cm} (guanylate kinase)

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

Hydroxyurea inhibits this enzyme: chemotherapeutic use

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

[Diagram showing the conversion of ribonucleotides to deoxyribonucleotides with regulatory mechanisms.]
Nucleoside Diphosphate Kinase

\[ N_1DP + N_2TP \leftrightarrow N_1TP + N_2DP \]

\[ dN_1DP + N_2TP \leftrightarrow dN_1TP + N_2DP \]

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

PRPP

IMP

GMP

ATP + GTP

AMP

GTP

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

- **Adenosine**
  - → **Inosine**
    - Adenosine deaminase (ADA)
    - $\text{H}_2\text{O}$, $\text{NH}_4^+$
  - $\text{p}_i$, ribose - 1 - p
  - **Hypoxanthine**
    - Purine nucleoside phosphorylase
  - $\text{NH}_4^+$

- **Guanosine**
  - → **Guanine**
    - Purine nucleoside phosphorylase
  - $\text{H}_2\text{O}$, $\text{NH}_4^+$
  - **Xanthine**
    - Guanine deaminase
  - $\text{NH}_4^+$

- **Uric acid**
  - 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 → Hypoxanthine

2-deoxyribose → 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...

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

...used for pyrimidine synthesis

carbamoyl phosphate  

aspartate  
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:

5-fluorodeoxuryridine monophosphate (FdUMP)

\[
\text{FdUMP} \rightarrow \text{thymidylate synthase} \rightarrow \text{deoxothymidine monophosphate}
\]

\[
\text{FdUMP} \rightarrow \text{N}^5,\text{N}^{10}\text{methylene tetrahydrofolate} \rightarrow \text{dihydrofolate} \rightarrow \text{THF} \rightarrow \text{DHFR} \rightarrow \text{NADH}
\]

\[
\text{FdUMP} \rightarrow \text{NAD}^+ \rightarrow \text{methylene donor}
\]
Complicated Pathways for Pyrimidinede 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:

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

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

5-FU \rightarrow \rightarrow \text{FdUMP} \rightarrow \text{inactivation of TS}

+ methylene-THF + Thymidylate Synthase

 Degradation
(via dihydropyrimidine dehydrogenase, DPD)

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

Cytosine arabinoside (araC) activation and inactivation: