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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

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

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

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

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

Hydroxyurea inhibits this enzyme: chemotherapeutic use

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

[Diagram showing the relationship between PRPP and IMP, and the subsequent conversion to GMP, AMP, GTP, and ATP]
Feed-forward regulation by PRPP

PRPP

IMP

ATP +

GMP

GTP +

AMP

GTP

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

- Adenosine → Inosine
  - Adenosine deaminase (ADA)
  - Purine nucleoside phosphorylase

- Inosine → Hypoxanthine
  - Purine nucleoside phosphorylase
  - xanthine oxidase

- Guanosine → Guanine
  - Purine nucleoside phosphorylase
  - Guanine deaminase

- Guanine → Xanthine
  - xanthine oxidase

- Xanthine → Uric acid
  - xanthine oxidase
“Salvage” Pathways for Purine Nucleotides

Hypoxanthine  +  Hypoxanthine-guanine phosphoribosyl transferase  →  Inosine monophosphate

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

Deoxyadenosine → dAMP → dADP → dATP
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

H₂O → NH₃

myoadenylate deaminase

Adenosine monophosphate

Inosine monophosphate

Fumarate

To TCA Cycle

Asp, GTP → GDP + Pi
Carbamoyl phosphate synthetase II - a *cytoplasmic* enzyme...

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

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:

5-fluorodeoxyuridine monophosphate (FdUMP) is converted by thymidylate synthase to deoxythymidine monophosphate. The reaction involves the conversion of $N^5, N^{10}$-methylene tetrahydrofolate to dihydrofolate, with methylene donor THF and DHFR catalyzing the process. The reaction is inhibited by FdUMP, indicated by the red cross.
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:

\[
\begin{align*}
\text{Acyclovir} & \xrightarrow{\text{HSV thymidine kinase}} \text{AcycloGMP} \\
\text{5-fluorouracil} + \text{deoxyribose-1-phosphate} & \xrightarrow{\text{uridine kinase}} \text{fluorodeoxyuridine} \\
\text{fluorodeoxyuridine} & \xrightarrow{\text{phosphorylase}} \text{fluorodeoxyuridine monophosphate (FdUMP)}
\end{align*}
\]
5-FU efficacy depends on rate of degradation vs activation

Degradation
(via dihydropteridine dehydrogenase, DPD)

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

Cytosine arabinoside (araC) activation and inactivation: