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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.
Nucleic Acid metabolism

Click on any blue rectangle to see details.

Purine Salvage

- amino acids, folate
- IMP
- Purine MP
- dNTP
- NTP
- Purine Degradation
- Uric Acid

Purine Biosynthesis

- PRPP

Pyrimidine Biosynthesis

- Carbamoyl Phosphate
- OMP
- Pyrimidine MP
- dNTP
- NTP
- Pyrimidine Degradation
- (energy)

Ribonucleotide reductase

DNA
RNA

Pyrimidine Salvage
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

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

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

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

Hydroxyurea inhibits this enzyme: chemotherapeutic use

$$\text{O}$$

$$\text{HONH}^-\text{C}^-\text{NH}_2$$
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

GPCP

ATP

↓

GTP

AMP

GTP

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

Adenosine $\xrightarrow{\text{H}_{2}\text{O}, \text{NH}_{4}^{+}}$ Inosine $\xrightarrow{\text{purine nucleoside phosphorylase}}$ Hypoxanthine

Adenosine deaminase (ADA)

Inosine $\xrightarrow{\text{purine nucleoside phosphorylase}}$ Hypoxanthine

Guanosine $\xrightarrow{\text{purine nucleoside phosphorylase}}$ Guanine $\xrightarrow{\text{Guanine deaminase}}$ Xanthine

Guanine $\xrightarrow{\text{xanthine oxidase}}$ Uric acid
“Salvage” Pathways for Purine Nucleotides

Hypoxanthine + PRPP \rightarrow \text{Hypoxanthine-guanine phosphoribosyl transferase} \rightarrow \text{Inosine monophosphate} + PP_i

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

Deoxyadenosine → dAMP → dADP → dATP

Deoxyadenosine

Adenosine deaminase (ADA) → Deoxyinosine

2-deoxyribose → Hypoxanthine

Deoxyinosine → 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...

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

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) inhibits the thymidylate synthase reaction to form deoxythymidine monophosphate.
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 $\rightarrow$ thymidine
(NOT thymidine monophosphate!)

Enzyme: Thymidine kinase - adds the monophosphate back
Thymidine + ATP $\rightarrow$ thymidine monophosphate

Herpes Simplex Virus carries its own tk gene
Certain drugs act via the pyrimidine salvage pathway:

![Chemical structures and reactions]

- Acyclovir is converted to AcycloGMP by HSV thymidine kinase.
- 5-fluorouracil, deoxyribose-1-phosphate, fluorodeoxyuridine, and fluorodeoxyuridine monophosphate (FdUMP) are involved in the pathway through phosphorylation and kinase reactions.
5-FU efficacy depends on rate of degradation vs activation

\[
5\text{-FU} \rightarrow \text{FdUMP} + \text{methylene-THF} + \text{Thymidylate Synthase} \rightarrow \text{inactivation of TS}
\]

Degradation
(via dihydropyrimidine dehydrogenase, DPD)

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

Cytosine arabinoside (araC) activation and inactivation: