Nucleic Acid metabolism

Click on any blue rectangle to see details.

Purine Salvage

- IMP
- Purine MP
- NTP
- Uric Acid
- Purine Degradation

Pyrimidine Salvage

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

- PRPP
- Carboxylase
- Ribonucleotide reductase
- DNA
- RNA

- amino acids, folate
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

AMP + ATP $\leftrightarrow$ 2ADP  (adenylate kinase)

GMP + ATP $\leftrightarrow$ GDP + ADP  (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

\[ \text{N}_1\text{DP} + \text{N}_2\text{TP} \rightleftharpoons \text{N}_1\text{TP} + \text{N}_2\text{DP} \]

\[ \text{dN}_1\text{DP} + \text{N}_2\text{TP} \rightleftharpoons \text{dN}_1\text{TP} + \text{N}_2\text{DP} \]

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

Adenosine $\xrightarrow{\text{H}_2\text{O}, +\text{NH}_4^+} \text{Inosine}$

$\xrightarrow{\text{Adenosine deaminase (ADA)}} \text{Hypoxanthine}$

$\xrightarrow{\text{purine nucleoside phosphorylase}} \text{Guanosine}$

$\xrightarrow{\text{Guanylate deaminase}} \text{Xanthine}$

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

Hypoxanthine + PRPP $\xrightarrow{\text{Hypoxanthine-guanine phosphoribosyl transferase}}$ Inosine monophosphate + PP$_i$

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...

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

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 to deoxythymidine monophosphate by thymidylate synthase. The reaction involves the transfer of a methyl group from N^5, N^10-methylene tetrahydrofolate to deoxyuridine monophosphate (dUMP) in the presence of NADH. The methyl donor is tetrahydrofolate (THF), and the reduction of NAD+ to NADH is catalyzed by dihydrofolate reductase (DHFR).
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:

- **Acyclovir**
  - **HSV thymidine kinase**
  - **AcycloGMP**

- **5-fluorouracil**
  - **pyrimidine phosphorylase**
  - **fluorodeoxyuridine**
  - **fluorodeoxyuridine monophosphate (FdUMP)**
5-FU efficacy depends on rate of degradation vs activation

![Chemical reaction diagram]

5-FU $\rightarrow$ FdUMP

$\rightarrow$ inactivation of TS

Degradation
(via dihydopyrimidine dehydrogenase, DPD)

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

Cytosine arabinoside (araC) activation and inactivation: