Nucleic Acid metabolism
Click on any blue rectangle to see details.

- **Purine Salvage**
  - IMP
  - Purine MP
  - Purine Degradation
  - NH₄

- **Purine Biosynthesis**
  - PRPP
  - Ribonucleotide reductase
  - dNTP
  - NTP

- **Pyrimidine Biosynthesis**
  - Carbamoyl Phosphate
  - OMP
  - Pyrimidine MP
  - Ribonucleotide reductase
  - dNTP
  - NTP

- **Pyrimidine Salvage**
  - DNA
  - RNA
  - (energy)
Formation of PRPP: Phosphoribose pyrophosphate

PRPP Use in Purine Biosynthesis:

H₂O

phosphoribose - 1 pyrophosphate

glutamine

glutamate

NH₂

phosphoribose - 1 pyrophosphate
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

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

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

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

![Diagram showing the regulation of IMP by PRPP, leading to GMP and AMP, with further regulation by ATP and GTP to GTP and ATP.](image-url)
Feed-forward regulation by PRPP
Feed-forward regulation by PRPP
Feed-forward regulation by PRPP

Diagram showing the regulation of IMP, AMP, GTP, ATP, GMP, and PRPP.
Degradation of the Purine Nucleosides:

Adenosine $\overset{\text{H}_2\text{O}}{\text{H}}_{\text{NH}_4}\overset{+}{\text{NH}_4}\overset{\text{Adenosine deaminase (ADA)}}{\rightarrow}$ Inosine

Inosine $\overset{p_i}{\text{ribose - 1-P}}\overset{\text{purine nucleoside phosphorylase}}{\rightarrow}$ Hypoxanthine

Hypoxanthine $\overset{\text{xanthine oxidase}}{\rightarrow}$ Guanine

Guanosine $\overset{p_i}{\text{ribose - 1-P}}\overset{\text{purine nucleoside phosphorylase}}{\rightarrow}$ Guanine

Guanine $\overset{\text{Guanine deaminase}}{\rightarrow}$ Xanthine

Xanthine $\overset{\text{xanthine oxidase}}{\rightarrow}$ Uric acid
“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

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...

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

carbamoyl phosphate

...used for pyrimidine synthesis

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

5-fluorodeoxyuridine monophosphate (FdUMP)

thymidylate synthase

N5, N10-methylene tetrahydrofolate

dihydrofolate

DHFR

methylene donor

THF

NADH

NAD+
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 acid urea 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:

\[
\begin{align*}
\text{Acyclovir} & \xrightarrow{\text{HSV thymidine kinase}} \text{AcycloGMP} \\
\end{align*}
\]

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

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

Degradation
(via dihydropyrimidine dehydrogenase, DPD)

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

Cytosine arabinoside (araC) activation and inactivation: