Nucleotide metabolism

Chem 454: Biochemistry II
University of Wisconsin-Eau Claire
<table>
<thead>
<tr>
<th>Base</th>
<th>Ribonucleoside</th>
<th>Ribonucleotide (5’-monophosphate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenine (A)</td>
<td>Adenosine</td>
<td>Adenylate (AMP)</td>
</tr>
<tr>
<td>Guanine (G)</td>
<td>Guanosine</td>
<td>Guanylate (GMP)</td>
</tr>
<tr>
<td>Uracil (U)</td>
<td>Uridine</td>
<td>Uridylate (UMP)</td>
</tr>
<tr>
<td>Cytosine (C)</td>
<td>Cytidine</td>
<td>Cytidylate (CMP)</td>
</tr>
</tbody>
</table>

**DNA**

<table>
<thead>
<tr>
<th>Base</th>
<th>Deoxyribonucleoside</th>
<th>Deoxyrribonucleotide (5’-monophosphate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenine (A)</td>
<td>Deoxyadenosine</td>
<td>Deoxyadenylate (dAMP)</td>
</tr>
<tr>
<td>Guanine (G)</td>
<td>Deoxyguanosine</td>
<td>Deoxyguanylate (dGMP)</td>
</tr>
<tr>
<td>Thymine (T)</td>
<td>Thymidine</td>
<td>Thymidylate (TMP)</td>
</tr>
<tr>
<td>Cytosine (C)</td>
<td>Deoxycytidine</td>
<td>Deoxycytidylate (dCMP)</td>
</tr>
</tbody>
</table>

Table 25-1

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**SALVAGE PATHWAY**

Activated ribose (PRPP) + base

↓

Nucleotide

**DE NOVO PATHWAY**

Activated ribose (PRPP) + amino acids + ATP + CO₂ + ...

↓

Nucleotide
Figure 25-2

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Bicarbonate $\xrightarrow{\text{ATP, ADP}}$ Carboxyphosphate $\xrightarrow{\text{NH}_3, P_i}$ Carbamic acid

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2 ATP-Grasp domains

Glutamine

$\text{NH}_3$

Carbamic acid

Carbamoyl phosphate

Figure 25-4
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Generic Mechanism: ATP-grasp domains (nucleotide syntheses too)

\[
\begin{align*}
\text{C} &= \text{ATP} \quad \text{ADP} \\
\text{Phosphorylation} &\quad \text{Displacement} \\
\text{C} &= \text{Nu}
\end{align*}
\]

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http://cathwww.biochem.ucl.ac.uk/cgi-bin/cath/GotoCath.pl?cath=3.30.1490.20
To start off:

Figure 25-5
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Figure 25-6
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Figure 25-8
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Ribonucleotide reductase

Products of ribonucleotide reductase

Further processing yields dNTP

ADP → dADP
GDP → dGDP
CDP → dCDP
UDP → dUDP

dATP  dGTP  dCTP  TTP
Ribonucleotide Reductase

R1 dimer

R2 dimer

Glu
Cys
Cys
Cys

Active site

Tyrosyl-radical site
Figure 25-12

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Fluorouracil

\[ \downarrow \]

Fluorodeoxyuridylate (suicide inhibitor)

\[ \downarrow \]

\[ \text{dUMP} \rightarrow \text{dTMP} \]

Thymidylate synthase

\[ \text{N}^5, \text{N}^{10}-\text{Methylene-tetrahydrofolate} \]

Glycine

Serine

Tetrahydrofolate

\[ \text{Dihydrofolate} \rightarrow \text{NADPH + H}^+ \]

NADP^+

Aminopterin and methotrexate (amethopterin)
Suicide Inhibition

Fluorodeoxyuridylate + $N^5,N^{10}$-Methylene-tetrahydrofolate → Stable adduct

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Pyrimidine regulation

Aspartate + carbamoyl phosphate → carbamoylaspartate → UMP → UDP → UTP → CTP

ATCase

ATP

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Purine regulation

[Diagram showing the regulation of purine synthesis and the conversion of IMP to AMP and GMP through various substrates and inhibitors.]
Regulation of overall activity

\[
\begin{align*}
\text{ADP} & \rightarrow \text{Ribonucleotide reductase} & \text{ATP} \\
\text{GDP} & \rightarrow \text{dADP} \\
\text{UDP} & \rightarrow \text{dGDP} \\
\text{CDP} & \rightarrow \text{dUDP} \\
\end{align*}
\]

\[
\begin{align*}
\text{dATP} & \rightarrow \text{dGTP} \\
\text{dGDP} & \rightarrow \text{TTP} \\
\text{dUDP} & \rightarrow \text{dCTP} \\
\end{align*}
\]

Regulation of substrate specificity

\[
\begin{align*}
\text{ADP} & \rightarrow \text{dADP} & \rightarrow \text{dATP (ATP)} \\
\text{GDP} & \rightarrow \text{dGDP} & \rightarrow \text{dGTP} \\
\text{UDP} & \rightarrow \text{dUDP} & \rightarrow \text{TTP} \\
\text{CTP} & \rightarrow \text{dCTP} & \rightarrow \text{dCTP} \\
\end{align*}
\]

Figure 25-16b
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Purine Degradation

**GENE THERAPY!!**

![Diagram of purine degradation]

**The Gout**  James Gillray (1757-1815), artist