Lecture 30: Gluconeogenesis, Pathway Regulation

Gluconeogenesis:
Location: cytosol (liver & kidney cells)
Input: pyruvate
Output: glucose

General properties of Catabolic and Anabolic pathways:

<table>
<thead>
<tr>
<th>Catabolic (e.g. glycolysis)</th>
<th>Anabolic (e.g. gluconeogenesis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Input → out</td>
<td>Simple → Complex</td>
</tr>
<tr>
<td>Redox</td>
<td>Reducing: NADH/FADH₂ required (electron donors)</td>
</tr>
<tr>
<td>Energy</td>
<td>Consumed</td>
</tr>
</tbody>
</table>

Gluconeogenesis: The formation of glucose is essential for the maintenance of constant blood glucose levels. The liver, and to a lesser extent the kidneys, are the only organs that carry out this process. All of our other tissues and organs (especially the brain) require this newly-synthesized glucose during periods of fasting, i.e. between meals and during sleep. This process is particularly important during strenuous exercise, where the lactic acid produced during anaerobic metabolism in the muscle is returned to the liver and converted back to glucose.

To maintain flux through the pathway it is essential to have ΔG<0 for each step in the pathway. The free-energy changes in gluconeogenesis are inverted compared to glycolysis by the following:

- Steps that have ΔG=0 in glycolysis are reversible and catalyzed by the same enzyme in both pathways. The sign of ΔG is flipped by indirect coupling by the large energy change from the hydrolysis of G-6-P at the end of gluconeogenesis.
- Steps in glycolysis with ΔG<0 in glycolysis cannot be reversed by indirect coupling, so the reactions have to be done by a different mechanism.

There are three steps that are done differently.

i) Pyruvate → PEP
   Use of ATP and GTP (=ATP in energy) to convert Pyr to PEP.

ii) Fructose 1,6P → F-6-P
    Spontaneous hydrolysis of Phos.

iii) Glucose-6-P → Glucose
    Spontaneous hydrolysis of Phos

\[ \Delta G^\circ = -15 \text{kJ/mol} \]

\[ \text{[fructose-1,6-bisphosphatase]} \]

\[ \text{[phosphoglycerate mutase]} \]

\[ \text{[PEP carboxylase]} \]

\[ \text{[pyruvate carboxylase]} \]

\[ \text{[pyruvate kinase]} \]

\[ \text{[glyceroldehyde-3-P dehydrogenase]} \]

\[ \text{[phosphoglycerate kinase]} \]

\[ \text{[3-phosphoglycerate]} \]

\[ \text{[fructose-1,6-bisphosphatase]} \]

\[ \text{[glyceroldehyde-3-P dehydrogenase]} \]
Regulation of Biochemical Pathways:
**General Properties of Regulation:**
- Step below a convergence point is usually regulated — coordinate regulation of many compounds.
- Step that has a high energy drop ($\Delta G < 0$) is usually regulated (e.g. PFK).
- Opposing pathways are coordinately regulated, usually at the same step. (e.g. glucose synthesis/degradation, glycogen synthesis/degradation).

**Mechanisms of Regulation**
(slow $\rightarrow$ fast)
1. **Change in levels of enzymes** by regulation of the synthesis/degradation.
   \[
   v = E_T k_{CAT} [S] / (K_M + [S])
   \]
2. Change in the activity of enzymes by covalent modification, e.g. phosphorylation.

3. **Feedback regulation (FB)** - change in the activity of enzymes due to an allosteric inhibition or activation by a chemical that is near the end of the pathway (e.g. ATP & PFK), or in another pathway (e.g. citrate & PFK).

4. **Product inhibition (PI).** e.g. hexose kinase via G-6P.

5. **Substrate availability** (all enzymes, $K_M = [S]_{in vivo}$). $v \propto [S]$