**Lecture 30: Gluconeogenesis, Pathway Regulation**

**Gluconeogenesis:**

1. **Location**: cytosol
2. **Input**: pyruvate
3. **Output**: glucose
4. **Energetics**: 6 ATP, 2 NADH *required*
5. **Key Reg. Step**: F 1-6 phosphatase.

**Regulation:**

1. General Properties & Mechanisms
2. Local pathway sensing.
3. Inter-pathway communication.
4. Energy Sensing.

**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 is returned to the liver and converted back to glucose.

Steps in the forward pathway that have large negative Gibbs energy are usually accomplished in the reverse pathway by performing the reaction in a different way with a different enzyme. The allows the reverse pathway to operate with a negative Gibbs energy at each step. The use of different enzymes in each pathway also provides a mechanism for coordinated regulation. There are three such steps in glycolysis / gluconeogenesis:



i) Glucose → Glucose-6-P

ii) Fructose-6-P → Fructose 1,6 P

iii) PEP → Pyruvate

These energetically favorable reactions in glycolysis are reversed in gluconeogenesis by:

iii) Use of ATP and GTP (=ATP) to convert Pyr to PEP.

ii) & i) Spontaneous hydrolysis of the phosphate from the sugar.

**General properties of Catabolic and Anabolic pathways:**

|  |  |  |
| --- | --- | --- |
|  | **Catabolic** | **Anabolic** |
| Energy | Produce | Consume |
| Input→out | Complex→Simple | Simple→ Complex |
| Redox | Oxidizing\*:  NADH/ FADH2 produced  (electron acceptors) | Reducing:  NADH/ FADH2 required (electron donors) |

\*lose electrons → oxidation

**Regulation of Biochemical Pathways:**

**General Properties of Regulation:**

* Step *below* a convergence point is usually regulated
* Step that has a high energy change (ΔGo, ΔG) 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 (**fromslow →fast**)**

* **Change in levels of enzymes** by regulation of the synthesis/degradation.
* Change in the activity of enzymes by **covalent modification** ( **phosphorylation**) of the enzyme\*.

\*Indirectly regulates glycolysis/gluconeogenesis.

* **Feedback regulation (FB)** - change in the activity of enzymes due 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)
* **Product** **inhibition (PI)**. e.g. hexose kinase via G-6P
* **Substrate availability** (all enzymes, KM≈[S]in vivo).

**ATP Balance in Cells:**



* ATP is hydrolyzed to produce energy for cellular activities, ADP + inorganic phosphate (Pi)
* ATP is re-synthesized from ADP in oxidative phosphorylation.
* ADP is also converted to ATP by the enzyme **adenylate kinase**, producing AMP as well.
* ATP levels are kept relatively constant; however AMP and ADP levels can change dramatically.

**Regulation of Glycolysis/Gluconeogenesis by Energy Sensing:**

|  |  |  |  |
| --- | --- | --- | --- |
| A cell has **HIGH** energy reserves when: | | **Glycolysis (Glucose→ATP)** | **Gluconeogenesis (→Glucose)** |
| ATP |  |  |  |
| AMP, ADP |  |

|  |  |  |  |
| --- | --- | --- | --- |
| A cell has **LOW** energy reserves when: | | **Glycolysis (Glucose→ATP)** | **Gluconeogenesis (→Glucose)** |
| ATP |  |  |  |
| AMP, ADP |  |

**Allosteric control of – PFK:**



|  |  |
| --- | --- |
| T-state stabilized by | R stabilized by |
| ***ATP***  *Citrate (TCA)* | ***ADP, AMP***  *F2,6P (Hormone)* |

**Allosteric control of Fructose bis-phosphatase-1:**

|  |  |
| --- | --- |
| T-state stabilized by | R stabilized by |
| ***AMP***  *F2,6P (hormone)* | *nothing* |