Glycolysis I

Glycolytic endpoints - depending on which cell and conditions, glucose metabolism results in the production of ethanol, lactate and CO_2, H_2O via pyruvate

- This is the predominate fate of glucose in mammalian cells
- Limited potential energy w/o O_2 . Captured as ATP
- Pathway is found in all cells of the body
- This is primarily a cytosolic pathway

Net reaction:

$$\text{Glucose} + 2\text{ ADP} + 2\text{ P}_i + 2\text{ NAD}^+ \Leftrightarrow 2\text{ Pyruvate} + 2\text{ ATP} + 2\text{ NADH}$$

The overall metabolism can be considered to be in two stages. In the first stage there is a cost of energy (in the form of ATP). Glucose is metabolized to two trisoses - 3 phosphoglycerate. In essence the carbohydrate is activated and prepared for energy production by phosphorylation. The second stage results in the partial oxidation to pyruvate and the formation of energy currency (NADH and ATP).

There are a few items you need to keep in mind when looking at metabolism.

- The structure of the reactants and products
- Where did the carbons come from. Be able to trace the carbons from glucose through each step of glycolysis
- What are the important points for each enzyme... regulation, reaction mechanism, isozymes ...
- The overall control of glycolysis and the fate of the metabolism
- This is more than just memorizing the pathway but you do need to know that too.

Nomenclature points -

- bis vs. di phosphates - two phosphoryl groups bonded by a phosphodiester bond is a "di" phosphate (ADP). While a "bis" phosphate means that two phosphates are bonded onto the molecule on different sites.
- Enolates - "ene" is descriptive for a double bond the "ol" refers to an alcohol group. If there is a phosphate on the OH of an enolate then it is a enol phosphate. This is different than an acyl phosphate. Both enol phosphates and acyl phosphates are high energy bonds.

Structures of glycolysis -

Glucose and phosphate derivatives

Glucose Glucose -6-phosphate

Fructose phosphate

Fructose 6-phosphate -

Ketones

Dihydroxyacetone- Dihydroxyacetone -phosphate-

Aldehydes

Glyceraldehyde- Glyceraldehyde -phosphate-

Sugar acids

Glycerate 3- Phosphoglycerate- Pyruvate-

Reactions of Glycolysis Metabolism

Glucokinase / Hexokinase - (**GK**/**HK**) - key glycolytic enzyme

- Glucokinase in liver only (maintenance of blood glucose levels)
- Hexokinase in nearly all tissues - non specific for various hexoses
- HK has a low affinity for glucose while GK has a high affinity.
- The function of GK is to remove glucose from the blood following a meal
- 1 ATP is consumed - is considered an irreversable step. Also a key glycolytic step
- Mg^{+2} is a common cofactor for the kinases. - the metal forms a complex with the α and β phosphates and allows the γ phosphate to be reactive. EDTA is often used as an inhibitor or kinase reactions - why?
- Phosphorylation helps trap sugar in cells -transport across membranes
- The specific transfer of a phosphoryl from ATP to glucose instead of water is possible due to the conformational change in HK/GK once ATP and glucose is bound. (this is an example of induced fit)

Phosphoglucose Isomerase (**PGI**)

- Isomerase reaction
- Phosphohexose isomerase = phosphoglucose isomerase
- The reaction is a controlled sequence of ->open structure / reaction / close ring
- Acid/ base catalyst mechanism
- Fructose 6-P produced - no energy input

Phosphofructokinase - (**PFK**) key glycolytic enzyme

- ATP consumed, another phosphoryl transfer (kinase) reaction
- Rate determining reaction - first commited step in glycolysis
- Allosterically regulated. Activated by low energy signal AMP. Inhibited by high energy signals, ATP and Citrate. A feedforward and feedback mechansim.
- Fructose -1-6- di P produced

Aldolase

- Molecule split in equal carbons -glyceraldehyde -3-P (GAP) and dihydroxyacetone P (DHAP)
- Two classes of aldolase - class I use a Schiff base and are found in plants and animals. Class II aldolases use Zn^{+2} in the active site.
- Enolate intermediate
- Note where the carbons come from.
- Why not just phosphorylate and split glucose rather than fructose? - F1,6P allow two equal length phosphorylated trioses. These phosphates will later yield ATP!

Triose Phosphoisomerase (**TPI**)
intraconversion of GAP and DHAP
allows for production of 2 molecules of glyceraldehyde 3-P

Glyceraldehyde 3-Phosphate Dehydrogenase (**GAPDH**)
withdraws 2 electrons / NAD+ is acceptor
production of ATP via ox phos later
produces phosphoanhydride bond
leads to production of DPG allosteric regulator of hemoglobin

7) Phosphoglycerate Kinase (**PGK**)
ATP produced through substrate level phosphorylation

8) Phosphoglycerate Mutase (**PGM**)
isomerase reaction

9) Enolase
removal of water - high energy product
floride inhibits by forming tightly bound complex with Mg at active site

10) Pyruvate Kinase (**PK**) key glycolytic enzyme
substrate level phosphorylation / ATP produced
spontaneous shift to keto form

Energy of glycolysis
- which reactions are exothermic and endothermic how does this relate to regulation
- total amount of ATP produced by metabolism of glucose to pyruvate - net gain of 2 ATP (fate of NADH depends on cell type and oxidation state)