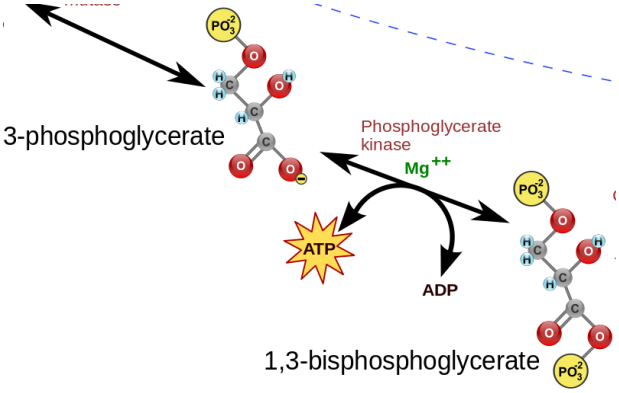
Name:

1. Proteins are major components of all living organisms, which are made as a long polymer of simpler subunits. Yet, they have amazing diversity of shape and function. Describe levels of structure in proteins (primary, secondary etc.) and how that makes it possible to have so much diversity.

   Describe: primary, sequence of amino acids as dictated by DNA; secondary, folding into alpha helices and beta sheets; tertiary, arrangement of full 3-d structure bringing the helices and sheets together; where it occurs, quaternary, linking two or more folded polypeptide chains together into a larger structure.

   A protein's 3-d structure determines its function. Because proteins fold into a vast number of different structures, their functions seem endlessly variable.

2. As shown in the diagram below, in the second part of glycolysis, the molecule 1,3 bisphosphoglycerate is acted on by an enzyme called phosphoglycerate kinase, which removes the phosophate from 1,3 bisphosphoglycerate and transfers it to ADP, releasing ATP.



   a. What is important about this particular reaction in glycolysis?

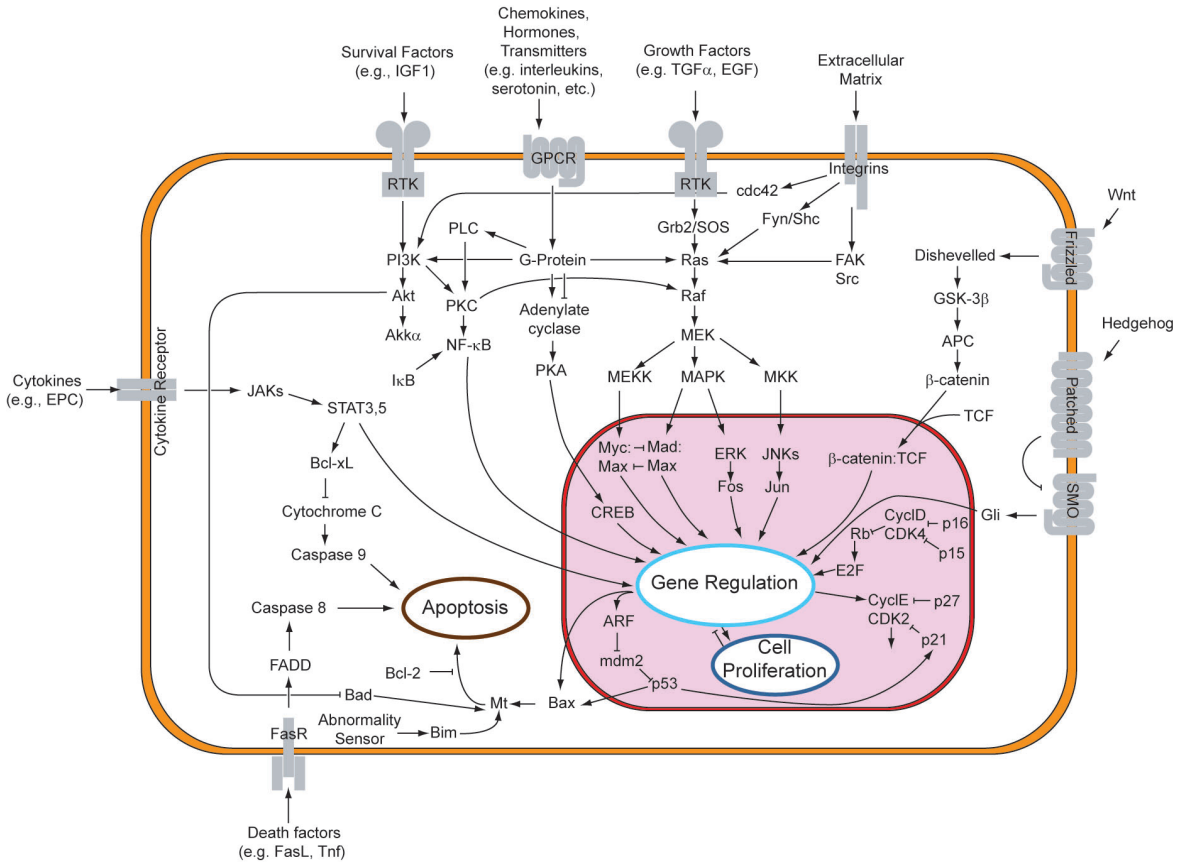
      It is one of the substrate-level phosphorylation steps that generates ATP for use as a source of chemical PE.

   b. Some persons are born with a partially functional phosphoglycerate kinase. The main symptom of this genetic disease is that their red blood cells die. Hypothesize why red blood cells are particularly sensitive to this mutation (hint: you might want to look up details of the structure of red blood cells…how they are different from others.

      RBCs have no mitochondria (or nuclei, for that matter). Thus, they are dependent on glycolysis for ATP. As an aside, they are among the few cells that actually do live in a solution of glucose (~50mM)

Name:

3. OK, this will be fun, I promise. I want you to look up the following four experimental cancer drugs: Navitoclax; U0126; OPB-31121; and T-5224. For the last 3, you may have to include the word "drug" in your search (I didn't have to, but google knows what I like). Figure out where on the diagram below each of these acts and discuss with each other their role in cell signaling and regulating the cell cycle. Below, briefly describe that role and why these are being developed to treat cancer.



Navitoclax is an inhibitor of Bcl-2 and Bcl-xL. Since Bcl-2 and xL are inhibitors of apoptosis, blocking its function (inhibiting the inhibitor), increases sensitivity to apoptotic signals. Thus, it increases apoptosis of cancer cells in response to chemotherapy or to immune system signals.

U0126 is an inhibitor of MEK, which is also known as Map Kinase Kinase. The role of the different MEK proteins is a little complicated to cover here. Trials suggest that this drug results in death of anchorage-independent cells. That is, most cells outside of blood have to be adhered to the extracellular matrix, usually via integrins. The signal from the pathway feeds into general cell-survival pathways. Cancer cells become independent of cell adhesion, which makes them able to migrate to other tissues (metastasize). This drug inhibits MEK enough to make them anchorage dependent again, but not enough to kill normal cells (or, that is the hope). If it works, cells that are in the process of metastasizing will die…good for the patient.

OPB-31121. This is a STAT3 inhibitor, according to its initial publication, maybe STAT2 as well. This inhibitor reduces STAT-induced gene activation. which reduces the stimulatory effects of cytokines. Also, STAT3 stimulates Bcl-xL inhibits apoptosis, inhibiting it makes the cells more sensitive to apoptotic signals (inhibiting the activator of the inhibitor…gets weird, huh?). Block STAT, therefore don't activate Bcl-xL, therefore don't inhibit apoptosis.

T-5224: This one acts directly at the regulation of gene activation. As we will soon see, transcriptional activation (turning "on" genes) is in growth-stimulated cells is mediated by the protein Fos. This drug blocks the activation of Fos and therefore blocks the activation of genes needed for cell growth etc.