Seminar 1 problem collection

Material and energy budget

1. Cancer cells often have highly active glycolysis, and can convert as much as 1pmol of glucose to lactate every hour. At this rate, how long does it take for a cancer cell to consume its own weight in glucose? (Assume some typical mass of a human cell.) What does this mean for a patient with a large tumor?

2. Vitamins are required in minute amounts by human cells. For example, human cells contain about 30 uM folate. What is the rate of folate uptake needed for proliferating cells to maintain folate levels? Compare with glucose! What is the dietary requirement for folate?

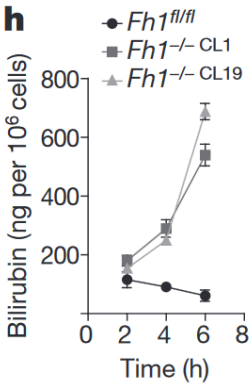
3. How energy-rich is glucose really? Livesey (1984) estimates the actual yield of ATP to be about 12 mol ATP per MJ “metabolizable energy” for sugar, and about 10 mol ATP/ MJ for protein. The “metabolizable energy” is the one commonly found in food nutrient declarations. How much ATP do you get from one gram of glucose or protein? How much from 1 glucose molecule, or from one “average” amino acid residue in protein?

Livesey 1984: http://www.ncbi.nlm.nih.gov/pubmed/6689941

4. Cells in culture need about 1 pmol ATP per hour for basal metabolism. How long could a cell survive by oxidizing its own protein contents for energy?

5. ATP concentration in cells is about 5mM. How long would you expect a cell to survive if ATP synthesis was completely blocked?

6. Frezza et al (Nature 2011) reported that cells with a genetic defect (Fh1-/-) in the TCA cycle can produce some ATP by producing bilirubin as a waste product (an “escape valve”) which allows cells to respire. For each bilirubin produced, about 5 ATP could be obtained. The authors' bilirubin data is shown in the figure. Is the mechanism reasonable from a quantitative standpoint?



7. How much ammonia would an average cell produce per hour if oxidizing only protein for energy? Ammonia becomes toxic at around 5mM. How long would it take for ammonia to reach toxic levels in cell culture? In human tissues?

8. A human adipocyte can be 100uM in diameter. How long could an adipocyte survive if it would oxidize all of its fat contents for energy? Assume that the fat is similar to palmitate, and yield of about 100 ATP for a palmitate molecule.

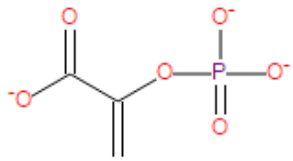
9. An average adult turns requires about 10,000 kJ (2500 kcal) of energy per day. How many ATP equivalents (Gibb's energy of hydrolysis) does this correspond to if translated directly? Do you think the estimate is realistic?

10. Proliferating cells must renew all their components every cell cycle. Based on biomass composition, what metabolites are in highest demand? What consumes the most carbon – biomass synthesis or ATP production?

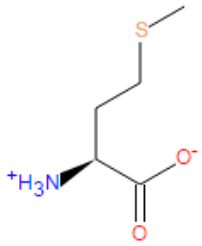
11. ATP and other high-energy molecules are only intermediates in metabolism that carry energy. In the end, where does all the energy consumed by cells (or people) go?

Oxidation and reduction

1. What is the definition of an oxidation number? What are the oxidation numbers for the various carbons in the metabolites below?



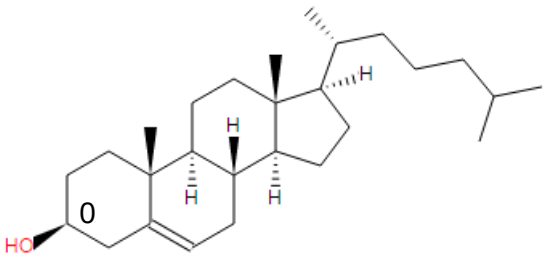
phosphoenolpyruvate



methionine

guanine

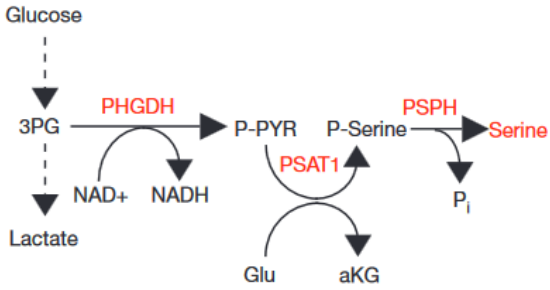
2. Cholesterol (below) is a rather complex, hydrophobic molecule which is synthesized by a complicated pathway, starting from acetyl-CoA. Without looking at this pathway, can you tell if it is oxidative or reductive? What electron carrier do you expect to be active in the pathway? Does the synthesis require energy?



3. Purine nucleotides like guanine (problem 1, above) are synthesized from amino acids and formyl (aldehyde) groups. Is this an oxidative or reductive pathway?

4. The first step in catabolism of amino acids is usually an aminotransferase. For example, look up alanine aminotransferase. Is this a redox enzyme? (Are carbons being oxidized / reduced?) Does the reaction require energy?

5. Synthesis of the amino acid serine from the glycolytic intermediate 3-phosphoglycerate (Figure left, from Possemato et al, Nature 2011) is considered an important pathway in proliferating cells. Which reactions in this pathway are redox-reactions? What is being oxidized, reduced? Is energy required for serine synthesis?



6. What are the major electron carriers for oxidative and reductive metabolism, respectively? Why are the two processes separated? What enzymes of pathways can you find that use each electron carrier?

7. Look up the structure for NAD and identify the redox active site. Compare with the structure of NADP. What function does the extra phosphate group in NADP serve? What "metabolites" (moieties) does NAD(P) consist of? How many electrons are transferred when NAD(P) is reduced to NAD(P)H?

8. Flavin adenine dinucleotide (FAD) is another major electron carrier. How many electrons are transfered when it is reduced to $FADH_2$? What is the major difference in function between FAD and NAD(P) ?

9. The amino acid cysteine has a --SH group that is prone to conversion to cysteine dimers, --S-S--, in the presence of oxygen. Is this an oxidation or reduction? What atom is being oxidized / reduced ? What does this means for cells that need to keep --SH groups intact?

Carbohydrates

1. What is the yield of ATP and NADH when catabolizing glucose to lactate? Which are the ATP-yielding enzymes?

2. What happens with the cytosolic NADH produced by glycolysis?

3. Acid-base homeostasis is an important factor for glycolysis. Which reactions of glycolysis produce protons? What is the overall balance of H+ when glucose is converted to pyruvate, or to lactate?

4. Some cell types take up lactate from their surroundings as fuel, converting it to pyruvate which is then oxidized in the mitochondrion. What does this mean for NAD/NADH balance in the cytosol? How does it affect H+ balance?

5. Intermediates of the glycolytic pathway are also used for biosynthesis of other compounds. For example, dihydroxyacetone-phosphate can be converted to glycerol for synthesis of various lipids, and 3-phosphoglycerate can be converted to serine. What is the energetic cost when these compounds are "drained" from glycolysis?

6. What would (theoretically) happen to cellular pH if lactate dehydrogenase is blocked experimentally in a glycolytic cell? Consider all components of the reaction.

7. While glucose is the main blood sugar in humans, glyceraldehyde is the precursor of the energy-yielding steps in lower glycolysis. Would it not be more advantageous for a cell to take up and catabolize glyceraldehyde? Can you think of reasons why glyceraldehyde is *not* the main blood sugar?

8. Fructose is an important sugar in the human diet, on par with glucose in abundance. Look up the pathway that catabolized fructose. How does it differ from / relate to glycolysis? Is the energy yield of fructose catabolism comparable to glucose?

9. Galactose is another dietary sugar. It is catabolized via the Leloir pathway. Lookup the pathway in humancyc. How does it compare to that of glucose or fructose? Are there corresponding enzymes? At what point do the pathways "connect" ? Compare with the bow-tie model of metabolism.

10. Glucose-6-phosphate pool can be obtained from glycogen instead of glucose. Lookup / draw the pathway leading from glycogen to glucose-6-phosphate. What is the ATP yield when catabolizing glycogen to lactate? Compare this with the yield of glycolysis from glucose. What is the difference?

11. The liver can contain 3--7% glycogen w/w in the fasted state. How much glucose does this represent? How long would its energy sustain basal BMR, or heavy exercise?