CMB311 Fall 2017

Wednesday, October 11

Lecture 13 Notes

Metabolism Overview

Metabolism can be defined as the sum of all the chemical processes or biochemical pathways that occur inside the cell. That's a pretty vague definition, and we'd prefer to think of metabolism in more precise terms. Metabolism serves two main puposes: the aquisition of carbon for the biosynthesis of molecules to suit the cell's needs, and the aquisition of energy to carry out those processes. Remember that one way to think of biology is as a system of chemical reactions, many of which are driven away from equilibrium. Life is entropically unfavorable, and energy is required to produce the highly complex molecules needed for life. Most notable in this regard are the macromolecules (proteins and nucleic acids) which left on their own would eventually break down to amino acids and nucleotides. Thus, cells need energy and a carbon source.

In any case, metabolic processes are all catalyzed by enzymes, almost all of which are proteins. We studied enzyme kinetics in some detail earlier in the course, as purified entities removed from all other cellular components. Of course, this is a situation that's very different from the environment in which enzymes normally find themselves. In particular, enzyme reactions carried out in a laboratory eventually reach equilibrium, a situation that does not occur inside a cell. *In vivo*, substrates are constantly replenished, as they are the products of a previous step in a pathway, and reaction products do not accumulate, as they are consumed as substrates for the next step in a pathway. As a result, reactions that may not have favorable $\Delta G^{\circ'}$ values can nevertheless be driven forward by the rapid removal of reaction products by the next enzyme.

We can think of metabolism as the sum of two distinct processes, *catabolism* and *anabolism*. Metabolism thus includes the synthesis of molecules to suit the cell's needs, as well as the breakdown of molecules to yield energy to fuel macromolecular synthesis. We can define catabolism and anabolism as follows:

Catabolism = the breakdown of big molecules into little ones, yielding energy. This also involves the transfer of electrons to acceptor molecules. The overall process is one of oxidation.

Anabolism = the synthesis of precursors for macromolecular synthesis. This requires energy and involves the transfer of electrons to donor molecules. The overall process is one of reduction.

Redox reactions are central to metabolism. As stated above, catabolism involves oxidation reactions, while anabolism involves reduction reactions. You should be able to ascertain whether a reaction is an

oxidation or a reduction reaction based on the functional groups being changed. For instance, carbonyls are more oxidized than alcohols. So, going from the more reduced to the more oxidized would be alkane, alcohol, carbonyl, carboxylic acid, CO_2.

Biological Redox reactions involve the participation of coenzymes. The most important ones are NAD (nicotinamide adenine dinucleotide), FMN (flavin mononucleotide) and FAD (flavin adenine dinucleotide). These molecules act as electron acceptors and are reduced during metabolism. They are subsequently re-oxidized to generate ATP via electron transport and oxidative phosphorylation, which we will discuss in future lecture.

There is a great deal of diversity in how organisms carry out metabolism. Nevertheless, all forms of metabolism require three things.

1. Energy Source (light, organic molecules, or reduced inorganic molecules)
2. Carbon Source (organic molecules or CO_2)
3. Terminal electron acceptor (O_2 or oxidized inorganic compounds)

The oxidation of organic molecules can yield a great deal of energy. The complete oxidation of glucose to $6CO_2$ and $6H_2O$ yields 2878.4 kJ/mol. While such reactions taking place in a test tube release energy as heat, cells capture this energy in the form of chemical bonds, which is useful for doing work such as biosynthesis of biomolecules. This is done via the coupling of oxidation reactions to the formation of high-energy compounds, specifically adenosine triphosphate or ATP. ATP is synthesized by phosphorylation of adenosine diphosphate or ADP, a process requiring 30.5 kJ/mol. Our example of the oxidation of glucose to CO_2 therefore yields a lot of energy in the form of ATP, but only a small amount of ATP is *directly* produced by oxidation of glucose. Oxidation requires a concurrent reduction reaction in which hydrogens and their associated electrons are transferred to electron carriers such as nicotinamide adenine dinucleotide (NAD^+) or flavin adenine dinucleotide (FAD) to produce NADH and $FADH_2$, respectively, which in turn carry electrons to the electron transport system to generate ATP using a proton motive force (more about that in a few weeks). Just remember that the oxidation of organic molecules generates energy primarily by the transfer of electrons to this system. Ultimately, electrons need to be transferred to a terminal electron acceptor, which in our case is O_2.

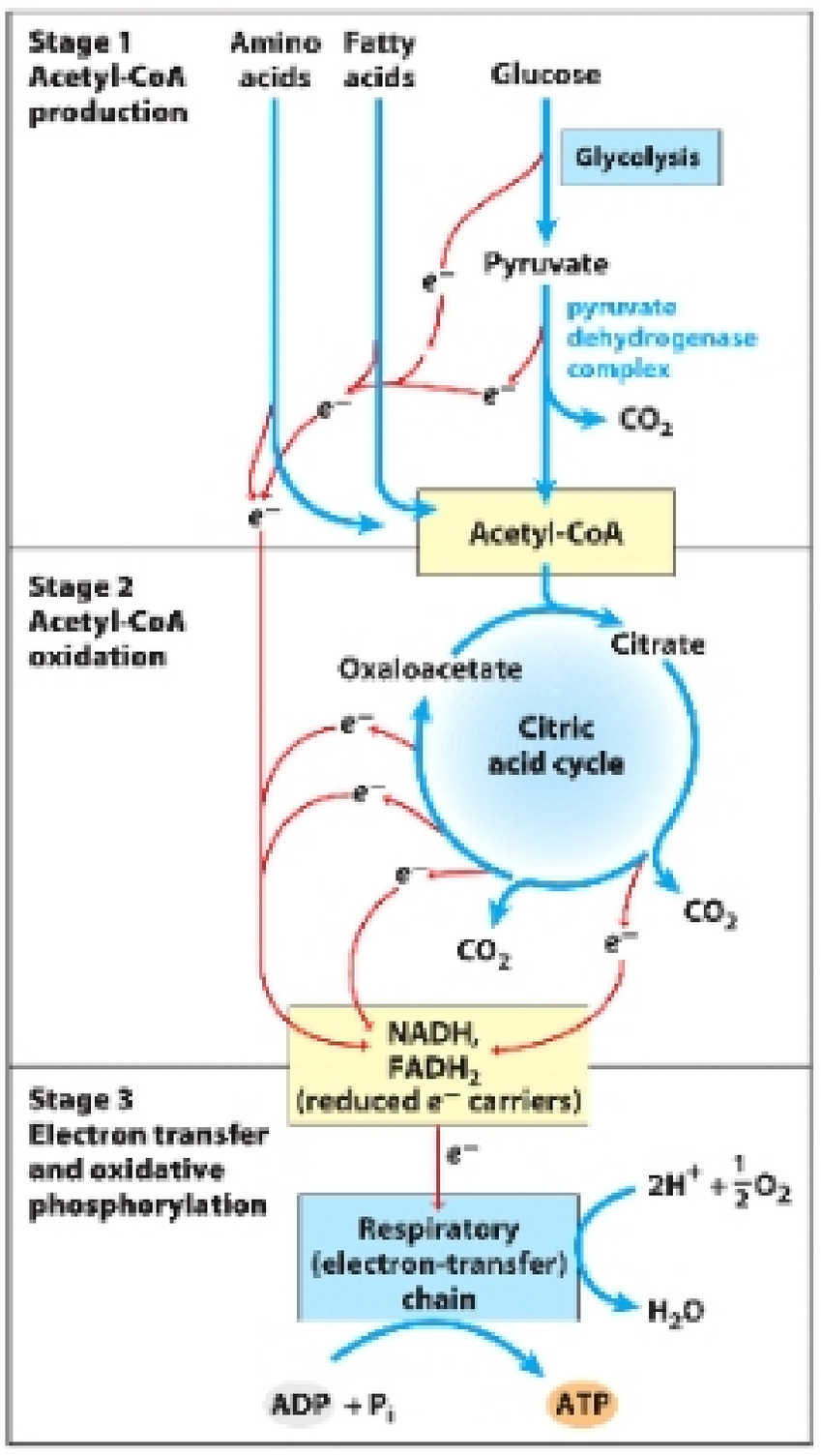
Once formed, ATP can then be used for processes that require energy, such as the biosynthesis of more complex biomolecules. These processes involve the oxidation of the cofactors reduced during catabolism, e.g. oxidation of NADH to NAD^+ (actually a phophorylated form of NAD called NADP, NADPH) and $FADH_2$ to FAD. Note that for us, organic molecules such as glucose serve as both (1) a carbon source for biosynthesis and (2) an energy source, i.e. as electron donors. Some organisms us CO_2 as a carbon source and obtain energy from reduced inorganic molecules, which serve as electron donors for energy

production. Plants and photosynthetic bacteria use CO_2 as a carbon source, visible light as an energy source, H_2O as an electron donor, and O_2 as a terminal electron acceptor.

ATP is often referred to as the cell's energy currency. This is because the phosphate bonds are high-energy bonds, and their hydrolysis yields large amounts of energy ($\Delta G^{\circ\prime}$ -30.5 kJ/mol). The high energy yield is due to three factors:

1. Relief of electrostatic repulsion of the three negative charges on the phosphates.
2. Stabilization of the resonance of the phosphate ion (even distribution of the negative charge among the four oxygen atoms.
3. Hydration of the phosphate ion; also the high concentration of H_2O favors hydrolysis.

There are other important organophosphates. One of these is phosphoenol pyruvate (PEP), which is an intermediate in glycolysis. PEP has the highest energy phosphate bond known ($\Delta G^{\circ\prime}$ -62 kJ/mol). In the case of PEP, hydrolysis is also favored by the ability of the resulting product, pyruvate, to alternate between an enol tautomer and a keto tautomer, preventing the reverse reaction.



An important concept in metabolism is the coupling of reactions. While many reactions release energy (are **exergonic**), many require energy (are **endergonic**). One way to provide energy for an endergonic reaction is to couple it to a second reaction that involves the breaking of high-energy bonds, such as the phosphate bonds of ATP. The $\Delta G^{\circ\prime}$ of a coupled reaction can be calculated simply by adding the $\Delta G^{\circ\prime}$ values of the individual reactions. Although reactions are often written as if they involve the hydrolysis of ATP, what actually happens is the transfer of phosphate groups from ATP to something else. For instance, the conversion of glutamic acid to glutamine involves the addition of an ammonia to the carboxylate of glutamate coupled to ATP hydrolysis with the release of ADP and P_i. What actually happens is that a phosphate is transferred from ATP to the glutamate carboxyl group in the first step, which is replaced by ammonia in the second step.

An important cofactor is coenzyme A. This molecules is involved in acyl group transfers. Many molecules are eventually broken down to two-carbon molecules that are carried by CoA, which in turn enters the TCA