Cellular Respiration

1. To perform cell work, cells require energy.
   a. A cell does three main kinds of work:
      i. **Mechanical work**, such as the beating of cilia, contraction of muscle cells, and movement of chromosomes during cellular reproduction.
      ii. **Transport work**, the pumping of substances across membranes against the direction of spontaneous movement.
      iii. **Chemical work**, driving endergonic reactions such as the synthesis of polymers from monomers.
   b. Cells manage their energy resources to do this work by **energy coupling,** using an exergonic reaction (one that releases energy) to drive an endergonic one (one that absorbs energy).
   c. Basically, enzymes catalyze the breakdown of high energy organic molecules to simpler, low energy products. Some of the released energy is used to do work; the rest is lost as heat. Specifically, 40% is converted to ATP while 60% of the energy from glucose is lost as heat. Some of that heat is used to maintain our high body temperature (37°C).
   d. Cells harvest the chemical energy stored in these organic molecules and use it to make ATP, the molecule that is the energy source for most cell work. This process is called **cellular respiration**.
      i. Although carbohydrates, fats, and proteins can all be used as the fuel, most cells prefer to use glucose:

         $C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O$ + Energy (ATP + heat)
      ii. **ATP (adenosine triphosphate)** is a type of nucleotide consisting of the nitrogenous base adenine, the sugar ribose, and a chain of three phosphate groups.
      iii. The bonds between phosphate groups can be broken by hydrolysis. Hydrolysis of the end phosphate group forms adenosine diphosphate. Because the phosphate bonds of ATP are high-energy bonds, they are unstable, and their hydrolysis yields energy because the products are more stable. The release of energy during the hydrolysis of ATP comes from the change to a state of lower energy, not from the phosphate bonds themselves.
      iv. Why does the hydrolysis of ATP yield so much energy?
         (1) Each of the three phosphate groups has a negative charge.
         (2) These three like charges are crowded together, and their mutual repulsion contributes to the instability of this region of the ATP molecule.
   e. In the cell, the energy from the hydrolysis of ATP is directly coupled to endergonic processes by the transfer of the phosphate group to another molecule.
      i. This recipient molecule is now said to be **phosphorylated** and is now more reactive (less stable) than the original unphosphorylated molecule.
      ii. To perform work, a phosphate group is transferred from ATP to another molecule and the phosphorylated molecule undergoes a change that performs work.
   f. ATP is a renewable resource that can be regenerated by the addition of a phosphate group to ADP.
      i. The energy to phosphorylate ADP comes from catabolic reactions in the cell.
      ii. A working muscle cell recycles its entire pool of ATP once each minute.
      iii. More than 10 million ATP molecules are consumed and regenerated per second per cell. (1 Cal = 8.2×10^{19} ATP)
   g. Mitochondria (singular, mitochondrion)

i. In eukaryotic cells, cellular respiration occurs in the mitochondria.
ii. Mitochondria have two membranes, an inner and an outer. All the equipment the cell needs for cellular respiration is on the inner membrane. To maximize the amount of energy produced, the inner membrane is highly folded to provide a huge surface area.

h. The large amount of energy in glucose is released in many small steps to produce the small, useable amount in ATP.

2. Catabolic pathways transfer the electrons stored in food molecules closer to more electronegative atoms, releasing energy that is used to synthesize ATP.
   a. Reactions release energy when electrons move closer to electronegative atoms.
   b. Reactions that result in the transfer of one or more electrons from one molecule to another are called oxidation-reduction reactions, or **redox reactions**. In biology, the transfer of electrons is usually not complete but results in a change in the amount of sharing of the electrons.
      i. The loss of electrons is called **oxidation**.
      ii. The addition of electrons is called **reduction**.
      iii. In general: $Xe^- + Y \rightarrow X + Ye^-$
         (1) X, the electron donor, is the **reducing agent** and reduces Y.
         (2) Y, the electron recipient, is the **oxidizing agent** and oxidizes X.
         (3) Redox reactions require both a donor and acceptor.
   c. Energy is released when electrons move toward electronegative atoms (such as oxygen); energy must be added to pull electrons away from electronegative atoms. The more electronegative the atom, the more energy is involved in moving electrons toward or away from it.
   d. Oxidation is always accompanied by a net release of energy, producing products that are more stable than the reactants. Reduction is the opposite.
   e. H^+ and electrons (and their energy) are removed from glucose and accepted by NAD^+ which becomes NADH (a reduction); NADH is the carrier of electrons.
      i. Dehydrogenase enzymes strip two hydrogen atoms from the fuel (*e.g.*, glucose), oxidizing it. The enzyme passes two electrons and one proton to NAD^+. The other proton is released as H^+ to the surrounding solution.
      ii. This explains why lipids (which have lots of H atoms) have much more energy than carbohydrates.
   f. The process of cellular respiration is, basically, a big oxidation - glucose is oxidized to carbon dioxide.
      i. Cellular respiration does not oxidize glucose in a single step that transfers all the hydrogen in the fuel to oxygen at one time. Rather, glucose and other fuels are broken down in a series of steps, each catalyzed by a specific enzyme. At key steps, electrons are stripped from the glucose.
   g. Cellular respiration has three major steps: glycolysis, the Krebs cycle, and electron transport.

3. **Glycolysis** occurs in the cytoplasm and begins catabolism by breaking glucose into two molecules of pyruvate.
   a. During glycolysis, glucose, a six carbon-sugar, is split into two three-carbon sugars.
   b. The steps of glycolysis can be divided into two phases: an energy investment phase and an energy payoff phase.

i. In the energy investment phase, the cell invests 2 ATP to provide activation energy by phosphorylating glucose.
ii. In the energy payoff phase, 4 ATP are produced and NAD^+ is reduced to **NADH** by electrons released by the oxidation of glucose.

c. The NADH produced passes the electrons to the electron transport chain.
d. Note in step 5 that the energy released from the oxidation is used to attach a phosphate to **PGAL**. The resulting 2 phosphate compound immediately gives up one of the phosphates to ADP and two ATP are created. The cell has capitalized on the fact that oxidation reactions release energy.
e. The product, **pyruvate** (or pyruvic acid) is the starting material for the next step (the Krebs cycle) and it enters the mitochondrion where that occurs.
f. Note that glycolysis can occur whether O_2 is present or not.

4. The **citric acid cycle** (or **Krebs Cycle**) occurs in the mitochondrial matrix. It completes the breakdown of glucose by oxidizing pyruvate to carbon dioxide.
   a. More than three-quarters of the original energy in glucose is still present in the two molecules of pyruvate (remember the yield is only two ATP).
   b. If oxygen is present, pyruvate enters the mitochondrion where the enzymes of the citric acid cycle complete the oxidation of the fuel to carbon dioxide.
   c. The purpose of the cycle is to produce NADH, the electron carrier, which passes these electrons to the electron transport chain.
   d. Notice that CO_2 is a highly oxidized, therefore low energy, product.
   e. The cycle produces ATP, NADH, and CO_2.

5. <u>**E**</u>lectron <u>**T**</u>ransport <u>**C**</u>hain
   a. Cellular respiration uses an **electron transport chain** to break the fall of electrons to O_2 into several steps.
   b. The electron transport chain is a collection of molecules embedded in the folded inner membrane of the mitochondrion. The folding of the membrane increases its surface area, providing space for thousands of copies of the chain in each mitochondrion.
   c. In the electron transport chain, the electrons move from molecule to molecule until they combine with molecular oxygen and hydrogen ions to form water. As they are passed along the chain, the energy carried by these electrons is transformed in the mitochondrion into a form that can be used to synthesize ATP in a process called **oxidative phosphorylation.**
      i. Oxidative phosphorylation produces almost 90% of the ATP generated by respiration. Some ATP is also formed directly during glycolysis and the citric acid cycle by **substrate-level phosphorylation.**
         (1) Here an enzyme transfers a phosphate group from an organic substrate to ADP, forming ATP.
   d. Electrons released from food are shuttled by NADH to the "top" higher-energy end of the chain. At the "bottom" lower-energy end, oxygen captures the electrons along with H^+ to form water.
   e. The electrons are passed to stronger and stronger electron acceptors and, each time, energy is transformed into a form that can be used to synthesize ATP.
      i. The electron transport chain generates no ATP directly. Its function is to break the large amount of energy in food in manageable amounts.
   f. Each component of the chain becomes reduced when it accepts electrons from its "uphill" neighbor, which is less electronegative. It then returns to its oxidized form as it passes

electrons to its more electronegative "downhill" neighbor.

g. The last acceptor of the chain passes its electrons to oxygen, which is very electronegative. Each oxygen atom also picks up a pair of H^+ to form water. Note that water is a low energy product which shows that most of the energy in the original fuel has been extracted.

h. The function of the chain is to release the large amount of energy from food in a series of small steps, in manageable amounts. The overall net energy yield from cellular respiration is 36-38 ATP/glucose molecule.

i. The mitochondrion couples electron transport and energy release to ATP synthesis using a mechanism called **chemiosmosis.**

   i. A protein complex, **ATP synthase,** in the folds of the inner membrane actually makes ATP from ADP and P.

   ii. The chain is an energy converter that uses the exergonic flow of electrons to pump H^+ from the matrix into the intermembrane space.

      (1) Certain members of the electron transport chain accept and release H^+ along with electrons such that protons are accepted from the mitochondrial matrix and deposited in the intermembrane space.

      (2) The H^+ gradient that results is the **proton-motive force.**

   iii. The protons pass back to the matrix through a channel in ATP synthase, using the exergonic flow of H^+ to drive the phosphorylation of ADP.

6. Fermentation (fermentum, L - yeast, or to leaven) enables some cells to produce ATP in the absence of oxygen.

   a. Without oxygen to accept electrons in the electron transport chain, most of cellular respiration stops, but fermentation provides a mechanism by which some cells can continue to oxidize organic fuel and generate ATP.

   b. In glycolysis, glucose is oxidized to two pyruvate molecules with NAD^+ being reduced to NADH. Fermentation can generate ATP from glucose by substrate-level phosphorylation as long as there is a supply of NAD^+ to accept electrons. If the NAD^+ pool is exhausted, glycolysis shuts down.

   c. Under aerobic conditions, NADH transfers its electrons to the electron transfer chain, recycling NAD^+. Under anaerobic conditions, pyruvate then accepts electrons from NADH, oxidizing it back to NAD^+. The NAD^+ is then available to oxidize more glucose.

   d. Because the pyruvate does not enter the citric acid cycle, there is still a lot of energy which is not removed from the fuel. This is evident in yeast fermentation where the end product is alcohol - a high energy fuel.

   e. Human muscle cells switch from aerobic respiration to lactic acid fermentation to generate ATP when O_2 is scarce. When O_2 is absent, the ETC stops; therefore pyruvate accepts electrons, forming lactic acid. This waste product causes muscle fatigue and cramping, but it is eventually converted back to pyruvate in the liver.

   f. Under aerobic respiration, a molecule of glucose yields 36-38 ATP, but the same molecule of glucose yields only 2 ATP under anaerobic respiration.

7. Glycolysis can accept a wide range of carbohydrates as fuel

   a. Polysaccharides like starch or glycogen can be hydrolyzed to glucose monomers that enter glycolysis.

   b. Other monosaccharides, such as galactose and fructose, can also be modified to undergo glycolysis.

   c. The other two major fuels, proteins and fats, can also enter the respiratory pathways used by carbohydrates.

    i. Proteins must first be digested to individual amino acids which then have their amino groups removed.
    ii. The nitrogenous waste is excreted as ammonia, urea, or another waste product.
    iii. The carbon skeletons are modified by enzymes and enter into glycolysis or the citric acid cycle, depending on their structure.

d. Fats must be digested to glycerol and fatty acids.
    i. Glycerol can enter glycolysis.
    ii. The rich energy of fatty acids is accessed as fatty acids are split into two-carbon molecules that enter the citric acid cycle.
e. Intermediates in glycolysis and the citric acid cycle can be diverted to anabolic pathways.
    i. For example, a human cell can synthesize about half the 20 different amino acids by modifying compounds from the citric acid cycle.
    ii. Glucose can be synthesized from pyruvate; fatty acids can be synthesized from acetyl CoA.
    iii. Excess carbohydrates and proteins can be converted to fats through intermediaries of glycolysis and the citric acid cycle.

8. The rate of catabolism is also regulated, typically by the level of ATP in the cell.
    a. If ATP levels drop, catabolism speeds up to produce more ATP.
    b. The third step of glycolysis is catalyzed by phosphofructokinase. Allosteric regulation of phosphofructokinase sets the pace of respiration.
        i. It is inhibited by ATP and stimulated by AMP (derived from ADP).
        ii. When ATP levels are high, inhibition of this enzyme slows glycolysis. As ATP levels drop and ADP and AMP levels rise, the enzyme becomes active again and glycolysis speeds up.
        iii. Citrate, the first product of the citric acid cycle, is also an inhibitor of phosphofructokinase.
        iv. This synchronizes the rate of glycolysis and the citric acid cycle.
        v. If intermediaries from the citric acid cycle are diverted to other uses (e.g., amino acid synthesis), glycolysis speeds up to replace these molecules.