Chapter 9 - Cellular Respiration: Harvesting Chemical Energy

Overview: Life Is Work

- To perform their many tasks, living cells require energy from outside sources.
- Energy enters most ecosystems as sunlight and leaves as heat.
- In contrast, the chemical elements essential for life are recyled.
- Photosynthesis generates oxygen and organic molecules that the mitochondria of eukaryotes (including plants and algae) use as fuel for cellular respiration.
- Cells harvest the chemical energy stored in organic molecules and use it to regenerate ATP, the molecule that drives most cellular work.
- Respiration has three key pathways: glycolysis, the citric acid cycle, and oxidative phosphorylation.

Concept 9.1 Catabolic pathways yield energy by oxidizing organic fuels.

- Catabolic metabolic pathways release the energy stored in complex organic molecules.
- Electron transfer plays a major role in these pathways.
- The arrangement of atoms of organic molecules represents potential energy.
- Enzymes catalyze the systematic degradation of organic molecules that are rich in energy to simpler waste products that have less energy.
- Some of the released energy is used to do work; the rest is dissipated as heat.
- One type of catabolic process, **fermentation**, leads to the partial degradation of sugars without the use of oxygen.
- A more efficient and widespread catabolic process, **aerobic respiration,** consumes oxygen as a reactant to complete the breakdown of a variety of organic molecules.
    - Most eukaryotic and many prokaryotic organisms can carry out aerobic respiration.
    - Some prokaryotes use compounds other than oxygen as reactants in a similar process called *anaerobic respiration*.
    - Although **cellular respiration** technically includes both aerobic and anaerobic processes, the term is commonly used to refer only to the aerobic process.
- Aerobic respiration is similar in broad principle to the combustion of gasoline in an automobile engine after oxygen is mixed with hydrocarbon fuel.
    - Food is the fuel for respiration. The exhaust is carbon dioxide and water.
- The overall catabolic process is: organic compounds + O_2 CO_2 + H_2O + energy (ATP + heat).
- Carbohydrates, fats, and proteins can all be used as the fuel, but it is most useful to consider glucose:

$$C_6H_{12}O_6 + 6O_2 \quad 6CO_2 + 6H_2O + \text{energy (ATP + heat)}$$

- The catabolism of glucose is exergonic, with $G = -686$ kcal per mole of glucose.
- Some of this energy is used to produce ATP, which can perform cellular work.
- *Redox reactions release energy when electrons move closer to electronegative atoms*.
- Catabolic pathways transfer the electrons stored in food molecules, releasing energy that is used to synthesize ATP.
- Reactions that result in the transfer of one or more electrons (e^-) from one reactant to another are oxidation-reduction reactions, or **redox reactions**.
    - The loss of electrons from a substance is called **oxidation**.
    - The addition of electrons to another substance is called **reduction**.

- *Adding* electrons is called *reduction* because negatively charged electrons added to an atom *reduce* the amount of positive charge of that atom.

- The formation of table salt from sodium and chloride, $Na + Cl \rightarrow Na^+ + Cl^-$, is a redox reaction.
  - Sodium is oxidized, and chlorine is reduced (its charge drops from 0 to –1).
- More generally: $Xe^- + Y \rightarrow X + Ye^-$.
  - X, the electron donor, is the **reducing agent** and reduces Y by donating an electron to it.
  - Y, the electron recipient, is the **oxidizing agent** and oxidizes X by removing its electron.
- Redox reactions require both a donor and an acceptor.
- Redox reactions also occur when the transfer of electrons is not complete but involves a change in the degree of electron sharing in covalent bonds.
- In the combustion of methane to form water and carbon dioxide, the nonpolar covalent bonds of methane (C—H) and oxygen (O=O) are converted to polar covalent bonds (C=O and O—H).
- When methane reacts with oxygen to form carbon dioxide, electrons end up farther away from the carbon atom and closer to their new covalent partners, the oxygen atoms, which are very electronegative.
  - In effect, the carbon atom has partially "lost" its shared electrons. Thus, methane has been oxidized.
- The two atoms of the oxygen molecule (O_2) share their electrons equally.

- When oxygen reacts with the hydrogen from methane to form water, the electrons of the covalent bonds are drawn closer to the oxygen.
  - In effect, each oxygen atom has partially "gained" electrons, and so the oxygen molecule has been reduced.
  - Oxygen is very electronegative and is one of the most potent of all oxidizing agents.
- Energy must be added to pull an electron away from an atom.
- The more electronegative the atom, the more energy is required to take an electron away from it.
- An electron loses potential energy when it shifts from a less electronegative atom toward a more electronegative one.
- A redox reaction that relocates electrons closer to oxygen, such as the burning of methane, releases chemical energy that can do work.
- *Organic fuel molecules are oxidized during cellular respiration.*
- Respiration, the oxidation of glucose and other molecules in food, is a redox process.
- In a series of reactions, glucose is oxidized and oxygen is reduced.
- The electrons lose potential energy along the way, and energy is released.
- Organic molecules that contain an abundance of hydrogen are excellent fuels.
- The bonds of these molecules are a source of "hilltop" electrons, whose energy may be released as the electrons "fall" down an energy gradient when they are transferred to oxygen.
- As hydrogen is transferred from glucose to oxygen, the energy state of the electron changes.
- In respiration, the oxidation of glucose transfers electrons to a lower energy state, releasing energy that becomes available for ATP synthesis.
- The main energy foods, carbohydrates and fats, are reservoirs of electrons associated with hydrogen.
- These molecules are stable because of the barrier of activation energy.
  - Without this barrier, a food molecule like glucose would combine almost

instantaneously with O_2.

- If activation energy is supplied by igniting glucose, it burns in air, releasing 686 kcal (2,870 kJ) of heat per mole of glucose (about 180 g).
- This reaction cannot happen at body temperatures.
- Instead, enzymes within cells lower the barrier of activation energy, allowing sugar to be oxidized in a series of steps.

- *The "fall" of electrons during respiration is stepwise, via NAD^+ and an electron transport chain.*
- 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.
- In many oxidation reactions, the electron is transferred with a proton, as a hydrogen atom.
- The hydrogen atoms are not transferred directly to oxygen but are passed first to a coenzyme called **NAD^+** (nicotinamide adenine dinucleotide).
- As an electron acceptor, NAD^+ functions as an oxidizing agent during respiration.
- How does NAD^+ trap electrons from glucose?
  - Dehydrogenase enzymes strip two hydrogen atoms from the substrate (glucose), thus oxidizing it.
  - The enzyme passes two electrons and *one* proton to NAD^+.
  - The other proton is released as H^+ to the surrounding solution.
- By receiving two electrons and only one proton, NAD^+ has its charge neutralized when it is reduced to NADH.
  - NAD^+ functions as the oxidizing agent in many of the redox steps during the breakdown of glucose.
- The electrons carried by NADH lose very little of their potential energy in this process.
- Each NADH molecule formed during respiration represents stored energy. This energy is tapped to synthesize ATP as electrons "fall" down an energy gradient from NADH to oxygen.
- How are electrons extracted from glucose and stored in NADH finally transferred to oxygen?
- Unlike the explosive release of heat energy that occurs when H_2 and O_2 are combined (with a spark for activation energy), cellular respiration uses an **electron transport chain** to break the fall of electrons to O_2 into several steps.

- The electron transport chain consists of several molecules (primarily proteins) built into the inner membrane of a mitochondrion of eukaryotic cells and the plasma membrane of aerobically respiring prokaryotes.
- 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.
- Electron transfer from NADH to oxygen is an exergonic reaction with a free-energy change of –53 kcal/mol.
- Electrons are passed to increasingly electronegative molecules in the chain until they reduce oxygen, the most electronegative receptor.
- Each "downhill" carrier is more electronegative than, and thus capable of oxidizing, its "uphill" neighbor, with oxygen at the bottom of the chain.
- The electrons removed from glucose by NAD^+ fall down an energy gradient in the electron

transport chain to a far more stable location in the electronegative oxygen atom.

- In summary, during cellular respiration, most electrons travel the following "downhill" route: glucose NADH electron transport chain oxygen.
- *The stages of cellular respiration: a preview*.
- Respiration occurs in three metabolic stages: glycolysis, the citric acid cycle, and the electron transport chain and oxidative phosphorylation.
- **Glycolysis** occurs in the cytosol. It begins catabolism by breaking glucose into two molecules of pyruvate.
- The **citric acid cycle** occurs in the mitochondrial matrix of eukaryotic cells or in the cytoplasm of prokaryotes. It completes the breakdown of glucose by oxidizing a derivative of pyruvate to carbon dioxide.
- Several steps in glycolysis and the citric acid cycle are redox reactions in which dehydrogenase enzymes transfer electrons from substrates to NAD^+, forming NADH.
- In the third stage of respiration, the electron transport chain accepts electrons from the breakdown products of the first two stages (most often via NADH).
- 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 the electrons are passed along the chain, the energy released at each step in the chain is stored in a form the mitochondrion (or prokaryotic cell) can use to make ATP.
- This mode of ATP synthesis is called **oxidative phosphorylation** because it is powered by the redox reactions of the electron transport chain.
- In eukaryotic cells, the inner membrane of the mitochondrion is the site of electron transport and chemiosmosis, the processes that together constitute oxidative phosphorylation.
- In prokaryotes, these processes take place in the plasma membrane.
- 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**, in which an enzyme transfers a phosphate group from an organic substrate molecule to ADP, forming ATP.
- For each molecule of glucose degraded to carbon dioxide and water by respiration, the cell makes as many as 38 ATP, each with 7.3 kcal/mol of free energy.
- Respiration uses the small steps in the respiratory pathway to break the large denomination of energy contained in glucose into the small change of ATP.
    - The quantity of energy in ATP is more appropriate for the energy level of work required in the cell.

Concept 9.2 Glycolysis harvests chemical energy by oxidizing glucose to pyruvate.

- During *glycolysis*, glucose, a six-carbon sugar, is split into two three-carbon sugars.
- These smaller sugars are then oxidized and rearranged to form two molecules of pyruvate, the ionized form of pyruvic acid.
- Each of the ten steps in glycolysis is catalyzed by a specific enzyme.
- These steps can be divided into two phases.
    1. In the energy investment phase, the cell spends ATP.
    2. In the energy payoff phase, this investment is repaid with interest. ATP is produced by substrate-level phosphorylation, and NAD^+ is reduced to NADH by electrons released by the oxidation of glucose.
- The net yield from glycolysis is 2 ATP and 2 NADH per glucose.
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    - No CO_2 is produced during glycolysis.
- Glycolysis can occur whether or not O_2 is present.
- If O_2 *is* present, the chemical energy stored in pyruvate and NADH can be extracted by the citric acid cycle and oxidative phosphorylation.

Concept 9.3 The citric acid cycle completes the energy-yielding oxidation of organic

molecules.

- More than three-quarters of the original energy in glucose is still present in the two molecules of pyruvate.
- If molecular oxygen is present in eukaryotic cells, pyruvate enters the mitochondrion, where enzymes of the citric acid cycle complete the oxidation of the organic fuel to carbon dioxide.
    - In prokaryotic cells, this process occurs in the cytoplasm.
- After pyruvate enters the mitochondrion via active transport, it is converted to a compound called acetyl coenzyme A, or **acetyl CoA**.
- This step, the junction between glycolysis and the citric acid cycle, is accomplished by a multienzyme complex that catalyzes three reactions.
    1. A carboxyl group is removed as CO_2. The carbon dioxide is fully oxidized and thus has little chemical energy.
    2. The remaining two-carbon fragment is oxidized to form acetate. An enzyme transfers the pair of electrons to NAD^+ to form NADH.
    3. Acetate combines with coenzyme A to form the very reactive molecule acetyl CoA.
- Due to the chemical nature of the CoA group, a sulfur-containing compound derived from a B vitamin, acetyl CoA has a high potential energy.
    - In other words, the reaction of acetyl CoA to yield lower-energy products is highly exergonic.
- Acetyl CoA is now ready to feed its acetyl group into the citric acid cycle for further oxidation.
- The citric acid cycle is also called the tricarboxylic acid cycle or the Krebs cycle.
    - The latter name honors Hans Krebs, who was largely responsible for elucidating the cycle's pathways in the 1930s.
- The citric acid cycle oxidizes organic fuel derived from pyruvate.
- Three CO_2 molecules are released, including the one released during the conversion of pyruvate to acetyl CoA.
- The cycle generates one ATP per turn by substrate-level phosphorylation.
- Most of the chemical energy is transferred to NAD^+ and a related electron carrier, the coenzyme FAD, during the redox reactions.
- The reduced coenzymes, NADH and $FADH_2$, transfer high-energy electrons to the electron transport chain.
- The citric acid cycle has eight steps, each catalyzed by a specific enzyme.
    - The acetyl group of acetyl CoA joins the cycle by combining with the compound oxaloacetate, forming citrate.
    - The next seven steps decompose the citrate back to oxaloacetate.
    - It is the regeneration of oxaloacetate that makes this process a *cycle*.
- For each acetyl group that enters the cycle, 3 NAD^+ are reduced to NADH.
- In one step, electrons are transferred to FAD instead of NAD^+.
- Then FAD accepts 2 electrons and 2 protons to become $FADH_2$.

- In the cells of plants, bacteria, and a few animal tissues, the citric acid cycle forms an ATP molecule by substrate-level phosphorylation.
- In most animal tissue cells, guanosine triphosphate (GTP) is formed by the same process of substrate-level phosphorylation.
- GTP may be used to synthesize an ATP or to directly power work in the cell.
- The output from this step is the only ATP generated directly by the citric acid cycle.
- Most of the ATP produced by respiration results from oxidative phosphorylation, as the NADH and $FADH_2$ produced by the citric acid cycle relay the electrons extracted from

food to the electron transport chain.

- This process supplies the necessary energy for the phosphorylation of ADP to ATP.

Concept 9.4 During oxidative phosphorylation, chemiosmosis couples electron transport to ATP synthesis.

- Only 4 of 38 ATP ultimately produced by the respiration of glucose are produced by substrate-level phosphorylation.
    - Two ATP are produced during glycolysis, and 2 ATP are produced during the citric acid cycle.
- NADH and $FADH_2$ account for most of the energy extracted from glucose.
- These reduced coenzymes link glycolysis and the citric acid cycle to oxidative phosphorylation, which uses energy released by the electron transport chain to power ATP synthesis.
- *The inner mitochondrial membrane couples electron transport to ATP synthesis.*
- The electron transport chain is a collection of molecules embedded in the cristae, the folded inner membrane of the mitochondrion.
    - In prokaryotes, the electron transport chain is located in the plasma membrane.
- The folding of the inner membrane to form cristae increases its surface area, providing space for thousands of copies of the chain in each mitochondrion.
- Most components of the chain are proteins that exist in multiprotein complexes numbered I–IV.
- Tightly bound to these proteins are *prosthetic groups,* nonprotein components essential for catalysis.
- Electrons drop in free energy as they pass down the electron transport chain.
- During electron transport along the chain, electron carriers alternate between reduced and oxidized states as they accept and donate electrons.
    - 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.
- Electrons carried by NADH are transferred to the first molecule in the electron transport chain, a flavoprotein.
- In the next redox reaction, the flavoprotein returns to its oxidized form as it passes electrons to an iron-sulfur protein.
- The iron-sulfur protein then passes the electrons to a compound called ubiquinone, a small hydrophobic molecule and the only member of the electron transport chain that is not a protein.
- Most of the remaining electron carriers between ubiquinone and oxygen are proteins called **cytochromes.**
    - The prosthetic group of each cytochrome is a heme group with an iron atom that accepts and donates electrons.
- The last cytochrome of the chain, cyt a_3, passes its electrons to oxygen, which is *very* electronegative.
- Each oxygen atom also picks up a pair of hydrogen ions from the aqueous solution to form water.
- The electrons carried by $FADH_2$ have lower free energy and are added at a lower energy level than those carried by NADH.
    - The electron transport chain provides about one-third less energy for ATP synthesis when the electron donor is $FADH_2$ rather than NADH.

- The electron transport chain generates no ATP directly.
- Its function is to break the large free-energy drop from food to oxygen into a series of smaller steps that release energy in manageable amounts.
- *Chemiosmosis couples electron transport and energy release to ATP synthesis*.
- A protein complex in the cristae, **ATP synthase**, actually makes ATP from ADP and P_i.

- ATP synthase works like an ion pump running in reverse.
    - Ion pumps usually use ATP as an energy source to transport ions against their gradients.
    - Enzymes can catalyze a reaction in either direction, depending on the *G* for the reaction, which is affected by the local concentrations of reactants and products.
    - Rather than hydrolyzing ATP to pump protons against their concentration gradient, under the conditions of cellular respiration, ATP synthase uses the energy of an existing ion gradient to power ATP synthesis.
- The power source for the ATP synthase is a difference in the concentrations of H^+ on opposite sides of the inner mitochondrial membrane.
    - This is also a pH gradient.
- This process, in which energy stored in the form of a hydrogen ion gradient across a membrane is used to drive cellular work such as the synthesis of ATP, is called **chemiosmosis**.
    - Here, *osmosis* refers to the flow of H^+ across a membrane.
- From studying the structure of ATP synthase, scientists have learned how the flow of H^+ through this large enzyme powers ATP generation.
- ATP synthase is a multisubunit complex with four main parts, each made up of multiple polypeptides.
- Protons move one by one into binding sites on one of the parts (the rotor), causing it to spin in a way that catalyzes ATP production from ADP and inorganic phosphate.
-     - ATP synthase is the smallest molecular rotary motor known in nature.
- Part of the complex actually spins around in the membrane when the reaction proceeds in the direction of ATP *hydrolysis*.
- Biochemists assumed that the same rotational mechanism was responsible for ATP *synthesis,* but they lacked experimental evidence.
- In 2004, *nanotechnology* techniques (involving control of matter on the molecular scale) were used to demonstrate that the direction of rotation of one part of the complex in relation to another is solely responsible for either ATP synthesis or ATP hydrolysis by this enzyme.
- How does the inner mitochondrial membrane or the prokaryotic plasma membrane generate and maintain the H^+ gradient that drives ATP synthesis in the ATP synthase protein complex?
    - Establishing the H^+ gradient is the function of the electron transport chain.
    - The chain is an energy converter that uses the exergonic flow of electrons to pump H^+ across the membrane from the mitochondrial matrix into the intermembrane space.
    - The H^+ has a tendency to diffuse down its gradient.
- The ATP synthase molecules are the only place where H^+ can diffuse back to the matrix.
- The exergonic flow of H^+ is used by the enzyme to generate ATP.
- This coupling of the redox reactions of the electron transport chain to ATP synthesis is an example of chemiosmosis.
- How does the electron transport chain pump protons?
    - Certain members of the electron transport chain accept and release H^+ along with

electrons.
    - At certain steps along the chain, electron transfers cause H^+ to be taken up and released into the surrounding solution.
    - The electron carriers are spatially arranged in the membrane in such a way that protons are accepted from the mitochondrial matrix and deposited in the intermembrane space.
    - The H^+ gradient that results is the **proton-motive force**, a gradient with the capacity to do work.
    - The force drives H^+ back across the membrane through the specific H^+ channels provided by ATP synthases.
- *Chemiosmosis is an energy-coupling mechanism that uses energy stored in the form of an H^+ gradient across a membrane to drive cellular work.*
- In mitochondria, the energy for proton gradient formation comes from exergonic redox reactions, and ATP synthesis is the work performed.
- Chemiosmosis in chloroplasts also generates ATP, but light drives the electron flow down an electron transport chain and H^+ gradient formation.
- Prokaryotes generate H^+ gradients across their plasma membrane.
- Prokaryotes use the proton-motive force not only to generate ATP but also to pump nutrients and waste products across the membrane and to rotate their flagella.
- *Here is an accounting of ATP production by cellular respiration.*
- During cellular respiration, most energy flows as follows: glucose NADH electron transport chain proton-motive force ATP.
- Let's consider the products generated when cellular respiration oxidizes a molecule of glucose to six molecules of CO_2.

- Four ATP molecules are produced by substrate-level phosphorylation during glycolysis and the citric acid cycle.
- Many more ATP molecules are generated by oxidative phosphorylation.
- Each NADH from the citric acid cycle and the conversion of pyruvate contributes enough energy to the proton-motive force to generate a maximum of 3 ATP.
- There are three reasons we cannot state an exact number of ATP molecules generated by one molecule of glucose.
    1. Phosphorylation and the redox reactions are not directly coupled to each other, so the ratio of the number of NADH to the number of ATP is not a whole number.
        * One NADH results in 10 H^+ being transported across the inner mitochondrial membrane.
        * Between 3 and 4 H^+ must reenter the mitochondrial matrix via ATP synthase to generate 1 ATP.
        * Therefore, 1 NADH generates enough proton-motive force for the synthesis of 2.5–3.3 ATP.
        * We round off and say that 1 NADH generates 3 ATP.
        * The citric acid cycle also supplies electrons to the electron transport chain via $FADH_2$, but because it enters later in the chain, each molecule of this electron carrier is responsible for the transport of only enough H^+ for the synthesis of 1.5–2 ATP.
        * There is also a slight energetic cost of moving the ATP formed in the mitochondrion out into the eukaryotic cytoplasm where it will be used.
    2. The ATP yield varies slightly depending on the type of shuttle used to transport electrons from the cytosol into the mitochondrion.
        * The mitochondrial inner membrane is impermeable to NADH, so the two

electrons of the NADH produced in glycolysis must be conveyed into the mitochondrion by one of several electron shuttle systems.
    * In some shuttle systems, the electrons are passed to NAD^+, which generates 3 ATP. In others, the electrons are passed to FAD, which generates only 2 ATP.
3. The proton-motive force generated by the redox reactions of respiration may drive other kinds of work, such as mitochondrial uptake of pyruvate from the cytosol.
    * If *all* the proton-motive force generated by the electron transport chain were used to drive ATP synthesis, one glucose molecule could generate a maximum of 34 ATP by oxidative phosphorylation plus 4 ATP (net) from substrate-level phosphorylation to give a total yield of 36–38 ATP (depending on the efficiency of the shuttle).

- How efficient is respiration in generating ATP?
    - Complete oxidation of glucose releases 686 kcal/mol.
    - Phosphorylation of ADP to form ATP requires at least 7.3 kcal/mol.
    - Efficiency of respiration is 7.3 kcal/mol times 38 ATP/glucose divided by 686 kcal/mol glucose, which equals 0.4, or 40%.
    - Approximately 60% of the energy from glucose is lost as heat.
    - Some of that heat is used to maintain our high body temperature (37°C).
- Cellular respiration is remarkably efficient in energy conversion.
    - For example, the most efficient automobile converts only about 25% of the energy stored in gasoline to energy that moves the car.

Concept 9.5 Fermentation and anaerobic respiration enable some cells to produce ATP without the use of oxygen.

- Without electronegative oxygen to pull electrons down the transport chain, oxidative phosphorylation ceases.
- However, there are two general mechanisms by which certain cells can oxidize organic fuel and generate ATP *without* the use of oxygen: fermentation and anaerobic respiration.
    - An electron transport chain is present in aerobic respiration but not in fermentation.
- Anaerobic respiration takes place in organisms that have an electron transport chain but do not use oxygen as a final electron acceptor at the end of the chain.
    - Some "sulfate-reducing" marine bacteria, for instance, use the electronegative sulfate ion (SO_4^{2-}) at the end of their respiratory chain.
    - Operation of the chain builds up a proton-motive force used to produce ATP, but H_2S (hydrogen sulfide) is produced as a by-product rather than H_2O (water).
- Fermentation provides a mechanism by which some cells can oxidize organic fuel and generate ATP without the use of oxygen or any electron transport chain (that is, without cellular respiration).
    - In glycolysis, glucose is oxidized to two pyruvate molecules with NAD^+ as the oxidizing agent.
    - Glycolysis is exergonic and produces 2 ATP (net) by substrate-level phosphorylation.
- If oxygen *is* present, additional ATP can be generated when NADH delivers its electrons to the electron transport chain.
- However, glycolysis generates 2 ATP whether oxygen is present **(aerobic)** or not **(anaerobic)**.
- Fermentation can generate ATP from glucose by substrate-level phosphorylation as long as there is a supply of NAD^+ to accept electrons during the oxidation step of glycolysis.
    - If the NAD^+ pool is exhausted, glycolysis shuts down.
- Under aerobic conditions, NADH transfers its electrons to the electron transfer chain,

recycling NAD^+.

- *Fermentation pathways recycle NAD^+ by transferring electrons from NADH to pyruvate or derivatives of pyruvate.*
- In **alcohol fermentation**, pyruvate is converted to ethanol in two steps.
    1. Pyruvate is converted to a two-carbon compound, acetaldehyde, by the removal of CO_2.
    2. Acetaldehyde is reduced by NADH to ethanol.
- This process regenerates the supply of NAD^+ needed for the continuation of glycolysis.
    - Alcohol fermentation by yeast is used in brewing, baking, and winemaking.
- During **lactic acid fermentation**, pyruvate is reduced directly by NADH to form lactate (the ionized form of lactic acid) without the release of CO_2.
    - Lactic acid fermentation by some fungi and bacteria is used to make cheese and yogurt.
- Human muscle cells switch from aerobic respiration to lactic acid fermentation to generate ATP when O_2 is scarce. This may occur in the early stages of strenuous exercise.
    - The waste product, lactate, was previously thought to cause muscle fatigue and pain, but recent research suggests instead that increased levels of potassium ions (K^+) may be to blame; lactate appears to enhance muscle performance.
    - Excess lactate is gradually carried away by the blood to the liver, where it is converted back to pyruvate by liver cells.
- *Fermentation and cellular respiration are compared.*
- Fermentation and cellular respiration are anaerobic and aerobic alternatives, respectively, for producing ATP from sugars.
    - Both use glycolysis to oxidize sugars to pyruvate with a net production of 2 ATP by substrate-level phosphorylation.
    - Both use NAD^+ as an oxidizing agent to accept electrons from food during glycolysis.
- The two processes differ in their mechanism for oxidizing NADH to NAD^+, which is required to sustain glycolysis.
    - In fermentation, the electrons of NADH are passed to an organic molecule such as pyruvate (lactic acid fermentation) or acetaldehyde (alcohol fermentation), in order to regenerate NAD^+.
    - In cellular respiration, the electrons of NADH are ultimately passed to O_2, generating ATP by oxidative phosphorylation.
- More ATP is generated from the oxidation of pyruvate in the citric acid cycle.
    - Without oxygen, the energy still stored in pyruvate is unavailable to the cell.
    - Under aerobic respiration, a molecule of glucose yields 38 ATP, but the same molecule of glucose yields only 2 ATP under anaerobic respiration.
- *Organisms vary in the pathways available to them to break down sugars.*
- **Obligate anaerobes** carry out only fermentation or anaerobic respiration and cannot survive in the presence of oxygen.
- A few cell types, such as the cells of the vertebrate brain, can carry out only aerobic oxidation of pyruvate, not fermentation.
- Yeast and many bacteria are **facultative anaerobes** that can survive using either fermentation or respiration.
    - At a cellular level, human muscle cells can behave as facultative anaerobes.
- For facultative anaerobes, pyruvate is a fork in the metabolic road that leads to two

alternative routes.

- Under aerobic conditions, pyruvate is converted to acetyl CoA and oxidation continues in the citric acid cycle.
- Under anaerobic conditions, pyruvate serves as an electron acceptor to recycle NAD^+.

- To make the same amount of ATP, a facultative anaerobe must consume sugar at a much faster rate when fermenting than when respiring.
- *The role of glycolysis in both fermentation and respiration has an evolutionary basis.*
- Ancient prokaryotes used glycolysis to make ATP long before oxygen was present in Earth's atmosphere.
- The oldest bacterial fossils are more than 3.5 billion years old, appearing long before appreciable quantities of O_2 accumulated in the atmosphere about 2.7 billion years ago.
  - Cyanobacteria produced this O_2 as a by-product of photosynthesis.

- The first prokaryotes may have generated ATP exclusively from glycolysis, which does not require oxygen.
- The fact that glycolysis is a ubiquitous metabolic pathway and occurs in the cytosol without membrane-enclosed organelles suggests that this pathway evolved very early in the history of life on Earth.

Concept 9.6 Glycolysis and the citric acid cycle connect to many other metabolic pathways.

- Glycolysis and the citric acid cycle are major intersections of various catabolic and anabolic (biosynthetic) pathways.
- *A variety of organic molecules can be used to make ATP.*
- Glycolysis can accept a wide range of carbohydrates for catabolism.
  - Polysaccharides like starch or glycogen can be hydrolyzed to glucose monomers that enter glycolysis and the citric acid cycle.
  - The digestion of disaccharides, including sucrose, provides glucose and other monosaccharides as fuel for respiration.
- The other two major fuels, proteins and fats, can also enter the respiratory pathways used by carbohydrates.
- Proteins must first be digested to individual amino acids.
  - Many of the amino acids are used by the organism to build new proteins.
  - Amino acids that will be catabolized must have their amino groups removed via deamination.
  - The nitrogenous waste is excreted as ammonia, urea, or another waste product.
  - The carbon skeletons are modified by enzymes and enter as intermediaries into glycolysis or the citric acid cycle, depending on their structure.
- Catabolism can also harvest energy stored in fats obtained from food or from storage cells in the body.
- Fats must be digested to glycerol and fatty acids.
  - Glycerol can be converted to glyceraldehyde phosphate, an intermediate of glycolysis.
- The rich energy of fatty acids is accessed as fatty acids are split into two-carbon fragments via **beta oxidation**.
- These molecules enter the citric acid cycle as acetyl CoA.
- NADH and $FADH_2$ are also generated during beta oxidation; they can enter the electron transport chain, leading to further ATP production.
- A gram of fat oxidized by respiration generates twice as much ATP as a gram of carbohydrate.

- *The metabolic pathways of respiration also play a role in anabolic pathways of the cell.*
- In addition to calories, food must provide the carbon skeletons that cells require to make their own molecules.
- Some organic monomers obtained from digestion can be used directly.
- Intermediaries in glycolysis and the citric acid cycle can be diverted to anabolic pathways as precursors from which the cell can synthesize the molecules it requires.
    - For example, a human cell can synthesize about half the 20 different amino acids by modifying compounds from the citric acid cycle. The rest are "essential amino acids" that must be obtained in the diet.
    - Glucose can be synthesized from pyruvate; fatty acids can be synthesized from acetyl CoA.
- Anabolic, or biosynthetic, pathways do not generate ATP but instead consume it.
- Glycolysis and the citric acid cycle function as metabolic interchanges that enable cells to convert one kind of molecule to another as needed.
    - For example, excess carbohydrates and proteins can be converted to fats through intermediaries of glycolysis and the citric acid cycle.
    - If we eat more food than we need, we store fat even if our diet is fat-free.
- Metabolism is remarkably versatile and adaptable.
- *Feedback mechanisms control cellular respiration.*
- Basic principles of supply and demand regulate the metabolic economy.
- If a cell has an excess of a certain amino acid, it typically uses feedback inhibition to prevent the diversion of intermediary molecules from the citric acid cycle to the synthesis pathway of that amino acid.
- The rate of catabolism is also regulated, typically by the level of ATP in the cell.
    - If ATP levels drop, catabolism speeds up to produce more ATP.
    - When there is plenty of ATP to meet demand, respiration slows down, sparing valuable organic molecules for other functions.
- Control of catabolism is based mainly on regulating the activity of enzymes at strategic points in the catabolic pathway.
- One strategic point occurs in the third step of glycolysis, catalyzed by phosphofructokinase, an enzyme that functions as the pacemaker of respiration.
- Phosphofructokinase catalyzes the earliest step that irreversibly commits the substrate to glycolysis.
- Phosphofructokinase is an allosteric enzyme with receptor sites for specific inhibitors and activators.
- Phosphofructokinase is inhibited by ATP and stimulated by AMP (derived from ADP).
    - 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.
- Citrate, the first product of the citric acid cycle, is also an inhibitor of phosphofructokinase.
    - This synchronizes the rate of glycolysis and the citric acid cycle.
- If intermediaries from the citric acid cycle are diverted to other uses (for example, amino acid synthesis), glycolysis speeds up to replace these molecules.
- Metabolic balance is augmented by the control of other enzymes at other key locations in glycolysis and the citric acid cycle.
- Cells are thrifty, expedient, and responsive in their metabolism.
- Cellular respiration functions in the broad context of energy flow and chemical cycling in ecosystems.
- The energy that keeps us alive is *released,* not *produced,* by cellular respiration.