

1  *Cellular Respiration*  
Chapter 9

2  **Introduction**

- Living is work.
- To perform their many tasks, cells require transfusions of energy from outside sources.
  - ◆ In most ecosystems, energy enters as sunlight.
  - ◆ Light energy trapped in organic molecules is available to both photosynthetic organisms and others that eat them.

3  *Energy flow*

4  **Cellular respiration and fermentation are catabolic, energy-yielding pathways**

- Organic molecules store energy in their arrangement of atoms.
- Enzymes catalyze the systematic degradation of organic molecules that are rich in energy to simpler waste products with less energy.
- Some of the released energy is used to do work and the rest is dissipated as heat.

5

- Metabolic pathways that release the energy stored in complex organic molecules are catabolic.
- One type of catabolic process, **fermentation**, leads to the partial degradation of sugars in the absence of oxygen.
- A more efficient and widespread catabolic process, **cellular respiration**, uses oxygen as a reactant to complete the breakdown of a variety of organic molecules.
  - ◆ Most of the processes in cellular respiration occur in mitochondria.

6  **Overall Equation for Respiration**

- Cellular respiration is similar to the combustion of gasoline in an automobile engine.
- The overall process is:
  - ◆ Organic compounds + O<sub>2</sub> -> CO<sub>2</sub> + H<sub>2</sub>O + Energy

7  **More than one fuel**

- Carbohydrates, fats, and proteins can all be used as the fuel, but it is traditional to start learning with glucose.
  - ◆ C<sub>6</sub>H<sub>12</sub>O<sub>6</sub> + 6O<sub>2</sub> -> 6CO<sub>2</sub> + 6H<sub>2</sub>O + Energy (ATP + heat)
- The catabolism of glucose is exergonic with a delta G of - 686 kcal per mole of glucose.
  - ◆ Some of this energy is used to produce ATP that will perform cellular work.

8  **Cells recycle the ATP they use for work**

- ATP, adenosine triphosphate, is the pivotal molecule in cellular energetics.
- It is the chemical equivalent of a loaded spring.
  - ◆ The close packing of three negatively-charged phosphate groups is an unstable, energy-storing arrangement.
  - ◆ Loss of the end phosphate group “relaxes” the “spring”.

9  **Recycling inorganic phosphate**

- The price of most cellular work is the conversion of ATP to ADP and inorganic phosphate ( $P_i$ ).
- An animal cell regenerates ATP from ADP and  $P_i$  by the catabolism of organic molecules.

10  **Phosphorylation**

- The transfer of the terminal phosphate group from ATP to another molecule is phosphorylation.
  - ◆ This changes the shape of the receiving molecule, performing work (transport, mechanical, or chemical).
  - ◆ When the phosphate groups leaves the molecule, the molecule returns to its alternate shape.

11  **Addition or removal of  $P_i$  alters molecular shape**

12  **Redox reactions release energy when electrons move closer to electronegative atoms**

- Catabolic pathways relocate 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 from one reactant to another are oxidation-reduction reactions, or **redox reactions**.
  - ◆ The loss of electrons is called **oxidation**.
  - ◆ The addition of electrons is called **reduction**.

13   **$e^-$  donor and acceptor required**

- The formation of table salt from sodium and chloride is a redox reaction.
  - ◆  $\text{Na} + \text{Cl} \rightarrow \text{Na}^+ + \text{Cl}^-$
  - ◆ Here sodium is oxidized and chlorine is reduced (its charge drops from 0 to -1).
- More generally:  $\text{Xe}^- + \text{Y} \rightarrow \text{X} + \text{Ye}^-$ 
  - ◆ X, the electron donor, is the **reducing agent** and reduces Y.
  - ◆ Y, the electron recipient, is the **oxidizing agent** and oxidizes X.
- Redox reactions require both a donor and acceptor.

14  **Redox involves change in  $e^-$  sharing**

- Redox reactions also occur when the movement of electrons is not complete but involve 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).

15  *Methane redox couplet*

- ◆ Oxygen is one of the most potent oxidizing agents.

16

- When these bonds shift from nonpolar to polar, the electrons move from positions equidistant between the two atoms for a closer position to oxygen, the more electronegative atom.
- An electron loses energy as it shifts from a less electronegative atom to a more electronegative one.
- A redox reaction that relocates electrons closer to oxygen releases chemical energy that can do work.
- To reverse the process, energy must be added to pull an electron away from an atom.

17  ***Electrons “fall” from organic molecules to oxygen during cellular respiration***

- In cellular respiration, glucose and other fuel molecules are oxidized, releasing energy.
- In the summary equation of cellular respiration:  
$$\text{C}_6\text{H}_{12}\text{O}_6 + 6\text{O}_2 \rightarrow 6\text{CO}_2 + 6\text{H}_2\text{O}$$
- Glucose is oxidized, oxygen is reduced, and electrons lose potential energy.
- Molecules that have an abundance of hydrogen are excellent fuels because their bonds are a source of “hilltop” electrons that “fall” closer to oxygen.

18  *Electrons harvested from macromolecules*

- The cell has a rich reservoir of electrons associated with hydrogen, especially in carbohydrates and fats.
- However, these fuels do not spontaneously combine with O<sub>2</sub> because they lack the activation energy.
- Enzymes lower the barrier of activation energy, allowing these fuels to be oxidized slowly.

19  ***The “fall” of electrons during respiration is stepwise, via NAD<sup>+</sup> 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 gradually in a series of steps, each catalyzed by a specific enzyme.
- At key steps, hydrogen atoms are stripped from glucose and passed first to a coenzyme, like **NAD<sup>+</sup>** (nicotinamide adenine dinucleotide).

20  *Freeing e<sup>-</sup> and p<sup>+</sup>*

- Dehydrogenase enzymes strip two hydrogen atoms from the fuel (e.g., glucose), pass two electrons and one proton to NAD<sup>+</sup> and release H<sup>+</sup>.
  - ◆  $\text{H-C-OH} + \text{NAD}^+ \rightarrow \text{C=O} + \text{NADH} + \text{H}^+$
- This changes the oxidized form, NAD<sup>+</sup>, to the reduced form NADH.

- 21  *NAD<sup>+</sup> functions as the oxidizing agent*
- 22  *Nicotinamide*
- The electrons carried by NADH lose very little of their potential energy in this process.
  - This energy is tapped to synthesize ATP as electrons “fall” from NADH to oxygen.
- 23  *Transforming energy in steps*
- Unlike the explosive release of heat energy that would occur when H<sub>2</sub> and O<sub>2</sub> combine, cellular respiration uses an electron transport chain to break the fall of electrons to O<sub>2</sub> into several steps.
- 24  *Controlled release of energy*
- 25
- The electron transport chain, consisting of several molecules (primarily proteins), is built into the inner membrane of a mitochondrion.
  - NADH shuttles electrons from food to the “top” of the chain.
  - At the “bottom”, oxygen captures the electrons and H<sup>+</sup> to form water.
  - The free energy change from “top” to “bottom” is -53 kcal/mole of NADH.
  - Electrons are passed by increasingly electronegative molecules in the chain until they are caught by oxygen, the most electronegative.
- 26  ***Respiration involves glycolysis, the Krebs cycle, and electron transport***
- Respiration occurs in three metabolic stages: glycolysis, the Krebs cycle, and the electron transport chain and oxidative phosphorylation.
- 27  *2 main stages of aerobic respiration*
- Glycolysis occurs in the cytoplasm.
    - ◆ It begins catabolism by breaking glucose into two molecules of pyruvate.
  - The Krebs cycle occurs in the mitochondrial matrix.
    - ◆ It degrades pyruvate to carbon dioxide.
- 28  *Oxidation of NAD feeds e<sup>-</sup> to electron transport chain*
- Several steps in glycolysis and the Krebs cycle transfer electrons from substrates to NAD<sup>+</sup>, forming NADH.
  - NADH passes these electrons to the electron transport chain.
- 29  ***ETC***
- In the electron transport chain, the electrons move from molecule to molecule until they combine with oxygen and hydrogen ions to form water.
  - As they are passed along the chain, the energy carried by these electrons is

stored in the mitochondrion in a form that can be used to synthesize ATP via oxidative phosphorylation.

- ◆ Oxidative phosphorylation produces almost 90% of the ATP generated by respiration.

30  ***Substrate phosphorylation***

- Some ATP is also generated in glycolysis and the Krebs cycle by substrate-level phosphorylation.

- ◆ Here an enzyme transfers a phosphate group from an organic molecule (the substrate) to ADP, forming ATP.

31  ***Stepping down energy allows more ATP to be formed***

- 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 level of work required in the cell.

- Ultimately 38 ATP are produced per mole of glucose that is degraded to carbon dioxide and water by respiration.

32  ***view***

- Little sound byte

33  ***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 oxidized and rearranged to form two molecules of pyruvate.

- Each of the ten steps in glycolysis is catalyzed by a specific enzyme.

- These steps can be divided into two phases: an energy investment phase and an energy payoff phase.

34  ***Energy Investment Phase***

- In the energy investment phase, ATP provides activation energy by phosphorylating glucose.

- ◆ This requires 2 ATP per glucose.

- In the energy payoff phase, ATP is produced by substrate-level phosphorylation and NAD<sup>+</sup> is reduced to NADH.

- 4 ATP (net) and 2 NADH are produced per glucose.

35  *Energy Investment phase*

36

37

38  *Glycolysis is substrate phosphorylation*

- The net yield from glycolysis is 2 ATP and 2 NADH per glucose.
  - ◆ No CO<sub>2</sub> is produced during glycolysis.
- Glycolysis occurs whether O<sub>2</sub> is present or not.
  - ◆ If O<sub>2</sub> is present, pyruvate moves to the Krebs cycle and the energy stored in NADH can be converted to ATP by the electron transport system and oxidative phosphorylation.

39  *The Krebs cycle completes the energy-yielding oxidation of organic molecules*

- More than three quarters of the original energy in glucose is still present in two molecules of pyruvate.
- If oxygen is present, pyruvate enters the mitochondrion where enzymes of the Krebs cycle complete the oxidation of the organic fuel to carbon dioxide.

40

- As pyruvate enters the mitochondrion, a multienzyme complex modifies pyruvate to **acetyl CoA** which enters the Krebs cycle in the matrix.
  - ◆ A carboxyl group is removed as CO<sub>2</sub>.
  - ◆ A pair of electrons is transferred from the remaining two-carbon fragment to NAD<sup>+</sup> to form NADH.
  - ◆ The oxidized fragment, acetate, combines with coenzyme A to form acetyl CoA.

41  *Krebs= citric acid cycle*

- The Krebs cycle is named after Hans Krebs who was largely responsible for elucidating its pathways in the 1930's.
  - ◆ This cycle begins when acetate from acetyl CoA combines with oxaloacetate to form citrate.
  - ◆ Ultimately, the oxaloacetate is recycled and the acetate is broken down to CO<sub>2</sub>.
  - ◆ Each cycle produces one ATP by substrate-level phosphorylation, three NADH, and one FADH<sub>2</sub> (another electron carrier) per acetyl CoA.

42  *The Krebs cycle consists of eight steps.*

43

- The conversion of pyruvate and the Krebs cycle produces large quantities of electron carriers.

44  ***The inner mitochondrial membrane couples electron transport to ATP synthesis***

- Only 4 of 38 ATP ultimately produced by respiration of glucose are derived from substrate-level phosphorylation.
- The vast majority of the ATP comes from the energy in the electrons carried by NADH (and FADH<sub>2</sub>).
- The energy in these electrons is used in the electron transport system to power ATP synthesis.

45  ***ETC etcetcetcetcetcetc***

- Thousands of copies of the electron transport chain are found in the extensive surface of the cristae, the inner membrane of the mitochondrion.
  - ◆ Most components of the chain are proteins that are bound with prosthetic groups that can alternate between reduced and oxidized states as they accept and donate electrons.
- Electrons drop in free energy as they pass down the electron transport chain.

46

- Electrons carried by NADH are transferred to the first molecule in the electron transport chain, flavoprotein.
  - ◆ The electrons continue along the chain which includes several **cytochrome** proteins and one lipid carrier.
- The electrons carried by FADH<sub>2</sub> have lower free energy and are added to a later point in the chain.

47

- Electrons from NADH or FADH<sub>2</sub> ultimately pass to oxygen.
  - ◆ For every two electron carriers (four electrons), one O<sub>2</sub> molecule is reduced to two molecules of water.
- 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.
- The movement of electrons along the electron transport chain does contribute to chemiosmosis and ATP synthesis.

48

- A protein complex, **ATP synthase**, in the cristae actually makes ATP from ADP and P<sub>i</sub>.
- ATP used the energy of an existing proton gradient to power ATP synthesis.
  - ◆ This proton gradient develops between the intermembrane space and the matrix.

49  ***Proton Motive Force***

- The proton gradient is produced by the movement of electrons along the electron transport chain.

- Several chain molecules can use the exergonic flow of electrons to pump H<sup>+</sup> from the matrix to the intermembrane space.
  - ◆ This concentration of H<sup>+</sup> is the proton-motive force.

50  *ETC*

51  *Chemiosmosis*

- The ATP synthase molecules are the only place that will allow H<sup>+</sup> to diffuse back to the matrix.
- This exergonic flow of H<sup>+</sup> is used by the enzyme to generate ATP.
- This coupling of the redox reactions of the electron transport chain to ATP synthesis is called chemiosmosis.

52

- The mechanism of ATP generation by ATP synthase is still an area of active investigation.
  - ◆ As hydrogen ions flow down their gradient, they cause the cylinder portion and attached rod of ATP synthase to rotate.
  - ◆ The spinning rod causes a conformational change in the knob region, activating catalytic sites where ADP and inorganic phosphate combine to make ATP.

53  *Chemiosmosis*

- Chemiosmosis is an energy-coupling mechanism that uses energy stored in the form of an H<sup>+</sup> gradient across a membrane to drive cellular work.

54  *Significance of chemiosmosis*

- ◆ In the mitochondrion, chemiosmosis generates ATP.
- ◆ Chemiosmosis in chloroplasts also generates ATP, but light drives the electron flow down an electron transport chain and H<sup>+</sup> gradient formation.
- ◆ Prokaryotes generate H<sup>+</sup> gradients across their plasma membrane.
  - They can use this proton-motive force not only to generate ATP but also to pump nutrients and waste products across the membrane and to rotate their flagella.

55  ***Cellular respiration generates many ATP molecules for each sugar molecule it oxidizes***

- During respiration, most energy flows from glucose → NADH → electron transport chain → proton-motive force → ATP.
- Considering the fate of carbon, one six-carbon glucose molecule is oxidized to six CO<sub>2</sub> molecules.
- Some ATP is produced by substrate-level phosphorylation during glycolysis and the Krebs cycle, but most comes from oxidative phosphorylation.

56

- Each NADH from the Krebs cycle and the conversion of pyruvate contributes enough energy to generate a maximum of 3 ATP (rounding up).
  - ◆ The NADH from glycolysis may also yield 3 ATP.
- Each FADH<sub>2</sub> from the Krebs cycle can be used to generate about 2ATP.
- In some eukaryotic cells, NADH produced in the cytosol by glycolysis may be worth only 2 ATP.

- ◆ The electrons must be shuttled to the mitochondrion.
- ◆ In some shuttle systems, the electrons are passed to NAD<sup>+</sup>, in others the electrons are passed to FAD.

57  4 + 34

- Assuming the most energy-efficient shuttle of NADH from glycolysis, a maximum yield of 34 ATP is produced by oxidative phosphorylation.
- This plus the 4 ATP from substrate-level phosphorylation gives a bottom line of 38 ATP.
  - ◆ This maximum figure does not consider other uses of the proton-motive force.

58

59  *How efficient is respiration in generating ATP?*

- ◆ Complete oxidation of glucose releases 686 kcal per mole.
- ◆ Formation of each ATP requires at least 7.3 kcal/mole.
- ◆ Efficiency of respiration is  $7.3 \text{ kcal/mole} \times 38 \text{ ATP/glucose} / 686 \text{ kcal/mole glucose} = 40\%$ .
- ◆ The other approximately 60% is lost as heat.
- Cellular respiration is remarkably efficient in energy conversion.

60  **Fermentation enables some cells to produce ATP without the help of oxygen**

- Oxidation refers to the loss of electrons to any electron acceptor, not just to oxygen.
  - ◆ In glycolysis, glucose is oxidized to two pyruvate molecules with NAD<sup>+</sup> as the oxidizing agent, not O<sub>2</sub>.
  - ◆ Some energy from this oxidation produces 2 ATP (net).
  - ◆ If oxygen is present, additional ATP can be generated when NADH delivers its electrons to the electron transport chain.
- Glycolysis generates 2 ATP whether oxygen is present (**aerobic**) or not (**anaerobic**).

61  **Fermentation**

- Anaerobic catabolism of sugars can occur by fermentation.
- Fermentation can generate ATP from glucose by substrate-level phosphorylation as long as there is a supply of NAD<sup>+</sup> to accept electrons.
  - ◆ If the NAD<sup>+</sup> pool is exhausted, glycolysis shuts down.
  - ◆ Under aerobic conditions, NADH transfers its electrons to the electron transfer chain, recycling NAD<sup>+</sup>.
- Under anaerobic conditions, various fermentation pathways generate ATP by glycolysis and recycle NAD<sup>+</sup> by transferring electrons from NADH to pyruvate or derivatives of pyruvate.

62

- In **alcohol fermentation**, pyruvate is converted to ethanol in two steps.
  - ◆ First, pyruvate is converted to a two-carbon compound, acetaldehyde by the removal of CO<sub>2</sub>.
  - ◆ Second, acetaldehyde is reduced by NADH to ethanol.
  - ◆ Alcohol fermentation by yeast is used in brewing and winemaking.

63

- During **lactic acid fermentation**, pyruvate is reduced directly by NADH to form lactate (ionized form of lactic acid).
  - ◆ Lactic acid fermentation by some fungi and bacteria is used to make cheese and yogurt.
  - ◆ Muscle cells switch from aerobic respiration to lactic acid fermentation to generate ATP when  $O_2$  is scarce.
    - The waste product, lactate, may cause muscle fatigue, but ultimately it is converted back to pyruvate in the liver.

64

- 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 electron acceptor.
- In fermentation, the electrons of NADH are passed to an organic molecule, regenerating  $NAD^+$ .

65

- In respiration, the electrons of NADH are ultimately passed to  $O_2$ , generating ATP by oxidative phosphorylation.
- In addition, even more ATP is generated from the oxidation of pyruvate in the Krebs 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.

66

- Some organisms (**facultative anaerobes**), including yeast and many bacteria, can survive using either fermentation or respiration.
- At a cellular level, human muscle cells can behave as facultative anaerobes, but nerve cells cannot.
- For facultative anaerobes, pyruvate is a fork in the metabolic road that leads to two alternative routes.

67

- The oldest bacterial fossils are over 3.5 billion years old, appearing long before appreciable quantities of  $O_2$  accumulated in the atmosphere.
- Therefore, the first prokaryotes may have generated ATP exclusively from glycolysis.

- The fact that glycolysis is also the most widespread metabolic pathway and occurs in the cytosol without membrane-enclosed organelles, suggests that glycolysis evolved early in the history of life.

68  ***Glycolysis and the Krebs cycle connect to many other metabolic pathways***

- Glycolysis can accept a wide range of carbohydrates.
  - ◆ Polysaccharides, like starch or glycogen, can be hydrolyzed to glucose monomers that enter glycolysis.
  - ◆ Other hexose sugars, like galactose and fructose, can also be modified to undergo glycolysis.
- The other two major fuels, proteins and fats, can also enter the respiratory pathways, including glycolysis and the Krebs cycle, used by carbohydrates.

69

- Proteins must first be digested to individual amino acids.
- 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 Krebs cycle depending on their structure.

70

- The energy of fats can also be accessed via catabolic pathways.
- 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 Krebs cycle as acetyl CoA.
- In fact, a gram of fat will generate twice as much ATP as a gram of carbohydrate via aerobic respiration.

71

- Carbohydrates, fats, and proteins can all be catabolized through the same pathways.

72

- The metabolic pathways of respiration also play a role in anabolic pathways of the cell.
- Not all the organic molecules of food are completely oxidized to make ATP.
- Intermediaries in glycolysis and the Krebs cycle can be diverted to anabolic pathways.
  - ◆ For example, a human cell can synthesize about half the 20 different amino acids by modifying compounds from the Krebs cycle.
  - ◆ Glucose can be synthesized from pyruvate and fatty acids from acetyl CoA.

73

- Glycolysis and the Krebs 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 Krebs cycle.
- Metabolism is remarkably versatile and adaptable.

74  **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 more intermediary molecules from the Krebs 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.

75

- 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.

76

- Allosteric regulation of phosphofructokinase sets the pace of respiration.
  - ◆ This enzyme is inhibited by ATP and stimulated by AMP (derived from ADP).
    - It responds to shifts in balance between production and degradation of ATP:  $ATP \leftrightarrow ADP + P_i \leftrightarrow AMP + P_i$ .
  - ◆ Thus, when ATP levels are high, inhibition of this enzyme slows glycolysis.
  - ◆ When ATP levels drop and ADP and AMP levels rise, the enzyme is active again and glycolysis speeds up.

77

- Citrate, the first product of the Krebs cycle, is also an inhibitor of phosphofructokinase.
  - ◆ This synchronizes the rate of glycolysis and the Krebs cycle.
  - ◆ Also, if intermediaries from the Krebs cycle are diverted to other uses (e.g., 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 Krebs cycle.
- Cells are thrifty, expedient, and responsive in their metabolism.