Overview: Life Is Work

• Living cells require energy from outside sources

• Some animals, such as the giant panda, obtain energy by eating plants, and some animals feed on other organisms that eat plants
• Energy flows into an ecosystem as sunlight and leaves as heat

• Photosynthesis generates $O_2$ and organic molecules, which are used in cellular respiration

• Cells use chemical energy stored in organic molecules to regenerate ATP, which powers work
Light energy

ECOSYSTEM

Photosynthesis in chloroplasts

CO$_2$ + H$_2$O

Cellular respiration in mitochondria

Organic molecules + O$_2$

ATP

ATP powers most cellular work

Heat energy
Catabolic Pathways and Production of ATP

• The breakdown of organic molecules is exergonic

• **Fermentation** is a partial degradation of sugars that occurs without $O_2$

• **Aerobic respiration** consumes organic molecules and $O_2$ and yields ATP

• Anaerobic respiration is similar to aerobic respiration but consumes compounds other than $O_2$
Cellular respiration includes both aerobic and anaerobic respiration but is often used to refer to aerobic respiration.

Although carbohydrates, fats, and proteins are all consumed as fuel, it is helpful to trace cellular respiration with the sugar glucose:

\[ C_6H_{12}O_6 + 6 \, O_2 \rightarrow 6 \, CO_2 + 6 \, H_2O + \text{Energy (ATP + heat)} \]
Redox Reactions: Oxidation and Reduction

- The transfer of electrons during chemical reactions releases energy stored in organic molecules
- This released energy is ultimately used to synthesize ATP
The Principle of Redox

- Chemical reactions that transfer electrons between reactants are called oxidation-reduction reactions, or redox reactions.
  - In **oxidation**, a substance loses electrons, or is oxidized.
  - In **reduction**, a substance gains electrons, or is reduced (the amount of positive charge is reduced).
Fig. 9-UN1

Na + Cl → Na⁺ + Cl⁻

becomes oxidized (loses electron)

becomes reduced (gains electron)
• The electron donor is called the **reducing agent**

• The electron receptor is called the **oxidizing agent**

• Some redox reactions do not transfer electrons but change the electron sharing in covalent bonds

• An example is the reaction between methane and $O_2$
Reactants becomes oxidized

\[ \text{CH}_4 + 2\text{O}_2 \rightarrow \text{CO}_2 + \text{Energy} + 2\text{H}_2\text{O} \]

Methane (reducing agent) becomes oxidized

Oxygen (oxidizing agent) becomes reduced

Products

Carbon dioxide

Water
Oxidation of Organic Fuel Molecules During Cellular Respiration

- During cellular respiration, the fuel (such as glucose) is oxidized, and \( \text{O}_2 \) is reduced:

\[
\text{C}_6\text{H}_{12}\text{O}_6 \quad + \quad 6 \text{ O}_2 \quad \rightarrow \quad 6 \text{ CO}_2 \quad + \quad 6 \text{ H}_2\text{O} \quad + \quad \text{Energy}
\]

\[
\text{H--C--OH} \quad + \quad \text{NAD}^+ \quad \rightarrow \quad \text{C}==\text{O} \quad + \quad \text{NADH} \quad + \quad \text{H}^+
\]
Stepwise Energy Harvest via NAD$^+$ and the Electron Transport Chain

• In cellular respiration, glucose and other organic molecules are broken down in a series of steps.

• Electrons from organic compounds are usually first transferred to NAD$^+$, a coenzyme.

• As an electron acceptor, NAD$^+$ functions as an oxidizing agent during cellular respiration.

• Each NADH (the reduced form of NAD$^+$) represents stored energy that is tapped to synthesize ATP.
Dehydrogenase

Reduction of NAD$^+$

Oxidation of NADH

$2e^- + 2H^+$

$2e^- + H^+$

NAD$^+$ + 2[H]

Nicotinamide (oxidized form)

Nicotinamide (reduced form)
• NADH passes the electrons to the electron transport chain

• Unlike an uncontrolled reaction, the electron transport chain passes electrons in a series of steps instead of one explosive reaction

• $O_2$ pulls electrons down the chain in an energy-yielding tumble

• The energy yielded is used to regenerate ATP
(a) Uncontrolled reaction

\[ \text{H}_2 + \frac{1}{2} \text{O}_2 \rightarrow \text{H}_2\text{O} \]

Explosive release of heat and light energy

(b) Cellular respiration

\[ 2 \text{H} + \frac{1}{2} \text{O}_2 \rightarrow \text{H}_2\text{O} \]

(from food via NADH)

\[ 2 \text{H}^+ + 2 e^- \rightarrow \text{H}_2\text{O} \]

Controlled release of energy for synthesis of ATP

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The Stages of Cellular Respiration: A Preview

- Cellular respiration has three stages:
  - **Glycolysis** (breaks down glucose into two molecules of pyruvate)
  - The **citric acid cycle** (completes the breakdown of glucose)
  - **Oxidative phosphorylation** (accounts for most of the ATP synthesis)
Mitochondrion

Substrate-level phosphorylation

ATP

Electrons carried via NADH

Glycolysis

Glucose → Pyruvate

Cytosol

ATP

Substrate-level phosphorylation

Electrons carried via NADH and FADH\textsubscript{2}

Citric acid cycle

Oxidative phosphorylation: electron transport and chemiosmosis
• The process that generates most of the ATP is called oxidative phosphorylation because it is powered by redox reactions.

• Oxidative phosphorylation accounts for almost 90% of the ATP generated by cellular respiration.

• A smaller amount of ATP is formed in glycolysis and the citric acid cycle by substrate-level phosphorylation.
Enzyme \[ \text{ADP} \] Substrate \[ \text{ATP} + \text{Product} \]
Concept 9.2: Glycolysis harvests chemical energy by oxidizing glucose to pyruvate

- Glycolysis ("splitting of sugar") breaks down glucose into two molecules of pyruvate
- Glycolysis occurs in the cytoplasm and has two major phases:
  - Energy investment phase
  - Energy payoff phase
Energy investment phase

Glucose

2 ADP + 2 P \rightarrow 2 ATP used

Energy payoff phase

4 ADP + 4 P \rightarrow 4 ATP formed

2 NAD^+ + 4 e^- + 4 H^+ \rightarrow 2 NADH + 2 H^+

2 Pyruvate + 2 H_2O

Net

Glucose \rightarrow 2 Pyruvate + 2 H_2O

4 ATP formed – 2 ATP used \rightarrow 2 ATP

2 NAD^+ + 4 e^- + 4 H^+ \rightarrow 2 NADH + 2 H^+
Fig. 9-9-9

**Triose phosphate dehydrogenase**

2 NAD\(^+\) + 2 H\(^+\) → 2 NADH + 2 P\(_i\)

**Phosphoglycerokinase**

2 ATP + 2 ADP → 2 ADP + 2 ATP

**Phosphoglyceromutase**

2 3-Phosphoglycerate → 2 2-Phosphoglycerate

**Enolase**

2 2-Phosphoglycerate → 2 3-Phosphoglycerate + 2 H\(_2\)O

**Phosphoenolpyruvate**

2 ADP → 2 ATP

**Pyruvate kinase**

2 Pyruvate kinase + 2 ATP → 2 ATP + 2 ADP

2 ADP → 2 ATP
Concept 9.3: The citric acid cycle completes the energy-yielding oxidation of organic molecules

- In the presence of $O_2$, pyruvate enters the mitochondrion

- Before the citric acid cycle can begin, pyruvate must be converted to **acetyl CoA**, which links the cycle to glycolysis
Pyruvate transport protein

1. Pyruvate is converted to CO₂ and Coenzyme A.
2. NAD⁺ is reduced to NADH + H⁺.
3. Acetyl CoA is formed.

CYTOSOL

MITOCHONDRION
The citric acid cycle, also called the Krebs cycle, takes place within the mitochondrial matrix.

The cycle oxidizes organic fuel derived from pyruvate, generating 1 ATP, 3 NADH, and 1 FADH$_2$ per turn.
Pyruvate $\rightarrow$ Acetyl CoA

$\text{NAD}^+ \rightarrow \text{NADH} + \text{H}^+$

Acetyl CoA

Citric acid cycle

$\text{FADH}_2 \rightarrow \text{FAD}$

$\text{NAD}^+ \rightarrow 3 \text{NADH} + 3 \text{H}^+$

$\text{CO}_2 \rightarrow 2 \text{CO}_2$

$\text{ATP} \rightarrow \text{ADP} + \text{P}_i$

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• 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 oxaloacetate, forming citrate.

• The next seven steps decompose the citrate back to oxaloacetate, making the process a cycle.

• The NADH and FADH$_2$ produced by the cycle relay electrons extracted from food to the electron transport chain.
Fig. 9-12-8

The diagram illustrates the citric acid cycle, also known as the Krebs cycle. The cycle begins with Acetyl CoA and progresses through the following steps:

1. Oxaloacetate + Acetyl CoA → Citrate + CoA
2. Citrate → Isocitrate + H₂O
3. Isocitrate → α-Ketoglutarate + NAD⁺ + H⁺
4. α-Ketoglutarate → Succinyl CoA + NAD⁺ + CO₂ + H⁺
5. Succinyl CoA → Succinate + CoA
6. Succinate → Fumarate + FADH₂
7. Fumarate → Malate + H₂O
8. Malate → Oxaloacetate + NADH + H⁺

The cycle is accompanied by the production of ATP through substrate-level phosphorylation and the reduction of NAD⁺ to NADH, which can be oxidized to generate additional ATP.

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

- Following glycolysis and the citric acid cycle, NADH and FADH$_2$ account for most of the energy extracted from food.
- These two electron carriers donate electrons to the electron transport chain, which powers ATP synthesis via oxidative phosphorylation.
The Pathway of Electron Transport

- The electron transport chain is in the cristae of the mitochondrion
- Most of the chain’s components are proteins, which exist in multiprotein complexes
- The carriers alternate reduced and oxidized states as they accept and donate electrons
- Electrons drop in free energy as they go down the chain and are finally passed to O₂, forming H₂O
Fig. 9-13

Free energy change ($\Delta G$) relative to $O_2$ (kcal/mol)

NADH $\rightarrow$ NAD$^+$

FADH$_2$ $\rightarrow$ FAD

Multiprotein complexes

FMN $\rightarrow$ Q $\rightarrow$ Cyt b $\rightarrow$ Cyt c $\rightarrow$ Cyt a $\rightarrow$ Cyt a$_3$

(Number of electrons $e^-$ transferred)

(from NADH or FADH$_2$)

$2H^+$ + $\frac{1}{2}O_2$ $\rightarrow$ $H_2O$

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Electrons are transferred from NADH or FADH$_2$ to the electron transport chain

Electrons are passed through a number of proteins including cytochromes (each with an iron atom) to O$_2$

The electron transport chain generates no ATP

The chain’s function is to break the large free-energy drop from food to O$_2$ into smaller steps that release energy in manageable amounts
Chemiosmosis: The Energy-Coupling Mechanism

- Electron transfer in the electron transport chain causes proteins to pump $H^+$ from the mitochondrial matrix to the intermembrane space.
- $H^+$ then moves back across the membrane, passing through channels in ATP synthase.
- ATP synthase uses the exergonic flow of $H^+$ to drive phosphorylation of ATP.
- This is an example of chemiosmosis, the use of energy in a $H^+$ gradient to drive cellular work.
Fig. 9-14

INTERMEMBRANE SPACE

Rotor
H+
Stator

H+

Internal
rod

Catalytic
knob

ADP
+ 

P_i

MITOCHONDRIAL MATRIX

ATP
**EXPERIMENT**

An electromagnet is used to manipulate a sample. The sample contains a magnetic bead, an internal rod, a catalytic knob, and a nickel plate.

**RESULTS**

The results show the number of photons detected in sequential trials.

- **Rotation in one direction**: Bar heights vary from approximately 20 to 30, with a peak around 25.
- **Rotation in opposite direction**: Similar bar heights to the above, with a peak around 25.
- **No rotation**: Bar heights range from 15 to 20, with a peak around 20.

Graphically, the bars are color-coded: yellow for rotation in one direction, light blue for rotation in the opposite direction, and gray for no rotation.
The energy stored in a $\text{H}^+$ gradient across a membrane couples the redox reactions of the electron transport chain to ATP synthesis.

The $\text{H}^+$ gradient is referred to as a proton-motive force, emphasizing its capacity to do work.
Protein complex of electron carriers

Electron transport chain

1. Electron transport chain

Chemiosmosis

2. Chemiosmosis

Oxidative phosphorylation

- **NADH** (carrying electrons from food)
- **FADH$_2$**
- **FAD**
- **Q**
- **Cyt c**
- **II**
- **III**
- **IV**
- **2 H$^+$ + $\frac{1}{2}$O$_2$**
- **H$_2$O**
- **2 H$^+$ + 1/2O$_2$**
- **ADP + P$_i$**
- **ATP synthase**
- **ATP**
An Accounting of ATP Production by Cellular Respiration

• During cellular respiration, most energy flows in this sequence:
  
glucose $\rightarrow$ NADH $\rightarrow$ electron transport chain $\rightarrow$ proton-motive force $\rightarrow$ ATP

• About 40% of the energy in a glucose molecule is transferred to ATP during cellular respiration, making about 38 ATP
Maximum per glucose: About 36 or 38 ATP

Glycolysis: Glucose → 2 Pyruvate

Citric acid cycle: 2 Acetyl CoA

Oxidative phosphorylation: electron transport and chemiosmosis

Electron shuttles span membrane between CYTOSOL and MITOCHONDRION.
Concept 9.5: Fermentation and anaerobic respiration enable cells to produce ATP without the use of oxygen

- Most cellular respiration requires $O_2$ to produce ATP
- Glycolysis can produce ATP with or without $O_2$ (in aerobic or anaerobic conditions)
- In the absence of $O_2$, glycolysis couples with fermentation or anaerobic respiration to produce ATP
• Anaerobic respiration uses an electron transport chain with an electron acceptor other than O$_2$, for example sulfate

• Fermentation uses phosphorylation instead of an electron transport chain to generate ATP
Types of Fermentation

• Fermentation consists of glycolysis plus reactions that regenerate NAD$^+$, which can be reused by glycolysis

• Two common types are alcohol fermentation and lactic acid fermentation
  
  – In **alcohol fermentation**, pyruvate is converted to ethanol in two steps, with the first releasing CO2
    
    • Alcohol fermentation by yeast is used in brewing, winemaking, and baking
  
  – In **lactic acid fermentation**, pyruvate is reduced to NADH, forming lactate as an end product, with no release of CO$_2$
    
    • Lactic acid fermentation by some fungi and bacteria is used to make cheese and yogurt
    
    • Human muscle cells use lactic acid fermentation to generate ATP when O$_2$ is scarce
Fig. 9-18

(a) Alcohol fermentation

2 ADP + 2 $\text{P}_i$ $\rightarrow$ 2 ATP

Glucose $\rightarrow$ Glycolysis

2 NAD$^+$ $\rightarrow$ 2 NADH $\rightarrow$ 2 Ethanol $\rightarrow$ 2 Acetaldehyde

2 Pyruvate $\rightarrow$ 2 $\text{CO}_2$

(b) Lactic acid fermentation

2 ADP + 2 $\text{P}_i$ $\rightarrow$ 2 ATP

Glucose $\rightarrow$ Glycolysis

2 NAD$^+$ $\rightarrow$ 2 NADH $\rightarrow$ 2 Lactate $\rightarrow$ 2 Pyruvate

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Fermentation and Aerobic Respiration Compared

• Both processes use glycolysis to oxidize glucose and other organic fuels to pyruvate.

• The processes have different final electron acceptors: an organic molecule (such as pyruvate or acetaldehyde) in fermentation and \( O_2 \) in cellular respiration.

• Cellular respiration produces 38 ATP per glucose molecule; fermentation produces 2 ATP per glucose molecule.
- **Obligate anaerobes** carry out fermentation or anaerobic respiration and cannot survive in the presence of $O_2$

- Yeast and many bacteria are **facultative anaerobes**, meaning that they can survive using either fermentation or cellular respiration.

- In a facultative anaerobe, pyruvate is a fork in the metabolic road that leads to two alternative catabolic routes.
Glucose

<table>
<thead>
<tr>
<th>Glycolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytosol</td>
</tr>
<tr>
<td>No O₂ present: Fermentation</td>
</tr>
<tr>
<td>O₂ present: Aerobic cellular respiration</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pyruvate</th>
</tr>
</thead>
<tbody>
<tr>
<td>MITOCHONDRION</td>
</tr>
<tr>
<td>Acetyl CoA</td>
</tr>
<tr>
<td>Citric acid cycle</td>
</tr>
<tr>
<td>Ethanol or lactate</td>
</tr>
</tbody>
</table>
The Evolutionary Significance of Glycolysis

- Glycolysis occurs in nearly all organisms
- Glycolysis probably evolved in ancient prokaryotes before there was oxygen in the atmosphere
Concept 9.6: Glycolysis and the citric acid cycle connect to many other metabolic pathways

- Glycolysis and the citric acid cycle are major intersections to various catabolic and anabolic pathways
The Versatility of Catabolism

- Catabolic pathways funnel electrons from many kinds of organic molecules into cellular respiration
- Glycolysis accepts a wide range of carbohydrates
- Proteins must be digested to amino acids; amino groups can feed glycolysis or the citric acid cycle
• Fats are digested to glycerol (used in glycolysis) and fatty acids (used in generating acetyl CoA)

• Fatty acids are broken down by beta oxidation and yield acetyl CoA

• An oxidized gram of fat produces more than twice as much ATP as an oxidized gram of carbohydrate
Proteins → Carbohydrates → Fats

Amino acids → Sugars → Glycerol → Glycerol-3-Phosphate

Glycolysis:
- Glucose → Glyceraldehyde-3-Phosphate
- Pyruvate

Acetyl CoA

Citric acid cycle

Oxidative phosphorylation
Biosynthesis (Anabolic Pathways)

- The body uses small molecules to build other substances
- These small molecules may come directly from food, from glycolysis, or from the citric acid cycle
Regulation of Cellular Respiration via Feedback Mechanisms

• Feedback inhibition is the most common mechanism for control

• If ATP concentration begins to drop, respiration speeds up; when there is plenty of ATP, respiration slows down

• Control of catabolism is based mainly on regulating the activity of enzymes at strategic points in the catabolic pathway
Fig. 9-21

Glucose

Glycolysis
Fructose-6-phosphate

Phosphofructokinase

Fructose-1,6-bisphosphate

Pyruvate

Inhibits

AMP
Stimulates

Inhibits

ATP

Acetyl CoA

Citrate

Citric acid cycle

Oxidative phosphorylation
Fig. 9-UN5

Inputs

Glucose

Glycolysis

Outputs

Pyruvate

2 ATP

2 NADH
Inputs

- 2 Acetyl CoA
- 2 Oxaloacetate

Outputs

- 2 ATP
- 6 NADH
- 2 FADH₂

Citric acid cycle
You should now be able to:

1. Explain in general terms how redox reactions are involved in energy exchanges.

2. Name the three stages of cellular respiration; for each, state the region of the eukaryotic cell where it occurs and the products that result.

3. In general terms, explain the role of the electron transport chain in cellular respiration.
4. Explain where and how the respiratory electron transport chain creates a proton gradient

5. Distinguish between fermentation and anaerobic respiration

6. Distinguish between obligate and facultative anaerobes