**Chapter X: Cellular Metabolism**

**Introduction**

After a long day at school, you may first enter your room, turn on the lights, plug in your phone to charge, and turn on your computer to surf the Internet. Those three things, and many more everyday conveniences, require electricity to run. Where does this energy come from? In most cases, the electricity is generated at a power plant. Another form of energy, like from a running river, blowing wind, burning coal, or even nuclear interactions, is converted to electrical energy and used to power numerous households and businesses. Much like these power plants, living things need to convert different forms of energy into useable forms. At a cellular level, this process is conversion of complex compounds into adenosine triphosphate (ATP) and certain electron carriers, which are used to power countless reactions within a cell. Cells have many ways of producing this much-needed energy source, and they can use different methods to adapt under different stressors or environmental factors. In this chapter, we will discuss the function of electron carriers and ATP within a cell. We will also cover one of the main ways a cell can produce these forms of energy: through glycolysis, the citric acid cycle, and oxidative phosphorylation.

**X.1—Energy within the Cell**

Energy within a cell is packaged within two kinds of molecules: triphosphate molecules like ATP, which are an active source for cellular energy, and electron carriers like NADH and FADH­­2, which transport electrons to the mitochondria to produce more ATP. These molecules are produced in many metabolic reactions within the cell that break down complex molecules like glucose.

*ATP in the Cell*

Adenosine triphosphate (ATP) is a ubiquitous energy carrier in all cells. Certain reactions within the cell are considered thermodynamically unfavorable; under normal circumstances, the reaction would not proceed due to a lack of energy input. ATP is used to power these normally unfavorable reactions by breaking the terminal phosphate bond to produce adenosine diphosphate (ADP) and a lone inorganic phosphate (Pi). ATP functions not only to power cellular reactions but also to control the amount of energy released at one time. If the cell released all of its gathered energy at once, the output would be deadly for the cell. Too little energy release would cause the reaction to fail; too much energy release could damage the cell. How does the cell address this conundrum? Since the cell cannot store free energy alone, it stores energy in the form of chemical bonds, namely in the phosphate bonds of ATP.

To break the terminal phosphate bond of ATP, the cell utilizes a hydrolysis reaction. This reaction splits a water molecule (H2O) into a proton (H+) and hydroxide group (OH-) and adds the resulting ions to the larger molecule. The interactions of the added groups and the phosphates cause the terminal phosphate bond to be broken, resulting in the formation of ADP and Pi. This bond breakage releases a set amount of energy which powers reactions, allowing the cell to control how much energy is released at one time to maximize efficiency. The cell has a limited pool of ATP and ADP, so as it breaks down ATP to ADP to power reactions, the cell needs to replenish ATP. The cell can break down macromolecules like glucose in order to produce energy. This energy is then stored into the phosphate bond used to convert ADP and Pi back into ATP. Much like a rechargeable battery, the cell continually uses its energy from ATP and replenishes its energy stores by reattaching a phosphate group to ADP. This addition of a phosphate group to ADP is done by enzymes called kinases throughout the various metabolic processes in cells. Phosphorylation occurs at two levels within the cell. Substrate-level phosphorylation is the direct addition of phosphate to ADP to produce ATP. Meanwhile, oxidative phosphorylation uses electron carriers and a proton gradient to phosphorylate ADP to form ATP.

*Electron Carriers*

Metabolic reactions in the cell can directly produce ATP, but the amount of ATP produced from substrate level phosphorylation alone is rather low. To remedy this, many steps in the metabolism of macromolecules release electrons. However, electrons cannot flow freely within the cell; they must be bound to some other molecule or compound. These electrons are therefore transferred to compounds known as electron carriers, whose specific purpose is to shuttle electrons from one reaction site to another. Electrons are transferred from one compound to another through oxidation-reduction reactions, or redox reactions. These reactions involve one compound losing an electron or electrons (oxidation) and the other compound gaining said electron(s) (reduction).

In the cell, the most common electron carriers in metabolism are nicotinamide adenine dinucleotide (NAD) and flavin adenine dinucleotide (FAD). The carriers in their oxidized state are NAD+ and FAD. These carriers act as oxidizing agents to many compounds formed within metabolic processes, meaning that they cause the oxidation of another compound and are therefore reduced. Reducing agents, which are oxidized in the redox reaction, pass their electrons to these carriers in the form of hydrogen atoms. The reduced carriers, which are NADH and FADH2, respectively, then transport the received electrons to the mitochondria. There, they release their hydrogens to supplement ATP formation via oxidative phosphorylation. The now oxidized carriers can then return to metabolic sites and uptake electrons, continuing the energy production cycle.

**X.2—Glycolysis**

Almost all cells, from bacteria to cells in our bodies, can utilize glucose to create energy. The process that initiates the metabolism of glucose is called glycolysis. It takes place in the cytoplasm of cell, and it is present in nearly all cells. This process is part of substrate-level phosphorylation; it does not use oxygen and is therefore anaerobic. The main goals of glycolysis are to break down glucose into pyruvate for further metabolism and to produce energy in the form of ATP and NADH. However, there are many steps between the starting and ending products of glycolysis that modify glucose to be more easily metabolized. The first half of glycolysis actually invests energy in the form of ATP to prepare glucose for metabolism, while the second half actually produces ATP and NADH.

The steps of glycolysis are as follows:

1. *Glucose 🡪 Glucose-6-phosphate*. This reaction adds a phosphate from ATP to six-carbon sugars (in this case, glucose). Since ATP is being used in this reaction, it is considered an energy-consuming reaction. This phosphorylation activates glucose to be further broken down in glycolysis. It also prevents the glucose from leaving the cell since the charged phosphate group cannot cross the uncharged plasma membrane of the cell.
2. *Glucose-6-phosphate🡪 Fructose-6-phosphate*. This reaction is an isomerization, where one molecule is changed to another form without major chemical formula changes. In the reaction, G6P is converted to an isomer form, F6P.
3. *Fructose-6-phosphate🡪 Fructose-1,6-bisphosphate*. A kinase enzyme adds another phosphate group to F6P, creating a compound with two phosphate groups. Prior to this reaction, glucose and its other forms can be shuttled out of glycolysis and used for other purposes. This would occur when ATP levels are high and the cell needs to focus on other means of energy storage. Once this reaction proceeds forward, the sugar is locked into breakdown through glycolysis. Because of this, it is considered the rate-limiting step of glycolysis.
4. *Fructose-1,6-bisphosphate🡪 Glyceraldehyde-3-phosphate + dihydroxyacetone phosphate.* F16BP, still a six-carbon sugar, is now split into two three-carbon sugars, G3P and DHAP. G3P continues further down into glycolysis, but DHAP must be converted into G3P to be further metabolized. This is accomplished by another isomerization reaction like in step 2.
5. *Glyceraldehyde-3-phosphate🡪 1,3-bisphosphoglycerate.* This step begins the energy-producing half of glycolysis. In this step, electrons are removed from G3P, and a phosphate group is added. These electrons (which are moved via hydrogen) are transferred to NAD+, forming the reduced NADH. This NADH then goes on to supply electrons for oxidative phosphorylation or to be oxidized to NAD+ via fermentation.
6. *1,3-bisphosphoglycerate🡪 3-phosphoglycerate.* Here, a phosphate group is removed from the bisphosphoglycerate to form a “mono”-phosphoglycerate. The removed phosphate is added to ADP to form ATP. This is the first step to directly produce ATP in glycolysis.
7. *3-phosphoglycerate🡪 2-phosphoglycerate.* This step involves an isomerization that moves the phosphate group from the third carbon to the second.
8. *2-phosphoglycerate🡪 Phosphoenolpyruvate.* The reaction removes a water from 2-PG through a dehydration reaction. This dehydration causes the formation of a double bond between carbons adjacent to the phosphate group, which increases the phosphate bond’s potential energy prior to removal.
9. *Phosphoenolpyruvate🡪 Pyruvate.* The final step of glycolysis involves the removal of the phosphate group from PEP to form pyruvate. Like in reaction 6, this phosphate is transferred to ADP to form ATP.

Following these reactions, pyruvate goes on to be further metabolized through other cellular processes. Using one glucose, the cell has already invested two ATP. However, for each G3P, the cell produces two ATP and one NADH per cycle of glycolysis. Since we obtain two G3P per one glucose through conversion of DHAP, we actually make four ATP and two NADH per one glucose. Thus, the net total of energy produced is two ATP and two NADH. In the next section, we will discuss how the end product, pyruvate, is further metabolized in the cell.

**X.3—Pyruvate Dehydrogenase and the Citric Acid Cycle**

Now that glucose has been broken down into two three-carbon molecules, it can be further metabolized via the citric acid cycle. Unlike glycolysis, the citric acid cycle takes place in the mitochondria of cells. The citric acid cycle does not necessarily have an end product. It takes acetyl coenzyme A (CoA) and adds it to oxaloacetate to form citrate, which is then metabolized by various enzymes back to oxaloacetate so that the cycle can begin anew. However, the citric acid cycle produces more electron carriers, CO2, and guanine triphosphate (GTP), which is equivalent to ATP. Since two pyruvates are formed from one glucose, the cycle runs through twice per one glucose.

Before pyruvate enters the citric acid cycle, it must be converted to acetyl CoA. This process is catabolized by pyruvate dehydrogenase, and the conversion process takes place in three steps. First, a carboxyl group is removed from pyruvate (3C) and released as CO2, forming a hydroxyethyl group (2C). Then, the hydroxyethyl group is oxidized, transferring electrons to NAD+ and forming one NADH and producing an acetyl group (2C). Finally, the CoA is added to the acetyl group, forming acetyl CoA. This molecule then can move to the mitochondrial matrix and participate in the citric acid cycle.

The steps of the citric acid cycle are as follows:

1. *Acetyl CoA (2C)+ Oxaloacetate(4C)🡪 Citrate (6C).* This condensation reaction uses water to join the acetyl group and oxaloacetate to form a six-carbon molecule, citrate. Meanwhile, the CoA is removed as CoA-SH, which will combine with another acetyl group via pyruvate dehydrogenase activity. This is an irreversible step in the citric acid cycle and commits the acetyl CoA to the pathway. When ATP levels are high, this step is inhibited and prevents the cycle from continuing.
2. *Citrate(6C)🡪* *Isocitrate (6C).* A water is removed from citrate, and it is converted to an isomer form, isocitrate.
3. *Isocitrate (6C)🡪 α-Ketoglutarate (5C).* Isocitrate loses a carboxyl group as CO2, forming a five-carbon molecule. This molecule is oxidized to form α-Ketoglutarate; the electrons lost are used to form another molecule of NADH.
4. *α-Ketoglutarate (5C)🡪 Succinyl CoA (4C).* In this reaction, α-Ketoglutarate loses another carbon as CO2 and is oxidized to form another NADH molecule. However, CoA-SH is also added to form another CoA molecule, succinyl CoA.
5. *Succinyl CoA (4C)🡪 Succinate (4C).* Here, the CoA is removed from succinyl CoA as CoA-SH, and a phosphate group forms a high-energy bond in its place. This bond is then broken, and the phosphate is bound to guanine diphosphate (GDP) to form GTP. Again, GTP has the same function as ATP.
6. *Succinate (4C)🡪 Fumarate (4C).* Succinate is oxidized via dehydration to form fumarate, losing two hydrogens. These hydrogens are transferred to FAD to form another reduced electron carrier, FADH2.
7. *Fumarate (4C)🡪 Malate (4C).* Water is added to fumarate, reducing it to malate.
8. *Malate (4C)🡪 Oxaloacetate (4C).* In the final step of the citric acid cycle, malate is oxidized to reform oxaloacetate, which can recombine with another acetyl CoA to begin

the cycle again. Another molecule of NADH is produced in this step.

Per one glucose molecule, glycolysis produces two pyruvate. These are then converted to acetyl CoAs through pyruvate dehydrogenase, producing one NADH and one CO2 per molecule. Each acetyl CoA enters the citric acid cycle to form three NADH, one FADH2, two CO2, and one GTP per cycle. For one glucose, the citric acid cycle produces double the amount of these since one glucose makes two acetyl CoA.

So far, the cell has made a net total of three ATP equivalents and many electron carriers like NADH and FADH2. Most cells cannot run effectively on such an inefficient exchange of energy, especially within the human body. The majority of the energy is instead produced through electron transport across the mitochondrial membrane using the electron carriers made throughout glycolysis and the citric acid cycle. In the next section, we will take a look at how a cell can mass produce ATP through oxidative phosphorylation.

**X.4—Oxidative Phosphorylation**

The previous two sections discussed anaerobic processes of producing energy within a cell. However, the jackpot of ATP comes from utilizing a concentration gradient of hydrogen ions across a mitochondrial membrane. These ions are removed from electron carriers produced from glycolysis and the citric acid cycle and pumped to the other side of the membrane, building up an imbalance of charge within the intermembrane space. In an attempt to rebalance the charge gradient, hydrogen ions flow back into the mitochondrial matrix through an enzyme called ATP synthase, which uses the energy of the proton flow to synthesize ATP. This is known as oxidative phosphorylation. In this section, we will discuss the individual complexes of the electron transport chain and ATP synthase.

*Complex I*—Complex I accepts electrons from NADH (which was produced during glycolysis and the citric acid cycle), oxidizing it back to NAD+. It receives the hydrogens through a prosthetic group. A prosthetic group is a non-protein component of a protein that is essential for its function. The electrons on the hydrogens are transferred to another electron transporter. The reduced transporter then shuttles its electrons to Complex III. This causes the hydrogens to be oxidized into protons. The protons are then pumped into the intermembrane space.

*Complex II*—Complex II receives electrons from FADH2, which is oxidized back to FAD. The electrons are transferred to a protein transporter like in Complex I. However, Complex II cannot pump protons like the other complexes, so it does not contribute as much energy per electron to the ATP producing process.

*Complex III*—This complex receives electrons from QH2. It pumps the protons into the intermembrane space like Complex I. However, it transfers the received electrons to another protein transporter. The transporter then passes its electron onto the fourth complex of the chain.

*Complex IV*—The final complex contains proteins that tightly hold an oxygen. Electrons are passed to this oxygen to reduce it. Upon complete reduction (O22-), the oxygen is unbound and picks up hydrogen from its surroundings, forming H2O. Complex IV pumps out protons removed from the system, contributing to the overall ATP production.

*ATP Synthase*—So far, three of the four complexes have pumped protons into the intermembrane space, creating an imbalance of protons across the mitochondrial membrane. Since the charged protons cannot cross the nonpolar phospholipid membrane, they must use a protein transporter to reenter the mitochondrial matrix and attempt to rebalance the electrochemical gradient. ATP synthase acts as this proton channel. As hydrogen ions move down the concentration gradient through the channel, part of ATP synthase turns through the force of the proton flow. This rotation powers the addition of a phosphate to ADP to generate ATP. This process produces about 90 percent of the ATP generated in the metabolism of glucose.

The main idea behind oxidative phosphorylation is that electrons are transferred from electron carriers into complex proteins, and the remaining protons are pumped out of the membrane to form a proton gradient. This gradient force is used to drive protons back into the membrane through ATP synthase, which uses the force of the reentering proton to make ATP. Since many protons can be pumped out and back in, a lot of ATP can be generated at once.

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