

Aerobic Respiration

Slide 2 In our previous lesson on glycolysis, we saw that during glycolysis, 6-carbon molecules of glucose are partially oxidized to produce two 3-carbon molecules of pyruvate. This process releases some, but not all, of the energy stored in the bonds of the glucose molecule, and results in a net production of 2 ATP molecules and 2 molecules of reduced $\text{NADH} + \text{H}^+$. For many organisms, however, glycolysis is only the beginning of the story in terms of energy production. Organisms that are able to perform aerobic respiration can fully oxidize glucose and utilize more of its energy through glycolysis and three more pathways that occur after glycolysis. These three pathways, in the order that they occur, are pyruvate oxidation, the citric acid cycle, and oxidative phosphorylation.

The complete oxidation of glucose through these pathways, as you might expect, releases more energy than glycolysis alone. This energy, in turn, is ultimately captured in the bonds of ATP. In fact, the pathways of aerobic respiration release around 34 more molecules of ATP per molecule of glucose, resulting in a total of 36 molecules of ATP per molecule of glucose – 18 times the amount of energy produced by glycolysis alone!

Slide 3 The pathways of aerobic respiration begin where glycolysis ended – with pyruvate. Pyruvate oxidation occurs at the inner mitochondrial membrane of eukaryotic cells, and at the cell membrane of prokaryotic cells. During this process, 3-carbon pyruvate is oxidized to 2-carbon acetate, which is then bound to a second molecule, called Coenzyme A. The energy-releasing oxidation reaction is coupled to the energy-requiring reduction of NAD^+ to $\text{NADH} + \text{H}^+$. The energy and electrons thus captured in $\text{NADH} + \text{H}^+$ will play an important role later, so don't forget this molecule.

In addition, note that one carbon molecule from pyruvate is completely oxidized and released as carbon dioxide. What does this mean in terms of our original 6-carbon glucose molecule? Remember that each glucose molecule produces two 3-carbon pyruvate molecules. When each of these molecules goes through pyruvate oxidation, it loses one fully oxidized carbon. This means that a total of two carbons of our original glucose molecule are now fully oxidized. Two down, four to go!

The product of pyruvate oxidation, called acetyl-CoA, may now enter the next pathway of aerobic respiration, the citric acid cycle.

Slide 4 Three things are accomplished in the citric acid cycle:

- (1) Acetyl-CoA is oxidized to produce two molecules of carbon dioxide.
- (2) The energy released from these oxidation reactions is used to reduce the electron carriers NAD^+ and FAD^+ to produce $\text{NADH} + \text{H}^+$ and FADH_2 , and to produce ATP by substrate-level phosphorylation.
- (3) citric acid cycle intermediates are rearranged to regenerate oxaloacetate -- the same

molecule that initiates the cycle by condensing with acetyl-CoA.

So let's take a closer look at the steps involved in this process.

When acetyl-CoA enters the citric acid cycle - which is also called the Krebs cycle or the tricarboxylic acid cycle - it reacts with a 4 carbon molecule, oxaloacetate, to form a 6 carbon compound, citrate.

A series of reactions follows where citrate is rearranged. This is accompanied by the loss of a carbon atom in the form of carbon dioxide, and the formation of α -ketoglutarate.

Oxidation of α -ketoglutarate results in reduction of $\text{NADH} + \text{H}^+$, the formation of another molecule of carbon dioxide, and the production of succinyl-CoA, a 4 carbon molecule. By this point in the cycle two molecules of reduced $\text{NADH} + \text{H}^+$ have been formed and two molecules of carbon dioxide have been released.

Succinyl-CoA enters a sequence of reactions that results in the reformation of oxaloacetate. During this part of the cycle two more molecules of $\text{NADH} + \text{H}^+$ and FADH_2 are produced, and ATP is formed. This completes the cycle.

Now, step back and try to see the big picture. First, a four carbon molecule and a two carbon molecule are combined to form a six carbon molecule. Second, two carbon atoms are completely oxidized, producing 2 molecules of carbon dioxide. The energy produced from the oxidation reactions of this cycle is captured in the bonds of ATP, $\text{NADH} + \text{H}^+$ and FADH_2 . Third, there is a series of reactions that regenerates the original four carbon molecule that started the cycle. Can you see it?

Slide 5 The final stage of aerobic respiration is oxidative phosphorylation. The key event of this stage is the formation of a proton gradient that drives the synthesis of ATP. Here's how it happens.

In the first step, an electron carrier (such as $\text{NADH} + \text{H}^+$) donates electrons to the first protein in the chain, resulting in the protein becoming reduced. This is followed by the sequential oxidation and reduction of a "chain" of proteins and other molecules that comprise the electron transport chain. These events are accompanied by the transfer of protons across the membrane. The energy needed to "pump" these protons across the membrane is derived from the redox reactions that occur.

The electron transport chain consists of several proteins and other compounds that are associated with the inner membrane of mitochondria, or the cell membrane of prokaryotes. In the first step, the electron carrier NADH donates electrons to the first protein in the chain - the NADH-Q reductase complex. Once NADH-Q reductase is reduced, it can in turn become oxidized by reducing the next component of the chain, ubiquinone. Ubiquinone then may become oxidized by reducing the next component of the chain, and so on. Note that each component of the chain undergoes a cycle of being reduced and then oxidized as it gains and then donates electrons.

At the end of the electron transport chain, the electrons are finally used to reduce the “terminal electron acceptor”, which in aerobic metabolism is oxygen. The reduction of oxygen yields water - the final product of this process.

At this point you may say “A-ha!”, because you have finally found where oxygen takes part in aerobic respiration, or, in other words, why aerobic respiration is ‘aerobic.’ In fact, this is the only step in aerobic respiration that directly requires molecular oxygen. If oxygen is not present, however, oxidative phosphorylation, the citric acid cycle, and pyruvate oxidation are not able to occur. We will discuss the reason for this in the lesson on fermentation.

The sequence of reduction and oxidation reactions allows energy to be gradually released, and it is productively used to transport protons (H^+) across the membrane. The transport of protons requires energy because it is accompanied by the formation of a chemical gradient. As we’ve seen before, a chemical gradient is a form of potential energy – remember this energy, we’ll see how it is used to produce ATP in just a moment.

Slide 6 Electrons can actually enter the electron transport chain at several stages in the process. Precisely where they enter depends on the redox potential of the electron donor and the redox potential of the electron acceptor (if this doesn’t make sense to you, then it might be useful to review basic redox chemistry in a chemistry textbook).

On this slide you can see an example of electrons entering the electron transport chain at a place that differs from that used by $NADH + H^+$. As you recall, in the citric acid cycle FAD^+ is reduced to form $FADH_2$. The electrons carried by $FADH_2$ enter the electron transport chain at ubiquinone. From this point on, the electrons follow the same path as with $NADH + H^+$ and are ultimately used to reduce oxygen.

Two other important features of electron transport are illustrated on this slide. First, notice that each time a redox reaction occurs, the amount of free energy present decreases. In other words, each time an electron is transferred between carriers, a small amount of energy is released. This, again, is the energy that is used to build a proton gradient across the membrane.

Second, it is important to notice that all components of electron transport chains share a common feature - they are all capable of undergoing oxidation and reduction. As a result, they cycle from being oxidized, to being reduced, to being oxidized, and so on. This has several important implications, one of which is that the $NADH + H^+$ produced during metabolism of glucose is continually being re-oxidized to form NAD^+ that can cycle back to participate in glycolysis, pyruvate oxidation, and the citric acid cycle.

Slide 7 Like many other membranes in cells, the inner mitochondrial membrane is highly selective and H^+ cannot readily cross it. This is a very important feature since it provides a way to form a H^+ gradient. If you’ll remember, during electron transport protons are pumped across the membrane via the electron transport chain, forming just

such a gradient. Given a chance, protons will diffuse back across the membrane toward equilibrium. In order for H^+ to move back across the membrane, however, they must pass through special channels within the ATP synthase complex. The passage of H^+ through the channels is “driven” by the electrochemical gradient that exists due to the difference in the H^+ concentrations on either side of the membrane. This electrochemical gradient, which is also called the proton motive force, provides the energy needed by ATP synthase to synthesize ATP from ADP and inorganic phosphate. As protons flow down their electrochemical gradient and through ATP synthase, they cause part of the synthase complex to rotate. The energy thus provided is used to form ATP from ADP and inorganic phosphate.

Slide 8 To recap the process of aerobic respiration, let’s look again at how ATP is produced throughout the whole process.

Note that only a small proportion of ATP is produced during glycolysis and the citric acid cycle - these processes only net 4 ATP.

The reduced electron carriers $NADH + H^+$ and $FADH^2$ cycle energetic electrons to the electron transport chain from glycolysis, pyruvate oxidation, and the citric acid cycle.

The vast majority of the ATP is produced as a result of oxidative phosphorylation. In fact, 32 (!) molecules of ATP are produced for each molecule of glucose that is metabolized.

The yield of energy from aerobic respiration is important since many cells need a lot of ATP to function and grow. Just how much ATP do cells need? Here’s a staggering example: a working muscle cell may recycle ATP at a rate of 10 million molecules per second! Maybe sugar isn’t so bad for you after all!