Cellular respiration

Cellular respiration is the set of the metabolic reactions and processes that take place in the cells of organisms to convert biochemical energy from nutrients into adenosine triphosphate (ATP), and then release waste products.[1] The reactions involved in respiration are catabolic reactions, which break large molecules into smaller ones, releasing energy in the process as weak so-called "high-energy" bonds are replaced by stronger bonds in the products. Respiration is one of the key ways a cell gains useful energy to fuel cellular activity. Cellular respiration is considered an exothermic redox reaction. The overall reaction is broken into many smaller ones when it occurs in the body, most of which are redox reactions themselves. Although technically, cellular respiration is a combustion reaction, it clearly does not resemble one when it occurs in a living cell. This difference is because it occurs in many separate steps. While the overall reaction is a combustion reaction, no single reaction that comprises it is a combustion reaction.

Nutrients that are commonly used by animal and plant cells in respiration include sugar, amino acids and fatty acids, and a common oxidizing agent (electron acceptor) is molecular oxygen (O₂). The energy stored in ATP (its third phosphate group is weakly bonded to the rest of the molecule and is cheaply broken allowing stronger bonds to form, thereby transferring energy for use by the cell) can then be used to drive processes requiring energy, including biosynthesis, locomotion or transportation of molecules across cell membranes.
Aerobic respiration

Aerobic respiration requires oxygen in order to generate ATP. Although carbohydrates, fats, and proteins can all be processed and consumed as reactants, it is the preferred method of pyruvate breakdown in glycolysis and requires that pyruvate enter the mitochondrion in order to be fully oxidized by the Krebs cycle. The product of this process is carbon dioxide and water but the energy transferred is used to break strong bonds in ADP as the third phosphate group is added to form ATP (adenosine triphosphate), by substrate-level phosphorylation, NADH and FADH₂.

\[
\begin{align*}
\text{Simplified reaction:} & \quad C_6H_{12}O_6 (s) + 6 O_2 (g) \rightarrow 6 CO_2 (g) + 6 H_2O (l) + \text{heat} \\
\Delta G & = -2880 \text{ kJ per mole of } C_6H_{12}O_6
\end{align*}
\]

The negative ΔG indicates that the reaction can occur spontaneously.

The reducing potential of NADH and FADH₂ is converted to more ATP through an electron transport chain with oxygen as the "terminal electron acceptor". Most of the ATP produced by aerobic cellular respiration is made by oxidative phosphorylation. This works by the energy released in the consumption of pyruvate being used to create a chemiosmotic potential by pumping protons across a membrane. This potential is then used to drive ATP synthase and produce ATP from ADP and a phosphate group. Biology textbooks often state that 38 ATP molecules can be made per oxidised glucose molecule during cellular respiration (2 from glycolysis, 2 from the Krebs cycle, and about 34 from the electron transport system). However, this maximum yield is never quite reached due to losses (leaky membranes) as well as the cost of moving pyruvate and ADP into the mitochondria's matrix and current estimates range around 29 to 30 ATP per glucose.

Aerobic metabolism is up to 15 times more efficient than anaerobic metabolism (which yields 2 molecules ATP per 1 molecule glucose). However some anaerobic organisms, such as Methanogen are able to continue with anaerobic respiration, yielding more ATP by using other inorganic molecules (not oxygen) as a final electron acceptors in the electron transport chain. They share the initial pathway of glycolysis but aerobic metabolism continues with the Krebs cycle and oxidative phosphorylation. The post glycolytic reactions take place in the mitochondria in eukaryotic cells, and in the cytoplasm in prokaryotic cells.
**Glycolysis**

Glycolysis is a metabolic pathway that takes place in the cytosol of cells in all living organisms. This pathway can function with or without the presence of oxygen. Aerobic conditions produce pyruvate and anaerobic conditions produce lactate. In aerobic conditions, the process converts one molecule of glucose into two molecules of pyruvate (pyruvic acid), generating energy in the form of two net molecules of ATP. Four molecules of ATP per glucose are actually produced; however, two are consumed as part of the preparatory phase. The initial phosphorylation of glucose is required to increase the reactivity (decrease its stability) in order for the molecule to be cleaved into two pyruvate molecules by the enzyme Aldolase. During the pay-off phase of glycolysis, four phosphate groups are transferred to ADP by substrate-level phosphorylation to make four ATP, and two NADH are produced when the pyruvate are oxidized. The overall reaction can be expressed this way:

\[
\text{Glucose} + 2 \text{NAD}^+ + 2 \text{P}_i + 2 \text{ADP} \rightarrow 2 \text{pyruvate} + 2 \text{NADH} + 2 \text{ATP} + 2 \text{H}^+ + 2 \text{H}_2\text{O} + \text{heat}
\]

Starting with glucose, 1 ATP is used to donate a phosphate to glucose to produce glucose 6-phosphate. Glycogen can change into glucose 6-phosphate as well with the help of glycogen phosphorylase. During Energy metabolism, glucose 6-phosphate turns into fructose 6-phosphate. An additional ATP is used to phosphorylate fructose 6-phosphate into fructose 1,6-disphosphate by the help of phosphofructokinase. Fructose 1,6-diphosphate then splits into two phosphorylated molecules with three carbon chains that later degrades into pyruvate.

**Oxidative decarboxylation of pyruvate**

Pyruvate is oxidized to acetyl-CoA and CO\(_2\) by the pyruvate dehydrogenase complex (PDC). The PDC contains multiple copies of three enzymes and is located in the mitochondria of eukaryotic cells and in the cytosol of prokaryotes. In the conversion of pyruvate to acetyl-CoA, one molecule of NADH and one molecule of CO\(_2\) is formed. This step is also known as the **link reaction or transition step**, as it links glycolysis and the Krebs cycle.

**Citric acid cycle**

This is also called the **Krebs cycle** or the **tricarboxylic acid cycle**. When oxygen is present, acetyl-CoA is produced from the pyruvate molecules created from glycolysis. When oxygen is present, the mitochondria will undergo aerobic respiration which leads to the Krebs cycle. However, if oxygen is not present, fermentation of the pyruvate molecule will occur. In the presence of oxygen, when acetyl-CoA is produced, the molecule then enters the citric acid cycle (Krebs cycle) inside the mitochondrial matrix, and gets oxidized to CO\(_2\) while at the same time reducing NAD to NADH. NADH can be used by the electron transport chain to create further ATP as part of oxidative phosphorylation. To fully oxidize the equivalent of one glucose molecule, two acetyl-CoA must be metabolized by the Krebs cycle. Two waste products, H\(_2\)O and CO\(_2\), are created during this cycle.

The citric acid cycle is an 8-step process involving different enzymes and co-enzymes. Throughout the entire cycle, acetyl-CoA(2 carbons) + Oxaloacetate(4 carbons) → Citrate(6 carbons) is rearranged to a more reactive form called Isocitrate(6 carbons). Isocitrate(6 carbons) modifies to become α-Ketoglutarate(5 carbons), Succinyl-CoA, Succinate, Fumarate, Malate, and finally, Oxaloacetate. The net energy gain from one cycle is 3 NADH, 1 FADH\(_2\).
and 1 GTP; the GTP may subsequently be used to produce ATP. Thus, the total energy yield from one whole glucose molecule (2 pyruvate molecules) is 6 NADH, 2 FADH$_2$, and 2 ATP.

**Oxidative phosphorylation**

In eukaryotes, oxidative phosphorylation occurs in the mitochondrial cristae. It comprises the electron transport chain that establishes a proton gradient (chemiosmotic potential) across the inner membrane by oxidizing the NADH produced from the Krebs cycle. ATP is synthesized by the ATP synthase enzyme when the chemiosmotic gradient is used to drive the phosphorylation of ADP. The electrons are finally transferred to exogenous oxygen and, with the addition of two protons, water is formed.

**Efficiency of ATP production**

The table below describes the reactions involved when one glucose molecule is fully oxidized into carbon dioxide. It is assumed that all the reduced coenzymes are oxidized by the electron transport chain and used for oxidative phosphorylation.

<table>
<thead>
<tr>
<th>Step</th>
<th>coenzyme yield</th>
<th>ATP yield</th>
<th>Source of ATP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycolysis preparatory phase</td>
<td>-2</td>
<td></td>
<td>Phosphorylation of glucose and fructose 6-phosphate uses two ATP from the cytoplasm.</td>
</tr>
<tr>
<td>Glycolysis pay-off phase</td>
<td>4</td>
<td></td>
<td>Substrate-level phosphorylation</td>
</tr>
<tr>
<td></td>
<td>2 NADH</td>
<td>4</td>
<td>Oxidative phosphorylation – Each NADH produces net 2 ATP due to NADH transport over the mitochondrial membrane</td>
</tr>
<tr>
<td>Oxidative decarboxylation of pyruvate</td>
<td>2 NADH</td>
<td>5</td>
<td>Oxidative phosphorylation</td>
</tr>
<tr>
<td>Krebs cycle</td>
<td>2</td>
<td>15</td>
<td>Oxidative phosphorylation</td>
</tr>
<tr>
<td></td>
<td>2 FADH$_2$</td>
<td>3</td>
<td>Oxidative phosphorylation</td>
</tr>
<tr>
<td><strong>Total yield</strong></td>
<td><strong>31 ATP</strong></td>
<td></td>
<td>From the complete oxidation of one glucose molecule to carbon dioxide and oxidation of all the reduced coenzymes.</td>
</tr>
</tbody>
</table>

Although there is a theoretical yield of 38 ATP molecules per glucose during cellular respiration, such conditions are generally not realized due to losses such as the cost of moving pyruvate (from glycolysis), phosphate, and ADP (substrates for ATP synthesis) into the mitochondria. All are actively transported using carriers that utilise the stored energy in the proton electrochemical gradient.

- Pyruvate is taken up by a specific, low km transporter to bring it into the mitochondrial matrix for oxidation by the pyruvate dehydrogenase complex.
- The phosphate carrier (PiC) mediates the electroneutral exchange (antiport) of phosphate $\text{H}_2\text{PO}_4^-$ (Pi) for $\text{OH}^-$ or symport of phosphate and protons $\text{H}^+$ across the inner membrane and the driving force for moving phosphate ions into the mitochondria is the proton motive force.
- The ATP-ADP translocase (also called adenine nucleotide translocase, ANT) is an antiporter and exchanges ADP and ATP across the inner membrane. The driving force is due to the ATP ($-4$) having a more negative charge than the ADP ($-3$) and thus it dissipates some of the electrical component of the proton electrochemical gradient.

The outcome of these transport processes using the proton electrochemical gradient is that more than 3 $\text{H}^+$ are needed to make 1 ATP. Obviously this reduces the theoretical efficiency of the whole process and the likely maximum is closer to 28–30 ATP molecules. In practice the efficiency may be even lower due to the inner
membrane of the mitochondria being slightly leaky to protons. Other factors may also dissipate the proton gradient creating an apparently leaky mitochondria. An uncoupling protein known as thermogenin is expressed in some cell types and is a channel that can transport protons. When this protein is active in the inner membrane it short circuits the coupling between the electron transport chain and ATP synthesis. The potential energy from the proton gradient is not used to make ATP but generates heat. This is particularly important in brown fat thermogenesis of newborn and hibernating mammals.

According to some of newer sources the ATP yield during aerobic respiration is not 36-38, but only about 30-32 ATP molecules / 1 molecule of glucose, because:

- **ATP : NADH+H⁺** and **ATP : FADH₂** ratios during the oxidative phosphorylation appear to be not 3 and 2, but 2.5 and 1.5 respectively. Unlike in the substrate-level phosphorylation, the stoichiometry here is difficult to establish.

- ATP synthase produces 1 ATP / 3 H⁺. However the exchange of matrix ATP for cytosolic ADP and Pi (antiport with OH⁻ or symport with H⁺) mediated by ATP–ADP translocase and phosphate carrier consumes 1 H⁺ / 1 ATP due to regeneration of the transmembrane potential changed during this transfer, so the net ratio is 1 ATP / 4 H⁺.

- The mitochondrial electron transport chain proton pump transfers across the inner membrane 10 H⁺ / 1 NADH+H⁺ (4+2+4) or 6 H⁺ / 1 FADH₂ (2+4).

So the final stoichiometry is

\[
\begin{align*}
1 \text{ NADH}+\text{H}^+ & : 10 \text{ H}^+ : 10/4 \text{ ATP} = 1 \text{ NADH}+\text{H}^+ : 2.5 \text{ ATP} \\
1 \text{ FADH}_2 & : 6 \text{ H}^+ : 6/4 \text{ ATP} = 1 \text{ FADH}_2 : 1.5 \text{ ATP}
\end{align*}
\]

- **ATP : NADH+H⁺** coming from glycolysis ratio during the oxidative phosphorylation is

  - 1.5 like for FADH₂ if hydrogen atoms (2H⁺+2e⁻) are transferred from cytosolic NADH+H⁺ to mitochondrial FAD by the glycerol phosphate shuttle located in the inner mitochondrial membrane.
  - 2.5 in case of malate-aspartate shuttle transferring hydrogen atoms from cytosolic NADH+H⁺ to mitochondrial NAD⁺

So finally we have / 1 molecule of glucose

- **Substrate-level phosphorylation:** 2 ATP from glycolysis + 2 ATP (directly GTP) from Krebs cycle
- **Oxidative phosphorylation**
  - 2 NADH+H⁺ from glycolysis: 2 × 1.5 ATP (if glycerol phosphate shuttle transfers hydrogen atoms) or 2 × 2.5 ATP (malate-aspartate shuttle)
  - 2 NADH+H⁺ from the oxidative decaboylation of pyruvate and 6 from Krebs cycle: 8 × 2.5 ATP
  - 2 FADH₂ from the Krebs cycle: 2 × 1.5 ATP

Altogether it gives 4 + 3 (or 5) + 20 + 3 = 30 (or 32) ATP / 1 molecule of glucose

The total ATP yield in ethanol or lactic acid fermentation is only 2 molecules coming from glycolysis, because pyruvate is not transferred to the mitochondrion and finally oxidized to the carbon dioxide (CO₂), but reduced to ethanol or lactic acid in the cytoplasm. These simple additional reactions are not energy source, but only regenerate for glycolysis NAD⁺ from NADH+H⁺, which can't be converted back to NAD⁺ in the mitochondrial electron transport chain inactive in anaerobic conditions, normally main source of ATP.
Fermentation

Without oxygen, pyruvate (pyruvic acid) is not metabolized by cellular respiration but undergoes a process of fermentation. The pyruvate is not transported into the mitochondrion, but remains in the cytoplasm, where it is converted to waste products that may be removed from the cell. This serves the purpose of oxidizing the electron carriers so that they can perform glycolysis again and removing the excess pyruvate. Fermentation oxidizes NADH to NAD+ so it can be re-used in glycolysis. In the absence of oxygen, fermentation prevents the build up of NADH in the cytoplasm and provides NAD+ for glycolysis. This waste product varies depending on the organism. In skeletal muscles, the waste product is lactic acid. This type of fermentation is called lactic acid fermentation. In strenuous exercise, when energy demands exceed energy supply, the respiratory chain cannot process all of the hydrogen atoms joined by NADH. During anaerobic glycolysis, NAD+ regenerates when pairs of hydrogen combine with pyruvate to form lactate. Lactate formation is catalyzed by lactate dehydrogenase in a reversible reaction. Lactate can also be used as an indirect precursor for liver glycogen. During recovery, when oxygen becomes available, NAD+ attaches to hydrogen from lactate to form ATP. In yeast, the waste products are ethanol and carbon dioxide. This type of fermentation is known as alcoholic or ethanol fermentation. The ATP generated in this process is made by substrate-level phosphorylation, which does not require oxygen.

Fermentation is less efficient at using the energy from glucose since only 2 ATP are produced per glucose, compared to the 38 ATP per glucose produced by aerobic respiration. This is because the waste products of fermentation still contain plenty of energy. Ethanol, for example, can be used in gasoline (petrol) solutions. Glycolytic ATP, however, is created more quickly. For prokaryotes to continue a rapid growth rate when they are shifted from an aerobic environment to an anaerobic environment, they must increase the rate of the glycolytic reactions. For multicellular organisms, during short bursts of strenuous activity, muscle cells use fermentation to supplement the ATP production from the slower aerobic respiration, so fermentation may be used by a cell even before the oxygen levels are depleted, as is the case in sports that do not require athletes to pace themselves, such as sprinting.

Anaerobic respiration

Cellular respiration is the process by which biological fuels are oxidised in the presence of an inorganic electron acceptor (such as oxygen) to produce large amounts of energy, to drive the bulk production of ATP.

Anaerobic respiration is used by some microorganisms in which neither oxygen (aerobic respiration) nor pyruvate derivatives (fermentation) is the final electron acceptor. Rather, an inorganic acceptor such as sulfate or nitrate is used.

Many high-school biology textbooks incorrectly refer to fermentation (e.g., to lactate) as anaerobic respiration.

References

External links

- A detailed description of respiration vs. fermentation (http://www2.ufp.pt/~pedros/bq/respi.htm)
- Kimball's online resource to cellular respiration (http://users.rcn.com/jkimball.ma.ultranet/BiologyPages/C/CellularRespiration.html)
- Cellular Respiration and Fermentation (http://biology.clc.uc.edu/courses/bio104/cellresp.htm) at Clermont College