15.2: The Citric Acid Cycle

Learning Outcomes

- Describe the citric acid cycle (Krebs Cycle).
- Name the products of the citric acid cycle.
- Identify the energy carrier molecules produced in the citric acid cycle.
- Describe what happens to pyruvate before it enters the citric acid cycle.

Aerobic Respiration

Enticing clues - volcanic gases, vast iron ore sediments, and bubbles of ancient air trapped in amber - suggest dramatic changes during the history of earth's atmosphere. Correlating these clues with the fossil record leads to two major conclusions: that early life evolved in the absence of oxygen, and that oxygen first appeared between 2 and 3 billion years ago (see figure below) because of photosynthesis by the blue green bacteria, cyanobacteria. The chemistry of cellular respiration reflects this history. Its first stage, glycolysis, is universal and does not use oxygen.

Absolutely dependent on oxygen gas, we find it difficult to imagine that its appearance must have been disastrous for the anaerobic organisms that evolved in its absence. But oxygen is highly reactive, and at first, its effect on evolution was so negative that some have named this period the "oxygen catastrophe". However, as oxygen gradually formed a protective **ozone layer**, life rebounded. After the first organisms evolved to use oxygen to their advantage, the diversity of aerobic organisms exploded. According to the Theory of Endosymbiosis, engulfing of some of these aerobic bacteria led to eukaryotic cells with mitochondria, and **multicellularity**, the evolution of multicellular eukaryotic organisms, followed. Today, we live in an atmosphere which is 21% oxygen, and most of life follows glycolysis with the last two, aerobic stages of cellular respiration.

Recall the purpose of cellular respiration: to release energy from glucose to make ATP, the universal molecule of energy for cellular work. The following equation describes the overall process, although it summarizes many individual chemical reactions.

$$6\,O_2 + \underbrace{C_6H_{12}O_6}_{\text{stored chemical energy, deliverable}} + 398\,Pi \xrightarrow{\text{mitochondia}} 38\,ATP + 6\,O_2 + 6\,H_2O \tag{15.2.1}$$

Once again, the first stage of this process, glycolysis, is ancient, universal, and anaerobic. In the cytoplasm of most cells, glycolysis breaks each 6-carbon molecule of glucose into two 3-carbon molecules of **pyruvate**. Chemical energy, which had been stored in the now broken bonds, is transferred to 2 ATP and 2 NADH molecules.

The fate of pyruvate depends on the species and the presence or absence of oxygen. If oxygen is present to drive subsequent reaction, pyruvate enters the mitochondria, where the **citric acid cycle** (also known as the **Krebs Cycle**) (Stage 2) and **electron transport chain** (Stage 3) break it down and oxidize it completely to CO_2 and H_2O. The energy released builds many more ATP molecules, though of course some is lost as heat. Let's explore the details of how mitochondria use oxygen to make more ATP from glucose by aerobic respiration.

The Citric Acid Cycle: Capturing Energy from Pyruvate

Aerobic respiration begins with the entry of the product of glycolysis, pyruvate, into the mitochondria. For each initial glucose molecule, two pyruvate molecules will enter the mitochondria. Pyruvate, however, is not the molecule that enters the citric acid cycle. Prior to entry into this cycle, pyruvate must be converted into a 2-carbon acetyl-CoenzymeA (acetyl-CoA) unit.

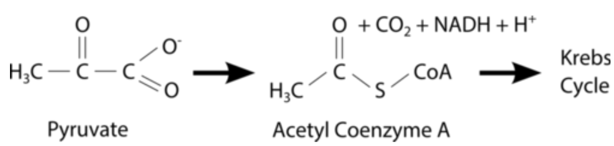

Figure 15.2.1: After glycolysis, two 3-carbon pyruvates enter the mitochondria, where they are converted to two 2-carbon acetyl-CoenzymeA (CoA) molecules. Acetyl-CoA then enters the Krebs Cycle. Note that the carbons removed become carbon dioxide, accounting for two of the six such end products of glucose oxidation. The energy released by this breakdown is carried by NADH.

The conversion of pyruvate into acetyl-CoA is referred to as the pyruvate dehydrogenase reaction. It is catalyzed by the pyruvate dehydrogenase complex. This process produces one NADH electron carrier while releasing a CO_2 molecule. This step is also known as the link reaction or transition step, as it links glycolysis and the citric acid cycle. Of course, as two pyruvates result from glycolysis, two acetyl-CoAs are produced as are 2 NADH molecules.

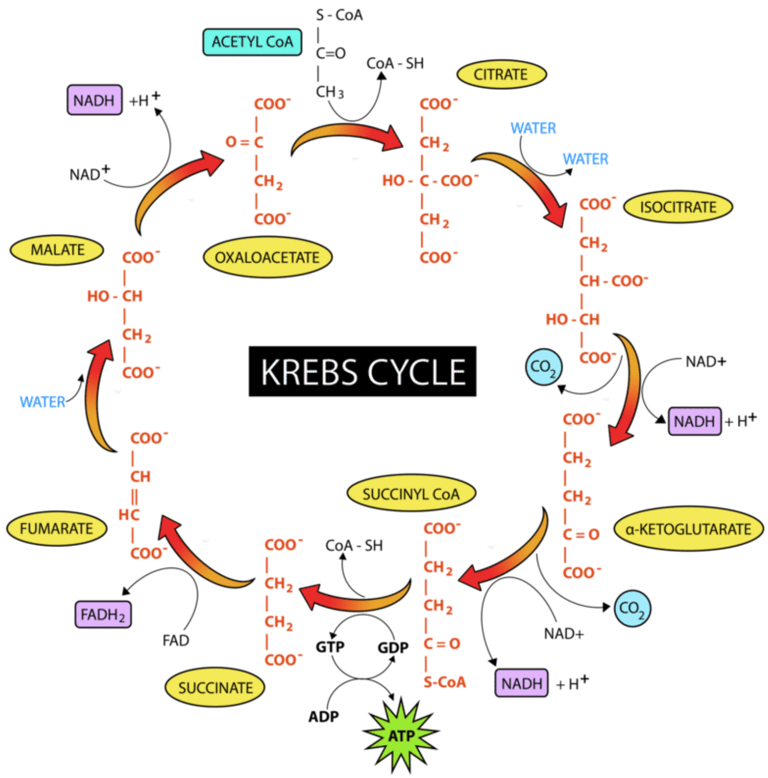

Figure 15.2.2: The Krebs Cycle completes the breakdown of glucose begun in glycolysis. If oxygen is present, pyruvate enters the mitochondria and is converted to acetyl-CoA. Acetyl-CoA enters the cycle by combining with 4-carbon oxaloacetate. Study the diagram to confirm that each turn of the cycle (two for each glucose) stores energy in 3 NADH $+H^{+}$, one $FADH_2$, and one ATP (from GTP), and releases 2 CO_2. The Krebs Cycle is also known as the citric acid cycle or the tricarboxylic acid cycle (TCA cycle).

1. Within the mitochondria, each pyruvate is broken apart and combined with a coenzyme known as CoA to form a 2-carbon molecule, acetyl-CoA, which can enter the Krebs Cycle. A single atom of carbon (per pyruvate) is "lost" as carbon dioxide. The energy released in this breakdown is captured in two NADH molecules. See the figure above. Fatty acids can also break down in to acetyl-CoA. By this means, lipids, like fats, can be "burned" to make ATP using the citric acid cycle.
2. The Krebs Cycle (see figure above) begins by combining each acetyl-CoA with a four-carbon carrier molecule to make a 6-carbon molecule of citric acid (or citrate, its ionized form).
3. The cycle carries citric acid through a series of chemical reactions which gradually release energy and capture it in several carrier molecules. For each acetyl-CoA which enters the cycle, 3 NAD^{+} are reduced to NADH, one molecule of FAD (another temporary energy carrier) is reduced to \(**FADH_2\)**, and one molecule of ATP (actually a precursor, GTP, guanine triphosphate) is produced. Study the figure above to locate each of these energy-capturing events.
4. Note what happens to carbon atoms (black dots in the figure above). For each 2-carbon acetyl-CoA which enters the cycle, two molecules of carbon dioxide are released, completing the breakdown of the original 6-carbon glucose molecule. The final step regenerates the original 4-carbon molecule which began the cycle, so that another acetyl-CoA can enter the cycle.

In summary, the citric acid cycle completes the breakdown of glucose which began with glycolysis. Its chemical reactions oxidize all six of the original carbon atoms to CO_2, and capture the energy released in 2 ATP, 6 NADH, and 2 $FADH_2$. These energy carriers join the 2 ATP and 2 NADH produced in glycolysis and the 2 NADH produced in the conversion of 2 pyruvates to 2 acetyl-CoA molecules.

At the conclusion of the citric acid cycle, glucose is completely broken down, yet only four ATP have been produced. Moreover, although oxygen is required to drive the citric acid cycle, the cycle's chemical reactions do not themselves consume O_2. The conclusion of cellular respiration, stage 3, produces the majority of the ATP.

Supplemental Resources

- Citric Acid Cycle (aka Krebs Cycle): virtuallabs.stanford.edu/other/biochem/TCA.swf
- Krebs Cycle (aka Citric Acid Cycle): http://johnkyrk.com/krebs.html

Contributors and Attributions

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