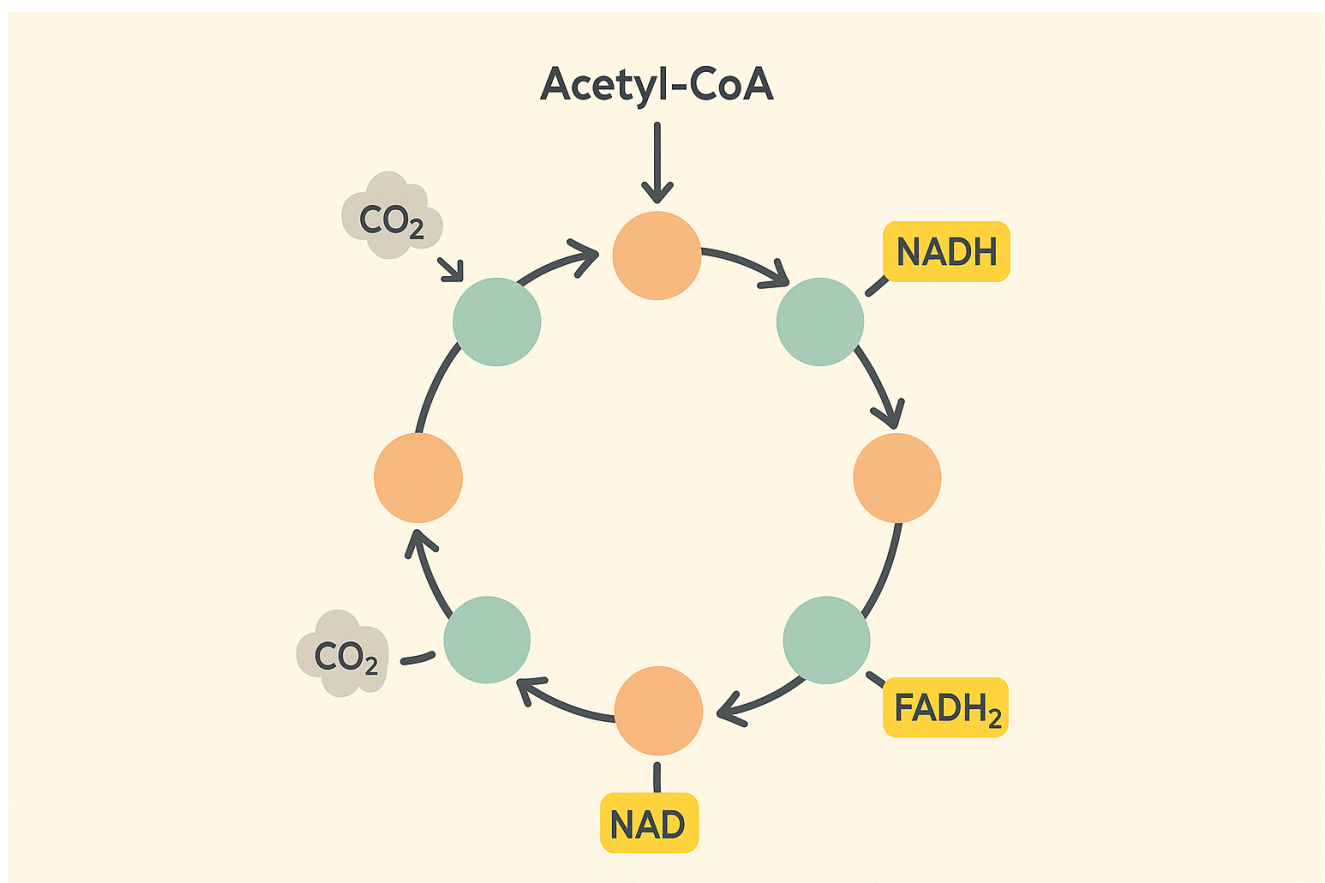


Krebs Cycle

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The Krebs cycle, also called the citric acid cycle or the TCA (tricarboxylic acid) cycle, is the second stage of aerobic cellular respiration. It runs inside the mitochondrial matrix, takes in acetyl-CoA produced from pyruvate, runs through eight enzymatic steps in a closed loop, and produces NADH, FADH₂, GTP/ATP, and CO₂. The cycle's job is not to make a lot of ATP directly; it's to strip electrons from carbon and load them onto NADH and FADH₂ carriers that then deliver the electrons to the electron transport chain for the big ATP payoff. Hans Krebs worked out the cycle in 1937 and won the 1953 Nobel Prize for the discovery.

The cycle exports reduced electron carriers as well as a small direct ATP-equivalent yield. Pyruvate oxidation is a separate preceding step.



The Krebs cycle, acetyl-CoA enters, CO₂ exits, and NADH plus FADH₂ carry electrons to the electron transport chain.

Where the Krebs Cycle Sits

The Krebs cycle is stage 2 of aerobic cellular respiration. It's preceded by **glycolysis** (cytoplasm) and followed by oxidative phosphorylation (inner mitochondrial membrane).

- **Stage 1, Glycolysis (cytoplasm):** glucose splits into 2 pyruvate, producing 2 ATP and 2 NADH per glucose.
- **Pyruvate oxidation (mitochondrial matrix):** each pyruvate becomes acetyl-CoA, releasing 1 CO₂ and producing 1 NADH.
- **Stage 2, Krebs cycle (mitochondrial matrix):** acetyl-CoA enters the cycle; covered in detail below.
- **Stage 3, Oxidative phosphorylation (inner membrane):** NADH and FADH₂ deliver electrons; oxygen is the final acceptor; produces ~26-28 ATP per glucose.

The Krebs cycle is the bridge between glycolysis and the big ATP-generating stage. Strip electrons from carbon, hand them to NADH and FADH₂, send them down the road to the electron transport chain.

The Cycle's Input and Output Per Acetyl-CoA

One turn of the Krebs cycle consumes one acetyl-CoA (2 carbons) and produces:

- 3 NADH (electron carriers)
- 1 FADH₂ (electron carrier)
- 1 GTP (which converts to ATP by substrate-level phosphorylation)
- 2 CO₂ (released as waste)

Per glucose (which produces 2 pyruvates → 2 acetyl-CoA), the cycle runs twice, doubling all those outputs. Combined with the pyruvate-oxidation step and glycolysis, the running total entering oxidative phosphorylation is 10 NADH, 2 FADH₂, 4 ATP, and 6 CO₂.

The Eight Steps of the Cycle

The cycle has eight enzymatic steps, each catalyzed by a specific enzyme. The key chemistry is carbon-by-carbon stripping of electrons via oxidation reactions.

1. **Citrate synthase** joins acetyl-CoA (2C) with oxaloacetate (4C) to form citrate (6C). This is the cycle's entry step.

2. **Aconitase** rearranges citrate into isocitrate (still 6C).
3. **Isocitrate dehydrogenase** oxidizes isocitrate to alpha-ketoglutarate (5C). Releases 1 CO₂ and produces 1 NADH. First decarboxylation.
4. **Alpha-ketoglutarate dehydrogenase** oxidizes alpha-ketoglutarate to succinyl-CoA (4C). Releases 1 CO₂ and produces 1 NADH. Second decarboxylation.
5. **Succinyl-CoA synthetase** converts succinyl-CoA to succinate, producing 1 GTP (which equals 1 ATP). Substrate-level phosphorylation.
6. **Succinate dehydrogenase** oxidizes succinate to fumarate, producing 1 FADH₂. This enzyme is also Complex II of the electron transport chain, it sits in the inner mitochondrial membrane, not the matrix.
7. **Fumarase** adds water to fumarate, producing malate.
8. **Malate dehydrogenase** oxidizes malate back to oxaloacetate, producing the final 1 NADH. Oxaloacetate is now available to accept another acetyl-CoA, restarting the cycle.

Notice the symmetry: the cycle takes in a 2-carbon acetyl group, runs it around, and releases the 2 carbons as 2 CO₂ molecules. The carbons that leave are not the same ones that entered (the cycle rearranges atoms), but the carbon balance is exact.

Why the Cycle Matters Beyond ATP

The Krebs cycle is not just an energy-extraction loop. Many of its intermediates are starting materials for biosynthesis.

- **Alpha-ketoglutarate** is the precursor for the amino acid glutamate, which is in turn the precursor for many other amino acids.
- **Oxaloacetate** is the precursor for aspartate, which is the precursor for several more amino acids.
- **Succinyl-CoA** is required for heme synthesis (the iron-binding group in hemoglobin).
- **Citrate** can leave the mitochondrion to serve as a building block for fatty acid synthesis in the cytoplasm.

Because intermediates are drawn off for biosynthesis, the cycle would eventually run out of oxaloacetate to accept incoming acetyl-CoA. The cell compensates with anaplerotic reactions, replenishment reactions that produce new oxaloacetate from pyruvate via pyruvate carboxylase, for example.

Regulation

The Krebs cycle is regulated at three key enzymes: citrate synthase, isocitrate dehydrogenase, and alpha-ketoglutarate dehydrogenase. The regulation logic is simple, when the cell has plenty of ATP and NADH, slow the cycle down. When ATP is low and ADP/NAD⁺ are accumulating, speed it up. The cycle is driven by demand, not by supply.

Related study notes: [Cellular Respiration](#), [Mitochondria](#), [Enzyme](#), [Protein](#).

The [OpenStax biology textbooks](#) develop the biological processes discussed here with additional diagrams and explanations.

One Turn and One Glucose

One acetyl-CoA entering a standard cycle turn gives 3 NADH, 1 FADH₂, 1 GTP or ATP equivalent and 2 CO₂, while oxaloacetate is regenerated. One glucose normally supplies 2 acetyl-CoA for 2 turns.

The 2 turns therefore give 6 NADH, 2 FADH₂, 2 GTP/ATP equivalents and 4 CO₂. Pyruvate oxidation supplies an additional 2 NADH and 2 CO₂ before those turns. Combining the steps correctly accounts for the original 6 glucose carbons without assigning all CO₂ to the cycle itself.

Where the 6 CO₂ Come From

Glycolysis

1 glucose → 2 pyruvate

0 CO₂



Pyruvate Oxidation

2 pyruvate → 2 acetyl-CoA

2 CO₂



Krebs Cycle

2 turns per glucose

4 CO₂

Total: 2 + 4 = 6 CO₂ per glucose.

Per glucose, glycolysis releases no carbon dioxide, pyruvate oxidation releases 2 molecules, and the Krebs cycle releases 4, totaling 6.

The points to check in this example are:

- Acetyl-CoA is the entry substrate in this cycle accounting.
- Most captured energy leaves in reduced electron carriers.
- The cycle does not directly consume molecular oxygen, but aerobic continuation depends on regenerating oxidized carriers.

Check Your Understanding

Try the questions before reading the answers.

Question 1. How much CO₂ comes from 2 cycle turns?

Answer. 4 molecules per glucose-derived pair of acetyl-CoA.

Question 2. Where do the remaining 2 glucose-derived CO₂ arise?

Answer. Pyruvate oxidation.

Practice Questions

Work each question before reading its solution. The set runs from direct recall and substitution to the applied questions that exams actually use to separate grades. The downloadable PDF includes these questions and their solutions.

Question 1. Where does the Krebs cycle occur, and what must happen to pyruvate before it can enter?

Solution. In the mitochondrial matrix. Pyruvate from glycolysis is first converted by the pyruvate dehydrogenase complex into acetyl-CoA, losing 1 CO₂ and reducing 1 NAD⁺ to NADH per pyruvate. Acetyl-CoA, not pyruvate, is the cycle's true fuel.

Question 2. List the products of 1 turn of the Krebs cycle.

Solution. 3 NADH, 1 FADH₂, 1 ATP (as GTP in many cells), and 2 CO₂, while regenerating the starting molecule oxaloacetate. The cycle's main export is not ATP but loaded electron carriers.

Question 3. One glucose molecule powers how many turns of the cycle, and what is the combined cycle output?

Solution. Glycolysis splits glucose into 2 pyruvate, giving 2 acetyl-CoA, so 2 turns: 6 NADH, 2 FADH₂, 2 ATP, and 4 CO₂. Adding the 2 CO₂ from pyruvate conversion accounts for all 6 carbons of glucose leaving as CO₂.

Question 4. The first step condenses acetyl-CoA with a 4-carbon acceptor. Name the acceptor, the product, and the enzyme.

Solution. Acetyl-CoA (2C) joins oxaloacetate (4C) to form citrate (6C), catalyzed by citrate synthase. Citrate gives the cycle its alternative name, the citric acid cycle, and this committed step is a major regulation point.

Question 5. Why is the cycle described as catalytic rather than consumptive?

Solution. Oxaloacetate is regenerated every turn, so 1 molecule of it can process endless acetyl-CoA, the way a single wrench tightens endless bolts. The cycle consumes only what it burns; its own machinery molecules are recycled.

Question 6. Where do the NADH and FADH₂ go, and what are they worth?

Solution. To the electron transport chain on the inner mitochondrial membrane, where their electrons drive proton pumping for oxidative phosphorylation. Each NADH yields roughly 2.5 ATP and each FADH₂ about 1.5 ATP, which is why the cycle's 3 NADH + 1 FADH₂ per turn dwarf its single direct ATP.

Question 7. Does the Krebs cycle use oxygen directly? Why does it stop without oxygen anyway?

Solution. No step consumes O₂. But the electron transport chain needs oxygen as its final electron acceptor to reoxidize NADH and FADH₂ back to NAD⁺ and FAD. Without O₂ those carriers

stay loaded, the cycle's supply of NAD^+ runs out, and it halts. Oxygen dependence is indirect but absolute.

Question 8. High ATP and NADH levels slow the cycle. Name this control logic and explain why it is efficient.

Solution. Feedback inhibition: the products throttle the enzymes that make them, chiefly citrate synthase, isocitrate dehydrogenase, and α -ketoglutarate dehydrogenase. When energy is abundant the cell stops burning fuel it does not need; when ADP rises the brakes release. Supply follows demand automatically.

Question 9. Beyond energy, the cycle supplies building blocks. Give 2 examples of intermediates drawn off for biosynthesis.

Solution. α -ketoglutarate leaves to build glutamate and other amino acids; oxaloacetate feeds aspartate synthesis and gluconeogenesis; citrate exports acetyl units for fatty acid synthesis. The cycle is a metabolic roundabout, and anaplerotic reactions top the intermediates back up.

Question 10. Trace the carbon: you feed a cell glucose with radioactive carbon. Where does the label finally leave the body?

Solution. In exhaled CO_2 . Two carbons leave during pyruvate-to-acetyl-CoA conversion and 4 more during the 2 Krebs turns; the bloodstream carries the CO_2 to the lungs. The carbon you breathe out tonight was sugar this morning; the cycle is where food carbon becomes breath.

Frequently Asked Questions

What is the Krebs cycle in simple terms?

The Krebs cycle (also called the citric acid cycle or TCA cycle) is the second stage of aerobic cellular respiration. It happens inside the mitochondrial matrix and runs in a circle, accepting acetyl-CoA from pyruvate, stripping electrons onto NADH and FADH_2 , releasing CO_2 , and producing a small amount of ATP. The big ATP payoff comes later, in oxidative phosphorylation, using the NADH and FADH_2 from this cycle.

Where does the Krebs cycle take place?

In the matrix of the mitochondrion (the innermost compartment). All eight enzymes of the cycle are dissolved in the matrix, except succinate dehydrogenase, which sits in the inner mitochondrial membrane because it also functions as Complex II of the electron transport chain.

How much ATP does the Krebs cycle produce per glucose?

Directly, the cycle produces only 2 ATP per glucose (1 per acetyl-CoA, and one glucose yields 2 acetyl-CoA). The cycle's real contribution is the 6 NADH and 2 FADH₂ per glucose, which feed the electron transport chain and produce roughly 26-28 ATP per glucose downstream. So indirectly, the Krebs cycle drives the bulk of cellular ATP production.

Who discovered the Krebs cycle?

Hans Krebs worked out the cycle in 1937 while at the University of Sheffield. He won the 1953 Nobel Prize in Physiology or Medicine for the discovery (shared with Fritz Lipmann, who discovered coenzyme A). The name 'citric acid cycle' refers to citrate, the first intermediate after acetyl-CoA enters; 'TCA cycle' stands for tricarboxylic acid cycle, since citrate has three carboxyl groups.

What's the difference between the Krebs cycle and cellular respiration?

Cellular respiration is the whole process of extracting energy from glucose, glycolysis, the Krebs cycle, and oxidative phosphorylation together. The Krebs cycle is the middle stage. Cellular respiration produces about 30-32 ATP per glucose total; the Krebs cycle is responsible for about 2 of those directly and another 26 indirectly via NADH and FADH₂.

Does the Krebs cycle require oxygen?

Not directly, none of the eight enzymes use oxygen. But the cycle depends on the regeneration of NAD⁺ and FAD from NADH and FADH₂, which only happens when the electron transport chain is running. The electron transport chain requires oxygen as the final electron acceptor. So in practice, the Krebs cycle stops when oxygen runs out, because NADH and FADH₂ accumulate and there's no NAD⁺ or FAD left to accept electrons.