CELL BIOLOGY

Krebs Cycle

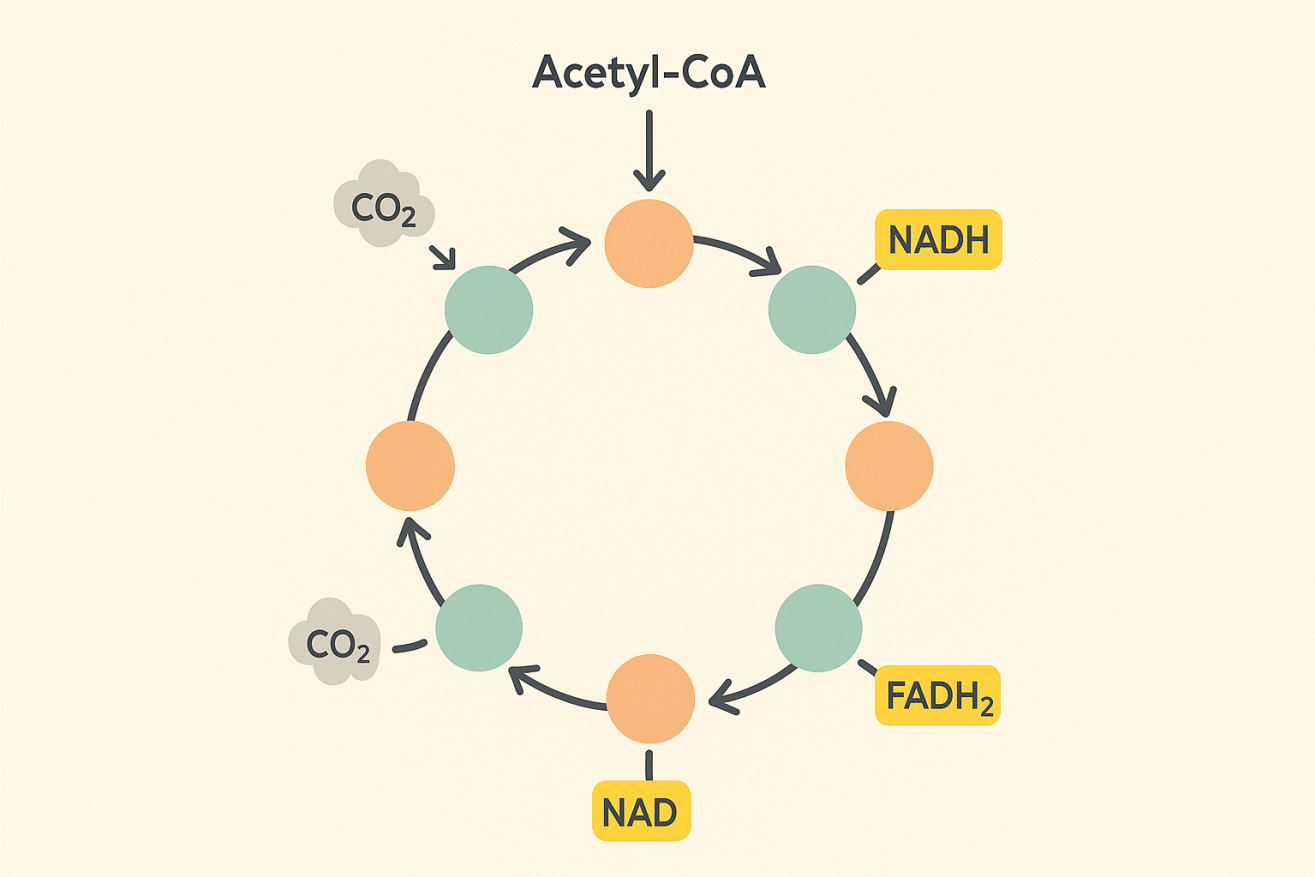
Where the cycle sits in respiration, what one turn produces, the regulation logic, and a 10-question practice set with full solutions.

SUBJECT	LEVEL	INCLUDES
Biology	High school and early college	Practice set, answer key, revision sheet

Read this note online, with updates: gauravtiwari.org/study-notes/krebs-cycle

INSIDE

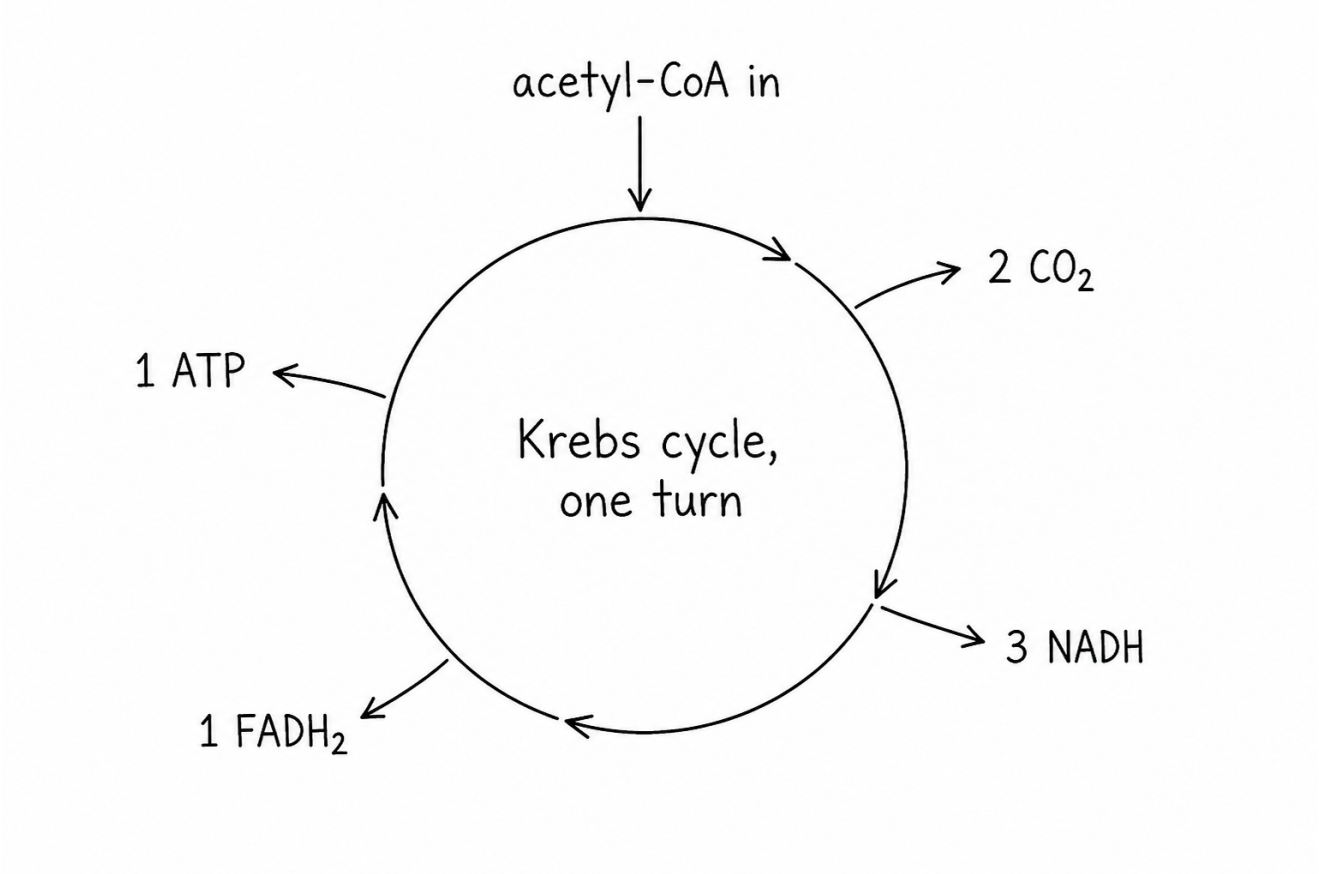
The Krebs cycle, also called the citric acid cycle or the TCA (tricarboxylic acid) cycle, is the second stage of aerobic cellular respiration. It runs inside the mitochondrial matrix, takes in acetyl-CoA produced from pyruvate, runs through eight enzymatic steps in a closed loop, and produces NADH, FADH2, 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 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).



One turn of the cycle: 1 acetyl-CoA in, 2 CO_2 out, and the real payload, 3 NADH + 1 $FADH_2$, off to the electron transport chain.

- **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.

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.

Q1. 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 CO_2 and reducing 1 NAD^+ to NADH per pyruvate. Acetyl-CoA, not pyruvate, is the cycle's true fuel.

Q2. List the products of 1 turn of the Krebs cycle.

SOLUTION

3 NADH, 1 $FADH_2$, 1 ATP (as GTP in many cells), and 2 CO_2, while regenerating the starting molecule oxaloacetate. The cycle's main export is not ATP but loaded electron carriers.

Q3. 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 $FADH_2$, 2 ATP, and 4 CO_2. Adding the 2 CO_2 from pyruvate conversion accounts for all 6 carbons of glucose leaving as CO_2.

Q4. 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.

Q5. 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 sin-

gle wrench tightens endless bolts. The cycle consumes only what it burns; its own machinery molecules are recycled.

Q6. Where do the NADH and $FADH_2$ 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 $FADH_2$ about 1.5 ATP, which is why the cycle's 3 NADH + 1 $FADH_2$ per turn dwarf its single direct ATP.

Q7. Does the Krebs cycle use oxygen directly? Why does it stop without oxygen anyway?

SOLUTION

No step consumes O_2. But the electron transport chain needs oxygen as its final electron acceptor to reoxidize NADH and $FADH_2$ back to NAD^+ and FAD. Without O_2 those carriers stay loaded, the cycle's supply of NAD^+ runs out, and it halts. Oxygen dependence is indirect but absolute.

Q8. 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.

Q9. 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.

Q10. 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.

Answer Key

QUICK ANSWERS

Q1 matrix; pyruvate → acetyl-CoA first **Q2** 3 NADH, 1 $FADH_2$, 1 ATP, 2 CO_2 **Q3** 2 turns: 6 NADH, 2 $FADH_2$, 2 ATP, 4 CO_2 **Q4** oxaloacetate + acetyl-CoA → citrate **Q5** oxaloacetate is regenerated each turn

Q6 to the electron transport chain; ~2.5 and ~1.5 ATP **Q7** no direct use; it starves of NAD^+ without O_2 **Q8** feedback inhibition by ATP and NADH **Q9** e.g. α-ketoglutarate and oxaloacetate **Q10** exhaled as CO_2

Revision Sheet

Location and fuel

Mitochondrial matrix; runs on acetyl-CoA (from pyruvate, fats, or amino acids).

First step

Acetyl-CoA (2C) + oxaloacetate (4C) → citrate (6C), via citrate synthase.

Per turn

3 NADH, 1 $FADH_2$, 1 ATP, 2 CO_2; oxaloacetate re-generated.

Why it needs oxygen

Only indirectly: the electron transport chain must recycle NAD^+ and FAD.

Per glucose

2 turns: 6 NADH, 2 $FADH_2$, 2 ATP, 4 CO_2.

Regulation

Feedback inhibition by ATP and NADH; activated by ADP. Supply follows demand.

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