

Cellular Respiration and the Role of Mitochondria

Study Notes — Biochemistry & Cell Biology

1. Introduction

Cellular respiration is the set of metabolic reactions by which cells break down organic fuel molecules — chiefly glucose — and harvest the released chemical energy in the form of adenosine triphosphate (ATP), the universal energy currency of the cell. In eukaryotes the process begins in the cytoplasm and is completed inside the mitochondrion, which is why the organelle is often called the “powerhouse of the cell.”

Aerobic respiration (in the presence of O_2) is far more efficient than anaerobic fermentation because it allows the complete oxidation of glucose to carbon dioxide and water, releasing almost all of the energy stored in its chemical bonds.

Overall (summary) equation:



2. The Four Stages of Aerobic Respiration

Aerobic cellular respiration proceeds through four linked stages. The first occurs in the cytoplasm; the remaining three occur inside the mitochondrion.

Stage	Location	Key inputs	Key outputs
1. Glycolysis	Cytoplasm (cytosol)	1 Glucose, 2 ATP, 2 NAD^+	2 Pyruvate, net 2 ATP, 2 NADH
2. Pyruvate oxidation (link reaction)	Mitochondrial matrix	2 Pyruvate, 2 NAD^+ , CoA	2 Acetyl-CoA, 2 NADH, 2 CO_2
3. Krebs cycle (citric acid cycle)	Mitochondrial matrix	2 Acetyl-CoA, ADP, NAD^+ , FAD	6 NADH, 2 $FADH_2$, 2 ATP, 4 CO_2
4. Oxidative phosphorylation	Inner mitochondrial membrane	NADH, $FADH_2$, O_2 , ADP + Pi	$\approx 26\text{--}28$ ATP, H_2O

Glycolysis splits one 6-carbon glucose molecule into two 3-carbon pyruvate molecules through a ten-step enzymatic sequence, yielding a small net gain of 2 ATP (substrate-level phosphorylation) and 2 NADH. It does not require oxygen.

Pyruvate oxidation converts each pyruvate into a 2-carbon acetyl group carried by coenzyme A (acetyl-CoA), releasing one CO_2 and reducing one NAD^+ to NADH per pyruvate.

The Krebs cycle (citric acid cycle) oxidises the acetyl group completely, releasing two more CO_2 per turn and generating the bulk of the electron carriers (NADH and $FADH_2$) that power the next stage. Since one glucose yields two acetyl-CoA, the cycle turns twice per glucose molecule.

Oxidative phosphorylation — the electron transport chain (ETC) coupled to chemiosmosis — uses the electrons carried by NADH and $FADH_2$ to pump protons across the inner mitochondrial membrane, and lets those protons flow back through ATP synthase to generate the majority of the cell's ATP, with O_2 as

the final electron acceptor, forming water.

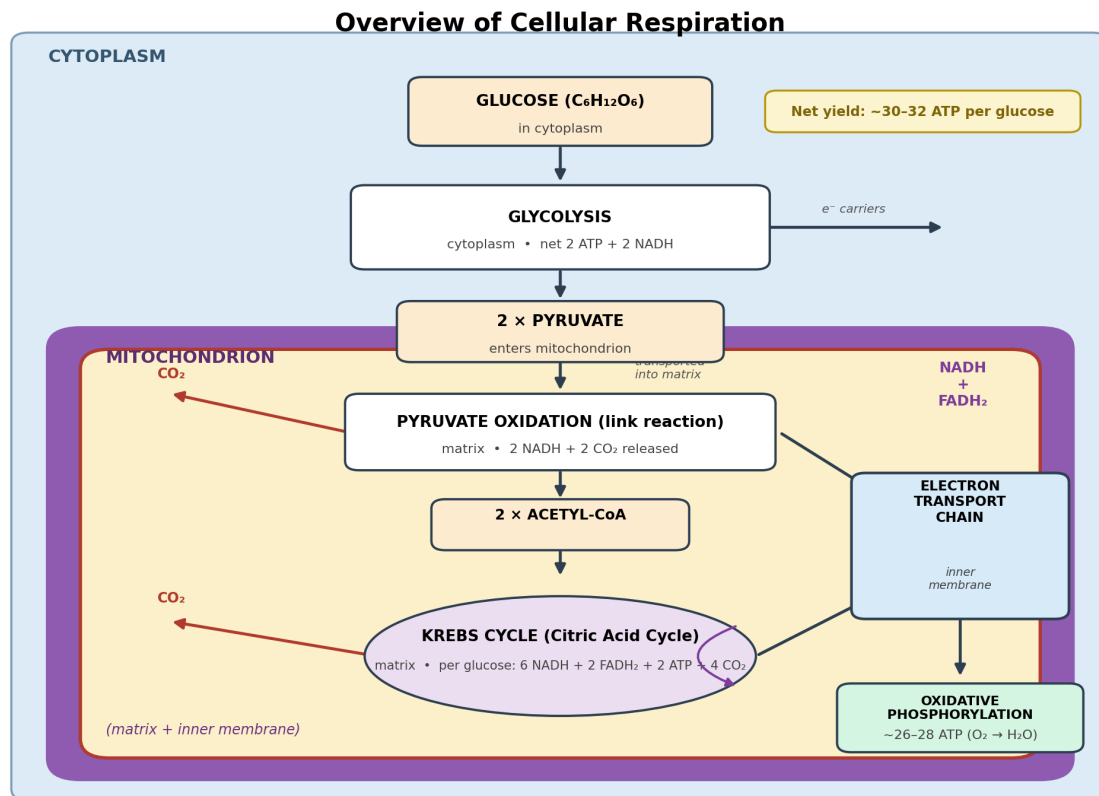


Figure 1. Overview of the four stages of cellular respiration and where each occurs within the cell.

3. The Mitochondrion: Structure and Function

Mitochondria are double-membrane-bound organelles found in almost all eukaryotic cells, and their number per cell (from a few hundred to several thousand) broadly tracks a cell's energy demand — cardiac muscle, liver, and kidney cells are especially rich in them.

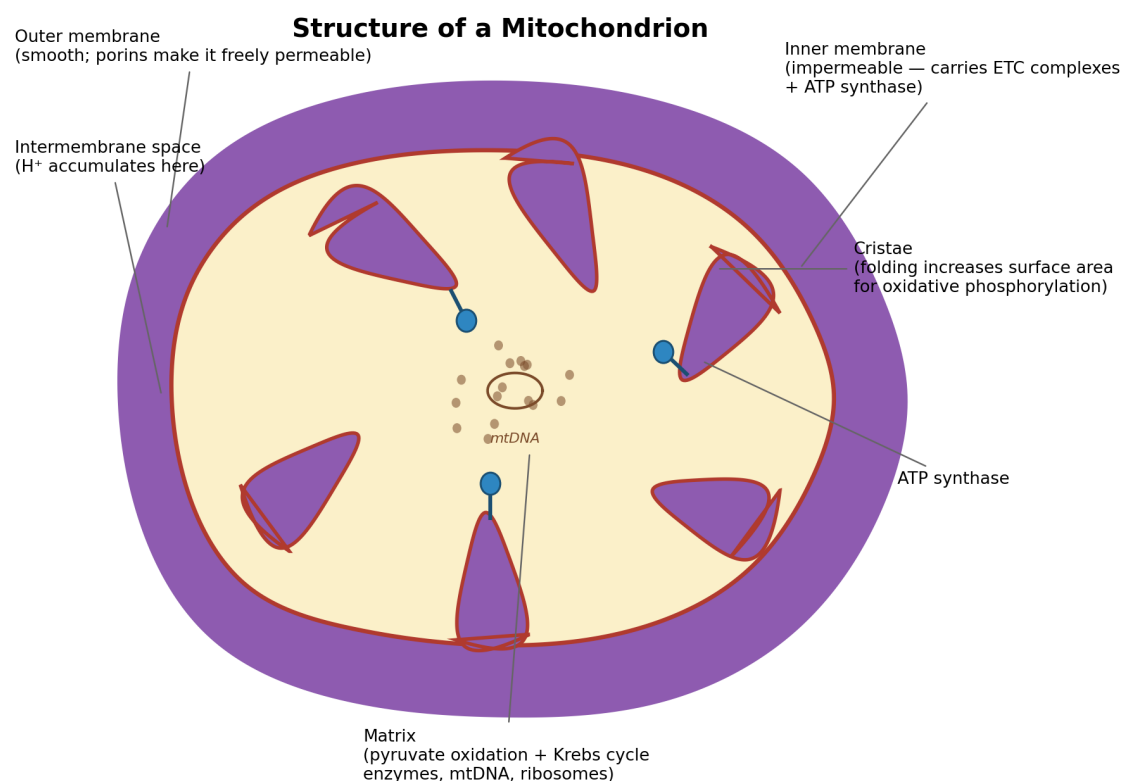


Figure 2. Labelled structure of a mitochondrion in cross-section.

Component	Structure	Function
Outer membrane	Smooth; studded with porin proteins	Freely permeable to ions and small molecules ($< \sim 5$ kDa)
Intermembrane space	Narrow space between the two membranes	Site of H^+ accumulation during the electron transport chain
Inner membrane	Highly folded, impermeable to most ions	Houses ETC complexes I–IV, ATP synthase, and transporters
Cristae	Finger-like folds of the inner membrane	Greatly increase surface area for oxidative phosphorylation
Matrix	Gel-like interior; contains mtDNA, ribosomes, enzymes	Site of pyruvate oxidation and the Krebs cycle

3.1 Why mitochondria are central to respiration

- They are the exclusive site of pyruvate oxidation, the Krebs cycle, and oxidative phosphorylation — together responsible for roughly 90% of the ATP generated from one glucose molecule.
- The cristae-folded inner membrane maximises the surface area available for the electron transport chain and ATP synthase, directly increasing ATP output per organelle.
- The double-membrane architecture creates the intermembrane space needed to build the proton (H^+) gradient that drives chemiosmotic ATP synthesis.

- Mitochondria carry their own circular DNA (mtDNA) and ribosomes, reflecting their evolutionary origin as free-living bacteria that entered an ancestral eukaryotic cell (the endosymbiotic theory) — they still divide independently of the cell cycle by binary fission.
- Beyond ATP production, mitochondria regulate apoptosis (programmed cell death), calcium buffering, and heat generation (via uncoupling proteins in brown adipose tissue).

4. Electron Transport Chain and Chemiosmosis

The electron transport chain (ETC) is a series of four large protein complexes (I–IV) embedded in the inner mitochondrial membrane, linked by two mobile electron carriers: ubiquinone (coenzyme Q) and cytochrome c.

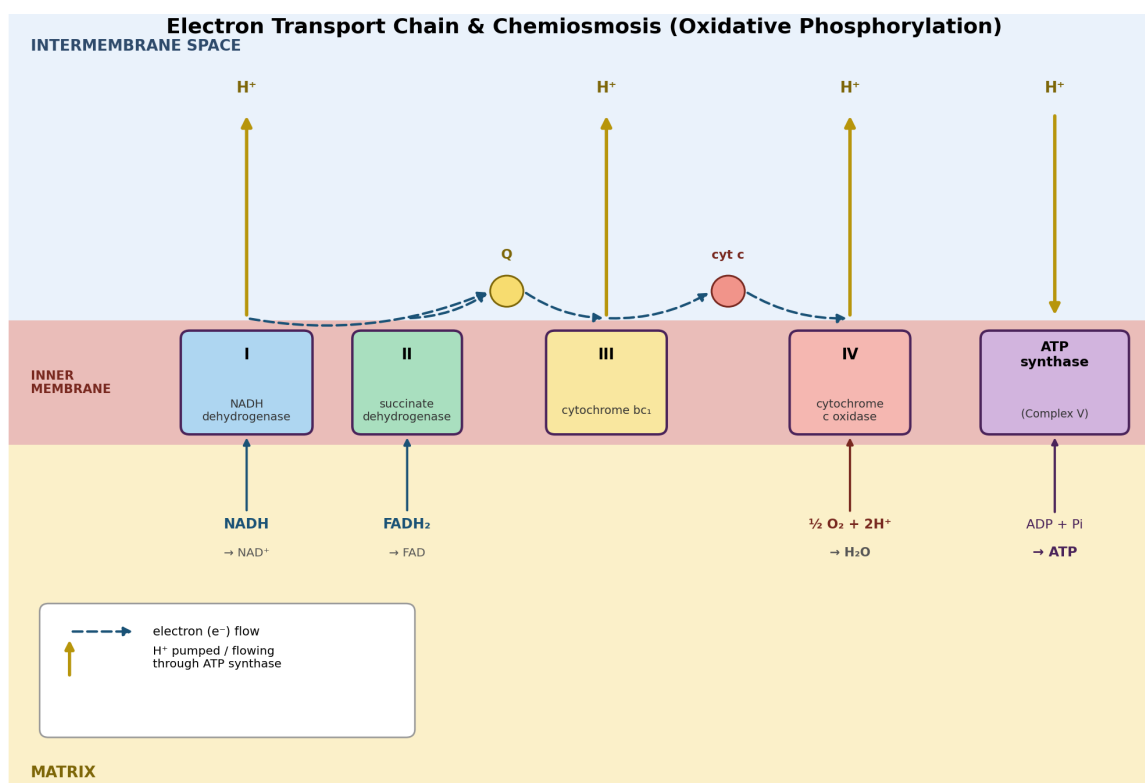


Figure 3. Electron flow through Complexes I–IV drives proton (H⁺) pumping into the intermembrane space; protons flow back through ATP synthase (chemiosmosis) to phosphorylate ADP.

- **Complex I (NADH dehydrogenase):** accepts electrons from NADH, pumps H⁺ into the intermembrane space, and passes electrons to coenzyme Q.
- **Complex II (succinate dehydrogenase):** accepts electrons from FADH₂ directly into the chain via coenzyme Q; it does not pump protons, which is why FADH₂ yields less ATP than NADH.
- **Complex III (cytochrome bc₁):** transfers electrons from coenzyme Q to cytochrome c while pumping additional H⁺.
- **Complex IV (cytochrome c oxidase):** transfers electrons to the final acceptor, molecular oxygen, forming water, while pumping more H⁺.
- **ATP synthase (Complex V):** protons flow back down their electrochemical gradient through this rotary enzyme, and the mechanical rotation drives the phosphorylation of ADP to ATP — a process called **chemiosmosis**, first proposed by Peter Mitchell.

Because oxygen is required as the final electron acceptor, blocking O₂ supply (or ETC poisons such as cyanide) halts electron flow, collapses the proton gradient, and stops ATP synthesis almost entirely — illustrating why oxidative phosphorylation accounts for the vast majority of ATP yield.

5. ATP Yield Summary

Stage	ATP (direct)	NADH	FADH ₂	ATP from ETC*
Glycolysis	2	2	—	≈ 3–5
Pyruvate oxidation (×2)	—	2	—	≈ 5
Krebs cycle (×2 turns)	2	6	2	≈ 14–18
Total per glucose	4	10	2	≈ 26–28

* Modern estimates give ≈ 30–32 ATP per glucose overall (≈2.5 ATP per NADH and ≈1.5 ATP per FADH₂ oxidised via the ETC); older textbooks that assume fixed P/O ratios quote a theoretical maximum of 36–38 ATP. The lower, more realistic figure accounts for the energy cost of shuttling cytosolic NADH into the mitochondrion and of transporting ATP out.

6. Key Takeaways

- Cellular respiration oxidises glucose in four stages — glycolysis (cytoplasm), pyruvate oxidation, the Krebs cycle, and oxidative phosphorylation (all three inside the mitochondrion).
- The mitochondrion's double-membrane structure — especially the cristae-folded inner membrane — is what makes efficient, large-scale ATP production possible.
- Oxidative phosphorylation (ETC + chemiosmosis) contributes the large majority (≈85–90%) of total ATP yield and absolutely requires O₂ as the final electron acceptor.
- Mitochondria are semi-autonomous organelles with their own DNA, consistent with their proposed bacterial, endosymbiotic origin.

7. Practice Questions

7.1 Multiple Choice Questions

1. Which of the following is **not** a direct product of glycolysis?
a) Pyruvate b) NADH c) FADH_2 d) Net ATP
2. The Krebs cycle takes place in the:
a) Cytoplasm b) Outer mitochondrial membrane c) Mitochondrial matrix d) Intermembrane space
3. Which complex of the electron transport chain does **not** pump protons into the intermembrane space?
a) Complex I b) Complex II c) Complex III d) Complex IV
4. The final electron acceptor at the end of the electron transport chain is:
a) NAD^+ b) FAD c) Oxygen d) Pyruvate
5. ATP synthase is also referred to as:
a) Complex I b) Complex II c) Complex IV d) Complex V
6. The net ATP yield from substrate-level phosphorylation during glycolysis (per glucose) is:
a) 4 b) 2 c) 6 d) 8
7. The proton (H^+) gradient generated by the electron transport chain is used directly to drive:
a) Glycolysis b) The Krebs cycle c) Chemiosmotic ATP synthesis d) Pyruvate oxidation
8. The presence of circular mtDNA and 70S ribosomes in mitochondria is cited as evidence for the:
a) Autogenous theory b) Endosymbiotic theory c) Chemiosmotic theory d) Fluid mosaic model

7.2 Short-Answer Questions

- 1. Explain why the oxidation of FADH_2 via the electron transport chain yields fewer ATP than the oxidation of NADH.
- 2. Describe how the cristae of the inner mitochondrial membrane contribute to the efficiency of ATP production.
- 3. Differentiate between substrate-level phosphorylation and oxidative phosphorylation, giving one example of each from cellular respiration.
- 4. With reference to chemiosmosis, explain why cyanide poisoning is lethal to aerobic organisms.

Answer Key

MCQs: 1–c, 2–c, 3–b, 4–c, 5–d, 6–b, 7–c, 8–b

Short answers (key points): (1) FADH_2 feeds electrons in at Complex II, bypassing the proton-pumping of Complex I, so fewer H^+ are translocated and less ATP is made per FADH_2 (≈ 1.5) than per NADH (≈ 2.5). (2) Cristae fold the inner membrane to greatly increase its surface area, allowing more copies of the ETC complexes and ATP synthase to be packed in, raising total ATP output. (3) Substrate-level phosphorylation forms ATP directly from a high-energy substrate (e.g. in glycolysis and the Krebs cycle); oxidative phosphorylation forms ATP via the proton-gradient-driven ATP synthase during the electron transport chain. (4) Cyanide blocks Complex IV, halting electron flow and collapsing the H^+ gradient, so ATP synthase stops — cells (especially in the brain and heart) rapidly run out of ATP.