Aerobic Respiration

BCH 100 — Introductory Biochemistry · Dr. Radi

By the end of this unit, you can…

- Explain the pyruvate dehydrogenase complex — the link reaction to acetyl-CoA — its cofactors and its allosteric + covalent regulation
- Walk all eight reactions of the TCA cycle with the running NADH/$FADH_2$/GTP ledger, and explain its regulated, amphibolic, and anaplerotic roles
- Describe the pentose phosphate pathway — its oxidative and non-oxidative phases and its NADPH and ribose-5-phosphate products
- Trace electron flow through the four ETC complexes, driven by reduction potential, pumping protons to build the gradient
- Explain chemiosmosis and ATP synthase's rotary catalysis, the NADH shuttles, and the total ATP yield from one glucose
- Describe the regulation of respiration, uncouplers (thermogenin), and ETC poisons (cyanide, rotenone)

Today's route

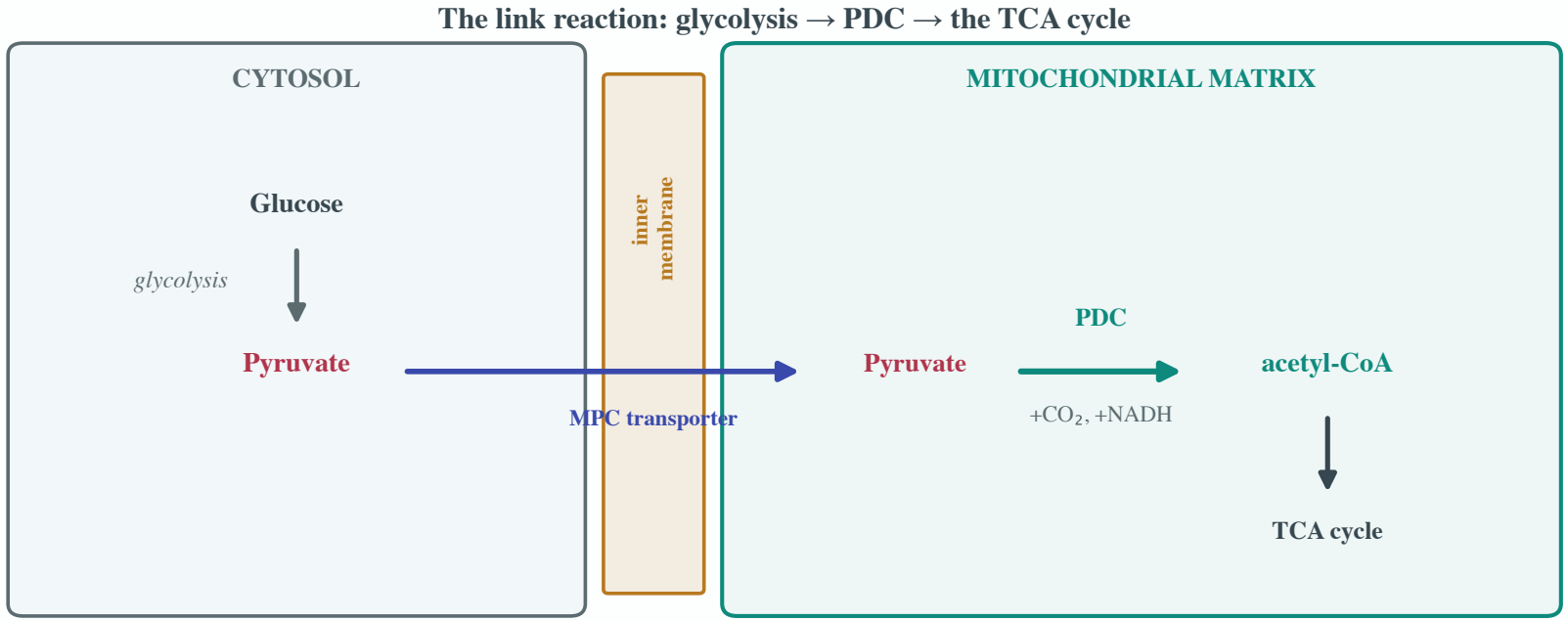
1. The Pyruvate Dehydrogenase Complex
2. The TCA Cycle
3. The Pentose Phosphate Pathway
4. The Electron Transport Chain
5. Oxidative Phosphorylation
6. Regulation, Poisons & Uncouplers

1 · The Pyruvate Dehydrogenase Complex

"The bridge from glycolysis to the TCA cycle — meet the giant complex that turns pyruvate into acetyl-CoA."

The bridge to aerobic metabolism

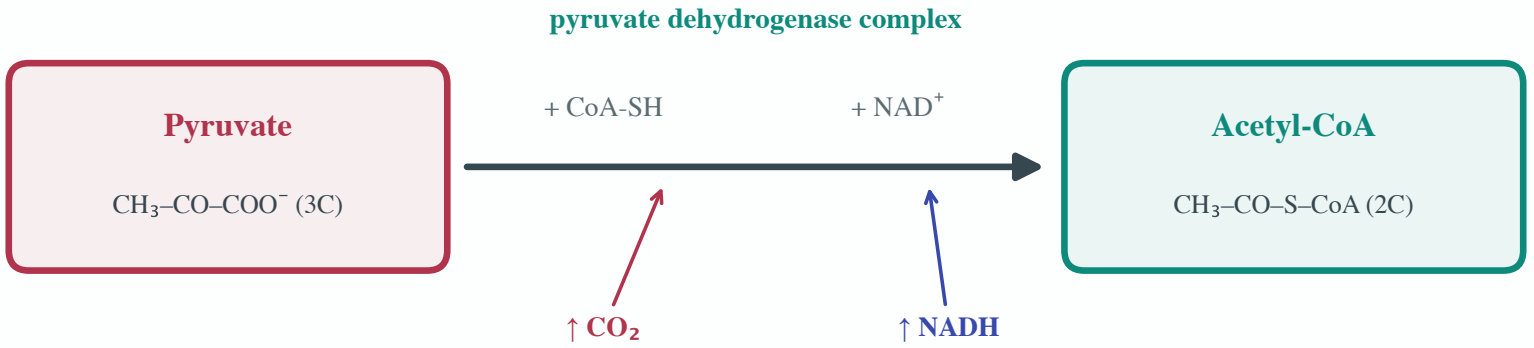
Glycolysis ends with **pyruvate** in the **cytosol** — but the real energy harvest happens in the **mitochondrion**. So pyruvate is shuttled across the inner membrane (by the **MPC transporter**) into the **matrix**, where both the **PDC** and the **TCA cycle** live. There the **pyruvate dehydrogenase complex** turns pyruvate into **acetyl-CoA** — the fuel the cycle actually burns.



The link reaction

Pyruvate + CoA + NAD^+ → acetyl-CoA + CO_2 + NADH. In one move the PDC does three things: **chops off a carbon** (as CO_2), **oxidizes** what's left (banking an **NADH**), and **attaches CoA** to make the reactive **acetyl-CoA**. It's **irreversible** — the true point of no return for glucose oxidation.

Oxidative decarboxylation — lose a carbon, bank an NADH, activate the rest as acetyl-CoA



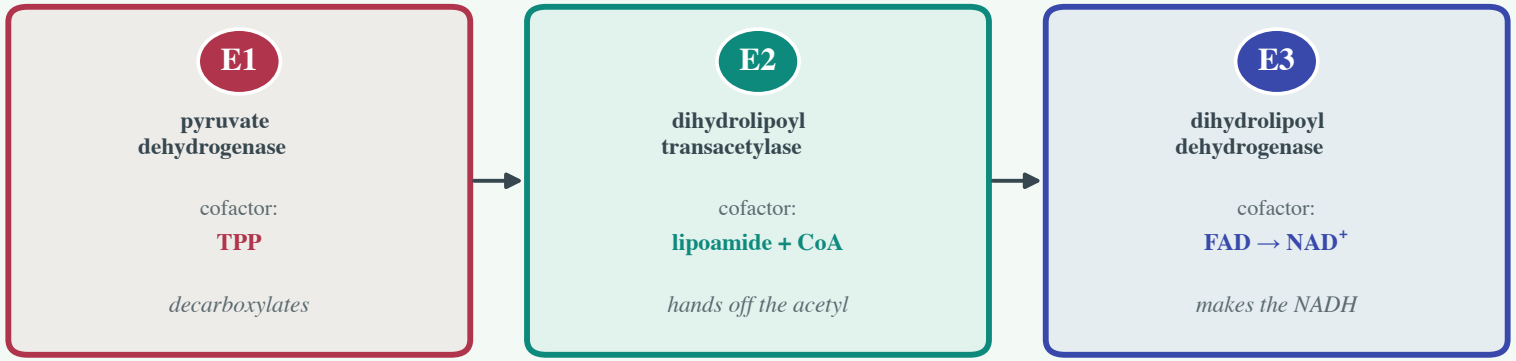
Irreversible — the true committed step of glucose oxidation.

One complex, three enzymes, five cofactors

The PDC is a **giant** — three enzymes working as one, with **five** cofactors handing the substrate down an assembly line.

- **E1** (with **TPP**) decarboxylates pyruvate
- **E2** (with **lipoamide + CoA**) hands off the acetyl group
- **E3** (with **FAD → NAD⁺**) resets the machine and makes the **NADH**
- Remember the cofactors: **"Tender Loving Care For Nancy"** → **T**PP · **L**ipoamide · **C**oA · **F**AD · **N**AD⁺

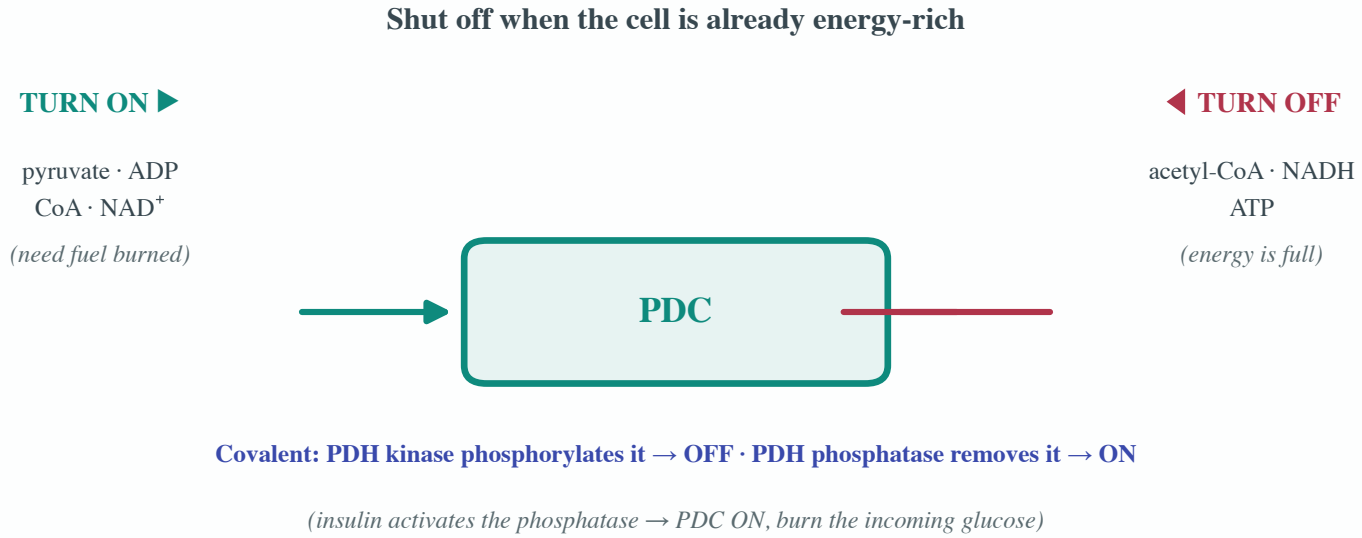
One giant complex, three enzymes, five cofactors



Mnemonic: "Tender Loving Care For Nancy" — TPP · Lipoamide · CoA · FAD · NAD⁺

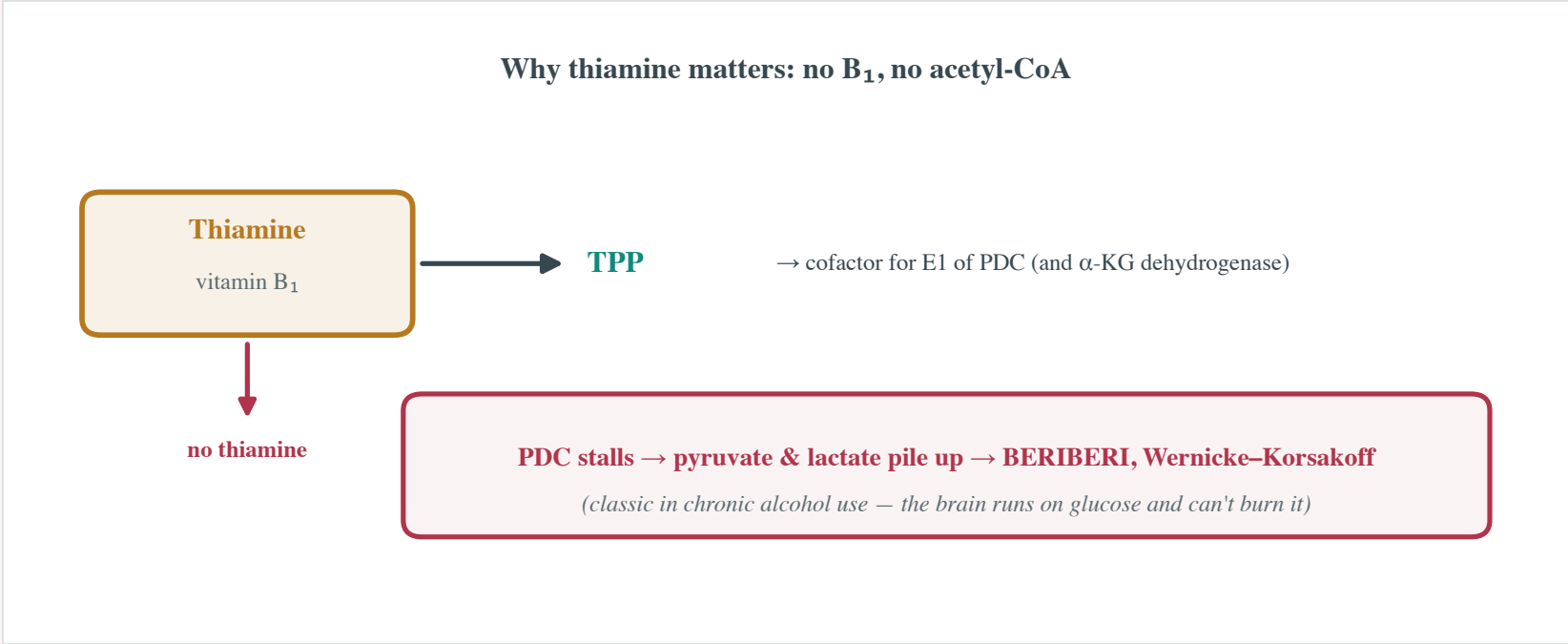
Turned off when you're full

The PDC is a **committed, irreversible** step, so it's **tightly regulated** — and the theme is simple: **don't burn fuel you don't need**. Its own products (**acetyl-CoA, NADH**) and **ATP** shut it **off**; **pyruvate** and **ADP** turn it **on**. A **kinase/phosphatase** pair adds the covalent layer — **phosphorylation switches it OFF**, and **insulin** (fed) flips the phosphatase back **on** to burn the incoming glucose.



No B_1, no acetyl-CoA

TPP — the E1 cofactor — is made from **thiamine (vitamin B_1)**. Without it, the PDC (and α-ketoglutarate dehydrogenase) **stall**, so pyruvate and lactate **pile up**. The result is **beriberi** and **Wernicke–Korsakoff** syndrome — classically in **chronic alcohol use**, where the glucose-hungry brain suddenly can't burn its fuel.

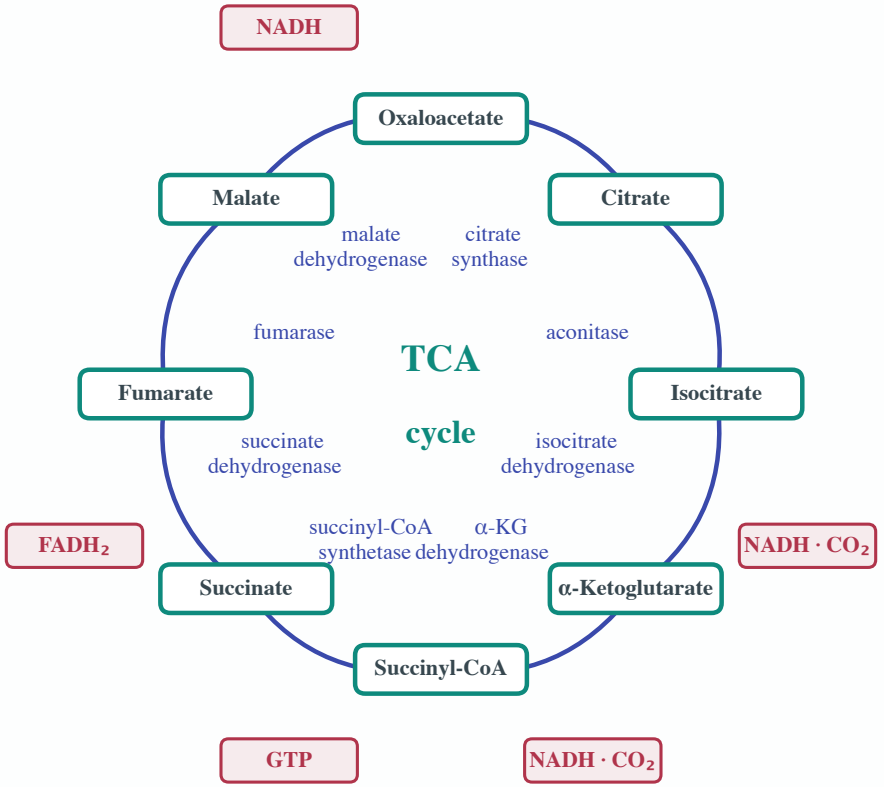


2 · The TCA Cycle

"NOT the Kreb's cycle — the TCA cycle! Walk all eight reactions, bank 3 NADH + 1 $FADH_2$ + 1 GTP per turn, and meet the hub of all metabolism."

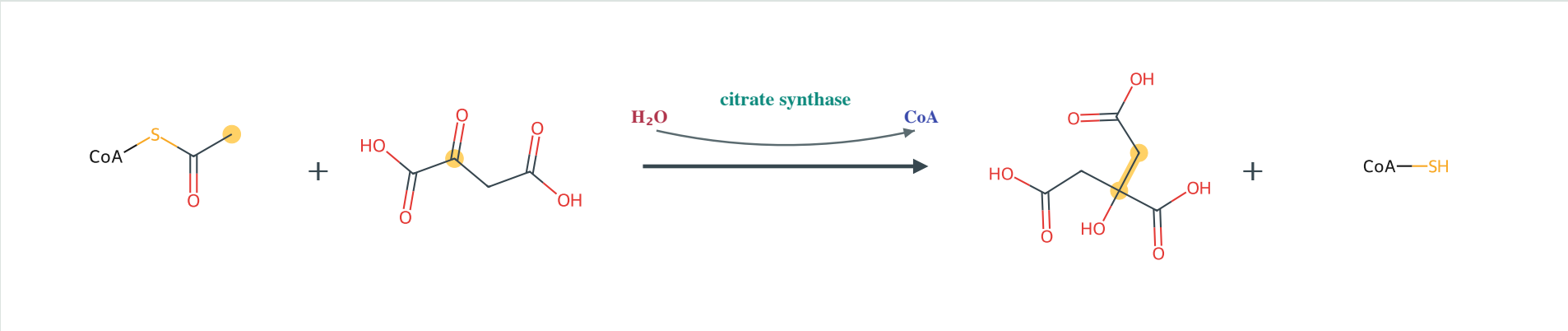
NOT the Kreb's cycle – the TCA cycle!

Acetyl-CoA hands its **two carbons** to the cycle, which oxidizes them all the way to **two CO_2** – and captures the energy as **reducing power**. Eight enzymes, one full turn, and oxaloacetate comes back out ready to grab the next acetyl-CoA. Watch what gets tapped off each step.



Step 1: Citrate synthase

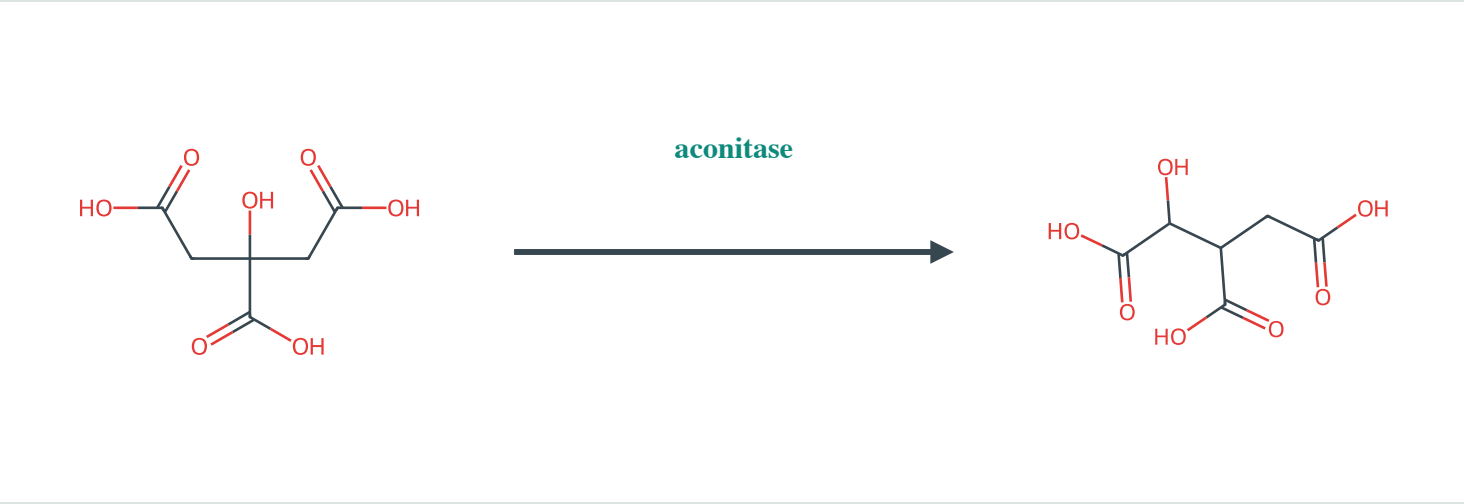
Acetyl-CoA + oxaloacetate → citrate. The 2-carbon acetyl group is welded onto the 4-carbon **oxaloacetate** to make the 6-carbon **citrate**, and the CoA is released. This first step is **irreversible** and a key **control point**.



no carriers yet · running: –

Step 2: Aconitase

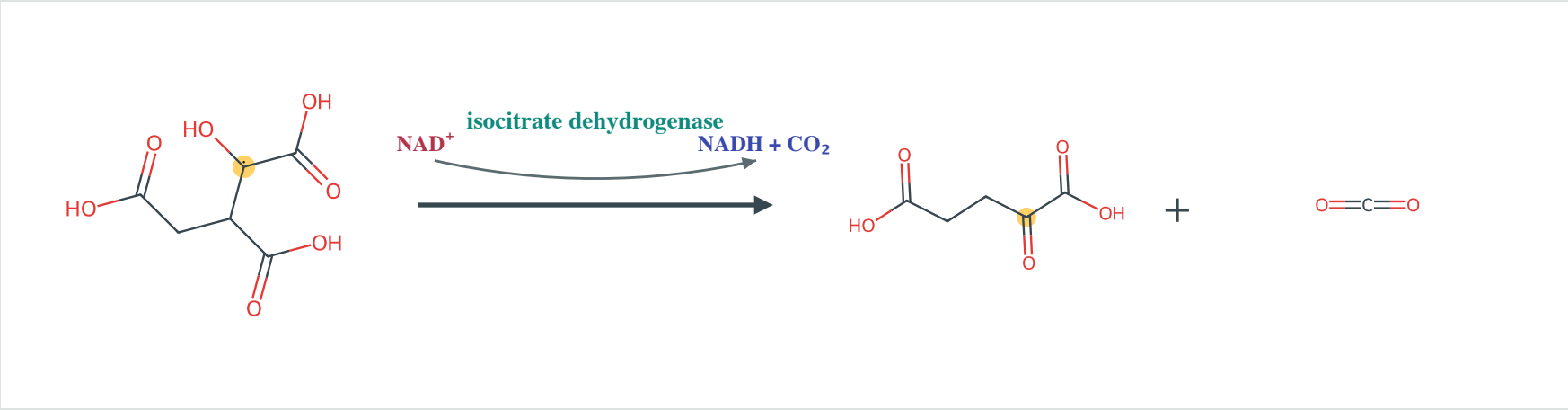
Citrate → isocitrate. Just a rearrangement — the **hydroxyl moves** to a neighboring carbon (via a **cis**-aconitate intermediate). Why? Citrate's –OH is on a carbon that can't be oxidized; isocitrate's can. Setting up the next step. **Reversible.**



no carriers yet · running: –

Step 3: Isocitrate dehydrogenase

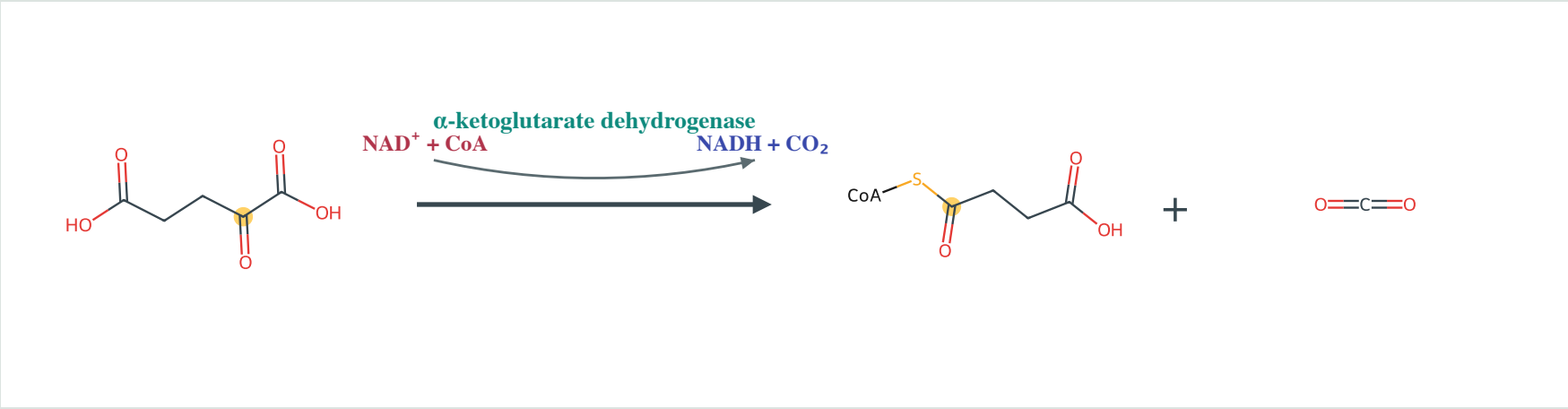
Isocitrate → α-ketoglutarate + CO_2. The **first oxidation** and the **first CO_2 lost**: isocitrate is oxidized (making our **first NADH**) and immediately decarboxylated. This is the cycle's **rate-limiting, most-regulated** step.



NADH +1 · CO_2 ↑ · running: 1 NADH

Step 4: α-Ketoglutarate dehydrogenase

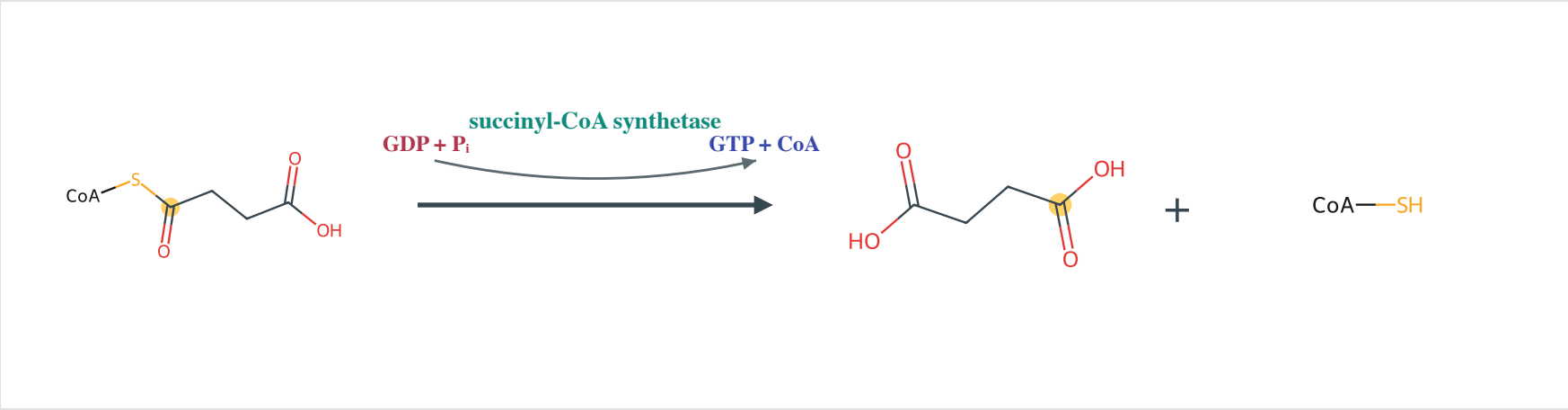
α-Ketoglutarate → succinyl-CoA + CO_2. The **second oxidative decarboxylation** — a giant complex just like the PDC (same 5 cofactors!). It banks a **second NADH**, releases the **second CO_2**, and attaches CoA to make the high-energy thioester **succinyl-CoA**.



NADH +1 · CO_2 ↑ · running: 2 NADH

Step 5: Succinyl-CoA synthetase

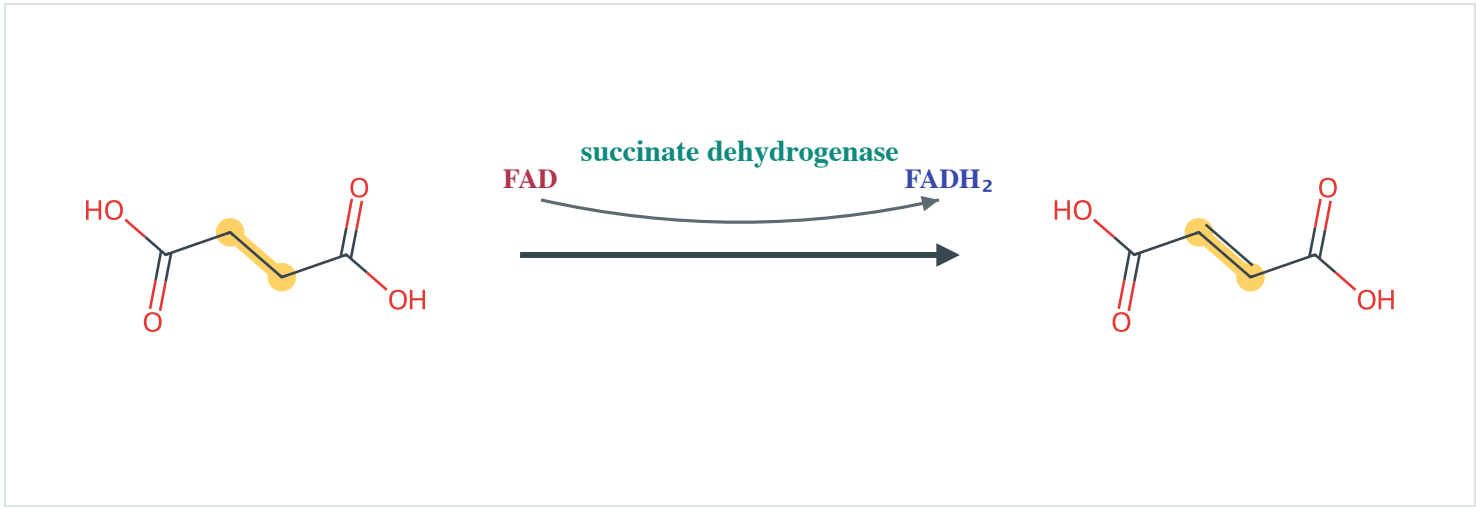
Succinyl-CoA → succinate + GTP. The thioester bond is **high-energy** — snapping it powers a **substrate-level phosphorylation**, making one **GTP** (= 1 ATP). This is the cycle's **only** direct high-energy phosphate. **Reversible.**



GTP +1 · running: 2 NADH, 1 GTP

Step 6: Succinate dehydrogenase

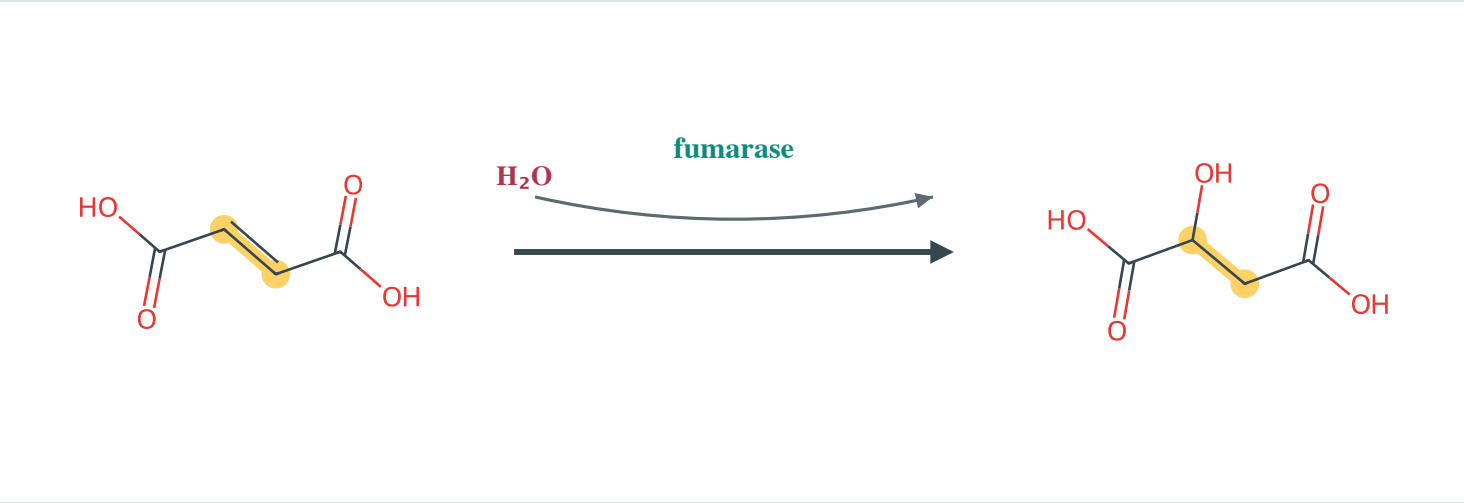
Succinate → fumarate. An oxidation that forms a **double bond** — and its electrons are a bit lower-energy, so they go to **FAD → $FADH_2$** instead of NAD^+. Fun fact: this enzyme is **embedded in the inner membrane** — it **is** Complex II of the electron transport chain!



$FADH_2$ +1 · running: 2 NADH, 1 $FADH_2$, 1 GTP

Step 7: Fumarase

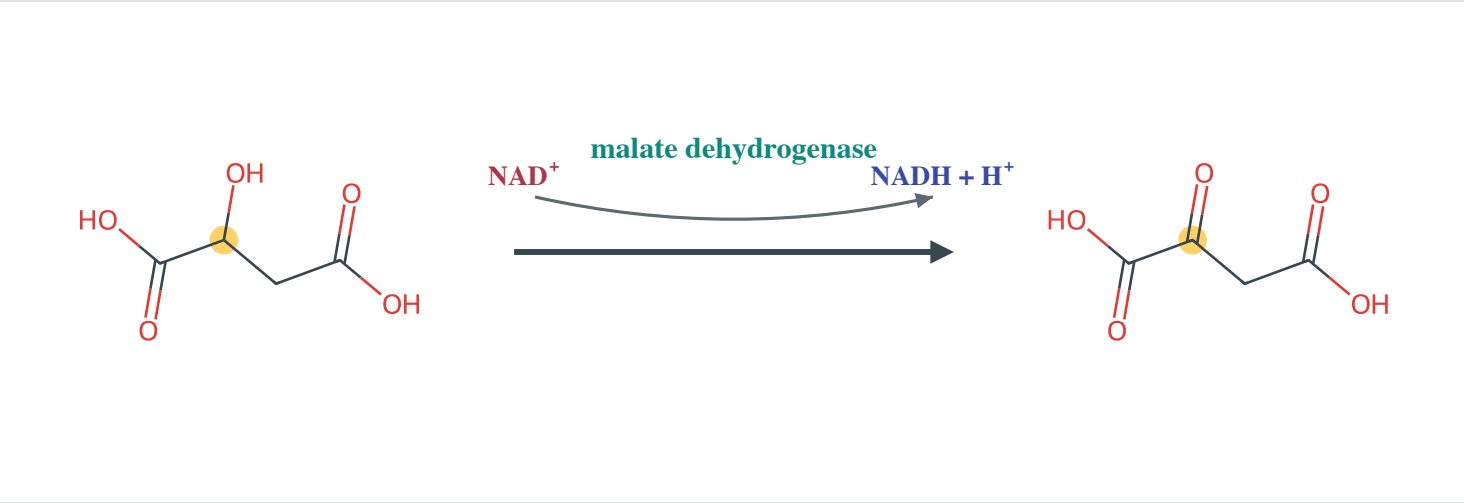
Fumarate + H_2O → malate. A simple **hydration** – water adds across the double bond, putting a hydroxyl back on. No energy captured; we're setting up the final oxidation. **Reversible.**



no carriers · running: 2 NADH, 1 $FADH_2$, 1 GTP

Step 8: Malate dehydrogenase

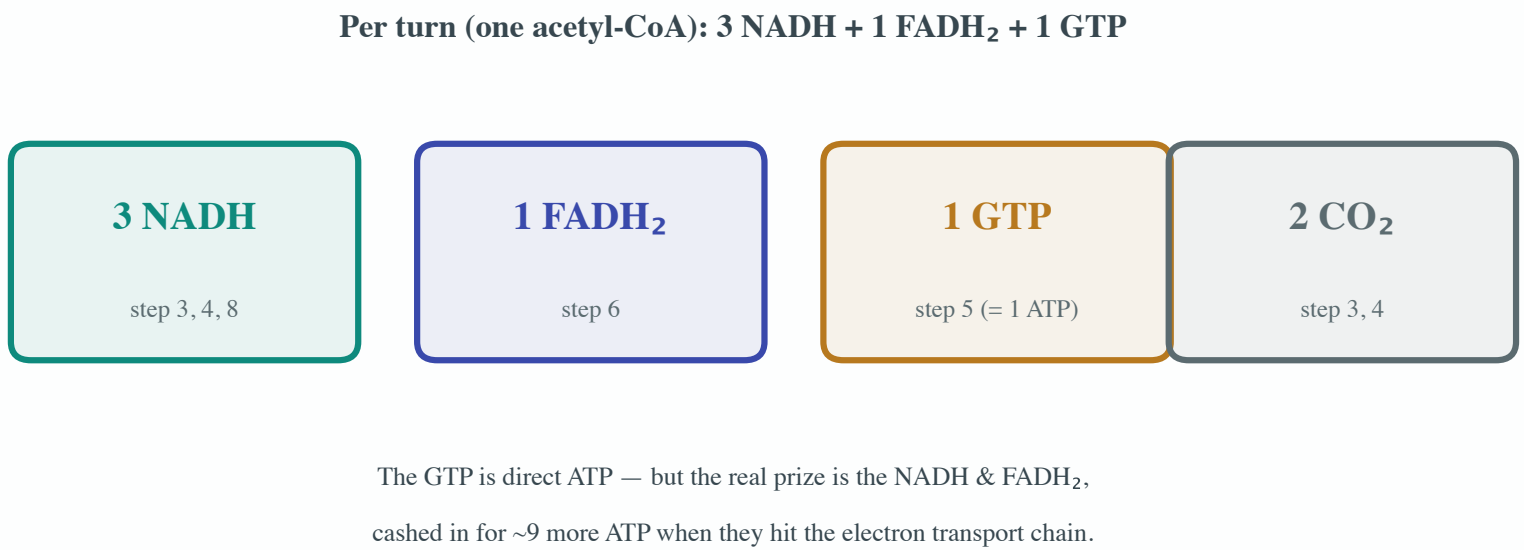
Malate → oxaloacetate. The last oxidation banks a **third NADH** and regenerates **oxaloacetate** – ready to accept the next acetyl-CoA. The cycle is closed! Per turn we've made **3 NADH + 1 $FADH_2$ + 1 GTP** and released **2 CO_2**.



NADH +1 · running: 3 NADH, 1 $FADH_2$, 1 GTP **→ per turn**

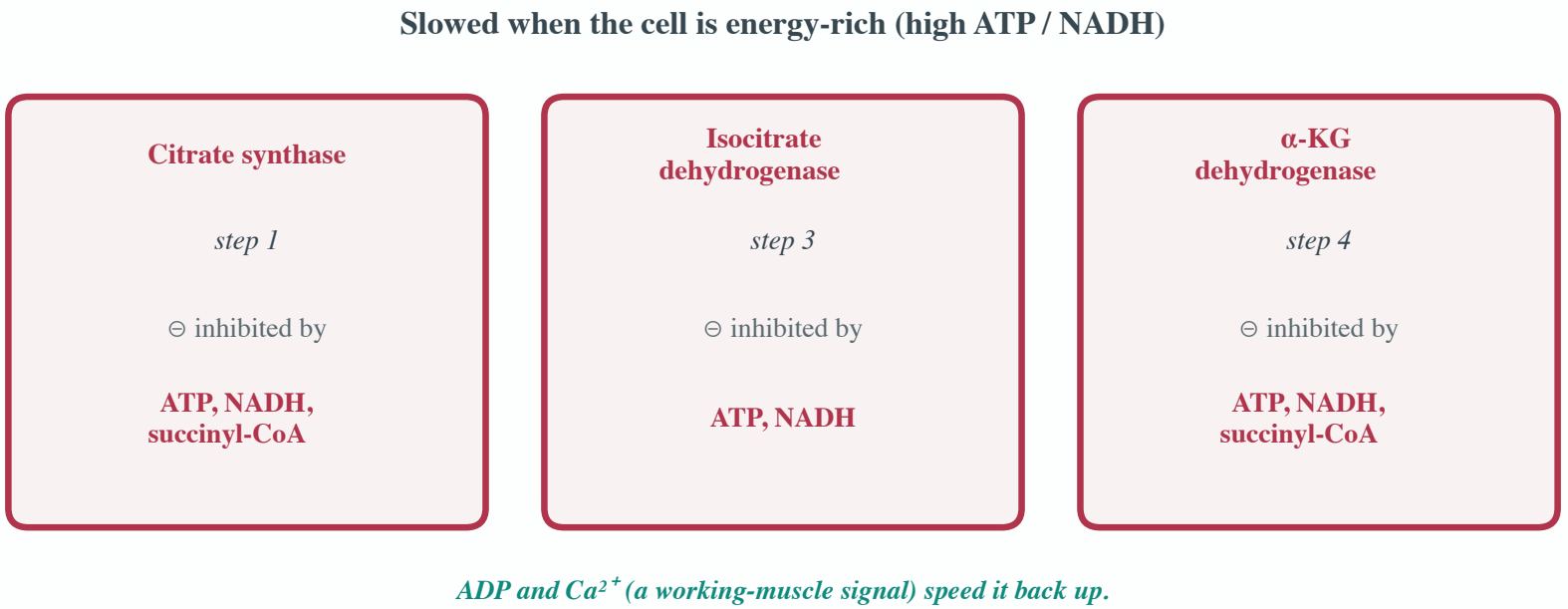
Tallying one turn

So one acetyl-CoA yields **3 NADH + 1 $FADH_2$ + 1 GTP**. The GTP is a **direct** ATP — but the real prize is the **reducing power**: those NADH and $FADH_2$ are worth **~9 more ATP** once they reach the electron transport chain. That's where aerobic metabolism gets its huge payoff.



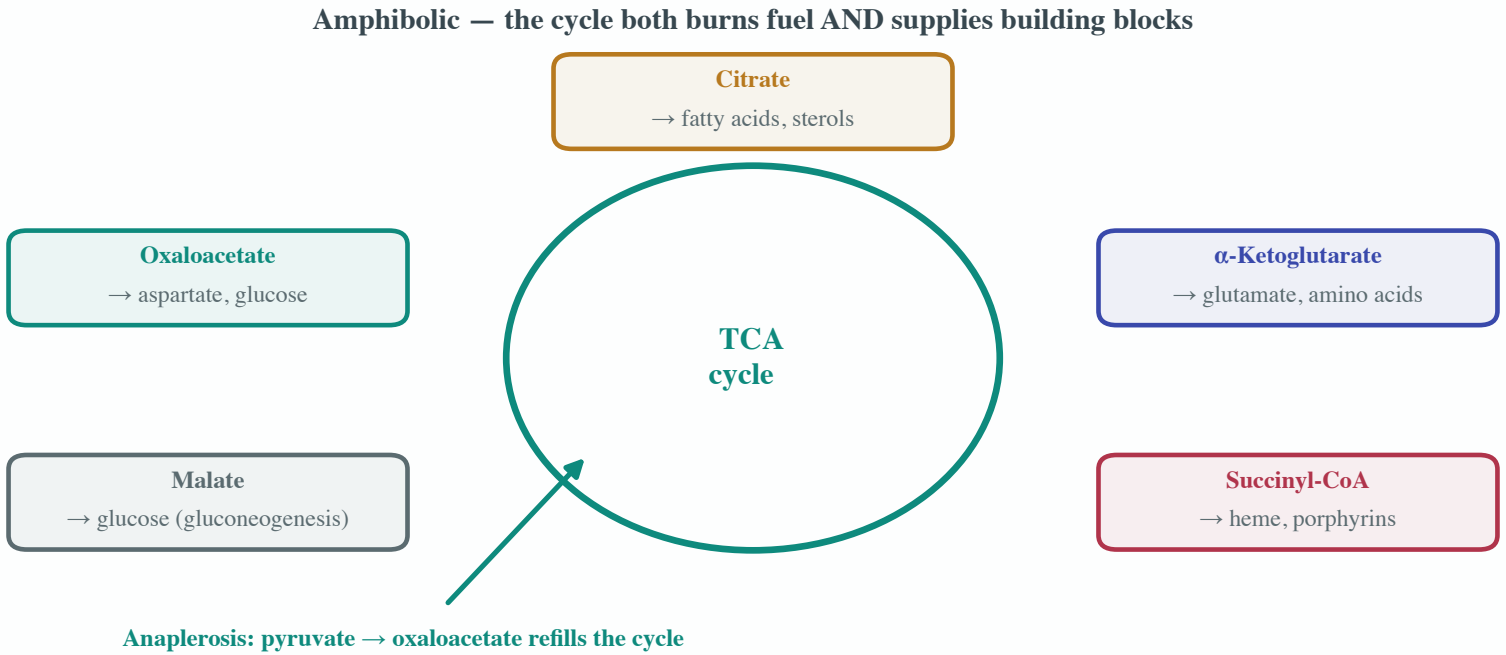
Regulation: read the energy charge

Three enzymes are the control points — **citrate synthase**, **isocitrate dehydrogenase**, and **α-ketoglutarate dehydrogenase**. All are **slowed** when the cell is energy-rich (high **ATP**, **NADH**), and sped up by **ADP** and **Ca^{2+}** (the working-muscle signal). Don't oxidize fuel you don't need.



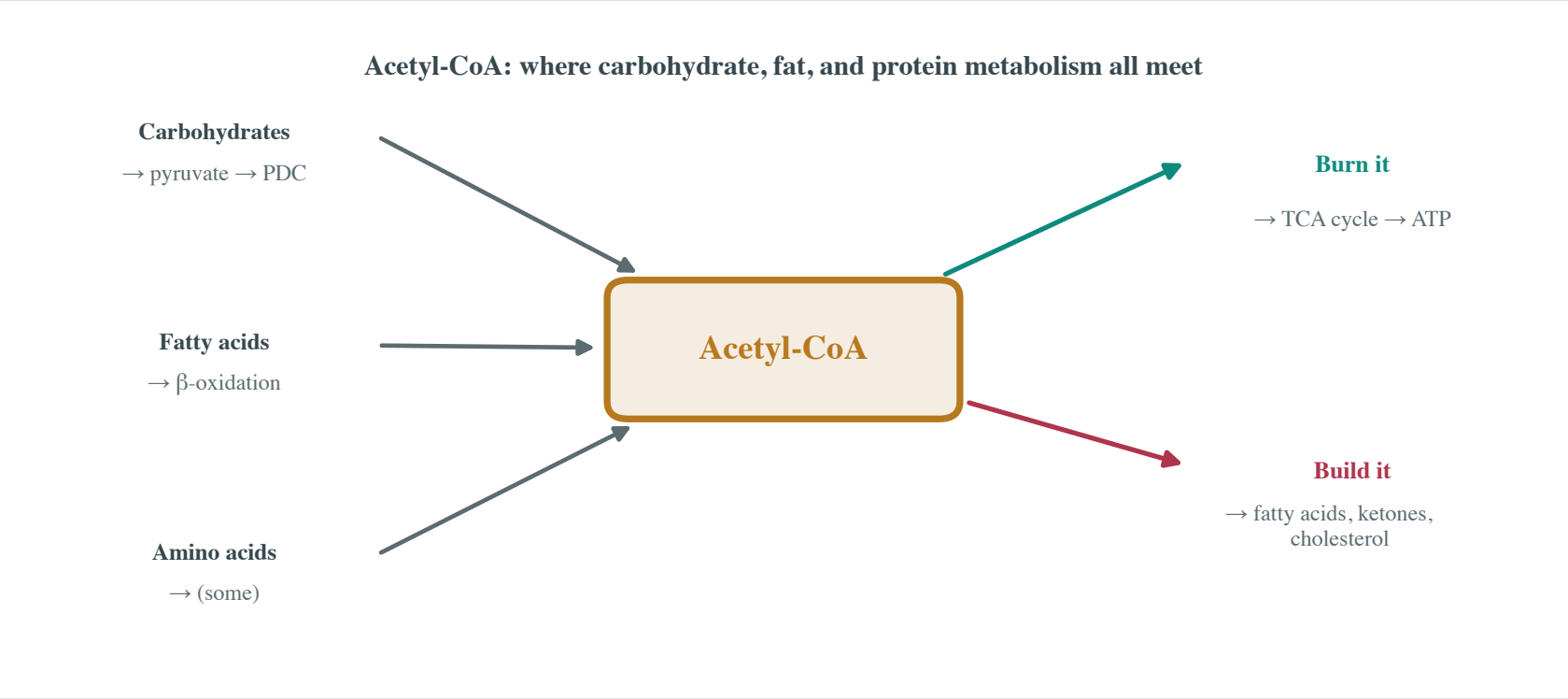
Amphibolic – it builds as it burns

The TCA cycle isn't **only** for energy. Its intermediates get **pulled off for biosynthesis** – citrate → **fatty acids**, α-ketoglutarate → **amino acids**, succinyl-CoA → **heme**. When they're drained, **anaplerotic** reactions top the cycle back up (pyruvate → oxaloacetate). It runs **both directions of metabolism at once**.



Acetyl-CoA: the crossroads of everything

Carbs, fats, and proteins all funnel into acetyl-CoA — then it either **burns** in the TCA cycle or gets **built** into fatty acids, ketones, and cholesterol. One catch: because acetyl-CoA's two carbons **leave as CO_2** each turn, you can't make **net** glucose from it — which is exactly **why you can't turn fat into sugar**.

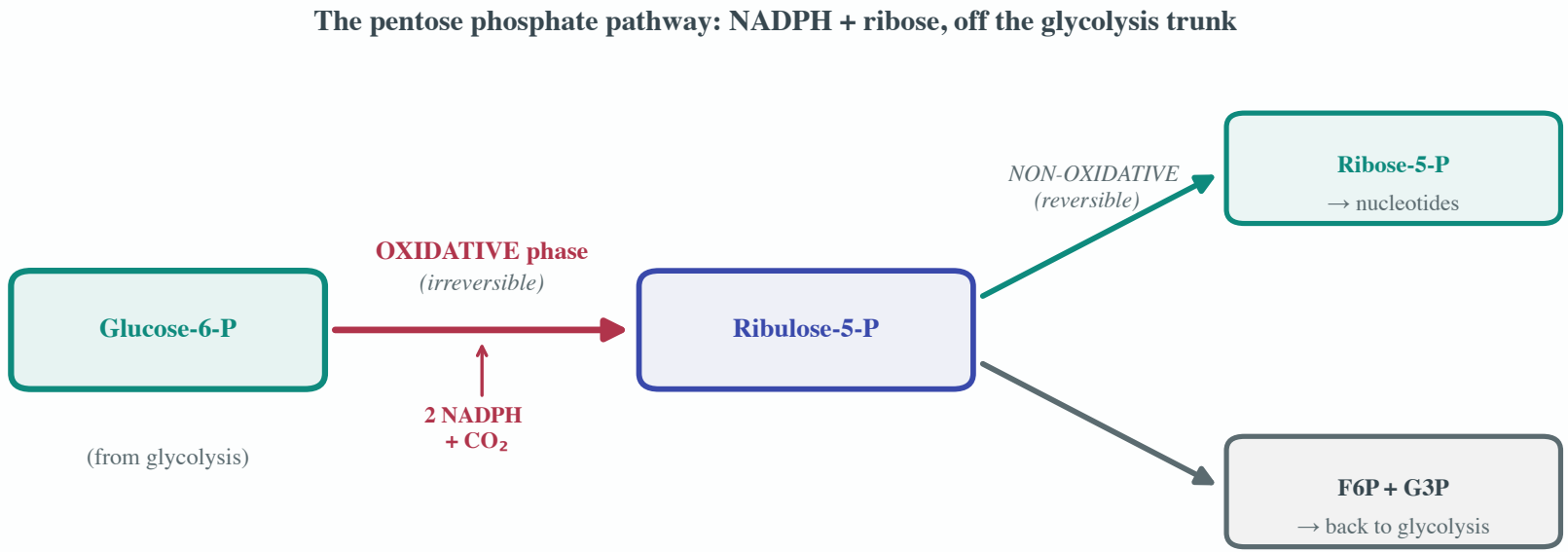


3 · The Pentose Phosphate Pathway

"A branch off glycolysis that makes something ATP can't — NADPH for building and defense, plus ribose for your DNA."

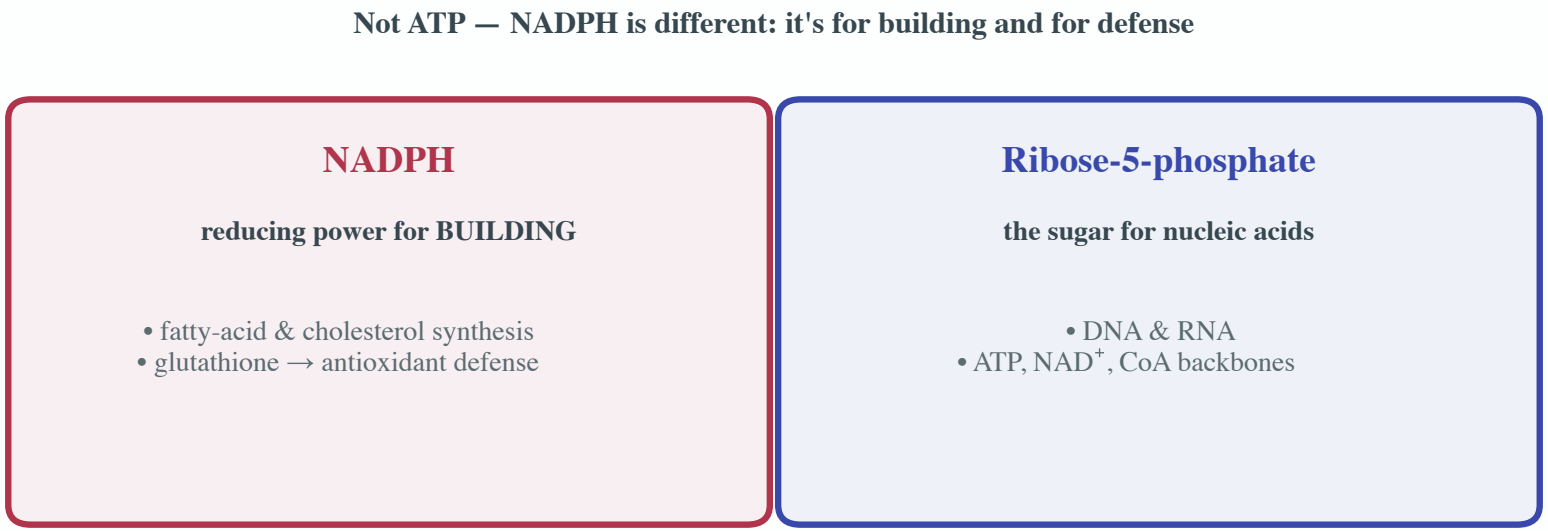
Not everything is about ATP

Glucose-6-phosphate can take a **detour** off glycolysis: the **pentose phosphate pathway**. It runs in **two phases** — an **oxidative** phase (irreversible) that makes **NADPH**, and a **non-oxidative** phase (reversible) that shuffles sugars around. The 5-carbon **ribulose-5-P** in the middle can become **ribose-5-P** or fold **back into glycolysis**.



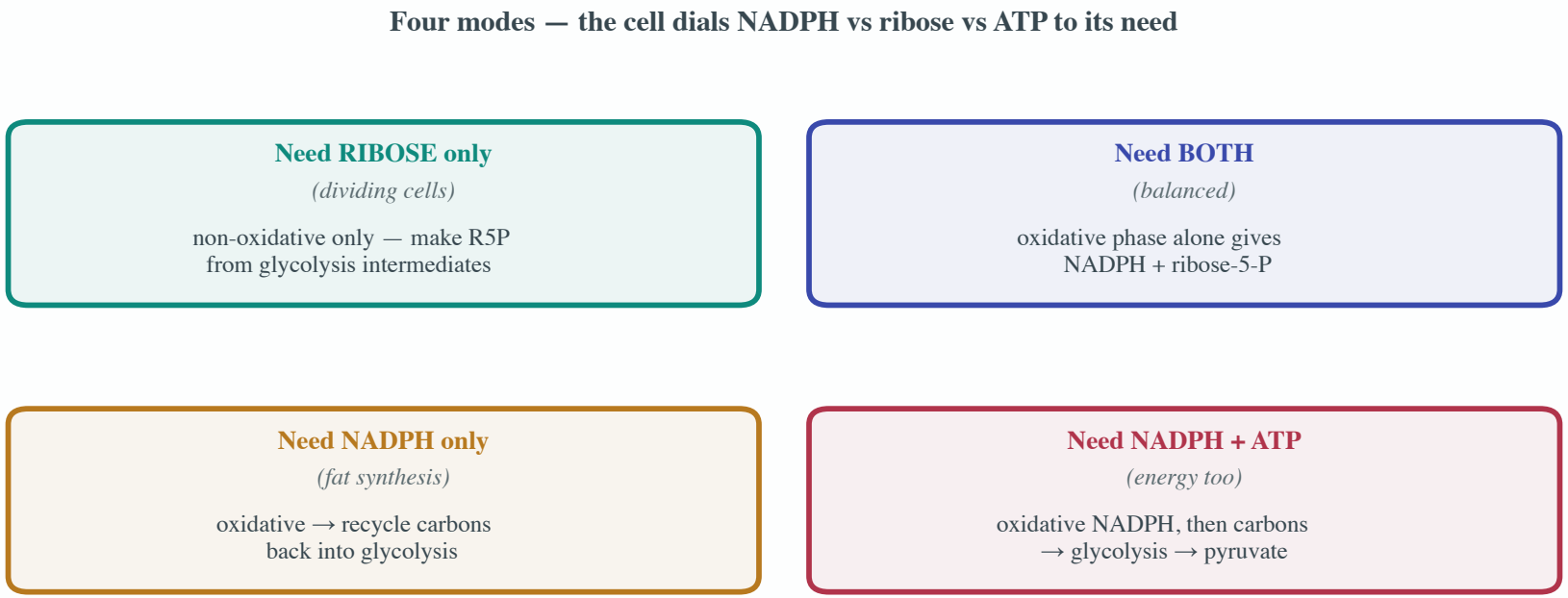
Two products worth having

NADPH looks like NADH but does a totally different job: it's **reducing power for building** — fatty acids, cholesterol — and for **antioxidant defense** (it keeps glutathione charged). **Ribose-5-phosphate** is the sugar backbone of your **nucleic acids** (**RNA** directly; **DNA** once it's reduced) and of cofactors like ATP and NAD^+. Energy? That's glycolysis's job — this pathway supplies **materials**.



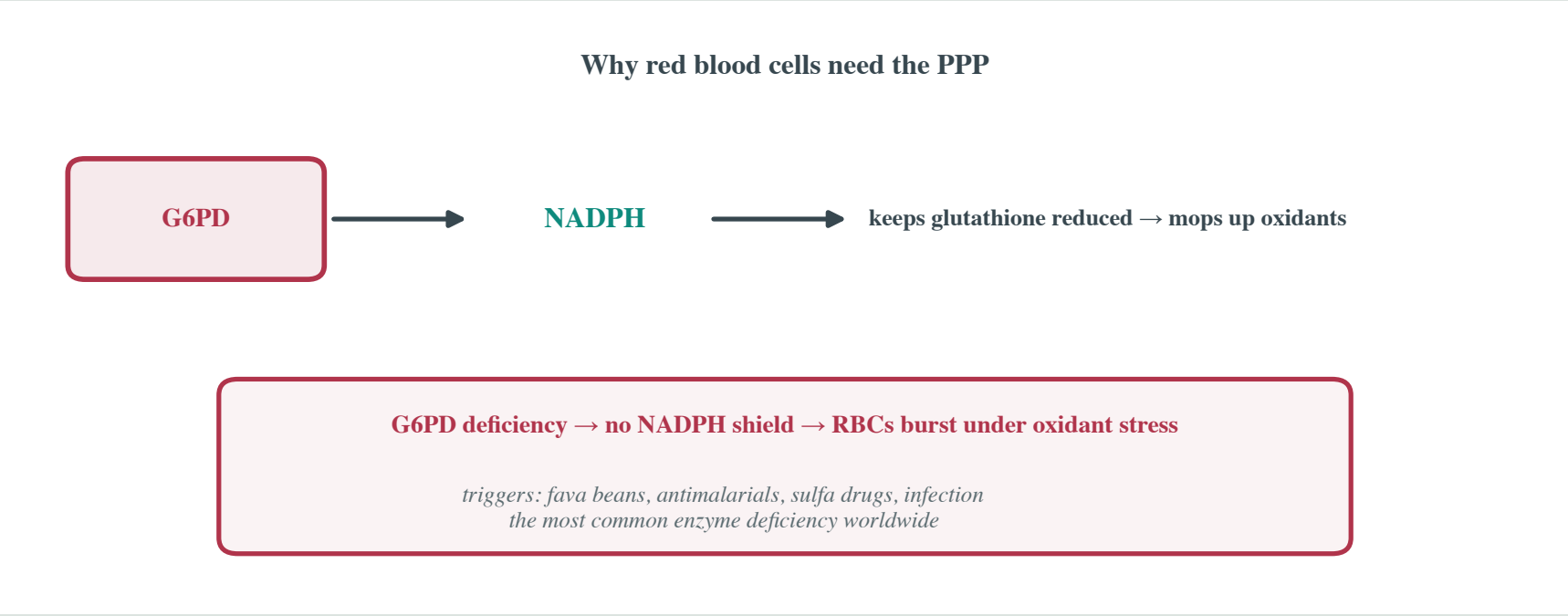
It flexes to what the cell needs

The beauty of the PPP is that it's **flexible**. Need only **ribose** (a dividing cell)? Run just the non-oxidative phase. Need **NADPH** (a fat-making liver cell)? Run oxidative, then recycle the carbons back into glycolysis. Need **both**, or **NADPH plus ATP**? There's a mode for that too — **four paths**, one pathway.



Why your red blood cells depend on it

G6PD (glucose-6-phosphate dehydrogenase) starts the oxidative phase — so it's the **NADPH supply**. Red blood cells use that NADPH to keep **glutathione** charged and neutralize oxidants. In **G6PD deficiency** — the world's **most common enzyme defect** — that shield fails, and RBCs **burst** when hit by oxidative stress: **fava beans**, antimalarials, sulfa drugs, or infection.

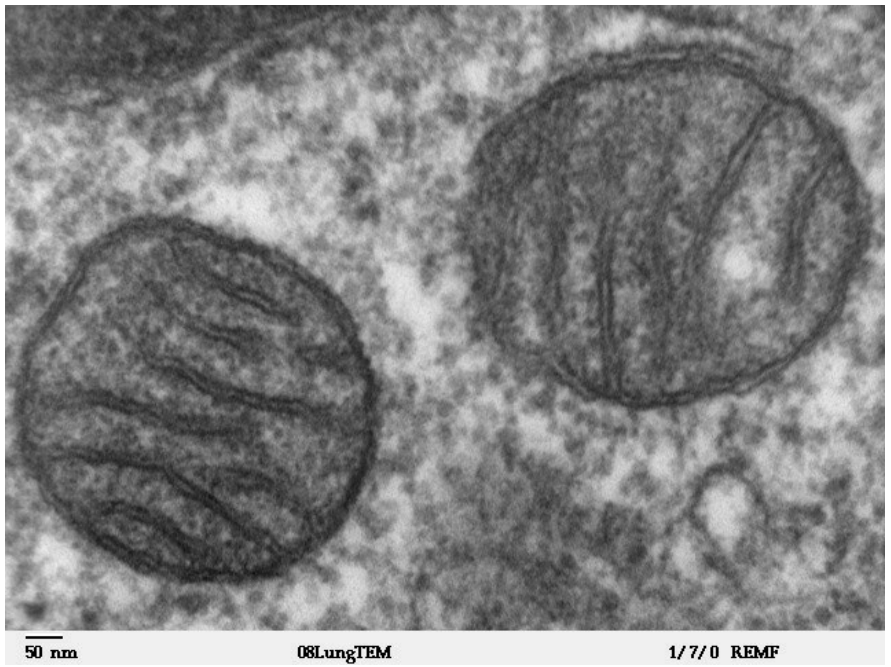


4 · The Electron Transport Chain

"Cash in all that NADH and $FADH_2$ – watch electrons tumble down four complexes to oxygen, pumping protons the whole way."

Where the real ATP is made

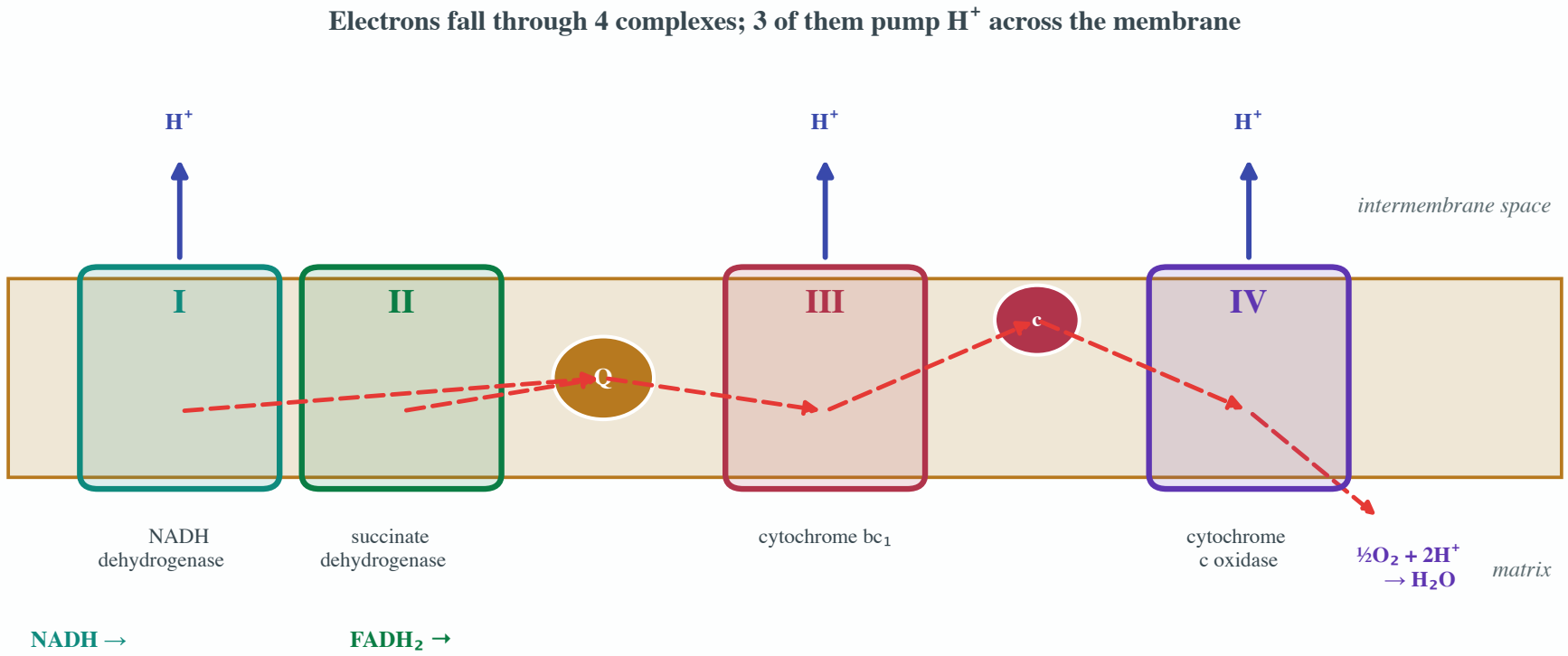
Glycolysis and the TCA cycle made only a little ATP directly — their real haul was **NADH and $FADH_2$**. Now we cash them in. It all happens on the **inner mitochondrial membrane**, folded into **cristae** to pack in as much surface area (and as many chains) as possible. You can see those folds in this real electron micrograph.



TEM: Louisa Howard, public domain (Wikimedia Commons)

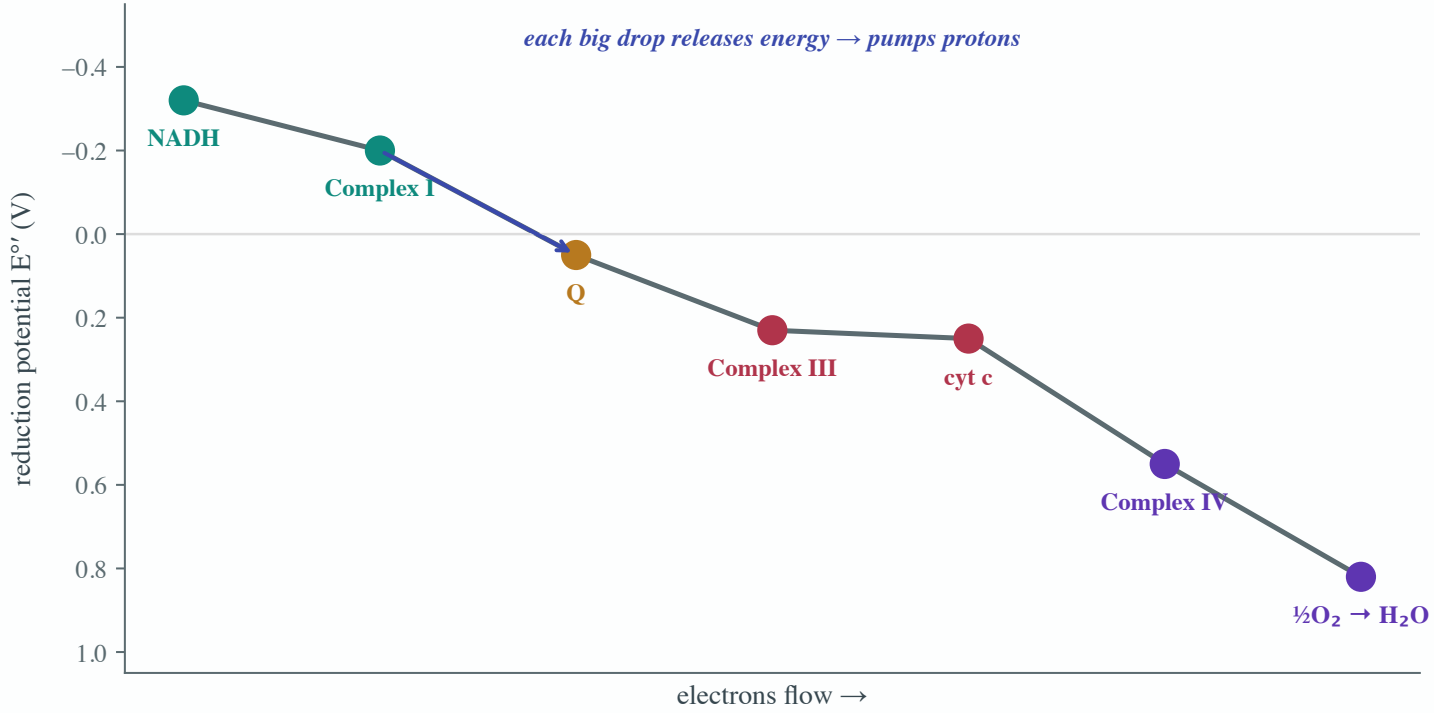
Four complexes, one chain

The chain is **four protein complexes** in the membrane. Electrons are handed from one to the next — NADH drops them at **Complex I**, $FADH_2$ at **Complex II** — and mobile carriers **Q** (ubiquinone) and **cytochrome c** ferry them along. Three of the complexes (**I, III, IV**) use the released energy to **pump H^+** out into the intermembrane space.



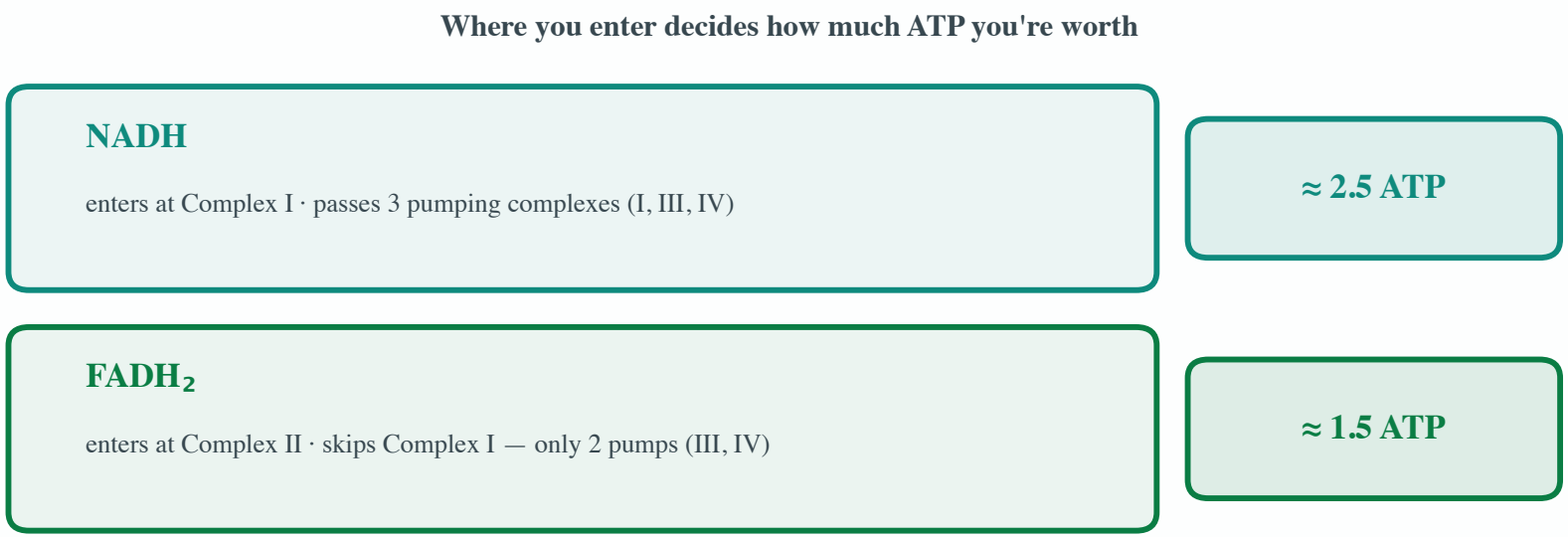
Downhill all the way to oxygen

Why do electrons flow **this** direction? Each carrier has a **reduction potential** — a "grabbiness" for electrons. Electrons fall from **low** potential (**NADH**) to **high** (**O_2**, the greediest of all), and every big drop **releases energy** to pump protons. At the end, **Complex IV** hands them to **O_2**, making **water** — which is why you must **breathe**.



NADH vs $FADH_2$: entry matters

Here's why NADH is worth more than $FADH_2$. **NADH** enters at **Complex I** and drives **all three** proton pumps. **$FADH_2$** enters later, at **Complex II**, so it **skips Complex I** – only two pumps. Fewer protons pumped means less ATP: about **2.5** for NADH versus **1.5** for $FADH_2$.

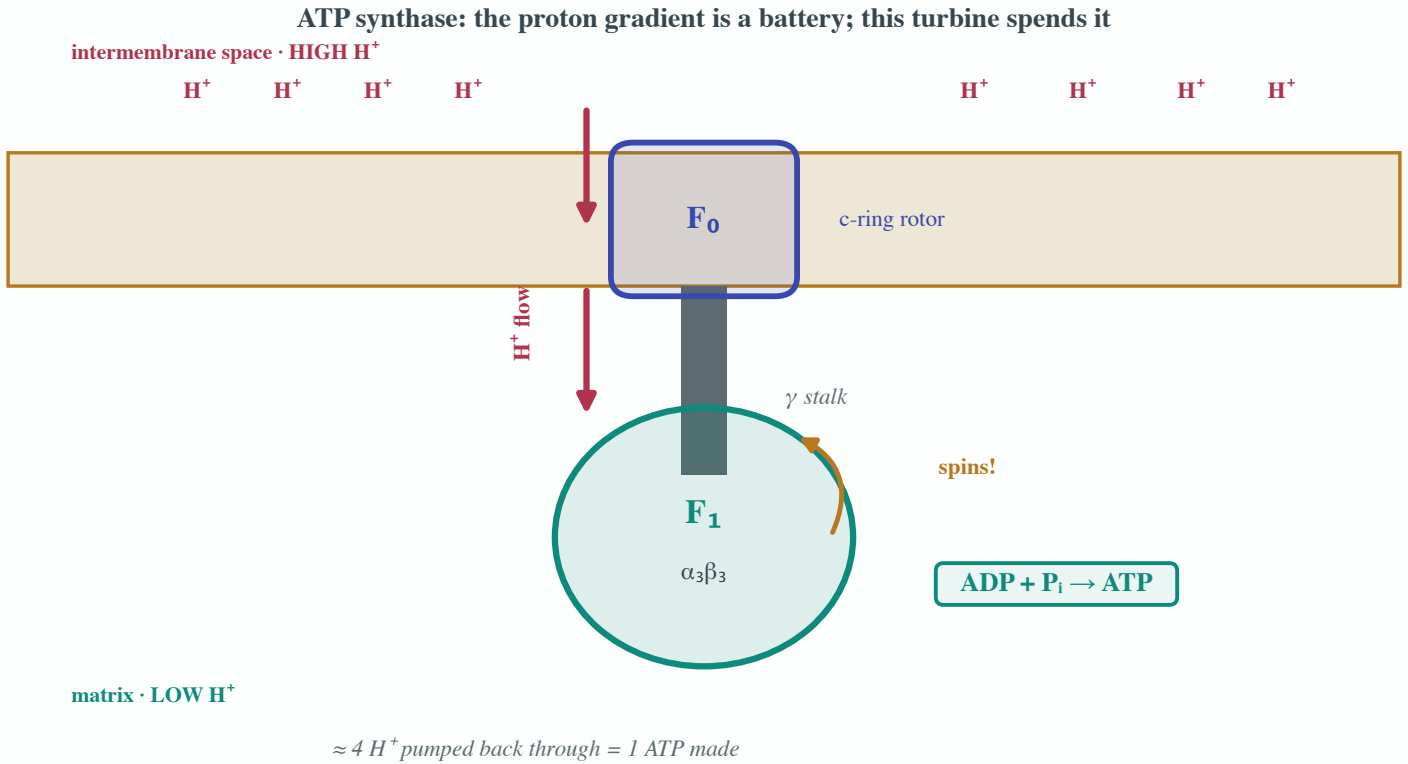


5 · Oxidative Phosphorylation

"The payoff — the proton gradient spins a molecular turbine into ATP. Add it all up: one glucose, ~30 ATP."

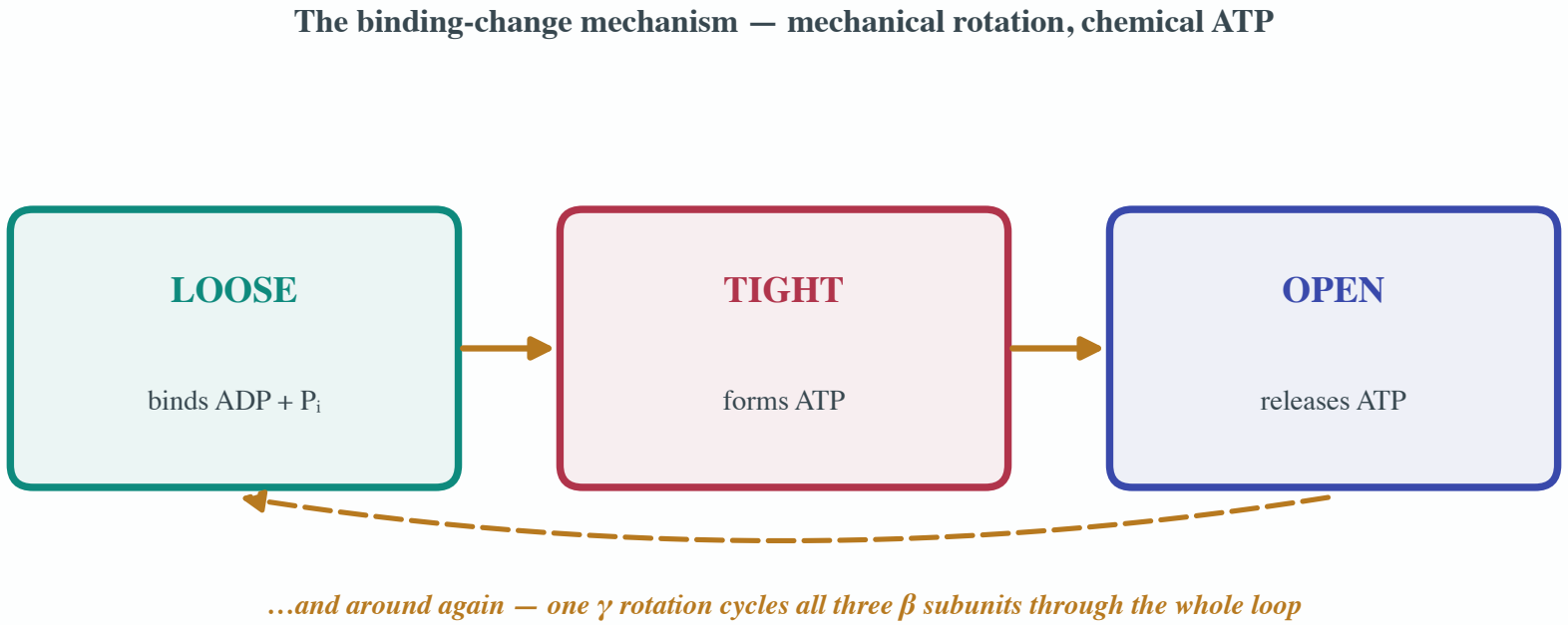
The gradient is a battery

All that proton-pumping charged up a **gradient** across the inner membrane — more H^+ outside than in. That's **stored energy** (the proton-motive force), and it wants to flow back. The only door back in is through **ATP synthase**, and as protons rush through, they **spin it like a turbine** — that's **chemiosmosis**, and it's where most of your ATP is made.



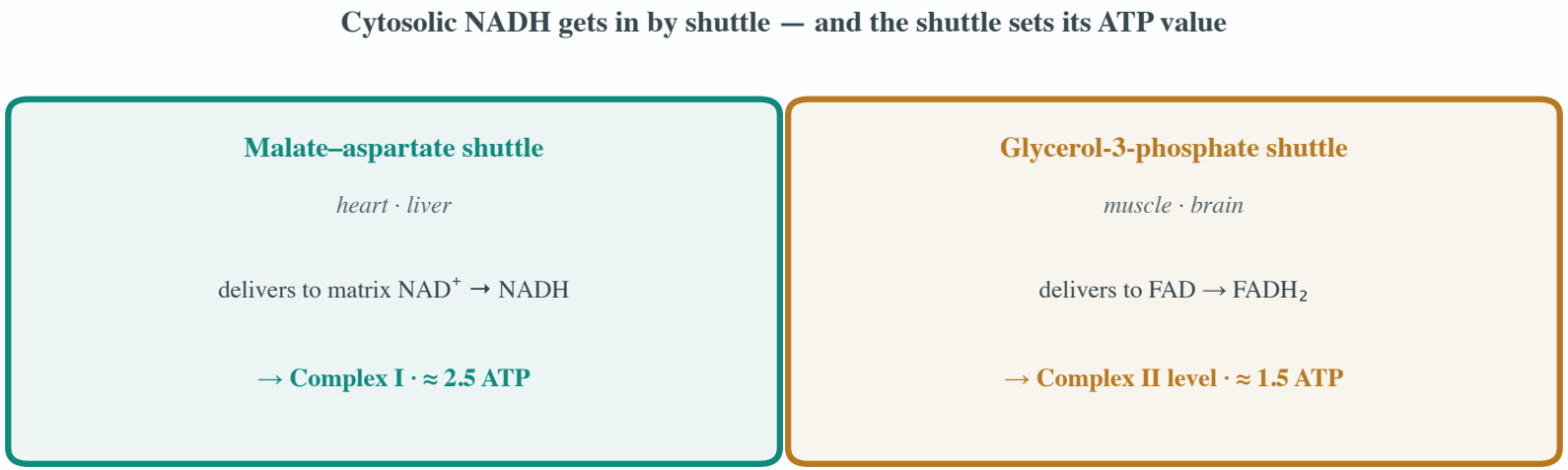
How a spinning motor makes ATP

ATP synthase has two parts: **F_o** (a **rotor** in the membrane that the protons turn) and **F_1** (the **$\alpha_3\beta_3$** head in the matrix that does the chemistry), joined by a **γ stalk**. As γ spins, it shoves each **β subunit** through three shapes — **Loose** (grab ADP + P_i), **Tight** (squeeze them into ATP), **Open** (let ATP go). Mechanical motion → chemical bond.



Getting cytosolic NADH into the game

One problem: the **NADH made in glycolysis** is stuck in the **cytosol** — the inner membrane won't let it cross. So its **electrons** are ferried in by a **shuttle**. The **malate–aspartate** shuttle (heart, liver) hands them to **NADH** (worth ~2.5 ATP); the **glycerol-3-phosphate** shuttle (muscle, brain) hands them to **$FADH_2$** (only ~1.5 ATP).



That's why "ATP per glucose" is a range, not a fixed number.

Adding it all up

Here's the whole harvest from **one glucose**. A little **direct** ATP (2 from glycolysis, 2 GTP from the TCA cycle) — but the bulk comes from cashing in **10 NADH + 2 $FADH_2$** at the electron transport chain. All told: **about 30–32 ATP**, depending on which shuttle carried the cytosolic NADH. **That's** why we breathe.

Adding it all up: one glucose, fully oxidized

stage	direct	carriers → ETC
Glycolysis	2 ATP	2 NADH
Pyruvate → acetyl-CoA (×2)	—	2 NADH
TCA cycle (×2 turns)	2 GTP	6 NADH + 2 $FADH_2$
totals	**4 ATP**	**10 NADH + 2 $FADH_2$**

GRAND TOTAL ≈ 30–32 ATP per glucose

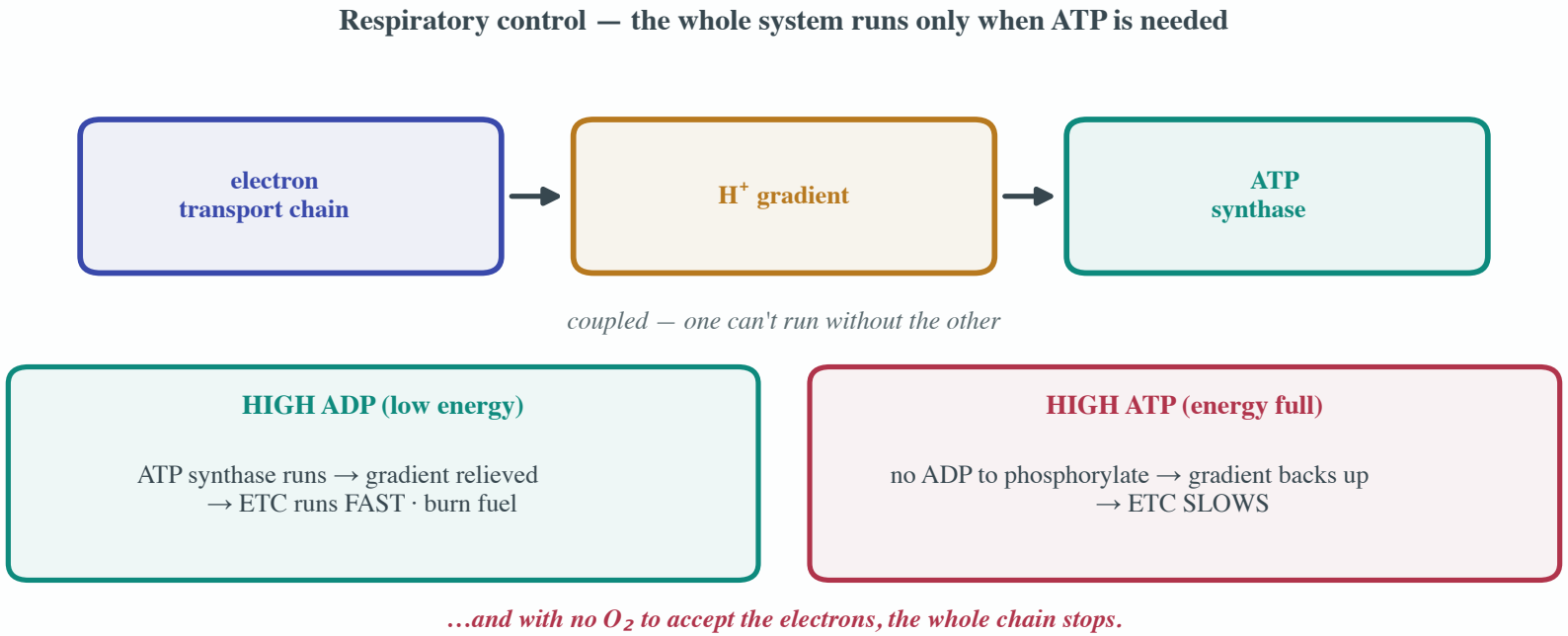
4 direct + (10 NADH ×2.5) + (2 $FADH_2$ ×1.5) = 32
slightly less if the glycerol-P shuttle is used

6 · Regulation, Poisons & Uncouplers

"What sets the pace of respiration — and what happens when you poison it or short-circuit it for heat."

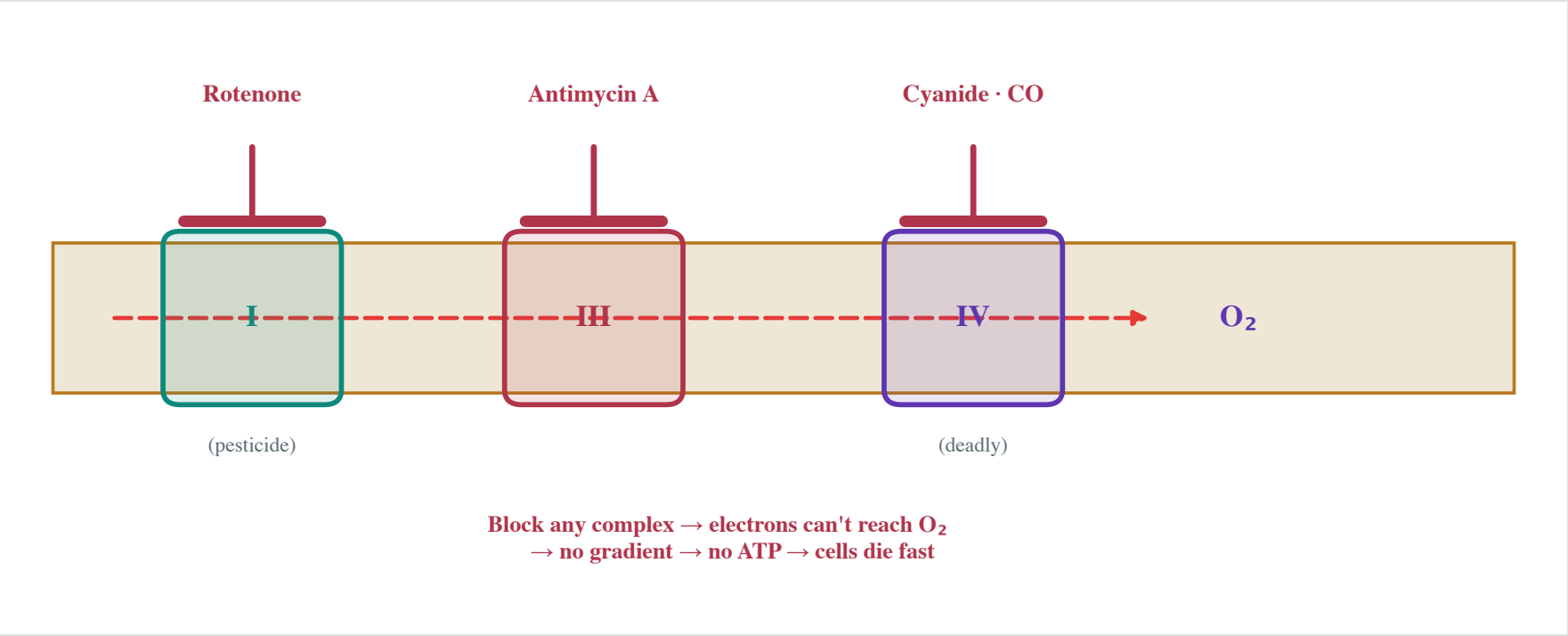
What sets the pace: ADP

The electron transport chain and ATP synthase are **coupled** — chained together by the proton gradient, so **one can't run without the other**. That makes **ADP the throttle** (called **respiratory control**): when **ADP is high** (you're low on energy), ATP synthase runs, the gradient is relieved, and the chain burns **fast**. When **ATP is high**, everything **slows**. And with **no O_2** to catch the electrons at the end, the whole chain simply **stops**.



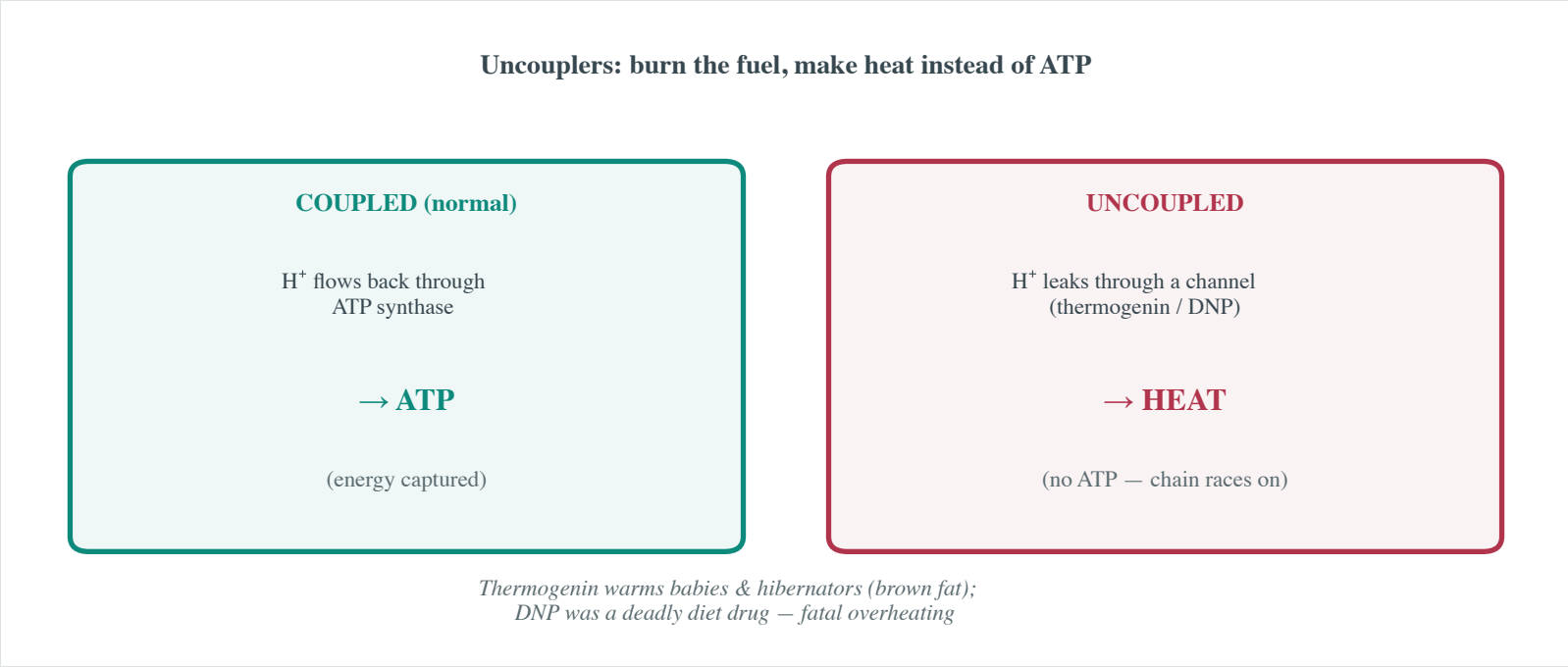
Poisons that stop the chain

Because every complex passes electrons to the next, **blocking any one** jams the whole line. **Rotenone** (a pesticide) blocks **Complex I**; **antimycin A** blocks **Complex III**; **cyanide** and **carbon monoxide** block **Complex IV**. Electrons can't reach O_2, the gradient collapses, ATP synthesis halts — and cells die **fast**. This is exactly how cyanide kills.



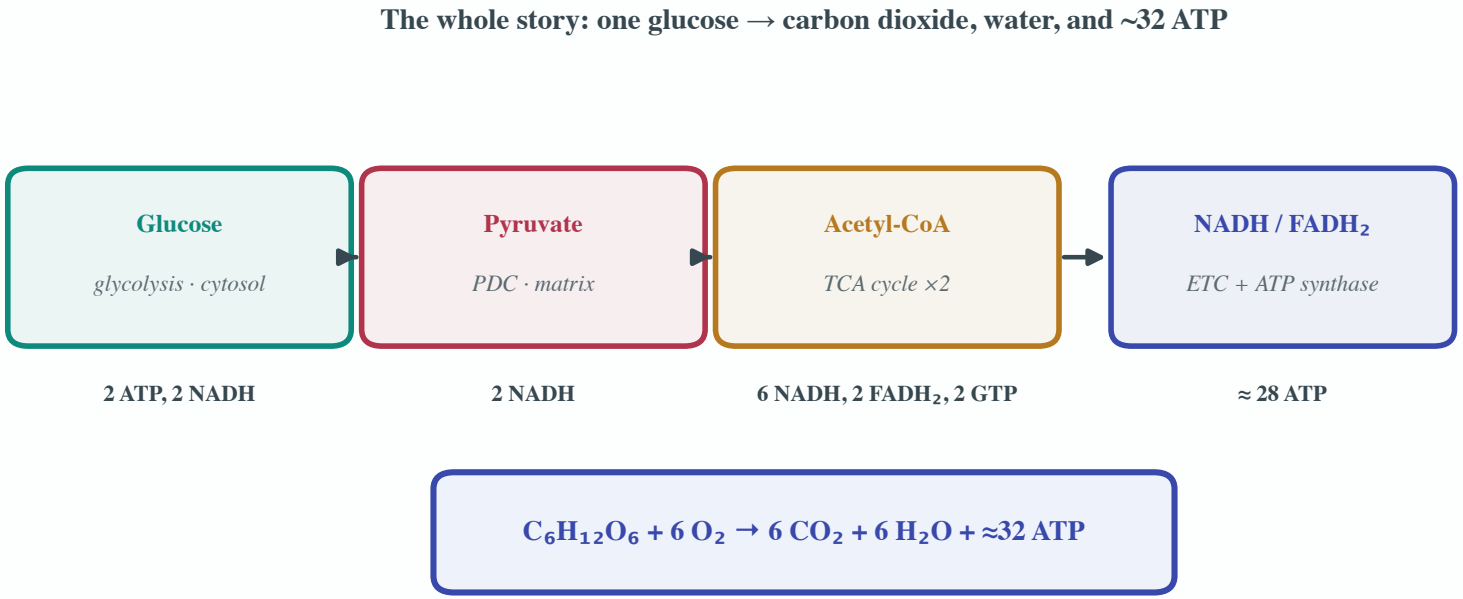
Uncouplers: heat instead of ATP

There's another way to wreck it: an **uncoupler** lets **H^+ leak back across** the membrane **without** passing through ATP synthase — so the energy comes out as **heat**, not ATP. Your **brown fat** does this **on purpose** with **thermogenin** to keep babies warm; the diet drug **DNP** did it too — and cooked people to death.



The whole story, one glucose

Step back and look at it all: **glucose** is split in the **cytosol**, its pyruvate shipped into the **mitochondrion**, oxidized by the **TCA cycle**, and the harvested **NADH and $FADH_2$** cashed in at the **electron transport chain** to spin out ATP. One glucose, fully burned to **CO_2 and water**, yields about **32 ATP**. **That's** why you breathe.



Can you…?

- □ explain the pyruvate dehydrogenase complex — the link reaction to acetyl-CoA — its cofactors and its allosteric + covalent regulation?
- □ walk all eight reactions of the TCA cycle with the running NADH/$FADH_2$/GTP ledger, and explain its regulated, amphibolic, and anaplerotic roles?
- □ describe the pentose phosphate pathway — its oxidative and non-oxidative phases and its NADPH and ribose-5-phosphate products?
- □ trace electron flow through the four ETC complexes, driven by reduction potential, pumping protons to build the gradient?
- □ explain chemiosmosis and ATP synthase's rotary catalysis, the NADH shuttles, and the total ATP yield from one glucose?
- □ describe the regulation of respiration, uncouplers (thermogenin), and ETC poisons (cyanide, rotenone)?

If any box stays empty, the practice site has a drill for it.

🧪