BIO102-Foundations of Biology (I)

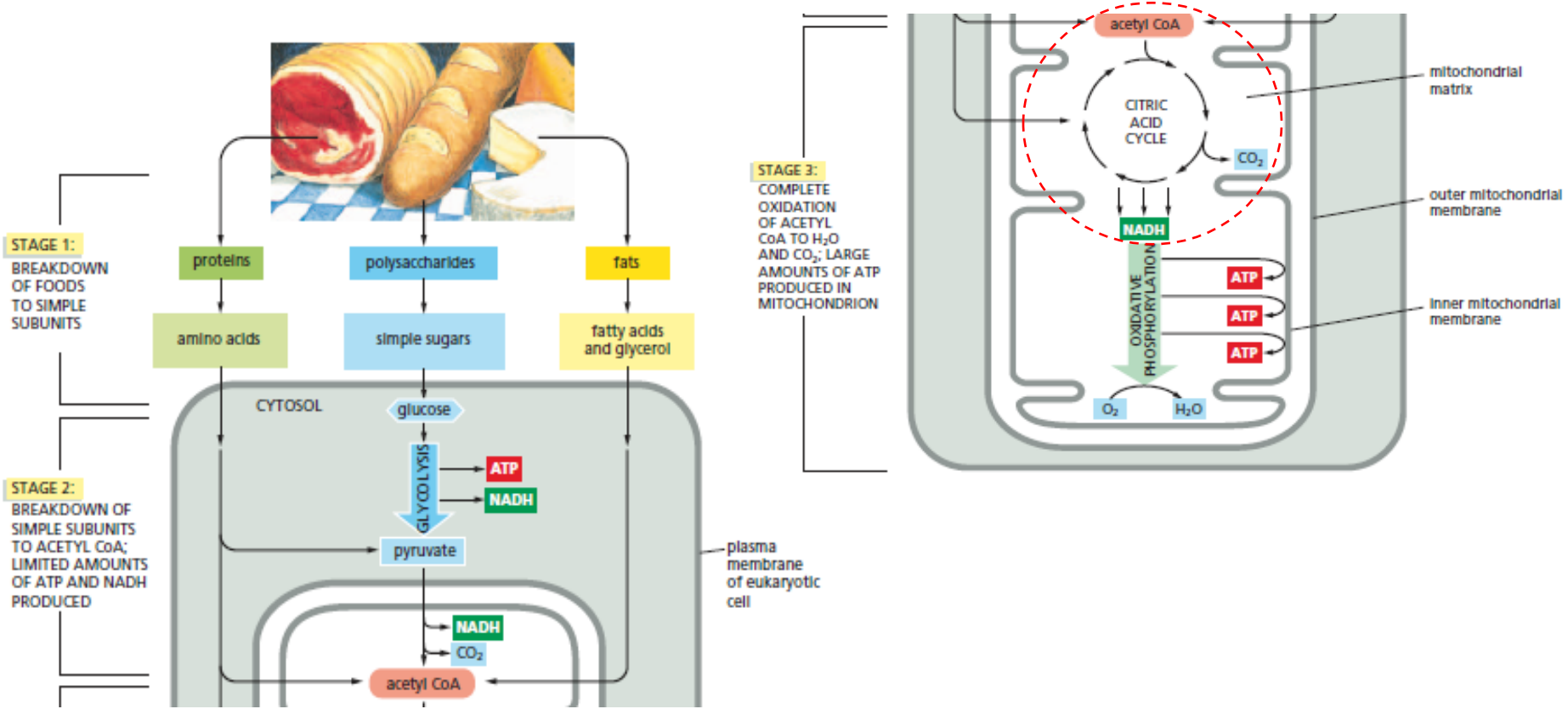
Glucose metabolism

INDRAPRASTHA INSTITUTE *of*
INFORMATION TECHNOLOGY **DELHI**

Dr. Jaspreet Kaur Dhanjal
Assistant Professor, Center for Computational Biology
Email ID: jaspreet@iiitd.ac.in

February 17, 2025

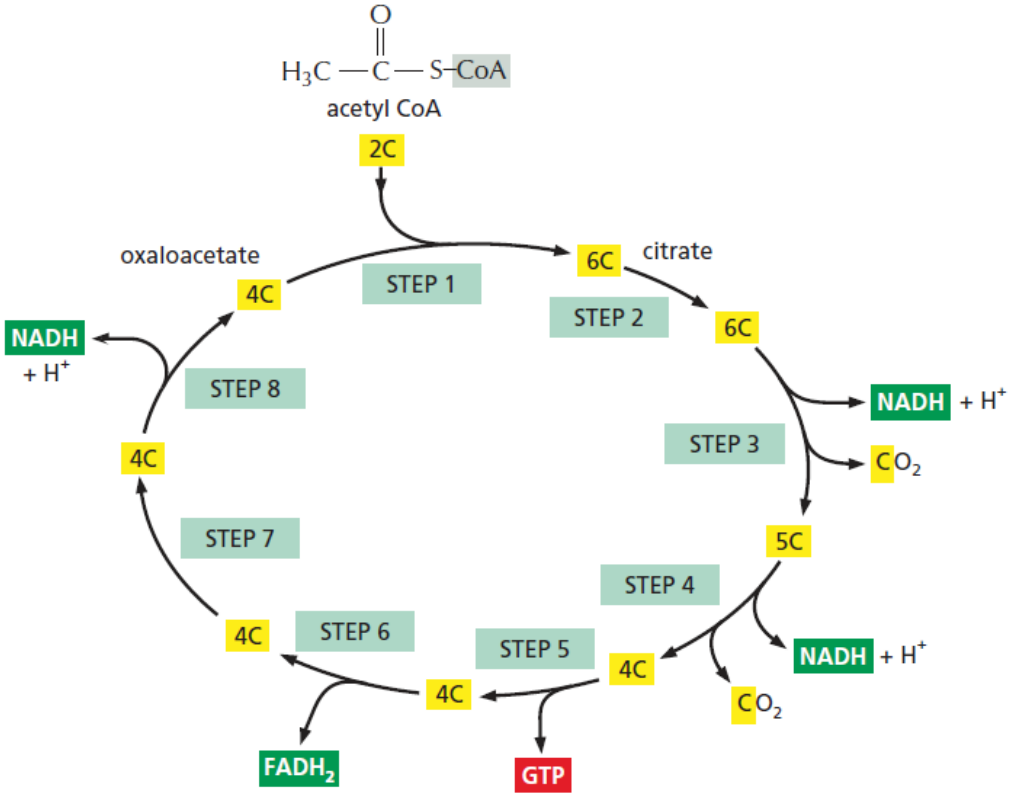
Food molecules are broken down in three stages



The Citric Acid Cycle

- Catabolism does not end with the production of acetyl CoA.
- In the process of converting food molecules to acetyl CoA, only a small part of their stored energy is extracted and converted into ATP, NADH, or $FADH_2$. Most of that energy is still locked up in acetyl CoA.
- The next stage in cell respiration is the citric acid cycle, in which the acetyl group in acetyl CoA is oxidized to CO_2 and H_2O in the mitochondrial matrix.
- Citric acid cycle is also called the tricarboxylic acid cycle or the Krebs cycle.
- The citric acid cycle catalyzes the complete oxidation of the carbon atoms of the acetyl groups in acetyl CoA, converting them into CO_2. The acetyl group is not oxidized directly, however. Instead, it is transferred from acetyl CoA to a larger four-carbon molecule, oxaloacetate, to form the six-carbon tricarboxylic acid, citric acid. The citric acid molecule (also called citrate) is then progressively oxidized, and the energy of this oxidation is harnessed to produce activated carriers. The chain of eight reactions forms a cycle, because the oxaloacetate that began the process is regenerated at the end.

The Citric Acid Cycle

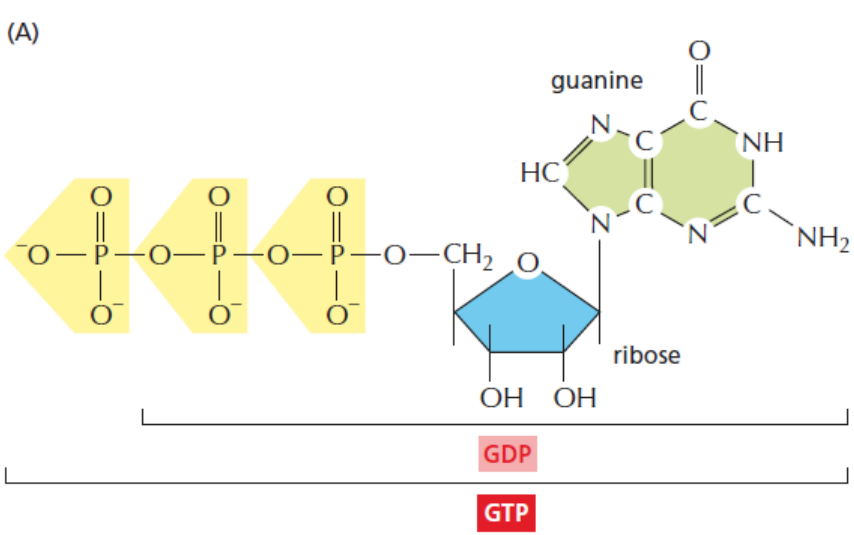


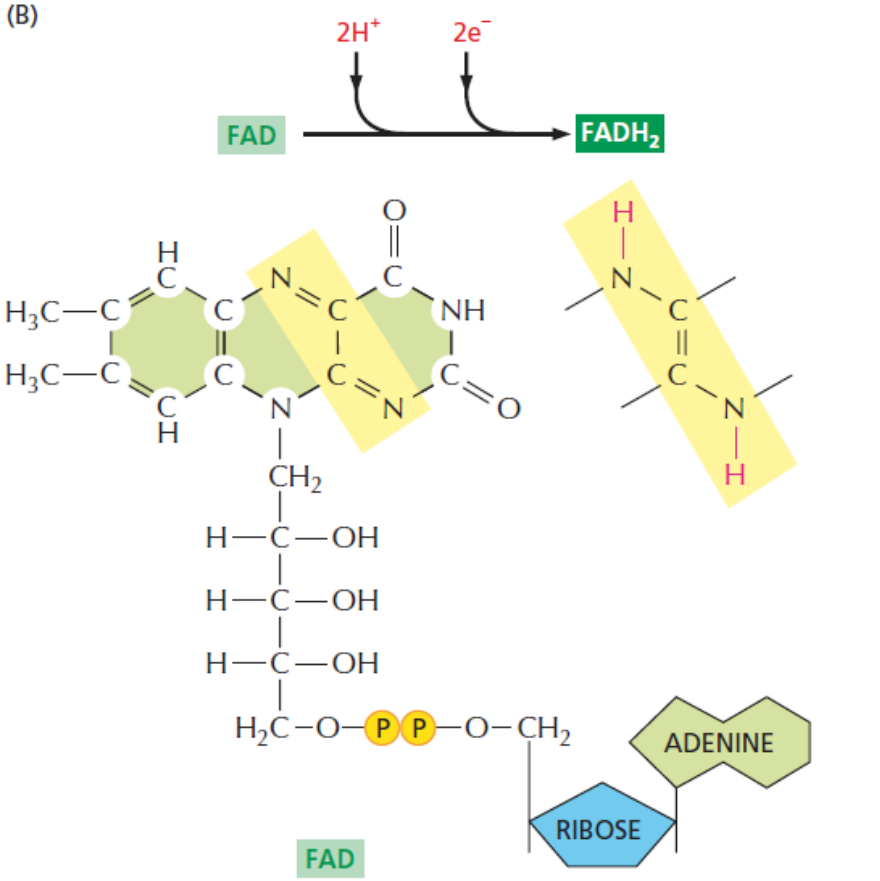
NET RESULT: ONE TURN OF THE CYCLE PRODUCES THREE NADH, ONE GTP, AND ONE $FADH_2$, AND RELEASES TWO MOLECULES OF CO_2

In addition to three molecules of NADH, each turn of the cycle also produces one molecule of $FADH_2$ (reduced flavin adenine dinucleotide) from FAD and one molecule of the ribonucleoside triphosphate GTP (guanosine triphosphate) from GDP.

GTP is a close relative of ATP, and the transfer of its terminal phosphate group to ADP produces one ATP molecule in each cycle. Like NADH, $FADH_2$ is a carrier of high-energy electrons and hydrogen.

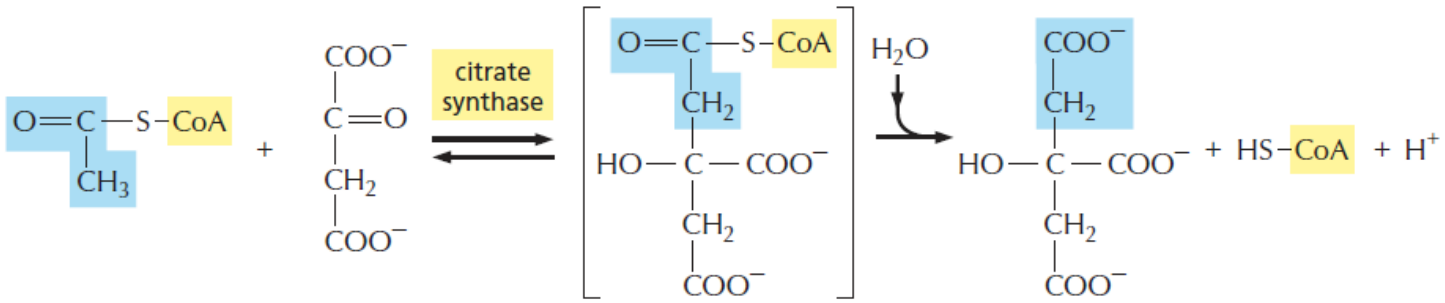
The Citric Acid Cycle





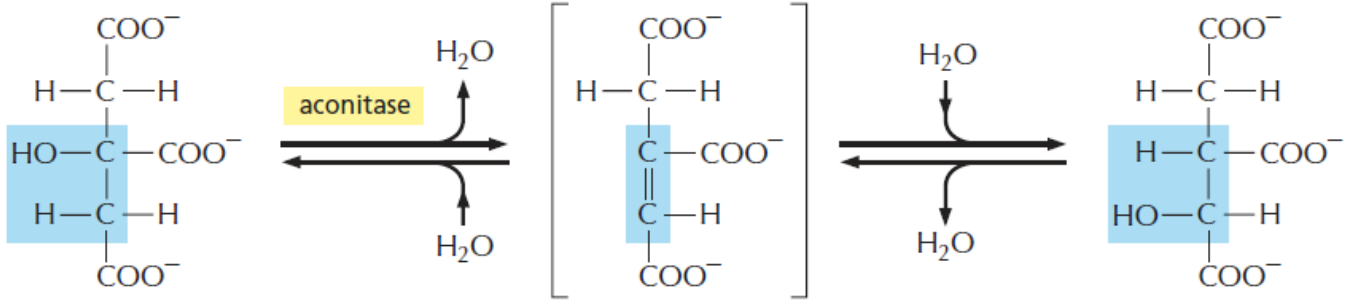
The Citric Acid Cycle

Step 1 After the enzyme removes a proton from the CH_3 group on acetyl CoA, the negatively charged CH_2^- forms a bond to a carbonyl carbon of oxaloacetate. The subsequent loss by hydrolysis of the coenzyme A (HS–CoA) drives the reaction strongly forward.



acetyl CoA | oxaloacetate | S-citryl-CoA intermediate | citrate

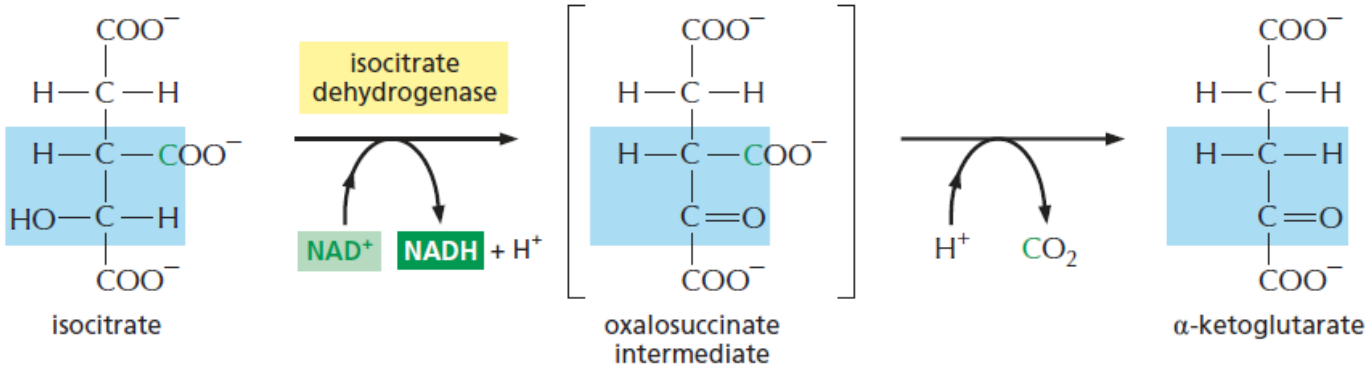
Step 2 An isomerization reaction, in which water is first removed and then added back, moves the hydroxyl group from one carbon atom to its neighbor.



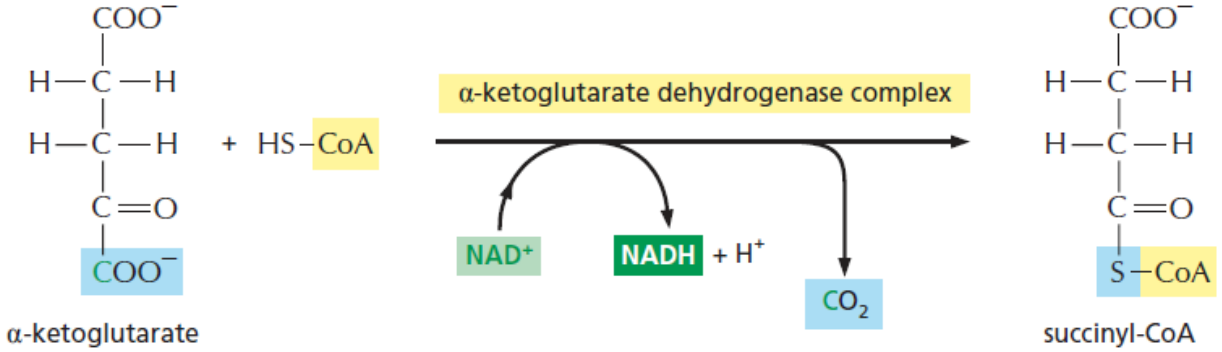
citrate | *cis*-aconitate intermediate | isocitrate

The Citric Acid Cycle

Step 3 In the first of four oxidation steps in the cycle, the carbon carrying the hydroxyl group is converted to a carbonyl group. The immediate product is unstable, losing CO_2 while still bound to the enzyme.

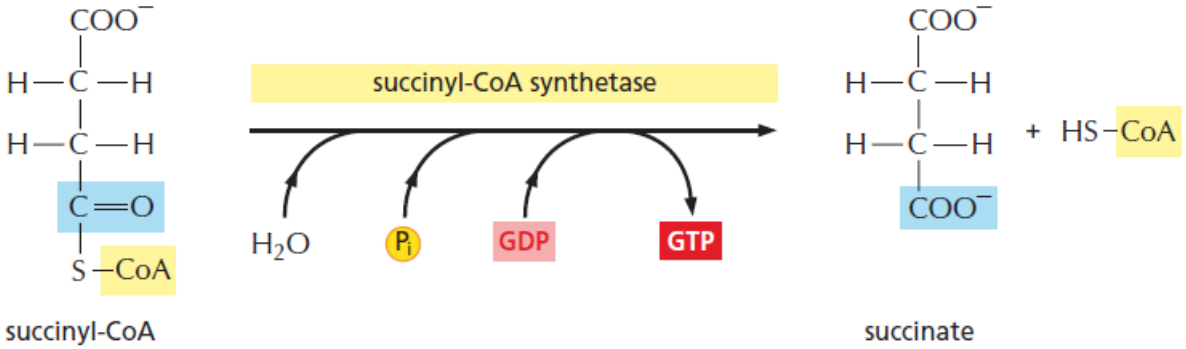


Step 4 The *α-ketoglutarate dehydrogenase complex* closely resembles the large enzyme complex that converts pyruvate to acetyl CoA, the *pyruvate dehydrogenase* complex in Figure 13–10. It likewise catalyzes an oxidation that produces NADH, CO_2, and a high-energy thioester bond to coenzyme A (CoA).



The Citric Acid Cycle

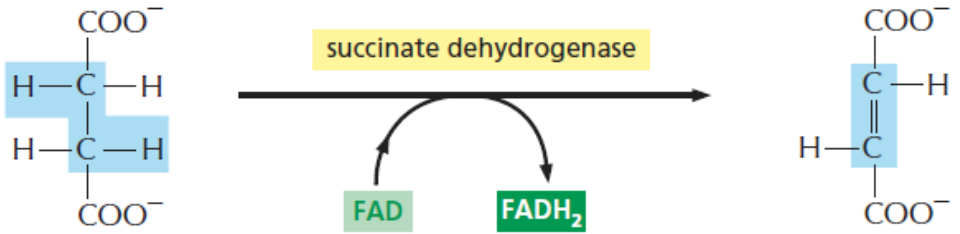
Step 5 A phosphate molecule from solution displaces the CoA, forming a high-energy phosphate linkage to succinate. This phosphate is then passed to GDP to form GTP. (In bacteria and plants, ATP is formed instead.)



succinyl-CoA

succinate

Step 6 In the third oxidation step in the cycle, FAD accepts two hydrogen atoms from succinate.

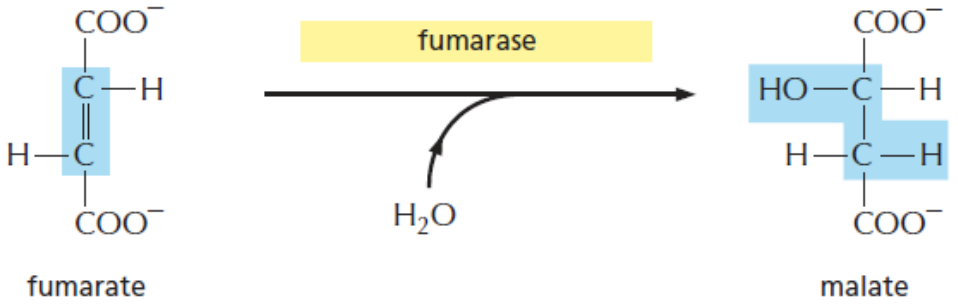


succinate

fumarate

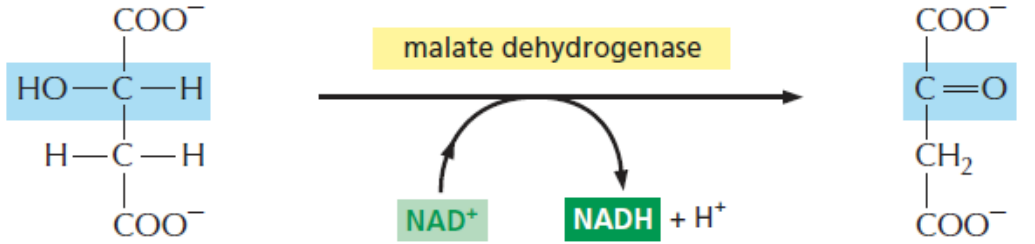
The Citric Acid Cycle

Step 7 The addition of water to fumarate places a hydroxyl group next to a carbonyl carbon.



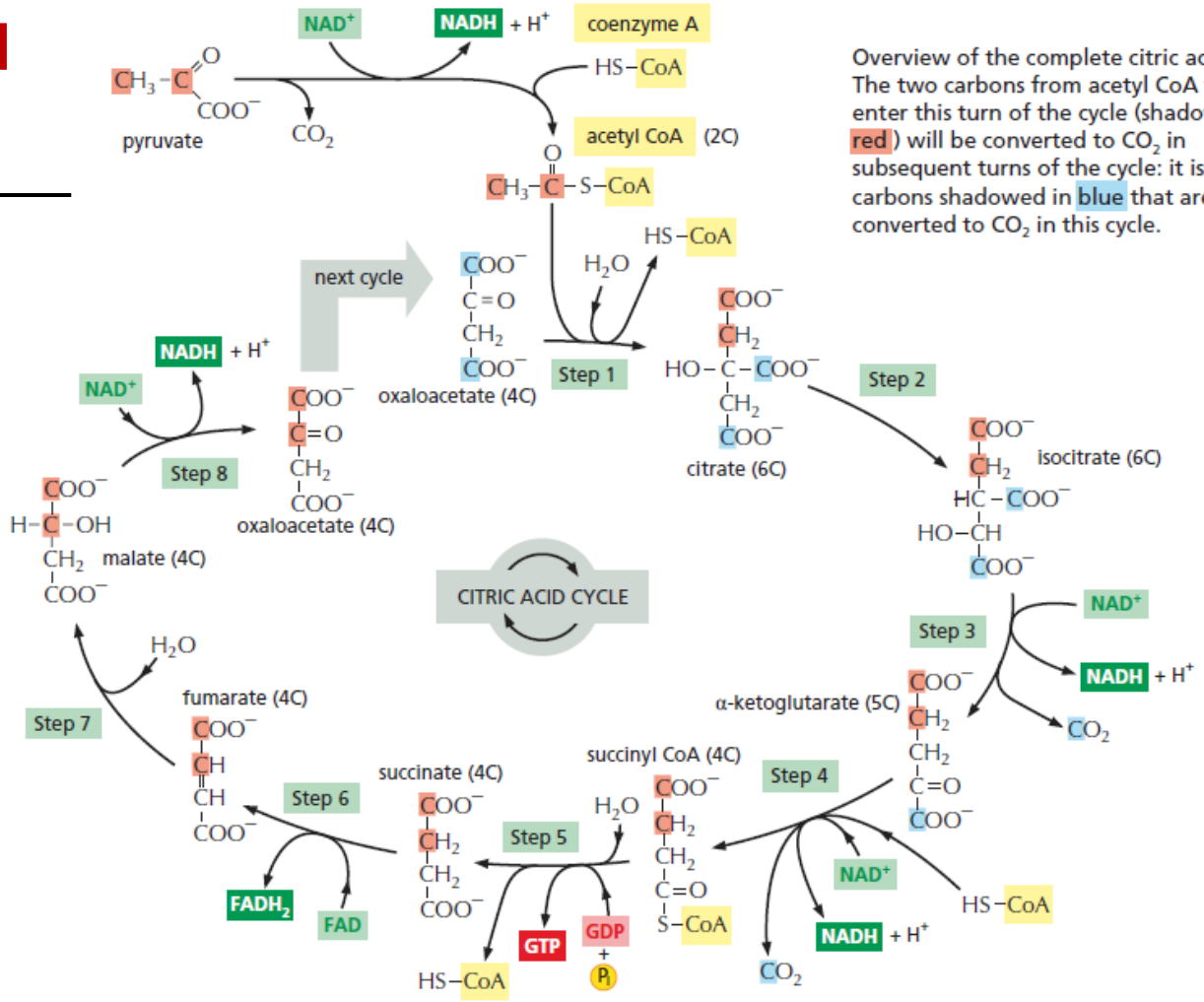
fumarate malate

Step 8 In the last of four oxidation steps in the cycle, the carbon carrying the hydroxyl group is converted to a carbonyl group, regenerating the oxaloacetate needed for step 1.



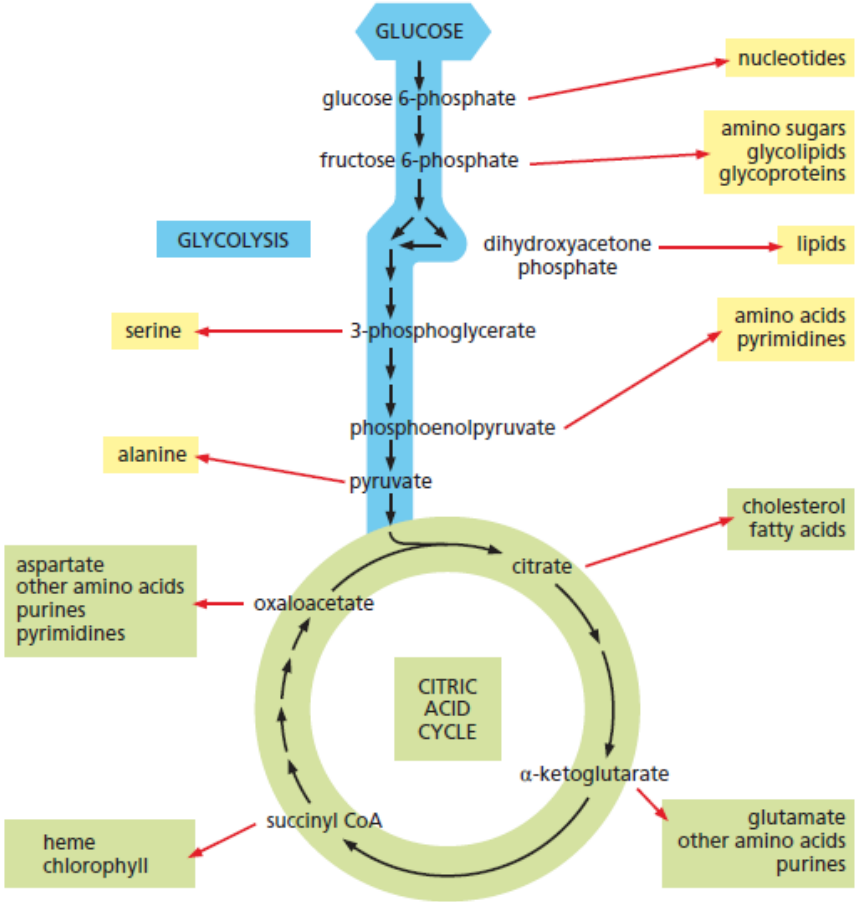
malate oxaloacetate

The Citric Acid Cycle



Overview of the complete citric acid cycle. The two carbons from acetyl CoA that enter this turn of the cycle (shadowed in red) will be converted to CO_2 in subsequent turns of the cycle: it is the two carbons shadowed in blue that are converted to CO_2 in this cycle.

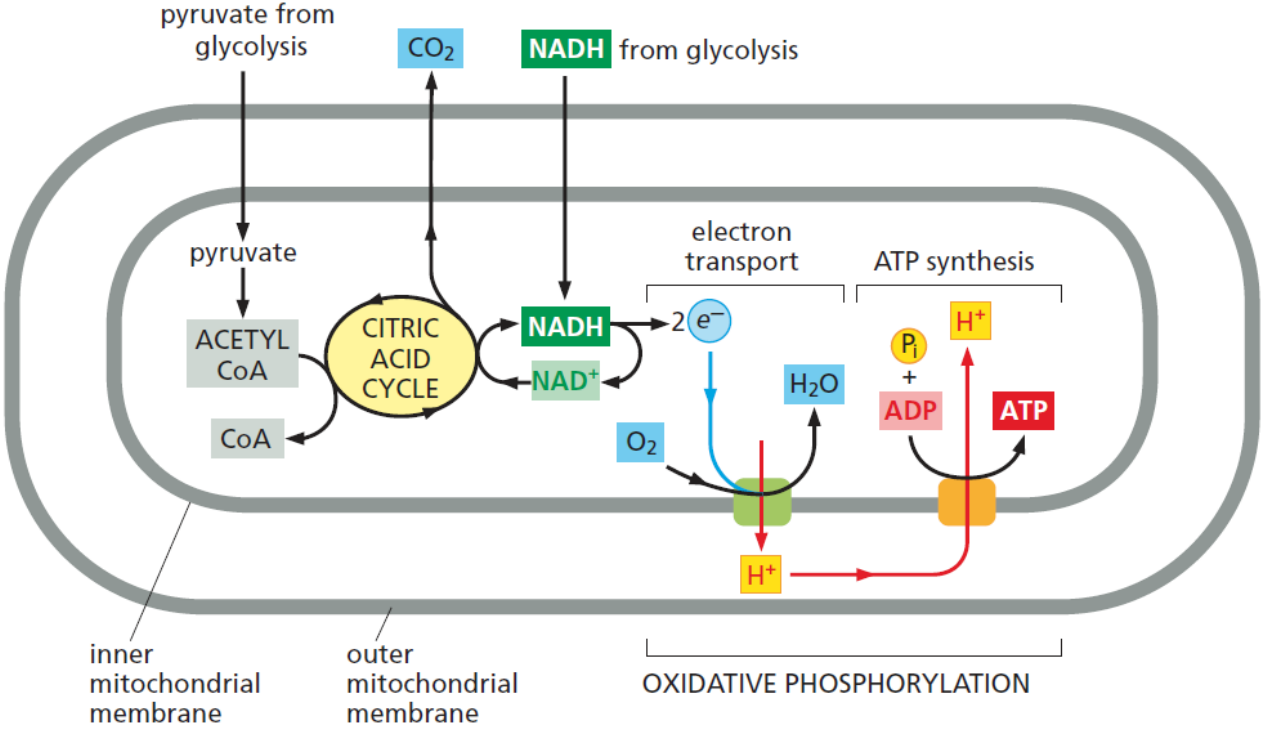
Glycolysis or Citric acid cycle serve precursor molecules



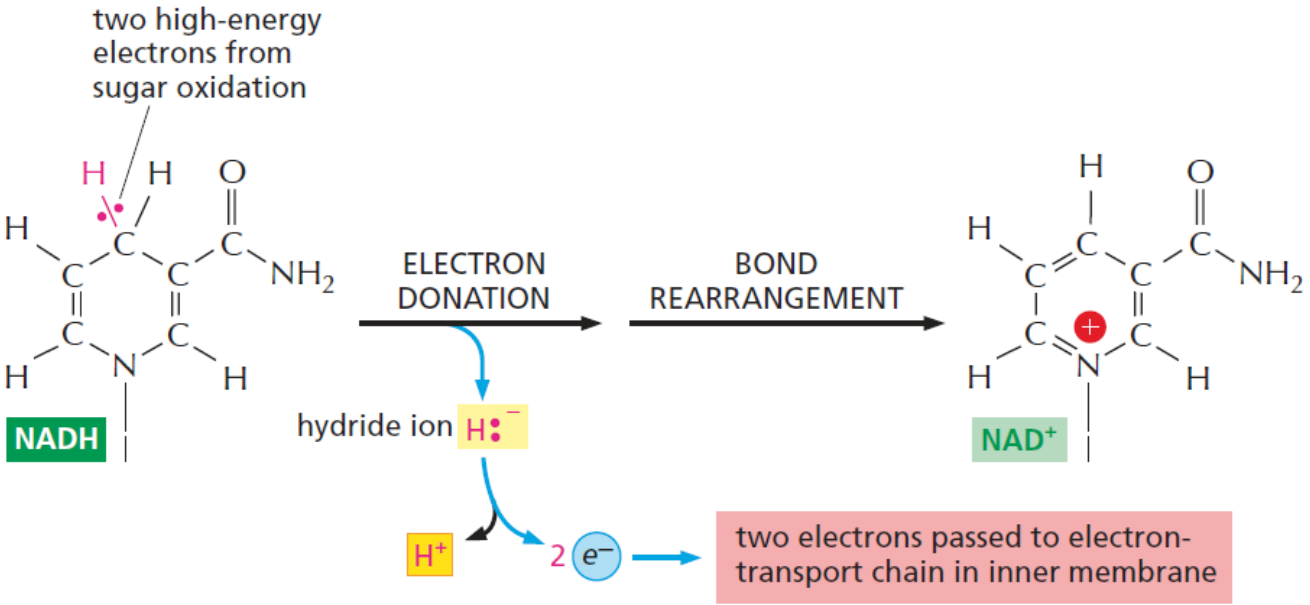
- Catabolic reactions like glycolysis and the citric acid cycle, produce both energy for the cell and the building blocks from which many other organic molecules are made.
- Many intermediates formed in glycolysis and the citric acid cycle are used by anabolic pathways to be converted by series of enzyme-catalyzed reactions into amino acids, nucleotides, lipids, and other small organic molecules that the cell needs.
- Oxaloacetate and α-ketoglutarate from the citric acid cycle, for example, are transferred from the mitochondrial matrix back to the cytosol, where they serve as precursors for the production of many essential molecules, such as the amino acids aspartate and glutamate, respectively.

Oxidative Phosphorylation

Oxidative phosphorylation completes the catabolism of food molecules and generates the bulk of the ATP made by the cell.



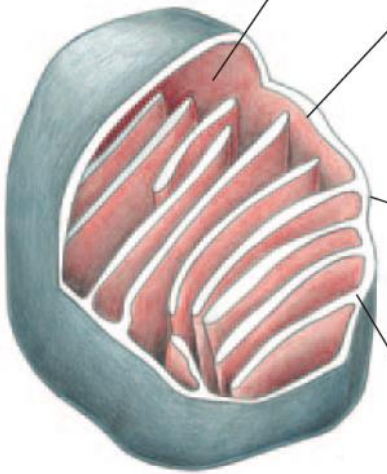
High-energy electrons



Mitochondria is the site for oxidative phosphorylation

- Mitochondria are present in nearly all eukaryotic cells, where they produce the bulk of the cell's ATP. Without mitochondria, eukaryotes would have to rely on the relatively inefficient process of glycolysis for all of their ATP production.
- The importance of mitochondria - patients with an inherited disorder called myoclonic epilepsy and ragged red fiber disease (MERRF) are deficient in multiple proteins required for electron transport. As a result, they typically experience muscle weakness, heart problems, epilepsy, and often dementia. Muscle and nerve cells are especially sensitive to mitochondrial defects, because they need so much ATP to function normally.

Structure of Mitochondria

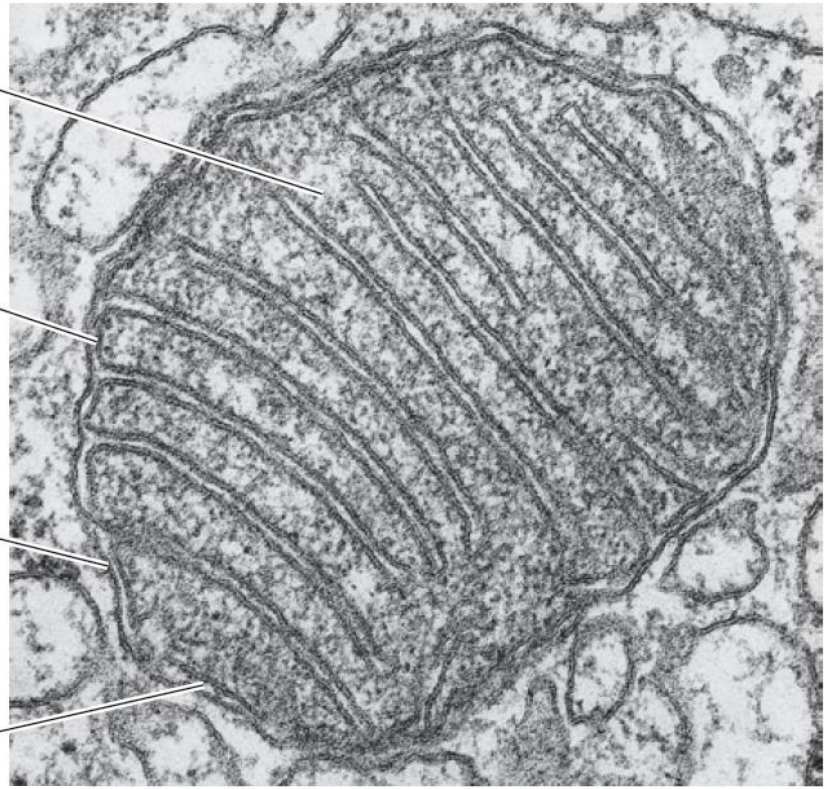


Matrix. This space contains a highly concentrated mixture of hundreds of enzymes, including those required for the oxidation of pyruvate and fatty acids and for the citric acid cycle.

Inner membrane. Folded into numerous cristae, the inner membrane contains proteins that carry out oxidative phosphorylation, including the electron-transport chain and the ATP synthase that makes ATP.

Outer membrane. Because it contains large channel-forming proteins (called porins), the outer membrane is permeable to all molecules of 5000 daltons or less.

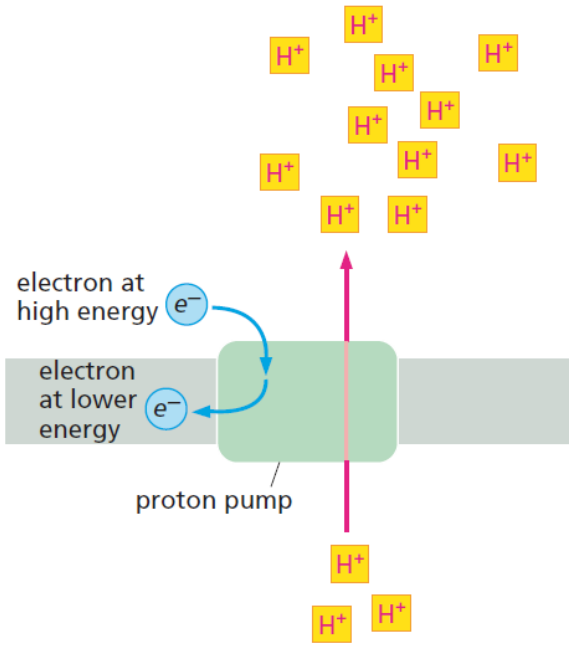
Intermembrane space. This space contains several enzymes that use the ATP passing out of the matrix to phosphorylate other nucleotides. It also contains proteins that are released during apoptosis (discussed in Chapter 18).



Energy generation by a membrane-based mechanism

- The main chemical energy currency in cells is ATP.
- Small amounts of ATP are generated during glycolysis in the cytosol of all cells. But for the majority of cells, most of their ATP is produced by oxidative phosphorylation.
- The generation of ATP by oxidative phosphorylation differs from the way ATP is produced during glycolysis, in that it requires a membrane.
- In eukaryotic cells, oxidative phosphorylation takes place in mitochondria, and it depends on an electron-transport process that drives the transport of protons (H^+) across the inner mitochondrial membrane.
- This membrane-based process for making ATP consists of two linked stages: one sets up an electrochemical proton gradient, the other uses that gradient to generate ATP.

Energy generation by a membrane-based mechanism



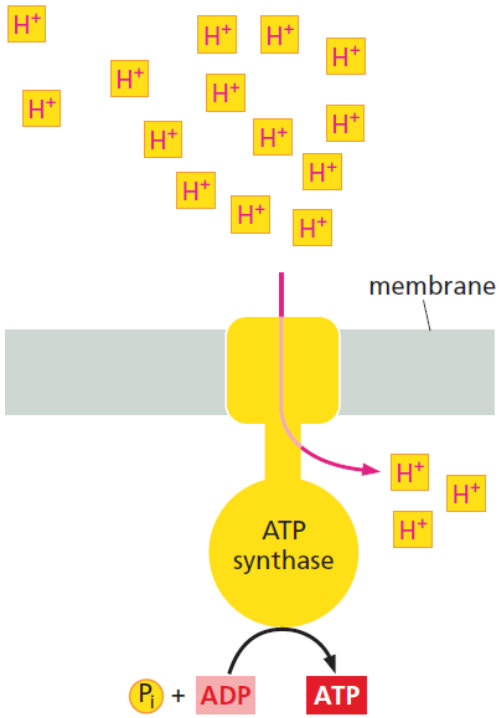
STAGE 1: ENERGY OF ELECTRON TRANSPORT IS USED TO PUMP PROTONS ACROSS MEMBRANE

In Stage 1, high-energy electrons derived from the oxidation of food molecules are transferred along a series of electron carriers—called an electron-transport chain—embedded in the membrane.

These electron transfers release energy that is used to pump protons, derived from the water in cells, across the membrane and thus generate an electrochemical proton gradient.

An ion gradient across a membrane is a form of stored energy that can be harnessed to do useful work when the ions are allowed to flow back across the membrane down their electrochemical gradient

Energy generation by a membrane-based mechanism



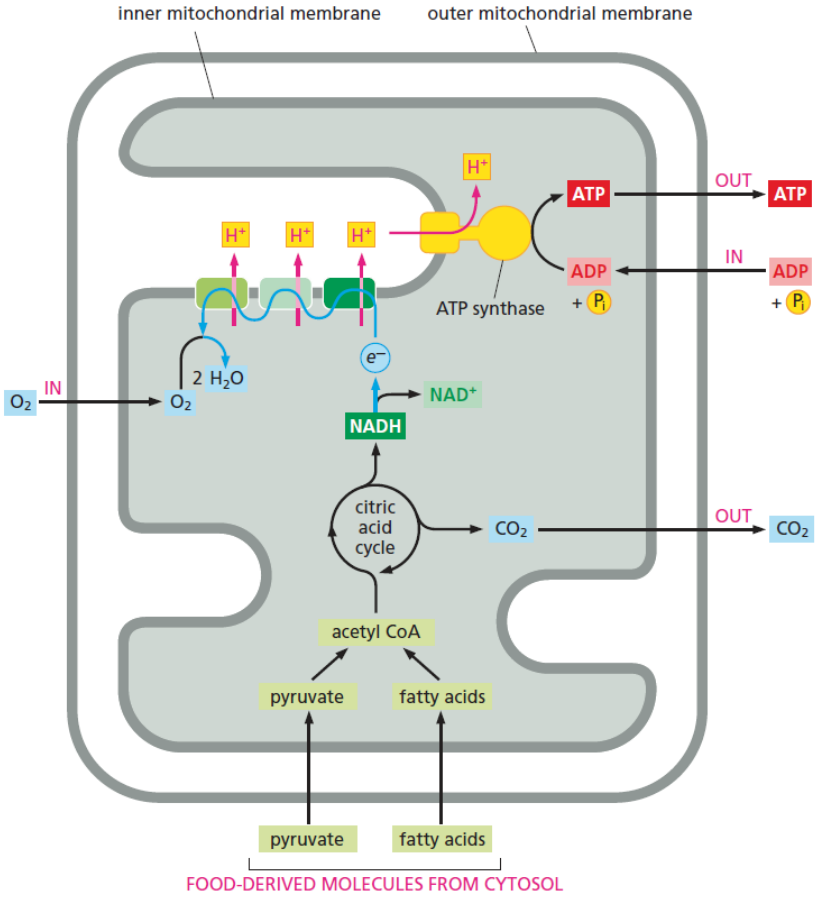
STAGE 2: ENERGY IN THE PROTON GRADIENT IS HARNESSED BY ATP SYNTHASE TO MAKE ATP

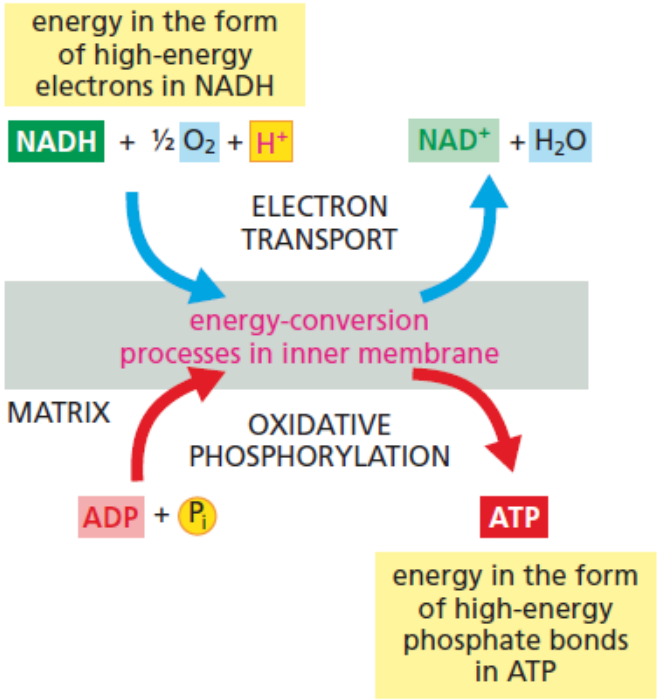
In Stage 2 of oxidative phosphorylation, protons flow back down their electrochemical gradient through a protein complex called ATP synthase, which catalyzes the energy-requiring synthesis of ATP from ADP and inorganic phosphate (Pi).

This ubiquitous enzyme functions like a turbine, permitting the proton gradient to drive the production of ATP.

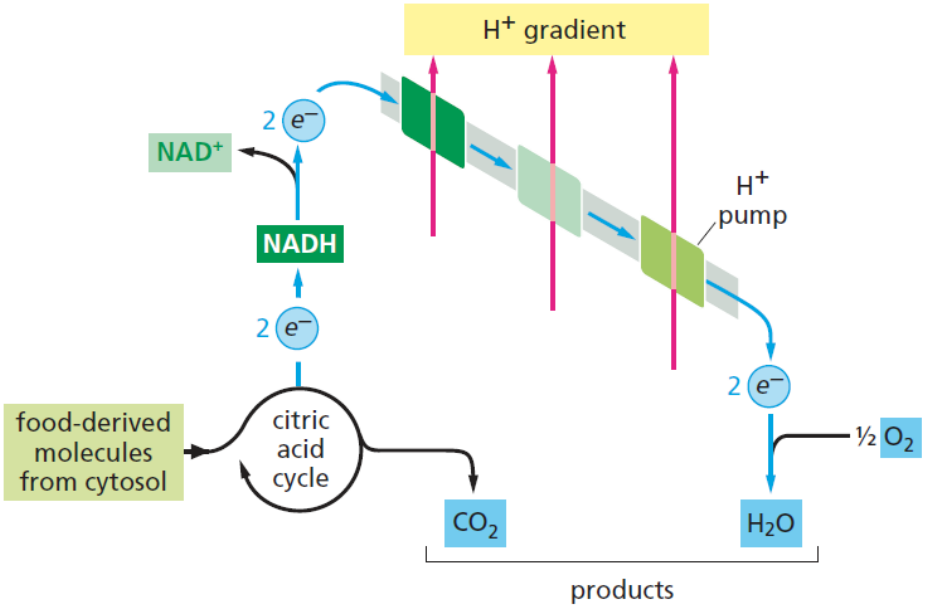
This mechanism for generating energy is called the chemiosmotic hypothesis, because it linked the chemical bond-forming reactions that synthesize ATP ("chemi-") with the membrane transport processes that pump protons ("osmotic," from the Greek osmos, "to push").

Overview of oxidative phosphorylation





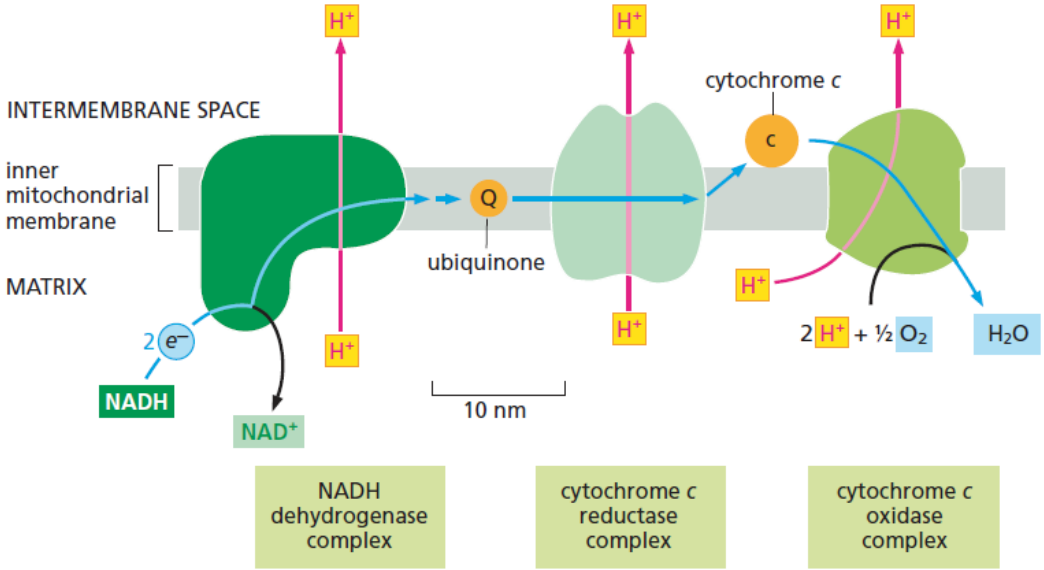
Movement of electrons is coupled with proton pumping



The chemiosmotic generation of energy begins when the activated carriers NADH and $FADH_2$ donate their high-energy electrons to the electron-transport chain in the inner mitochondrial membrane, becoming oxidized to NAD^+ and FAD in the process. The electrons are quickly passed along the chain to molecular oxygen (O_2) to form water (H_2O). The stepwise movement of these high-energy electrons through the components of the electron-transport chain releases energy that can then be used to pump protons across the inner membrane.

Proteins in the Electron-Transport Chain

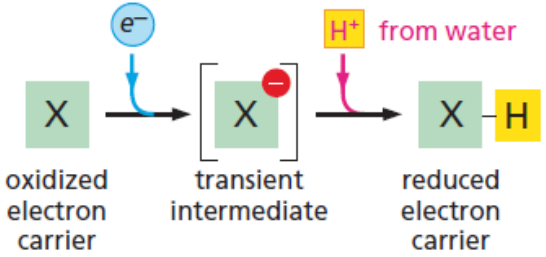
The electron-transport chain—or respiratory chain—that carries out oxidative phosphorylation is present in many copies in the inner mitochondrial membrane. Each chain contains over 40 proteins, grouped into three large respiratory enzyme complexes. These complexes each contain multiple individual proteins, including transmembrane proteins that anchor the complex firmly in the inner mitochondrial membrane.

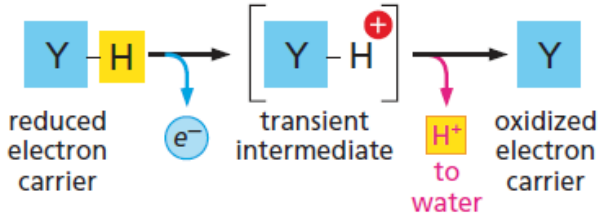


Ubiquinone (Q) and cytochrome c (c) serve as mobile carriers that ferry electrons from one complex to the next.

Electron-Transport Chain

The protons in water are highly mobile: by rapidly dissociating from one water molecule and associating with its neighbor, they can rapidly flit through a hydrogen bonded network of water molecules. Thus water, which is everywhere in cells, serves as a ready reservoir for donating and accepting protons.



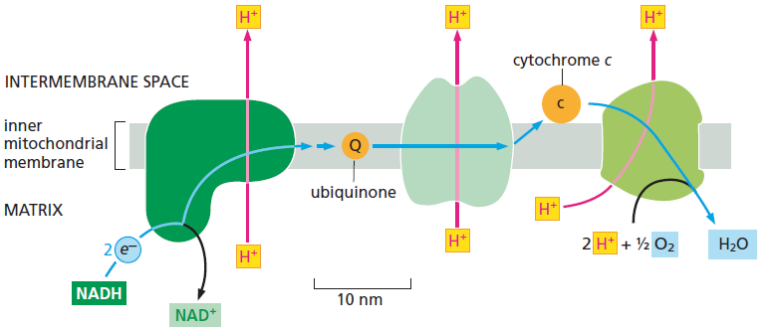


When a molecule is reduced by acquiring an electron (e^-), the electron brings with it a negative charge; in many cases, this charge is immediately neutralized by the addition of a proton from water, so that the net effect of the reduction is to transfer an entire hydrogen atom, $H^+ + e^-$.

Similarly, when a molecule is oxidized, it often loses an electron from one of its hydrogen atoms: in most instances, the electron is transferred to an electron carrier, and the proton is passed on to water.

Electron-Transport Chain

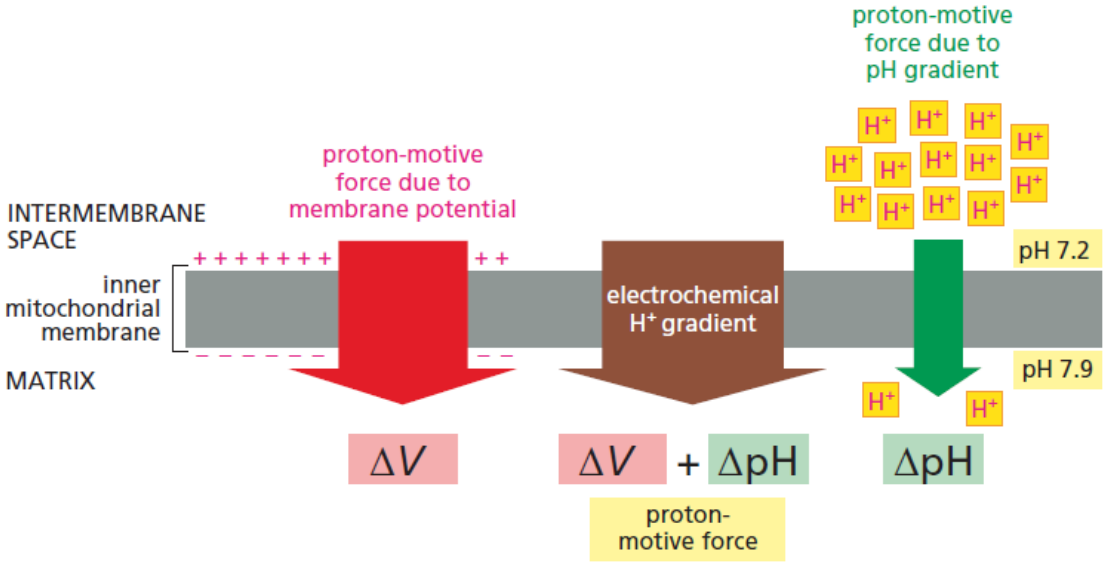
Therefore, in a membrane in which electrons are being passed along an electron-transport chain, it is a relatively simple matter, in principle, to move protons from one side of the membrane to the other. All that is required is that the electron carrier be oriented in the membrane in such a way that it accepts an electron—along with a proton from water—on one side of the membrane, and then releases that proton on the other side of the membrane when the electron is passed on to the next electron carrier molecule in the chain.



This transfer of electrons is energetically favorable: the electrons are passed from electron carriers with weaker electron affinity to those with stronger electron affinity, until they combine with a molecule of O_2 to form water.

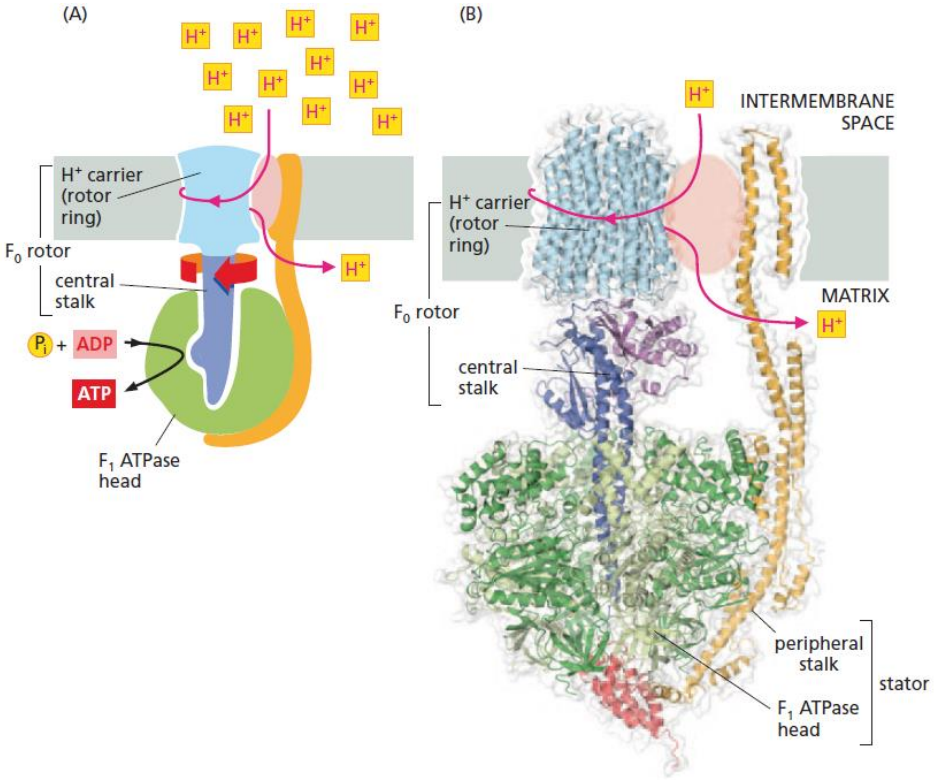
This final reaction is the only oxygen-requiring step in cell respiration, and it consumes nearly all of the oxygen that we breathe.

Proton-motive force



The electrochemical H^+ gradient across the inner mitochondrial membrane includes a large force due to the membrane potential (ΔV) and a smaller force due to the H^+ concentration gradient—that is, the pH gradient (ΔpH). Both forces combine to generate the proton-motive force, which pulls H^+ back into the mitochondrial matrix.

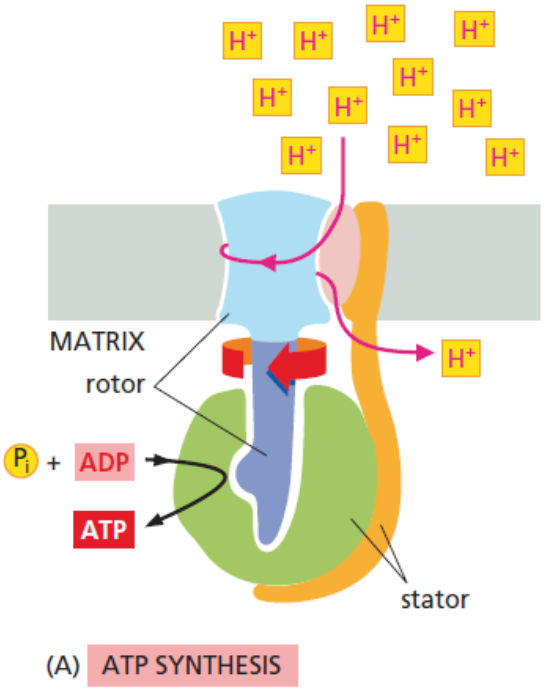
ATP Synthase finally produces ATP



If protons in the intermembrane space were allowed simply to flow back into the mitochondrial matrix, the energy stored in the electrochemical proton gradient would be lost as heat. Such a seemingly wasteful process allows hibernating bears to stay warm.

In most cells, however, the electrochemical proton gradient across the inner mitochondrial membrane is used to drive the synthesis of ATP from ADP and Pi. The device that makes this possible is ATP synthase, a large, multi-subunit protein embedded in the inner mitochondrial membrane.

ATP Synthase finally produces ATP



The part of the protein that catalyzes the phosphorylation of ADP is shaped like a lollipop head and projects into the mitochondrial matrix; it is attached by a central stalk to a transmembrane H^+ carrier. The passage of protons through the carrier causes the carrier and its stalk to spin rapidly, like a tiny motor.

As the stalk rotates, it rubs against proteins in the stationary head, altering their conformation and prompting them to produce ATP. In this way, a mechanical deformation gets converted into the chemical-bond energy of ATP. This fine-tuned sequence of interactions allows ATP synthase to produce more than 100 molecules of ATP per second—3 molecules of ATP per revolution.

ATP Synthase finally produces ATP

- Much of the energy carried by NADH and $FADH_2$ is ultimately converted into the bond energy of ATP. How much ATP each of these activated carriers can produce depends on several factors, including where its electrons enter the respiratory chain.
- The NADH molecules produced in the mitochondrial matrix during the citric acid cycle pass their high energy electrons to the NADH dehydrogenase complex—the first complex in the chain. As the electrons pass from one enzyme complex to the next, they promote the pumping of protons across the inner mitochondrial membrane at each step along the way. In this way, each NADH molecule provides enough net energy to generate about 2.5 molecules of ATP.
- $FADH_2$ molecules, on the other hand, bypass the NADH dehydrogenase complex and pass their electrons to the membrane-embedded mobile carrier ubiquinone. Because these electrons enter further down the respiratory chain than those donated by NADH, they promote the pumping of fewer protons: each molecule of $FADH_2$ thus produces only 1.5 molecules of ATP.

Product yield from glucose metabolism

Process	Direct product	Final ATP yield per molecule of glucose
Glycolysis	2 NADH (cytosolic)	3*
	2 ATP	2
Pyruvate oxidation to acetyl CoA (two per glucose)	2 NADH (mitochondrial matrix)	5
Complete acetyl CoA oxidation (two per glucose)	6 NADH (mitochondrial matrix)	15
	2 $FADH_2$	3
	2 GTP	2
	TOTAL	30

*NADH produced in the cytosol yields fewer ATP molecules than NADH produced in the mitochondrial matrix because the mitochondrial inner membrane is impermeable to NADH. Transporting NADH into the mitochondrial matrix—where it encounters NADH dehydrogenase—thus requires energy.