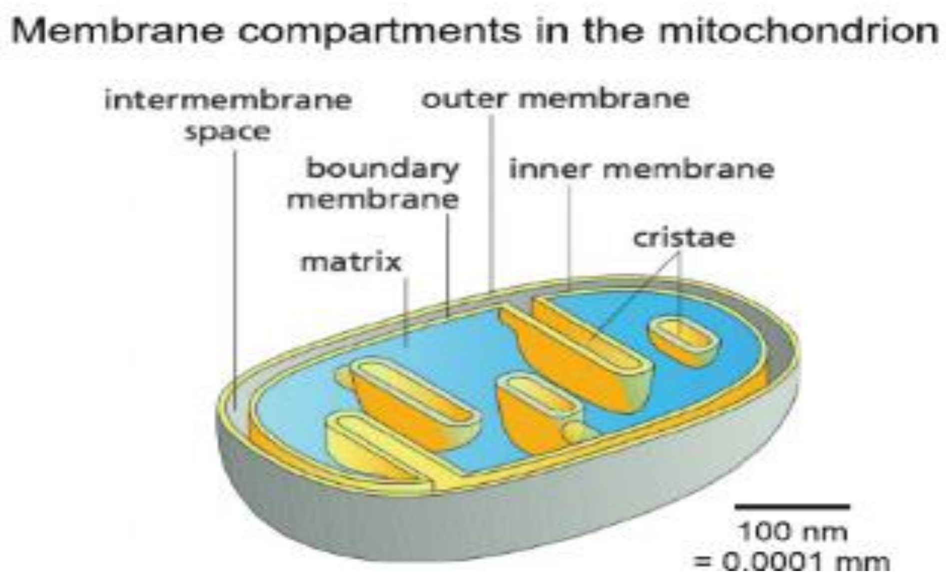
MITOCHONDRIAL MEMBRANES

The mitochondrion (plural mitochondria) is a double membrane-bound organelle found in most eukaryotic organisms. Some cells in some multicellular organisms may, however, lack them (for example, mature mammalian red blood cells). Mitochondria are the powerhouses of the cell. In all eukaryotes that do not depend on photosynthesis, the mitochondria are the main source of adenosine triphosphate (ATP), the energy-rich compound that drives fundamental cell functions.

Structure of the mitochondrial membranes

A mitochondrion contains outer and inner membranes composed of phospholipid bilayers and proteins. The two membranes have different properties. There are five distinct parts:

1. the outer mitochondrial membrane,
2. the intermembrane space (the space between the outer and inner membranes),
3. the inner mitochondrial membrane,
4. the cristae space (formed by infoldings of the inner membrane), and
5. the matrix (space within the inner membrane).



1- Outer membrane:

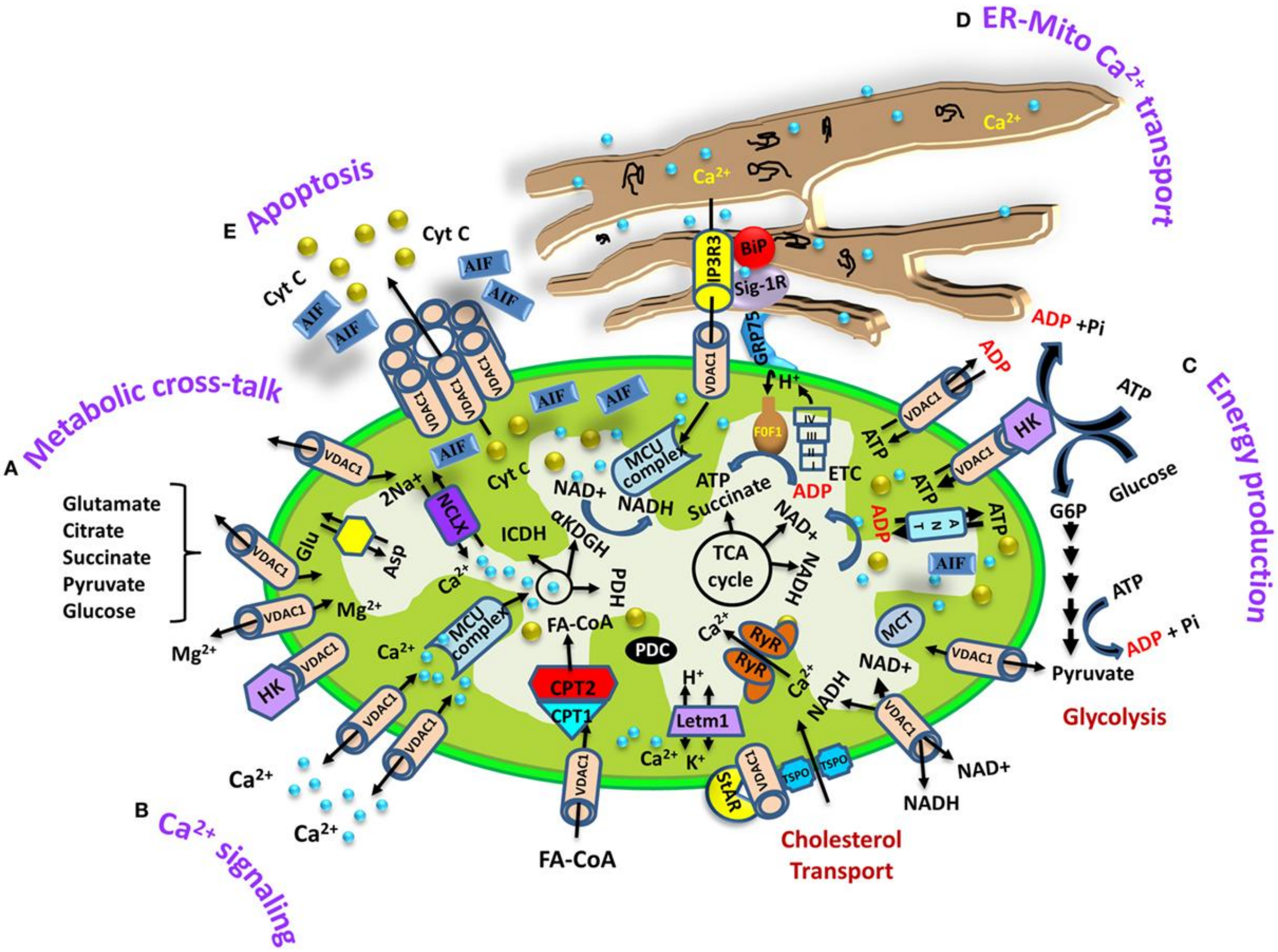
The outer mitochondrial membrane, which encloses the entire organelle, is 60 to 75 angstroms (Å) thick. It has a protein-to-phospholipid ratio similar to that of the cell membrane (about 1:1 by weight).

It contains large numbers of integral membrane proteins called porins. Porin forms a voltage-dependent anion-channel (VDAC) that behaves as a general diffusion pore for small hydrophilic molecules. The VDAC is the primary transporter of nucleotides, ions, and metabolites between the cytosol (intracellular fluid or cytoplasmic matrix) and the intermembrane space.

Larger proteins can enter the mitochondrion if a signaling sequence at their N-terminus binds to a large multisubunit protein called translocase in the outer membrane, which then actively moves them across the membrane.

The outer membrane also contains enzymes involved in such diverse activities as the elongation of fatty acids, oxidation of epinephrine, and the degradation of tryptophan.

The mitochondrial outer membrane can associate with the endoplasmic reticulum (ER) membrane, in a structure called MAM (mitochondriaassociated ER-membrane). This is important in the ER-mitochondria calcium signaling and is involved in the transfer of lipids between the ER and mitochondria.



2- Intermembrane space:

The mitochondrial intermembrane space is the space between the outer membrane and the inner membrane. It is also known as perimitochondrial space.

Because the outer membrane is freely permeable to small molecules, the concentrations of small molecules, such as ions and sugars, in the intermembrane space is the same as in the cytosol.

However, large proteins must have a specific signaling sequence to be transported across the outer membrane, so the protein composition of this space is different from the protein composition of the cytosol. One protein that is localized to the intermembrane space in this way is cytochrome c.

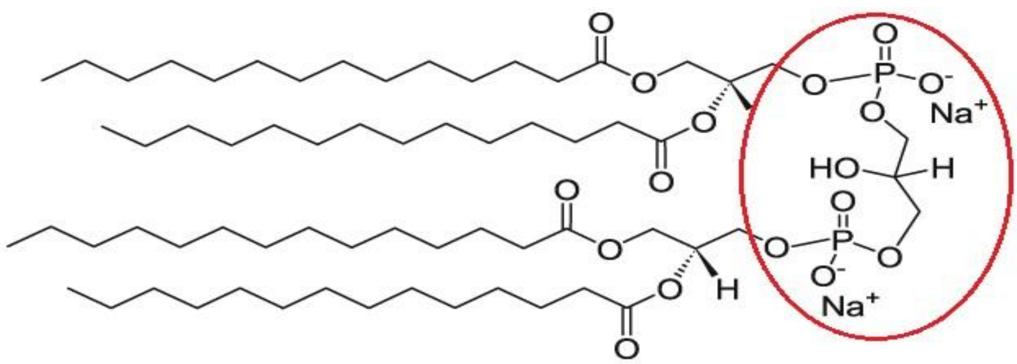
3- Inner membrane:

The inner mitochondrial membrane contains proteins with five types of functions:

1. Those that perform the redox reactions of oxidative phosphorylation
2. ATP synthase, which generates ATP in the matrix
3. Specific transport proteins that regulate metabolite passage into and out of the mitochondrial matrix
4. Protein import machinery
5. Mitochondrial fusion and fission protein

It contains more than 151 different polypeptides and has a very high protein-to-phospholipid ratio. The inner membrane is home to around 1/5 of the total protein in a mitochondrion.

In addition, the inner membrane is rich in an unusual phospholipid, cardiolipin. This phospholipid was originally discovered in cow hearts in 1942 and is usually characteristic of mitochondrial and bacterial plasma membranes. Cardiolipin contains four fatty acids rather than two and may help to make the inner membrane impermeable.



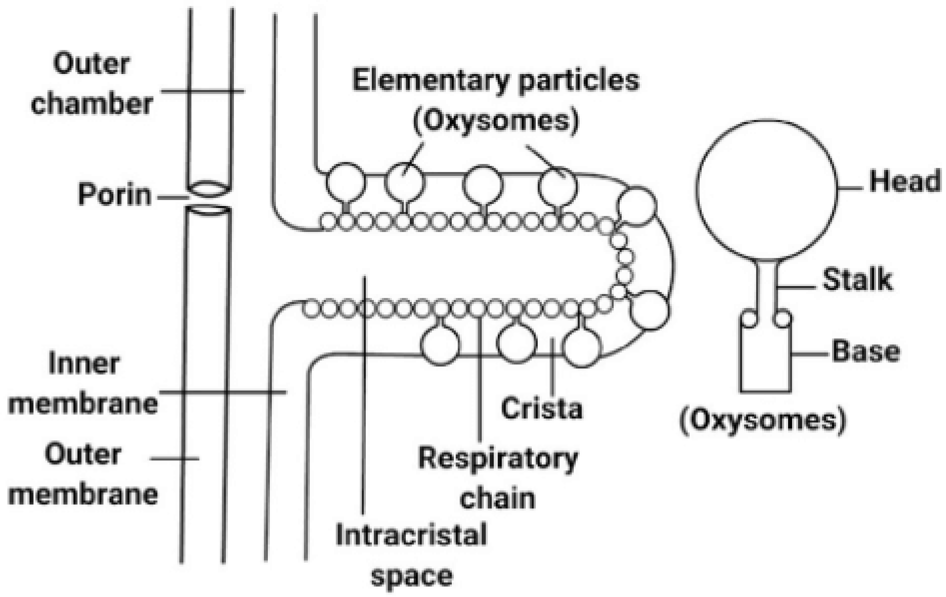
Unlike the outer membrane, the inner membrane does not contain porins and is highly impermeable to all molecules. Almost all ions and molecules require special membrane transporters to enter or exit the matrix. Proteins are ferried into the matrix via the translocase of the inner membrane (TIM) complex. In addition, there is a membrane potential across the inner membrane, formed by the action of the enzymes of the electron transport chain.

4- Cristae:

The inner mitochondrial membrane is compartmentalized into numerous cristae, which expand the surface area of the inner mitochondrial membrane, enhancing its ability to produce ATP.

For typical liver mitochondria, the area of the inner membrane is about five times as large as the outer membrane. This ratio is variable and mitochondria from cells that have a greater demand for ATP, such as muscle cells, contain even more cristae. Mitochondria within the same cell can have substantially different crista-density, the ones that are required to produce more energy, have much more crista-membrane surface.

These folds are studded with small round bodies known as F1 particles or oxysomes. These are not simple random folds but they can affect overall chemiosmotic function. Oxysome has three parts, the bottom or base part is embedded in the membrane. It is known as the F0 particle. The second part extends from the base and it is a protein and is known as F5-F6 particle or the stock part. The third part is enlarged which is also a protein and is attached to the stock part. It is known as F1 particles or the head of the oxysome. The head part acts as ATPase so it helps in the synthesis of ATP due to this reason it is also known as ATP synthetase. The number of oxysome also varies, it can be 1000 to 100000 in a mitochondrion depending on the activity of the cell.



5- Matrix:

The matrix is the space enclosed by the inner membrane. It contains about 2/3 of the total protein in a mitochondrion. The mitochondrial matrix contains the mitochondria's DNA, ribosomes, soluble enzymes, small organic molecules, nucleotide cofactors, and inorganic ions. The enzymes in the matrix facilitate reactions responsible for the production of ATP, such as the citric acid cycle, oxidative phosphorylation, oxidation of pyruvate, and the beta-oxidation of fatty acids. Mitochondria have their own genetic material and the machinery to manufacture their own RNAs and proteins .

Transport systems in the inner mitochondrial membrane

The inner mitochondrial membrane must be impermeable to most molecules, yet much exchange has to take place between the cytosol and the mitochondria. This exchange is mediated by an array of membrane-spanning transporter proteins.

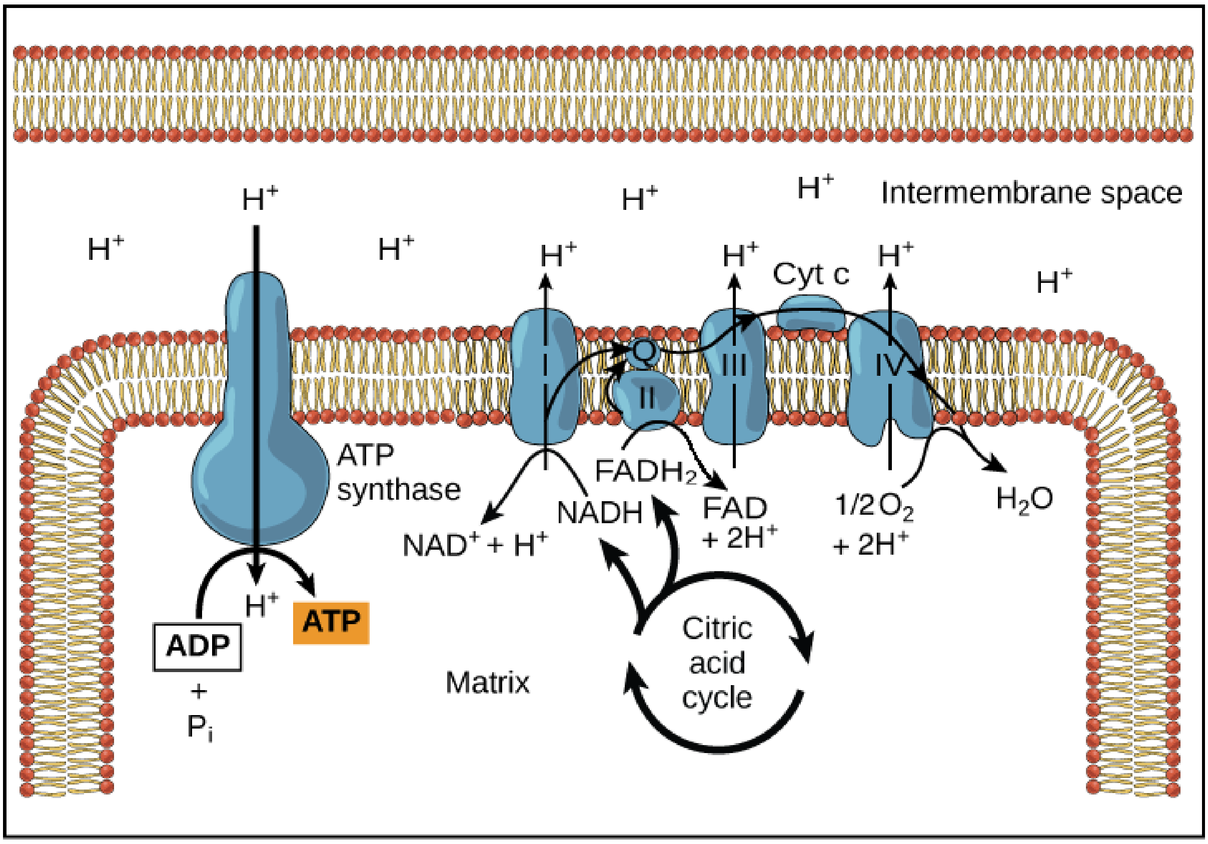
ATP, ADP and phosphate transport:

Oxidative phosphorylation is made up of two closely connected components: the electron transport chain and chemiosmosis. In the electron transport chain, electrons are passed from one molecule to another, and energy released in these electron transfers is used to form an electrochemical gradient. In chemiosmosis, the energy stored in the gradient is used to make ATP.

The **electron transport chain** is a collection of membrane-embedded proteins and organic molecules, most of them organized into four large complexes labeled I to IV. As the electrons travel through the chain, they go from a higher to a lower energy level, moving from less electron-hungry to more electron-hungry molecules. Energy is released in these "downhill" electron transfers, and several of the protein complexes use the released energy to pump protons from the mitochondrial matrix to the intermembrane space, forming a proton gradient.

In the matrix, NADH deposits two electrons at Complex I, turning into NAD^+ and releasing a proton into the matrix. $FADH_2$ in the matrix deposits two electrons at Complex II, turning into FAD and releasing 2 H^+. The electrons from Complexes I and II are passed to the small mobile carrier Q. Q transports the electrons to Complex III, which then passes them to Cytochrome C. Cytochrome C passes the electrons to Complex IV, which then passes them to oxygen in the matrix, forming water. It takes two electrons, 1/2 O_2, and 2 H^+ to form one water molecule. Complexes I, III, and IV use the energy released as electrons move from a higher to a lower energy level to pump protons out of the matrix and into the intermembrane space, generating a proton gradient.

All of the electrons that enter the transport chain come from NADH and $FADH_2$ molecules produced during earlier stages of cellular respiration: glycolysis, pyruvate oxidation, and the citric acid cycle.



Chemiosmosis is the process in which energy from a proton gradient is used to make ATP. The proton motive force will cause H^+ ions to move down their electrochemical gradient and diffuse back into matrix. This diffusion of protons facilitated by the transmembrane enzyme ATP synthase. As the H^+ ions move through ATP synthase they trigger the molecular rotation of the enzyme, synthesising ATP.

NADH enters the ETC at complex I and produces a total of 10 H^+ ions (4 H^+ from complex I, 4 H^+ from complex III, and 2 H^+ from complex IV). ATP-synthase synthesizes 1 ATP for 4 H^+ ions. Therefore, 1 NADH = 10 H+, and 10/4 H+ per ATP = 2.5 ATP per NADH (**some sources round up**).

- Reaction 1: NADH $\longrightarrow$ H^+ + NAD^+ + 2 e-

$FADH_2$ enters the ETC at complex II and produces a total of 6 H+ ions (4 H^+ from complex III, and 2 H^+ from complex IV) ATP-synthase synthesizes 1 ATP for 4 H^+

ions. Therefore, 1 $FADH_2$ = 6 H^+, and 6/4 H^+ per ATP = 1.5 ATP per $FADH_2$ (**some sources round up**).

- Reaction 2: $FADH_2 \longrightarrow 2H^+ + FAD^+ + 2e^-$