Chapter 8
Mitochondria and Cellular Respiration

Cellular respiration is the process of oxidizing food molecules, like glucose, to carbon dioxide and water. The energy released is trapped in the form of **ATP** for use by all the energy-consuming activities of the cell. The process occurs in two phases:

1. **Glycolysis**, the breakdown of glucose to pyruvic acid
2. The complete **oxidation of pyruvic acid** to carbon dioxide and water

In eukaryotes, glycolysis occurs in the cytosol. The remaining processes take place in **mitochondria**.

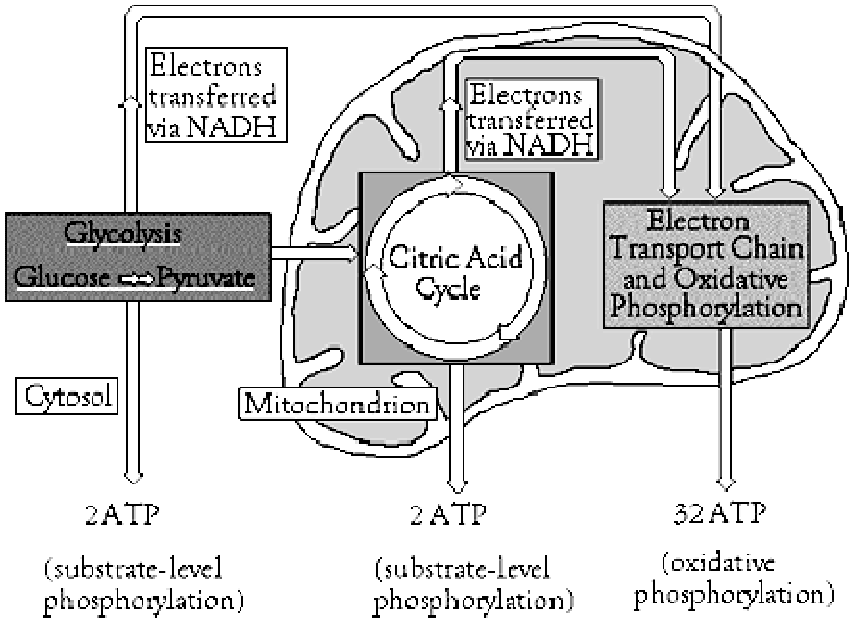

Fig.8.1. Pathways of Cellular Respiration

8.1. Glycolysis

Glycolysis is the **anaerobic catabolism** of glucose. It occurs in virtually all cells. In eukaryotes, it occurs in the cytosol.

$$C_6H_{12}O_6 + 2NAD^+ \rightarrow 2C_3H_4O_3 + 2NADH + 2H^+$$

The free energy stored in 2 molecules of **pyruvic acid** is somewhat less than that in the original glucose molecule. Some of this difference is captured in 2 molecules of **ATP**.

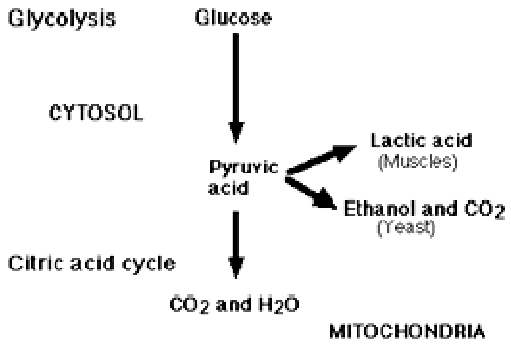

Fig.8.2. Glycolysis

(a) The Fates of Pyruvic Acid

(i) In YEAST

Pyruvic acid is decarboxylated and reduced by NADH to form a molecule of carbon dioxide and one of ethanol.

$$C_3H_4O_3 + NADH + H^+ \rightarrow CO_2 + C_2H_5OH + NAD^+$$

This accounts for the bubbles and alcohol in, for examples, beer and champagne. The process is called **alcoholic fermentation**. The process is energetically wasteful because so much of the free energy of glucose (some 95%) remains in the alcohol (a good fuel!).

(ii) In active MUSCLES

Pyruvic acid is reduced by NADH forming a molecule of **lactic acid**.

$$C_3H_4O_3 + NADH + H^+ \rightarrow C_3H_6O_3 + NAD^+$$

The process is called **lactic acid fermentation**. The process is energetically wasteful because so much free energy remains in the lactic acid molecule. (It can also be debilitating because of the drop in pH as the lactic acid produced in overworked muscles is transported out into the blood.)

(iii) In MITOCHONDRIA

Pyruvic acid is oxidized completely to form carbon dioxide and water. The process is called **cellular respiration**. Approximately 40% of the energy in the original glucose molecule is trapped in molecules of **ATP**.

8.2. Mitochondria

Mitochondria are membrane-enclosed organelles distributed through the cytosol of most eukaryotic cells. Their main function is the conversion of the potential energy of food molecules into ATP.

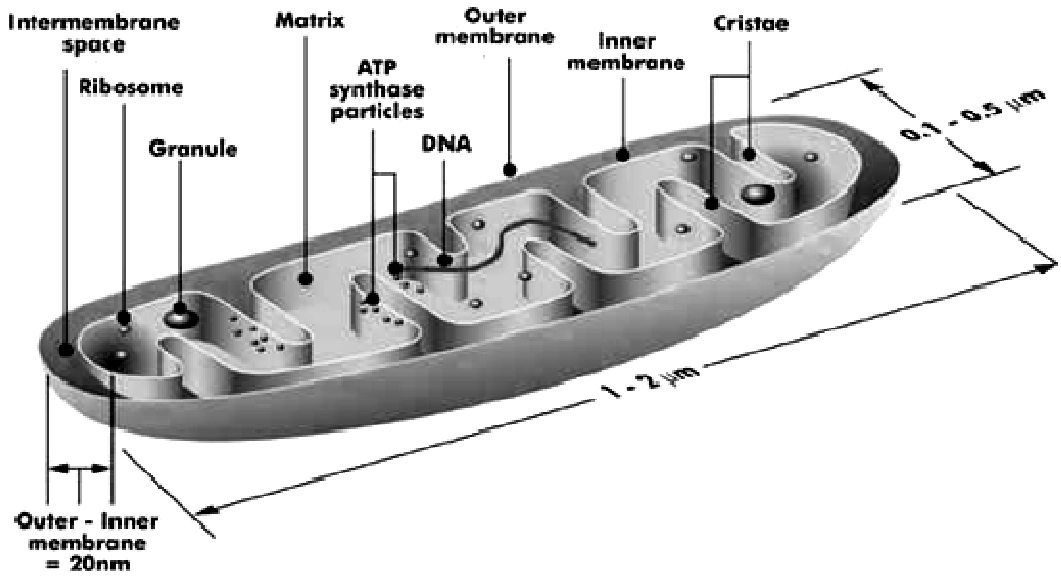

Fig.8.3. Structure of a mitochondrion

Mitochondria have an **outer membrane** that encloses the entire structure an **inner membrane** that encloses a fluid-filled **matrix** between the two is the **intermembrane space**. The inner membrane is elaborately folded with shelflike **cristae** projecting into the matrix. A small number (some 5–10) circular molecules of **DNA**

(a) The Outer Membrane

The outer membrane contains many complexes of integral membrane proteins that form channels through which a variety of molecules and ions move in and out of the mitochondrion.

(b) The Inner Membrane

The inner membrane contains 5 complexes of integral membrane proteins:

1. **NADH dehydrogenase** (Complex I)
2. Succinate dehydrogenase (Complex II)
3. **Cytochrome C Reductase** (Complex III; also known as the cytochrome b-c_1 complex)
4. **cytochrome C Oxidase** (Complex IV)
5. **ATP synthase** (Complex V)

(c) The Matrix

The matrix contains a complex mixture of soluble enzymes that catalyze the respiration of pyruvic acid and other small organic molecules. Here pyruvic acid is oxidized by NAD^+ producing NADH + H^+ decarboxylated producing a molecule of carbon dioxide (CO_2) and a 2-carbon fragment of acetate bound to coenzyme A forming acetyl-CoA

8.3. The Citric Acid Cycle

This 2-carbon fragment is donated to a molecule of **oxaloacetic acid**. The resulting molecule of **citric acid** (which gives its name to the process) undergoes the series of enzymatic steps shown in the diagram. The final step regenerates a molecule of oxaloacetic acid and the cycle is ready to turn again.

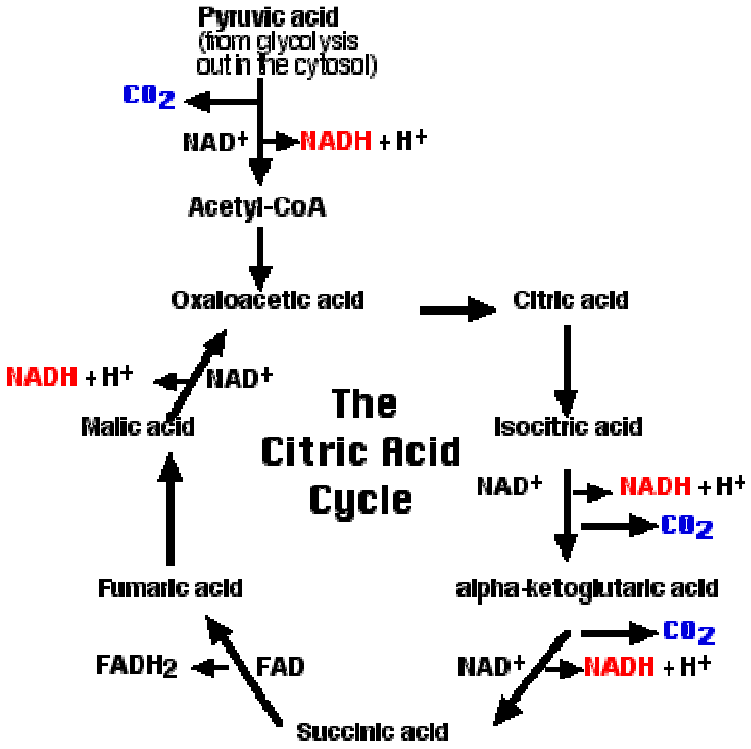

Fig.8.2. Citric Acid Cycle

Summary:

1. Each of the 3 carbon atoms present in the pyruvate that entered the mitochondrion leaves as a molecule of carbon dioxide (**CO_2**).
2. At 4 steps, a pair of electrons (**$2e^-$**) is removed and transferred to **NAD^+** reducing it to **$NADH + H^+$**.
3. At one step, a pair of electrons is removed from succinic acid and reduces **FAD** to **$FADH_2$**.

The electrons of NADH and $FADH_2$ are transferred to the **electron transport chain**.

8.4. The Electron Transport Chain

The electron transport chain consists of 3 complexes of integral membrane proteins the **NADH dehydrogenase** complex (I), the **cytochrome c reductase** complex (III), the **cytochrome c oxidase** complex (IV) and two freely-diffusible molecules **ubiquinone** and **cytochrome c** that shuttle electrons from one complex to the next.

The electron transport chain accomplishes:

1. The stepwise transfer of electrons from **NADH** (and **$FADH_2$**) to **oxygen** molecules to form (with the aid of protons) water molecules (**H_2O**); (Cytochrome c can only transfer one electron at a time, so cytochrome c oxidase must wait until it has accumulated 4 of them before it can react with oxygen.)
2. Harnessing the energy released by this transfer to the pumping of protons (**H^+**) from the **matrix** to the **intermembrane space**.
3. Approximately 20 protons are pumped into the intermembrane space as the 4 electrons needed to reduce oxygen to water pass through the respiratory chain.

4. The gradient of protons formed across the inner membrane by this process of active transport forms a miniature battery.
5. The protons can flow back down this gradient, re-entering the matrix, only through another complex of integral proteins in the inner membrane, the **ATP synthase** complex.

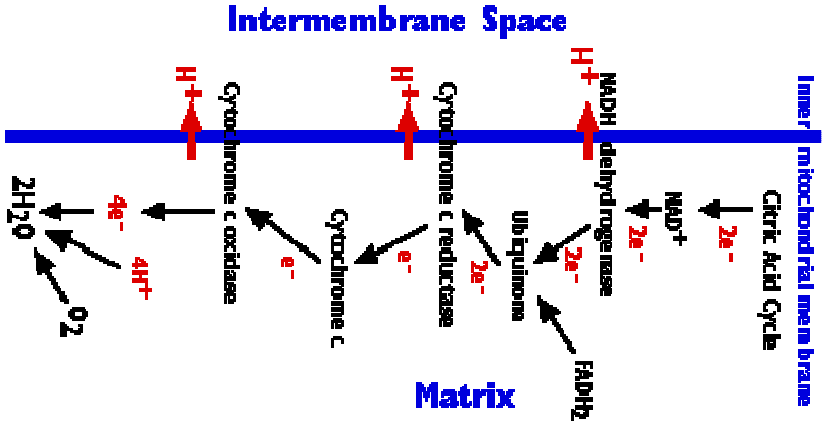

Fig.8.4. The Electron Transport Chain

8.5. Chemiosmosis in Mitochondria

The energy released as electrons pass down the gradient from NADH to oxygen is harnessed by three enzyme complexes of the respiratory chain (I, III, and IV) to pump **protons** (H^+) **against** their concentration gradient **from the matrix** of the mitochondrion **into the intermembrane space** (an example of active transport).

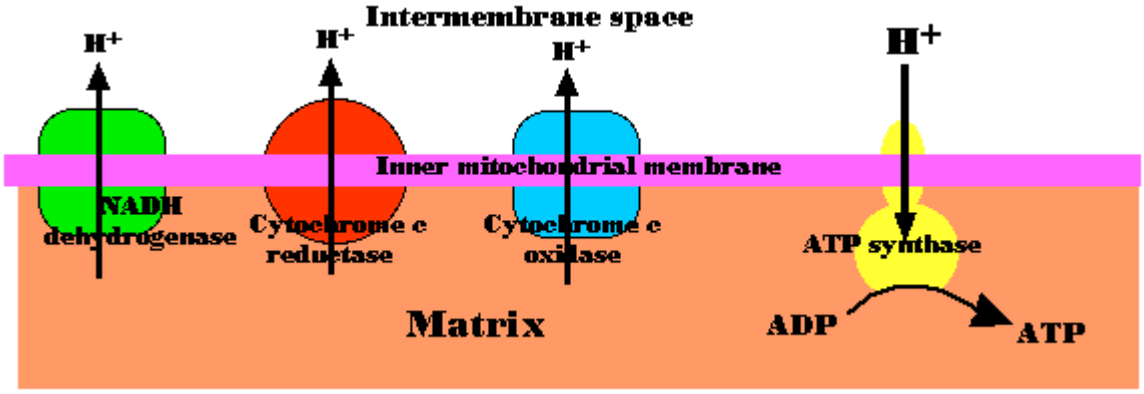

Fig.8.5. Chemiosmosis in Mitochondria

As their concentration increases there (which is the same as saying that the pH decreases), a strong diffusion gradient is set up. The only exit for these protons is through the **ATP synthase** complex. As in **chloroplasts**, the energy released as these protons flow down their gradient is harnessed to the synthesis of **ATP**. The process is called **chemiosmosis** and is an example of **facilitated diffusion**.

8.6. ATPs Balance Sheet

It is tempting to try to view the synthesis of ATP as a simple matter of stoichiometry (the fixed ratios of reactants to products in a chemical reaction). But (with 3 exceptions) **it is not**. Most of the ATP is generated by the proton gradient that develops across the inner

mitochondrial membrane. The number of protons pumped out as electrons drop from NADH through the respiratory chain to oxygen is theoretically large enough to generate, as they return through ATP synthase, 3 ATPs per electron pair (but only 2 ATPs for each pair donated by $FADH_2$). With 12 pairs of electrons removed from each glucose molecule, 10 by NAD^+ (so 10x3=30); and 2 by $FADH_2$ (so 2x2=4), this could generate 34 ATPs. Add to this the 4 ATPs that are generated by the 3 exceptions and one arrives at 38. But the energy stored in the proton gradient is also used for the **active transport** of several molecules and ions through the inner mitochondrial membrane into the matrix. NADH is also used as **reducing agent** for many cellular reactions. So the actual yield of ATP as mitochondria respire varies with conditions. It probably seldom exceeds **30**.
The three exceptions to this are that there is a stoichiometric production of ATP does occur at one step in the citric acid cycle yielding 2 ATPs for each glucose molecule. This step is the conversion of **alpha-ketoglutaric** acid to **succinic acid** and at two steps in **glycolysis** yielding 2 ATPs for each glucose molecule.

8.7. The Interconversion of Fuels

The immediate source of energy for most cells is **glucose**. How energy is extracted from glucose is described in **Glycolysis** and in **Cellular Respiration**. But glucose is not the only fuel on which cells depend. Other **carbohydrates**, **fats** and even **proteins**
may in certain cells or at certain times be used as a source of **ATP**. The complexity of the mechanism by which cells use glucose may make you fervently hope that a similarly-constructed system is not needed for each kind of fuel. And indeed it is not. One of the great advantages of the step-by-step **oxidation** of glucose into CO_2 and H_2O is that several of the intermediate compounds formed in the process link glucose **metabolism** to the metabolism of other food molecules. For example, when fats are used as fuel, the **glycerol** portion of the molecule is converted into **PGAL** and enters the **glycolytic pathway** at that point**. Fatty acids** are converted into molecules of **acetyl-CoA** and enter the **respiratory pathway** to be oxidized in the mitochondria.
The **amino acids** liberated by the **hydrolysis** of proteins can also serve as fuel. First, the nitrogen is removed, a process called **deamination**. The remaining fragments then enter the respiratory pathway at several points. For examples, the amino acids **Gly, Ser, Ala,** and **Cys** are converted into pyruvic acid and enter the mitochondria to be respired. The acetyl-CoA and several intermediates in the **citric acid cycle** serve as entry points for other amino acid fragments.
These links thus permit the respiration of excess fats and proteins in the diet. No special mechanism of cellular respiration is needed by those animals that depend largely on ingested fats (e.g., many birds) or proteins (e.g., carnivores) for their energy supply. Much of the protein we consume is ultimately converted into glucose (a process called **gluconeogenesis**) to provide fuel for the brain and other tissues.
Although all our foods are interconvertible to some extent, they are not completely so. In other words, no single food can supply all our anabolic needs. We can indeed synthesize many fats from glucose, but certain unsaturated fats cannot be synthesized and must be taken in directly in our diet. These are **linoleic acid, linolenic acid,** and **arachidonic acid**. All are unsaturated; that is, have double bonds. Although we can synthesize 11 of the amino acids from carbohydrate **precursors,** we must obtain 9 others (the "**essential amino acids**") directly.

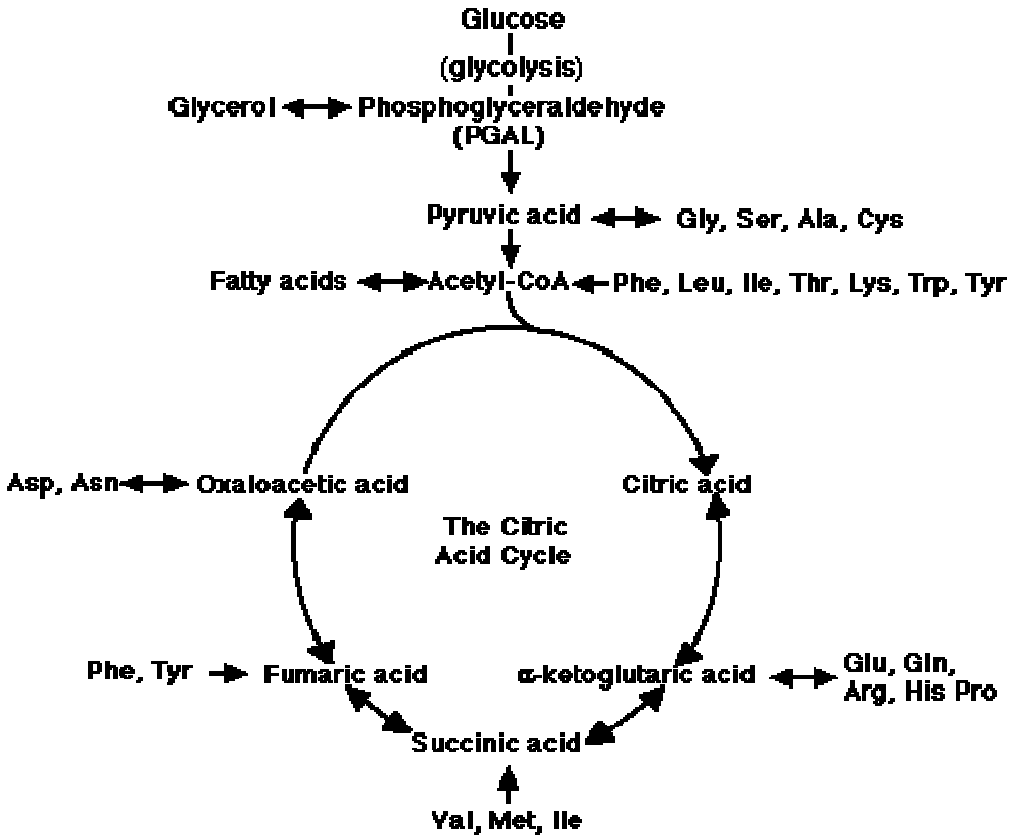

Fig.8.6. Pathways of The Interconversion of Fuels

Many of the points that connect carbohydrate metabolism to the catabolism of fats and proteins serve as two-way valves (indicated in the figure by double-headed arrows). They provide points of entry not only for the catabolism (cellular respiration) of fatty acids, glycerol, and amino acids, but for their synthesis (anabolism) as well. Thus the catabolic breakdown of starches can lead (through acetyl-CoA and PGAL) to the synthesis of fat.

8.8. Mitochondrial DNA (mtDNA)

The human mitochondrion contains 5–10 identical, circular molecules of DNA. Each consists of 16,569 base pairs carrying the information for **37 genes** which encode 2 different molecules of **ribosomal RNA** (**rRNA**), 22 different molecules of **transfer RNA** (**tRNA**) (at least one for each amino acid) and **13 polypeptides.** The **rRNA** and **tRNA** molecules are used in the machinery that synthesizes the 13 polypeptides. The 13 polypeptides are subunits of the protein complexes in the inner mitochondrial membrane, including subunits of **NADH dehydrogenase**, **cytochrome c oxidase**, and **ATP synthase**. However, each of these protein complexes also requires subunits that are encoded by nuclear genes, synthesized in the cytosol, and imported from the cytosol into the mitochondrion. Nuclear genes also encode hundreds of other proteins that must be imported into the mitochondrion.

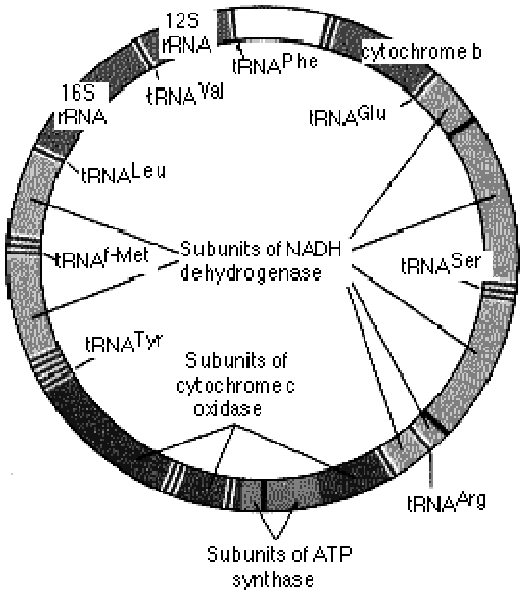

Fig.8.7. Mitochondrial DNA

Many of the features of the mitochondrial genetic system resemble those found in bacteria. This has strengthened the theory that mitochondria are the evolutionary descendants of a bacterium that established an **endosymbiotic** relationship with the ancestors of eukaryotic cells early in the history of life on earth. However, many of the genes needed for mitochondrial function have since moved to the nuclear genome.

The recent sequencing of the complete genome of **Rickettsia prowazekii** has revealed a number of genes closely related to those found in mitochondria. Perhaps **rickettsias** are the closest living descendants of the **endosymbionts** that became the mitochondria of eukaryotes.