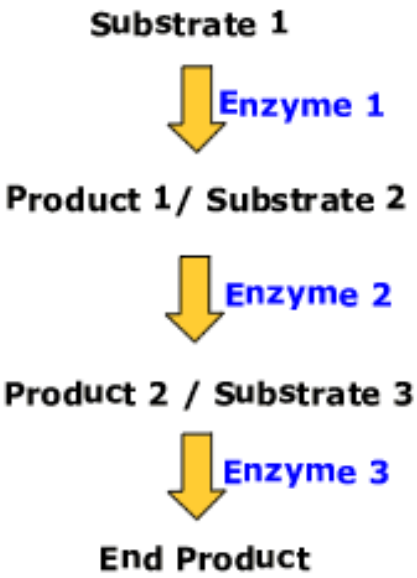
# Metabolism

It is a series of chemical reactions inside the cell with the help of different types of enzymes. The chemical compounds involved in this process known as metabolites. This process can be linier (Glycolysis), cyclic (Krebs cycle) or spiral (Fatty acid synthesis).

It's divided in two pathways on the basis of synthesis and breakdown of compounds.

(1) Anabolic pathway: It's involve synthesis of compounds and usually endergonic in nature.

(2) Catabolic pathway: Its involve breakdown of compounds and usually exergonic in nature.




**Characteristics of metabolic pathway are:**

(1) They are usually irreversible.

(2) Those in eukaryotic cells occurs in specific cellular locations.

(3) Each one has a first committed step.

(4) They are regulated. Regulation occurs in following different ways :

(i) Availability of substrate, the rate of reaction depends on substrate concentration.

(ii) Allosteric regulation of enzyme by a metabolic intermediate or co-enzyme.

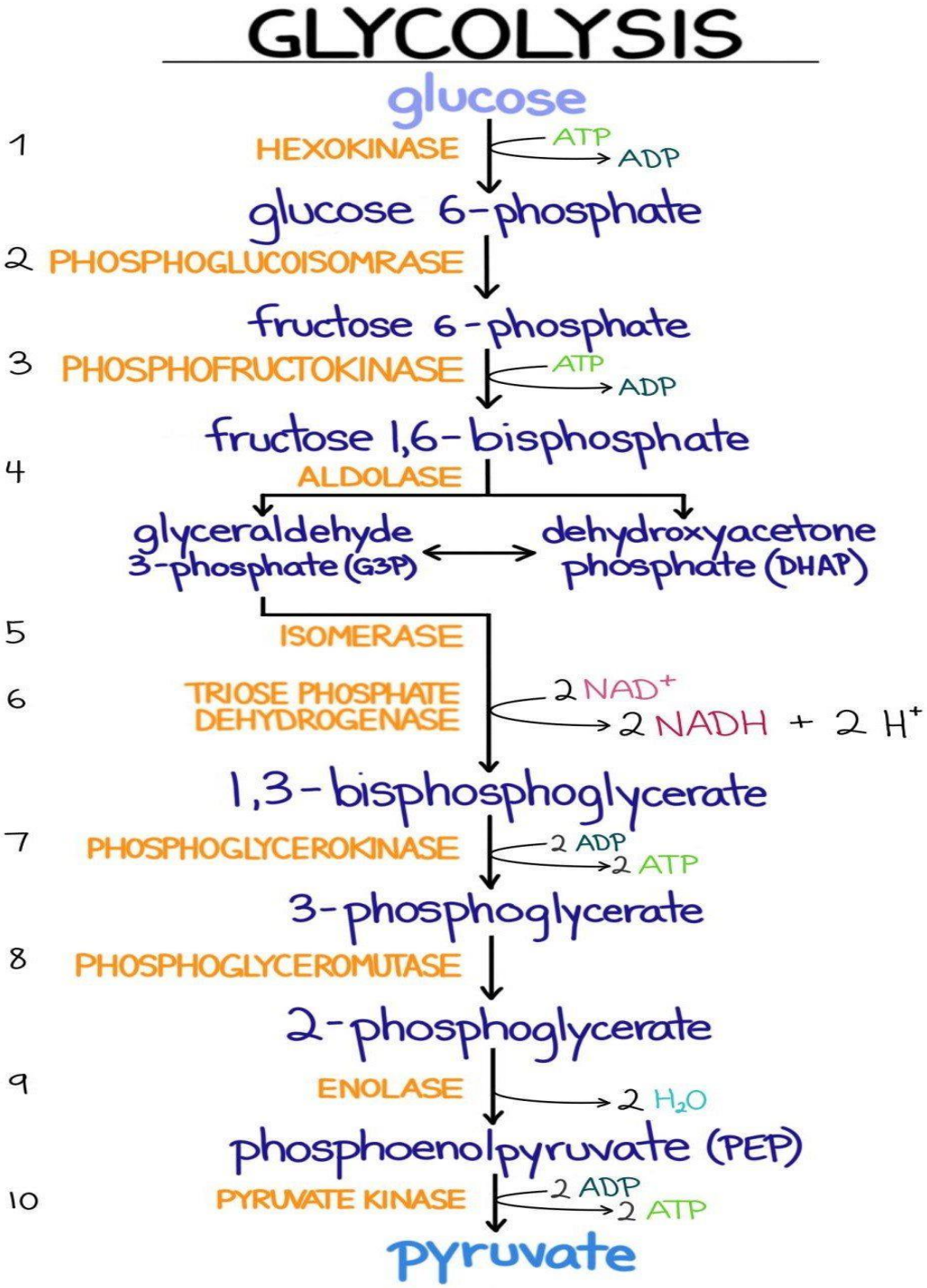
(iii) By extra cellular signal such as growth factors and hormones that act from outside the cell in multicellular organisms changes the cellular concentration of a enzyme by altering the rate of its synthesis or degradation.

# Glycolysis

Glycolysis means lysis or breakdown of sugar (Glucose).it's also known as *Embden-Meyerhof* pathway. Glycolysis is a catabolic process which take place inside the cytosol of the cell. Glycolysis is an oxidative process in which one mole of glucose is partially oxidized in to two mole of pyruvate in a series reactions. It is a unique pathway that occurs in both aerobic and anaerobic condition. On the basis of energy utilization and energy production further classified in two phase

(1) Preparatory phase: first to five steps are included in this phase because in these steps utilization of energy take place.

(2) Payoff phase: Six to last steps are included in this phase because in these steps generation of energy take place.




**Steps of glycolysis**

**1 (Phosphorylation) -** In this steps glucose molecule phosphorylated by ATP and gets converted in to Glucose-6- Phosphate with the help of enzymes Hexokinase. Hexokinase requires metal ions such as $Mg^{2+}$ for activity. It is an irreversible step

**2 (Isomerization)** A readily reversible rearrangement of the chemical structure (isomerization) moves from carbon 1 to carbon 2, to form a ketos from an aldose sugar with the help of phosphor-glucoisomerase enzymes.

**3 (Phosphorylation**) fructose -6-phosphate is phosphorylated by ATP to fructose 1,6 bis phosphate with the help of enzyme phosphofructokinase.

**4 (Cleavage)** The fructose 1,6 bis phosphate each cleaved to produce 2,3 carbon molecules glyceraldehyde-3-phosphate (G3P) and dihydroxyacetone phosphate (DHAP) with the help of enzyme Aldolase.

**5 (Isomerization)** The enzyme triose-phosphate isomerase rapidly inter- converts the molecules dihydroxyacetone phosphate (DHAP) and glyceraldehyde 3-phosphate (GAP). Glyceraldehyde phosphate is removed / used in next step of Glycolysis**.**

**6-(Glyceraldehyde-3-phosphate Dehydrogenase)** In this step, two main events take place: 1) glyceraldehyde-3-phosphate is oxidized by the coenzyme nicotinamide adenine dinucleotide (NAD); 2) the molecule is phosphorylated by the addition of a free phosphate group. The enzyme that catalyzes this reaction is glyceraldehyde-3-phosphate dehydrogenase (GAPDH).

**7-(Phosphoglycerate Kinase)** In this step, 1,3 bis-phosphoglycerate is converted to 3-phosphoglycerate by the enzyme phosphoglycerate kinase (PGK). This reaction involves the loss of a phosphate group from the starting material. The phosphate is transferred to a molecule of ADP that yields our first molecule of ATP. Since we actually have two molecules of 1,3 bis-phosphoglycerate (because there were two 3-carbon products from stage 1 of glycolysis), we actually synthesize two molecules of ATP at this step. With this synthesis of ATP, we have cancelled the first two molecules of ATP that we used, leaving us with a net of 0 ATP molecules up to this stage of glycolysis.

**8-** (**Phosphoglycerate Mutase)** This step involves a simple rearrangement of the position of the phosphate group on the 3 phosphoglycerate molecule, making it 2 phosphoglycerate. The molecule responsible for catalysing this reaction is called phosphoglycerate mutase (PGM). A mutase is an enzyme that catalyzes the transfer of a functional group from one position on a molecule to another.

**9-(Enolase)** This step involves the conversion of 2 phosphoglycerate to phosphoenolpyruvate (PEP). The reaction is catalyzed by the enzyme enolase. Enolase works by removing a water group, or dehydrating the 2 phosphoglycerate.

**10- (Pyruvate Kinase)** The final step of glycolysis converts phosphoenolpyruvate into pyruvate with the help of the enzyme pyruvate kinase. As the enzyme's name suggests, this reaction involves the transfer of a phosphate group. The phosphate group attached to the 2′ carbon of the PEP is transferred

to a molecule of ADP, yielding ATP. Again, since there are two molecules of PEP, here we actually generate 2 ATP molecules**.**

**Total energy gain from Glycolysis –**

**Steps 1 and 3 = – 2ATP**

**Steps 7 and 10 = + 4 ATP**

**Net "visible" ATP produced = 2.**

## Formation of Acetyl CoA:

**Pyruvate formed in glycolysis enters the mitochondrial matrix. It undergoes oxidative decarboxylation to form two molecules of Acetyl CoA. The reaction is catalysed by pyruvate dehydrogenase enzyme.**

$$2Pyruvate + 2NAD^{+} + 2CoA \xrightarrow{Pyruvate\ dehydrogenase} 2AcetylCoA + 2NADH + CO_2$$

## Krebs cycle (TCA or Citric Acid Cycle):

It is the common pathway for complete oxidation of carbohydrates, proteins and lipids as they are metabolised to acetyl coenzyme A or other intermediates of the cycle. The Acetyl CoA produced enters the Tricarboxylic acid cycle or Citric acid cycle. Glucose is fully oxidized in this process. The acetyl CoA combines with 4-carbon compound oxaloacetate to form 6C citrate. In this process, 2 molecules of CO2 are released and oxaloacetate is recycled. Energy is stored in ATP and other high energy compounds like NADH and FADH2.

**Krebs cycle Steps**

It is an eight-step process. Krebs cycle takes place in the matrix of mitochondria under aerobic condition.

Step 1: The first step is the condensation of acetyl CoA with 4-carbon compound oxaloacetate to form 6C citrate, coenzyme A is released. The reaction is catalysed by *citrate synthase*.

Step 2: Citrate is converted to its isomer, isocitrate. The enzyme *aconitase* catalyses this reaction.

Step 3: Isocitrate undergoes dehydrogenation and decarboxylation to form 5C **α**-ketoglutarate. A molecular form of $CO_2$ is released. *Isocitrate dehydrogenase* catalyses the reaction. It is an $NAD^+$ dependent enzyme. $NAD^+$ is converted to NADH.

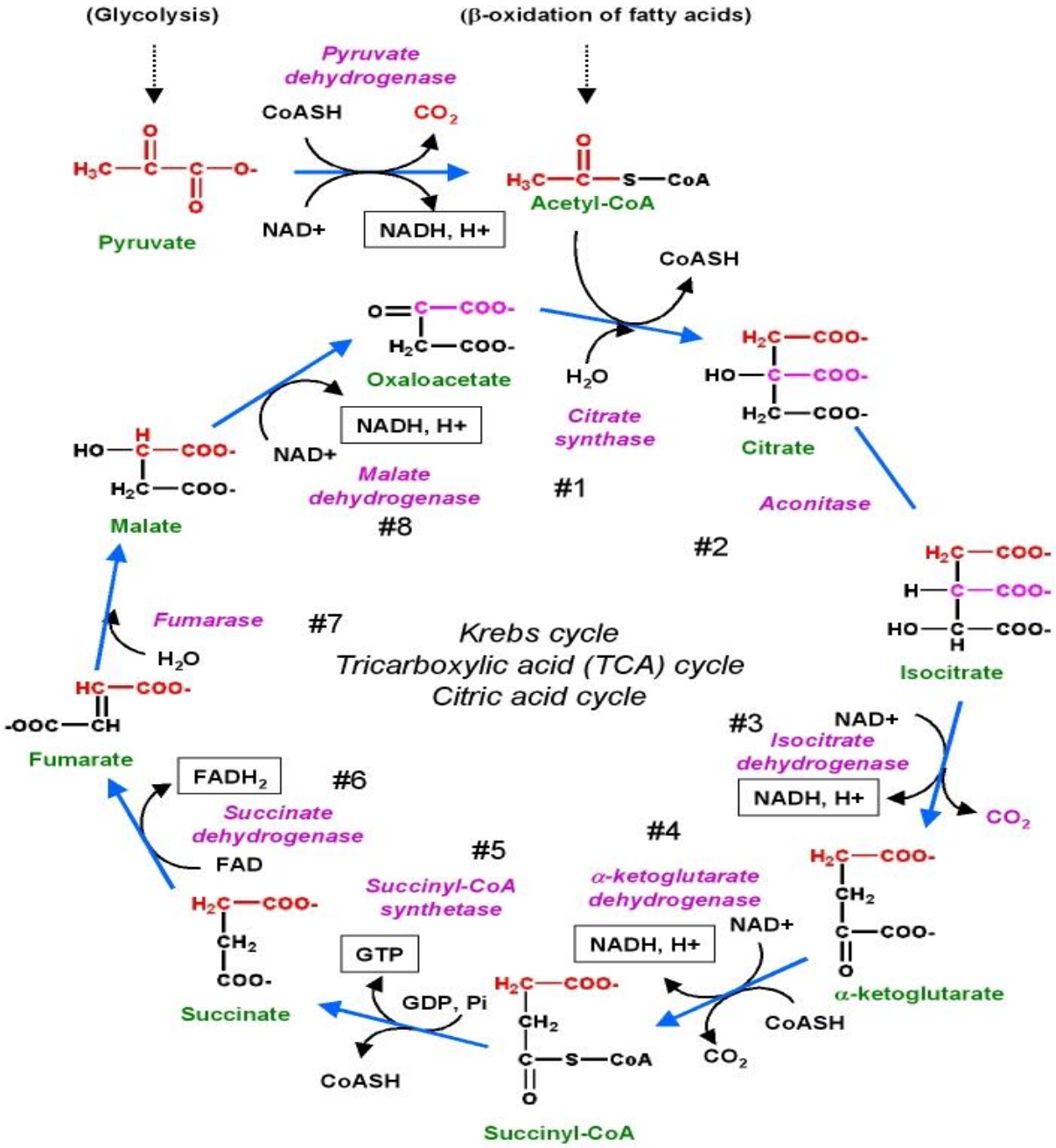
Step 4: **α**-ketoglutarate undergoes oxidative decarboxylation to form succinyl CoA, a 4C compound. The reaction is catalyzed by ***α-ketoglutarate dehydrogenase*** enzyme complex. One molecule of $CO_2$ is released and $NAD^+$ is converted to NADH.

Step 5: Succinyl CoA forms succinate. The enzyme *succinyl CoA synthetase* catalyses the reaction. This is coupled with substrate-level phosphorylation of GDP to get GTP. GTP transfers its phosphate to ADP forming ATP.

Step 6: Succinate is oxidised by the enzyme *succinate dehydrogenase* to fumarate. In the process, FAD is converted to $FADH_2$.

Step 7: Fumarate gets converted to malate by addition of one $H_2O$. The enzyme catalysing this reaction is *fumarase*.

Step 8: Malate is dehydrogenated to form oxaloacetate, which combines with another molecule of acetyl CoA and starts the new cycle. Hydrogens removed, get transferred to $NAD^+$ forming NADH. *Malate dehydrogenase* catalyses the reaction.




**Krebs cycle Summary**

**Location**: Krebs cycle occurs in the mitochondrial matrix

**Krebs cycle reactants:** Acetyl CoA, which is produced from the end product of glycolysis, i.e. pyruvate and it condenses with 4 carbon oxaloacetate, which is generated back in the Krebs cycle

**Krebs cycle products**

**Each citric acid cycle forms the following products:**

- **2 molecules of $CO_2$ are released. Removal of $CO_2$ or decarboxylation of citric acid takes place at two places:**
    1. In the conversion of isocitrate (6C) to **α**-ketoglutarate (5C)
    2. In the conversion of **α**-ketoglutarate (5C) to succinyl CoA (4C)

- 1 ATP is produced in the conversion of succinyl CoA to succinate
- 3 $NAD^+$ are reduced to NADH and 1 $FAD^+$ is converted to $FADH_2$ in the following reactions:
    1. Isocitrate to **α**-ketoglutarate → NADH
    2. **α**-ketoglutarate to succinyl CoA → NADH
    3. Succinate to fumarate → $FADH_2$
    4. Malate to Oxaloacetate → NADH

Note that 2 molecules of Acetyl CoA are produced from oxidative decarboxylation of 2 pyruvates so two cycles are required per glucose molecule.

**To summarize, for complete oxidation of a glucose molecule, Krebs cycle yields 4 $CO_2$, 6NADH, 2 $FADH_2$ and 2 ATPs.**

**Each molecule of NADH can form 2-3 ATPs and each $FADH_2$ gives 2 ATPs on oxidation in the electron transport chain.**

**Krebs cycle equation**

**To Sum up**

$$2Acetyl\ CoA + 6NAD^+ + 2\ FAD\ +\ 2\ ADP\ +\ 2\ P_i\ +\ 2\ H_2O \rightarrow\ 4\ CO_2\ +\ 6\ NADH\ +\ 2\ FADH_2\ +\ 2\ ATP\ +\ 2\ CoA$$

**Significance of Krebs Cycle**

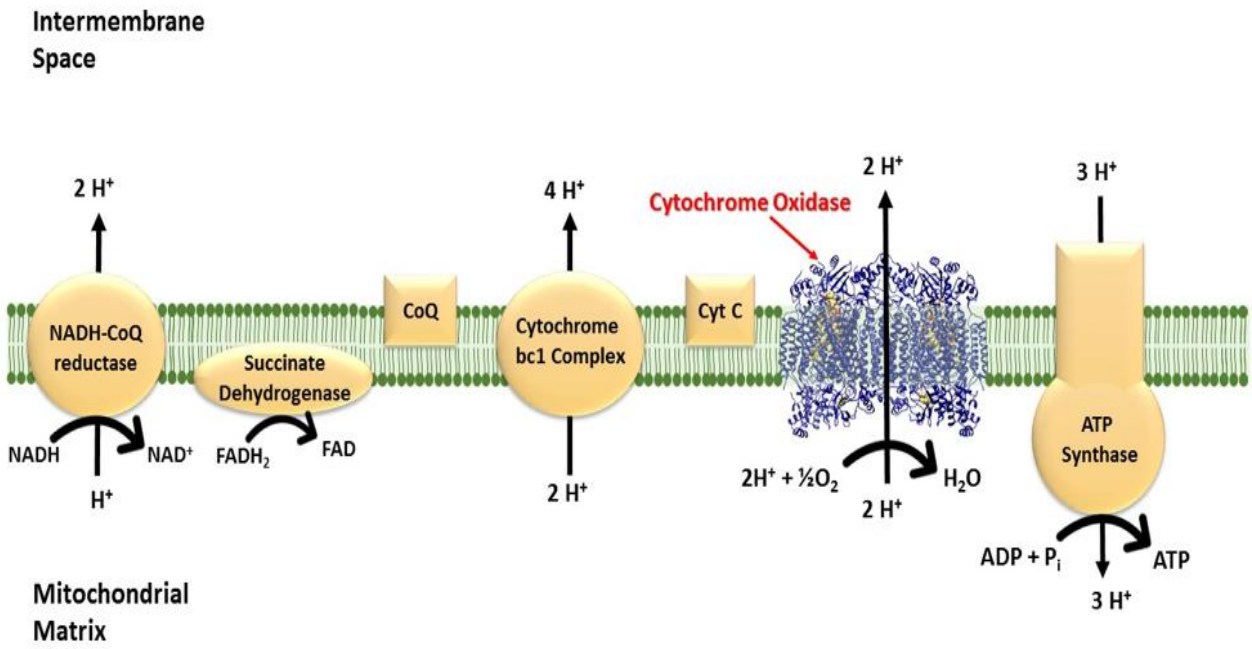
- Krebs cycle or Citric acid cycle is the final pathway of oxidation of glucose, fats and amino acids
- Many animals are dependent on nutrients other than glucose as an energy source
- Amino acids (metabolic product of proteins) are deaminated and get converted to pyruvate and other intermediates of the Krebs cycle. They enter the cycle and get metabolised e.g. alanine is converted to pyruvate, glutamate to **α**-ketoglutarate, aspartate to oxaloacetate on deamination
- Fatty acids undergo ***β***-oxidation to form acetyl CoA, which enters the Krebs cycle
- It is the major source of ATP production in the cells. A large amount of energy is produced after complete oxidation of nutrients
- It plays an important role in gluconeogenesis and lipogenesis and interconversion of amino acids
- Many intermediate compounds are used in the synthesis of amino acids, nucleotides, cytochromes and chlorophylls, etc.
- Vitamins play an important role in the citric acid cycle. Riboflavin, niacin, thiamin and pantothenic acid as a part of various enzymes cofactors (FAD, NAD) and coenzyme A
- Regulation of Krebs cycle depends on the supply of $NAD^+$ and utilization of ATP in physical and chemical work
- The genetic defects of the Krebs cycle enzymes are associated with neural damage
- As most of the biological processes occur in the liver to a significant extent, damage to liver cells has a lot of repercussions. Hyperammonemia occurs in liver diseases and leads to

convulsions and coma. This is due to reduced ATP generation as a result of the withdrawal of **α**-ketoglutarate and formation of glutamate, which forms glutamine

## Electron transport system

Electron Transport Chain is a series of compounds where it makes use of electrons from electron carrier to develop a chemical gradient. It could be used to power oxidative phosphorylation. The molecules present in the chain comprises enzymes that are protein complex or proteins, peptides and much more. Large amounts of ATP could be produced through a highly efficient method termed oxidative phosphorylation. ATP is a fundamental unit of metabolic process. The electrons are transferred from electron donor to the electron acceptor leading to the production of ATP. It is one of the vital phases in the electron transport chain. Compared to any other part of cellular respiration the large amount of ATP is produced in this phase.

Electron transport is defined as a series of redox reaction that is similar to the relay race. It is a part of aerobic respiration. It is the only phase in glucose metabolism that makes use of atmospheric oxygen. When electrons are passed from one component to another until the end of the chain the electrons reduce molecular oxygen thus producing water. The requirement of oxygen in the final phase could be witnessed in the chemical reaction that involves the requirement of both oxygen and glucose.



# Electron Transport Chain in Mitochondria

A complex could be defined as a structure that comprises a weak protein, molecule or atom that is weakly connected to a protein. The plasma membrane of prokaryotes comprises multi copies of the electron transport chain.

**Complex 1- NADH-Q oxidoreductase:** It comprises enzymes consisting of iron-sulfur and FMN. Here two electrons are carried out to the first complex aboard NADH. FMN is derived from vitamin B2.

**Q and Complex 2- Succinate-Q reductase:** FADH2 that is not passed through complex 1 is received directly from complex 2. The first and the second complexes are connected to a third complex through compound ubiquinone (Q). The Q molecule is soluble in water and moves freely in the hydrophobic core of the membrane. In this phase, an electron is delivered directly to the electron protein chain. The number of ATP obtained at this stage is directly proportional to the number of protons that are pumped across the inner membrane of the mitochondria.

**Complex 3- Cytochrome c reductase:** The third complex is comprised of Fe-S protein, Cytochrome b, and Cytochrome c proteins. Cytochrome proteins consist of the heme group. Complex 3 is responsible for pumping protons across the membrane. It also passes electrons to the cytochrome c where it is transported to the 4th complex of enzymes and proteins. Here, Q is the electron donor and Cytochrome C is the electron acceptor.

**Complex 4- Cytochrome c oxidase:** The 4th complex is comprised of cytochrome c, a and a3. There are two heme groups where each of them is present in cytochromes c and a3. The cytochromes are responsible for holding oxygen molecule between copper and iron until the oxygen content is reduced completely. In this phase, the reduced oxygen picks two hydrogen ions from the surrounding environment to make water.