AEROBIC RESPIRATION

Aerobic respiration is a vital biological process through which organisms execute the complete oxidation of glucose, harnessing its stored energy to synthesize a substantial number of ATP molecules essential for cellular metabolism. Primarily occurring within the mitochondria of eukaryotic cells, this intricate process is reliant upon the presence of oxygen (O_2). By engaging in aerobic respiration, organisms achieve the comprehensive breakdown of organic substances in the presence of oxygen, resulting in the liberation of carbon dioxide (CO_2), water, and a significant amount of energy embedded within the substrate. This mode of respiration predominates among higher organisms.

For aerobic respiration to occur within the mitochondria, the pyruvic acid generated during glycolysis is translocated from the cytoplasm into the mitochondria. The pivotal events in aerobic respiration encompass:

- The thorough oxidation of pyruvate through the gradual removal of all hydrogen atoms, leading to the formation of three molecules of CO_2. This process unfolds in two stages:
- Formation of Acetyl coenzyme A.
- Tricarboxylic acid cycle (TCA cycle) or Krebs cycle or Citric acid cycle, which transpires within the mitochondrial matrix.
- The conveyance of the electrons extracted as part of the hydrogen atoms to molecular O_2, concurrently facilitating the synthesis of ATP via the Electron Transport System (ETS). This phase unfolds on the inner membrane of the mitochondria.

Formation of Acetyl coenzyme A or Oxidative decarboxylation:

- Pyruvate, derived from the glycolytic breakdown of carbohydrates in the cytosol, undergoes oxidative decarboxylation upon entry into the mitochondrial matrix. This process, catalyzed by pyruvate dehydrogenase, necessitates several coenzymes such as NAD^+ and Coenzyme A.

$$\underset{(3C)}{\text{Pyruvic acid}} + \text{CoA} + \text{NAD}^+ \xrightarrow[\text{Pyruvate dehydrogenase}]{\text{Mg}^{2+}} \underset{(2C)}{\text{Acetyl}}\ \text{CoA} + \text{CO}_2 + \text{NADH} + \text{H}^+$$

- The conversion of pyruvic acid into Acetyl CoA yields two molecules of Acetyl CoA, $2CO_2$, and $2NADH + 2H^+$ from two molecules of pyruvic acid, a reaction referred to as the link reaction or transition reaction of aerobic respiration. The resultant $NADH_2$ molecules subsequently partake in the mitochondrial electron transport system to facilitate energy release.

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

- Acetyl CoA initiates a cyclic pathway known as the Krebs cycle. Named after the scientist Hans Krebs, who first elucidated it, this cycle involves the removal of hydrogen atoms from Acetyl CoA, which are then transferred to coenzymes for further processing within the electron transport system.
- Also termed the Citric Acid Cycle or TCA cycle due to the formation of citric acid in its initial step, this cycle's reactions necessitate the presence of oxygen and are confined to the mitochondrial matrix. Serving as a common oxidative pathway for carbohydrates, fats, and proteins, all enzymes involved in the Krebs cycle are soluble within the mitochondrial matrix, except succinate dehydrogenase (SDH), which is bound to the inner mitochondrial membrane.

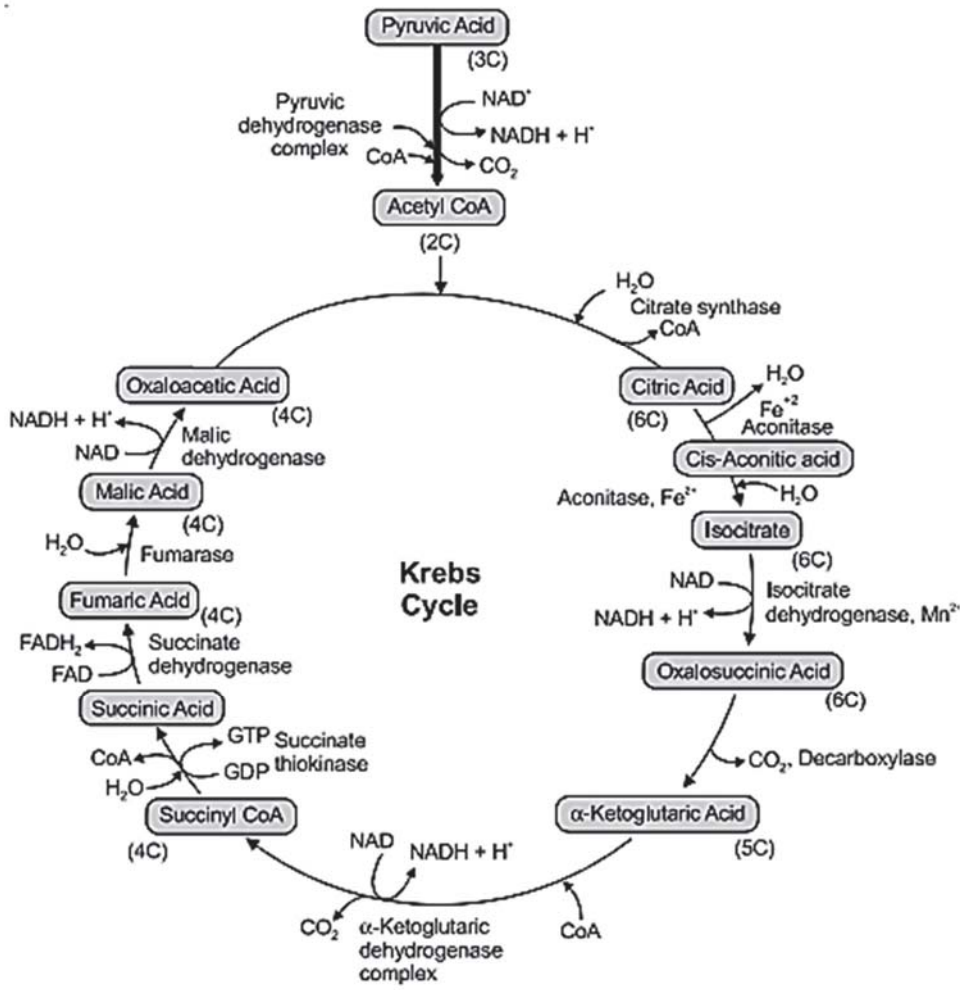

Fig. : The Krebs cycle

The Krebs cycle unfolds through the following steps:

- Commencing with the condensation of the acetyl group with oxaloacetic acid (OAA) and water, citric acid is generated catalytically by citrate synthase, accompanied by the release of a CoA molecule.
- Citric acid transforms into cis-aconitic acid via aconitase, and then into isocitrate, a process known as isomerization catalyzed by the same enzyme.
- Isocitrate undergoes conversion into oxalo-succinate, yielding one molecule of $NADH_2$. Subsequently, oxalosuccinate is transformed into α-ketoglutaric acid.
- Acting upon α-ketoglutaric acid, the α-ketoglutaric dehydrogenase complex facilitates its conversion into succinyl CoA, releasing CO_2 and reducing$NAD +$ to $NADH + H^+$.
- Succinate thiokinase or succinyl CoA synthetase catalyzes the conversion of succinyl CoA into succinic acid, concurrently releasing CoA and generating one molecule of GTP from GDP through substrate-level phosphorylation. In a coupled reaction, GTP is converted to GDP, facilitating the synthesis of ATP from ADP.
- Fumaric acid is produced from succinic acid via succinate dehydrogenase, with FAD being reduced to $FADH_2$.
- Fumarase catalyzes the transformation of fumaric acid into malic acid through the addition of a water molecule.

- The final step involves the regeneration of oxaloacetic acid, facilitated by malic dehydrogenase, which reduces NAD + to NADH + H^+ by extracting hydrogen from malic acid.

For each molecule of acetyl CoA oxidized, one molecule of ATP (via direct GTP), three $NADH_2$, one $FADH_2$, and two molecules of CO_2 are released. Considering that two molecules of pyruvic acid are generated from one glucose molecule during glycolysis, the TCA cycle must occur twice for every glucose molecule respired, resulting in the formation of 2 ATP, 6 $NADH_2$, and 2 $FADH_2$ from 2 molecules of acetyl CoA originating from one glucose molecule.
The sustained oxidation of acetyl CoA through the TCA cycle necessitates the continual replenishment of oxaloacetic acid, the cycle's initial constituent, along with the regeneration of NAD+ and FAD+ from NADH and $FADH_2$, respectively. The summative equation for this respiratory phase (Oxidative decarboxylation + Kreb cycle) can be expressed as follows:

Pyruvic acid + $4NAD^+ + FAD^+ + 4H_2O + ADP + Pi$

$$\xrightarrow{\text{Mitochondrial matrix}} 3CO_2 + 4NADH + 4H^+ + FADH_2 + ATP + H_2O.$$

Electron Transport System (ETS) and Oxidative Phosphorylation

Up to this point, we have observed the complete breakdown of glucose without direct involvement of oxygen (O_2) or the generation of a significant number of ATP molecules. The subsequent stages in the respiratory process aim to release and harness the energy stored in NADH + H+ and FADH2. This is achieved through their oxidation via the electron transport system (ETS), where electrons are sequentially passed along a series of carriers until they reach oxygen (O_2), resulting in the formation of water (H_2O). The metabolic pathway facilitating the transfer of electrons from one carrier to another is known as the electron transport system, which unfolds within the inner mitochondrial membrane. This process progresses through the following steps:

- Electrons derived from NADH, produced in the mitochondrial matrix during the citric acid cycle, undergo oxidation by an NADH dehydrogenase (Complex I).
- Subsequently, these electrons are transferred to ubiquinone, situated within the inner membrane.
- Ubiquinone also receives reducing equivalents via FADH2 (Complex II), which is generated during the oxidation of succinate in the citric acid cycle.
- The reduced ubiquinone (ubiquinol) is then oxidized, with electrons being transferred to cytochrome c via the cytochrome bc1 complex (Complex III).
- Cytochrome c, a small protein anchored to the outer surface of the inner membrane, serves as a mobile carrier, facilitating the transfer of electrons between Complexes III and IV. The cytochrome c oxidase complex, comprising cytochromes a and a3 and two copper centers, is denoted as Complex IV.
- Oxygen serves as the terminal electron acceptor. Upon receiving electrons, it becomes reactive and combines with protons to generate metabolic water.

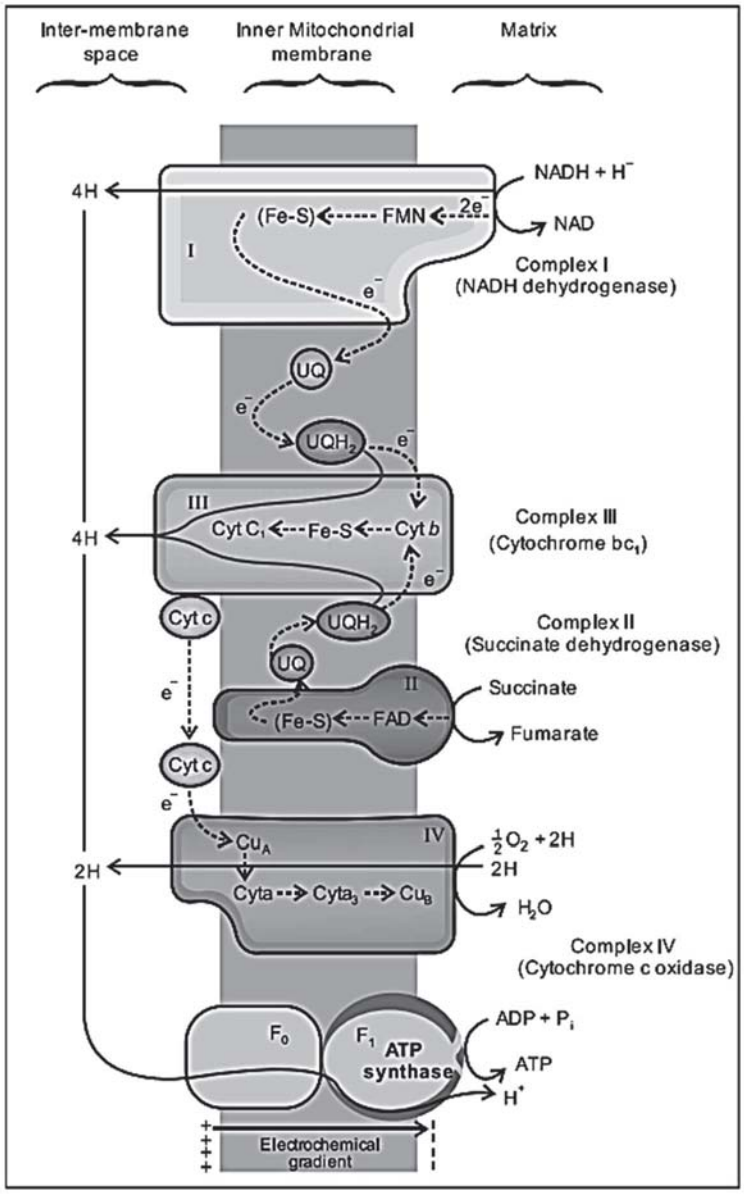

Fig. : Electron Transport System (ETS)

Oxidative phosphorylation

Oxidative phosphorylation, a crucial aspect of cellular respiration, involves the transfer of electrons through various carriers (from complex I to IV) in the electron transport chain. This electron movement is coupled to ATP synthase (complex V), resulting in the conversion of ADP and inorganic phosphate into ATP. The key features of oxidative phosphorylation are detailed as follows:

- As electrons traverse the electron transport chain complexes I to IV, they are coupled with ATP synthase (complex V), a process that leads to the synthesis of ATP from ADP and inorganic phosphate.
- The generation of a proton gradient or proton motive force (PMF) necessary for phosphorylation is achieved through the energy derived from oxidation-reduction reactions. Hence, this process is termed oxidative phosphorylation. The chemiosmotic hypothesis, proposed by Peter Mitchell, elucidates the mechanism of membrane-linked ATP synthesis.

- Protons move across the inner mitochondrial membrane only in the region of $F_0 - F_1$, also known as elementary particles or ATP synthase.
- The energy liberated during the electron transport system is employed in the synthesis of ATP with the aid of ATP synthase (complex V). This complex comprises two major components: F_1 and F_0.
- The F_1 headpiece, a peripheral membrane protein complex, houses the site responsible for ATP synthesis from ADP and inorganic phosphate. F_0, on the other hand, is an integral membrane protein complex that forms the channel facilitating the movement of protons across the inner membrane.
- The passage of protons through the channel is linked to the catalytic site of the F_1 component, leading to the production of ATP. For every ATP produced, $2H^+$ traverse F_0 from the intermembrane space to the matrix, following the electrochemical proton gradient.
- During the oxidation of each NADH + H^+, three pairs of protons are pushed, while the oxidation of each $FADH_2$ results in the pushing of two pairs of protons.
- The complete oxidation of NADH yields 3ATP molecules, whereas one molecule of $FADH_2$ leads to the formation of 2ATP molecules. This differential ATP production is a reflection of the varying contribution of NADH and $FADH_2$ to the electron transport chain.

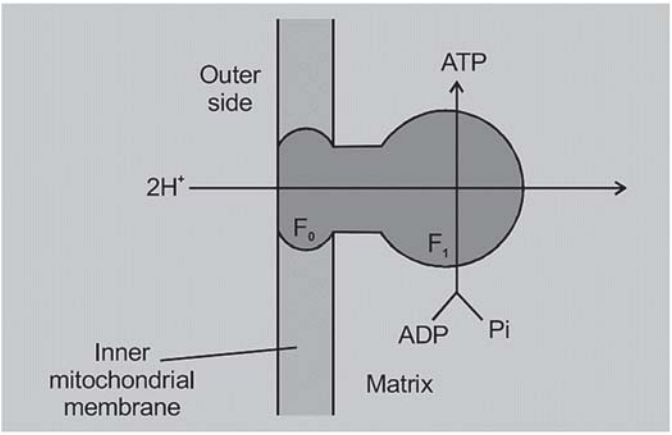

Fig. : Diagrammatic presentation of ATP synthesis in mitochondria