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Electron Transport Chain: Role in Reactive Oxygen Species Production and Aging

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Abstract: Mitochondria have captured the interest of biochemists for more than 50 years. They have been studied intensively in the past decades, not least because they are abundant and can be isolated easily from different tissues. Mitochondria have lately moved into the spotlight of other exciting areas, namely the study of apoptosis, evolutionary biology and molecular medicine. Cellular respiration is the oxidative, chemical attack on energy-rich molecules to provide useful energy for the cell. Cellular respiration involves four phases: glycolysis, the preparatory reaction, the citric acid cycle, and the electron transport chain. Electron transport chains are biochemical reactions that produce ATP, which is the energy currency of life. The generation of monomitochondrial ROS is a consequence of oxidative phos-phorylation, a process that uses the controlled oxida-tion of NADH or FADH to generate a potential energy for protons across the mitochondrial inner mem-brane. ROS can directly modulate protein complexes within the mitochondrial electron transport chain, activate caspases and trigger cell death. In apoptosis there is typically a rapid reduction in the mitochondrial membrane potential lead to block of respiratory function due to the cleavage and inactivation of electron transport chain constituents by activated caspases. The mitochondrial theory of ageing predicts that Oxidative damage induced mtDNA mutations that impair either the assembly or the function of the respiratory chain will in turn trigger further accumulation of ROS, which results in a vicious cycle leading to energy depletion in the cell and ultimately cell death.
Keywords: Mitochondria, Cellular respiration, ETC, ROS production, Apoptosis, Aging

INTRODUCTION

The Mitochondria

The Mitochondria (Greek : mitos- thread ; chondros – grnaule) are membrane bound cytoplasmic organelle concerned mainly with cellular respiration and energy metabolism. It produces the energy required for cellular functions, so it regarded as “Power house of the cell”. Mitochondria are about 0.5 – 1 µm in diameter and up to 7 µm long with rod shape filamentous bodies.

Mitochondrial shape and number per cell depends on the particular tissue. The number of mitochondria per cells varies depending on the energy requirements: tissues with a high capacity to perform aerobic metabolic functions such as skeletal muscle, kidney, heart muscle and in live sperm will have a larger number of mitochondria. In the birds, during the flight, requirement of energy is higher, so they have the larger number of mitochondria in their cell. Mammalian cells have 800 to 2,500 mitochondria per cell.

Mitochondrion contains its own DNA, which is responsible for many enzymatic actions. It is the only organelle other than nucleus, which has it’s own DNA. Mitochondria are remarkably mobile organelles. Time lapse photography shows that they are constantly moving and changing shape. In some cells they are anchored by attachment to the cell’s cytoskeleton so that they remain fixed at one cellular location to target a site of high ATP utilization. In heart muscle for example the mitochondria are anchored close to the contractile muscle, in sperm they are wrapped tightly around the motile flagellum. Mitochondria have a main role in production of energy, for synthesizing the ATP and in apoptosis [1].

Mitochondria – structure

Mitochondria is mainly composed of :
(1) Outer membrane
(2) Inner membrane
(3) Cristae and (4) Matrix [2].

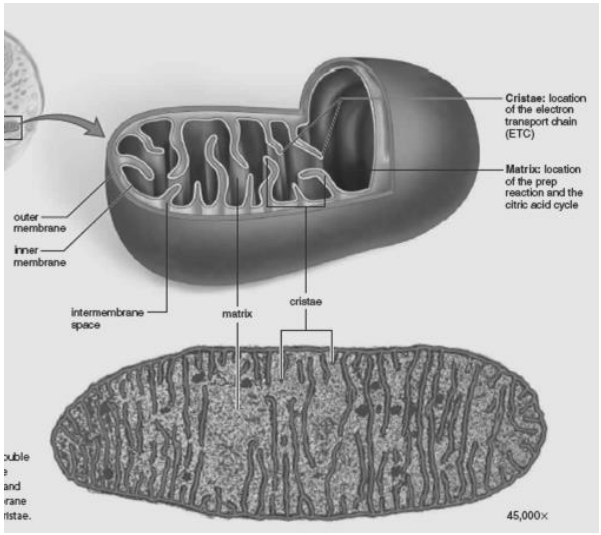

Fig-1: Mitochondrial Structure

Mitochondrial membranes are composed of a phospholipid bilayer. Both membranes are quite distinct in appearance and in physico-chemical properties, thus determining the biochemical function of each membrane.

(1) Outer membrane: The outer membrane contains porins which are transmembrane proteins rich in ß - sheets which allow molecules of low molecular weight (<10,000 dalton) freely diffuse in and out.

(2) Inner membrane: The inner mitochondrial membrane is packed with proteins which account for 80% of the membranes molecular weight. The inner membrane is impermeable to molecules and ions. Metabolites that must cross the inner mitochondrial membrane are carried across by specific transport proteins. The inner mitochondrial membrane is, in fact, an electrical insulator and chemical barrier. Sophisticated ion transporters exist to allow specific molecules to cross this barrier. There are several antiport systems embedded in the inner membrane, allowing exchange of anions between the cytosol and the mitochondrial matrix. Examples of these are a phosphate- OH^- exchanger, the adenine nucleotide translocase.

(3) Cristae: The inner membrane is folded into numerous cristae, which greatly increase the surface area of the inner membrane. Within this membrane are the proteins involved in the electron transport chain, ATP synthase and transport proteins.

(4) Matrix: The large internal space enclosed by inner mitochondrial membrane is called the matrix. It is densely packed with hundreds of enzymes, including pyruvate dehydrogenase, pyruvate carboxylase, and the soluble enzymes of the citric acid cycle. There are the enzymes involved in the oxidation of fatty and amino acids. The matrix also contains the mitochondrial genome, the mitochondrial ribosomes, tRNA's and the enzymes required for the expression of mitochondrial genes.

The space between the inner and outer mitochondrial membranes is called the intermembrane space. Within this space enzymes find which utilize ATP such as creatine kinase and adenylate kinase.

Mitochondria and Cellular Respiration

Cellular respiration is the oxidative, chemical attack on energy-rich molecules to provide useful energy for the cell. Enzymes catalyze the oxidation reactions. These reactions are known as *catabolic reactions* because they break molecules down to release energy. Cellular respiration involves four phases: glycolysis, the preparatory reaction, the citric acid cycle, and the electron transport chain.

Glycolysis takes place outside the mitochondria and does not require the presence of oxygen. Therefore, glycolysis is anaerobic. The other phases of cellular respiration take place inside the mitochondria, where oxygen is the final acceptor of electrons. Because they require oxygen, these phases are called aerobic.

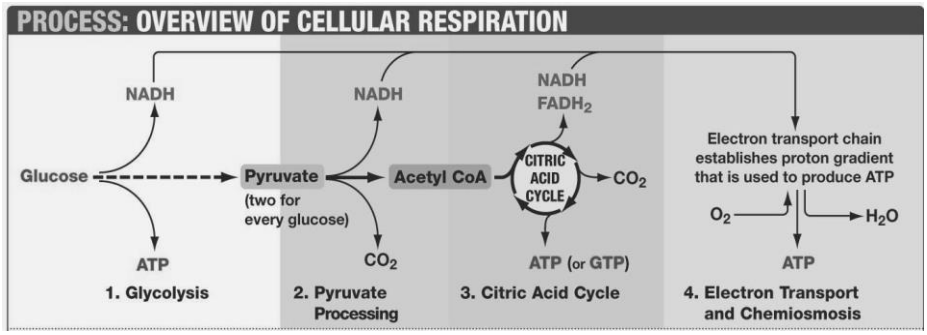

Fig-2: Cellular respiration

(1) Glycolysis: Glycolysis is the oldest energy-harvesting process and is universal to all of life. Glycolysis occurs in the cytosol of the cytoplasm. Glycolysis [Greek : *glycos – sugar and lysis -, splitting*] is the breakdown of glucose (6 C) to two

molecules of pyruvate (3 C). Glycolysis produces two pyruvates, two ATP and two NADH.

(2) The Preparatory (prep) reaction: The preparatory phase takes place in the matrix of the mitochondrion. Pyruvate is broken down from a 3-carbon (C_3) to a 2-carbon (C_2) acetyl group, and a 1-carbon CO_2 molecule is released. Since glycolysis ends with two molecules of pyruvate, the prep reaction occurs twice per glucose molecule.

(3) The Citric acid cycle: It also takes place in the matrix of the mitochondrion. Each 2-carbon acetyl group matches up with a 4-carbon molecule, forming two 6-carbon citrate molecules. As citrate bonds are broken and oxidation occurs, NADH and $FADH_2$ are formed, and two CO_2 per citrate are released. The citric acid cycle is able to produce one ATP per turn Oxidation results in NADH and provides enough energy for the net gain of two ATP molecules.

(4) The Electron Transport Chain (ETC): Electron transport chain is a series of carriers on the cristae of the mitochondria. NADH and $FADH_2$ give up their high-energy electrons to the chain. Energy is released and captured as the electrons move from a higher-energy to a lower-energy state during each redox reaction.

Electron Transport Chain (ETC)

Electron transport chains (also called Electron Transfer Pathways - ETP) are biochemical reactions that produce ATP, which is the energy currency of life. The transfer of electrons from a high energy molecule (the donor) to a lower energy molecule (the acceptor) can be *spatially* separated into a series of intermediate redox reactions. ETC produce energy in the form of a transmembrane electrochemical potential gradient. The gradient can be used to transport molecules across membranes. It can be used to produce ATP and NADH, high-energy molecules that are necessary for growth. Hydrogen and electrons flow through a negative to positive redox potential from NAD^+/NADH to $O_2/2H_2O$ redox pair [3].

Components of Electron Transport Chain:

Mainly five components of ETC present at various places in mitochondria -

(1) NADH (Nicotinemide Adenosine DeHydrogenase)
(2) Flavoproteins
(3) Coenzyme Q
(4) Cytochromes
(5) Iron – sulphur proteins

(1) NADH: NADH is generated in the matrix by the reactions of pyruvate dehydrogenase, isocitrate dehydrogenase, α ketoglutarate dehydrogenase and malate dehyrogenase. The electron transport chain begins with reoxidizing NADH to form NAD^+ and channeling the electrons into the formation of reduced coenzymes. NADH transfers 2 electrons at a time in the form of a hydride[3].

$$NAD^+ + 2\,e^- + H^+ \rightarrow NAD$$

(2) Flavoproteins: Flavoproteins have either a FAD (flavin adenosine dinucleotide) or a FMN (flavin mononucleotide) prosthetic group. Flavoproteins can accept or donate electrons one at time or two at a time. Thus they are often intermediaries between two electron acceptors/donors and one electron acceptors/donors [3].

$$FAD + 2e^- + 2H^+ \rightarrow FADH_2;$$
$$FMN + 2e^- + 2H^+ \rightarrow FMNH_2$$

(3) Coenzyme Q: Coenzyme Q is a versatile cofactor because it is a soluble electron carrier in the hydrophobic bilipid layer of the inner mitochondrial membrane. CoQ acts as a mobile component of the respiratory chain that collects reducing equivalents from the more fixed flavoprotein complexes and passes them on to the cytochromes. CoQ is also known as ubiquinone. It can accept / donate electrons one at a time or two at a time. CoQ exists in the oxidized quinone or reduced quinol form under aerobic or anaerobic conditions, respectively[3].

$$Q + 2e^- + 2H^+ \rightarrow QH_2;$$
$$Q + e^- + H^+ \rightarrow \cdot QH;$$
$$\cdot QH + e^- + H^+ \rightarrow QH_2$$

(4) Cytochromes : Cytochromes are proteins contain heme prosthetic groups which function as one electron carriers. The heme iron is involved in one electron transfers involving the Fe^{2+} and Fe^{3+} oxidation states. Important cytochromes are cytochrome a, b, c, c_1 and a_3 [3].

(5) Iron-Sulfur proteins: Iron-sulfer proteins which participate in one e^- transfers involving the Fe^{2+} and Fe^{3+}oxidation states. These are non-heme iron-sulfur proteins. e.g. FeS, Fe_2S_2 , Fe_3s_4 [3].

Complexes of Electron Transport Chain

The components of the electron transport chain are organized into 4 complexes. Each complex contains several different electron carriers.

Table 1: Complexes of ETC

Complex I	NADH-coenzyme Q reductase or NADH dehydrogenase.
Complex II	Succinate-coenzyme Q reductase or succinate dehydrogenase
Complex III	Coenzyme Q reductase.
Complex IV	Cytochrome c reductase

Complex I accepts electrons from NADH and serves as the link between glycolysis, the citric acid cycle, fatty acid oxidation and the electron transport chain. Complex II includes succinate dehydrogenase and serves as a direct link between the citric acid cycle and the electron transport chain. Complex III transfers the electrons from $CoQH_2$ to reduce cytochrome *c* which is the substrate for Complex IV. Complex IV transfers the electrons to reduce molecular oxygen into water [3].

(1) Complex I: Electrons are carried from NADH to CoQ by the NADH-CoQ reductase complex. In complex I, two electrons first flow from NADH to FMN , to produce $FMNH_2$. Each electron is accepted together with a hydrogen ion, H^+, such that two electrons and two H^+ are accepted in total.

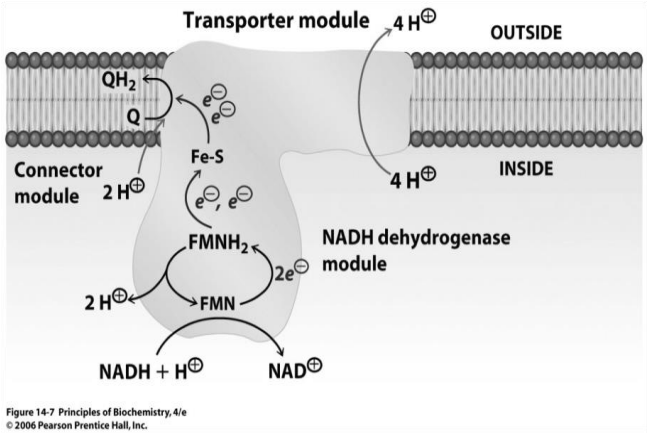

Fig-3: Complex I

Electrons are then transferred, within Complex I, to iron–sulfur clusters (FeS) in iron–sulfur proteins. Within a FeS cluster, an electron is carried by the iron atom which, on accepting the electron, changes from the Fe^{3+} (ferric) state to the Fe^{2+} (ferrous) state. As the electron is passed to another electron carrier, the iron atom of the FeS cluster changes back again to the Fe^{3+} state. Electrons from the FeS clusters of Complex I are passed on to ubiquinone (CoQ).Released energy is used to transport four protons across the inner membrane per molecule of NADH oxidized by the NADH-CoQ reductase complex.

(2) Complex II: Succinate dehydrogenase, the enzyme that oxidizes a molecule of succinate to fumarate in the citric acid cycle, is localized to the inner mitochondrial membrane. This enzyme is an integral component of the succinate-CoQ reductase. The two electrons released in conversion of succinate to fumarate are transferred first to FAD, then to an iron-sulfur carrier, and finally to CoQ, forming the reduced $CoQH_2$.

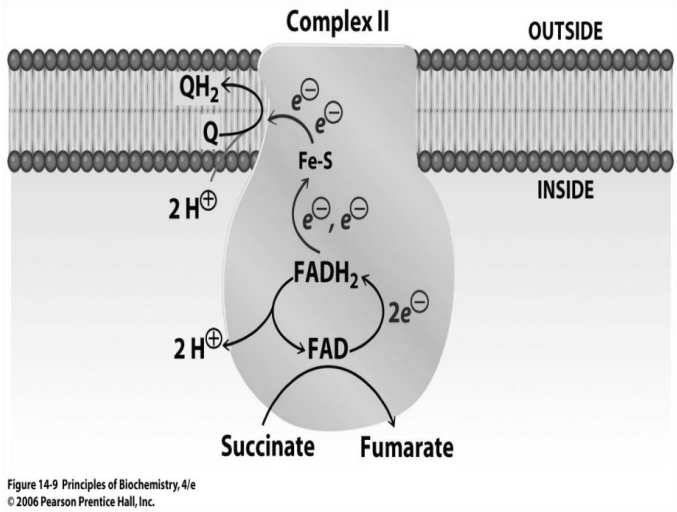

Fig-4: Complex II

Succinate + **CoQ** → **Fumarate** + **$CoQH_2$**
(Reduced) (Oxidised) (Oxidised) (Reduced)

(3) Complex III: When ubiquinol ($CoQH_2$) donates its two electrons to the next carrier in the chain, the Q-cytochrome *c* reductase (Complex III), the H^+ ions are released once more. This complex contains two types of cytochromes, cytochrome *b* and cytochrome c_1, as well as an FeS protein.Electrons passing from ubiquinol ($CoQH_2$) through the cytochrome *b*, FeS and cytochrome c_1 components of the complex to the next electron carrier, *cytochrome c*.

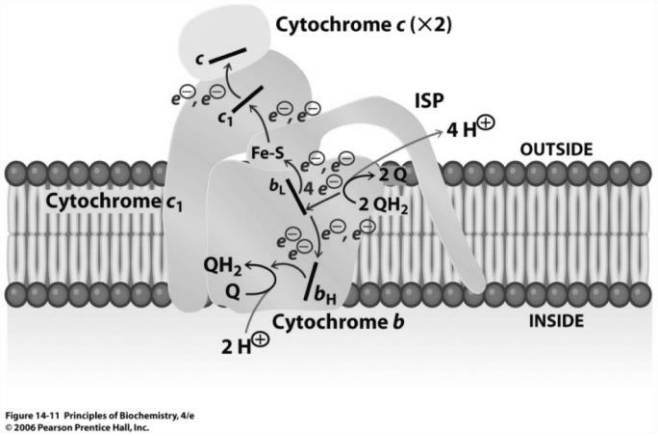

Fig-5: Complex IV

(4) Complex IV:- Cytochrome *c*, after being reduced by the CoQH – cytochrome *c* reductase complex, transports electrons, one at a time, to the cytochrome *c* oxidase complex. Within this complex, electrons are transferred, again one at a time, first to a pair of copper ions (Cu_a^{2+}), then to cytochrome *a*, then to a complex of a second copper ion (Cu_b^{2+}), and cytochrome a_3 and finally to O_2 , the ultimate electron acceptor, yielding H_2O.

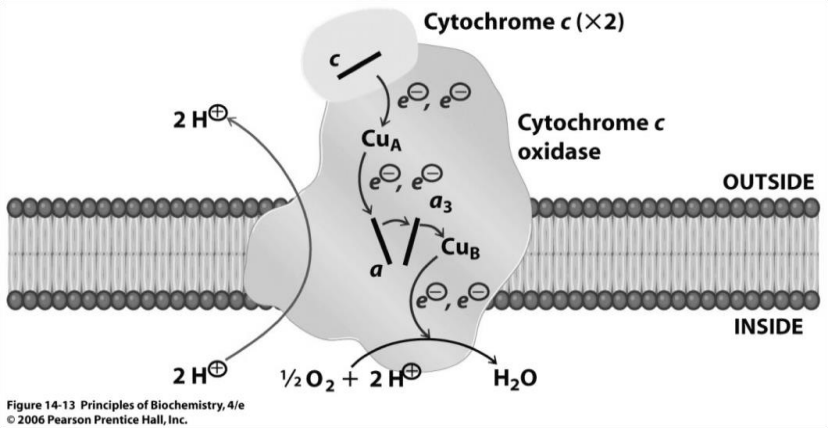

Fig-6: Complex V

Oxidative Phosphorylation

Oxidative phosphorylation is the name given to the synthesis of ATP (*phosphorylation)* that occurs when NADH and $FADH_2$ are oxidized (hence oxidative) by *e*lectron transport through the respiratory chain. The complex V of the inner mitochondrial membrane is the site of oxidative phosphorylation. It works on a very different mechanism was proposed by Peter Mitchell in 1961, the chemiosmotic hypothesis [4].

Chemiosmotic Hypothesis

Electron transport down the respiratory chain from NADH oxidation causes H ions to be pumped out of the mitochondrial matrix across the inner mitochondrial membrane into the intermembrane space by the three H^+ pumps; Complex I, III and IV. The pumping out of the H^+ ions generates a higher concentration of H^+ ions in the intermembrane space and an electrical potential, with the side of the inner mitochondrial membrane facing the intermembrane space being positive. Thus, an electrochemical proton gradient is formed (Fig 7).

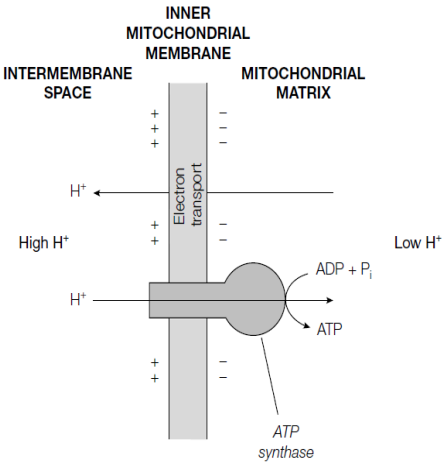

Fig-7: Proton gradient

The protons flow back into the mitochondrial matrix through the ATP synthase and this drives ATP synthesis. The ATP synthase is driven by proton-motive force, which is the sum of the pH gradient (i.e. the chemical gradient of H ions) and the membrane potential (i.e. the electrical charge potential across the inner mitochondrial membrane). The actual synthesis of ATP is carried out by an enzyme called ATP synthase, located in the inner mitochondrial membrane.

ATP synthase

The ATP synthase can be seen as spherical projections from the inner membrane. ATP synthase also known as Complex V (F_0F_1 Complex) has two distinct components: F_1 is a peripheral membrane protein and F_0 which is integral to the membrane.

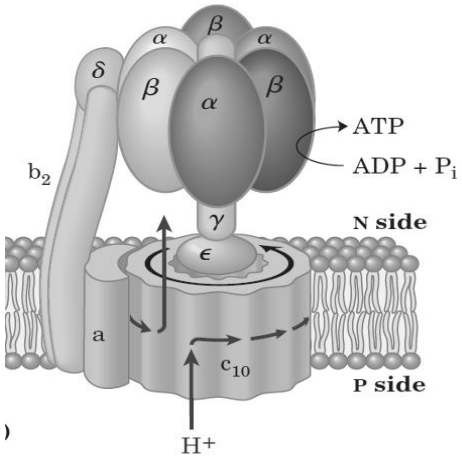

Fig-8: ATP Synthase

(i) F_0 consists of a ring of 10 to 14 **c** subunits sitting in the inner mitochondrial membrane. This contacts a single **a** subunit that links to two **b** subunits and the single δ subunit to form a long column that connects to the head of the F_1 ATPase.

(ii) The F_1 ATPase consists of five types of polypeptides in the following ratio: α3, β3, γ, δ, ε. The six α and β subunits are arranged alternately in a ring, with a central stalk formed by the γ and ε subunits.

Rotary motor model for ATP generation

Paul Boyer in 1964 proposed that a conformational change in the mitochondrial membrane proteins leads to the synthesis of ATP. The original Boyer hypothesis consider as rotary motor / engine driving model / binding change model or rotational catalysis mechanism (Fig 9).

In response to the proton flux, the gamma subunit physically rotates. This induces conformational changes in the $ß_3$ subunits that finally lead to the release of ATP. According to the binding change mechanism, the three ß subunits of F_1-ATP synthase adopt different conformations. One subunit has open (O) conformation; the second has loose (L) conformation while the third one has tight (T) conformation [3].

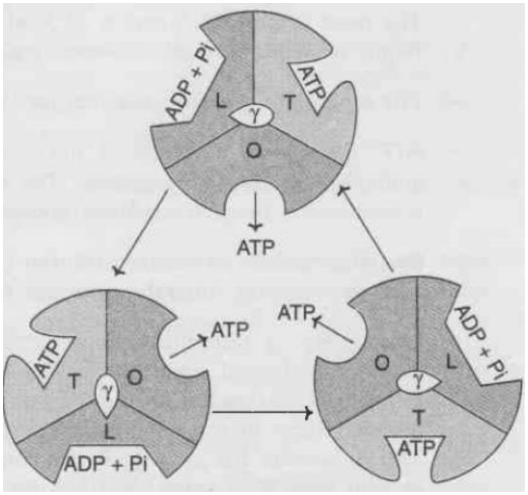

Fig-9: Rotary model for ATP production

Mechanism involves the three active sites of F_1 take turns catalyzing ATP synthesis. The streaming of protons through the F_o "pore" causes the cylinder of c subunits and the attached gamma subunit to rotate about the long axis of, which is perpendicular to the plane of the membrane. The gamma subunit passes through the centre of the 33 spheroid, which is held stationary relative to the membrane surface by the ß2 and Ɛ subunits [3].

A given ß subunit starts in the ß-ADP conformation, which binds ADP and Pi from the surrounding medium. The subunit now changes conformation, assuming the ß-ATP form that tightly binds and stabilizes ATP, bringing about the ready equilibration of ADP + Pi with ATP on the enzyme surface.

Finally, the subunit changes to the ß-empty conformation, which has very low affinity for ATP, and the newly synthesized ATP leaves the enzyme surface. The conformational changes central to this mechanism, are driven by the passage of protons through the F_o portion of ATP synthase. The three ß subunits interact in such a way that when one assumes the ß -empty conformation, its neighbour to one side must assume the ß -ADP form, and the other neighbour the ß -ATP form. Thus one complete rotation of the gamma *subunit* causes each ß subunit to cycle through all three of its possible conformations, and for each rotation, three ATP are synthesized and released [3].

ATP release in O conformation is energy dependent and very crucial in rotary motor model for ATP generation. The enzyme ATP synthase acts as a proton driving motor, and is an example of rotary catalysis. Thus, ATP synthase is the world's smallest molecular motor.

Inhibitors of ETC

The inhibitors bind to one of the components of ETC and block the transport of electrons. It causes the accumulation of reduced components before the inhibitor blockade step and oxidized components.

Table 2: Inhibitors of ETC

Compounds	Site of Action	Effect
CCCP 2,4 - Dinitrophenol (uncoupler)	Inner membrane	Ionophores that disrupt the proton gradient by carrying protons across a membrane. This ionophore uncouples proton pumping from ATP synthesis because it carries protons across the inner mitochondrial membrane [5].
Rotenone (fish poison)	Complex I	Prevents the transfer of electrons from complex I to ubiquinone by blocking the ubiquinone binding site [6].
Antimycin A (antibiotic)	Complex III	Binds to the Qi site of cytochrome c reductase, thereby inhibiting the oxidation of ubiquinol.
Cyanide, Carbon monoxide, Azide, Hydrogen sulfide (poisons)	Complex IV	Inhibit the electron transport chain by binding more strongly than oxygen to the Fe–Cu center in cytochrome c oxidase, preventing the reduction of oxygen [7].
Oligomycin (antibiotic)	Complex V	Inhibits ATP synthase by blocking the flow of protons through the F_o subunit [8].

ETC and ROS production

The generation of monomitochondrial ROS is a consequence of oxidative phos-phorylation, a process that uses the controlled oxida-tion of NADH or FADH to generate a potential energy for protons across the mitochondrial inner mem-brane. This potential energy is in turn used to phosphorylate ADP via the F1-F0 ATPase. At several sites along the cytochrome chain, electrons derived from NADH or FADH can directly react with oxygen or other electron oxidaacceptors and generate free radicals. In the past, the generation of ROS or other free radicals was thought of as "slippage" or an unproductive side reaction. More recently, it has been proposed that mitochondrial ROS may actually be important in various redox-dependent signaling processes as well as aging clock [9-11].

- Reactive oxygen species (ROS) are often generated following inhibition of the mitochondrial Electron Transport Chain (mETC) [14]. Inhibition of the various mitochondrial electron transport chain complexes induces cell death [12].
- Generally, complex I and complex III are considered as the major $O_2^{\bullet-}$ sources [13]. Complex I releases $O_2^{\bullet-}$ to matrix, complex III can release $O_2^{\bullet-}$ to [14] both sides of the inner mitochondrial membrane.
- At site III, Q cycle contributing to the generation of O_2^{-} through reduced ubisemiquinone either on the inner or outer membrane surface [15]. Ubiquinone within the electron transport chain cycles between the quinone (fully oxidized) to semiquinone (one-electron reduction product) to quinol (fully reducedby two electrons) states, there is a tendency for an electron to pass to oxygen directly instead of to the next electron carrier in the chain.
- Manipulations that increase the redox potential of site I or site III generally increase the rate of ROS generation, supporting the notion that the redox potential of these reactive sites is important in free radical formation [16].
- ROS produced from the mETC inhibition by rotenone and TTFA mediate autophagy and autophagic cell death in transformed cells and cancer cell lines.
- Cytochrome c delivers electrons from cytochrome bc1 to cytochrome c oxidase, the complete loss of cytochrome c could similarly lead to accumulation of electrons in the chain and oxygen radical formation.
- The iron sulfur groups and FMN sites [17] have been implicated in ROS generation.

ROS production by mitochondria can lead to oxidative damage to mitochondrial proteins, membranes and DNA, impairing the ability of mitochondria to synthesize ATP and to carry out their wide range of metabolic functions, including the tricarboxylic acid cycle, fatty acid oxidation, the urea cycle, amino acid metabolism, haem synthesis and FeS centre assembly that are central to the normal operation of most cells [18]. Mitochondrial oxidative damage can also increase the tendency of mitochondria to release intermembrane space proteins such as cytochrome c (cyt c) to the cytosol by mitochondrial outer membrane permeabilization (MOMP) and thereby activate the cell's apoptotic machinery [19]. In addition, mitochondrial ROS production leads to induction of the mitochondrial permeability transition pore (PTP), which renders the inner membrane permeable to small molecules in situations such as ischaemia/reperfusion injury. Consequently, it is unsurprising that mitochondrial oxidative damage contributes to a wide range of pathologies. In addition, mitochondrial ROS may act as a modulatable redox signal, reversibly affecting the activity of a range of functions in the mitochondria, cytosol and nucleus.

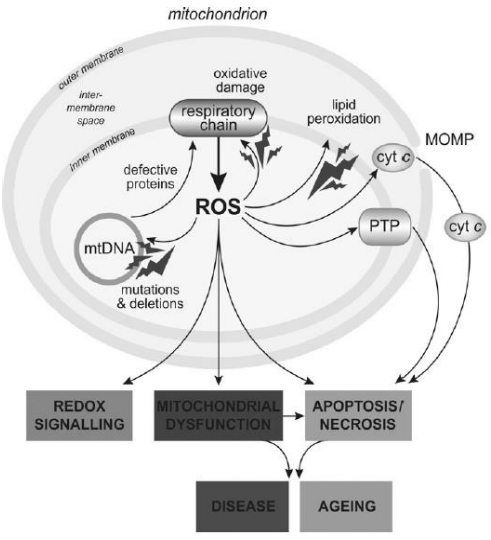

Fig-10: Overview of ROS production

ETC and Apoptosis

Apoptosis is characterized by cell shrinkage, blebbing of plasma membrane, maintenance of organelle integrity, condensation and fragmentation of DNA, followed by ordered removal of phagocytes [20]. It works like a "suicide" program and it causes minimal damage to surrounding tissues. Apoptosis has been sub classified into two types of death pathways, namely, the extrinsic pathway and the intrinsic pathway (mitochondria-mediated pathway). These two processes however, are not exclusive and evidence suggests that they can be linked and that molecules in one pathway can influence the other [21, 22].

Intrinsic Pathway for Apoptosis

- The mitochondria pathway of cell death can be activated by a variety of receptorindependent stimuli such as radiation, free radicals, viral infections and serum/growth factor withdrawal.
- Mitochondria contain many pro-apoptotic proteins such as Apoptosis Inducing Factor (AIF), Smac/DIABLO and cytochrome C (ETC carriar).
- Initially, it was demonstrated that these triggers invariably result in changes in the inner mitochondrial membrane permeability due to the opening of the mitochondrial permeability transition (MPT) pore.
- The major consequences of this change of permeability are the loss of the mitochondrial transmembrane potential ($\Delta\Psi$m), the release of pro-apoptotic proteins and the arrest of the bioenergetic function of the organelle [23].
- The proteins that are released can be broadly classified into two categories:

The first category comprises of proteins that can activate the caspase dependent pathway. This group includes proteins such as cytochrome *c* (cyt *c*) and Smac/DIABLO (second mitochondria-derived activator of caspases). The holocytochrome *c* induces Apaf-1 oligomerization, leading to the activation of caspase 9. This active cyt *c*/Apaf-1/caspase 9 complex forms the apoptosome and activates the executioner caspases 3 and 7 resulting in the dismantling of the cell through nuclear fragmentation. Smac/DIABLO binds to IAPs (inhibitor of apoptosis proteins) and deactivates them, thus preventing the IAPs from arresting the apoptotic process, permitting apoptotic progression. Over expression of Bcl-2, the founder oncogene of the Bcl-2 family has been shown to block apoptosis in certain cancer cells, which have been classified as type II cells, as compared to type I cells in which the execution of apoptosis program is Bcl-2-independent [24, 25].

The second group includes other pro-apoptotic proteins such as apoptosis inducing factor (AIF) and endonuclease G (Endo G). In some models, the release of these proteins is a late event in apoptosis, which occurs once the cells are committed to die. Following the release of AIF, it translocates to the nucleus where it promotes DNA fragmentation. Both AIF and Endo G act in a caspase-independent manner to execute cell death. Alternatively, AIF has also been recently proposed to participate in a different form of cell death, namely programmed necrosis [26].

- ROS can directly modulate protein complexes within the mitochondrial electron transport chain, activate caspases and trigger cell death.
- In apoptosis there is typically a rapid reduction in the mitochondrial membrane potential lead to block of respiratory function due to the cleavage and inactivation of electron transport chain constituents by activated caspases.

ETC and Ageing

Ageing can be defined as "A progressive, generalized impairment of function, resulting in an increased vulnerability to environmental challenge and a growing risk of disease and death"[27].

Though primary mitochondrial dysfunction affects aging, different cellular and metabolic alterations also contribute to the aging process by promoting secondary changes in mitochondrial energy production or mitochondrial biogenesis (Figure 11).

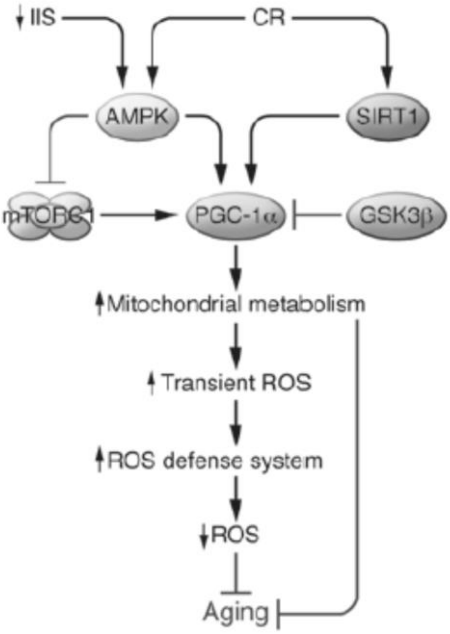

Fig-11: Model for Aging

Therefore, aging-associated phenotypes have been linked not only to mitochondrial dysfunction but also to aberrant mitochondrial biogenesis caused by impaired retrograde signaling regulated by nuclear genes and factors dependent on mitochondrial metabolism (e.g., ATP, Ca2+, ROS, NO, NAD+/NADH) [28]. Numerous studies have shown that mitochondrial metabolism is important in mediating longevity through nutrient-sensing pathways and dietary

restriction [29, 30, 31, 32]. Insulin/IGF-1 signaling (IIS) and target of rapamycin (TOR) signaling pathways are the two main nutrient-sensing pathways that have been linked to the regulation of life span. Reduced nutrient availability, also termed CR, extends life span in species ranging from yeast to mammals and improves the health status of rodents and primates [33, 34,35]. The effects of CR on longevity are very complex and include many organs and different pathways. Still, the exact underlying mechanisms are unknown. For instance, CR decreases the incidence of cardiovascular diseases in animals, and it has been suggested that the anti-aging effect of CR is propagated through a reduction of metabolic rate and oxidative damage, which consequently inhibits signaling pathways regulated by mitochondria-derived ROS [36] . It is important to note that both nutrient-sensitive pathways TOR and IIS activate the common downstream effector ribosomal protein S6 kinase 1 (S6K1), which plays a key role in the regulation of aging [37].

- Increasing age in mammals correlates with increased levels of mitochondrial DNA (mtDNA) mutations and a deteriorating respiratory chain function [38].
- The mitochondrial theory of ageing predicts that [39] Oxidative damage induced mtDNA mutations that impair either the assembly or the function of the respiratory chain will in turn trigger further accumulation of ROS, which results in a vicious cycle leading to energy depletion in the cell and ultimately cell death.
- Oxidative damage generated during oxidative phosphorylation of mitochondrial macromolecules such as mtDNA, proteins, or lipids is responsible for aging [40].
- As mitochondria play a critical role in regulation of apoptosis, which is implicated in the aging process, age-related mitochondrial oxidative stress may contribute to apoptosis upon aging [41].

However, there is a clear need for future experimental studies to determine whether the contribution of mitochondrial dysfunction to different age-related diseases is explained by a cellular bioenergetic deficiency or by changes in mitochondrial ROS production affecting oxidative damage and signaling.

CONCLUSIONS

- ✓ The mitochondrion is a chemical power plant and as a cellular compartment housing various biosynthetic pathways.
- ✓ Electron transport chain plays crucial role in oxidative phosphorylation, generation of oxygen radicals, dynamic morphological rearrangements, and permeability transition and ageing.
- ✓ ROS generated by ETC can cause damage to mitochondrial components and initiate degradative processes.
- ✓ Excessive ROS production by ETC results in oxidative stress which is a significant pathology in many diseases, including neurodegenerative disease.
- ✓ Studies that link mitochondrial electron transport chain, ATP production and longevity have given conflicting results that are not easy to reconcile in a unifying theory.
- ✓ More experiments are needed to clarify the role of mitochondrial biogenesis, mitochondrial respiration rate and ROS production in different aspects of ageing.

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