

### **MITOCHONDRIAL DYSFUNCTION AND THEIR MANAGEMENT BY ANTIOXIDANTS**

#### **ABSTRACT**

For normal cell functioning generation of ATP is very important, and it is produced by mitochondria, and they also an important organelle. When sometimes mitochondrial dysfunction occur produces high energy will be demanded, and it is critical for cells such as signal transmission between neuronal cells and also affects cardiomyocytes. Mitochondria and their role to act as power house of the cell and through reactive oxygen species they transmit signaling between molecule and also determination of cellular fate. But sometimes the reactive oxygen species generated more that time, for maintaining normal homeostatic mitochondrial function rapid activation of antioxidant defense system that is required by mitochondrial electron transport. But that time antioxidant defense system is not responded properly or absent that cause mitochondrial dysfunction is occurred at that time they produce degenerative diseases in human beings that is nervous system, and they significantly contribute to produce a cardiac pathology because mitochondria are more abundant in cardiac tissues due to mitochondrial dysfunction, and also they are involved in lung related diseases that is asbestos, lung cancer, chronic airway disease and lung fibrosis. When compared to nuclear DNA the mitochondrial DNA is more sensitive to oxidants because they encode the mitochondrial proteins. When damages to mitochondrial DNA, that case impairment occurs in electron transport chain and potential loss in mitochondrial membrane. In this review I concluded that by, oxidative stress induced mitochondrial dysfunction produced lung related heart related and neurological related disease and their one of the way of prevention is by antioxidant induced mitochondrial biogenesis.

**Keywords:** Mitochondrial dysfunction, Mitochondrial DNA, Degenerative disease, Mitochondria proteins, Electron transport chain, Antioxidants.

## **INTRODUCTION**

### **Mitochondria**

The Power houses of the cell called as Mitochondria. For driving fundamental cellular function, adenosine triphosphate is required and their main source is mitochondria, and they are also called as energy rich compound. And their function is biosynthesis, force generation that is contraction of muscle and cell division, protein degradation, membrane potential maintenance etc. Generation of ATP from ADP and phosphate ions by mitochondria, but mitochondria have also other some functions that is NADH production, amino acid biosynthesis, phospholipids synthesis for membrane biogenesis citric acid cycle of GTP. They have an ability to act on signaling of calcium [1], responses of stress [2] and cellular signaling are generally [3]. But if, mitochondria dysfunction occur they cause inherited disease in the way of maternally and also in apoptosis and aging, mitochondria are deeply implicated [4].

### **Morphology of Mitochondria**

In mitochondria the organelle are separated into four distinct compartments, and they have double membrane arrangements that is inner membrane, intermembrane space, outer membrane and matrix. Different functions are produced in each compartment. Porous is present in outer membrane by these porous membranes the small unchanged molecules and ions are freely transverse through proteins that is membrane of pore forming proteins such as anion channel VDAC and this is voltage dependent ion channel [5]. Proteins which are present in between space that is intermediate space plays a vital role in apoptosis and mitochondrial energetic. The responsible for the reaction of citric acid cycle by matrix because these contain most of the enzymes. Large components are present in inner membrane which contains total mitochondrial composition they act as transporters to matrix for carrying protein.

### **Shape and Structure**

From electron microscopy studies the description of mitochondrial structure are largely, then in various part of the cytoplasm mitochondria may be spherical or rod shaped structure, where uniform sphere or ovoid structure of mitochondria which are present in hepatocytes [6], and they are ovoid or rod shaped in native vascular smooth muscle [7, 8, 9, 10], a tubular mitochondrial network will be existed in endothelium [11], but the mitochondrial structure may be varied within the individual cells. Mitochondria are ovoid structure which is present in skeletal muscle, but they are existed in two ways that is first one is embedded in center point of myofibrils and other one is close present to the sarcoma [12]. The three groups of mitochondria may serve different functions as identified by the analyzing, with the help of specific type of cytosol  $Ca^{2+}$  signal that each group is activated independently [13].

### **Mitochondrial DNA**

There are 22 transfer RNAs are encodes in mtDNA, and two ribosomal RNAs, and for oxidative phosphorylation having 13 essential proteins and for ATP production the quintessential machinery is responded [14]. Absence of protective histone molecules and the limited mtDNA repair enzymes then mtDNA have a susceptibility to oxidative damage, and

also mtDNA have a chance to mutations, and finally produces mtDNA damages is occurred [15, 16, 17]. Aging and the number of human inherited mitochondrial disease which producing mutation in mtDNA and to accumulate [18]. That is demonstrated by mice through carry a mtDNA polymerase with mutation which leads to mtDNA proofreading activity of enzyme is to be disabled [17]. That result during mitochondrial replication the mtDNA mutation can be accumulated [17] and finally the mutant mice show pathologies [17].

### **Energy Production of Mitochondria and the release of Reactive Oxygen Species**

The enzyme involved in oxidative phosphorylation which is present in mitochondrial inner membrane of large surface area, and they act as impermeable for energy production from oxygen. Through flow of electrons together with electron transport chain of five molecular complexes which helps to production of ATP takes place. That time mitochondrial membrane potential will be created due to electron transfer that finally produces transfer of proton is to be reciprocated. As a result the by-product of Reactive Oxygen Species are produced and the electron acceptor finally during process of ATP production. The major producing of intracellular ROS in the cell by the electron transport chain of mitochondria and also they are the major target for damages by reactive oxygen species [19, 20]. Production of ROS is very important for maintaining signaling pathway, and they are tightly regulated by antioxidants and also other than use of normal cell functioning they are used for homeostasis of calcium and iron and also various cell signaling pathway [21].

### **Reactive Nitrogen Species**

Nitric Oxide which is produced during mitochondrial respiratory chain, and they also consist of free radical which is unpaired electrons, the other by-product of nitric oxide is called as reactive nitrogen species. For example during reaction of nitric oxide with superoxide anion, peroxynitrite is formed farther rapid and it is a one of the highly toxic molecule. The cytotoxic action of nitric oxide is thought to by peroxynitrite. But the nitric oxide have some physiological roles, but through oxidation, nitration, or nitrosylation the reactive nitrogen species produce detrimental effect in various cellular targets which includes nucleic acid, proteins and DNA and endogenous antioxidant product such as glutathione [22]. It has been proposed that, although this is by means no certain in mitochondrial form of NOS exists [23, 24].

### **Stress induced Mitochondrial Damages**

Oxidative stress due to decreased antioxidant defense system that majorly producing damages in nucleic acid, lipids and proteins within both cell and mitochondria. For example peroxidation will be occurred in cardiolipin in the mitochondrial lipid which is usually present in mitochondrial inner membrane plays an important role in energy metabolism due to peroxidation causes cytochrome C is dissociated and finally reduced ATP production and increased ROS production [20, 21, 25, 26]. Due to oxidation and peroxidation of the component enzyme the antioxidant systems are affected themselves due to presence of oxidative stress.

### **Mitochondrial DNA damages**

During that process mitochondrial DNA also damaged because they are very close to the electron transport chain. For maintaining electron transport and energy production they needed some polypeptide components so the mtDNA which encodes some polypeptide plus that is ribosomal RNA species and transfer RNA species. Expressed gene which is encodes in

mtDNA but the genomic DNA having many non coding sequence and thus the functional mutation their potential is higher [27]. When mtDNA damages can occur the electron transport enzymes loss their functions and that time generation of ROS is increased and may decrease the antioxidant defense systems that may cause cell death occur and this is called as toxic oxidative stress or mitochondrial catastrophe hypothesis [28].

### Mitochondria and apoptosis

In the respiratory chain cytochrome C is an essential component because they facilitate the electron transfer from complex 3 to complex 4 [29]. Finally, electron transport chain is disturbed due to membrane permeabilization in mitochondria, and mitochondrial dysfunctions, at last the oxidative stress they also affect cytochrome C functions [30]. At that time the release of cytochrome C from mitochondria to the cytosol that causes activation of caspases when it triggers downstream process and finally producing complex within the caspase-activated complex this process causes producing apoptosis and also in cellular component's degradation is occurred [31], and the release of cytochrome C also activates the caspase 3 and 9 in the cytosol through apoptosis complex will be formed by binding to and finally the apoptotic protease factor 1 is to be activated [32].

### Lipid Oxidation and Apoptosis

Lipid oxidation also plays a very important role in apoptosis inductions [33, 34]. Mitochondria-specific lipid is the cardiolipin whose oxidation is occurred that causes membrane permeability in mitochondria and also the recruitment of BAX and the pro apoptotic protein [33, 35, 36]. Normally cytochrome C is associated with cardiolipin which is usually present in inner membrane of mitochondria [37, 38]. As finally cardiolipin oxidation causes permeabilization in the mitochondrial membrane and dissociation of cytochrome C and then it release [38, 37, 39].

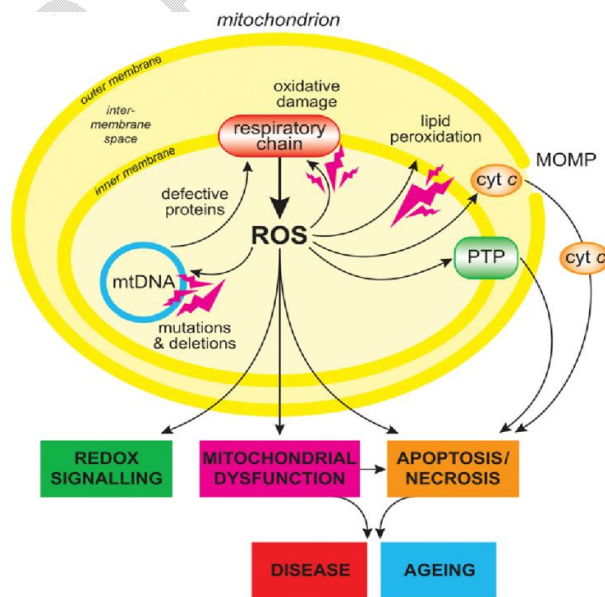


Fig 1: Oxidative Stress and Mitochondrial Dysfunction[40]

During electron transport chain mitochondria produce Reactive Oxygen Species can lead to oxidative damages to mitochondrial proteins, membranes and DNA, and also they causes impairing the ability of mitochondria to synthesis ATP and other essential functions. Oxidative damage in mitochondria also increases the tendency of mitochondria and to release the cytochrome C into cytosol by the Mitochondria Outer Membrane Permeabilization, this leads to apoptosis. Oxidative damage of mitochondria contributes a wide range of pathologies, and the ROS production of mitochondria act as a reversible redox signal modulating the activity of a range of cellular functioning [40].

### **Mitochondrial dysfunction in Neurodegenerative disease**

Normally the brain consists of only 2% of human body mass, but they consume body resting ATP production of 20% [41]. In studies demonstrate that when associated with mitochondria in neurodegenerative disorders produce manifest pathological events. These include oxidative stress, mitochondrial dysfunctions [42], apoptosis and autophagic dysfunctions.

### **Alzheimer's disease**

In most common of the neurodegenerative disease, Alzheimer disease (AD) is also one of that, but to estimate the worldwide Alzheimer patient is nearly 46.8 million [43]. AD is consisting of cognitive disorder, but they are related with  $\beta$ -amyloid peptide which is normally composed as senile plaques and also hyperphosphorylated tau which is also normally composed of neurofibrillary tangles [44]. But also deposition Amyloid  $\beta$  causes neurotoxicity also due to mitochondrial dysfunctions [44]. In report says that in amyloid precursor protein translocation occurs and to be accumulated in membrane of mitochondria [44], by  $\gamma$  secretary cleavage may be occurred and thus forming the  $A\beta$  peptide of toxic compounds [45, 46]. Number of mitochondrial proteins are affected due to  $A\beta$  peptide interacts and finally produces apoptosis by disturbs the membrane potential of mitochondria through cytochrome C release [47, 48].

### **Pathogenesis**

Oxidative damages to the mtDNA which produce the pathogenesis of Alzheimer's disease [49]. In AD patients showed increased mutations of regulatory regions of mtDNA [50]. These mutations produce mtDNA transcription and mtDNA copy number reduction of 50% and also increasing mitochondrial dysfunctions [50]. Due to mitochondrial dysfunction and to ensuring the ROS generation in AD patients is documented well. Mitochondria fusion is disrupted by  $A\beta$  that finally produces fragmentation occurred in mitochondria [51, 52]. Mitochondrial fusion and neuronal damages by the two crucial factors such as increased  $A\beta$  and their interaction with DRP1 [53]. The pathologic  $A\beta$  OR Tau mediated problems such as fragmentation of mitochondria, dysfunction of mitochondria and also synaptic depression in neuron, but they can be restored by conversely reduction or inhibition of DRP1 also with mitochondrial division inhibitor.

### **Cerebral Ischemia due to mitochondrial dysfunction**

Evidence says that reactive oxygen species, and they are produced by mitochondria partially produced the cerebral ischemia plays a vital role in this pathology. By using antioxidants helpful for slow down the appearance and symptoms in cerebral ischemic brain and the lifespan of organism will be increased.

### **Cerebral ischemia and their causing**

Cerebral ischemia may be defined as delivery of substrates are limited that is some main constituents are glucose, oxygen, and also energy requirement is decreased in brain [54]. At last, they may cause death, but now there is increasing evidence suggested that mitochondrial dysfunction plays a vital role in producing apoptotic and necrotic neuronal cell death when after cerebral ischemia will be occurred [55, 56]. Necrotic or apoptotic cell death are due to mitochondrial swelling, and they are induced by cerebral ischemia and also by mitochondrial permeability is to be opened leads to transition pore, so these are the reason for the cell death of after cerebral ischemia [57, 58, 59]. Reactive oxygen species overproduction from either by electron transport chain of mitochondria or from stimulation excessive in NAD(P)H, finally produces oxidative stress

### **Mitochondrial dysfunction in ischemic brain**

In life and death of cells, mitochondria play an important role and also they are very important in performing several functioning. Impairment of energy production in mitochondrial is the major cause of mitochondrial dysfunction and also disturb occurs on oxidative phosphorylation [60, 61]. Mitochondrial membrane potential maintenance is very important because these helps to activation of adenosine triphosphate and to generate high energy phosphates through proton gradient across the inner membrane these are totally disturbed during cerebral ischemia. When loss of mitochondrial membrane potential occurs, these are the common risk for ischemic destructive process and there are producing progression and initiation of cell death [62, 63]. In that disease I conclude that major target is mitochondria and these are the source for oxidative stress so excess oxidative stress has been producing the pathogenesis of cerebral ischemia. The main contributors for necrotic or delayed neuronal cell death by these oxygen free radicals and also these are the powerful initiators for the inflammation and apoptosis [64].

### **Antioxidant Protection**

In normal condition the antioxidants which protect the mitochondria from an oxidative damage of ROS through several interacting antioxidant systems, but when the antioxidant production is decreased oxidative stress initiates damages to nucleic acids, proteins, and lipids in mitochondria, this causes loss of enzyme function in the electron transport chain and finally mitochondrial dysfunction occurs and impairment of ATP production [65, 66]. Due to protein oxidation and peroxidation of cardiolipin the endogenous antioxidant system can also damage this leads to dissociation of cytochrome C, reduce ATP production and further increased generation of ROS. The antioxidant defense system present in mitochondria and they activates at several levels. They also use both enzymatic and non-enzyme pathway to scavenge mitochondrial ROS and also including some are manganese containing superoxide dismutase, the glutathione and thioredoxin systems, peroxiredoxins, cytochrome C, peroxidase and catalase [67, 68].

### **NATURALLY OCCURRING ANTIOXIDANTS**

Some evidence suggested that antioxidant treatment which helps to delay the disease progression in neurodegenerative disease of the animal model. Some natural antioxidants help to give protective effect in ischemic brain. That is

#### **SKQ1**

In aging process mitochondria are very important, one of the mitochondrial targeted antioxidant is lipophilic cation SKQ1 which is present more in inside of mitochondria, and

they are only formed by negatively charged compartment in the organelles of the cell. In inner mitochondrial membrane having high membrane potential they together with plasma membrane of membrane potential and the effective hydrophobicity of skq1 finally produce accumulation of skq1 in the inner leaflet of mitochondrial membrane of inner position [69]. After the scavenging of ROS oxidized skq1 is formed and it is rapidly reduced by the mitochondrial respiratory chain at last production or regeneration of reduced form of skq1. And also after cerebral ischemia skq1 helps to diminish the mitochondrial fragmentation then they help to prevent progression of apoptotic cascade [70].

### **Mito Q**

Mitochondrial are the major source for superoxide free radical and also vulnerable to the oxidative damage. In cerebral ischemia, oxidative damage is produced in mitochondria that contribute to mitochondrial dysfunction and cell death. A lipophilic triphenylphosphonium cation is called as MitoQ these helps to pass easily in the phospholipid bilayer of mitochondria [71, 72]. Numbers of animal model of diseases are tested by MitoQ where supplementation with MitoQ in rat which helps to decrease heart dysfunction, mitochondrial damage and cell death [73, 74]. And also they protected endothelial cell function, mitochondrial enzyme damage in rat model of oxidative stress [75].

### **CoQ10**

CoQ10, it is one of the fat soluble quinone with 10 five-carbon isoprenoid units, these helps to act as antioxidants and also they protect the cell against oxidative damage. It is an important component in mitochondrial electron transport chain, they are transferring electron in the respiratory chain and play an vital role in membrane stabilization [76]. It also improves neurological outcomes and they helps to prevent neuronal damage by reducing the free radical production and also preventing lipid peroxidation

### **CONCLUSION**

In this review, I conclude that mitochondria called as power houses of the cell, and they are very important is to energize ATP to the cell by metabolizing nutrients and these are the responsible for cellular process ranging from energy metabolism, generation of ROS and Ca<sup>2+</sup> homeostasis cell survival and death. Mitochondrial structural and functional changes cause ageing, cancer, metabolic syndrome, diabetics, obesity, heart related, lung related and neurodegenerative disease etc. Mitochondrial DNA is very sensitive to oxidants because they contain the mitochondrial proteins. When damage to mitochondrial DNA, causes impairment produce in electron transport chain and potential loss in mitochondrial membrane. So that time majorly affecting lung related, heart related and neurological related disease will be produced. One of the treatments is taking proper antioxidant and proper life style intervention (healthy diet and regular exercise) which helps for inducing mitochondrial biogenesis.

### **Abbreviations**

Not applicable

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