Mitochondrial Pharmacotherapeutics - Advancements and Applications

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Abstract. Mitochondria, known as the "powerhouse of the cell", plays an important role in the occurrence of multiple diseases and disorders. Mitochondria are believed to come into existence from the synergistic relationship between the proto-eukaryotic and primitive prokaryotic efficient by oxidative phosphorylation. It is the major hub of Adenosine Tri Phosphate production through the implementation of oxidative phosphorylation. It is the processing unit of the "Electron transport chain". Mitochondria is useful in dealing with various cancers, cardiovascular problems, fatty-acid oxidation disorders, and several kinds of tumours and also several cancers.

Keywords: Mitochondria, Evolution, Therapy, Reactive Oxygen Species, Apoptosis.

1 Introduction

Mitochondria is also called as "Powerhouse of the cell". They havea major role in many diseases and disorders as they have various functions.Mitochondriaplay animportantrole in bothi.e.,cellular and gross levels. Mitochondrial Pharmacotherapeutic is an upcomingstudy, where treating the disorders related to the functioning will influence the outcomes of diseases. In a review by Cowdry (1918), more than a dozen terms i.e., blepharoblast, chondriomites, mitogel, chondriokonts, chondrioplasts, parabasal bodies, plasmasomes, plastochondria, plastosomes, vermicules, sarcosomes, bioplasts,etc are used to name the structure which is now identified as mitochondria. Microbiologist Carl Benda coin the term "mitochondria" from the Greek word *mitos*"**thread**," *Khondrion* "**little granules**" in 1898[1].By improving straining techniques more proper etymological explanation obtained which display the granules were in some tissue seen as thread[2, 3].

Almost 120 years ago, by looking carefully in cells of higher organisms the relationship between bacteria and mitochondria was discovered. This belief was very helpful afterthe revealing of DNA in mitochondria[4]. The first origin hypothesis suggested that mitochondria originated from individual cells via the method of intracellular compartmentalization as well as working specialization. The second assumption suggested that mitochondria arose from a synergeticconnection by linking a proto-eukaryotic cell as well as primitive prokaryoticefficient oxidative phosphorylation. Out of these two,the 2nd presumptionis seriously considered because of the discovery of DNA in mitochondria and due to all the mitochondria containing DNA thatis present in Eukaryotic cells. The DNA present in mitochondria could be muted but it does not affect the activity of mitochondria to carry out oxidative phosphorylation and respiration. Mitochondrial DNA was equipped with very definite and special proteins, but adequate information cannot be encoded for free-livingorganisms. The proto-mitochondrial genetic code was transferred into the nucleus to accountfor the failure of genetic information as primordial proto-mitochondria[2, 5].

Evolution in mitochondrial studies

Altman unveiled a remarkable revelation in 1890, that subcellular granules bore remarkable similarities to bacteria in terms of their shape and mass, shedding light on the potential connection between these microscopic entities[6]. He named them bioblast and suggested that bioblasts are responsible for cellular activity. He believed that these bioblasts have independent existence like bacteria because of their colonial association in the cytoplasm of host cells[2, 7, 8].

During the turn of the century, Benda introduced the term "*mitochondrion"* which means thread-like granules. Around the same time, Michaelis developed a method for specifically staining mitochondria at around the same time called the supravital technique using the redox dye Janus green[9]. This discovery gives evidence that mitochondria tend to reduce dye and givesan exact benchmark for the cytological identification of organelle. In 1900-1940 for explaining the oxidation of substrate in aerobic organisms, Wieland stated that the substrate oxidized because of catalytic activation of abridged compound which can then react with molecular oxygen[3, 7].

Epicentrefor metabolism of energy (mitochondria)

Bensley and Hoerr experimented in 1932 where they extracted a granular fraction from the liver of guinea pigs, in which mitochondria were identified through analysis**.** The study was distrusted by cytologists because Bensley's work was not able to fulfillthe isolation fraction when tested for in-situ identification of mitochondria[10]. Hogeboom, Schneider, and Palade through their work and experimental results reported that about 80% of cytochrome succinate oxidase was isolated in the mitochondrial fraction. Green, Loomis, and Auerbech resulted that the complete citric acid cycle was somehow related to gritty fraction obtained from both kidney and liver homogenates which firstly were known as cyclophorase systemsand later showed that consistsof mitochondria[11]. By using Hogeboom, Schneider, and Palade methods,Lehninger proposed that the citric acid cycle and fatty oxidation occur in mitochondria[5, 7].

2 Structure and morphology

the tendency of mitochondria to reduce Janus Green dye plays an important role to find out the structure of mitochondria. Although electron microscopy and specimen preparation make the study of structure possible initially, the use of light microscopes for structural studies rehabilitated in the past few years. Mitochondria after staining with antibodies dyesi.e., TMRM (Tetramethylrhodamine methyl ester, perchlorate), could be viewed with the fluorescence microscope. Certain rhodamine derivatives and lipophilic "vital dyes" tendto concentrate in organelle and make it visible undera microscope and make important observations in mitochondrial studies. Rhodamine staining in living cell-associated time-lapse photography opened up that mitochondria keepon changing their shape and sizes[2, 5, 7].

As mentioned above mitochondria do not have a fixed shape, but in hepatocytes and fibroblasts, mitochondria are found to have asausage-like structure which is 3-4um in length and 1um in diameter. The number of mitochondria in each cell varies significantly because of differences in cell differentiation and specialization process[5, 8].

"A large mitochondrion's intramural cavity contains a network of circular DNA called the kinetoplast, which is home to numerous copies of the mitochondrial genome". Previously kinetoplast was found to be stainable with Janus green dye and give positive Feulgen reaction but electron microscopy reported cristae which are identical to those present in mitochondria and kinetoplast are reported to be present only in highly specific mitochondrion[3, 8].

Palade and his colleagues gave a new consideration to the morphology of mitochondria. He studied the mitochondrial profile in a thin section of mammalian tissue and recognized that mitochondria had an external limiting membrane and collection of inner covering pleats which he called"cristae mitochondrial". Later Fernandez-Moran reported that the inner mitochondrial covering is filled with sphere-shaped particles with a diameter of 90Angstrom using a negative staining technique. In 1965, Racker and his colleagues suggested that the internal membrane particles be bodily alike to F1 ATPase, this enzyme is involved in oxidative phosphorylation[5, 8].

In mitochondrial structure two membranes are present i.e., an outer mitochondrial membrane (OMM) and an inner mitochondrial membrane (IMM). Inner mitochondrial membranes include complexes I-V[8].

Complexes 1, 3, and 4 are vital in the production of electrochemical potential through the integration of electron transfer and proton conversion. They allow the movement of protons from the matrix to intermembrane space while facilitating electron transfer. ATP formation takes place in complex 5 as it uses this electrochemical gradient. Also, complex 2 assists in the transfer of electrons between complexes 1 and 3 and plays a significant role in the reduction of ubiquinone to ubiquinol [5, 8].

Fig.1 Interior membrane with mitochondrial complexes.**,** depicts the interior membrane of mitochondria where these complexes are situated on a framework made up of cardiolipin and several phospholipids. Complexes are denoted as 1 to 4, which are involved in the transfer of electrons. Coenzyme Q10 (Q) facilitates this electron transfer process with cytochrome c (CYT-C) in complexes 1 to 4. This transfer of electrons results in the generation of a powerful electric force, which drives adenosine triphosphate (ATP) synthesis via complex 5.

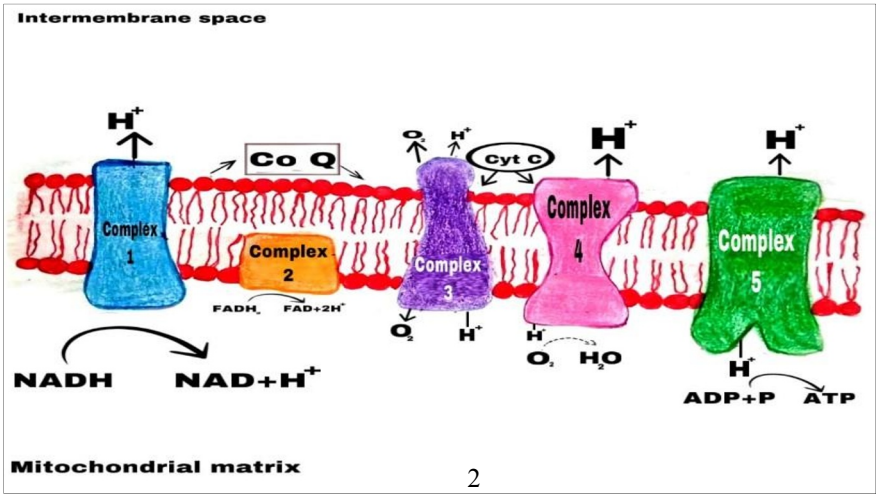

Fig.1 Interior membrane with mitochondrial complexes.

3Mitochondrial biogenesis

During cell division, organelle biogenesis is synonymous with organelle heritage. To lead two identical daughter cells, organelles must double their dimensions and separate. Mitochondrial biogenesis occurs through the development and distribution of pre-existing organelles[12]. Thus, the process by which cells increase their mitochondrial mass is known as mitochondrial biogenesis. New studies contain highlighted mitochondrial biogenesis as a possible aim for treating diseases that do not have an effective treatment. In cell mediation processes such as apoptosis, detoxification, buffering for $Ca^{2+,}$ and so on, mitochondria play an important part asthe main ROS producer as well as the major antioxidant producer. The mitochondrial main function makes it possible to cope with a wide variety of diseases. Pharmacology is possible to control mitochondrial biogenesis[13, 14].

Because of the endosymbiotic developmental beginning of this organelle, this study of mitochondrial biogenesis is particularly complex. Mitochondria are the most complicated as well as special organelles in which Eukaryotic andprokaryotic mechanismscoexist[15]. They have an internal along with an external membrane and have a minute genome. In addition, new mitochondrial biological pathways have formed along with endosymbiosis. To expand knowledge of the underlying mechanisms throughwhich mitochondriogenesis is induced in dissimilar tissues, they are important to use appropriate methods to quantify mitochondrial masses. Regulating mitochondrial content or mitochondrial mass in living cells is needed for the fine equilibrium of mitochondrial biogenesis, mitochondrial destruction, and mitochondrial mechanisms[14].

Free radicals are commonly considered damaging to cellular structures and senescence promoters. They also function as the next messenger by activating the signal that brings gene appearance. Free endogenous radicals also lead to mitochondriogenesis. Variable medications, including recognized nutrients and scavengers, can interact with these and other signals that lead to mitochondriogenesis such as NO donor, triterpenoid, erythropoietin, a thiazolidinedione, Metformin, AICAR, and many natural compounds. Therefore, the induction of mitochondrial and quality control biogenesis is a possible useful approach to the development of new therapies for mitochondrial damage and/or inflammation diseases.Recent findings have attracted much interest and have highlighted mitochondrial biogenesis as a crucial mechanism for extending life, for example, similar molecules and pathways and similar interventions in both processes[14, 16].

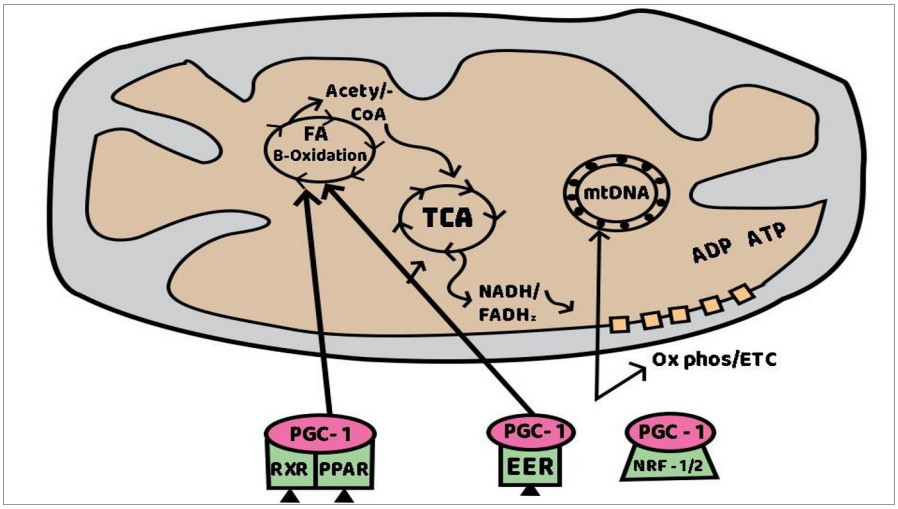

Fig.2PGC-1 regulation of the biogenesis of mitochondria.

In Fig.2, PGC-1 regulation of biogenesis of mitochondria has been demonstrated. Interaction between PGC-1 and unique transcriber factors is a complementary complement to the biogenesis of the PGI-1, which orchestrates the key functions of mitochondria, including fatty acid b-oxidation, and tricarboxylic acid cycle (TCA). To regulate the expression of several b-oxidation enzymes, PPARa interacts with its binding partner, the retinoid X receptors (RXR). NRF-1 and NRF-2 support mtDNA maintenance and multiple component expression of ETC.

4Functions

Mitochondria contributetoseveral important human metabolism reactions, including phosphorylation by oxidative substances, tricarboxylic acid cycle, oxidation by a fatty acid, iron sculpture, heme biosynthesis, and the metabolism of amino acids. In addition, mitochondria are essential to apoptotic cell death and modulate cell calcium flow. Superoxide is mitochondrial reactive oxygen (ROS), underlying redox signals in sensory hypoxia, cell differentiation, and innate immunity[17, 18].

MitochondriaRole in the Emergence ofROS

Mitochondria contain superoxide and other reactive species. The superoxide is prepared by the electron transport chain in mitochondria. Water is generated as an end product by the reduction of the cytochrome oxidase molecule by four electrons. The ROS is mainly produced in complex III by the method in which the proton revolves between ubiquinone, cytochrome b along with c1, as well as iron-sulfur proteins[19]. Mitochondria superoxide dismutase helps to convert superoxide into hydrogen peroxide which defuses out from mitochondria and enters intothe cytoplasm and in high iron concentration H_2O_2formsa highly reactive hydroxyl radical[20]. Natural protection mechanism neutralizes the ROS and their peroxidation components. Defencesystems contain glutathione peroxidase, phospholipid hydroperoxide glutathione peroxidase, and superoxide dismutase[21].ROS increase results from Ischemia-reperfusion, xenobiotic contact, inflammation, ultraviolet, and an impaired antioxidant protection mechanism. This rise in ROS results in mtDNA mutations,oxidation of lipid peroxidation proteins, and degradation of the cell and the entire organism[22]. The accumulation of ROS alters the function of many metabolic enzymes and electron transport chains which leadsto degenerative diseases like Parkinson's disease, Alzheimer's disease,Huntington's Disease, etc[18, 23]. Mitochondrial ROS developmentcan result in oxidative harm to mitochondrial membranes and DNA, affecting mitochondria's ability to synthesize ATP and conduct its wide range of metabolic activities, including tricarboxylic acid cycles, fatty acid oxidation, urea cycles, amino acid metabolism, haem synthesis, and FeS core assemblies, which are crucial to normal operations.

The propensity of mitocryansincreased due to mitochondrial oxidative injury which releases the cytosol from intermembrane spatial proteins such as cytochrome C (CYT-C) from mitochondrial outer membrane permeabilization (MOMP).In addition, mitochondrial ROS development contributes to the activation of the mitochondrial transition pore (PTP). In situations such as ischemia/reperfusion injury the inner membrane becomes permeable to small molecules. Therefore, a large variety of pathologies is caused by mitochondrial oxidative damage[18, 23].

System of electron transfer&synthesis of ATP

The mitochondrial respiratory chain, which is located inside the inner membrane of mitochondria, comprises enzymes and coenzymes that play a critical role in transferring H atoms or electrons and reducing equivalents from respiratory substrates to molecular O_2. It contributes to 70–80% of ATP synthesis by oxidative phosphorylation in mitochondria. The chain of electron transport uses energy created through the oxidation of NADH to transport protons from the mitochondrial matrix to the intermembrane space. This flow of protons causes an electrochemical gradient commonly known as the proton motive force. It facilitates the backflow of protons through the ATP synthase complex. Mitochondria have certain specific characteristics that contribute to their function in energy production. They generate a transmembrane electrical potential of up to 200 mV by separating a charge across the inner mitochondrial membrane. Also, it maintains the -ve charge within its core and an internal pH of about 8. Among these mitochondrial functions, the most significant one is their capacity to produce ATP from ADP and phosphate, which is vital for cellular energy production[19, 24].

Plants synthesize ATP by utilizing the proton gradient produced by the thylakoid lumen through an ATP synthase enzyme present in the thylakoid membrane and chloroplast stroma, which facilitates photosynthesis.

Significance of mitochondria in apoptosis

Mitochondria play a role in apoptotic programmed cell death. Apoptosisisinitiated by ligand binding to the dead receptor at the cell outside, in this way mitochondria is involved. Mitochondria releasea number of apoptogenic factors like cytochrome through its outer membrane. Incomplete self-digestion of the cell occurs due to the activation of intracellular protease of the caspase family[19, 23].

PT is usually detected by fluorescent dye loss for which the absorption and concentration in mitochondria is dependent on acid. A highly conserved porin VDAC is an intrinsic membrane pore homologous protein. VDAC plays a significant role in mitochondrial-mediated apoptosis, but the essence of its function is highly contradictory[19, 25].

Nonetheless, the ROS fraction which escapes catalytic extraction in mitochondria might root significant additional oxidative stress. ROS hasa main part to play in promoting mitochondrial CYT-C entry. In normal circumstances, CYT-C is connected with cardiolipin to the internal membrane. Cardiolipin peroxidation contributes to CYT-C dissociation and release into the cytosol from the external membrane. It is not clear through what mechanism CYT-Cis released

from the external membrane. Inside cytosol, CYT-C allows caspase 9 to be activated and in turn the caspase cascade to be activated[19, 26].

Fas-FasL binding mechanism does not involve in effects like DNA damage, decreased growth factors, etc these are initiated with some other mechanism. Unregulated apoptosis receptors, proteins BH3 (Bim, Bid, PUMA, NOXA, etc.) tell the cell to be subjected to apoptosis. If the cell has suffered DNA damage, it may have increased levels of expression due to increased P53 levels of BH3 Protein (PUMA, unregulated apoptosis modulator p53).

5Dysfunctions of mitochondria

Mitochondrial dysfunction is of two types-Primary dysfunction and Secondary dysfunction. Main dysfunction resulting from mtDNA or nDNA- encoded gene mutation. Secondary dysfunction is caused by pathological incidents which occur onthe external side of the mitochondria[27].

- In 1959,a paper, identified that three patients with hyper-metabolism had increased endogenous adenosine triphosphate production in the skeletal-muscle mitochondria and impaired regulation of cell respiration because of available phosphate acceptors.
- In patients, mitochondrial dysfunction is secondary to thyrotoxicosis[28].
- ATP production deficiency is linked to many mitochondrial diseases. In the respiratory chain, myoclonic epilepsy with ragged-red fibers (MERRF), recurrent progressive outer ophthalmias (CPEO) and mitochondrial myopathy, enceptal disorder, and stroke episodes (MELAS) are confirmed to have a defective disorder[29]. In addition to proteins, an electron transfer mechanism needs specific small molecules, including coenzyme Q10. There is also a possibility of mitochondrial therapy for these small molecules and proteins[30].
- The damage done by ROS affects the role of many of the metabolic enzymes, including the electron transport chain, within the mitochondrial matrix. Superoxide dismutase is an especially important protein that loses its function after oxidation.
- The absence or reduction of superoxide dismutase activity can impair the functionality of antioxidants and cause hyper-oxidative stress. This imbalance in oxidative processes has been linked to various degenerative disorders, such as Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis (ALS). The severity of these conditions has been associated with mitochondrial DNA damage.
- Medications suppress mitochondria, destroying cancer cells; defending cells from oxidative damage, and fixing defects. Different strategiesare needed for the mitochondrial use of various pharmacotherapeutic agents due to the complex nature of mitochondria[8, 27, 31]

Drugs that cause secondary mitochondrial dysfunction and its treatment

- The mitochondrial oxygen intake was inhibited with analgesic acetaminophen.
- HMG-CoA reductase (statins), which prevents the synthesis of endogenousCoQ10, is due to a reduction of CoQ10 levels as a consequence of myopathy.
- Cardiotoxicity caused by doxorubicin (Adriamycin) is due to oxidative stress and bioenergy deficiency because the complex I redox cycling is capable of producing superoxide[8, 27, 31].

5 Treatments

- Primary mitochondrial disorders treatments arenot very known except for replacement CoQ10 therapy in patients with CoQ10 synthesis defects[32].
- Different approaches to secondary mitochondrial disorders have been proposed. Such drugs un-target mitochondrial agents and drugs for the translation of mitochondrial genes have been identified as mitochondrial-target drugs[33].
- CoQ10 has been proposedas mitochondrial-targeted therapy for secondary mitochondrial disorders but a proper study has not been performed to support their efficacy.
- Another mitochondrial antioxidant, MitoTEMPO, used to reduce to minimize sepsis-induced acute kidney injury by decreasing mitochondrial superoxide rates and preservation of capillary blood flow was attempted to enhance the release of CoQ10 in the mitochondrial medium by combining the mitochondrial triphenylphosphonium ion (TPP+) in this difficulty[34].
- Targeted mitochondrial peptides are a promising treatment option for several causes of mitochondrial dysfunction[27]. The SS-31 peptide mentioned in this issue is most extensively examined.This peptide can penetrate the OMM and focus selectively on cardiolipin by securing an IMM which causes conformation changes that optimize the mitochondrial transport of electrons and ATP synthesis while inhibiting the peroxidation of cardiolipin[35]. In the pathophysiology of a wide range of diseases, mitochondrial dysfunction has proven to be of central importance and contributesto off-target drug effects[36].

6 Therapeutic applications

Mitochondrial Therapeutics for Cardio Protection

The heart is a highly active organ and mitochondria account for approximately 35% of adult cardiomyocytes volume. Cytochrome c, activation of caspase, and apoptosis may lead to severe consequences of defective mitochondria in the cell. Defective mitochondria can also allow the reactivation of proteases, lipases, and eventually necrotic cell deaths from reactive oxygen species (ROS) and calcium. Due to oxygen impoverishment during ischemia, oxidative phosphorylation is halted, intracellular ATP and Creatine phosphates are decreased and heart contractility is impaired[37-39].

The lactic acid aggregation and pH reduction during ischemia inhibit ATP generation from glycolysis[40]. To re-establish the pH of the antiporter Na+/H+ means the intracellular Na+ concentration is being simultaneously increased. In addition, the increase in the concentration of intracellular sodium slows or reverses the $Na+/Ca^{2+}$ path, which leads to a rise in Ca^{2+} concentration. Mitochondria are the buffer for intracellular calcium, and consequently the increasing levels of cytosoliccalcium cause an increase in the calcium levels in the mitochondria. The ROS development of the mitochondrial transfer systems I and III is thus increased and the antioxidantdefences are subsequently decreased. The production of ROS increases steadily during its chemicals and increases dramatically when oxygen stress increases[41].

Mitochondria perform important functions, including ATP manufacture by oxidative phosphorylation, heme biosynthesis, calcium signalling, and homeostasis. Nevertheless, defective mitochondria may have serious implications for the cell, causing caspase activation and apoptosis; via the discharge of cytochrome C. Defective mitochondria can allow the proteases reactivation, lipases as well as eventually necrotic cell deaths from reactive oxygen species and calcium. Giventhe serious effects of cell mitochondria, cells have evolved several mechanisms for preventing or repairing mitochondrial damage and for removing and replacing it if this is not possible[42].

Mitochondria and cancer

The mitochondrial role is important in the viability of cancers because the removal of mitochondrial DNA (mtDNAs) cells decreases the rate of growth of these mitochondrial DNA cells and increases their genetic tumorigenicity[43]. Increasing levels of succinate, fumarate, or R (-)-2-hydroxyglutarate are caused by mutations affecting mitochondrial metabolism in nuclear DNA genes, including succinate dehydrogenase (SDH), fumarate (FH) isocitrate dehydrogenase 1 (IDH1) and IDH2. These metabolic changes can inhibit different dioxygenases which rely on α-ketoglutarate and can activate the pathway to NFE2-related factor 2 (NRF2). This can all contribute to tumorigenesis[44].

Variations in mitochondrial metabolism may add to the synthesis of ROS and modify cell redox status, altering transcription factors like HIF1α and FOS – JUN to change the gene expression and promote the propagation of cancer cells. The reduction in mitochondrial membrane potential or the PML gene decreases Ca^{2+} intake and thereby decreases the activation of the mitochondrial intrinsic pathway of apoptosis. Reduced Ca^{2+} mitochondrial retention raises the concentration of Ca^{2+} cytosolic. In neighbouring stromal fibroblast cancer cells, ROS production inactivates caveolin 1. It improves mitophagy, decreases mitochondrial activity, and enhances lactate manufacture. Then, oxidative metabolism in cancer cells is carried by secreted stromal cell lactate, which promotes the growth and proliferation of tumours[45, 46].

Oxidation disorders of the mitochondrial fatty acids

Genetic fault in beta-oxidation of mitochondrial fatty acid contains at least 12 diseases with specific enzymes or carriers of defects[47]. The age and clinical severity of most such diseases are variable. The symptoms of mitochondria are typically episodic and related to mild infectious illness, physiologic stress, long-term exercise, and excessive fatty acid oxidation. Patients experience fasting hypoketotic, cardiomyopathy, rhabdomyolysis, hepatic dysfunction, or sudden death depending on the particular genetic defect[48].

The recognition depends on the result of different biochemical markersi.e., metabolites of acylcarnitine present in blood and urinary dicarboxylic acids, also in acylglycines. Positive testing includes both enzymatic studies and DNA analysis. Therapeutic methods as well as sudden death are typically effective in avoiding violent symptomatic episodes[49].

Gold (I) phosphine complexes cytotoxicity and antitumor activity mechanisms:possible function of mitochondria

Mitochondria are known for their anti-arthritis medicinal properties, as a possible anti-tumor agent with gold (I) phosphine derivatives. Gold drugs are also one of the active *in vivo* drugs. Auranofin, a linear phosphine complex of tetra acetylthioglucose gold (I), prolonged the lifespan of mice inoculated with P388 leukaemia, inhibited DNA polymerases, and was selectively cytotoxic to cells with altered mitochondria[50]. In some models of murine tumours*in vivo*, reproductible and important antitumor activity was identified in Bis[1,2-bis(diphenylphosphino)ethane]gold(I) chloride ([Au(dppe)2]Cl)[51].

In-vitro, DNA strands beaks formed of DNA and cross-links mediated DNA-protein, and with had anti-mitochondrial effects on the cells of P388 leukaemia and isolated hepatocytes, also injected tumours of the colony[52]. The bidentate pyridyl phosphine complexes in Tetrahedral-Au (I) have shown promising anti-tumour properties that are certainly their medical lipophilicity.While their intracellular targets are not obvious, they are directly cytotoxic and many tend to be

anti-mitochondrially active. Optimizing the hydrophilic/lipophilic balance may be necessary to boost the tumour mitochondrial selectivity of normal cell phosphorylation pathways[53].

Intracellular target of a boronated porphyrin photosensitizer: Functional Mitochondria

A boron-containing porphyrin photosensitizing derivative BOPP has been tested on 2 genetic configurations: p+ cells with normal mtDNA and mitochondrial respiratory function or pO cellswithout d-DNA & oxidative phosphorylation in mitochondria[54]. The BOPP is located selectively in Mitochondria. The BOPP (30 /xg / ml) after short cell uptake was not cytotoxic for 18 hours but showed strong phototoxicity in Namalwa p+ cells, followed by a substantial reduction in respiratory mitochondrial action[55]. BOPP has been shown to have a strong inhibitory effect on the mitochondrial p+ cell respiration immune to the azide. The present findings suggest that the removal and photoactivation of the functional mitochondrion is a significant cellular target *in vivo*[56, 57].

The increased fission of mitochondria promotes autophagy and hepatocellular cell survival via the NFKB and TP 53 pathways, which are coordinated with ROS modulations

Mitochondrial morphology in cells is dynamically restructured with fusion & fission and tumorigenesis includes dysregulation of this method. Nevertheless, in hepatocellular carcinoma (HCC), the process by which dynamic mitochondrial influences cancer cell survival is much less evident[58]. The variation of mitochondrial dynamics and their act throughout the control of the cells' artophagous and HCC survival have been systematically investigated[59]. In addition, the molecular and therapeutic processes behind the scenes were extensively investigated[60].

Elevated fission with mitochondrial due to forced expression of DNM1L or MFN1 prompted the *in vitro* as well as *in vivo* survival of HCC cells, primarily by making autophagy and mitochondrial-dependent apoptosis less difficult. Further, the task is demonstrated to promote survival of increased fission with mitochondria and was mediated by increased production of ROS[58, 61].

TP53 and the NFKB pathway interacted in the regulation of mitochondrial fission-mediated cell survival. Additionally, using an in vivo engraft nude mice model, mitochondrial division inhibitor-1 treatment significantly reduced the growth of tumours[59].

Targeting cellular antioxidants approaches for mitochondria: clinical implications

The mitochondrial function is important to regulate the life cycle of cells and is especially involved in cellular redox / oxidative balance[62]. It has a wide range of human diseases. Mitochondrial therapy has increased interest as a potentially effective treatment for a number of human diseases, especially those involving mitochondrial antioxidants. Over the last ten years, substantial progress was prepared in production as well as functional analysis of molecules targeting different mitochondria, and the compounds with antioxidant properties have been based in particular[63].

Talking about antioxidants and various redox active molecules, current work focuses on producingmoleculesthat can modulate certain processes that are regulated by mitochondria such as apoptosis and autophagy. As a delivery tool with wide-ranging mitochondrial manipulation opportunities, several chemical molecular strategies have been developed[64]. To establish the clinical significance of these molecules, further research is needed through in vivo studies performed under conditions that mimic physiological relevance. These studies are necessary to validate and confirm their practical importance in a clinical setting.

Newly developed multifunctional cancer therapy mitochondrial strategies

One key aim for cancer science is considered the realization of modified oncology which is the creation of multifunctional agents in simultaneous tumour targeting, imaging, and thesis[65]. Mitochondria participate in a variety of physiological activities and play a main model in the development and rise of cancer[44]. Increased work is being conducted to draw on different mitochondrial targets along with new mitochondrial medicine systems to improve cancer treatment strategies[66]. Present principles of tumour targeting and alternative approaches for mitochondrially targeted therapy are further extended by multifunctional nano-structures or multifunctional chemical compounds[67].

Differenttypes of systems using fake structures and sequences to aim and cure cancer have been developed to achieve success in the use of synthesizedcompounds to increase the right to use cancer mitochondria. A number of main outcomes show important promises of utilizing effective mitochondrial suppliers in various DLCs, amino acids, and peptides. Numeral mitochondrial unambiguous properties have been defined[67, 68].

It would significantly improve the selectivity of mitochondrially targeted anticancer drugs if we had a better understanding of the primary pathophysiological differences in mitochondrial function between cancer cells and normal cells[69]. With a better understanding, it will be possible to develop more specific and selective therapies that specifically target cancer mitochondria. There must however be substantial efforts to address numerous basic and

technological problems i.e. surface opsonization, retention along with the absorption of reticuloendothelial tissues, difficulty locating and penetrating tumours, and long-term fatalities and questions about poisoning[70].

Carbon Monoxide Activates autophagy by mitochondrial, reactive oxygen-forming cells

Autophagy is an autodigestive mechanism thatdegrades cell as well as protein organelles. Carbon monoxide (CO), a poisonous gas and a candidate therapeutic agent allows for cytoprotecting acute lung injury models in animals. The underlying mechanisms of CO-dependent protection of pulmonary cells and autophagy remain confused. Co-presentation in the lung of the mouse, as well as in human alveolar cells (A549) or bronchial cells, cultured human cells, has been increased by expression of the autophagous protein, the microtubule-associated protein–1 light chain-3 B (LC3B). In addition, CO increased the self-phagosome formation in electron microscopy of epithelial cells and puncta-assays for GFP-LC3 green-fluorescent protein. In stimulating autophagy, the reactive oxygen (ROS) species play an important role. CO up-regulated ROS generation in epithelial cells, depending on mitochondria, as tested with MitoSOX fluorescence[71-73].

Mitochondrial ROS production, CO promotes the self-reportable cycle. Relation between autophagic proteins and the hyperoxic stress model of CO-dependent cytoprotection.CO protected cells from death by hyperoxia and inhibited the development of ROS-related hyperoxia[74]. CO was affected in epithelial cells infected with LC3B-small RNA interfering (Si) which shows an autophageal protein role to protect against Hyperoxic cell mortality and activation from Caspase-3. Such experiments show a new protective mechanism for CO to promote the future medicinal use of this product[75, 76].

Mitochondria and cells death: BCL-2 family-driven therapeutic targeting:

Few have been carefully classified among preclinical and clinical compounds reported. Recorded in literature is limited by utilization of sufficient biochemical and biological resources (i.e. cell lines designed for different BCL2 proteins). In addition to rigorous studies, the growing amount of genuine BCL-2 inhibitors will have a positive impact on potential developments in this area. BH3mimetics has now grown in a mature phase in the treatment of tumours and suspected auto-immune diseases[77-79].

However, the production of compounds targeting specifically MCL-1 or A1, complementing the present range of available molecules, has been lagging. These agents assist in understanding the act of two main proteins for survival and provide resources to assess MCL-1 and A1 inhibition therapeutic relevance and health. The lack of established apoptosis inhibitors is also preventing significant progress toward establishing a definitive connection between higher-regulated apoptosis and neurodegeneration diseases[80, 81].

Resveratrol, a grape tumour suppressant, induces apoptosis via a new Bcl-2-controlled mitochondrial pathway

The phytoalexin in grapes and in other plant foods, which was resveratrol (3, 5, 4'-trihydroxy-trans-stilbene), caused a loss of mitochondrial potentials of transmembrane (Trenom) to intense lymphoblastic leukaemia cells, and swelling in isolated mitochondrial rats[82, 83]. The breakdown role in the induction process of apoptosis induced by resveratrol was not caused due to action of caspase 8 or bid, because there was no major cleavage of these proteins[84].

While due to the loss of f, ΔΨmwas not accompanied by translocation of cytochrome c to cytosol, with mitochondrial changes, caspase 9, -2, -3, and -6 were significantly activated. Inhibition by N-acetylcysteine or by excess expression of Bcl-2 protein, of a breakdown / ROS and ROS production prevented resveratrol induction of apoptosis[83]. Therefore, the tumour cells' Bcl-2 expression status should be considered as an anti-cancer agent for future clinical application of resveratrol[85, 86].

Organ-specific changes in mtDNAheteroplasm after systemic transmission of an endonuclease mitochondrial restriction

Pathogenic mitochondrial DNA (mtDNA) frequently exhibits heteroplasmic mutations, with mutant and wild-type mtDNA coexisting. In vivo, studies have revealed the presence of double-strand breaks (DSBs) in mtDNA, which contribute to the cleavage of mutant mtDNA and residual replication[87]. By utilizing mitochondrial restriction endonucleases, it is possible to target and eliminate the mutant mtDNA, allowing the proliferation of healthy, wild-type mtDNA in heteroplasmic cells or tissues. This targeted approach holds promise for addressing the pathological effects associated with heteroplasmic mtDNA mutations[88].

The growth in the proportion of New Zealand Black mtDNA within target tissue was observed in a study using an asymptomatic heteroplasmic mouse model (New Zealand Black/BALB mtDNA). This increase was specifically detected in the heart with a heart-tropic adenovirus type 5 and the liver with a liver-specific adenoassociated virus type 6. Mitochondrion-specific ApaLi, which preferentially cleaves BALB mtDNA at a single site while leaving New Zealand Black mtDNA unaffected, was used to target these tissues. Notably, despite the observed increase in the proportion of New Zealand Black mtDNA, there were no reductions in overall mtDNA levels or impairments in

cytochrome c oxidase activity in either the heart or the liver. These findings suggest that the presence of NZB mtDNA had no negative impact on these mitochondrial parameters in the tissues studied[87, 89].

These findings demonstrate the ability to deliver systems for the treatment of mitochondria-target restriction enzymes in mtDNA disorders from viral vectors to other bodies[90, 91].

hTERT downregulation by JNK/p38 pathway activation, Apoptosis of Pancreatic, oral cancer cells by Bufalin (mitochondrial dependant)

For dozens of human cancers, Bufalin is quite similar to digoxin which is an active component of the traditional Chinese medicine Chan Su. Apoptosis of cancer cell is induced by Bufalin based on the mitochondria but is largely unknown regarding detailed molecular mechanisms. HTERT is the telomerase catalytic subunit, protecting against mitochondrial damage and reducing mitochondrial ROS production by binding with mitochondrial DNA. Bufalin affected the CAPAN-2 of the human pancreas and CAL-27 of on their cell feasibility and damaged DNA as well as changed ROS and apoptosis. These cancerous cells feasibility was effectively reduced by bufalin[92, 93].

Increased ROS levels, DNA damage, and apoptosis were associated with decreased cell viability and decreased hTERT expression. In CAPAN-2 and CAL-27 cells, siRNAhTERT silenced hTERT, resulting in increased cell cleavage, DNA damage, and decreased cell viability. In CAPAN-9/-3 cells, bufalin treatment also caused decreased cell viability and mitochondrial-dependent apoptosis, as shown by an increase in cleavage. These findings suggest that Bufalin interferes with hTERT function, causing mitochondrial-dependent apoptosis in CAPAN-2 and CAL-27 cells. These cells' production of ROS and apoptosis appear to be regulated by the mitochondria. Notably, the JNK/p38 pathway was discovered to be involved in mediating these effects by down-regulating hTERT expression[93, 94].

Toxicological and clinical research for the use of isolated mitochondria:

Mitochondria are special organelles, which have a significant cellular role in the production of ATPs and control energy expenditure, apoptosis signals, and reactive oxygen species. The main key is there is no return for the apoptotic cycle. Though in recent decades we've learned much about mitochondria, mitochondrial research is a very fruitful field and there's certainly still a lot to be learned about new techniques[95].

Measuring the function of such organelles by intact with fresh tissue isolated mitochondria provides distinct information. This supports conformist mitochondrial tests, by using formerly cold tissue, as well as in In-vivo. Nevertheless, several studies by separated mitochondria show that the act of mitochondria remained in the ideal buffer at 4°C for up to 18 hours after homogenization[96].Notably, various forms of mitochondrial toxicants are occupied in mitochondrial dysfunction, which results in interfering with their function of oxidative phosphorylation, bio-activation of compounds or electrophilic intermediates, and eventually damage the mitochondrial DNA. Therefore, it is recommended that secluded mitochondria should be used in the detection of mitochondrial dysfunction. It also provides perfect information on energy metabolism malfunction, calcium homeostasis, and eventually detoxification and renovation procedures for the corresponding intact cells[95].

Somatic DNA accumulation in adult-derived human iPSCs, related to age: Age-related

Skin fibroblast, blood, and iPSCs were investigated in the study(MtDNAs) of young and old(24-72 years) due to the accumulation of the somatic mitochondrial genome.Even though pool-based skin and blood mtDNA contained low heteroplasmic point mutations but there was a growing amount of heteroplasmic and homoplasmic mutations in a panel of ten peoplewith iPSC lines from each tissue or clonally expanded fibrillation.It also suggests that the somatic mutations occur spontaneously within individual cells, but are not able to detect within entire tissues[97, 98].

A study of iPSC lines from ten people found that there were more heteroplasmic and homoplasmic mutations in the iPSC lines than in the pool-based skin and blood mtDNA. This suggests that the somatic mutations occur spontaneously within individual cells, but are not able to be detected within entire tissues. The mutations may be caused by a variety of factors, including environmental exposure, aging, and genetic predisposition [98, 99].

Available evidence indicates that the occurrence of mtDNA mutations in various age person tissues that result in pathogens reduction of respiratory ability, the degree and function of heteroplasmic or homoplasmicmtDNA mutations that can be identified at a high level remain unknown. In individual iPSC lines with mitochondrial genome integrity, particularly of elderly subjects, the cell of origin can be affected[100]. In the case of iPSCs, structural damage to the mtDNA genes is likely to reduce its metabolic functions in energy-consumption differentiated cells and thus limit its therapeutic potential[99].

In the case of chromosomal nuclear genes and mtDNA,the defect is therefore imperative to establish and analyse several iPSC lines and to identify optimal iPSC induction tissues[101].

Mitochondrial oxidative stress as a new clinical target in melanoma subpopulations to combat drug resistance:

Elesclomol – copper complexes that cause the oxidative stress of mitochondrial air chains or reactive oxygen species with indirect non-mitochondrial induction. Elesclomol was found to efficiently destroy the subpopulation of slow-cycling and to prevent selective slow-cycling enrichment which generally results after mono treatment[102]. They assume that elesclomol can in the future overcome slow-cycling melanoma cells' multidrug resistance and prevent tumour repopulation in patients with melanoma[103].

Clinical trials have been performed previously in patients with metastatic stage IV melanoma to assess the suitability of elesclomol as a clinical treatment. In the subgroup patients with normal baseline lactate dehydrogenase (LDH), PFS improved only in the following Phase III study which demonstrated a long progression-free survival (PFS) for the elesclomolplus paclitaxel combination compared to paclitaxel alone[104].

One potential explanation is that high levels of serum LDH may represent a fast-growing, hypoxic tumour burden that increases glycolysis dependence. Their pre-clinical finding indicates that elesclomol and simple therapeutic regimes such as vemurafenib,are a fast removal of rapidly expanded tumor mass. It can be overcome by multiple drug resistance to Slow-cycling Melanoma cells[105].

In the case of mitochondrial dependent and independent pathways, taurine protects rats from oxidizing stress and apoptosis caused by $NaASO_2$

A well-known inducer of toxicity is arsenic (As). However, new work indicates that it may be used therapeutically in the treatment of cancer. These dual roles have led to a renewed investigation into organ pathophysiology[106]. This study states that administration in the testicular tissue of experimental rats by activating caspase 3 and reciprocal control of Bcl2/Bad, induces acute apoptosis with the subsequent reduction of mitochondrial membrane potential and increased cytochrome C[85]. C is in the form ofNaAsO2 at a 2-day dose of 10 mg/kgbody weight orally[107]. The activation of mitogen-activated protein kinases (MAPK), Act, and Nf-B(p65) was also shown to cause the activation of arsenite in testicular tissue. Therefore, the testicular 5-3 -HSD and 17-HSD activity have decreased considerably and the plasma testosterone level, sperm count, and sperm motility have been substantially reduced[108].

Moreover, arsenite exposure has been observed to elevate levels of reactive oxygen species, increase serum TNF, and promote aggregation and peroxidation of lipids. And also degrades glutathione and antioxidant enzyme activity in testicular tissues[109]. Oxidative stress caused by arsenic is effectively reduced by taurine given orally at a dose of 100mg/kg body weight for 5 consecutive days, as well as attenuating testicular damage and boosting apoptosis in testicular tissues. Taurine has been beneficial via a mitochondrial-dependent pathway. This was evidenced by the reciprocal regulation of Ser473, phospo-p38, and NF-B[110].

The chosen target is mitochondria in human leukaemia HL60 cells in a-mangostin-induced apoptosis

In HL60, caspase- 3 dependent apoptosis induces a-mangostin, a xanthone from pericarps mangosteens. a-mangostin. The mechanism of a-mangostin-induced apoptosis in HL60 cells was studied in this present research. The HL60 cells treated with a-Mangostin showed that the mitochondrial pathway in the apoptosis could be activated by mitochondrial activation, but not by activation of caspase-8[111]. Intracellular ATP decreases and ROS accumulations and cytochrome c / AIF release were observed in a span of 1 to 2 hours after the treatment including swellings, and membrane potential loss (DWm)[112].

On the other hand, BCL-2 family protein expression and the activation of MAP kinases were affected by a-mangostin when treated. These results indicate that a-mangostin targets mitochondria preferentially in the early stage, resulting in apoptosis in HL60 cells. They also investigated the structure-activity relationships between xanthone derivatives and the potencies of DWm-loss in HL60 cells, including a-mangostin. Interestingly, its capacity has been greatly decreased by substituting the hydroxyl group for the methoxy group. A candidate for preventive and therapeutic applications for cancer treatment will be a mangostin and its analogues[113, 114].

Development of Ca DNA Enzymes with Possible Therapeutic Application Nuclease-resistant protein kinase

Small, stable, and cheap compounds that are active on physiological Mg2 are desirable for the therapeutic application of catalytic nucleic acids. In order to suppress the expression of protein kinase Ca (PKCa) in malignant cells, researchers have explored the possibility of utilizing the diverse 10-23 DNA catalytic center. They have developed stable catalysts with substantial in vitro cleavage activity by either inserting a 30-30 reverse nucleotide of thymidine or site-specific phosphorothioate modification into a PKCa DNA enzyme [115].

Sequence-specific inhibition of PKCa gene expression is ineffective as a DNA enzyme with reversed antisense arms.[116] Epifluorescence microscope analyses of 50 isothiocyanate-conjugated DNA transacted cells have revealed that the enzyme DNA molecules are located mainly in the nuclei.[117] Apoptosis has destroyed most DNA enzyme-treated cells.[118] The probability of apoptosis (apoptozymes) to malignant cells is demonstrated by the PKCa DNA enzymes described.[119,120] These agents may also be a powerful resource for gene function research[121-123].

7Conclusion

Mitochondria plays an important role in the treatment of various diseases. Mitochondria help in the production of ATP, apoptosis, Reactive oxygen species, and Electron transfer system in the body. Mitochondria are also known as the "Power House of Cell". Disturbance in mitochondrial function causes many diseases in the human body i.e., myoclonic epilepsy with rag-red fibres, myochondeencephalomyopathy, lactic acidosis, and stroke-like episodes. Depletion of ATP or Mutation in mtDNA can be the cause of mitochondrial diseases.

Mitochondria treat a number of diseases like cancer, cardiovascular disorders, fatty-acid oxidation disorders, and various kinds of tumours.The mitochondria play important roles in apoptosis induction through their interaction with BCL-2 family proteins. Drugs like Bufalin inhibit A549 cell proliferation and trigger mitochondrial-dependent apoptosis that indicates NSCLC therapeutics.

Targeting mitochondrial oxidative stress has come to light as it has emerged as a cutting-edge therapeutic strategy to counteract drug resistance in certain types of melanoma cell subpopulation. This approach aims to develop a therapeutic mechanism that gives sufficient time for the prevention of tumour repopulation as it gets rid of slow-cycling, multi-resistant cells. In cardio-protection mitochondria targeting is of utmost importance. Under a variety of disease mechanisms, and with normal aging, mitochondrial biogenesis will be the target of therapeutic intervention. Therefore, to move forward a better understanding of the mitochondrial structure and its mechanism and genetics of mitochondria is included. Mitochondria havethe potential to treat many chronic disorders the only need is furthermore advancement in therapeutic applications.

8References

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