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Review Article

Mitochondrial Stress by Toxic Elements - An Overview

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Abstract

Mitochondria (mT) are now considered as suitable targets of toxicity induced by various environmental xenobiotics. Mitochondrial dysfunction is the final outcome of their effects in cellular system. Human diseases *viz*. Alzheimer, parkinsonism, pancreatic β cell failure, insulin resistance and ageing have also been partially attributed to mitochondrial injury. Present review focuses mainly on mitochondrial stress induced by a few toxic elements i.e. cadmium, mercury, lead, copper, chromium, nickel and arsenic. General mechanisms that cause mT dysfunction including generation of reactive oxygen species, oxidative stress, apoptosis alterations in mT membrane permeability and energy disturbances have been discussed. Further, specific effects of toxic elements i.e. inhibition of ATPase, activation of caspases, enhanced release of cytochrome c and mT DNA damage have also been described. In few cases, cytokines were also involved in mT dysfunction. Their effects on mT biogenesis is also reported. Investigations on certain less understood paradigms *viz*. mitochondrial hormesis, mitophagy and mitokines are urgently needed.

Keywords: Mitochondrial dysfunction; Mitochondrial biogenesis; Toxic elements; Apoptosis; Oxidative stress; Mitochondrial DNA

Abbreviations

mT: mitochondria; nDNA: nuclear DNA; mTDNA: mitochondrial DNA; OXPHOS: Oxidative Phosphorylation; MOM: Mitochondrial Outer Membrane; MIM: Mitochondrial Inner Membrane; IBM: Inner Boundary Membrane; CJ: Cristae Junction; CM: Cristae Membrane; ROS: Reactive Oxygen Species; MPTP: Mitochondrial Permeability Transition Pore; Cd: Cadmium; HSP_{60}: Heat Shock Protein$_{60}$; Me-Hg: Methyl Mercury; Hg: Mercury; Pb: Lead; Cu: Copper; MDA: Malondialdehyde; NO: Nitric Oxide; SOD: Superoxide Dismutase; GSH: Reduced Glutathione; ATGs: Auotophagy Related Genes; ATO: Arsenic Trioxide; TNFα: Tumor Necrosis Factorα; IL-6: Interleukin 6; MRCC: Mitochondrial Respiratory Chain Complex

Introduction

Mitochondria (mT) evolved from α-proteobacteria captured within a host cell, two or three billion years ago. It was a symbiotic partnership between nucleus and cytosol in an eukaryotic organism [1,2]. Every eukaryotic cell possesses mitochondria that have been unequivocally recognized as the key producers of cellular energy in the form of ATP [3]. It controls cellular functions and its survival. Further, it plays an important role in cell differentiation [4]; calcium homeostasis [5]; immune cell function [6]; neurogenesis and cell death regulation [7,8].

Mitochondrial genome

In vertebrates, a small double stranded covalently closed circular DNA molecule of 16.5 kb makes its genome. The mitochondrial genome encompasses between one and two thousand nuclear DNA (nDNA) and thousands of copies of mitochondrial DNA (mtDNA) located in discrete zones called nucleoids. 13 most important OXPHOS genes are present in mtDNA while nDNA retains all the remaining OXPHOS genes as well as the genes for mitochondrial metabolism and biogenesis. In mammalian cells, nucleoids contain an average 5-7 genomes. They are stabilized by DNA binding proteins but not the histone. Absence of histones makes them more vulnerable to oxidative stress than nDNA [9,10]. The nDNA) encodes a large majority of mitochondrial proteins which are synthesized in cytosol and imported into the mitochondrion. Dedicated machinery of protein translocases in the Mitochondrial Outer Membrane (MOM) and Inner Membrane (MIM) facilitate this import [11].

Structure of mitochondria

Mitochondria consist of a double membrane system in which the MOM surrounds the MIM. The later constitutes the boundary of mitochondrial matrix compartment and contains many folds (cristae) that protrude into this compartment thereby enlarging the MIM surface area. MOM and MIM are separated by the inter-mitochondrial space and are partially connected via contact sites that are involved in cristae organization. Important structural features of the mitochondrial matrix and cristae system include the Inner Boundary Membrane (IBM), Cristae Junction (CJ) and Cristae Membrane (CM). Maintenance of mitochondrial integrity is important for its function. Further, external, internal morphology and positioning of mT differ amongst cell types and changes over time [12]. Morphological changes in mT are affected by processes *viz*. fission, fusion, chemiosmosis, physico-chemical properties of MOM and MIM and the nature of extracellular matrix.

Functions of mitochondria

Mitochondria perform several functions. These include regulation of energy production, modulation of redox status, generation of Reactive Oxygen Species (ROS), control of cytosolic Calcium (Ca^{2+}) levels, contribution to cytosolic biosynthetic precursors such as acetyl – coenzyme A and pyrimidines and initiation of apoptosis through activation of Mitochondrial Permeability Transition Pore (MPTP). Xenobiotics can change these functions and affect biosynthetic pathways, cellular signal transduction pathways, transcription factors

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and chromatin structure to transform a quiescent and differentiated cell into an actively proliferation one.

Morphological plasticity of mT allows mixing of its contents, redistribution of damaged proteins and lipids, local functioning of the subsets of mT within the cell and mitophagy. mT can not be generated *de novo* [13]. Therefore, mT fission is crucial to allow their inheritance during cell division. Transcellular exchange of individual mT via nanotubular structures (nanotunnelling) has been demonstrated under certain conditions [14]. mT DNA can be transferred between cells by extracellular vesicles [15].

Mitochondrial homeostasis

The maintenance/regulation of mitochondrial structure and function has been studied by a number of workers. Mitochondrial fission and fusion proteins significantly contribute to mT homeostasis. These processes are mediated by microRNAs that function as negative regulators for gene expression. They can inhibit mRNA translation or promote mRNA degradation [16]. Irreparable mT are removed by fusion, fission, autophagy or biogenesis. Damaged mT are removed either by general autophagy or priming of mT for selective autophagic recognition [17,18]. Certain protein receptors *viz*. autophagy related protein (Atg 32) in yeast; Nix/BCL2 interacting protein 3 like (Bnip3l), BCL2 interacting protein 3 (Bnip3) and FUN 14 domain containing 1 (Fundc1) in mammalian systems directly act in autophagy. mT can make multiple copies of their genome, however, lack nucleotide excision pathway. Therefore, DNA damaged by environmental chemicals is removed via mitochondrial fusion, fission, autophagy and biogenesis [19]. Principally, mitochondrial fusion and fission are considered as key processes in mitochondrial stress response and morphological changes in mitochondria [20].

Cellular export processes *viz* exocytosis may help in removing the damaged mT. Recent researches show that multiple signalling mechanisms i.e. nucleotides, biosynthetic intermediates, peptides, mT ROS, cardiolipin, mT unfolded protein response, reduced AMP/ATP ratio and calcium release are also involved in mT homeostasis [21-23].

Ca^{2+} plays a regulatory role in mT physiology [24]. mT can import Ca^{2+} through a uniporter, energized by an electrochemical gradient. ER membranes associated with mT bring ER type 3 Inositol Triphosphate Receptor (IP3R) Ca^{2+} release channels into juxtaposition with mT Ca^{2+} uninporter.

Defining mitochondrial stress

Many patho-physiological conditions or exposure to drugs/chemicals can cause mitochondrial dysfunction. These include metabolic disorders [25], cancer [26], diabetes [27] and neurodegenerative diseases [28]. Proper mitochondrial function in mammals requires -1200 genes {Mito carta 2.0) and (Mito-miner 4.0{ [29]. Only a small fraction of proteins is encoded in the mitochondrial DNA. A variety of chemicals/ drugs/ xenobiotics can disturb mT function by generating stress. Exposure of organisms to chemicals can cause mutations in mT DNA [30]. In turn, these mutations increase the sensitivity of mT to stress [31,32]. Stress can alter the morphology of mT [20].

In general, xenobiotics affect mT by inhibiting electron transfer. For instance, many herbicides and pesticides affect respiratory chain. While rotenone inhibits Complex –I, antimycin inhibits complex –III. Carbon monoxide, azide and cyanide bind to heme a^3 of complex IV, thereby inhibiting the oxidase activity. Most important, mT DNA encodes 13 proteins of the respiratory chain. Since mT DNA possesses no protective proteins, ROS easily damage mTDNA. Mutations in mTDNA generate dysfunctional proteins essential for respiratory chain, thus inhibiting the electron flow. Inhibition of the electron flow results into accumulation of reduced ubiquinone and reduced cytochrome C. Finally, reduced ubiquinone, complex I and complex III donate electrons directly to oxygen generating superoxide anions ($O_2^{\cdot-}$). ROS activate caspase pathway leading to apoptosis. Reduced ATP production (metabolic stress) activates autophagy.

Another group of xenobiotics are classified as energy transfer inhibitors. For example oligomycin inhibits ATP synthase. It reduces proton flow from the inter-membrane space to the matrix. Thus energy transfer inhibitors generate ROS.

Third category is known as uncouplers. Uncoupling is the state in which ATP synthase is inhibited by disruption of pH gradient. For example 2, 4 –Dinitrophenol (DNP) and Pentachlorophenol (PCP) are known as uncoupling agents. These compounds inhibit the production of ATP leading to metabolic stress**.** Metabolic stress induces autophagy. It activates p38 c-Jun N terminal Kinase (JNK) pathway. These pathways collectively lead to apoptosis, necrosis and mitophagic cell death.

Mitochondrial stress by environmental xenobiotics

Mitochondrial toxicity by drugs is better known than environmental pollutants. There were speculations that like drugs, environmental agents might also target mT [33]. Nonetheless, only a few studies demonstrated analogy between the effects of drugs and environmental toxins. Effects of paraquat, a pesticide, are similar to that of adriamycin that act by redox cycling [34]. While rotenone inhibits complex I, carbon monoxide and cyanide act as complex IV inhibitors [35]. Others that manifest their toxicity through mitochondria include particulate matter [36]; PAH quinines [37]; methoxychlor [38]; and pentachorophenol [39]. Many of these xenobiotics affect primary targets other than mT and thus effects on mT become secondary to these effects.

Mitochondrial stress by toxic elements

Amongst toxic elements, cadmium and copper [40]; manganese and lead [41]; arsenic [42] and mercury [43] have been demonstrated to cause toxicity through mT dysfunction/involvement. However, promising research on their effects on mT is wanting. This review focuses mainly on mT stress induced by toxic elements and presents directions for future research.

Cadmium (Cd)

mT represents key target organelle in cadmium Cd) intoxication. Exposure to Cd can cause different changes in mT *viz*. morphological changes; alterations in mT membrane permeability and potential; generation of ROS; mutation in mTDNA; altered gene expression and apoptosis. Biochemical mechanisms responsible for cadmium toxicity have been studied in a variety of *in vitro* and *in vivo* models [44]. It inactivates sulfydryl groups of essential proteins. It can cause functional changes in nucleus, mitochondria and endoplasmic reticulum [45,46]. Its effects on OXPHOS are considered as key

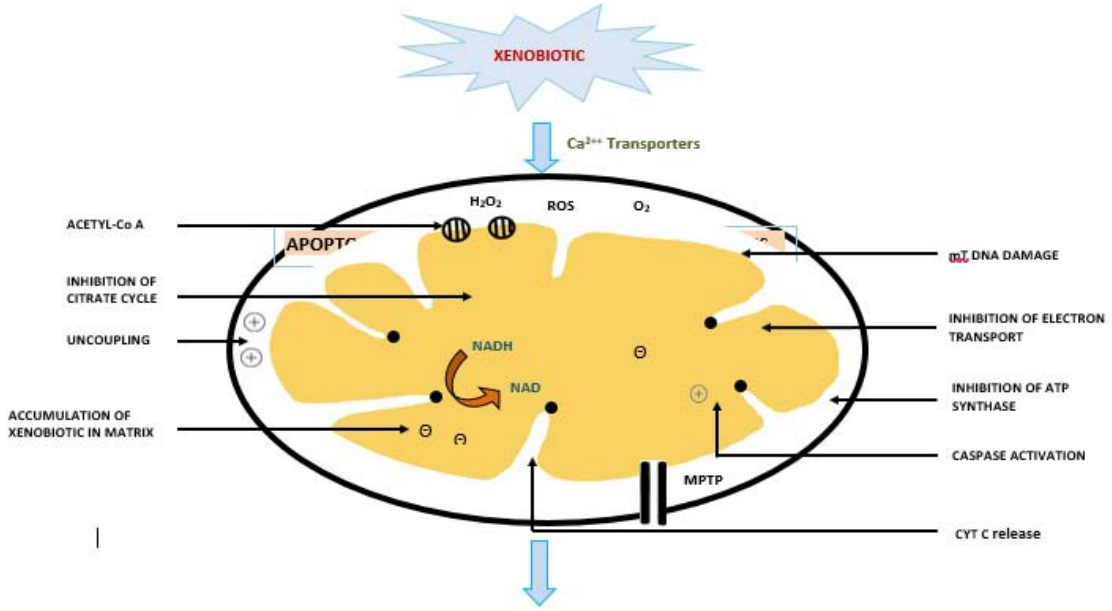

Figure 1: Generalized scheme of mitochondrial toxicity by xenobiotics.

factors affecting its toxicity [47]. The uncoupling effect of Cd on OXPHOS could be due to the acceleration of H^+ influx through the Pi/H^+ symporter [48]. Heat shock $protein_{60}$ (Hsp_{60}) mostly resides in mitochondrial matrix. Its over expression might exert a protective role assisting the cell in refolding and processing of damaged proteins [49]. Certain reports show that Cd affects mitochondrial electron transport chain by impairing electron flow through the cytochrome bc1 complex [50]. Cadmium can induce morphological changes too in mT. It could decrease the number of mT in the kidney of rat. Further, degenerated mT with reduced matrix density and loss of cristae were also observed [51]. Changes in the permeability of MIM caused opening of MPTP [52-54]. Exposure to cadmium is known to induce a massive accumulation of ROS [55]. These reactive species affect mT membrane potential and activate consequent events leading to apoptosis [56]. A quick survey of available literature showed that there were about 500 studies dealing with the effects of Cd on mT. Most of them dealt with indirect involvement of Cd in mitochondrial injury. A few reports dealt with the amelioration of mT dysfunction by treatment with antioxidants. It has now been accepted that Cd affects mT function through oxidative stress [57].

The role of Cd induced mTDNA mutations in neoplastic tissue formation is yet to be established. Cd is known to affect mT gene expression [58]. It upregulates HSP_{60} in HB2 cells [59]. The over expression of HSP_{60} may be protective or it can regulate programmed cell death [60].

Thus sufficient experimental evidence suggests mitochondrial participation in Cd induced cytotoxicity. Disruption in mT membrane permeability, generation of ROS and oxidative stress predominantly contribute to its toxic effects.

Mercury (Hg)

Mercury is a direct enzyme poison. It binds to sulfydryl, phosphoryl, carboxyl, amide and amine groups of proteins. On binding with mercury, these proteins become inactive. Inorganic and organic forms of mercury exhibit selective toxicity in organisms. Elemental mercury being lipid soluble can cross cell membranes and disrupt their structure and function. Organo -mercurials are classified as long chained aryl mercury compounds and short chained alkyl mercury compounds. Short chained alkyl compounds *viz.* methyl mercury are highly toxic [61].

The earliest report that suggested mT damage by mercury was published by Donaldson [62] who showed that moderate levels of mercuric chloride (200-300ppm) given to chicks in drinking water over an 8 week period adversely affected the integrity of mT membrane. Subsequently, it was shown by Sone et al. [63] that Me-Hg induced mT swelling. Stimulation of ATPase and energy dependent H^+ extrusion were equally dependent upon K^+. Its uptake by mT and the resulting loss of membrane potential was the major cause of uncoupling. Iida [64] studied the effects of various organic mercury compounds on OXPHOS in rat liver mT. While studying immunotoxic effects of methylmercury, it was demonstrated that methylmercury kills human lymphocytes by inducing apoptosis. It increased mT transmembrane potential (Ψm) and generated ROS that activated cell death signalling pathways [65]. Oxidative stress mechanisms were reported to alter mT activity in human THP1 monocytic cells exposed to Hg (II) in a dose dependent manner [66]. Further, effects of Me-Hg on mitochondrial function were found to be age dependent. Me-Hg reduced mitochondrial function as assessed by MTT reduction and mT membrane potential in the synaptosomes of early post-natal rats than those of greater age [67]. Mercury induced diseases like Multiple Sclerosis (MS) have also been associated with mitochondrial damage. Repeated administration of Hg induced mT swelling, generation of ROS, collapse of mitochondrial membrane potential and cytochrome c release [68]. *In vitro* studies made by Ma et al. [69] on mT isolated from Wistar rat liver confirmed that Hg^{2+} changes mT structure, causes mT swelling, alters mT membrane potential and membrane fluidity and influences cytochrome c release. mT were found to play a crucial role in neuronal apoptosis induced

by Me-Hg. Observations made on primary cultured neurones after exposure to 0,0.25; 0.5; or 1μM Me-Hg for 1-6 hr respectively showed that Me-Hg induced neuronal apoptosis through ER and mT pathways. Results on caspase-3' caspase-9 and cytochrome C release indicated disruption of mT dysfunction. Recently, diabetogenic effects of metals *viz*. Cd, Hg, Pb and Mo has been attributed to bioenergetic disruption of mT [70].

Information detailed above confirms that cell death signalling pathways are activated by Hg. Increase in transmembrane potential, enhanced generation of ROS, release of cytochrome c and activation of caspases are involved in its cytotoxicity.

Lead (Pb)

Lead is an ubiquitous element. It is known to cause serious health effects in man and animals. Lead has been found to cause anaemia in number of cases. It inhibits porphirobilinogen synthase and ferrochelatase preventing the synthesis of porphobilinogen and heme synthesis. It may cause ineffective synthesis and subsequently microcytic anaemia. Further, it blocks voltage dependent calcium channels. It does lead to encephalopathy and impaired respiratory function.

A few studies show its effects on mitochondria. It affects Ca^{2+} handling by heart mitochondria [71]. Glycine cleavage in rat liver mitochondria was also decreased by lead [72]. It was found to affect the structure and function of rat liver mT [73]. Synaptosomal fraction of the brain of a fresh water cat fish *Clarius batrachus* demonstrated increased generation of reactive oxygen species, decrease in protein thiols and Na^+ , K^+ ATPase activity and mitochondrial electron transport chain after exposure to 37.8 and 75.6mg/L for 20, 40, and 60 days [74]. Lead could cause mutations in mT DNA. This hypothesis was tested in yeast, *Saccharomyces cerevisae* by Sousa and Soares [75]. These workers attributed these effects to oxidative stress induced by lead. It has now been confirmed that Pb affects mT respiratory complex. This effect is the outcome of oxidative stress and MPT that lead to cell death signalling via opening of MPTP and cytochrome c release [76].

In brief, mitochondrial toxicity caused by lead includes its bindings with thiols, inhibition of Na^+ K^+ dependent ATPases, mutation in mT DNA and oxidative stress.

Copper (Cu)

Copper (Cu) is an essential transition element. It is a co-factor for many enzymes *viz*. Cu/Zn superoxide dismutase; cytochrome c oxidase; dopamine β hydroxylase and monoamine oxidase. Although mechanisms of copper toxicity are not completely understood, it has been implicated in the pathogenesis of neurodegenerative disorders i.e. Alzheimers' disease; Parkinsons' disease; familial amyotrophic lateral scelerosis and prion disorders. It binds with disease causing proteins *viz*. A-B peptide, a sinuclein and prion protein. This binding results into generation of free radicals and associated events of oxidative stress. Elevated tissue levels of copper have been associated with an autosomal recessive inherited disorder known as Wilsons' disease (hepatolenticular degeneration).

Role of mT in Cu induced cell injury has been studied by a few scientists. Reddy et al. [77] demonstrated that MPTP, oxidative stress and nitrosative stress play a major role in Cu induced toxicity in astrocytes. However, alterations in MPT had no contribution in its neural toxicity. Further, copper mediated oxidative stress is known to contribute to mT dysfunction which is considered as a major cause of neurodegeneration. In conditions of copper deficiency also, decreased activity of cytochrome c oxidase leads to mT dysfunction Role of Cu in neurodegenerative processes was further elaborated by Arnal et al. [78]. This group of scientists studied the effects of Cu and / or cholesterol on mT function in Wistar rats. Cu^+ induced a higher cholesterol/phospholipid ratio in mT membrane with a simultaneous decrease in glutathione content. Concentration of peroxidation products, conjugated dienes and lipid peroxides increased. These workers concluded that Cu and cholesterol potentiate the neurodegenerative process. Mitochondrial Cu homeostasis especially in Wilson disease patients was reviewed by Zischka and Einer [79]. This study concluded that Cu overlaod causes structural, biophysical and biochemical deficits during Wilsons' disease. Involvement of mT in copper induced oxidative stress and apoptosis was studied in chicken hepatocytes by Yang et al. [80]. Dose dependent increase in ROS levels, MDA, NO, SOD; decrease in GSH and upregulation of Bax, Bak1, Cyt c and apoptosis attributed these effects to changes in mT pathways. Briefly, Cu induced mT changes *viz*. nitrosative stress, opening of MPTP and oxidative stress promote cell death.

Arsenic (As)

Arsenic is historically known to inhibit cellular respiration and cause mitochondrial injury. Arsenic induced Reactive Oxygen Species (ROS) cause genetic mutations and cancer by promoting DNA damage, activating oncogenic kinases and activating lipids and proteins that inactivate DNA repair mechanisms.

It was hypothesized that mT, in particular the mT DNA are important targets of mutagenic effects of arsenic in mammalian cells. Partridge et al [81]. showed that arsenic did not induce nuclear mutations in mT DNA depleted cells. These authors showed that arsenic alters mT function by decreasing cytochrome c oxidase functions. Further, another study showed that arsenic alters mT DNA and telomere length in individuals possessing different arsenic metabolizing capacity [82]. In arsenic induced neurotoxicity also, mT oxidative stress and dysfunction were implicated [83]. Arsenic induced oxidative stress was linked to decreased mT biogenesis in rat liver. mT biogenesis was evident by decreased protein and mRNA expression of Nuclear Respiratory Factor (NRF-1), Nuclear Respiratory Factor 2 (NRF-2), peroxisome proliferator activator receptor γ co-activator 1 α(PGC-1α) and mitochondrial Transformation factor A (Tfam) in arsenic treated rat liver. Thus increased oxidative stress was found to be associated with decreased mT biogenesis. Arsenic induced neural damage in chicken was also found to be associated with oxidative stress and disruption in mT dynamics. Upregulation of Autophagy Related Genes (ATGs) was also observed [84]. Involvement of mT functions was demonstrated in female rats fed on sodium arsenate (2-4mg/kg body weight). Chandravanshi et al. [85] reported that increased oxidative stress and apoptosis in frontal cortex, hippocampus and corpus striatum of developing rats could be attributed to changes in mT function. Impairment of neurohormones, oxidative stress and mT dysfunction express synergistic behaviour during arsenic toxicity. Medda et al. [86] showed that arsenic directly affects cortex, cerebellum and microglial cells by inducing pro-inflammatory cytokines *viz*. TNF-α,

IL-6. Mitochondrial dysfunction has been implicated in the toxic effects of arsenic on spermatogonia. ATO damaged mT structure i.e mT cristae and mT vacuolar degeneration [87].

Certain reports indicate that antioxidants protect arsenic induced mT toxicity. Pace et al. [88] have identified 21 mitoprotective antioxidants that can effectively reverse mT dysfunction. Earlier reports suggest a protective role of ascorbic acid against arsenic induced mT toxicity [89]. Taken together, mT DNA damage, cytochrome c release and upregulation of autophagy related genes are important contributors of its cytotoxicity.

Chromium (Cr)

Chromium (Cr) is an important industrial metal. The stable oxidation states of Cr are trivalent chromium (Cr^{III}) and hexavalent Chromium (Cr^{VI}). It can enter the body through different portals i.e. inhalation, ingestion and absorption through skin. Cr^{VI} can enter the cell through anion transporters. Inside the cell, it can be reduced to lower oxidation states *viz*. pentavalent Chromium (Cr^{V}), and tetravalent Chromium (Cr^{IV}). It has been generally agreed that ROS plays a key role in Cr induced cytotoxicity. Experimental evidence indicates that Cr^{VI} affects Mitochondrial Respiratory Chain Complex I (MRCC I) to induce ROS [90]. MRCC I appears to be the new target and a new mechanism involved in Cr^{VI} induced apoptosis. Several metals might induce toxicity through MRCC (I-V) and disrupt the mT membrane structure and function [91]. Role of mT biogenesis in Cr induced hepatotoxicity in human liver cells was studied by Zhong et al. [92]. It was demonstrated that mT biogenesis, comprising the mT DNA copy number and mT mass was significantly increased HepG2 cells after exposure to low concentration of Cr. Moreover expression of genes related to mT function complex I and complex V was upregulated at low concentration of Cr^{VI}. mRNA and protein levels of key transcriptional regulators of mT biogenesis *viz*. the peroxisome–proliferator-activated receptor γ coactivator-1α (PGC-1α), NRF-1 and mitochondrial Transcription Factor A (TFAM) were also increased by low concentration of Cr^{VI} in HepG2 cells. Contrarily, high concentration of Cr^{VI} inhibited mT biogenesis [92]. Depletion of mitochondrial membrane potential in skin fibroblasts ScSF cells of Indo-Pacific hump back dolphin (*Sousa chinensis*) after exposure to Cr^{VI} was reported by Yu et al. [93]. This effect was attributed to decrease in ATP level, cytochrome c release from mT and the activation of caspase -9. Results of Cr^{III} may not support those obtained from Cr^{VI}. An *in vitro* study made in RAW 264.7 murine macrophages after exposure to 50-150 ppm Cr^{III} exhibited no mT dysfunction. A recent report from Seydi et al. [94] showed that Cr^{VI} caused Mt Membrane Potential (MMP) collapse in isolated human lymphocytes. In brief, a surge in the generation of ROS, inhibition of mT respiratory chain complex I and activation of caspase 9 mediate its effects on cell death.

Nickel (Ni)

Toxicity/ carcinogenic potential of nickel compounds has now been established. They are known to cause oxidative stress, genotoxicity, dermal and neurotoxicity. Role of mT in its toxicity has been studied by a few workers. Bemba-Meka et al. [95] reported that Ni3S2 induced changes in mT membrane potential in human lymphocytes in a dose and time dependent manner. These changes were mediated by oxidative stress. Antioxidants like N-acetyl cysteine inhibited the changes in mT membrane potential. Another study from Xu et al. [96] also confirmed that oxidative stress induced by nickel contributes in its neurotoxic effects. Melatonin, which is known to possess antioxidative properties inhibited neurotoxicity of Ni in mouse neuroblastoma cell lines (neuro2a) and cortical neurones. Oxidative damage to mT DNA might account for neurotoxicity of nickel. mT DNA nucleoid structure could also be affected by Ni. Xu et al. [97] confirmed that Ni could reduce mT DNA content and mT DNA transcripts. It decreased protein levels of Tfam, a key protein component of nucleoid organization. However, melatonin pretreatment attenuated oxidative damage to mT DNA. Protective effects of taurine, an antioxidant and essential for mT function, against Ni induced neurotoxicity have also been reported by the same group of scientists (Xu et al. Maiti et al. [98,99] attributed neurotoxicity of Ni induced in a cat fish, *Clarius batarchus* L. to inhibition of ATPase activity and mT respiratoty chain dysfunction. These studies emphasize the role of mT in nickel induced neurotoxicity.

Role of calcium in mitochondrial stress

Many xenobiotics impair mT function employing Ca^{2+} dependent signalling pathways [100,101]. Fleckenstein et al. for the first time showed that entry of the excess $Ca2^{+}$ in cardiomyocytes manifests cardiac pathology after ischemia. Intracellular compartmentalization of Ca^{2+} occur in mT. Increased generation of ROS facilitate changes in MPT that promote cell death [102]. It has been reported that mT in many pathological conditions accumulate Ca^{2+} that is subsequently released along with other matrix solutes [103]. Oxidative stress and impaired $Ca2^{+}$ homeostasis both contribute to mT mediated cell death [104]. Thus MPT remains to be the major mechanism of causing mT failure. It can lead to necrosis due to ATP depletion or to apoptosis due to caspase activation. However, further studies are needed to establish the role of specific elements on Ca^{2+} mediated mitochondrial permeability transition.

Conclusion and Future Perspectives

Mitochondrial biology remains central to our understanding on cell death and related mechanisms [105]. It offers a platform for interdisciplinary research on the aetiology of many complex diseases as well as ageing process. Though impressive research on mT dysfunction have been reported during last decades, many issues related to its dysfunction in different pathological conditions are yet to be resolved. A few of these include- elucidating the modulation of specific OXPHOS genes, mitochondrial hormesis, DNA methylation , mT- nuclear DNA interaction, retrograde signalling and adaptive mechanisms during cellular insult by toxic elements. Further, Antioxidant Responsive Elements (ARE) are to be identified. Detailed studies on fusion and fission of mT, induced by toxic elements are also awaited. There exists convincing evidence that certain signalling molecules known as mitokines may be secreted during mitochondrial stress. They may be proteins involved in retrograde signalling [106]. Further work is warranted to decipher the role of mitokines in metal toxicity. Finally, lack of inter-mitochondrial communication and quality control process in a pathologic state may play an important role in mT dysfunction. Efforts made by World Mitochondrial Society deserve appreciation. Next (12^{th} in the series) Berlin Congress proposed in Oct. 2021 is expected to add more information to our present knowledge on mitochondria.

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