Biochimica et Biophysica Acta xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbadis

Mitochondrial dysfunction and oxidative stress in metabolic disorders — A step towards mitochondria based therapeutic strategies☆

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ARTICLE INFO

Article history:
Received 4 August 2016
Received in revised form 2 November 2016
Accepted 3 November 2016
Available online xxxx

Keywords:
Metabolic syndrome
Mitochondria
Oxidative stress
Reactive oxygen species
Mitochondria-targeted antioxidants
Cardiovascular disease
Pre-diabetes
Type-2-diabetes
Obesity

ABSTRACT

Mitochondria are the powerhouses of the cell and are involved in essential functions of the cell, including ATP production, intracellular Ca^{2+} regulation, reactive oxygen species production & scavenging, regulation of apoptotic cell death and activation of the caspase family of proteases. Mitochondrial dysfunction and oxidative stress are largely involved in aging, cancer, age-related neurodegenerative and metabolic syndrome. In the last decade, tremendous progress has been made in understanding mitochondrial structure, function and their physiology in metabolic syndromes such as diabetes, obesity, stroke and hypertension, and heart disease. Further, progress has also been made in developing therapeutic strategies, including lifestyle interventions (healthy diet and regular exercise), pharmacological strategies and mitochondria-targeted approaches. These strategies were mainly focused to reduce mitochondrial dysfunction and oxidative stress and to maintain mitochondrial quality in metabolic syndromes. The purpose of our article is to highlight the recent progress on the mitochondrial role in metabolic syndromes and also summarize the progress of mitochondria-targeted molecules as therapeutic targets to treat metabolic syndromes. This article is part of a Special Issue entitled: Oxidative Stress and Mitochondrial Quality in Diabetes/Obesity and Critical Illness Spectrum of Diseases - edited by P. Hemachandra Reddy.

1. Introduction

Mitochondria are the intracellular organelles which play a significant role in the cells by metabolizing nutrients and producing the "energy currency" adenosine triphosphate (ATP) and responsible for various processes such as energy metabolism, generation of free radicals and calcium homeostasis, cell survival and death [1,2]. Their principal function is to synthesize ATP via oxidative phosphorylation (OXPHOS) in concurrence with the oxidation of metabolites by Krebs's cycle and β-oxidation of fatty acids. Currently, it is appreciated that pathophysiological alterations in mitochondria in aging and many other metabolic disorders are linked with impaired mitochondrial functions such as diminished oxidative capacity and antioxidant defense by the enhanced generation of reactive oxygen species (ROS), reduced OXPHOS, and decreased ATP production. Reduced mitochondrial biogenesis with age may be due to alterations in mitochondrial fission and fusion processes and the inhibition of mitophagy, a process which eliminates dysfunctional mitochondria [3]. ROS are a family of free radicals that includes superoxide anions, hydroxyl, peroxyl radicals and other non-radicals capable of generating free radicals [4]. Although the intracellular generation of ROS *per se* is an inevitable process, cells possess numerous defense systems to counter it. The overproduction of ROS has been associated with oxidative damage inflicted on lipids, DNA, and proteins [2,5]. It is evident from the previous studies that oxidative stress is associated with various pathophysiological conditions

Abbreviations: ATP, Adenosine triphosphate; OXPHOS, Oxidative phosphorylation; ROS, Reactive oxygen species; RNS, Reactive nitrogen species; TCA, Tricarboxylic acid; IR, Insulin resistance; MetS, Metabolic syndrome; ETC, Electron transport chain; SOD, Superoxide dismutase; (GPx), Glutathione peroxidase; (GSH), Glutathione; CAT, Catalase; PGC1α, Peroxisome proliferator-activated receptor gamma – coactivator 1 alpha; TNF-α, Tumor necrosis factor-alpha; T2DM, Type 2 diabetes mellitus; CR, Caloric restricted; MitoQ, Mitochondria-targeted quinone; SS31, Szeto-Schiller Peptide 31; NAC, N-acetylcysteine; mtDNA, Mitochondrial DNA; ERR, Estrogen related receptors.

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http://dx.doi.org/10.1016/j.bbadis.2016.11.010
0925-4439/

involving aging, cancer and age-related metabolic disorders and neurodegenerative diseases [6–16].

Metabolic syndrome (MetS) is a constellation of many metabolic abnormalities including hypertension, hyperglycemia, abdominal obesity and dyslipidemia represented by low-HDL-Cholesterol and hypertriglyceridemia. These conditions occurred together and increased the risk of type 2 diabetes and cardiovascular diseases (Fig. 1). It has been emerged as a major health problem in the modern society, associated with enormous social, personal, and economic burden in the developing and developed world [17–20]. Earlier studies demonstrated the interaction of genetic variants and environmental factors that contribute to the escalating situation of metabolic syndrome [21–24]. Several lines of evidence indicate the role of oxidative stress and mitochondrial dysfunction in the pathogenesis of aging, and age-related neurodegenerative and metabolic diseases [5,12,13,16,25–38]. Nevertheless, the basic mechanisms underlying the pathogenesis of metabolic syndrome remain largely unknown.

The present review article is focused to overview the basic mechanism of mitochondrial dysfunction and the link between oxidative stress/mitochondrial dysfunction and various components of metabolic syndrome. We specifically focused on heart disease, stroke, diabetes, and obesity, which are intimately related to oxidative damage induced by the enhanced generation of ROS that leads to mitochondrial dysfunction. Then, pharmacologic strategies translated from the bench to bedside will be provided to target mitochondrial dysfunction for the prevention of risk associated with metabolic syndrome.

2. Mitochondria: structure, function, and pathophysiology

Mitochondria are the double membrane, cytoplasmic organelles which contain their self-replicating genome. Mitochondria perform key biochemical functions essential for metabolic homeostasis and are arbiters of cell death and survival. In eukaryotes, mitochondria generate energy in the form of ATP via oxidative metabolism of nutrients using two major steps, 1) oxidation of NADH or FADH2 produced during the glycolysis, TCA cycle or β-oxidation of fatty acids, and 2) oxidative phosphorylation to generate ATP. All these processes are regulated by a complex of transcription factors in mitochondria. Each mitochondrion contains 800 to 1000 copies of mtDNA, which are maternally inherited and packaged in high-ordered nucleoprotein structures called nucleoids [39]. Although nucleoids are distributed throughout the mitochondrial matrix, they are often located in the proximity of the cristae, which carry the OXPHOS system. There is a small intermembrane space between the outer and inner mitochondrial membranes. Outer mitochondrial membrane and intermembrane space are relatively more permeable than the inner mitochondrial membrane. In contrast, the inner membrane has much more restricted permeability, contains enzymes involved in the process of electron transport chain and ATP generation. The inner membrane surrounds the mitochondrial matrix, wherein the electrons produced by TCA cycle are taken in by electron transport chain for the production of ATP. An electrochemical gradient generated across the inner membrane drives the process of OXPHOS [40]. Most of the body's cellular energy (>90%) is produced by mitochondria in the form of ATP via TCA cycle and the electron transport chain (ETC).

Mitochondrial ETC is composed of five multi-subunit enzyme complexes viz. I, II, III, IV and V located in the inner mitochondrial membrane [41]. The electrons donated by coenzymes, NADH and $FADH_2$ in TCA cycle are accepted and transferred to components of ETC at complex I (NADH ubiquinone reductase) or complex II (Succinate dehydrogenase), and then consecutively to complex III (Ubiquinol-cytochrome c reductase), complex IV (Cytochrome c oxidase) and finally to oxygen through complex V (F_0F_1 ATP synthase). This transfer of electrons along the electron transport chain is coupled with the transport of protons across the inner membrane, establishing the electrochemical gradient that generated ATP [42]. Mitochondria continuously function to metabolize oxygen and generate ROS (Fig. 2). However, either by accident or for a purpose, the flow of electrons through the ETC is an imperfect process in which 0.4 to 4% of oxygen consumed by mitochondria is incompletely reduced and leads to the production of ROS such as superoxide anion ($\bullet O_2^-$) designated as "primary" ROS [2,43]. Excessive generation of superoxide anion further interacts with many other compounds and generates "secondary" ROS [32,44]. It is earlier established that the interactions of hydroxyl radical (•OH) with DNA molecule damages the nitrogenous bases, purine and pyrimidine and deoxyribose backbone of DNA [2]. Also, the overproduction of ROS

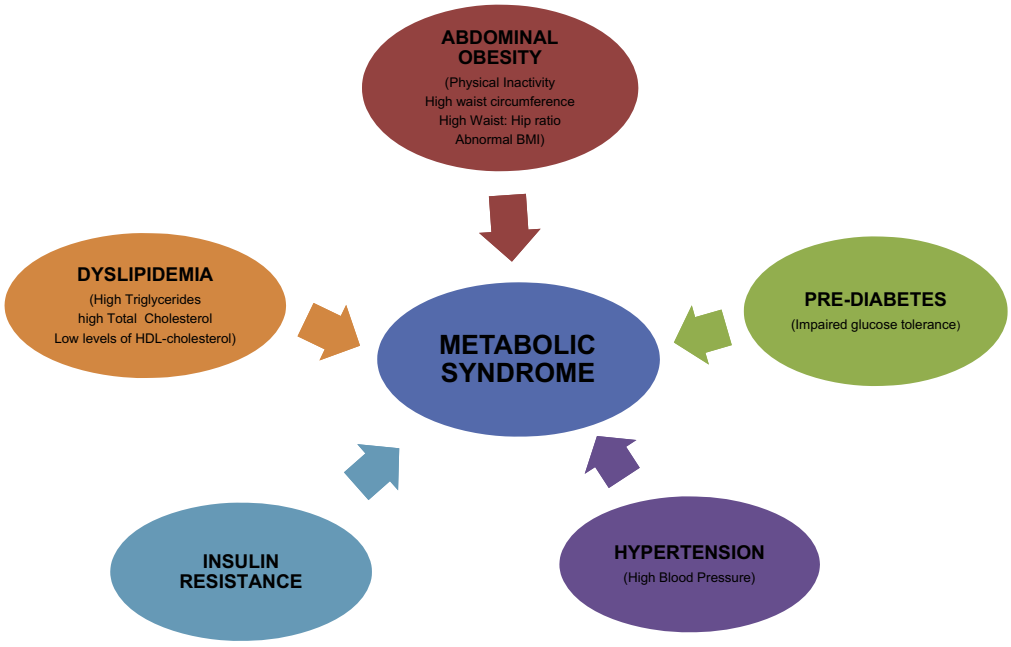

Fig. 1. Risk factors associated with metabolic syndrome. Metabolic syndrome is characterized by a group of metabolic abnormalities including hyperglycemia, abdominal obesity hypertension and dyslipidemia (Low HDL-cholesterol and elevated triglyceride levels).

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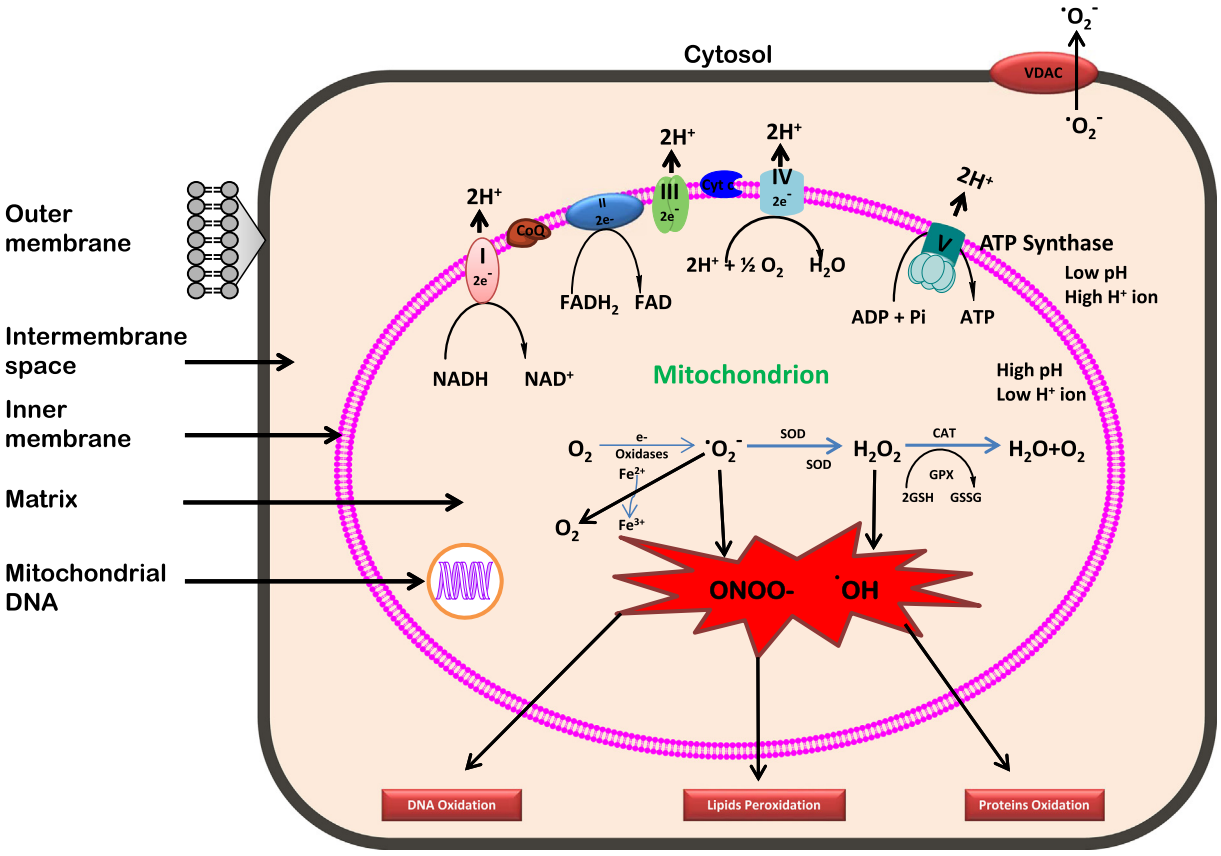

Fig. 2. Generation of reactive oxygen species in mitochondrion. Mitochondrial electron transport chain (ETC) is composed of five multi-subunit enzyme complexes located in the inner mitochondrial membrane. The electrons donated by coenzymes, NADH and $FADH_2$ in TCA cycle are accepted and transferred to components of ETC at complex I (NADH ubiquinone reductase) or complex II (Succinate dehydrogenase), and then consecutively to complex III (Ubiquinol-cytochrome c reductase), complex IV (Cytochrome c oxidase) and finally to oxygen through complex V (F_0F_1 ATP synthase). This transfer of electrons along the electron transport chain is coupled with the transport of protons across the inner membrane, establishing the electrochemical gradient that generated ATP. In a normal cell, mitochondria continuously function to metabolize oxygen and generate ROS such as superoxide anion ($^{\bullet}O_2^-$) designated as "primary" ROS. Transfer of electrons to O2 generates superoxide ($^{\bullet}O_2^-$) which is then converted to hydrogen peroxide (H_2O_2) by enzyme, superoxide dismutases (SOD) in mitochondria. H_2O_2 is then converted to water by glutathione peroxidase (GPx) or catalase (CAT). Excessive generation of ROS can oxidize proteins, lipids, or mitochondrial DNA (mtDNA).

damages the mitochondrial proteins/enzymes, membranes, and DNA, which leads to the interruption of ATP generation and other essential functions in mitochondria [32,43]. Besides superoxide anion and hydroxyl radicals, the ETC also generates other reactive species such as nitric oxide (NO) and reactive nitrogen species (RNS). Most of the cellular proteins and glutathione are affected through nitration induced by RNS. Free radicals are fundamental to any biochemical process and are continuously produced in the body. The cells have many ways to counter the effects of oxidative damage induced by ROS, either by directly diminishing the generation of free radicals or by scavenging the free radicals by an array of antioxidants, both enzymatic and non-enzymatic mechanisms.

Several defense mechanisms are used to alleviate the oxidative stress induced by the excessive generation of free radicals in the cells. Enzymatic defense system includes the ameliorative action of various antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), Glutathione Reductase (GR) and glutathione peroxidase (GPx). The other non-enzymatic defenses are the antioxidant compounds which protect the cells against oxidative stress. It includes Vitamin E and C, glutathione (GSH), various carotenoids and flavonoids. Under normal conditions, the overproduction of ROS is restricted in mitochondria to protect the cellular organelle from oxidative damage via enzymatic and non-enzymatic defense systems. On the other hand, when the antioxidant defenses are overwhelmed, there is an overproduction of ROS which then leads to oxidative damage to the proteins, DNA, and lipids in mitochondria [45]. This impaired the enzyme functions in the respiratory chain and ultimately leading to mitochondrial dysfunction, reduced mitochondrial biogenesis and a broad range of pathologic conditions such as aging, various metabolic diseases and neurodegenerative disorders [5,12,44,46–52]. Reduced mitochondrial number and capacity for oxidative phosphorylation in diabetes resulted in impaired mitochondrial biogenesis [53,54]. Mitochondria plays very critical role in the metabolic processes in mammalian cells and alterations in the mitochondrial structure and function lead to age-related neurodegenerative diseases as demonstrated by various studies in the past [34,55,56].

3. Regulation of mitochondrial biogenesis

Mitochondrial biogenesis maintains the number and size of mitochondria involving both nuclear and mitochondrial genomes. Several transcription factors are involved in the regulation of mitochondrial biogenesis, mediated by physiologic stimuli including physical exercise, dietary restrictions, temperature, and muscle myogenesis. Peroxisome proliferator-activated receptor (PPAR)-γ coactivator-1α (PGC-1α), is a co-transcriptional regulation factor that regulates the process of mitochondrial biogenesis by interacting with many transcription factors/proteins such as nuclear respiratory factors (NRF-1 and NRF-2), mitochondrial transcription factor A (Tfam), uncoupling proteins (UCP2), PPARs, thyroid hormone, glucocorticoid, oestrogen and estrogen related receptors (ERR) α and γ [57–59]. NRF-, NRF-2, and Tfam regulate the transcription of the main mitochondrial enzymes and mtDNA synthesis [60]. Besides these transcription factors, two important enzymes viewed as metabolic sensors that regulate mitochondrial biogenesis

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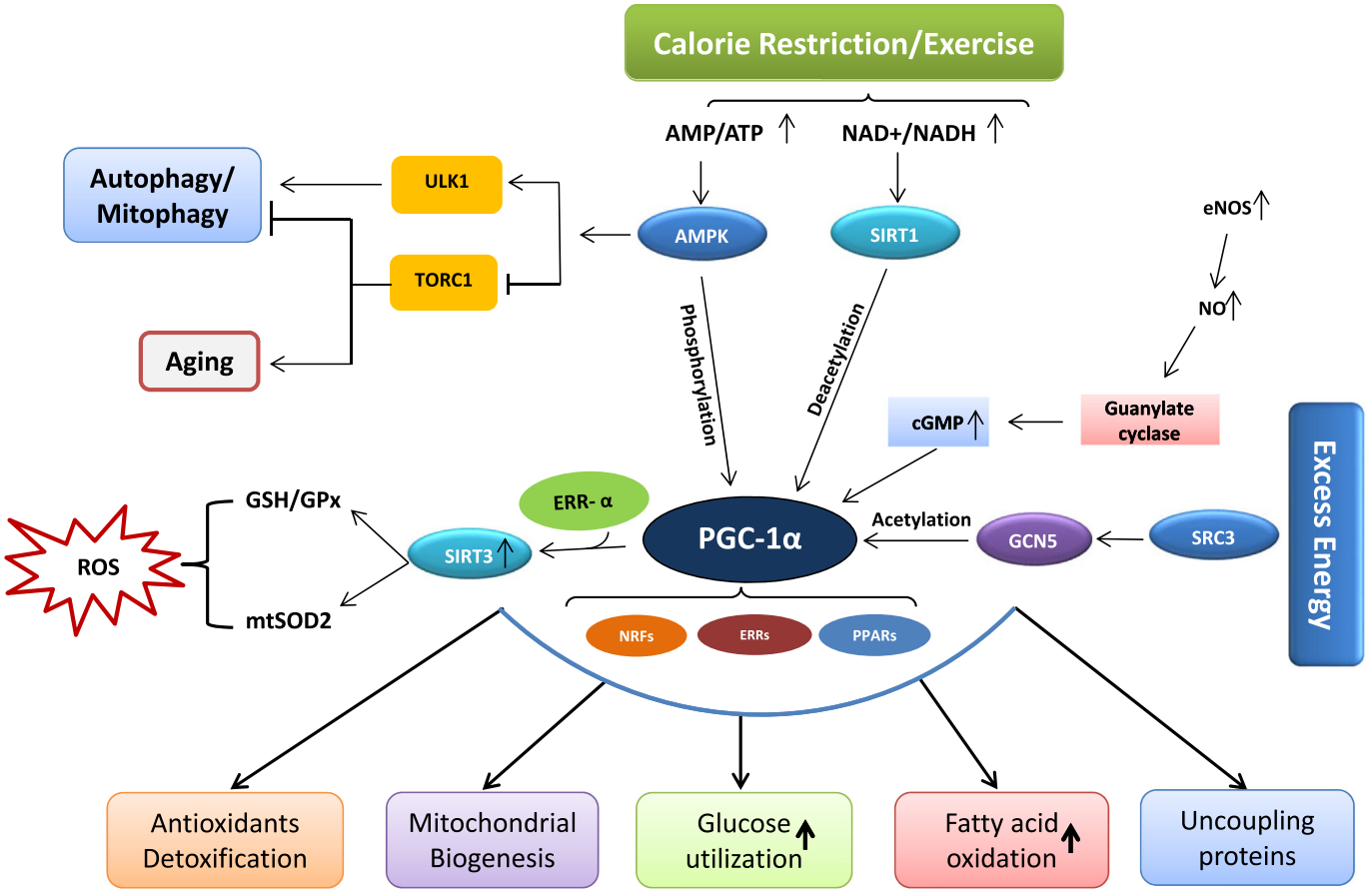

Fig. 3. Pathways involved in mitochondrial biogenesis. Mitochondrial biogenesis is activated via cellular stress or in response to environmental stimuli. Peroxisome proliferator-activated receptor (PPAR)-γ coactivator-1α (PGC-1α), a co-transcriptional regulation factor that regulate the process of mitochondrial biogenesis by interacting with many transcription factors/proteins such as nuclear respiratory factors (NRF-1 and NRF-2), mitochondrial transcription factor A (Tfam), uncoupling proteins (UCP2), PPARs, thyroid hormone, glucocorticoid, oestrogen and oestrogen related receptors (ERR) α and γ [57-59]. NRF-, NRF-2, and Tfam regulate the transcription of the main mitochondrial enzymes and mtDNA synthesis [60]. In calorie restriction or exercise, AMP-activated protein kinase (AMPK) and silent information regulator 2 (SIRT1) regulate PGC-1α through phosphorylation and deacetylation, respectively. Endothelial NO synthase (eNOS) display an increase in mtDNA content, cytochrome c and as well as PGC-1α, NRF-1 and Tfam mRNA expression. Activation of PGC-1α leads to increased fatty acid oxidation, uncoupling proteins, mitochondrial biogenesis, glucose utilization and ROS detoxification through PPARs, ERRs and NRFs.

are AMP-activated protein kinase (AMPK) and the mammalian counterpart of silent information regulator 2 (SIRT1). In energy deprived state, AMPK and SIRT1 regulate PGC-1α through phosphorylation and deacetylation, respectively [61]. Fig. 3 shows the role of PGC-1α and other transcriptional factors involved in mitochondrial biogenesis. Many experimental and clinical studies revealed the alterations in the morphology and number of mitochondria in heart, skeletal muscles and liver tissues in pathogenic conditions [1,62–66].

4. Mitochondrial dynamics

Mitochondrial dynamics is a delicate physiological balance between fission and fusion events of mitochondria, which is essential for their maintenance in the growing cells, regulation of cell death pathway, and removal of damaged mitochondria [67,68]. These mitochondrial events were first described in budding yeast [69]. Mitochondrial morphology varies tremendously in the cells and tissues in response to external stimuli and availability of nutrients. Mitophagy is an autophagy-lysosome system that removes dysfunctional mitochondria through fusion with lysosomes [70]. Mitochondrial fragmentation occurs in response to nutrient excess and cellular dysfunction escalates the prevalence of obesity, cancer, cardiovascular and neuromuscular disorders [71]. A mitochondrial defect leads to impaired oxidative capacity which then causes the overproduction of ROS. Over the past several years, many key regulators of fusion and fission have been identified. There are three GTPase genes that regulate the process of mitochondrial fusion viz. mitofusin 1 and 2 (Mfn1/2) and optic atrophy1 (Opa1), localized in the outer and inner mitochondrial membranes, respectively [72,73]. Mfn 1/2 are located on the outer mitochondrial membrane, whereas Opa 1 is localized to the inner mitochondrial membrane (Fig. 4). Mitochondrial fission, on the other hand, is regulated by highly conserved two GTPase genes, Fis1 and Drp1, located on outer membrane and in the cytosol, respectively. In the fusion process, mitochondrial content is intermixed and electrical conductivity maintained throughout the mitochondria [74–76]. Disturbed mitochondrial dynamics includes abnormal and/or impaired fission/fusion that occurs in response to nutrient excess and cellular dysfunction, directly impacts mitochondrial function, resulting in an excessive generation of ROS, altered mitochondrial enzymatic activities, impaired calcium homeostasis, diminished ATP production, and overall reduced energy metabolism in mammalian cells. Earlier studies documented the possible role of these mitochondrial alterations in escalation of metabolic and neurodegenerative disorders including aging, cancer, type 2 diabetes, obesity and dementia [34,36,56,77–88]. It also plays a pivotal role in the age-dependent decline in mitochondrial biogenesis. Increased ROS has been documented in the aging process. This increase may be primarily due to enhanced accumulation of mtDNA mutations which in turn could damage the mitochondrial structure and functions, consequently, altering antioxidant defense system, disturbed calcium homeostasis, low ATP generation and ultimately leading to many pathogenic conditions.

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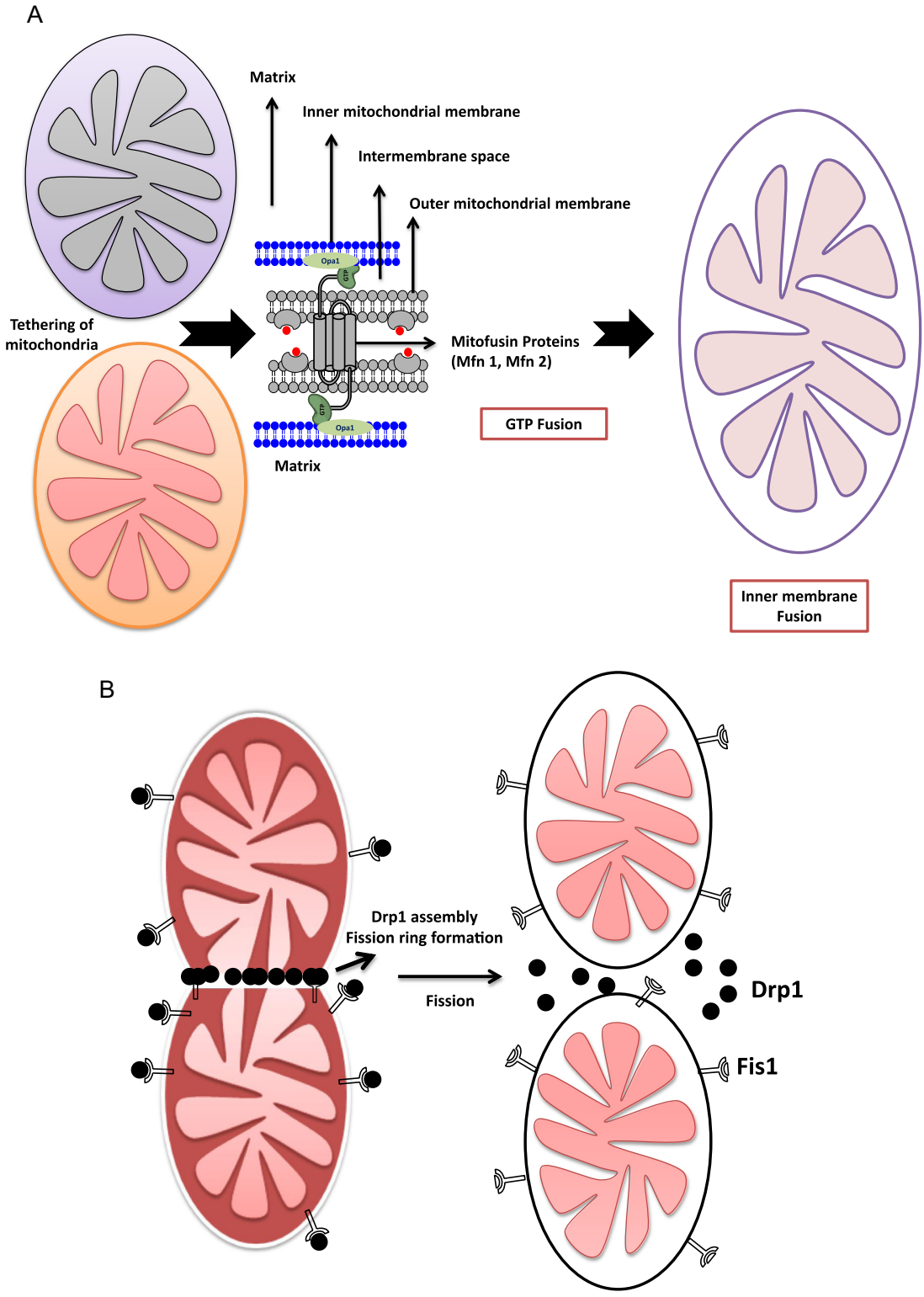

Fig. 4. (A) Mitochondrial fusion process. (B) Mitochondrial fission process. Mitochondrial fusion is regulated by three GTPase genes including mitofusin 1 (Mfn1), mitofusin 2 (Mfn 2), and optic atrophy 1 (Opa1); Mfn 1 and 2 are located on the outer mitochondrial membrane, whereas Opa 1 is localised on the inner mitochondrial membrane. On the other hand, mitochondrial fission is regulated by highly conserved two GTPase genes, Fis1 and Drp1, located on outer membrane and in the cytosol, respectively.

5. Oxidative stress and mitochondrial dysfunction

Oxidative stress refers to the imbalance of two opposite and antagonistic forces, production of ROS and antioxidants, wherein the damaging effects of ROS are more powerful compared to the compensatory effect of antioxidants in the cells. Mitochondrial dysfunction is defined as diminished mitochondrial biogenesis, altered membrane potential, and the decrease in mitochondrial number and altered activities of oxidative proteins due to the accumulation of ROS in cells and tissues [89]. Regular metabolism of oxygen generates reactive oxygen species as a by-product. Indeed, mitochondria are the most important source of ROS in most of the mammalian cells [43]. ROS produced in

mitochondria during OXPHOS process primarily triggered mitochondrial dysfunction by interacting with mitochondrial and cellular components such as DNA, proteins, lipids, and other molecules [90,91].

Metabolic syndrome represents a constellation of many risk factors such as obesity, higher blood pressure, abnormal levels of triglycerides and cholesterol which are involved in the higher prevalence of non-communicable diseases. Altered mitochondrial functioning has been implicated in the pathophysiology of type 2 diabetes, obesity, dyslipidemia, and cardiovascular diseases. The imbalance between energy production and its utilization - may lead to defective cell metabolism which is considered as the main culprits of metabolic syndrome [92]. Increased glucose levels enhance overproduction of ROS which leads to morphological changes in mitochondria [93]. Inhibition of insulin signaling pathway that caused the accumulation of lipids and free fatty acids (FFA) contributes to the metabolic disorders [94–99]. Also, it is evident that aging, altered mitochondrial biogenesis and decreased antioxidant defense capacity along with genetic factors caused insulin resistance which is the major cause of many metabolic diseases. In the following sections, we have established the link between mitochondrial dysfunction and individual components of metabolic syndrome.

6. Mitochondrial dysfunction and insulin resistance

Insulin resistance (IR) is characterized by diminished capacity of the cells to respond to the physiological levels of insulin. Various risk factors including aging, physical inactivity, abdominal obesity, and stress contribute to the pathophysiology of insulin resistance. Oxidative stress induced by an excess of ROS in mitochondria might also contribute to the development of insulin resistance [1,16,100]. It is evident from previous studies that oxidative stress and mitochondrial dysfunction are involved in the pathophysiology of many metabolic disease states such as insulin resistance, obesity diabetes, and many cardiovascular and neurodegenerative diseases [101–112]. However, it is still not clear whether insulin resistance is the primary cause of mitochondrial dysfunction or vice-versa. Nonetheless, many studies established the association of mitochondrial dysfunction with insulin resistance in various tissues [64,113–117]. In skeletal muscle, altered mitochondrial functions, reduced ATP synthesis, and increased ROS generation lead to insulin resistance and obesity/diabetes [66,118,119]. The imbalance between energy production and its utilization may result in impaired cell metabolism which is considered as the main culprits of metabolic syndrome [92]. Increased glucose levels enhance overproduction of ROS which lead to morphological changes in mitochondria [93]. Inhibition of insulin signaling pathway caused the accumulation of lipids and free fatty acids (FFA) which contributes to insulin resistance and other metabolic disorders [94–99]. Over the past decade, many studies on human subjects and rodents provide evidences for alterations in markers of mitochondrial metabolism in insulin resistant individuals. These observations led to the theory that compromised mitochondrial oxidative functions, particularly in skeletal muscle, causes excess lipid deposition, and development of insulin resistance. Considerable research indicates that decrease in fatty acid oxidation causes the inhibition of insulin signaling, which consequently leads to FFA and insulin resistance and further reduces the mitochondrial oxidative capacity and ATP synthesis in obese and insulin resistance models [92,100]. Indeed, further clinical research studies are necessary to investigate the role of antioxidants and antioxidant pathways that drive mitochondrial functions and insulin sensitivity in humans.

7. Mechanistic link between diabetes and oxidative stress/mitochondrial dysfunction

Over the past 20 years, there has been an explosive increase in the incidence and prevalence of type 2 diabetes and this increase becomes a major public health problem all over the world. Presently more than 382 million people are suffering from type 2 diabetes, and it is predicted that this number will rise to 438 million in 2030. India, China, and USA are the worst affected countries bearing the major burden of type 2 diabetes in the world. Although many experimental and clinical studies established the role of environmental and genetic factors associated with the pathophysiology of type 2 diabetes but the primary cause of this problem is still unknown. Both pancreatic β-cell dysfunction and insulin resistance in insulin sensitive tissues including adipocytes, myocytes, and hepatocytes have been implicated in the etiology of diabetes and related complications. Also, recent studies have indicated abnormal mitochondrial dynamics along with overproduction of ROS in diabetic patients [93,120]. T2DM results from a combination of reduced tissue sensitivity to insulin and inadequate insulin secretion. It usually develops in adults and is thought to stem from a complex interaction between obesity, physical inactivity, diet and genes [121]. A recent study done on diabetic and obese patients established the impaired glucose and lipid homeostasis in skeletal muscle [116]. Increased fat mass leads to several factors that inhibit insulin action including decreased glucose transporter type 4 (GLUT4), increased free fatty acids and other circulating molecules [122,123]. Due to reduced insulin response in sensitive tissues, excess glucose accumulates leading to chronic hyperglycemia [121].

Several studies have documented the role of mitochondrial dysfunction in the pathophysiology of T2DM [66,88,124–128]. Reduced mitochondrial respiration, ATP production and mitochondrial density and mRNA have been reported in the insulin resistance and type 2 diabetic patients [54,96,129–132]. A short-term high-calorie diet resulted in increased markers of oxidative stress and a transient increase in OXPHOS enzyme protein expression. The mtDNA is more predominantly susceptible to oxidative damage induced by the excess of ROS during OXPHOS process in mitochondria of the brain [133] in obesity and T2DM. Mitochondrial dysfunction inhibits insulin signaling pathway through the overproduction of ROS and interfering with oxidation of acetyl CoA, consequently resulting in increased lipid and diacylglycerol [1,48,66,134]. Mitochondrial biogenesis is reduced in the condition of diabetes and obesity [116,135,136]. PGC-1α also regulates the process of mitochondrial biogenesis [137,138]. Furthermore, mitochondrial dysfunction seems to play a vital role in the pathophysiology of IR and T2DM and may be considered as a target for therapeutic measures in metabolic diseases.

8. Mechanistic link between obesity and oxidative stress/mitochondrial dysfunction

Currently, obesity has become one of the major global health problems. It is one of the principal components of metabolic syndrome and known to be a major risk factor in the development of many metabolic disorders. Although obesity is caused by the interaction of genetic and environmental factors, the role of obesity in mitochondrial dysfunction has been revealed in many studies. Recent studies demonstrated the role of mitochondrial dysfunction in the pathogenesis of components of metabolic syndrome. There is an overproduction of ROS in adipose tissues with altered activities of NADPH oxidase and antioxidative enzymes in obese mice [139]. Intriguingly, abdominal obesity has been associated with defective mitochondrial biogenesis manifested by impaired mitochondrial dysfunction, oxidative metabolism, low mitochondrial gene expression and reduced ATP generation in rodents and humans [63,140–142]. Also, mtDNA, respiratory protein, and mtDNA transcription factor A (Tfam) gene expressions were markedly reduced in obese mice. Also altered mitochondrial dynamics plays a pivotal role in mitochondrial dysfunction linked to obesity as evident from reduced expression of mitofusin 2 gene in skeletal muscle [143].

9. Mechanistic link between heart disease and oxidative stress/mitochondrial dysfunction

Cardiovascular diseases (CVD) that include atherosclerosis, ischemic heart disease, cardiomyopathy, cardiac hypertrophy and heart failure

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are the leading cause of mortality, worldwide. CVD is multifactorial in nature involving the interactions of both environmental and genetic risk factors in cardiovascular diseases. It is evident from previous studies that oxidative stress may be associated with increased mtDNA damage in CAD patients. In the heart, the ROS can be generated in cardiac myocytes, endothelial cells, and neutrophils. *In vivo* and *ex vivo* studies have established the role of oxidative stress induced by the excess of ROS in a wide range of cardiovascular diseases [6,13,25,32,144–148]. The majority of ROS in the heart are generated by uncoupling of mitochondrial ETC complexes I and III [49,149]. However, there are other mechanisms such as NADPH oxidase, xanthine oxidoreductase, or NOS by which ROS are generated and induce oxidative damage in heart tissue. The excess of ROS leads to cellular injury and declined antioxidant capacity, which seems to be due to defects in mitochondrial functions and mtDNA damage, endothelial dysfunction and altered gene expression [6]. The reduced mitochondrial oxidative capacity contributes to cardiac dysfunction. The ROS are significantly enhanced in failing myocardium [51,148,150–152]. Recent findings have established the role of ROS, pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α), altered mitochondrial biogenesis and mtDNA damage, structural and morphological changes in mitochondria contributing to the development and progression of heart diseases such as heart failure and cardiac dysfunction [147,153,154]. Moreover, ROS stimulate contractile function, activate a variety of enzymes, transcription factors, and induce apoptosis. Thus ROS play a central role in the pathophysiology of cardiovascular diseases.

10. Mechanistic link between stroke and oxidative stress/mitochondrial dysfunction

Stroke is the fourth leading cause of adult disability and mortality in the developing world, associated with social and economic problems [155]. Oxidative stress is one of the contributing factors leading to cellular damage during ischemic brain injury [156]. Mitochondrial dysfunctions have been demonstrated as a key player in the development of brain stroke as evident by reduced ATP production, the starvation of glucose and oxygen to the tissues and influence on cell death pathways [157]. In experimental models of stroke, the diminished supply of glucose and oxygen leads to impaired oxidative metabolism in brain tissue [158]. The resultant oxygen-glucose deprivation in the brain tissue causes the accumulation of reducing intermediates and leads to enhanced ROS formation [156]. During oxidative stress, the excess of ROS alter antioxidant defense mechanism by reducing the scavenging capacity of antioxidant enzymes that could lead to altered mitochondrial functions by interacting with mitochondrial and cellular components such as DNA, proteins, and lipids [91,159]. In focal ischemia, the damaging action of oxidative stress in necrosis and apoptosis has been explained in previous studies [160,161]. Peroxynitrite radical also plays a significant role in the pathogenesis of brain stroke. Thus overproduction of ROS in mitochondria significantly induces oxidative damage in the ischemic and post-ischemic brain [157,162,163].

11. Pharmacologic strategies to target mitochondrial dysfunction

Mitochondrial stress pathways have been implicated in disease manifestations of mitochondrial dysfunction and could highlight promising therapeutic targets [164–166]. Several lines of evidence imply that mitochondrial dysfunction plays a central role in the pathophysiology of metabolic disorders, age, and age-related neurodegenerative diseases. So targeting mitochondria might be a promising strategy for potential therapeutic purposes in metabolic disorders and age-related neurodegenerative diseases. The following strategies might be employed to diminish the mitochondrial dysfunction caused by excessive generation of ROS that induced oxidative stress.

12. Lifestyle interventions

Mitochondrial dysfunction contributes to severity of many pathological conditions including skeletal muscle atrophy, diabetes, cardiovascular diseases and many metabolic disorders and neurodegenerative diseases. Recent studies indicated that physical activity offers many benefits through improved insulin sensitivity and mitochondrial biogenesis in skeletal muscles in T2D patients. Also, a significant increase in muscle mitochondrial respiration and mitochondrial content, oxidative enzyme activity and mitochondrial density were observed in T2D patients after exercise [61,167–173]. Exercise stimulates AMPK, leading to activation of PGC 1 by direct phosphorylation of threonine and serine residues [174]. This phosphorylation event may ultimately promote mitochondrial biogenesis. Also, regular exercise triggers many other signalling pathways involved in skeletal muscle mitochondrial biogenesis, dynamics and metabolism in healthy and aged persons [174,175]. Aging causes loss of muscle mass and structural changes in the neuromuscular components resulting in impaired contractile function. Exercise induces beneficial adaptations that slow down the progression of age-related muscle functional decline. Reduced physical activity and sedentary lifestyle are also the major contributing factors for escalating the prevalence of obesity, type 2 diabetes and many other metabolic disorders [176]. Several studies established the pleiotropic effect of physical exercise on mitochondrial dynamics in aging skeletal muscle [177]. Nutrients control the glucose homeostasis through a complex of PGC-1α and SIRT1 [178]. Reduced energy results increased AMP/ATP ratio and activate AMPK which then regulate PGC-1α through phosphorylation. Calorie restriction or exercise also increases tissue NAD + content thereby activates SIRT1, which then activates PGC-1α through deacetylation [178]. Nitric oxide also appears to be an important regulator of mitochondrial biogenesis. Previous studies shows that defect in PGC-1α are associated with insulin sensitivity in type 2 diabetic patients [54].

In addition to regular exercise, calorie restriction (CR) without malnutrition is also a promising non-genetic and non-pharmacologic nutritional intervention that prolongs the lifespan of a variety of organisms and helps in the prevention of age-related metabolic disorders [179–181]. However, the molecular mechanisms of calorie restrictions induced benefits in aging and related disorders are still not clear. Indeed, earlier studies reported that CR reduces the overproduction of ROS and oxidative damage, leading to enhanced mitochondrial function in humans and be an effective remedy for the treatment of obesity and insulin resistance [182–185]. CR has been also been reported to substantially elevate the insulin sensitivity in many species including humans, nonhuman primates, dogs, mice, and rats [186,187]. Recent studies demonstrated that CR leads to increased Akt2 activity and glucose uptake by insulin-stimulated skeletal muscle in aged rats [188,189]. Finally, data from various epidemiological, clinical and experimental studies have shown that CR exerts additional beneficial health effects by inhibiting key nutrient-sensing and inflammatory pathways and remains the cornerstone in the prevention and treatment of metabolic disorders [190].

13. Pharmacological interventions

The recent literature revealed that oxidative stress in the cell leads to structural and functional changes in the mitochondria. These mitochondrial changes trigger cell signaling pathways and generate uncontrollable ROS which ultimately lead to organ failure and diseases. Therefore pharmaceutical drugs that can limit the overproduction of ROS in the cells may be the potential therapeutic solution to improve mitochondrial health in a wide range of diseases. Although the molecular mechanisms of mitochondria-mediated diseases are uncertain, oxidative stress induced by overproduction ROS in mitochondria seems to be the major risk for development of metabolic and neurodegenerative diseases. Growing shreds of evidence demonstrated that

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NAD-dependent deacetylase family (Sirtuins), SIRT1 is involved in many cellular processes including regulation of glucose and lipid metabolism, through insulin signaling in the liver, adipose tissue, and skeletal muscles [191–202]. Newer pharmacologic approaches have been proposed to improve mitochondrial function. Resveratrol, an activator of SIRT1, found in grapes have strong antioxidant properties and improves insulin resistance. Activation of SIRT1 gene protects the cells against inflammation and oxidative stress. It activates PGC-1α that promotes glucose uptake and mitochondrial biogenesis [195,203, 204]. Mitochondrial fission has been implicated in various metabolic conditions, the inhibitors of mitochondrial fission may be used as therapeutic targets to treat patients with metabolic disorders [205]. Three inhibitors of mitochondrial fission have been identified as Mdivi 1, P110, and Dynasore [206–208] which play an ameliorative role against mitochondrial oxidative stress.

14. Mitochondria-targeted antioxidants

Metabolic syndrome affects 20%–30% of the world's population. The involvement of oxidative stress and mitochondrial dysfunction in the pathophysiology of metabolic disorders has been widely established. The mitochondria targeted antioxidant therapies could be potential treatment for a number of pathologic conditions including neurodegenerative or metabolic diseases. Recently, *in vivo* and *in vitro* studies done in experimental animals and humans, reported ameliorative role of mitochondria targeted antioxidants against metabolic disorders [209–212]. The commonly used vitamins (vitamin E and C) and other chemical compounds with antioxidant properties such as coenzyme Q, a-lipoic acid, N-acetylcysteine (NAC) have been used to reduce the excess generation of ROS in various metabolic conditions [213–215]. In the recent years, antioxidant compounds incorporating ubiquinone (MitoQ) or vitamin E (MitoVit E) specifically targeted to mitochondria have been successively used against mitochondrial dysfunctions [216] (Fig. 5). Recent studies have demonstrated that mitochondria-targeted antioxidants are far better in reducing oxidative damage in mitochondria [216–219].

MitoQ is a potent mitochondria-targeted therapeutic antioxidant in which lipophilic triphenylphosphonium (TPP) cation is bound to ubiquinone antioxidant moiety of the endogenous antioxidant coenzyme Q10 [220]. The lipophilic nature of TPP-cation enables MitoQ to cross phospholipid bilayers that leads to its accumulation many hundred-fold within mitochondria and reduce ROS in the mitochondria and protect against age-related mitochondrial insult in brain tissue [216,217,220]. Recent studies established the defensive action of MitoQ in metabolic syndrome by affecting the redox signaling pathways [221,222]. These findings support the understanding that increased ROS in mitochondria may contribute to the etiology of a wide variety of diseases [223–226]. Nowadays MitoQ has been extensively used as a potential therapeutic molecule for the treatment of neurodegenerative diseases [227–229]. Like MitoQ, MitoVitE, a TPP-conjugated vitamin E is another mitochondria-targeted vitamin E derivative, which can easily pass through the lipid bilayers and accumulate 100 to 1000-fold within mitochondria [230,231]. It also protects mitochondria against oxidative damage induced by the excess of ROS in many pathogenic conditions [217,220,230]. It also protects mitochondria against oxidative damage induced by the excess of ROS in many pathogenic conditions [217,220, 230]. MitoVit E has been shown to be 350-fold more potent than untargeted vitamin E in protecting against cell death induced by mitochondrial oxidative damage [219].

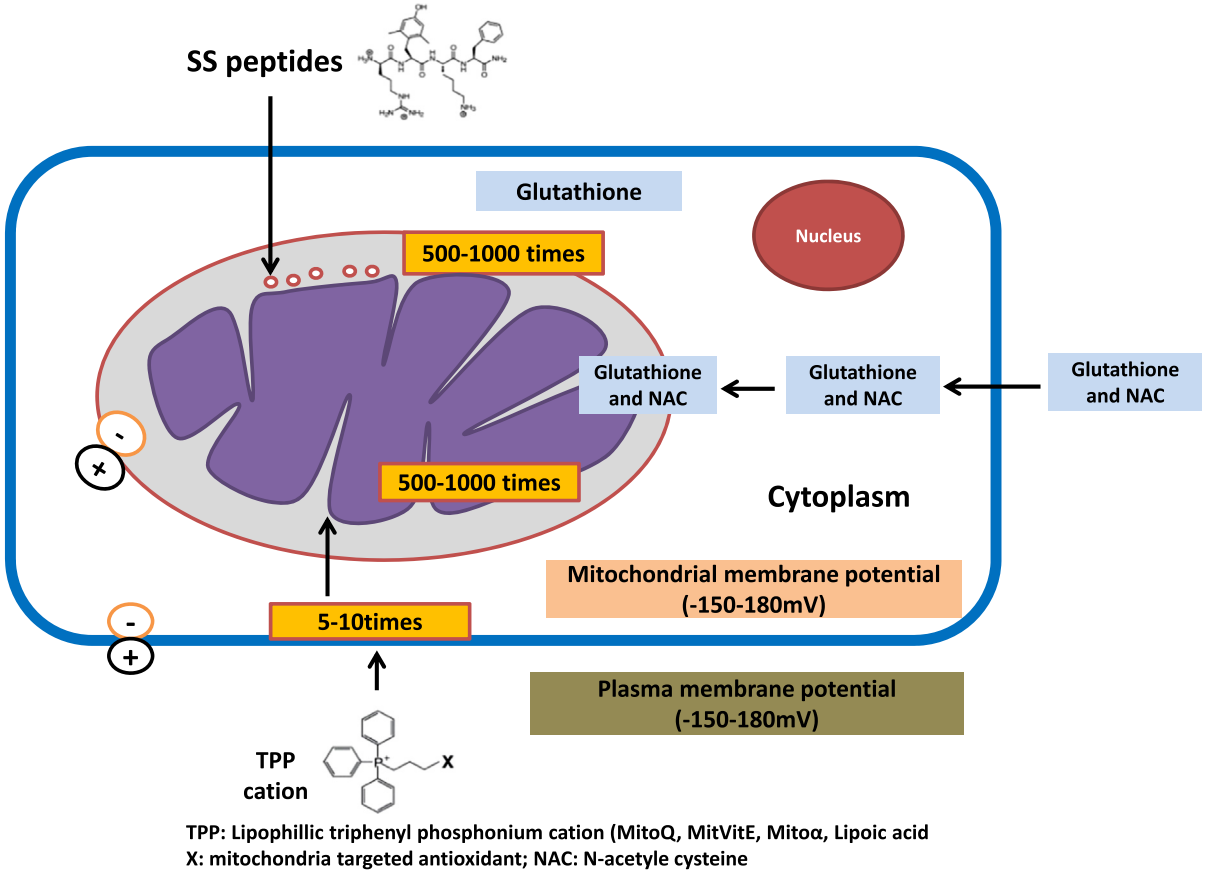

Fig. 5. Mitochondria-targeted antioxidants. A representative mitochondrial-targeted antioxidant (MitoQ) is constructed by an attachment of an antioxidant molecule – quinone to the lipophilic triphenylphosphonium cation - TPP. MitoQ accumulate several folds in the cytoplasm, and further accumulates several hundred folds in the mitochondria. Mitochondrial antioxidants scavenge free radicals.

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15. Conclusions and future perspectives

Mitochondria are the cytoplasmic organelles responsible for cell survival and cell death. The major function of mitochondria is to 'energize' adenosine triphosphate (ATP) to the cells by metabolizing nutrients and responsible for cellular processes ranging from energy metabolism, generation of reactive oxygen species and Ca^{2+} homeostasis, cell survival, and death. Mitochondrial structural and functional changes are reported to involve in aging, cancer, metabolic syndromes, including stroke, ischemia, pre-diabetes, diabetes, obesity, hypertension, dyslipidemia, heart disease, alcohol injury, and neurodegenerative diseases. Recent research revealed that mitochondrial abnormalities, including impaired mitochondrial dynamics, defects in mitochondrial biogenesis, mitochondrial dysfunction, and oxidative stress are primarily involved in metabolic syndromes. Recent research also revealed that maintaining mitochondrial dynamics (fission-fusion balance) and mitochondrial function are necessary to treat patients with metabolic syndromes. To reduce and/or delay the progression of disease in metabolic syndromes, many therapeutic approaches are useful, including – lifestyle intervention (healthy diet & regular exercise), pharmaceutical strategies, and treating patients with mitochondrial-targeted molecules. However, molecular links between metabolic syndromes and mitochondrial structural/functional changes are not well understood. Further genetics and genetic susceptibility to patients with metabolic syndromes, in relation to aging, are poorly understood. The role of epigenetics in patients with metabolic syndromes is unclear. Also, current generalized treatments to patients with metabolic syndromes may not be efficient and work because of body physiology different from population to population. Further research is urgently needed to answer these questions.

Transparency document

The Transparency document associated with this article can be found, in online version.

Acknowledgments

Work presented in this article is supported by NIH grants AG042178, AG047812 and the Garrison Family Foundation. Dr. Jasvinder Singh Bhatti is financially supported by the University Grants Commission, India under Raman Post-Doctoral Research Fellowship in USA [F.No. 5-82/2016 (IC)].

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Please cite this article as: J.S. Bhatti, et al., Mitochondrial dysfunction and oxidative stress in metabolic disorders — A step towards mitochondria based therapeutic strategies, Biochim. Biophys. Acta (2016), http://dx.doi.org/10.1016/j.bbadis.2016.11.010

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Please cite this article as: J.S. Bhatti, et al., Mitochondrial dysfunction and oxidative stress in metabolic disorders — A step towards mitochondria based therapeutic strategies, Biochim. Biophys. Acta (2016), http://dx.doi.org/10.1016/j.bbadis.2016.11.010

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Please cite this article as: J.S. Bhatti, et al., Mitochondrial dysfunction and oxidative stress in metabolic disorders — A step towards mitochondria based therapeutic strategies, Biochim. Biophys. Acta (2016), http://dx.doi.org/10.1016/j.bbadis.2016.11.010