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

Jasvinder Singh Bhatti [a,b,*], Gurjit Kaur Bhatti [c], P. Hemachandra Reddy [b,d,e,f,g,h]

[a] Department of Biotechnology and Bioinformatics, Sri Guru Gobind Singh College, Sector-26, Chandigarh 160019, India
[b] Garrison Institute on Aging, Texas Tech University Health Sciences Center, 3601 4th Street, MS 9424, Lubbock, TX 79430, United States
[c] UGC Centre of Excellence in Nano applications, Panjab University, UIPS building, Chandigarh 160014, India
[d] Cell Biology & Biochemistry Department, Texas Tech University Health Sciences Center, 3601 4th Street, MS 9424, Lubbock, TX 79430, United States
[e] Neuroscience & Pharmacology Department, Texas Tech University Health Sciences Center, 3601 4th Street, MS 9424, Lubbock, TX 79430, United States
[f] Neurology Department, Texas Tech University Health Sciences Center, 3601 4th Street, MS 9424, Lubbock, TX 79430, United States
[g] Speech, Language and Hearing Sciences Departments, Texas Tech University Health Sciences Center, 3601 4th Street, MS 9424, Lubbock, TX 79430, United States
[h] Garrison Institute on Aging, South West Campus, Texas Tech University Health Sciences Center, 6630 S. Quaker Suite E, MS 7495, Lubbock, TX 79413, United States

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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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* Corresponding author at: Department of Biotechnology and Bioinformatics, Sri Guru Gobind Singh College, Sector-26, Chandigarh 160019, India.
E-mail address: jasvinderbhatti@yahoo.com (J.S. Bhatti).

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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

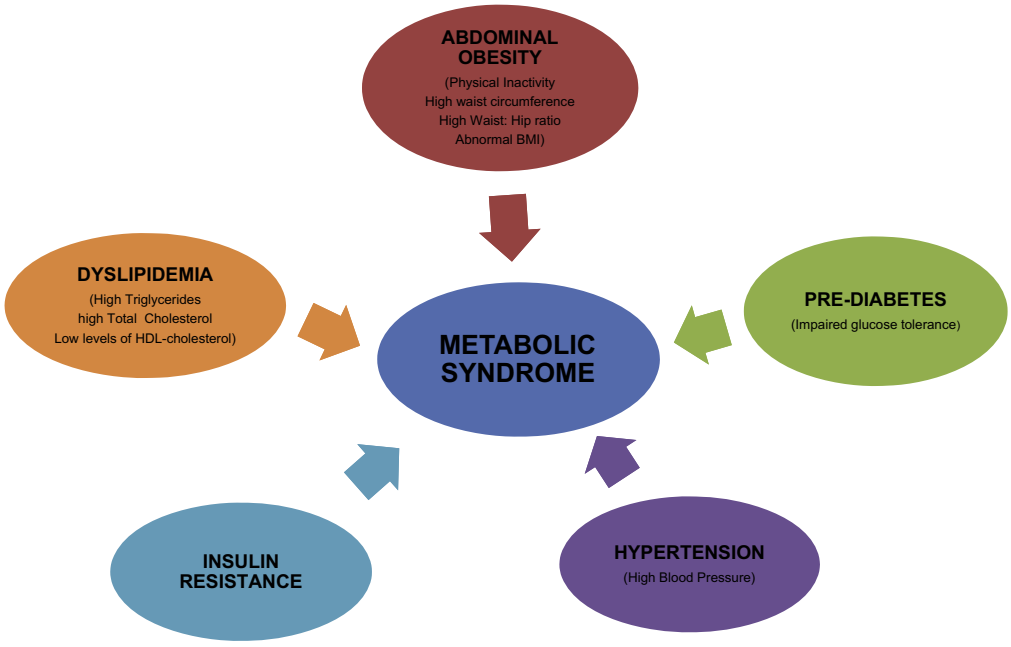

Fig. 1. Risk factors associated with metabolic syndrome. Metabolic syndrome is characterized by a group of metabolic abnormalities including hyperglycemia, abdominal obesity hypertension and dyslipidemia (Low HDL-cholesterol and elevated triglyceride levels).

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