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Linking mitochondrial dysfunction, metabolic syndrome and stress signaling in Neurodegeneration☆

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ABSTRACT

Mounting evidence suggests a link between metabolic syndrome (MetS) such as diabetes, obesity, non-alcoholic fatty liver disease in the progression of Alzheimer's disease (AD), Parkinson's disease (PD) and other neurodegenerative diseases (NDDs). For instance, accumulated Aβ oligomer is enhancing neuronal Ca^{2+} release and neural NO where increased NO level in the brain through post translational modification is modulating the level of insulin production. It has been further confirmed that irrespective of origin; brain insulin resistance triggers a cascade of the neurodegeneration phenomenon which can be aggravated by free reactive oxygen species burden, ER stress, metabolic dysfunction, neuorinflammation, reduced cell survival and altered lipid metabolism. Moreover, several studies confirmed that MetS and diabetic sharing common mechanisms in the progression of AD and NDDs where mitochondrial dynamics playing a critical role. Any mutation in mitochondrial DNA, exposure of environmental toxin, high-calorie intake, homeostasis imbalance, glucolipotoxicity is causative factors for mitochondrial dysfunction. These cumulative pleiotropic burdens in mitochondria leads to insulin resistance, increased ROS production; enhanced stress-related enzymes that is directly linked MetS and diabetes in neurodegeneration. Since, the linkup mechanism between mitochondrial dysfunction and disease phenomenon of both MetS and NDDs is quite intriguing, therefore, it is pertinent for the researchers to identify and implement the therapeutic interventions for targeting MetS and NDDs. Herein, we elucidated the pertinent role of MetS induced mitochondrial dysfunction in neurons and their consequences in NDDs. Further, therapeutic potential of well-known biomolecules and chaperones to target altered mitochondria has been comprehensively documented. 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

For the maintenance of energy metabolism and cellular homeostasis mitochondria is an important organelle which is also known as the power house of cells and predominantly required for determining many cellular functions ranging from metabolic to catabolic activities. Mitochondria performs numerous crucial functions within the cell, which include cellular ATP production, Ca^{2+} buffering, regulation of apoptotic process and involvement in the synthesis of key metabolites. Nevertheless, it also acts as a primary source of endogenous reactive oxygen species (ROS) under oxidative stress. Additionally, mitochondria provides most of the ATP for the metabolic and cellular reaction within the cell, which is mainly coupled with electron transport system (ETS) [1,2]. However, research in the past few decades has recognized various factors, such as mutations in mitochondrial DNA and environmental toxins causing homeostatic imbalances, consequently leading to the damage of normal mitochondrial dynamics. Such alterations include altered mitophagy, decelerated ATP production, disturbed Ca^{2+} homeostasis, reduced mitochondrial membrane potential and compromised mitochondrial respiration [3]. Since, the potential mechanistic role played by altered mitochondria and their associated risk factors in MetS and NDDs remain unsettled, and their possible interlinking is still needed to be investigated. This review extensively covers the involvement of mitochondrial dysfunction in both MetS and neuronal dysfunction. Further, implementation of several biomolecules and chaperones for targeting MetS and NDDs induced by mitochondrial dysfunction has also been elaborated.

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2. Metabolic syndrome and mitochondrial dysfunction: A complex interplay

Metabolic syndrome (MetS) is a cluster of aberrations of metabolic origin that augments the risk for cardiovascular disease, stroke, morbidity and mortality from type-2 diabetes (T2D) [4]. Characteristic features of these complex pathological aberrations include lipid accumulation, impaired glucose metabolism and hypertension [5]. Furthermore, obesity is also one of the most critical factors that have been linked with metabolic disturbances to facilitate tissue stress and dysfunction [6]. The obese individuals are having a greater risk for prolonged diseases and usually manifest clinical features of MetS including hypertension, insulin resistance (IR), hyperglycemia and systemic markers of chronic low-grade inflammation [7]. The central pathophysiological mechanism behind MetS is IR, which is closely related to mitochondrial dysfunctioning. However, mitochondrial dysfunction is a complicated process, but it is known to be triggered by genetic factors from both mitochondrial and nuclear genome. Additionally, mitochondrial DNA polymorphisms are also associated with the components of MetS [8]. Further, environmental risk factors, for instance, life style (food intake and physical activity), various chemicals and drugs, glucolipotoxicity, and homeostatic imbalances are also responsible for MetS associated with mitochondrial dysfunctioning and IR as well (Fig. 1) [3]. Recently, it has been reported that serum levels of many mitochondrial toxins, for instance, persistent organic pollutants (POPs) are associated with MetS. However, further investigation to reveal its precise mechanism is still unclear [9]. Likewise, deficiency of Co-enzyme Q10 (Co-Q10), an important element of the mitochondrial electron transport chain has been reported in a couple of clinical outcomes, including hypertension, heart failure, obesity, which all together leads to MetS [10]. Increasing evidence suggests that an altered or excessive glucocorticoid secretion and oxidative stress strongly lead to IR associated with MetS [11]. Furthermore, oxidative stress is also a key player in the progression of MetS, which is caused due to the loss of redox homeostasis which leads to pro-inflammatory and profibrotic pathways. These events enhance the destructions in insulin signaling, diminished endothelial-mediated vaso-relaxation and associated renal and cardiovascular risks [12]. Similarly, acute hypoxia in the body is accumulating extracellular and cytosolic irons that damage the cardiovascular tissue which is also a reason of redox homeostatic imbalance that leads to hypertension and progression of metabolic dysregulation [13].

Since, regulation of cellular energy depends on complex signaling networks that act in response to fuel availability and metabolic demands. Any imbalance in the cellular energy network also paves the way for metabolic diseases, including obesity and MetS [14]. Currently, chronic sympathetic nerve activation has been reported to promote

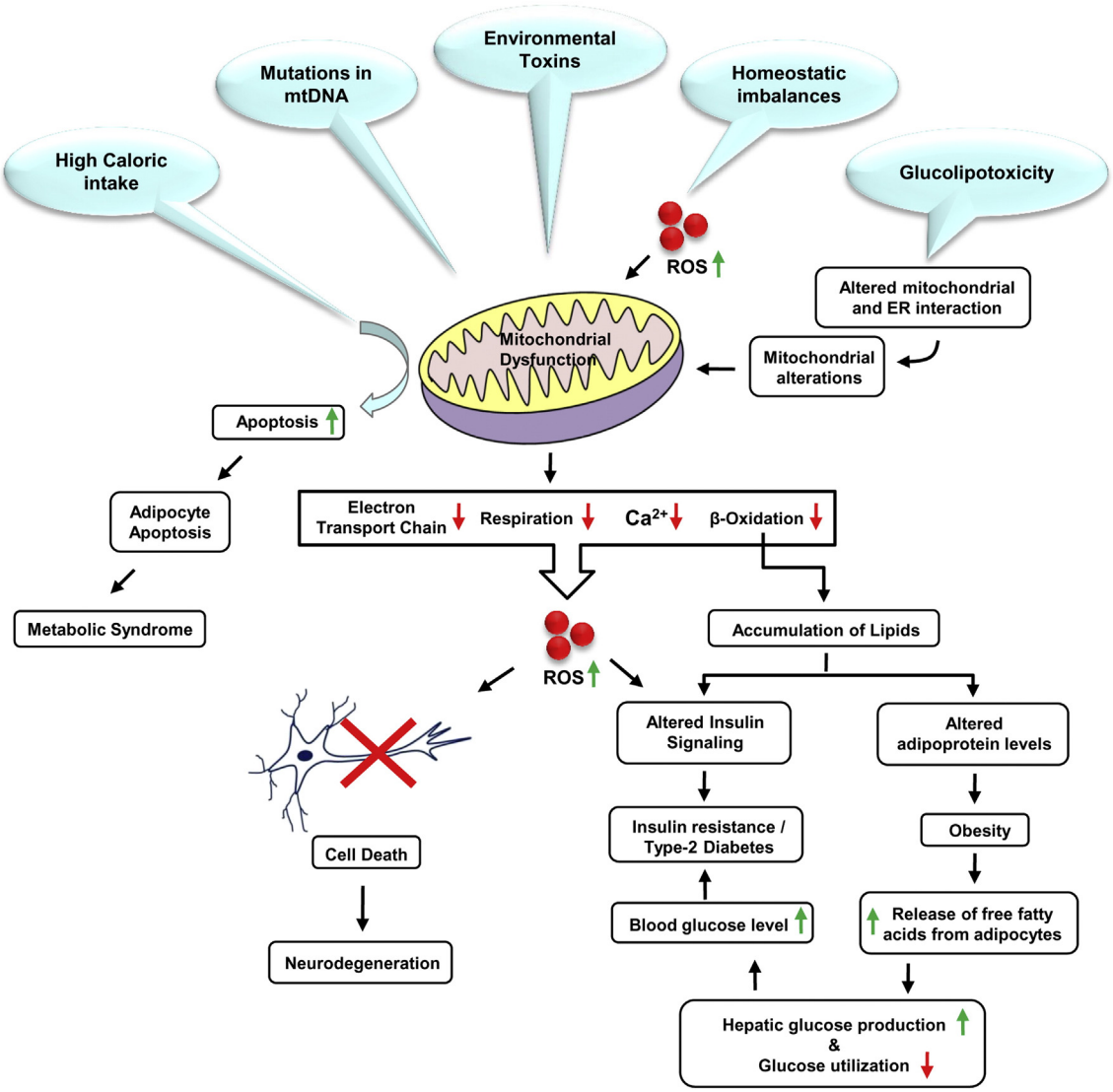

Fig. 1. Schematic illustration showing the association of mitochondrial dysfunction with clinical symptoms of metabolic syndrome as well as its associated factors.

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