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Review

Role of AMPK-mediated adaptive responses in human cells with mitochondrial dysfunction to oxidative stress☆

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ABSTRACT

Background: Mitochondrial DNA (mtDNA) mutations are an important cause of mitochondrial diseases, for which there is no effective treatment due to complex pathophysiology. It has been suggested that mitochondrial dysfunction-elicited reactive oxygen species (ROS) plays a vital role in the pathogenesis of mitochondrial diseases, and the expression levels of several clusters of genes are altered in response to the elevated oxidative stress. Recently, we reported that glycolysis in affected cells with mitochondrial dysfunction is upregulated by AMP-activated protein kinase (AMPK), and such an adaptive response of metabolic reprogramming plays an important role in the pathophysiology of mitochondrial diseases.
Scope of review: We summarize recent findings regarding the role of AMPK-mediated signaling pathways that are involved in: (1) metabolic reprogramming, (2) alteration of cellular redox status and antioxidant enzyme expression, (3) mitochondrial biogenesis, and (4) autophagy, a master regulator of mitochondrial quality control in skin fibroblasts from patients with mitochondrial diseases.
Major conclusion: Induction of adaptive responses via AMPK–PFK2, AMPK–FOXO3a, AMPK–PGC-1α, and AMPK–mTOR signaling pathways, respectively is modulated for the survival of human cells under oxidative stress induced by mitochondrial dysfunction. We suggest that AMPK may be a potential target for the development of therapeutic agents for the treatment of mitochondrial diseases.
General significance: Elucidation of the adaptive mechanism involved in AMPK activation cascades would lead us to gain a deeper insight into the crosstalk between mitochondria and the nucleus in affected tissue cells from patients with mitochondrial diseases. This article is part of a Special Issue entitled Frontiers of Mitochondrial Research.

1. Introduction

Mitochondrial diseases are a clinically heterogeneous group of disorders that are usually progressive and multi-systemic, which have contributed to the difficulties in definitive diagnosis of mitochondrial diseases [1,2]. Generally, clinical manifestations are mostly found in affected organs/tissues with a high energy demand, including skeletal and cardiac muscles, brain, retina, endocrine organs, kidney, non-mucosal components of the intestinal tract, and the central nervous system, respectively [3]. However, virtually any organ or tissue can be involved. The clinical features of mitochondrial diseases can be divided into two groups: (1) central neurological features including encephalopathy, stroke-like episodes, seizures, dementia and ataxia, and (2) peripheral neurological degeneration including myopathy, ophthalmoplegia, and peripheral neuropathy [4]. It has been documented that some patients have a mixture of central and peripheral features, whereas others have a pure clinical phenotype of central or peripheral neuropathy. At the biochemical level, the first evidence of mitochondrial diseases characterized by mitochondrial dysfunction was reported in 1962 by Dr. Luft [5]. Up to date, specific defects in the enzymes involved in the citric acid cycle, β-oxidation, the urea cycle, and the respiration and oxidative phosphorylation (OXPHOS) system, respectively, have been reported to be associated with the pathogenesis of mitochondrial diseases [6,7]. Mitochondrial diseases may arise from mutations in nuclear DNA (nDNA) or mitochondrial DNA (mtDNA), which have been involved in the replication and maintenance of mtDNA, and biogenesis and

Abbreviations: AMPK, AMP-activated protein kinase; CaMKs, calmodulin-dependent protein kinases; CPEO, chronic progressive external ophthalmoplegia; CREB, cAMP-responsive element-binding protein; FOXO, forkhead box O transcription factor; G6PD, glucose 6-phosphate dehydrogenase; GPx, glutathione peroxidase; GSH, reduced glutathione; H_2O_2, hydrogen peroxide; MELAS, mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes; MERRF, myoclonic epilepsy with ragged-red fibers; Mn-SOD, manganese-dependent superoxide dismutase; mtDNA, mitochondrial DNA; NAD^+, nicotinamide adenine dinucleotide; NADPH, reduced nicotinamide adenine dinucleotide phosphate; OXPHOS, oxidative phosphorylation; PTPs, permeability transition pores; PFK1/2, phosphofructokinase 1/2; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1α; PPP, pentose phosphate pathway; ROS, reactive oxygen species; SIRT1, silent information regulator 1

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bioenergetic function of mitochondria, respectively [8]. However, a large portion of mitochondrial diseases are caused by pathogenic mtDNA mutations including point mutations in the tRNA, rRNA or structural genes, and deletion, duplication or depletion of mtDNA, which culminate in mitochondrial dysfunction. Since mitochondria function as a power plant, in which several metabolic pathways act in a coordinative manner to supply energy for the cells, the defects in the respiratory chain would cause inefficient ATP generation accompanied by an overproduction of reactive oxygen species (ROS) in the affected tissues and impaired cells. Incomplete reduction of molecular oxygen and/or leak of electrons from the respiratory chain may result in the production of oxygen-derived free radicals. Under physiological condition, approximately 1–3% of the O_2 consumed by cells was metabolized to ROS in mitochondria, and the byproducts of oxidative metabolism include superoxide anions, hydrogen peroxide (H_2O_2), and hydroxyl radicals. It has been generally suggested that mitochondrial production of ROS occurs primarily at two sites, Complex I (NADH dehydrogenase) and Complex III, where the ubisemiquinone–cytochrome *b* cycle takes place [4]. The cells harboring a pathogenic mtDNA mutation usually display increased production of ROS due to enhanced leak of electrons from defective respiratory chain. Subsequently, ROS may trigger accumulation of secondary mtDNA mutations and exacerbate mitochondrial respiratory chain defects, and consequently increase the production of ROS and lipid peroxides in mitochondria [9–11]. Therefore, it has been suggested that oxidative stress plays a vital role in the pathophysiology of mitochondrial diseases.

In this review, we set out to discuss recent findings regarding the adaptive response of oxidative stress and to identify the proteins involved in the survival of affected tissue cells of patients with distinct mitochondrial diseases. The molecular mechanism involved in the retrograde signaling pathways triggered by defective mitochondria has been a subject of intensive research in recent years [12,13]. We and several foreign research groups have demonstrated that the expression levels of a wide spectrum of genes have been reported to be altered in affected cells of the patients with mitochondrial diseases such as myoclonic epilepsy with ragged-red fibers (MERRF) syndrome [10,14]. We highlight the role of AMP-activated protein kinase (AMPK) in the response of affected cells from patients with mitochondrial disease to cope with elevated oxidative stress that is elicited by overproduction of ROS by defective mitochondria. AMPK is the downstream target of a protein kinase cascade acting as an intracellular energy sensor, which regulates the energy status by stimulating catabolic processes such as glycolysis, to increase ATP production when cells encounter an energy crisis [15]. However, several adaptive responses mediated by AMPK signaling pathways in response to oxidative stress have been recently demonstrated in mammalian cells and a mouse model, receptively [16,17]. These studies showed that AMPK can be activated under some physiological and pathological conditions, which are characterized by concomitant increase of intracellular levels of ROS. Moreover, AMPK activation has been reported in affected tissues of patients with diseases associated with oxidative stress, which include neurodegenerative diseases, cardiovascular diseases, diabetes, and mitochondrial diseases, respectively [18–20]. Based on the findings of recent studies including our own research, we suggest that mitochondrial dysfunction-elicited ROS can induce various adaptive responses such as metabolic reprogramming in affected cells, which play an important role in the pathophysiology of mitochondrial diseases and conditions associated with mitochondrial defects.

2. Molecular features of mitochondrial diseases

More than two hundred mutations and/or deletion of mtDNA have been detected in affected tissues from patients with mitochondrial myopathy and encephalomyopathies, which underscore the importance of genetic defects in the pathogenesis of mitochondrial diseases [21–23]. The majority of patients with mitochondrial diseases often display multi-system disorders and affected tissue cells often harbor pathogenic mtDNA mutations leading to mitochondrial dysfunction [1,2]. Clinically, these mtDNA mutations include (1) point mutations: existed in patients with MERRF syndrome, mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS), Leber's hereditary optic neuropathy (LHON) and Leigh syndrome; and (2) large-scale deletions: found in patients with chronic progressive external ophthalmoplegia (CPEO) and Kearns–Sayre syndrome (KSS), respectively. Although these debilitating diseases are characterized by well-defined clinical symptoms, the correlation between clinical phenotype and genotype is rather poor for most of the mitochondrial diseases. Aside from clinical examinations, unraveling of the disease progression and pathological changes in affected tissues at the molecular and cellular levels is important for a better understanding of the pathophysiology of mitochondrial diseases.

2.1. Oxidative stress in mitochondrial diseases

It has been suggested that mitochondrial dysfunction-elicited ROS can increase oxidative damage to various biological molecules in affected tissue cells and are thus detrimental to patients with mitochondrial disease [9–11]. Abundant experimental evidence has suggested that ROS and oxidative damage elicited by a pathogenic mtDNA mutation play a key role in the pathophysiology and progression of mitochondrial diseases [24–27]. For example, one of our previous studies revealed that the skeletal muscle with the ragger-red fibers (RRFs) had a significantly higher level of 8-OHdG in the cellular DNA, and that muscle fibroblasts had an increased intracellular content of H_2O_2 in patients with CPEO syndrome [24]. In addition, Majora et al. observed that the average mitochondrial ROS levels in the primary culture of skin fibroblasts from KSS patients were higher than those of age-matched normal controls [25]. Moreover, the oxidative damage to proteins in the muscle biopsies of patients with MELAS syndrome was significantly higher than those of age-matched normal subjects [26]. On the other hand, it is worthy of noting that the elevation of oxidative stress in affected cells with defective mitochondria would cause the opening of the permeability transition pores (PTPs) in mitochondrial membranes, which in turn led to the simultaneous collapse of the mitochondrial membrane potential [28]. The opening of PTPs has been postulated to play a role in the induction of apoptosis and autophagy of affected mitochondria from patients with mitochondrial disease. Specifically, the mitophagy targeting at dysfunctional mitochondria was observed in the primary cultures of skin fibroblasts from MERRF and MELAS patients, respectively [29,30]. In addition, the disruption of mitochondrial PTPs can also cause the dysregulation of mitochondrial Ca^{2+} ions resulting in an increase of the cytosolic levels of Ca^{2+} ions [31]. Indeed, defects in the handling of mitochondrial Ca^{2+} ions were observed in the primary cultures of skin fibroblasts from patients with MERRF syndrome, which exhibited a reduced uptake of Ca^{2+} ions by mitochondria in response to histamine stimuli [32]. Most importantly, mitochondrial dysfunction-elicited dysregulation of Ca^{2+} homeostasis can subsequently increase cell excitability due to the irregular activation of several Ca^{2+}-dependent protein kinases and thus render the affected cells to damage by impairment of Ca^{2+} sequestration, which in turn lead to excitotoxic lesions and epilepsy [33]. However, the mechanism by which a pathogenic mtDNA mutation affects Ca^{2+} homeostasis is still worthy of further investigation. It has been established that mitochondrial Ca^{2+} uptake is dependent on the mitochondrial membrane potential, and thus the mitochondrial dysfunction-elicited disruption of membrane potential plays an important role in defects of Ca^{2+} homeostasis and in the elevation of cytosolic Ca^{2+} levels. Based on these observations, we contend that the oxidative stress elicited by mitochondrial dysfunction can cause additional damage or mutation to mtDNA and further impair the respiratory function and Ca^{2+} homeostasis, which culminate in a ROS-driven vicious cycle and contribute to the pathophysiology and progression of mitochondrial diseases [9].