Biochimica et Biophysica Acta 1840 (2014) 1331–1344

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

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

Review

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

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ARTICLE INFO

Article history:
Received 2 July 2013
Received in revised form 6 October 2013
Accepted 22 October 2013
Available online 27 October 2013

Keywords:
AMPK
Mitochondrial disease
Oxidative stress
Metabolic reprogramming
Antioxidant enzyme
Autophagy

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

☆ This article is part of a Special Issue entitled Frontiers of Mitochondrial Research.

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http://dx.doi.org/10.1016/j.bbagen.2013.10.034

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].

2.2. Retrograde signaling in cells with mitochondrial dysfunction

H_2O_2 can activate several signaling protein kinases, such as extracellular signal-regulated kinase (ERK)1/2, mitogen-activated protein kinase (MAPK), protein kinases B and C (PKB and PKC), and apoptosis signal-regulating kinase 1 (ASK1), respectively, in different cell types [34]. Because these pathways regulate cellular mitogenesis, migration, proliferation, survival, and death responses, aberrant activation of any one of them has been suggested to be a potential mechanism of ROS-induced pathologies. Gough and Cotter [35] reported that the diverse roles of H_2O_2 as an oxidant and signaling molecule depend on the subcellular source, location, and duration of its production, respectively. Since mitochondria are the major source of ROS, mitochondria-derived H_2O_2 has been considered to initiate most of the redox signaling pathways due to the fact the H_2O_2 can diffuse across the mitochondrial membrane to the cytosol [36]. Mitochondrial retrograde signaling is thought to be a significant pathway of communication between mitochondria and the nucleus under normal and pathophysiological conditions [37]. Mitochondrial retrograde regulation encompasses a wide variety of cellular activities that are essential for the regulation of metabolic and organelle homeostasis [38]. As to the affected cells with mitochondrial dysfunction, several stress-sensitive signaling pathways that regulate gene expression are activated in response to the survival or death of cells. Either mitochondrial dysfunction-elicited ROS or the subsequent release of molecules from mitochondrial permeability transition pores has recently been considered as vital second messenger under pathophysiological conditions. It is worth mentioning that for some types of cells whose mitochondria exhibit negligible respiratory function, ROS can also be formed as the intracellular redox messenger by extra-mitochondrial mechanism. Human cord blood-derived hematopoietic stem cells are poor in oxidative phosphorylation due to its low amount of respiratory enzyme complexes, lower mitochondrial respiratory enzymatic activity and lower mitochondrial membrane potential [39]. It has been shown that about 50% of the extra-mitochondrial oxygen consumption in hematopoietic stem cells is contributed by NADPH oxidase, a plasma membrane enzyme, and NADPH oxidase-elicited superoxide anions in cytosol could serve as redox signaling molecules contributing to mitochondrial biogenesis, cell survival, and differentiation, respectively [40]. In addition, transient production of ROS elicited by NADPH oxidase is reported to mediate RANKL-induced osteoclast differentiation of bone marrow cells [41].

It is noteworthy that the details regarding the execution and regulation of the retrograde signaling were mostly obtained from studies on the budding yeast, in which several nuclear genes encoding polypeptides constituting the OXPHOS system and other genes involved in the function and maintenance of mitochondria are regulated in a delicate manner [38,42]. Nevertheless, in mammalian cells, these signaling pathways are modulated in part by metabolites, Ca^{2+}, ROS and the ADP/ATP and NAD^+/NADH ratios, but much less have been known about the downstream signaling mechanisms of these retrograde effectors [42]. Intriguingly, Ca^{2+}-mediated signaling is one of the well-established mechanisms that involve several pathways, including activation of Ca^{2+}-dependent protein kinase C (PKC), cAMP-responsive element-binding protein (CREB), AMPK, NF-κB, and JNK/MAPK signaling pathways. In addition, the transcriptional regulation of the PGC-1α (proliferator-activated receptor gamma coactivator 1-α) by CREB is responsible for the upregulation of the expression of mitochondrial biogenesis-related genes including NRF1, NRF2 (nuclear respiratory factors 1 and 2), and mtTFA (mitochondrial transcription factor A) in response to ROS elicited by mitochondrial dysfunction [43]. Indeed, alterations of the expression of nuclear genes involved in mitochondrial respiration and glycolysis are observed in affected tissues of patients with mitochondrial diseases [44]. However, the alterations of gene expression are highly diverse and inconsistent in a variety of mitochondrial disease models. Several factors greatly affect gene expression, including the type of tissue cells, the phenotype of disease, the type of mtDNA mutation, the genetic background of the patient, age factor, and the experimental design [45]. Therefore, it has remained inconclusive regarding the reciprocal regulation of the OXPHOS function and activities of glycolytic enzymes, which are necessary for a thorough understanding of the response of human cells to mitochondrial dysfunction. In spite of the above-mentioned confounding factors, it has been suggested that an increase in the transcription of specific genes only occurs when energy deficiency has reached a certain threshold [46]. High levels of mtDNA mutation are linked to an increased expression of mitochondrial biogenesis-related genes, nuclear OXPHOS genes and several glycolytic genes, which act concomitantly with an attempt to compensate for the energy deficiency.

3. Metabolic reprogramming in mitochondrial diseases

Glucose utilization provides a quick supply of energy and precursors for de novo biosynthesis of macromolecules, including DNA, RNA, fatty acids, and amino acids that are essential for cell growth and proliferation. Normal cells metabolize glucose to pyruvate and then generate ATP by coupling with further oxidation of pyruvate through TCA cycle and the respiratory chain in mitochondria. In the mitochondrial inner membrane, the oxidative phosphorylation (OXPHOS) system utilizes the proton gradient formed during electron flow from a reduced substrate to molecular oxygen to synthesize ATP from ADP and inorganic phosphate. Most of the intracellular ATP is generated by OXPHOS in normal cells, but in cancer cells, due to the absence of oxygen in the microenvironment, pyruvate is converted to lactate in the cytoplasm to sustain glycolysis. It is worthy of noting that the redistribution of glycolytic metabolites has recently been shown to be essential for cellular adaptation to oxidative stress or metabolic stress [47]. For example, in the ischemic heart, there was a decrease in oxidative metabolism of both fatty acids and glucose due to the diminished oxygen supply, but with an increase in glucose transport and glycolytic production of ATP to cope with the energy crisis [48]. A recent study showed that glucose metabolism was accelerated in response to exogenous oxidative stress elicited by tert-butylhydroperoxide in human erythrocytes [49]. Moreover, by sustained inhibition of the OXPHOS system in human fibroblasts with specific inhibitors, the cellular metabolism could be reprogrammed by shifting to glycolysis due to the observation of increased lactic acid production in affected cells [50]. Lactic acidosis is one of the common biochemical hallmarks of mitochondrial diseases resulting from enhanced glycolysis in affected tissues or cells [4,5]. Indeed, several studies including our recent research suggest that the primary cell cultures of affected tissues (e.g. skin and muscle) from patients with mitochondrial diseases exhibit a glycolytic phenotype, indicating a metabolic reprogramming in affected cells in response to mitochondrial dysfunction [51–53]. One explanation is that mitochondrial dysfunction transforms affected cells to a more glycolytic state, thereby providing energy-rich metabolites such as lactate and ketone bodies for the cells to cope with energy crisis.

3.1. Coordination of bioenergetic functions in mitochondrial diseases

In a previous study using the microarray analysis of yeast cells that lost their mtDNA (ρ^0 cells) and could not respire normally, it was found that the yeast cells compensated for the metabolic defect by an increase in the transcription of genes coding for peroxisomal biogenesis, oxidative stress response, and genes involved in anaplerotic pathways, mitochondrial biogenesis, and glycolytic enzymes, respectively [38]. Three positive retrograde (RTG) regulator factors, Rtg1p, Rtg2p and Rtg3P, and four negative regulatory factors, Mks1, Lst8p, Bmh1p and Bmh2p, have been demonstrated to control the basal and retrograde signaling cascades [54]. Likewise, mammalian cells also respond to a loss of mitochondrial function with changes in the expression of several nuclear genes. In cells with OXPHOS deficiency induced by mitochondrial inhibitors such as rotenone and oligomycin A or by depletion of

mtDNA (ρ^0 cells), it was shown that several glycolytic enzymes, particularly lactate dehydrogenase (LDH), were upregulated [55]. In addition, a coordinated induction of bioenergetic genes related to mitochondrial biogenesis and glycolysis was observed in the muscle biopsies harboring a pathogenic mtDNA mutation from patients with MERRF, MELAS, LHON, NARP, and CPEO syndrome, respectively [44,56]. The compensatory increase of mitochondrial biogenesis results in the so-called RRFs in affected skeletal muscle, which is one of the most prominent pathological hallmarks of MERRF syndrome [57,58]. Recently, we demonstrated that in the primary culture of skin fibroblasts from MERRF patients energy metabolism was shifted from mitochondrial respiration to glycolysis as revealed by a Seahorse XF24 Analyzer [51]. Our findings are in agreement with previous reports that transmitochondrial cytoplasmic hybrid cells (cybrids) harboring a pathogenic mtDNA mutation were highly dependent on anaerobic glycolysis for energy supply [51–53,59]. Taken the above-mentioned observations together, we suggest that the cells with mitochondrial dysfunction would rely more on the glycolytic pathway for supply of energy. That is to say, when affected cells are cultured in a medium containing galactose as the only carbon source, the cells are forced to use the defective OXPHOS system for the production of energy, and one could assess the cell viability under such a growth condition to determine whether the patient under examination has a mitochondrial dysfunction-related disease [60].

3.2. Metabolic reprogramming and cellular redox status

It has been recognized that metabolic changes are key regulators of stress responses. A previous study by Ralser et al. [61] showed that dynamic modulation of the metabolic flux through the pentose phosphate pathway (PPP), with a concomitant generation of the reduced nicotinamide adenine dinucleotide phosphate (NADPH), is a conserved response to oxidative stress. NADPH is particularly important during exposure to oxidants because it provides reducing equivalents for most antioxidant enzymes and redox regulatory proteins, including glutathione (GSH), glutaredoxin and thioredoxin systems that are the major antioxidants regulating cellular redox homeostasis. It is noteworthy that the PPP is directly connected to glycolysis, and glucose 6-phosphate (G6P) is an intermediate in both pathways. Any condition that influences glycolytic activity can potentially alter the flux of glucose metabolites through the PPP, leading to a change in the NADPH generation. For example, stimulation of glucose utilization in neurons and astrocytes has been proposed to elicit a protective action against H_2O_2 toxicity [62]. Such kind of activation has also been reported to be responsible for the self-protection of astrocytes against endogenous nitric oxide (NO)-mediated GSH oxidation [63]. Intriguingly, investigation of the mechanism responsible for such a rapid effect revealed that NO stimulated the activity of G6PD (the rate-limiting step of the PPP) in intact cells by a rapid, non-transcriptional activation pathway [64]. These results strongly suggest that glucose utilization through the PPP could play a key protective role in the cells to coping with oxidative stress. Another example is the metabolic profile of human pluripotent stem cells (hPSCs) [65]. With a higher glycolytic flux in hPSCs, it not only provides sufficient ATP for the maintenance of cell function, but also requires increased PPP activity for sufficient supply of NADPH to cells under oxidative stress. Nevertheless, as to how cells respond to mitochondrial dysfunction-elicited ROS, Filosto et al. [66] first reported that the NADPH-dependent generation of GSH was upregulated in affected tissues of patients with mitochondrial diseases, which were revealed by immunochemical staining. They also showed an abnormal upregulation of GSH content, which could be considered as an initial sign of respiratory chain dysfunction. We consider that this phenomenon is relevant to the glycolytic phenotype of affected cells, which is essential for cell survival at the early phase of disease progression. Taken together, we contend that increased understanding of cellular metabolism in response to oxidative stress could bring about a renewal of interest in the study of human diseases that are associated with mitochondrial dysfunction.

4. Role of AMPK activation in cells with mitochondrial dysfunction

To further unveil molecular mechanism involved in the regulation of metabolic reprogramming in cells with mitochondrial dysfunction, a recent study has demonstrated that several cellular regulators play important roles in response to mitochondrial dysfunction [67]. Among them, AMPK has been established to play a diverse role in the regulation of the cellular energetic and redox status, respectively [67,68]. We summarize the adaptive roles of AMPK activation in the pathophysiology of diseases including Huntington's disease (HD) [18], Alzheimer's disease (AD) [19], diabetes [69,70], cardiovascular disease [71,72] and mitochondrial disease [51], respectively (Table 1). However, whether AMPK activation is beneficial to the patients with mitochondrial disease is a subject of controversy. For example, it was reported that AMPK activation was found in neurons of brain with Alzheimer's disease (AD) and Huntington's disease, suggesting that AMPK plays an essential role in the neuroprotection [18,19]. However, abnormal AMPK activation in tangle- and pre-tangle-bearing neurons could promote neurodegeneration, which was suggested as a novel common determinant of tauopathies [20]. Some researchers have contended that at the early phase of disease progression, the AMPK signaling can repress and delay the appearance of AD pathology, but with increased neuronal stress, AMPK activation can trigger detrimental effects that augment the pathogenesis of AD at a later stage [20]. In spite of detrimental effects of AMPK activation, recent studies revealed that the decline with age in the sensitivity and responsiveness of AMPK has been shown to be associated with many age-associated diseases, including cardiovascular diseases, type 2 diabetes, and metabolic syndrome [73]. Therefore, AMPK could be a potential target for the development of therapeutic agents for the treatment of metabolic syndrome, cardiovascular disease and neurodegenerative diseases, and both 5-aminoimidazole-4-carboxamide ribonucleoside (AICAR) and metformin are shown to be potent activators of AMPK [74,75]. Based on these recent findings, we suggest that a deeper understanding of the signaling cascade induced by AMPK activation and its tissue-specific regulation may provide new targets for the treatment of obesity, insulin resistance, cardiovascular disease, and particularly mitochondrial dysfunction-related diseases.

4.1. The regulation of AMPK

AMPK is an evolutionarily conserved serine/threonine kinase, and orthologs of the AMPK subunits have been found in all eukaryotic species, such as Snf1 kinase in the yeast [76]. Functionally, AMPK switches on other ATP-generating pathways such as glycolysis and amino acid oxidation, while simultaneously switching off ATP-utilizing pathways such as biosynthesis of fatty acids and gluconeogenesis [77]. In mammals, AMPK is a heterotrimeric enzyme consisting of the catalytic α-subunits (α1 or α2), β-regulatory subunits (β1 or β2) and AMP-binding subunits (γ1, γ2 or γ3), which results in 12 possible combinations of the AMPK complex. The α-subunit contains an *N*-terminal kinase domain and a *C*-terminal domain that is involved in complex formation with β- and γ-subunits. It has been demonstrated that AMPK is activated by phosphorylation of the catalytic subunits at Thr^{172}, which is mediated by the AMPK kinases (AMPKKs) including a tumor suppressor, LKB1 kinase, and several Ca^{2+}/calmodulin-dependent protein kinases (CaMKs) [78]. The isoforms of the AMPK α subunit, α1 and α2, have been shown to have rather similar substrate specificities as well as distinct functions depending on the cell type [79]. The AMPK-α1 is ubiquitously expressed, whereas the AMPK-α2 isoform is enriched in the nucleus of several cell types, including pancreatic β-cells, neurons, and skeletal muscle. It seems that the α2 subunit of AMPK is mainly located in tissues with high energy

Table 1
Contribution of AMPK activation to cellular adaptive responses in the pathophysiology of human diseases.

Disease	Model	Effect	Reference
Huntington's disease	Mouse cortical neurons cells	Stimulated mitochondrial biogenesis	[18]
Alzheimer's disease	AD transgenic mice	Promoted Aβ peptide metabolism	[19]
MERRF syndrome	Human skin fibroblasts	Enhanced glycolysis and redox balance	[51]
Diabetes	Human endothelial cells	Inhibited mitochondrial ROS production	[71]
Diabetes	Human endothelial cells	Stimulated mitochondrial biogenesis	[72]
Endothelial dysfunction	Human endothelial cells	Increased thioredoxin expression	[73]
Cardiovascular diseases	Human endothelial cells	Enhanced Bcl-2 expression	[74]

demand (e.g., muscle and brain), but the α1 subunit of AMPK accounts for the majority of the activity in tissues such as the smooth muscle, endothelial cells, fibroblasts, leukocytes, and the tissues where the α2 subunit of AMPK is located. Using a knockout mouse model with AMPK α-1$^{(-/-)}$ and α-2$^{(-/-)}$ catalytic subunit genes deleted, there was no defect in glucose homoeostasis observed in AMPK α-1$^{(-/-)}$ mice [80]. However, AMPK α-2$^{(-/-)}$ mice presented high plasma glucose levels and low plasma insulin concentrations in the fed period and during the glucose tolerance test. Although differences between the two subunits have been suggested, their differential roles have not been clearly established. In addition to activation by phosphorylation, AMPK is also activated by AMP in an allosteric manner [78]. AMPK is the downstream component of a kinase cascade that acts as a gage of cellular energy levels and can be activated by an increase of AMP associated with low ATP. The γ subunits of AMPK present a sequence motif of about 60 residues repeated four times, which is known as a cystathionine γ-synthase domain and these domains are involved in the nucleotide binding to either AMP or ATP in a mutually exclusive manner. The activation of AMPK α subunit is modulated in an allosteric manner by AMP that promotes the phosphorylation on Thr^{172} by AMPKK, and by ATP that inhibits phosphorylation at this site. On the other hand, it was shown that AMPK could be also inhibited by glycogen in an allosteric manner, leading to inhibition of phosphorylation of AMPK α subunit at Thr^{172} by upstream kinases [81,82]. The β subunit of AMPK was referred to as the glycogen-binding domain or carbohydrate-binding module (CBM), which causes the AMPK complex to bind to glycogen [83]. By analysis of the sequences of β subunits of AMPK in different eukaryotic species, two conserved regions can be observed, one at the center and one at the C-terminus of the AMPK β subunit. McBride and Hardie then pinpointed that the central domain of AMPK β subunit was the glycogen-binding domain that allows the AMPK to act as a glycogen sensor [84]. Taken together, AMPK responds to the immediate energy availability by sensing the AMP/ATP ratio and is also able to sense the status of cellular energy reserves in the form of glycogen [85].

4.2. AMPK activation by oxidative stress

Interestingly, recent studies showed that AMPK can be activated by reactive oxygen/nitrogen species (ROS/RNS), which in turn lead to the increase of glycolysis and mitochondrial biogenesis, respectively. The activation of AMPK by ultraviolet (UV) irradiation, hydrogen peroxide (H_2O_2), nitric oxide (NO) and peroxynitrite ($^{\bullet}ONOO^{-}$), respectively, has been demonstrated in various human cell lines [13,86–88]. On the contrary, treatment of cells with the antioxidant, *N*-acetylcysteine, the H_2O_2-induced AMPK phosphorylation could be abolished [51,87]. In addition, it was found that the effects of hypoxia-elicited oxidative stress on AMPK activation in the embryos of pregnant mice could be prevented by the antioxidants GSH-ethyl ester and vitamin E, respectively [89]. Intriguingly, it has been demonstrated that hypoxic activation of AMPK is dependent on the levels of mitochondrial ROS in cybrids harboring a pathogenic mtDNA mutation [90]. Besides, Han et al. observed that mitochondria-derived superoxide anions and peroxynitrite are required for AMPK activation, and pretreatment of cells with mitochondria-targeted tempol (mito-tempol), an antioxidant nitroxide, can attenuate the AMPK activation [17]. More recently, Mackenzie et al. [69] showed that AMPK could be activated in response to elevated mitochondrial ROS levels in the endothelial cells from patients with type 2 diabetes. Not surprisingly, AMPK could be activated by metabolic stress induced by the inhibition of mitochondrial respiration and OXOPHOS function by antimycin A, azide, oligomycin A, and dinitrophenol, respectively. We also demonstrated in a previous study that the primary cultures of skin fibroblasts with MERRF syndrome showed higher mitochondrial ROS accompanied by increased expression of AMPK activation as compared to skin fibroblasts from age-matched normal subjects [51]. However, cells with depleted mtDNA in mitochondria, that lack functional electron transport chain are reported to be unable to generate mitochondrial ROS and could not normally regulate the redox potential [91]. Consequently, impairment of hypoxic activation of AMPK was observed in ρ^0-A549 cells [92], which were more sensitive to apoptotic cell death [93]. The molecular mechanism by which the aberrant redox signaling triggers cell death in ρ^0 cells is worthy of further investigation.

On the other hand, in addition to inducing the phosphorylation of AMPK by ROS, it was demonstrated that H_2O_2 exposure can cause *S*-glutathionylation of AMPK and thereby enhance its activity [94,95]. Protein glutathionylation is an oxidative modification of a cysteine residue via binding of glutathione (GSH) to its thiol group, which is often catalyzed by a strong oxidant. In response to physiological conditions, reversible *S*-glutathionylation not only modulates diverse protein function but also protects protein cysteine residues against further oxidation. Zmijewski and coworkers first found the glutathionylation of α and β subunits of AMPK in HEK 293 cells upon exposure to H_2O_2 [94]. They identified two modification sites at cysteine residues 299 and 304 of AMPK-α subunit, and further demonstrated that mutation of these two residues can abrogate H_2O_2-induced activation of AMPK. Similar activation mediated by *S*-glutathionylation of the AMPK-α subunit occurred in the lung tissues of mice treated with the catalase inhibitor, aminotriazole [96]. Emerging evidence indicates that protein glutathionylation is catalyzed by glutathione *S*-transferase (GST) and is reversely removed by glutaredoxin (GRx) in mammals [97]. Two isoforms of GST, GSTP and GSTM1, have been shown to interact with the AMPK-β subunit in rat liver. It was further demonstrated that a complex interaction between the two GSTs and AMPK promotes *S*-glutathionylation and kinase activity of AMPK in vitro. Taken together, these findings suggest a potential role of AMPK glutathionylation in the regulation of redox signaling when mammalian cells are subject to mild oxidative stress.

4.3. Contribution of AMPK activation to the increase of glycolysis in cells with mitochondrial dysfunction

Intriguingly, AMPK-mediated activation of glycolysis has been reported to be required for the protection of astrocytes against NO-induced apoptosis [98], and could inhibit low-flow ischemia and reperfusion-induced ROS in cardiomyocytes [99]. It was observed that phosphofructokinase-1 (PFK1) activity was increased in intact astrocytes in response to mitochondrial dysfunction-elicited ROS, possibly through prior stimulation of phosphofructokinase-2 (PFK2) activity by

phosphorylated AMPK. AMPK-mediated PFK2 activation can produce fructose-2,6-bisphosphate, which is the most potent positive effector of PFK1 and can thus increase the glycolytic flux. In addition, AMPK-mediated metabolic reprogramming (via PFK2 activation) can stimulate the production of NADPH (via activation of PPP), which is a cofactor required for the regeneration of glutathione for cytoprotection through the removal of ROS [100]. Similar to brain PFK2, the PFK2 in cardiomyocytes and skin fibroblasts were also reported to be phosphorylated by AMPK [45,99]. On the other hand, the glycolytic flux could be increased by AMPK-mediated upregulation of the expression of several glycolytic enzymes, such as GLUT1 in epithelial cells and GLUT4 in skeletal muscle cells in response to inhibition of mitochondrial OXPHOS function [101,102]. In addition, AMPK also can directly phosphorylate hexokinase (HK) of skeletal muscle to boost the glycolytic flux [103]. Recently, we demonstrated that AMPK activation plays a crucial role in the regulation of the intracellular NADPH level in primary cultures of skin fibroblasts from MERRF patients [45]. It is worthy of noting that glycolysis is regulated by the coordination of several transcription factors including AKT, c-MYC, HIF-1α, and p53 [104]. The upregulation of glucose transport, glycolytic enzymes and regulatory factors are all required for the increase of glycolytic flux. As to whether AMPK-mediated increase of glycolytic flux in skin fibroblasts could be achieved by direct or indirect upregulation of the expression of GLUT1 or glycolytic enzymes alone remains to be further investigated.

5. AMPK-mediated signaling pathways in response to oxidative stress

It has been reported that AMPK activation can promote cell survival by inducing autophagy, mitochondrial biogenesis, and expression of genes, respectively, which are involved in antioxidant defense in response to oxidative stress [105,106]. That is to say, AMPK might function as an early warning system in response to oxidants so as to attenuate oxidative injury. There are several lines of evidence indicating that H_2O_2, acting as a second messenger, can activate AMPK in several cell types resulting in the regulation of the expression of specific genes to maintain cellular homeostasis and to promote cell survival under stressful condition [34–36]. Whether H_2O_2 has a direct effect on AMPK or activates upstream effectors of AMPK or inhibits protein phosphatases, possibly by direct oxidation of cysteine residues in the active site of phosphatase, has remained to be determined. In a previous study, we demonstrated that AMPK was activated by H_2O_2 in a dose-dependent manner in human skin fibroblasts [51]. This adaptive response of AMPK activation induced by H_2O_2 in skin fibroblasts contributed to the increase of the intracellular levels of NADPH, which is the major reducing equivalent in human cells. Disruption of AMPK activation in cells under oxidative stress would trigger cell death via accumulation of oxidative damage caused by ROS. Recently, by knockdown of the catalytic AMPK-α1 subunit in human umbilical vein endothelial cells (HUVECs), the expression levels of the key components in the antioxidant defense system including Mn-SOD, catalase, thioredoxin, and γ-glutamylcysteine synthase (γGCS) were substantially attenuated. However, other genes which have been implicated in response to oxidative stress (e.g., heme oxygenase 1, HO-1; glutathione transferase P1, GSTP1; and aldehyde dehydrogenase 1A, ALDH1A) remained unchanged [107]. In addition, a deletion of the AMPK gene in mice was found to cause the elevation of systematic oxidative stress leading to a shortened life span of erythrocytes, RBC hemolysis, and anemia in vivo due to the down-regulation of the expression of antioxidant enzyme including catalase, Mn-SOD and GPx-1 [108]. However, there are some inconsistencies in the changes of the expression of AMPK-mediated antioxidant enzymes in different experimental systems. We showed in a recent study that the activation of AMPK was more pronounced in skin fibroblasts of a patient with MERRF syndrome [51]. It is thus appealing to investigate the molecular mechanism by which AMPK activation contributes to the upregulation of antioxidant enzymes in the primary culture of skin fibroblasts from patients with mitochondrial diseases [66].

5.1. AMPK-mediated control of intracellular redox status

It has been well documented that AMPK can regulate cellular defense system to cope with stress via a downstream network of signaling pathways, including PGC-1α CREB, forkhead box O transcription factor 3a (FOXO3a), mammalian target of rapamycin (mTOR) and silent information regulator 1 (SIRT1) [78,105]. Nevertheless, recent studies focused on the adaptive response of AMPK-FOXO3a signaling pathway, which is involved in the upregulation of antioxidant enzymes in response to oxidative stress [73,109,110]. Upon phosphorylation by AMPK, FOXO3a is able to bind to the promoters and induce the transcription of target genes, which are involved in the fine tuning of cell metabolism, including PGC-1α and mitochondrial uncoupling protein 2 (UCP2), and in coping with oxidative stress (e.g., Mn-SOD and catalase), respectively [111]. It has been well-documented that AMPK can directly phosphorylate the FOXO3a at six sites (Thr^{179}, Ser^{399}, Ser^{413}, Ser^{555}, Ser^{588}, and Ser^{626}), five of which are located at the transactivation domain of FOXO3a. Most importantly, it was revealed that the AMPK-mediated phosphorylation of FOXO3a at Ser^{413} is essential for the formation of subsequent transcription activation complex in the nucleus [112]. Antioxidant enzymes including thioredoxin, peroxiredoxin, Mn-SOD, and catalase, were found to be upregulated upon activation of the AMPK–FOXO3a signaling pathway that can reduce oxidant-induced ROS production in endothelial cells derived from human umbilical veins and pulmonary arteries [113]. On the other hand, activation of AMPK was also reported to be involved in the upregulation of the expression of UCP2 in endothelial cells, and thereby suppresses mitochondrial production of superoxide anions [114]. It is worthy of noting that activation of AMPK–FOXO3a pathway by oxidative stress is independent of the change in the intracellular AMP level [107]. Although AMPK plays a crucial role in FOXO3a-dependent transcription, it is possible that there exist other signaling pathways converging on the same residues to modulate the transcriptional activity of FOXO3a [112]. For example, it has recently been demonstrated that AMPK is able to modulate NAD^+ metabolism in cells under metabolic stress, and thereby interfere with the deacetylase activity of SIRT1, a well-known FOXO3a coactivator [115]. AMPK activation results in an increase of NAD^+ levels, which in turn leads to SIRT1 activation and deacetylation-induced activation of its downstream targets including PGC-1α and FOXO3a, respectively. On the other hand, we have demonstrated that AMPK-mediated increase of glycolysis can increase the intracellular NADPH levels via the activation of the PPP, which plays an imperative role in the survival of skin fibroblasts from MERRF patients [51]. We also noticed that the antioxidant enzymes including Mn-SOD, glutathione peroxidase, thioredoxin and peroxiredoxin were upregulated, and the level of phosphorylated FOXO3a was pronounced in MERRF skin fibroblasts as compared to age-matched normal subjects (Fig. 1). Therefore, it remains to be answered as to whether upregulation of antioxidant enzymes observed in MERRF skin fibroblasts is regulated by the AMPK–FOXO3a signaling pathway. In this regard, the activation of AMPK–FOXO3a signaling pathways by metformin and resveratrol, respectively, has been reported to be responsible for their effects in amelioration of the symptom of diabetes, reducing the risk of Alzheimer's disease, protecting chronic cardiomyopathy, and inhibiting proinflammatory response and preventing the onset of neurodegenerative diseases [116–118]. Therefore, we suggest that targeting to AMPK–FOXO3a signaling pathway could be beneficial to alleviate the intracellular oxidative stress and restore the energy production. This scenario may provide a new avenue for the development of better treatment for patients with mitochondrial diseases such as MERRF syndrome.

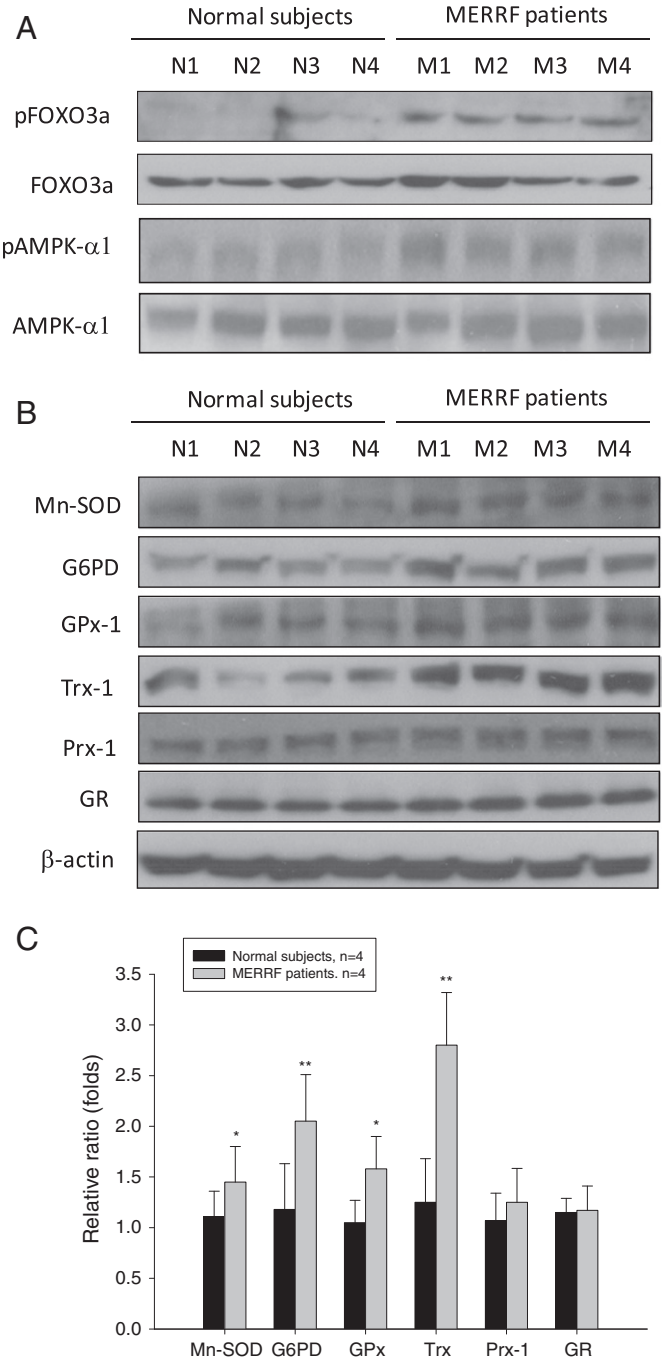

Fig. 1. Increased expression levels of phosphorylated FOXO3a, AMPK and antioxidant enzymes in the primary cultures of skin fibroblasts from MERRF patients. (A) By Western blot, phosphorylated FOXO3a and AMPK-α1, and (B) several antioxidant enzymes including Mn-SOD, G6PD, GPX-1, Trx-1, Prx-1, and GR were determined in the primary cultures of skin fibroblasts from MERRF patients (N = 4) and age-matched normal subjects (N = 4). (C) By densitometric analysis of three independent Western blots, the expression levels of indicated antioxidant enzymes were normalized with the expression level of corresponding β-actin. The representative histogram was constructed on the basis of the mean values of indicated proteins in the skin fibroblasts of MERRF patients and normal subjects, respectively. Data are presented as means ± SD of the results from three independent experiments (*$p < 0.05$, **$p < 0.01$ vs. the indicated group).

5.2. AMPK-mediated mitochondrial biogenesis

Upregulation of mitochondrial biogenesis has been well documented in affected tissue cells of patients with mitochondrial disease, which is considered a compensatory adaptation to compromised bioenergetic function due to defects in the mitochondrial OXPHOS system [44]. The compensatory induction of the expression of OXPHOS genes encoded by mtDNA and nDNA, respectively, to maintain cellular energy levels has been confirmed in the affected tissues of patients with specific mitochondrial diseases. The clinical diagnosis of RRFs is frequently made by Gomori trichrome staining on skeletal muscle of patients with mitochondrial diseases, which is a result of over-proliferation of abnormal mitochondria [119]. It has been reported that the expression levels of certain subunits of ATP synthase and succinate dehydrogenase (SDH), are increased in response to mitochondrial dysfunction [52]. However, it is unclear whether ROS plays a role in this pathological change. The abundance of mitochondria in a human cell is tightly controlled by a number of transcription factors involved in the regulation of mitochondrial biogenesis [10]. A number of studies have shown that several protein kinases are involved in the activation of a set of nuclear transcription factors, which link mitochondrial dysfunction-elicited oxidative stress to increased mitochondrial biogenesis in the affected tissues or cultured cells of patients with mitochondrial diseases [120,121]. PGC-1α has been reported to be a major upstream regulator of mitochondrial biogenesis and is pivotal in the regulation of OXPHOS, antioxidant enzyme system, β-oxidation of fatty acids, and adaptive thermogenesis, respectively [122]. PGC-1α upregulates the activity of transcription factors involved in mitochondrial biogenesis, such as NRF-1 which in turn modulates the expression of other factors such as mtTFA, which is important for the regulation of mtDNA replication and transcription. Overexpression of PGC-1α in cells from patients with mitochondrial diseases was reported to lead to a marked improvement on mitochondrial respiration due to increase of the function of the OXPHOS system [123,124]. This appears to be related to an increase in both the levels of OXPHOS limiting factors and the overall mitochondrial biogenesis, thereby increasing the electron transfer and ATP production per cell. Therefore, pharmacological manipulation of the PGC-1α activity has been shown to be a particularly promising strategy of restoring mitochondrial biogenesis to overcome a mitochondrial defect or to respond to an increase in energy demand. Recently, it was shown that the mRNA and protein levels of PGC-1α were significantly reduced in the AMPK-deficient HUVECs, suggesting that AMPK is an upstream regulator for PGC-1α [107]. In addition, the expression of PGC-1α has previously been demonstrated to be regulated by the transcription factor CREB, the activity of which is determined by its phosphorylation status [125]. Intriguingly, a clear reduction in the phosphorylation of CREB was found in the AMPK-deficient HUVECs, indicating that AMPK is an upstream regulator of the CREB [107]. Therefore, AMPK activation of HUVECs in response to hypoxia-induced oxidative stress could indirectly regulate PGC-1α gene expression through AMPK-CREB activation. On the other hand, recent studies showed that PGC-1α activity can be regulated by a variety of post-translational modifications including phosphorylation, ubiquitination and acetylation, which can affect the intrinsic activity, stability and the interaction of PGC-1α with other protein partners, respectively [126]. Among the posttranslational modification events, the reversible acetylation and phosphorylation have emerged as the key mechanisms in the modulation of the PGC-1α activity. It is probable that activation of the AMPK–SIRT1 pathway is involved in the aberrant biogenesis and altered function of mitochondria in the primary culture of skin fibroblasts from patients with mitochondrial diseases. This is justified by one of our previous studies showing that both phosphorylated AMPK and SIRT1 proteins were upregulated in MERRF and CPEO skin fibroblasts, respectively [127,128]. Therefore, the adaptive upregulation of AMPK and SIRT1 may be involved in the regulation of the transcriptional activity of PGC-1α, and thereby contributes to the compensatory proliferation of mitochondria in the affected tissues of patients with MERRF or CPEO syndrome.

6. Role of autophagy in cells with mitochondrial dysfunction

Autophagy is a major pathway for the delivery of proteins and organelles to lysosomes, where they are degraded and recycled

[129,130]. Autophagy is initiated by generation of a closed double-membrane phagophore, called autophagosome, which surrounds the cellular components targeted for degradation. The formation of autophagosome then fuses with a lysosome to become an autolysosome, and its content is degraded by lysosomal hydrolases. The molecular mechanism underlying autophagic processes has been a subject of extensive research in the past decade. Autophagy is mediated and regulated by a group of autophagy-related proteins (Atg) and lysosomal hydrolases [131]. In mammals, most Atg proteins form diverse molecular complexes to regulate the formation of autophagosome, including ULK1 complex, Beclin-PI3K complex, Atg9 complex and Atg8/LC3 conjugation, respectively [132]. Since autophagy plays a critical role in the maintenance of cellular homeostasis through preserving the balance between biogenesis and clearance of organelles and proteins, dysregulation of the autophagic process is often associated with the pathology of various human diseases, including aging, age-related neurodegenerative diseases, cardiomyopathy, and mitochondrial diseases, respectively [133–137]. Indeed, autophagy is emerging as an important mediator of pathological responses and is engaged in the crosstalk with ROS in both cell signaling and protein damage [138,139]. It has long been known that the conditions that regulate the activity of the autophagic process are associated with changes in the production of ROS. Induction of autophagy by mild oxidative stress is thought to be beneficial for cell survival, but excess oxidative damage caused by high levels of ROS would bypass autophagy induction, evoke apoptosis or necrosis, and lead to defective autophagic process, which would promote cell death [140]. Indeed, deficiency in the autophagic process would lead to a type of cell death, termed autophagic cell death (ACD), which is originally based on morphologic criteria that cell death is accompanied by massive autolysosomes [141]. Disruption of the late stages of autophagy has previously been reported to turn autophagy into a destructive process [142]. Therefore, the balance between the production of autophagosome and appropriate degradation of damaged biomolecules by the lysosomes is critical for the regulation of cell death and cell survival in response to stimuli that trigger the autophagic machinery. On the other hand, certain cells, especially those that display defects in apoptotic pathways, were reported to be prone to induction of ACD in response to a variety of cytotoxic stimuli [143]. Shimizu et al. demonstrated that when the apoptotic genes, Bax and Bak, are knocked-out from mice embryonic fibroblasts, the apoptosis-inducing reagents, etoposide and saurosporine, would induce ACD [144]. In addition, Yu et al. [145] pointed out that ACD requires the induction of Atg7 and Beclin 1, but most necessitates the inhibition of caspase-8 activation. Such observation unveils the significance that clinical therapies involving caspase inhibitors may arrest apoptosis but also have the unanticipated effect of promoting autophagic cell death. Since the mechanisms by which autophagy results in cell death are still poorly understood, we highlighted in this review the induction of autophagy in affected cells in the context of using it as an adaptive response against oxidative stress, particularly in response to the overproduction of ROS by defective mitochondria.

6.1. Induction of autophagy in response to oxidative stress

In response to oxidative stress, cells could protect themselves by induction of autophagy to remove damaged proteins or organelles, especially mitochondria that are a principal target of damage by oxidative stress. During nutrient deprivation, intracellular H_2O_2 produced from mitochondria is able to stabilize autophagosomes through induction, oxidation and inhibition of Atg4 that participates in the dissolution of autophagosomes via its deconjugation activity [146]. Indeed, accumulating evidence suggests that mitochondrial dysfunction-elicited ROS is a major signal for the activation of autophagy [147]. By treatment of human cells with sub-lethal levels of respiratory inhibitors (e.g., rotenone, a Complex I inhibitor), Chen et al. found that autophagy could be induced as a result of elevated oxidative stress [148]. They further demonstrated that starvation-induced autophagy was associated with an increase of oxidative stress, while overexpression of cells with Mn-SOD abolished autophagy triggered by ROS. On the other hand, accumulation of autophagosomes and p62, an autophagy adaptor that binds to ubiquitinated proteins and targets them to LC3-II to promote selective degradation of damaged proteins, also occurs in the neurons of patients with amyotrophic lateral sclerosis (ALS). ALS is a disease associated with mitochondrial dysfunction, abnormal protein aggregation and accumulation of excessive ROS in motor neurons [149], and similar increase of autophagy is also revealed in an animal model of ALS [150]. Most importantly, accumulation of autophagosomes and increased expression of autophagic proteins including Atg12, Beclin 1, and LC3-II were observed in skin fibroblasts of patients with MERRF and MELAS syndrome as compared with those found in age-matched normal subjects [29,151]. Electron and fluorescence microscopic studies showed a significant activation of autophagy in skin fibroblast and cybrids of MERRF and MELAS patients. In addition, increased autophagy in MELAS fibroblasts could be abolished by treatment with antioxidants NAC (N-acetylcysteine) or BHA (butylated hydroxyanisole), suggesting that ROS are involved in the induction of autophagy. Disruption of autophagy induction in the skin fibroblasts of MELAS patients resulted in significant apoptotic cell death, which indicates a protective role of autophagy in the affected tissue cells of patients with MELAS syndrome [29]. Similarly, our recent study also revealed that several autophagy-related regulators were upregulated in skin fibroblasts of MERRF patients (Fig. 2). Recently, it was demonstrated that increased mitochondrial ROS production and oxidation of mitochondrial lipids play a role in autophagy [138,139]. Taken together, we suggest that ROS-mediated signaling triggered by mitochondrial dysfunction plays a role in the regulation of autophagy and in the manifestation of the pathophysiological features of these mitochondrial diseases. However, the mechanistic details as to how ROS overproduction triggers autophagy remain to be elucidated.

6.2. AMPK-mediated redox signaling in the regulation of autophagy

In the past few years, AMPK has been revealed to promote autophagy through inhibiting the activation of mTORC1 (nutrient-sensitive mammalian target of rapamycin complex 1), which contains mTOR and its regulatory protein Raptor [152]. Under nutrient-rich conditions, activated mTOR functions as an inhibitor of the initial step of autophagy via phosphorylation of Atg13, which interferes the association of Atg13 with ULK and FIP200. However, activated AMPK induces the inactivation of mTOR either by phosphorylation of Raptor or by direct phosphorylation of TSC2 (tuberous sclerosis complex 2), an mTOR negative regulator, which triggers the dissociation of mTOC from the autophagy initiator complex [153]. In addition, Egan et al. [154] demonstrated that AMPK can regulate autophagy by direct phosphorylating and activating autophagic regulatory protein in the initial step of autophagy-mediated degradation. They identified ULK1 as a new interacting partner of AMPK, and showed that phosphorylation of ULK1 by AMPK is required for its function and subsequent activation of autophagy, which is required for cell survival during starvation. In addition, ROS-induced autophagy via AMPK activation is required for the survival of endothelial cells under metabolic stress [155]. It was reported that treatment of endothelial cells with 2-deoxyglucose (2-DG) increased AMPK phosphorylation and induction of autophagy, and that overexpression of catalase or treatment of cells with antioxidants NAC and Tempol, respectively, abolished the induction of autophagy [45,124]. Moreover, Sanchez et al. [156] demonstrated that autophagy induced by AMPK activation could be regulated by the activation of forkhead FoxO3a and interaction with Ulk1, which controls the mass of skeletal muscle in the mouse. They further showed that AMPK increases the

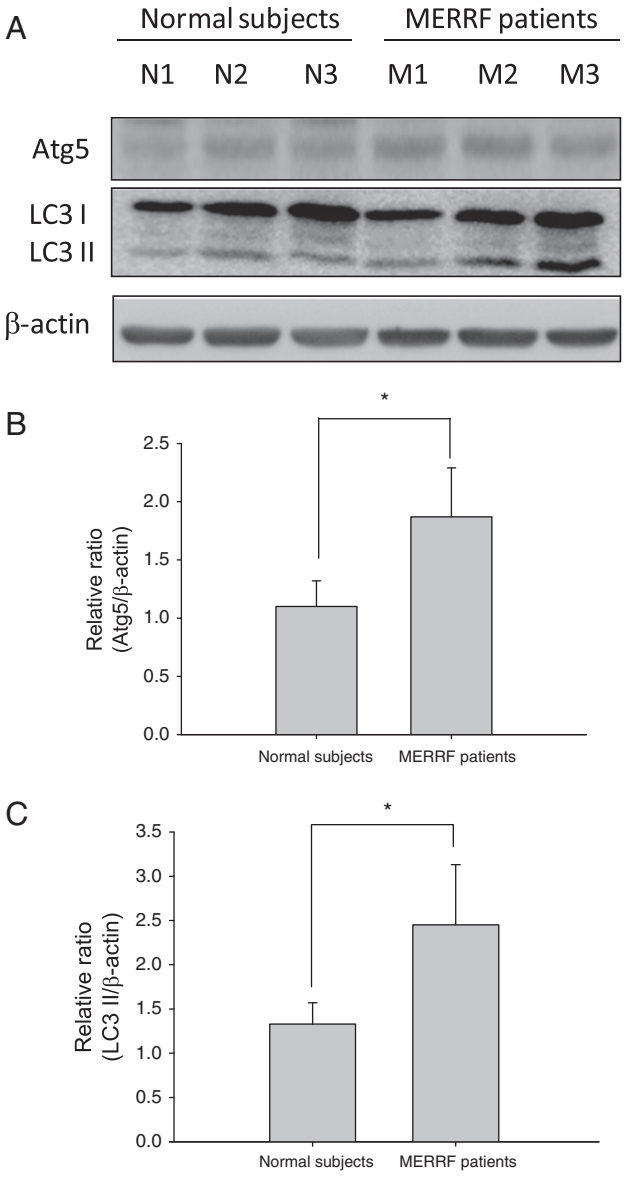

Fig. 2. Upregulation of Atg5 and LC3 II in the primary cultures of skin fibroblasts from MERRF patients. (A) By Western blots, Atg5 and LC3 II were determined in the primary cultures of skin fibroblasts from MERRF patients (N = 3) and age-matched normal subjects (N = 3). (B) and (C) By densitometric analysis of three independent Western blots, the expression levels of indicated autophagic proteins were normalized with the expression level of corresponding β-actin. The representative histogram was constructed on the basis of the mean values of indicated proteins in the skin fibroblasts of MERRF patients and normal subjects, respectively. Data are presented as means ± SD of the results from three independent experiments (*, $p < 0.05$ vs. the indicated group).

transcriptional activity of FOXO3a to induce the expression of the autophagy-related proteins, which include LC3B-II, Beclin1 and Gabarapl1, in the primary cultures of mouse myotubes. In addition, in skeletal muscle cells AMPK was found to directly interact with ULK1, which in turn promotes the formation of autophagosomes. Taken together, we suggest that AMPK-mediated signaling cascade plays a key role in regulating the response to oxidative stress, and that AMPK activation is involved in the regulation of cellular degradation process through redox signaling pathways, which may be associated with the induction of autophagy in mitochondrial diseases.

On the other hand, several regulators have recently been reported to be involved in the regulation of autophagy via cellular redox balance, which specifically affected the formation of autophagosomes [157–160]. The Nrf2 (nuclear factor-erythroid 2-related factor 2), a key regulator in redox signaling and response to ROS, was reported to activate autophagy by increasing the expression of p62, thereby enhancing the degradation of damaged proteins [157]. In addition, the p53 protein is also intimately linked to autophagy due to its role as a transcription sensor for ROS. Elevated expression of p53 in response to ROS has been shown to increase the expression of DRAM (damage-regulated autophagy modulator) and sestrin proteins, which in turn induce the activation of autophagy [158,159]. Moreover, Sirt1 has emerged as a potential regulator of autophagy due to the recent findings of its regulation of autophagy-related proteins. It was demonstrated that deacetylation of multiple Atg proteins and LC3 by Sitr1 could enhance autophagy through the increase of their activities during starvation or nutrient deprivation [160]. As a response to oxidative stress, AMPK, Sirt1, and FOXO3a are tightly regulated in a coordinate manner in affected cells. Therefore, it is possible that AMPK activates the autophagic process through different machineries, which are activated by Sirt1 and FOXO3a in the cells with mitochondrial dysfunction or those exposed to oxidative stress.

6.3. Activation of mitophagy in response to oxidative stress

In mammals, mitochondrial homeostasis is strictly regulated by autophagy and ubiquitin–proteasome degradation pathway [161]. Elimination of damaged mitochondria through a selective autophagic process, called mitophagy, is considered to be the main mechanism to maintain the integrity and quality of mitochondria. Accumulating evidence indicates that mitophagy can be rapidly induced to increase mitochondrial turnover and thus promote cell survival in response to metabolic stress or noxious environmental cues. Recently, mitophagy has been shown to play a crucial role in differentiation of red blood cells, in cellular response to nutrient deprivation or oxidative stress, and in pathological changes of neurodegenerative diseases and mitochondrial disorders [162,163]. A large number of depolarized mitochondria and mitophagy have been observed in skin fibroblasts derived from patients with CoQ_{10} deficiency [161]. Similarly, a massive accumulation of autophagosomes and increased degradation of mitochondria have been observed in MELAS and MERRF skin fibroblasts, respectively, as a result of the activation of mitophagy [29,151]. Not surprisingly, the mitophagy induced by mitochondrial dysfunction can be restored by supplementation of CoQ_{10} or other antioxidants. In the past few years, there has been rapid progress in unraveling the mechanism by which the damaged mitochondria are selectively removed by mitophagy and its pathophysiological role in neurodegenerative diseases. PINK–Parkin signaling pathway is an established mechanism underlying the selective degradation of impaired mitochondria by autophagy in mammalian cells [163]. PINK (PTEN-induced putative kinase protein) is a mitochondrial kinase, which can sense mitochondrial damage and subsequently recruit Parkin, an E3 ubiquitin ligase, from the cytosol to depolarized mitochondria. Under such condition, mitochondrial outer membrane proteins are ubiquitinated and engage LC3-II co-localization to trigger autophagic elimination of damaged mitochondria [162,163]. Importantly, Parkin recruitment to mitochondria was observed in cells that had been treated with respiratory inhibitors, and in cells harboring a pathogenic mtDNA mutation [163,164]. In cybrids harboring heteroplasmic *COXI* gene mutations, overexpression of Parkin was found to selectively eliminate mitochondria containing mutated *COXI* gene via the recruitment of Parkin and thereby restored cytochrome *c* oxidase activity [164]. Therefore, AMPK-mediated inhibition of mTOR, together with the recruitment of Parkin to defective mitochondria contributes to induction of mitophagy. That is to say, Parkin can selectively target severely defective mitochondria due to loss of mitochondrial membrane potential, coupled with increased AMPK activation, and then can selectively promote the removal of damaged mitochondria. On the other hand, emerging evidence has suggested that autophagic adapter protein p62 is involved in Parkin-promoted mitophagy [165]. Upon disruption of mitochondrial membrane potential by CCCP (carbonyl

cyanide 3-chlorophenylhydrazone), p62 can be recruited to mitochondria and bind to Parkin-ubiquitinated proteins such as VDAC and Mfn1, by which LC3-II can recognize impaired mitochondria for autophagic degradation. The scenario was further substantiated by the observation that mammalian cells with AMPK deficiency exhibited defective mitophagy [157,165]. It was demonstrated that AMPK phosphorylation of ULK1 was required for mitophagy upon nutrient deprivation. It was found that in AMPK knockout mice, AMPK loss led to aberrant accumulation of p62, ubiquitin aggregates, and abnormal mitochondria in the liver and primary hepatocytes of the animals.

7. Conclusion and future perspectives

It has been well established that most of the mitochondrial diseases are caused by mutations in mtDNA and/or nDNA. However, the molecular mechanisms underlying the pathophysiology of mitochondrial diseases are still poorly understood. It still remains a mystery as to how and why mutations in different genes of the mitochondrial genome lead to similar clinical symptoms. In addition, it is also unclear as to how the same mtDNA mutations manifest greatly varied clinical features in different patients. Based on the experimental data from this and other laboratories, we consider that bioenergetic dysfunction and accumulation of deleterious metabolic intermediates including ROS and lactate in affected tissue cells may be involved in the onset and progression of this prominent group of metabolic diseases [9–11]. A significant increase in oxidative stress and oxidative damage is often observed in the affected tissues and peripheral blood cells of most patients with mitochondrial diseases [27]. Once the damage persists too long or too pronounced to be repaired, the mitochondria could sense and integrate the extra-mitochondrial stress and signals to drive the cell into an irreversible death process such as apoptosis [166]. This scenario may explain the well-documented age-dependent progression and worsening of the symptoms in the majority of mitochondrial diseases. Therefore, to counteract the deleterious effects of oxidative stress, antioxidants have been utilized in the treatment of some mitochondrial diseases [167]. However, although the benefits of antioxidants have been extensively investigated in both cell culture and animal models for mitochondrial diseases, translation of these findings to the clinical setting has yielded inconsistent results. CoQ_{10} has been most often used due to its dual roles as a potent ROS scavenger and as a component of the respiratory chain. Clinical trials of CoQ_{10} with other antioxidants such as vitamins C, E and K as a form of "antioxidants cocktails" have been employed to treat some patients with mitochondrial diseases and neurodegenerative diseases, respectively [168]. Recently, reduction of the mitochondrial ROS has been shown to be beneficial to the patients with mitochondrial disorders, and thus the development of antioxidants targeting to mitochondria such as $MitoQ_{10}$ has been an intensive area of research [169,170]. At least, this line of research has revealed that most of the natural antioxidants are insufficiently targeted to the site of ROS generation, and instead are dispersed throughout the body. Therefore, antioxidants conjugated to lipophilic cations can pass easily through lipid bilayers and accumulate in mitochondria due to the large mitochondrial membrane potential dictated by the trans-membrane gradient of protons. Indeed, there has been much research and development in the design of the Mito-vitamin E, Mito-TEMPO, and Mito-NAC for the treatment of diseases caused by mitochondrial disorders [171]. On the other hand, the therapy of mitochondrial transfer or mitochondrial gene replacement has made some progress and is under intensive investigation [168]. Results from our recent studies together with others [172,173] have suggested some potential therapeutic interventions of mitochondrial diseases. However, there are many concerns, particularly the occurrence of adverse reactions (e.g., immunological or allergic) because these therapies require the delivery of foreign genes (or mitochondria) to the affected tissue cells, which is a similar problem encountered in many conventional gene therapy approaches. In consideration of the hurdles and potential risk of the mitochondrial gene therapy such as the choice of appropriate viral or non-viral vectors, and the high efficiency of the delivery of antioxidants to the affected tissues and the low incidence of adverse reactions, the redox therapy by mitochondria-targeting antioxidants is a promising treatment of patients with mitochondrial diseases and other diseases caused by mitochondrial dysfunction.

In order to further understand the pathophysiology of mitochondrial diseases, it is of fundamental interest and clinically relevant to reveal the mechanism of adaptive response to oxidative stress and to identify the protective proteins involved in the affected tissue cells. We contend that mitochondrial dysfunction-elicited oxidative stress can trigger a series of adaptive responses, including up-regulation of antioxidant enzymes, metabolic switch, increased mitochondrial proliferation and autophagy, to confer advantages for cells to survive (Fig. 3). In addition, we have discussed the roles of AMPK–PFK2, AMPK–FOXO3a, AMPK–PGC-1α, and AMPK–mTOR signaling pathways, respectively, in the modulation of the adaptive response in human cells under oxidative stress. It has been reported that the above-mentioned adaptive responses mediated by AMPK activation are involved in the protection of neurodegenerative disease, cardiovascular disease, and diabetes

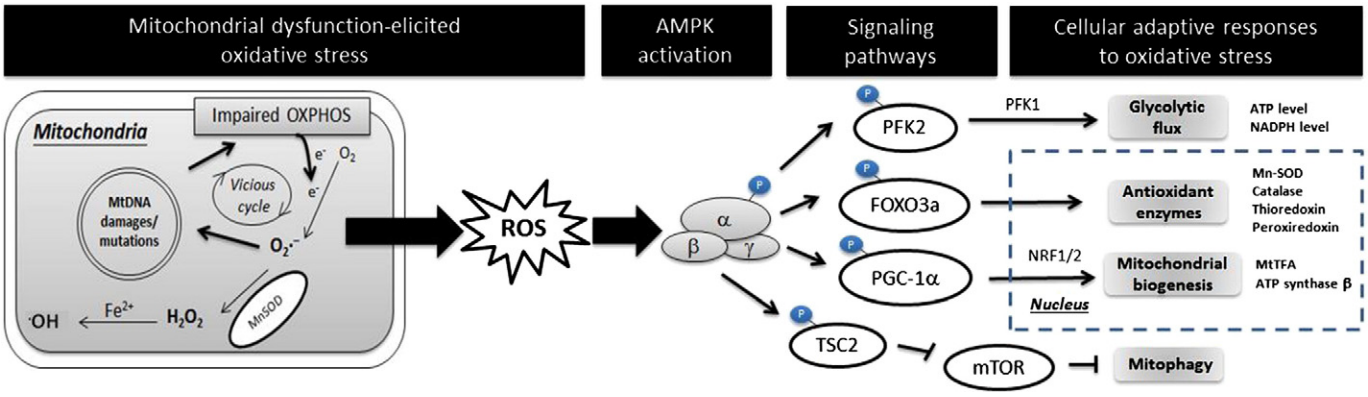

Fig. 3. AMPK-mediated adaptive responses of human cells to oxidative stress induced by mitochondrial dysfunction. In response to oxidative stress elicited by mtDNA mutation-induced mitochondrial dysfunction, AMPK activation (phosphorylation at Thr^{172}) would trigger several adaptive responses for cell survival. The activation of AMPK can increase the glycolytic flux by the activation of PFK2, so that the affected cells with mitochondrial dysfunction can not only obtain ATP but also replenish the intracellular NADPH pool via pentose phosphate pathway (PPP) to cope with the enhanced oxidative stress. In addition, AMPK can directly phosphorylate PGC-1α and FOXO3a, which in turn augment mitochondrial biogenesis (e.g., up-regulation of mtTFA and ATP synthase β, a subunit of mitochondrial Complex V) and antioxidant defense system (e.g., the up-regulation of thioredoxin, peroxiredoxin, Mn-SOD, and catalase), respectively, in response to oxidative stress. Moreover, AMPK-mediated TSC2 phosphorylation can activate cellular autophagy through the inhibition of mTOR activity in affected cells against elevated oxidative stress. Taken these responses together, we suggest that activation of AMPK plays a crucial role in the up-regulation of mitochondrial biogenesis, antioxidant enzymes, and glycolytic flux, respectively, as the adaptive responses to mitochondrial dysfunction-elicited oxidative stress for the survival of affected cells.

[18,19,69]. Since AMPK is substantially activated in MERRF skin fibroblasts [51], the AMPK activation signaling pathway is worthy of further investigation in relation to the pathophysiology of mitochondrial diseases. In addition, considering AMPK a potential therapeutic target, it is imperative to investigate whether activation of AMPK by compounds such as resveratrol or metformin is beneficial to patients with mitochondrial diseases. Taken together, the elucidation of the mechanism of AMPK-mediated adaptive responses has provided useful information for us to understand the cell physiological significance of the response to oxidative stress. This line of research has paved a new avenue for the development of better therapeutic agents for the treatment of patients with diseases caused by or associated with mitochondrial dysfunction.

Acknowledgements

Part of this article was prepared on the basis of our work supported by research grants from the National Science Council, the Executive Yuan, Taiwan (NSC100-2320-B-010-024-MY3 and NSC101-2811-B-010-029). The authors would like to acknowledge the support of an intramural research grant 982A01 from Mackay Medical College.

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