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REVIEW

Regulatory role of mitochondria in oxidative stress and atherosclerosis

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Abstract

Mitochondrial physiology and biogenesis play a crucial role in the initiation and progression of cardiovascular disease following oxidative stress-induced damage such as atherosclerosis (AST). Dysfunctional mitochondria caused by an increase in mitochondrial reactive oxygen species (ROS) production, accumulation of mitochondrial DNA damage, and respiratory chain deficiency induces death of endothelial/smooth muscle cells and favors plaque formation/rupture *via* the regulation of mitochondrial biogenesis-related genes such as peroxisome proliferator-activated receptor γ coactivator (PGC-1), although more detailed mechanisms still need further study. Based on the effect of healthy mitochondria produced by mitochondrial biogenesis on decreasing ROS-mediated cell death and the recent finding that the regulation of PGC-1 involves mitochondrial fusion-related protein (mitofusin), we thus infer the regulatory role of mitochondrial fusion/fission balance in AST pathophysiology. In this review, the first section discusses the possible association between AST-inducing factors and the molecular regulatory mechanisms of mitochondrial biogenesis and dynamics, and explains the role of mitochondria-dependent regulation in cell apoptosis during AST development. Furthermore, nitric oxide has the Janus-faced effect by protecting vascular damage caused by AST while being a reactive nitrogen species (RNS) which act together with ROS to damage cells. Therefore, in the second section we discuss mitochondrial ATP-sensitive K^+ channels, which regulate mitochondrial ion transport to maintain mitochondrial physiology, involved in the regulation of ROS/RNS production and their influence on AST/cardiovascular diseases (CVD). Through this review, we can further appreciate the multi-regulatory functions of the mitochondria involved in AST development. The understanding of these related mechanisms will benefit drug development in treating AST/CVD through targeted biofunctions of mitochondria.

Key words: Apoptosis; Atherosclerosis; ATP-sensitive K^+ channels; Free radical; Mitochondrial biogenesis

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INTRODUCTION

Cardiovascular diseases (CVD) are the leading cause of morbidity and mortality in many industrialized societies. Atherosclerosis (AST) is the major risk factor for the development of CVD based on arterial endothelial dysfunc-

tion caused by the impairment of endothelial dependent dilation[1,2]. AST is a chronic inflammatory syndrome with a predilection for sites within the walls of arteries. Common factors involved in the mechanism of AST include endothelial cells, vascular smooth muscle cells, macrophages, platelets, and protein substances such as low-density lipoproteins (LDL), growth factors, and cytokines. In the initial phase of AST development, LDL or other pro-inflammatory proteins stimulate endothelial cell expression of adhesion factors, chemokines, and growth factors, which attract circulating monocytes to the inflamed endothelial cells, and then the monocytes enter the intima where macrophage colony-stimulating factor induces monocyte-macrophage differentiation. The macrophages through the uptake of oxidatively modified LDL and cholesterol lead to foam cell formation, augmenting early lesion development. Meanwhile, T lymphocyte activation, smooth muscle cell proliferation and migration, and extracellular matrix deposition occur in the vascular intima. These deposits interact with molecules in the intima and lead to necrosis, causing the formation of fibrous plaques which contain a core of lipid-laden cells and a fibrous cap formed by smooth muscle cells and matrix. Slow progressive enlargement of plaques may eventually cause them to rupture and with blood flow produce stenosis or closure of the lumen of other arteries. In addition, as a result of plaque rupture, platelet activation may lead to thrombosis, in which a thrombus obstructs blood flow, further resulting in clinically acute CVD or stroke. AST is a dynamic process, exhibiting constant changes in size and composition of the blood vessels. This is known as remodeling of the vessel[3,4]. Two major forms of remodeling may progress within the affected artery. One is thickening and constrictive geometric remodeling in which the lumen of the affected artery becomes narrowed. The other is expansive remodeling in which the artery tends to preserve the lumen by expanding the vessel wall outward. These two remodeling responses by the vessels have been reported to depend on a variety of endogenous and environmental factors[3]. They can vary from vessel to vessel, with age and gender, and are modulated by known cardiovascular risk factors.

Reactive oxygen species (ROS) such as superoxide, hydrogen peroxide, and the extremely reactive hydroxyl radical, are risk factors for AST associated with lipid and protein oxidation in the vascular wall. ROS formation triggers a cascade of events such as oxidative modification of LDL, inflammation, cellular apoptosis and endothelium injury. ROS are produced by phagocytes and non-phagocytic cells through different mechanisms. The enzymes for ROS production in non-phagocytic cells such as vascular cells include xanthine oxidase, cytochrome P-450, uncoupled nitric oxide synthase (NOS), and NAD(P)H oxidase. Once ROS are produced, they play an important role in cell signaling[5]. They can also attack vital cell components such as polyunsaturated fatty acids, proteins, nucleic acids, and even carbohydrates. These reactions can alter cell membrane properties such as fluidity, ion transport, loss of enzyme activity, protein cross-linking, inhibition of protein synthesis, and DNA damage eventually leading to cell apoptosis. Mitochondria are the primary intracellular source of ROS, as they generate huge numbers of oxidative-reduction reactions and use massive amounts of oxygen. Overproduction of mitochondrial ROS (mtROS) not only leads to mitochondrial DNA (mtDNA) damage and mutation but also triggers proapoptotic protein release into the cytosol and could further impair cell viability. Therefore, mitochondrial redox balance is the key regulator of cell survival and death by controlling the accumulation of mtDNA mutations and net production of ROS. Aging is the driving force in a cycle that begins with age-related changes in the blood vessels including arterial thickening and stiffening, and thus can increase susceptibility to CVD[6]. Besides aging, the severity of mtDNA damage is higher in aortic samples from atherosclerotic patients than in non-atherosclerotic aortic samples from age-matched transplant donors[7].

Net production of mtROS is another crucial mechanism by which mitochondria are thought to contribute to a variety of pathologies, for instance, CVD, aging, ischemia/reperfusion and neurodegenerative diseases. The balance of mitochondrial redox reactions is coordinated with the processes and components involved in ROS synthesis, antioxidant defense and ROS release[8-11]. The role of mitochondria in ROS metabolism had been widely investigated in oxidative stress[12,13]. In 1997, one of the drugs involved in mitochondrial activation, diazoxide, was found to have strong cardioprotective activity. Diazoxide is a selective agonist of mitochondrial ATP-sensitive K^+ (mitoK$_{ATP}$) channels. Several studies have strongly implied that mitoK$_{ATP}$ channel opening benefited the decline of excessive mtROS preservation *via* a mitochondrial permeability transition pore (PTP)-mediated leak in ischemia/reperfusion-induced injury of the heart or kidney. However, the related role of mitoK$_{ATP}$ channels is still controversial[11,14,15]. Although most studies focused on the effect of mitoK$_{ATP}$ channels on ischemia/reperfusion[11,16], these channels are associated with known complex disorders induced by cardiovascular risk factors including hypertension[17], diabetes, and insulin resistance[18].

Oxidative stress plays an important role in the initial occurrence of CVD and has been previously discussed[19-21]. However, the molecular mechanisms responsible for mitochondria-mediated disease processes are not clear especially in mitochondrial physiology and in the balance of mitochondrial redox reactions during oxidative stress. Thus, the present study will review the mitochondrial biogenesis-mediated molecular mechanisms by which atherosclerotic risk factors could lead to mitochondrial dysfunction and subsequent vascular impairment. We will discuss (1) the role of mitochondrial dynamics in mitochondrial dysfunction and apoptosis; (2) the regulatory mechanism of mitochondrial biogenesis under AST-related stress; and (3) ROS/reactive nitrogen species (RNS)-mediated oxidative stress on mitochondrial biogenesis and physiology.

MITOCHONDRIAL DYNAMICS IN MITOCHONDRIAL DYSFUNCTION AND APOPTOSIS

Mitochondria are dynamic organelles in eukaryotic cells

and their heterogeneous morphology which results from equilibrium is dominated by the opposing processes of fission and fusion. The dynamic nature of mitochondria is a concept that includes the movement of mitochondria along the cytoskeleton, the regulation of mitochondrial architecture (morphology and distribution), and connectivity mediated by tethering and fusion/fission events[22]. This dynamic network is essential to maintain normal mitochondrial functions and participates in fundamental processes, including development, metabolic efficiency, apoptosis, and aging[23]. In recent years, at least four dynamin-related GTPase family proteins, including mitofusin 1 (MFN1), MFN2, optic atrophy 1 (OPA1), and dynamin-related protein 1 (DRP1), have been found to play significant roles in the regulation of mitochondrial fusion/fission[24]. Mitochondrial fusion controls mitochondrial morphology and is constituted by a multi-step process including fusion in the outer and inner membranes[24]. In outer membrane fusion, MFN1 and MFN2 which are located in the outer membrane help tether adjacent mitochondria by forming homo- and heterodimers. Furthermore, in mitochondrial inner membranes, OPA1 *via* oligomer formation is responsible for the formation of the cristae junction, ultimately resulting in mixing of matrix contents[25]. In contrast, mitochondrial fission is regulated by DRP1 in the outer membrane[26]. Fusion/fission balance plays a role in determining the fate of a depolarized mitochondrion. Mitochondrial fusion serves to maintain several mitochondrial functions or prevent stress-induced mitochondrial dysfunction. Besides the known fact that intact mitochondria can complement a damaged unit[23], it was later proved that the process can be regulated by a physiological mechanism; fission leading to selective fusion segregates dysfunctional mitochondria and allows autophagy to eliminate them[24]. Mitochondrial fission occurs when mitochondria are dysfunctional, probably caused by OPA1 cleavage[27]. However, preventing fission leads to mitochondrial dysfunction and loss of mtDNA[28]. Excessive mitochondrial fission and a lack of fusion results in breakdown of the mitochondrial network, loss of mtDNA, respiratory defects and an increase in ROS[29]. Additionally, the mitochondrial dynamics in cells with oxidative stress was further explored based on the importance of mitochondrial fission and fusion processes on cell survival[30,31]. Generally, in healthy cells the dynamic balance between mitochondrial fusion and fission maintains mitochondrial functions, but when cells are affected by excessive oxidative damage that results in apoptosis, the rate of mitochondrial fission outpaces that of fusion and stimulates fission protein DRP1-mediated release of cytochrome *c*. However, recently Tondera *et al*[31] offered a new concept for the distinct role of mitochondrial fusion in cells responding to stress using low levels of toxic agents such as cycloheximide, UV irradiation or actinomycin D. They found that cells subjected to low levels of stress-induced mitochondrial hyperfusion (SIMH), called the SIMH pathway, showed reduced mitochondrial fragmentation which occurs in full-blown apoptosis-induced cells. The mitochondria in SIMH fused into a closed network to confer resistance to further stress although eventually cells may succumb to apoptosis. Further supporting evidence showed that the mitochondrial inner membrane protein, *stomatin*-like protein 2 (SLP-2), is up-regulated under conditions of mitochondrial stress leading to increased protein turnover[32]. It is known that SLP-2 is significantly involved in the regulation of the stability of specific mitochondrial proteins. In HeLa cells, depletion of SLP-2 results in increased proteolysis of prohibitins and of subunits of the respiratory chain complexes I and IV[32]. Moreover, SLP-2 is essential in SIMH and is dependent on the correlation of OPA1 and MFN1[31].

The significance of cell death in AST has been demonstrated and clearly identified over the past few years in the related fields of key cellular, cytokine and molecular regulators within atherosclerotic lesions. The major consequence of AST in humans is mainly caused by apoptosis of vascular smooth muscle cells, endothelial cells and macrophages, possibly leading to promotion of plaque growth and procoagulation and induction of rupture[2,33]. Mitochondrial dynamics plays a unique role in cell apoptosis. An imbalance of mitochondrial fusion/fission results in excessive fragmentation or tubulation, with pathological consequences[30]. In addition to the influences of mitochondrial dysfunction and energetic deficiency on cell death, mitochondrial fission-related proteins also appear to participate in apoptosis and proteins associated with the regulation of apoptosis have been shown to affect mitochondrial ultrastructure[34]. Mitochondrial-mediated apoptosis upstream of caspase activation is regulated by two proapoptotic *Bcl-2* family members, *Bax and Bak,* whose activation is through regulating mitochondrial outer membrane permeability (MOMP). Apoptosis-associated MOMP is known to require Bax and/or Bak which reside on the mitochondrial outer membrane or translocate there in response to proapoptotic stimuli[35,36]. Bax then coalesces into foci with Drp1, mitofusins, and Bak, leading to mitochondrial division and release of cytochrome *c*[37]. When cytochrome *c* is released from the mitochondrial space between the inner and outer mitochondrial membranes to the cytosol, it binds apoptotic protease-activating factor 1 (APAF1), activating the assembly of the apoptosome that activates caspase 9 and subsequently the effectors caspase-3 and caspase-7[38]. The mitochondrial-triggered cytochrome *c* release is activated by an increase in fission. Blocking this mitochondrial fission inhibits cytochrome *c* release and delays cell death. Thus, mitochondrial fragmentation appears to be universally associated with apoptosis. However, excessive mitochondrial fragmentation is not linked to apoptosis such as in the cases of viral infection and stimulation by uncoupling agents[39]. Mitochondrial fragmentation is not required to induce cell death as shown in the studies of Sheridan *et al*[40] and Breckenridge *et al*[41]. Likewise, caspase inhibitors did not affect the apoptotic fragmentation of mitochondria[34].

Several studies have conclusively shown that activation of Bax and/or Bak rapidly leads to mitochondrial fragmentation[42-45]. The phenomenon seems to be unrelated to MOMP and cytochrome *c* release[46]. Interestingly, the study by Karbowski *et al*[47] found that, in Bax/Bak double-knockout cells, mitochondrial fusion was reduced and

inhibition of Drp1 activity did not promote elongation of mitochondria. The emerging role for the *Bcl-2 family* members, *Bax* and *Bak*, in regulation of mitochondrial dynamics was discussed recently[48]. These authors proposed that the role of Bcl-2 proteins in mitochondrial morphogenesis is functionally distinct from their role in apoptosis[48]. Bax and Bak can promote mitochondrial fusion by directly binding with Mfn1 and Mfn2 in normal cells and do not interfere with the normal fission process[37,47]. These results further explain the foregoing discussion on the non-dependent interaction between mitochondrial fragmentation and apoptosis. However, the detailed mechanism is unclear, for instance, how does the apoptotic-stimuli-induced Bax translocate to mitochondria without changing the Bax-Mfn2 interaction.

REGULATORY MECHANISM OF MITOCHONDRIAL BIOGENESIS UNDER AST-RELATED STRESS

Of the causes which induce AST, oxidative stress is the most frequent and major cause, and AST is further induced by common risk factors. Under most conditions, the rates of cellular ROS formation and elimination are balanced through mitochondrial and cellular mechanisms that sense relative ROS levels. However, a chronic imbalance in redox homeostasis contributes to various chronic diseases, especially AST, which is an inflammatory disease associated with the oxidation of lipids and proteins in the vascular wall[21,49]. Besides the influence of ROS/RNS formation, cytokines and chemoattractant chemokines recruit mononuclear leukocytes, and the migration, growth, and activation of the multiple cell types within atherosclerotic lesions are factors in the chronic inflammatory and fibroproliferative response central to AST. The role of oxidative damage in the cardiovascular risk factor-induced mitochondrial dysfunction in AST, such as aging, diabetes, dyslipidemia, hypertension homocysteinemia and cigarette smoking, has been reviewed in several literature studies[50-53]. However, the regulatory mechanisms of those factors in mitochondrial functions are still unclear, especially in pathophysiological processes. Therefore, in this section we will discuss the related regulatory mechanisms of mitochondrial physiology (biogenesis and fusion/fission) during the development of AST and CVD.

Poly(ADP-ribose) polymerase-1 (PARP-1), the most abundant isoform of the PARP enzyme family, is a nuclear enzyme involved in modulating chromatin structure, regulating gene transcription, and sensing and repairing DNA damage[54]. The protein is 116-kDa in size and is composed of three main domains: the N-terminal DNA-binding domain containing two zinc fingers, the automodification domain, and the C-terminal catalytic domain[54]. When PARP-1 is activated by single- and double-stranded DNA breaks, it forms homodimers and catalyzes the cleavage of NAD^+ into nicotinamide and ADP-ribose to form long branches of ADP-ribose polymers on the glutamic acid residues of a number of target proteins including PARP-1 itself. Although PARP-1 is essential for repairing stress-induced DNA damage, the massive DNA damage and overactivation of PARP-1 leading to irreversible cellular energy failure (with depletion of cellular NAD+ and its precursor ATP)[55,56], resulting in PARP-1 hyperactivation-induced necrosis has been implicated in several pathophysiological conditions[57-60]. Moreover, PARP-1 is also involved in regulation of the apoptotic cascade by mediating the translocation of apoptosis inducing factor (AIF) from the mitochondria to the nucleus in oxidatively injured cells[54,61]. The poly(ADP-ribose) polymer induced by PARP-1 activation had been demonstrated to be an AIF-releasing factor responsible for PARP-1-dependent cell death[62,63]. The role of PARP-1 in cardiovascular disorders has been widely discussed in recent years[59,64,65]. The major cause is dependent on PARP-1-regulated transcriptional levels of various proteins implicated in inflammation such as inducible NOS (iNOS), intercellular adhesion molecule-1, cyclooxygenase 2 and major histocompatibility complex Class Ⅱ[66]. Moreover, PARP-1 acts as the co-activator to regulate nuclear factor kappa-light-chain-enhancer of activated B cells and nuclear factor κB (NF-κB)-mediated transcription in the control of inflammatory cytokine/chemokine gene expression[66,67]. It is well-known that induction of cytokine/chemokine receptor-activated NF-κB signaling from activated endothelial cells and inflammatory cells in the vascular intima is an essential step in the development and progression of AST[68]. In addition, the formation of atherosclerotic plaques has been demonstrated to require PARP-1 by the use of chronic PARP inhibitor and genetic PARP1 deletion on plaque formation in AST-prone apolipoprotein E knockout mice[57]. Inhibition or genetic deletion of PARP-1 diminished the expression of inducible iNOS, vascular cell adhesion molecule-1, and P- and E-selectin[57]. Furthermore, pharmacological inhibition of PARP-1 reduced the number of plaque inflammatory cells and decreased features of plaque vulnerability[69]. In addition to AST, activation and overexpression of PARP-1 were also found in circulating mononuclear cells from unstable angina patients and had promoted PARP-1/NF-κB/DNA complex formation, leading to enhanced expression of TNF-α and interleukin-6[59]. In summary, the key pathophysiological roles of PARP-1 are shown in a simplified scheme in Figure 1. PARP-1 hyperactivation induced by excessive DNA damage during oxidative damage has various roles in promoting AST/CVD development *via* the regulation of AIF-dependent cell death, inflammatory gene transcription, cell adhesion molecules and the secretion of inflammatory cytokines.

PARP-1 *via* nuclear-mitochondrial crosstalk modulates the mitochondria-to-nucleus translocation of AIF which contributes to DNA fragmentation as previously described. However, the distinct role of PARP-1 in the regulation of mitochondrial biogenesis and fusion/fission has been explored recently. Hossain *et al*[70] showed that nuclear respiratory factor 1 can directly interact with PARP-1 by co-purifying the PARP-1·DNA-PK·Ku80·Ku70·topoisomerase Ⅱβ-containing protein complex. They suggested that NRF-1 can activate PARP1-mediated transcription by enhancing recruitment of RNA polymerase Ⅱ and/or by using enzymatic activities of

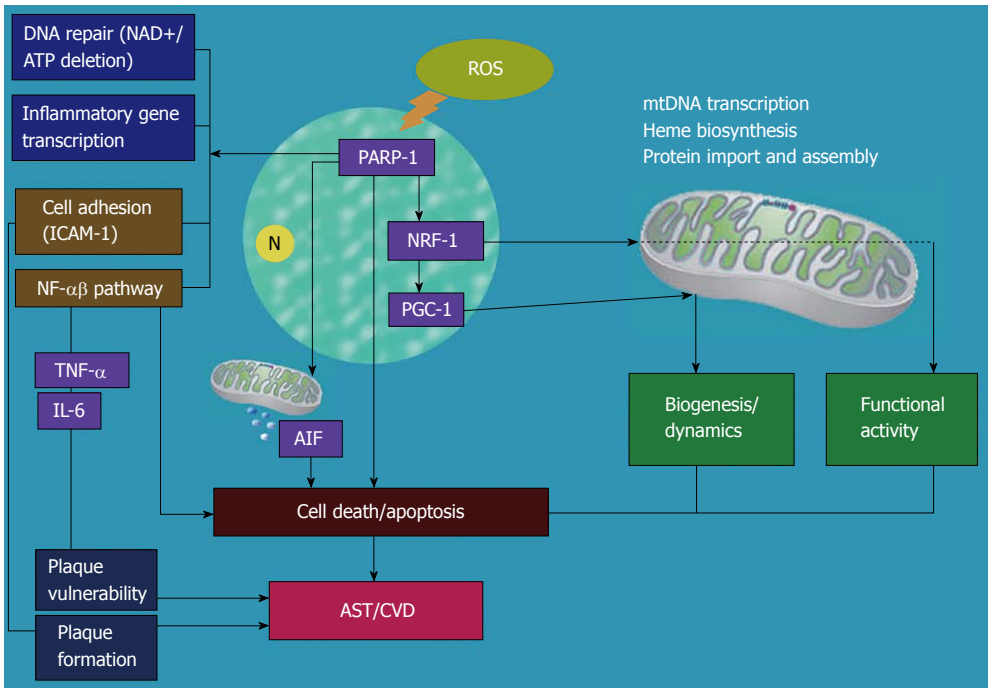

Figure 1 The molecular regulation of nuclear and mitochondrial cross-talk signaling on ROS-triggered AST/VCD development. ROS activate PARP-1 and cause AST primarily by increasing endothelial and smooth muscle cell death (mitochondria-dependent or not) and triggering inflammatory reactions. In addition, proinflammatory cytokines and chemokines induce plaque formation and plaque vulnerability that leads to deterioration in the later stages of AST. However, PARP-1 can also participate in NRF-1 regulation or indirectly activate PGC-1 to improve mitochondrial biofunctions such as biogenesis and fusion. This mechanism defends against ROS-induced progression of AST by inhibiting mitochondrial-mediated apoptosis and against the occurrence of AST at an early stage. ROS: Reactive oxygen species; PARP-1: Poly(ADP-ribose) polymerase-1; NRF-1: Nuclear respiratory factor 1; PGC-1: Peroxisome proliferator-activated receptor γ coactivator-1; mtDNA: Mitochondrial DNA; AIF: Apoptosis-inducing-factor; NF-κB: Nuclear factor κ-light-chain-enhancer of activated B cells; TNF-α: Tumor necrosis factor-α; IL-6: Interleukin-6; AST: Atherosclerosis; CVD: Cardiovascular diseases; N: Nucleus.

the PARP-1·DNA-PK·Ku80·Ku70·Topo Ⅱβ-containing complex. PARP-1 can also PARylate the DNA-binding domain of NRF-1 and negatively regulate the NRF-1·PARP-1 interaction[70]. Mitochondria contain their own genetic system consisting of a circular double-stranded DNA (mtDNA), which is responsible for the synthesis of 13 essential subunits of the inner membrane complexes of the respiratory apparatus. Because of myriad mitochondrial functions based on the limited coding capacity of mtDNA, most protein subunits consisting of five inner membrane complexes of the electron transport chain and oxidative phosphorylation system rely heavily on the expression of the nuclear encoding genes to maintain all the mitochondrial functions. NRF-1 is one of the transcriptional factors for nuclear-coded genes and has been linked to the expression of many genes required for mitochondrial respiratory functions[71]. The nuclear control of mitochondrial functions by NRF-1 was shown to include the regulation of mitochondrial translation, heme biosynthesis, and mtDNA transcription/replication[72].

Recent findings suggest that NRF-1 is also involved in the expression of key components of the protein import and assembly machinery in mitochondria and plays a broader role in orchestrating events in mitochondrial biogenesis beyond the regulation of respiratory chain-related genes[63,72,73]. NRF-1 is involved in the nucleomitochondrial interactions through interplay with the peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α), one of the transcriptional coactivator family (PGC-1α, PGC-1β, and PGC-1-related co-activator), to induce mitochondrial biogenesis[74,75]. PGC-1 α is mainly involved in the regulation of gluconeogenesis and has the potential to integrate the activities of a diverse collection of transcription factors implicated in the expression and function of the mitochondrial oxidative machinery[72]. Its transcriptional level is highly dependent on the increase in energy expenditure caused by cold exposure (in brown adipose tissue), fasting (in liver) or exercise (in muscle)[72,76]. These expressions differ somewhat from that of PGC-1β. For instance, PGC-1β expression occurs in distinct tissues and is unaffected by physiological processes as described above[76,77]. Even if PGC-1α and PGC-1β are functionally distinct in the regulation of mitochondrial biogenesis and uncoupling proteins[71,72,78,79], they both participate in the induction of mitochondrial biogenesis by utilizing NRF-1 or other transcription factors[72]. Thus, overexpression of either PGC-1α or PGC-1β contributes to an improvement in oxidative phosphorylation in cells with mtDNA mutation[80]. We further proposed that the interaction of NRF-1 and PGC-1α somehow affects the mitochondrial dynamics in maintaining proper mitochondrial morphology and activity during mitochondrial dysfunction. The hypothesis of mitochondrial biogenesis involving the balance of mitochondrial fission-fusion is further supported by the finding of Soriano *et al*[81], who showed that PGC-1α can induce Mfn2 transcription and regulate mitochon-

drial activity which depends on correct Mfn2 expression. Moreover, in 2008, Liesa *et al*[82] demonstrated that PGC-1β increases mitochondrial fusion using a multi-approach strategy that combined Mfn2 knockout cells, PGC-1β-overexpressing muscle cells and PGC-1β-ablated mice. They showed that reduced mitochondrial size observed in transcriptional regulator PGC-1β knockout mice was associated with a selective reduction in Mfn2 expression, and that PGC-1β increases mitochondrial fusion and elongates mitochondrial tubules by enhancement of *Mfn2* gene transcription through co-activated nuclear receptor estrogen related receptor α. Thus, these results prove that transcriptional regulators such as NRF-1 not only affect mitochondrial biofunction but also shift the balance between mitochondrial fusion and fission events through coordination of the PGC family to selectively control gene expressions (Figure 1). Here, we try to explain the distinct role of PPAR-1 during AST/CVD development. As shown in Figure 1, in the early stage of ROS-induced oxidative stress, cells can protect themselves from oxidative damage by activation of PARP-1-related signaling to support mitochondrial biofunctions and prevent mitochondrial-mediated cell apoptosis. When this is not enough to sustain the extensive ROS production, PARP-1 plays the opposite role by promoting the progression of AST/CVD. This phenomenon explains why mitochondrial hyperfusion is observed in cells suffering lower oxidative stress[31,32], as previously described.

ROS/RNS-MEDIATED OXIDATIVE STRESS ON MITOCHONDRIAL BIOGENESIS AND PHYSIOLOGY

ROS-mediated mitochondrial biogenesis was demonstrated through the upregulation and actions of NRF-1[83]. Moreover, ROS can also induce mitochondrial biogenesis through direct regulation of PGC-1α transcription[84,85]. Several reports link the expression of PGC-1α to exercise-induced mitochondrial biogenesis in skeletal muscle[74,85,86], but few have demonstrated the role of PGC-1α-mediated mitochondrial biogenesis in AST/CVD. As we know, the production of ROS is a crucial trigger for induction and progression of AST. ROS induce vascular inflammation *via* the proinflammatory cytokine/NF-κB pathway. Kim *et al*[87] found that overexpression of the PGC-1α gene in human aortic smooth muscle and endothelial cells leads to a significant reduction in intracellular and mtROS production as well as NAD(P)H oxidase activity which is induced by TNF-α. These findings implied that PGC-1α-mediated mitochondrial biogenesis in oxidatively injured cells seems to offer a good source of "healthy mitochondria" which detoxify mtROS by a large antioxidant defense system containing numerous redox enzymes of the electron-transport chain decreasing net ROS production. Thus, stimulation of PGC-1α expression in the vasculature benefits the prevention of AST development. Recently, another regulatory mechanism of PGC-1α-mediated apoptosis of endothelial cells was shown to support this inference. Adenoviral overexpression of PGC-1α prevented linoleic acid-induced increases in ROS generation and cell apoptosis in human aortic endothelial cells by increasing fatty acid oxidation, decreasing cytosolic fat metabolites and increasing ATP/ADP translocase activity[88]. Fatty acid oxidation affects metabolic and CVD by the regulation of adiponectin (adipocytokin), a circulating plasma protein secreted by adipocytes[89,90]. Adiponectin has insulin-sensitizing metabolic effects and vascular protective properties[91], and helps inhibit the inflammatory reaction induced by oxidative stress or TNF-α in endothelial cells[90]. In addition, adiponectin binds to the walls of catheter-injured vessels[92], and inhibits the expression of several TNF-α-induced adhesion molecules and monocyte adhesion in cultured endothelial cells[93]. Adiponectin also inhibits the production of CXC receptor 3 chemokine ligands in macrophages and reduces T-lymphocyte recruitment in atherogenesis[94]. Ouedraogo *et al*[95] showed that adiponectin suppresses excess ROS production induced by high-glucose conditions *via* a cAMP/PKA-dependent pathway. This implied a possible connection between mitochondrial biogenesis and adiponectin-mediated vascular protection. Indeed, it was demonstrated that adiponectin and adiponectin receptor 1 (AdipoR1) regulated mitochondrial functions by PGC-1α[96]. The binding of adiponectin and AdipoR1 increased PGC-1α expression and activity by Ca^{2+} signaling and by AMP-activated protein kinase and Sirtuin type 1, leading to increased mitochondrial biogenesis[96]. However, it still needs to be proved whether the regulatory mechanism observed in skeletal muscles to explain the causes of mitochondrial dysfunction and insulin resistance in diabetes, exists in endothelial cells and vascular smooth muscle cells to regulate AST/CVD.

Adiponectin has vascular actions which directly stimulate production of nitric oxide (NO) in endothelial cells through phosphatidylinositol 3-kinase-dependent pathways involving phosphorylation of endothelial NOS (eNOS)[75,97]. It is known that NO derived from eNOS acts as a maintenance factor for vascular structure integrity and has a variety of antiatherogenic effects in physiological conditions. Moreover, endothelial dysfunction which occurs early in the development of AST is characterized by a loss of NO bioactivity. Although NO plays a protective role in AST, it is still a reactive radical (RNS) that leads to nitrosative stress when excessive RNS generation in a biological system can not be neutralized. NO reacts strongly to ROS and produces peroxynitrite anion, which is a potent oxidizing agent capable of causing oxidative damage[50]. Thus, the Janus-faced role of eNOS in vascular disease is as a superoxide-producing enzyme especially in ROS-induced cardiovascular pathophysiology[98]. Under a high level of oxidative stress, the peroxynitrite anion from the strong interaction between NADPH oxidase-derived superoxide and eNOS-derived NO oxidizes tetrahydrobiopterin (BH4), an essential cofactor of eNOS, leading to a reduction in NO bioactivity and a further increase in ROS production (Figure 2). ROS are the major factors in the vascular inflammatory reaction leading to the development of atherosclerotic lesions. Mitochondrial dysfunction which induces the AST process not only depends on imbalanced mitochondrial dynamics as mentioned previously,

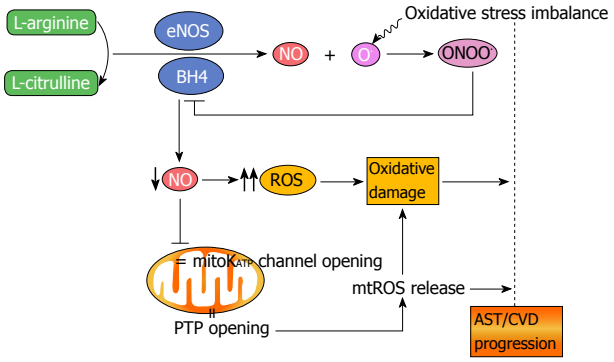

Figure 2 Proposed facilitation of AST progression *via* the opening of mitoK$_{ATP}$ channels. Decreased NO production by eNOS and increased expression of ROS induce AST. Excessive ROS with affinity for NO bind with it to produce the peroxynitrite anion ($ONOO^-$) which inhibits tetrahydrobiopterin (BH4), an essential cofactor of eNOS, leading to further reduction of NO. Significantly reduced NO not only increases ROS production, but also induces the opening of mitoK$_{ATP}$ channels, followed by activation of the permeability transition pore (PTP), leading to mtROS release and AST development. mtROS: Mitochondrial ROS; NO: Nitric oxide; mitoK$_{ATP}$: Mitochondrial ATP-sensitive K^+; eNOS: Endothelial nitric oxide synthase.

but also relies on the excess release of mtROS related to the important sources and targets of ROS in mitochondria[10,99]. Several studies have demonstrated that activation of mitoK$_{ATP}$ channels decreases ROS generation by preventing mtROS release and plays a protective role in the heart against ischemia-reperfusion injury[11,16,100] and mimics ischemic preconditioning[101]. The mitoK$_{ATP}$ channel opening improves the recovery of contractility and reduces myocardial infarct size in the reperfused heart[102,103] and could be associated with the mechanisms of mitochondrial calcium uptake prevention, the decrease in mtROS release and blockage of PTP[11,104]. As described previously, MOMP is a key participant in the machinery that controls mitochondrial fate and, consequently, cell fate. The opening of PTP causes cell death by increasing the release of cytochrome *c* and AIF[46] and triggering mtROS release *via* PTP[11]. Moreover, cytochrome *c*-catalyzed peroxidation of cardiolipin, a mitochondrial phospholipid, has been shown to reduce the binding of cytochrome *c* to the mitochondrial inner membrane and facilitate permeability of the outer membrane, which leads to mitochondrial dysfunction as well as the initial phase of the apoptotic process[105]. Recently, the role of mitoK$_{ATP}$ channel opening was further revealed by melatonin-mediated protection against heart ischemia-reperfusion injury[106]. The regulatory mechanism is related to inhibition of cardiolipin peroxidation in mitochondria and prevention of mitochondrial permeability transition and cytochrome c release[107]. Melatonin seems to have antiapoptotic actions in normal cells *via* the regulation of PTP and cytochrome *c* release[108,109] but the opposite regulation has been observed in different cell types such as tumor cells[110]. This suggests that considerable variability exists in the permeabilization of the outer membrane among different cell types treated with melatonin. Therefore, the role of mitoK$_{ATP}$ channels in the regulation of cytochrome *c* release and ROS-induced cell death needs to be considered carefully.

Although the role of the mitoK$_{ATP}$ channel-mediated mechanism in heart injury is mostly defined, its role in the occurrence and development of CVD such as AST is still unknown. Wajima *et al*[111] found that intravenous administration of BH4 has a cardioprotective effect in rats with myocardial infarction following ischemia/reperfusion, and its protective effect appeared to be involved in the opening of mitoK$_{ATP}$ channels through increased NO production. NO, as previously mentioned is one of the *antiatherogenic* factors, so we can hypothesize that NO protection in excessive ROS-induced progression of AST could result from the opening of mitoK$_{ATP}$ channels to trigger the blockage of PTP. This mechanism explains that a reduction in NO leads to a significant increase in ROS and induces oxidative injury in AST. Besides eNOS-dependent regulation, the reduction in NO inhibits mitoK$_{ATP}$ channel opening, and further increases oxidative stress caused by mtROS release (Figure 2). NO also benefits cardioprotection *via* the stimulation of mitoK$_{ATP}$ channel opening[112]. Although the activation of mitoK$_{ATP}$ channels by NO was observed in cardiomyocytes[111,113], the existence of a similar mechanism in endothelial or smooth muscle cells requires further research[108].

CONCLUSION

ROS-mediated cell apoptosis/death plays a major role in AST/CVD. Mitochondria are thought to augment intracellular oxidative damage by generating ROS and releasing cytochrome *c* and other *pro-apoptotic* proteins such as AIF. However, several defense systems in mitochondria which regulate ROS metabolism and outer membrane permeability simultaneously determine cell fate. During ROS-induced progression of AST/CVD, mitochondrial physiology including biogenesis, fusion/fission and mitoK$_{ATP}$ channel-mediated ROS release participates in related regulation *via* hyperactivation of PARP-1. PARP-1 not only promotes mitochondria-dependent cell death in injured cells and thus facilitates the development of AST/CVD, it also induces the defense functions in cells at the same time *via* the induction of mitochondrial biogenesis, hyperfusion and biofunctions in an early stage of AST/CVD progression. On the other hand, in terms of ROS/RNS imbalance as a major factor in AST/CVD occurrence, the role of mitoK$_{ATP}$ channels in ROS metabolism was further elucidated and showed that extensive ROS induce a dramatic decline in eNOS-mediated NO production, which inhibits the opening of mitoK$_{ATP}$ channels, leading to mtROS release from PTP during AST. Thus, ROS-induced progression of AST is facilitated. This review will benefit our understanding of the resistance mechanism in mitochondria against oxidative stress and offers distinct opinions on mitochondrial physiology in the progression of AST/CVD.

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