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Cardiac Response to Oxidative Stress Induced by Mitochondrial Dysfunction

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Abstract The heart works without resting, requiring enormous amounts of energy to continuously pump blood throughout the body. Because of its considerable energy requirements, the heart is vulnerable to oxidative stress caused by the generation of endogenous reactive oxygen species (ROS). Therefore, the heart has effective regulatory and adaptive mechanisms to protect against oxidative stress. Inherited or acquired mitochondrial respiratory chain dysfunction disrupts energy metabolism and causes excessive ROS production and oxidative stress. The physiological cardiac response to oxidative stress can strengthen the heart, but pathological cardiac responses or altered regulatory mechanisms can cause heart disease. Therefore, mitochondria-targeted antioxidants have been tested and some are used clinically. In this review, we briefly discuss the role of mitochondrial DNA mutations, mitochondrial dysfunction, and ROS generation in the development of heart disease and recent developments in mitochondria-targeted antioxidants for the treatment of heart disease.

Keywords Heart disease • Mitochondrial dysfunction • Mitochondrial medicine • Mitochondrial reactive oxygen species • Oxidative stress

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1 Introduction

Approximately 30 kg adenosine triphosphate (ATP) is generated and used by the human heart each day (Dorn 2013). Because the heart muscle has ATP reserves for only 20–40 strokes, it requires a highly efficient energy production system to enable continuous pumping of the blood throughout the body. Mitochondrial oxidative phosphorylation is capable of producing >30 ATP molecules per glucose molecule, providing the heart with >95% of the required ATP. To meet the energy demands of the heart, mitochondria comprise more than 30% of its mass (Page and McCallister 1973). Oxidative phosphorylation also produces various reactive oxygen species (ROS) and reactive nitrogen species (RNS), including superoxide radical anions ($O_2^{\cdot -}$), hydrogen peroxide (H_2O_2), hydroxyl radicals ($OH^{\cdot} + OH^-$), and peroxynitrite ($ONOO^-$) (Sovari et al. 2012). At physiological concentrations, ROS and RNS function as molecular messengers to modulate biological activities such as cell growth, anti-inflammatory responses, cell differentiation, and hormone synthesis. However, when produced in excess, ROS rapidly oxidize biomolecules (e.g., DNA, proteins, lipids), resulting in cellular dysfunction and cell death (Fig. 1). Therefore, effective systems for producing and clearing ROS are necessary for cell survival. For this purpose, various endogenous antioxidants including manganese or copper and zinc superoxide dismutase (MnSOD or Cu/ZnSOD), catalase, glutathione peroxidase, and peroxiredoxin existed in mitochondria or cell. An imbalance between ROS production and clearance leads to oxidative stress, which can cause a wide range of cardiovascular diseases including hypertension (de Champlain et al. 2004), coronary artery disease (Vichova and Motovska 2013), hypertrophy (Takimoto and Kass 2007), cardiomyopathy, and heart failure (Seddon et al. 2007). In this context, it is important to understand the role of ROS in both

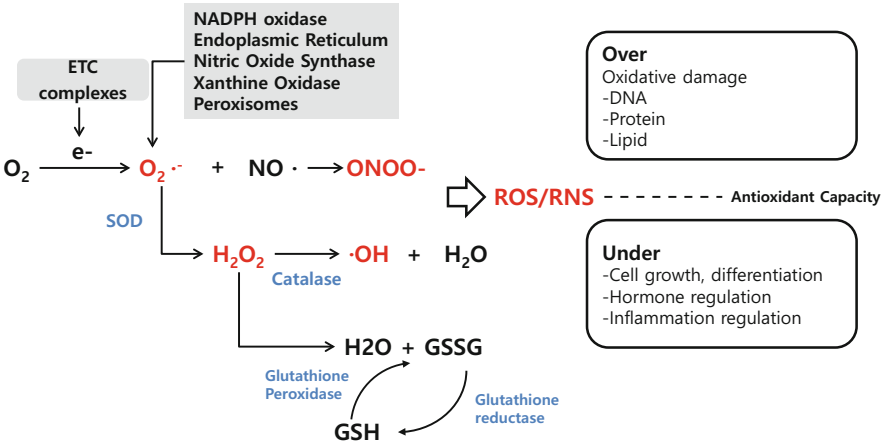

Fig. 1 Generation, clearance, and role of reactive oxygen species (ROS) and reactive nitrogen species (RNS). Sources of intracellular ROS generation are depicted in *gray boxes*; ROS/RNS are shown in *red* and antioxidants in *blue*. ROS/RNS function as signaling molecules that regulate physiological functions (*lower box*). Oxidative damage occurs when ROS/RNS production exceeds the cell's antioxidant capacity (*upper box*). *ETC* electron transport chain, *SOD* superoxide dismutase, *GSSG* oxidized glutathione, GSH, reduced glutathione

normal physiological processes and disease states and the cardiac response to ROS in ischemia/reperfusion injury, diabetes, hypertrophy, and endothelial shear stress.

2 Oxidative Stress and Mitochondrial Dysfunction

The cause-and-effect relationship between mitochondrial dysfunction and oxidative stress has not been completely elucidated. Oxidative stress induces mitochondrial dysfunction and apoptosis. As a result, the damaged mitochondrial electron transfer chain (ETC) complexes produce even more ROS, further increasing oxidative stress in the mitochondrion itself, as well as other subcellular organelles such as the endoplasmic reticulum (ER), sarcoplasmic reticulum, nucleus, and plasma membrane. The primary sources of mitochondrial ROS production are complex I and complex III; however, recent studies have implicated complexes II and IV in $O_2^{\bullet -}$ production in disease conditions (Chen and Zweier 2014). Specific cellular mechanisms underlying mitochondrial ROS generation are well explained in the excellent review by Chen and Zweier (2014).

A unique feature of mitochondria is that these organelles contain their own DNA. Human mitochondrial DNA (mtDNA) is a circular, covalently closed, double-stranded DNA molecule that contains 37 genes encoding 13 ETC component proteins, 2 ribosomal RNAs, and 22 transfer RNAs (Anderson et al. 1982). Recently, a fourteenth mitochondrial-derived peptide (humanin) was identified in

three different groups (Guo et al. 2003; Hashimoto et al. 2001; Ikonen et al. 2003). Humanin is encoded in the mitochondrial genome by the 16S ribosomal RNA gene. It has neuroprotective and cytoprotective roles and IGFBP-3 binding ability, which is involved in Alzheimer's disease, apoptosis regulation, and IGF-1 signaling (Guo et al. 2003; Hashimoto et al. 2001; Ikonen et al. 2003). Further detailed information of humanin is well described in the review of Cohen group (Yen et al. 2013).

Since mtDNA is located near the ETC, which is the major site of ROS generation, it is easily damaged, resulting in mutations or degradation (Shokolenko et al. 2009). Previously, it was thought that mtDNA lacks a DNA repair system, increasing its susceptibility to oxidative stress (Ames et al. 1995; Cadenas and Davies 2000). However, recent studies have described a mitochondrial DNA repair system similar to that of nuclear DNA, including base excision repair, single- and double-strand break repair, and mismatch repair (for review see (Alexeyev et al. 2013; Berneburg et al. 2006)). Mutations in mtDNA have been associated with a number of conditions including seizures, ataxia, cortical blindness, dystonia, diabetes, cardiomyopathy, hearing loss, kidney failure, and various cancers (DiMauro and Schon 2001; Lu et al. 2009; Wallace 1997). These findings suggest that mtDNA mutations impair mitochondrial function, thereby causing tissue-specific dysfunction or disease. This hypothesis has been supported by studies of mitochondrial dysfunction in mtDNA mutant cell lines (Ishikawa et al. 2008) and animal models (Ahlqvist et al. 2012; Dai et al. 2010; Hashizume et al. 2012; Hiona et al. 2010; Kolesar et al. 2014; Kujoth et al. 2005; Logan et al. 2014; Lu et al. 2009; Mito et al. 2013; Safdar et al. 2011; Trifunovic et al. 2004; Vermulst et al. 2008; Yamada et al. 2012).

Several research groups have generated mitochondrial DNA polymerase gamma mutant ($Polg^{D257A}$) mice (Kujoth et al. 2005; Trifunovic et al. 2004). These mice show a high frequency of mtDNA mutations in multiple tissues and a premature aging phenotype, with decreased oxidative phosphorylation and increased oxidative stress (Kujoth et al. 2005; Logan et al. 2014; Trifunovic et al. 2004; Trifunovic et al. 2005; Vermulst et al. 2008). The $Polg^{D257A}$ mice also exhibit sarcopenia, muscle weakness, cardiac hypertrophy, and dilatation, which are associated with significant defects in ETC complex I, III, and IV assembly (Dai et al. 2010; Hiona et al. 2010; Kolesar et al. 2014; Yamada et al. 2012). Similarly, a recently generated specific mtDNA mutation in the gene encoding NADH dehydrogenase subunit 6 (*ND6*) resulted in deficient complex I activity and ROS overproduction in a mouse tumor cell line, enhancing its metastatic potential (Ishikawa et al. 2008). Mice with the *ND6* G13997A mutation also showed deficient complex I activity and excessive ROS production in addition to lactic acidosis, diabetes, multiple tissue defects, and an elevated risk of lymphoma (Hashizume et al. 2012). Mutations in genes encoding proteins involved in mtDNA replication (e.g., mitochondrial transcription factor A (Wang et al. 1999), mitochondrial helicase TWINKLE (Milenkovic et al. 2013)) or the regulation of oxidative phosphorylation (e.g., adenine nucleotide transporter 1 (Narula et al. 2011)) result in the depletion of mtDNA, subsequent mitochondrial dysfunction, and cardiac diseases including hypertrophy, dilated cardiomyopathy, and conduction blocks (Kujoth et al. 2007).

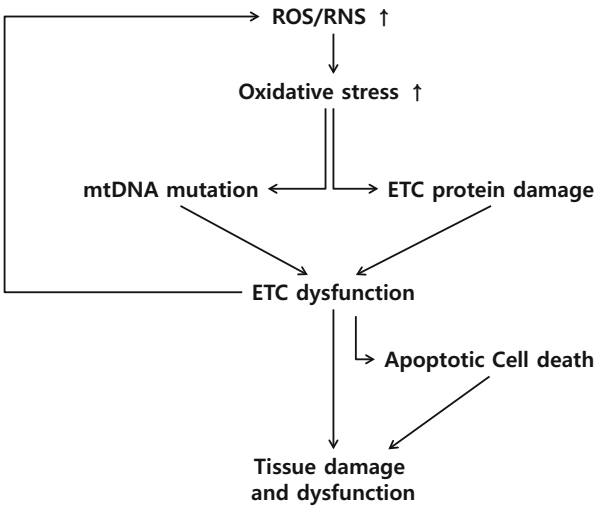

Fig. 2 Oxidative stress-induced mtDNA mutations result in mitochondrial dysfunction and tissue damage. Production of ROS/RNS that exceeds the cell's antioxidant capacity increases intracellular oxidative stress. The resulting damage to ETC proteins and mtDNA results in impaired oxidative phosphorylation and ROS overproduction, inducing apoptosis and causing tissue damage. *ETC* electron transport chain, *RNS* reactive nitrogen species, *ROS* reactive oxygen species

Conversely, overexpression of TWINKLE attenuates cardiac fibrosis and heart failure in mice with pressure overload hypertrophy (Tanaka et al. 2013). These results support the idea that oxidative stress increases mtDNA mutations and damages ETC proteins, thereby impairing oxidative phosphorylation and ultimately leading to cell death and tissue failure (Fig. 2).

3 Mitochondrial Quality Control System: Mitophagy and ROS

In addition to endogenous antioxidants, mitophagy acts as a mitochondrial quality control system to protect the cell. Mitophagy involves the autophagosomal degradation of abnormal mitochondria containing damaged components or producing excessive ROS. Pathological heart conditions including I/R injury, diabetic cardiomyopathy, and cardiac hypertrophy cause oxidative damage to cardiac mitochondria, leading to ROS overproduction, activation of inflammatory signals, and local tissue injury via NF-kappa B and NOD-like receptor family 3 (NLRP3) signaling (Gottlieb et al. 2011). In addition, mtDNA released from damaged mitochondria activates the NLRP3 inflammasome. By decreasing the number of damaged mitochondria, mitophagy decreases ROS production and inflammation to prevent further cardiac damage. Conversely, impairment of autophagy increases the number of

damaged mitochondria in cardiomyocytes, exacerbating inflammation, oxidative stress, and heart damage (Gottlieb et al. 2011). Autophagy is induced by starvation through AMPK signaling, and ROS play an important role in autophagy and mitophagy (Chen et al. 2009; Gottlieb and Carreira 2010; Korolchuk et al. 2010; Scherz-Shouval et al. 2007). A recent study by Scherz-Shouval demonstrated that starvation stimulates the formation of hydroperoxide, which is essential for autophagy, whereas antioxidant treatment prevents autophagosome formation and protein degradation (Scherz-Shouval et al. 2007). Excessive mitophagy can impair cardiac function; therefore, mitophagy must be carefully regulated to maintain normal heart function (Tang et al. 2015).

4 Non-mitochondrial Cytosolic ROS Sources

In addition to mitochondria, sources of ROS generation include NADPH oxidase (Nox) family (Griendling et al. 2000), ER (Dickinson and Chang 2011; Gross et al. 2006), nitric oxide synthase (NOS) (Landmesser et al. 2003; Umar and van der Laarse 2010; Zhang et al. 2012), xanthine oxidase (Kelley et al. 2010), and peroxisomes (Antonenkov et al. 2010), depending on the tissue and cell type. These intracellular ROS sources are closely linked, and the cumulative ROS levels modulate heart function under physiological and pathological conditions.

4.1 Cardiac NADPH Oxidase

As one of the major cellular sources of ROS, cardiac Nox plays an important role in a wide range of physiological and pathological processes including hypoxic adaptation, hypertrophy, apoptosis, and heart failure (Brandes et al. 2010). In particular, the isoforms Nox2 and Nox4 appear to have major roles within the myocardium, with Nox2 producing superoxide and Nox4 generating only hydrogen peroxide (Zhang et al. 2012). Nox2- and Nox4-derived $O_2 \cdot^-$ and H_2O_2 are involved in the growth response of vascular smooth muscle cells, cardiac cells, and fibroblasts; JNK/p38 MAPK and Akt signaling; and the expression of cardiovascular-related genes involved in hypertrophy and development of atherosclerosis and hypertension (Griendling et al. 2000).

4.2 Endoplasmic Reticulum: Ero1p and Nox4

The ER also produces ROS through Ero1p, an enzyme that transfers electrons from thiol substrates to molecular oxygen (Gross et al. 2006). In addition, Nox4 generates H_2O_2 from $O_2 \cdot^-$ in the ER by two-electron reduction (Chen et al. 2008). ROS

production and oxidative stress are closely related to ER stress and the unfolded protein response, which regulates intracellular signaling transduction and cell death (Santos et al. 2009). A recent study suggested that under ER stress, ROS production is increased by the Nox family of enzymes, which may contribute to the development of hypertension and other cardiovascular diseases (Santos et al. 2014). In cardiomyocytes, Nox4 mediates autophagy in response to energy stress by stimulating the protein kinase RNA-activated-like ER kinase signaling pathway (Sciarretta et al. 2013).

4.3 Nitric Oxide Synthases

Nitric oxide synthases produce NO, a highly reactive signaling molecule, through oxidative conversion of L-arginine to L-citrulline. In the heart, neuronal NOS and endothelial NOS constitutively produce NO in distinct subcellular locations, whereas inducible NOS is upregulated under certain pathological conditions such as I/R injury (Umar and van der Laarse 2010). Tetrahydrobiopterin is an essential cofactor for NO production by all three NOS isoforms. In the absence of tetrahydrobiopterin, NOS functions in an uncoupled state, producing ROS instead of NO. The lower NO bioavailability and increased oxidative stress in the heart lead to pathological cardiac remodeling (hypertrophy, fibrosis) and heart failure (Landmesser et al. 2003; Umar and van der Laarse 2010; Zhang et al. 2012).

4.4 Xanthine Oxidase

Another major source of ROS production in the heart is xanthine oxidase, which is converted from xanthine dehydrogenase by the oxidation of sulfhydryl residues or by limited proteolysis. Xanthine oxidase produces both $O_2^{\bullet -}$ and H_2O_2 through the oxidative hydroxylation of purine substrates. Under inflammatory conditions, xanthine oxidase levels are increased, resulting in excess ROS formation and oxidative damage in the cardiovasculature. Accordingly, xanthine oxidase inhibition attenuates oxidative damage in heart disease (Kelley et al. 2010; Kumar et al. 2011; Zhang et al. 2012).

4.5 Peroxisomes

Peroxisomes are multifunctional organelles that play an important role in maintaining oxidative balance. Peroxisomes degrade various biomolecules through alpha- and beta-oxidation, alone or in cooperation with mitochondria, producing H_2O_2 as a metabolic by-product (Antonenkov et al. 2010). The H_2O_2 is normally

broken down into water and oxygen by catalase or peroxidases; however, impairment of the antioxidant system allows ROS accumulation and subsequent damage to proteins, lipids, DNA, and organelles, resulting in neurodegenerative disease, type 2 diabetes, and cardiovascular disease (Fransen et al. 2012; Terlecky et al. 2012).

5 Cardiac Response to Oxidative Stress

Diseases caused by mtDNA mutations can be categorized as inherited or acquired mitochondrial disorders, depending on when the mtDNA mutation occurred. Approximately 40 different congenital mitochondrial diseases have been identified; they result in symptoms by 10 years of age and are associated with multiple tissue defects. The prevalence of mitochondrial mutations or disease is 4.7 in 100,000 in children and 11.5 in 100,000 for all ages (Schaefer et al. 2004). Inheriting a large mtDNA deletion or mutation results in one of the mitochondrial myopathies, which are functional defects of the mitochondrial respiratory chain, primarily affecting complexes I, III, and IV (Holt et al. 1988). Specific congenital conditions caused by mtDNA mutations include Kearns–Sayre syndrome, chronic progressive external ophthalmoplegia, mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes, myoclonic epilepsy with ragged-red fibers, neurogenic weakness with ataxia and retinitis pigmentosa, and Leigh syndrome (DiMauro and Davidzon 2005). These inherited diseases are associated with a wide range of heart dysfunctions including left ventricular hypertrophy, cardiac fibrosis, systo-diastolic dysfunction, and impaired conduction (Anan et al. 1995; Fayssoil 2009; Galetta et al. 2014; Thorburn and Rahman 1993), demonstrating the significant relationship between mtDNA mutations and heart disease in humans.

The prevalence of acquired mitochondrial dysfunction and related diseases (e.g., type 2 diabetes, Parkinson's disease, Alzheimer disease, cardiovascular disease) is considerably higher than that of inherited mitochondrial diseases. In acquired mitochondrial diseases, aging and oxidative stress lead to the accumulation of mtDNA mutations that impair oxidative phosphorylation. In turn, the damaged ETC further increases oxidative stress and mtDNA mutations, resulting in a vicious circle. Because the heart is the organ most dependent on mitochondrial oxidative phosphorylation, mitochondrial dysfunction often manifests as cardiomyopathy. In animal models, mtDNA mutations/deletions in the heart commonly cause defects in mitochondrial oxidative phosphorylation and severe cardiomyopathies, including dilated cardiac dysfunction (Zhang et al. 2000), cardiac hypertrophy (Esposito et al. 1999; Graham et al. 1997), and atrioventricular heart conduction blocks (Li et al. 2000b; Wang et al. 1999). These findings suggest that the integrity of mtDNA and mitochondrial oxidative phosphorylation are essential for normal cardiac function.

Age-dependent mitochondrial dysfunction and cardiomyopathy are closely associated with an imbalance between mitochondrial ROS production and

detoxification (Ames et al. 1995; Bratic and Trifunovic 2010; Cui et al. 2012; Dai et al. 2012). In the aging heart, increased ROS production is accompanied by decreased complex I and IV activity and state 3 respiration. This ETC impairment directly increases mitochondrial ROS generation (Dai and Rabinovitch 2009). However, the effect of age on antioxidant capacity or enzyme activity remains unclear (Rikans and Hornbrook 1997). It is generally accepted that antioxidant capacity increases through an adaptive response to aging-associated oxidative stress, but this increased capacity is not sufficient to prevent overwhelming oxidative stress and mitochondrial damage (Wei and Lee 2002). Thus, increased ROS generation in the aging heart induces cardiac abnormalities such as ventricular hypertrophy (Lakatta 2003), fibrosis, and diastolic dysfunction (Khouri et al. 2004). These age-related cardiac abnormalities are significantly attenuated in mice overexpressing mitochondrial catalase, providing further evidence for the role of elevated oxidative stress in mitochondrial dysfunction-induced heart disease (Dai and Rabinovitch 2009).

5.1 Ischemia/Reperfusion Injury

Loss of blood or coronary artery blockage can reduce the supply of blood to the cardiac myocardium. The resulting lack of oxygen and glucose (i.e., ischemia) eventually causes irreversible cardiac cell death, myocardial infarction, and cardiac dysfunction. Cardiomyocyte cell death is the result of depolarization of mitochondrial membrane potential, decreased oxidative phosphorylation and ATP generation, and increased ROS generation (Kim et al. 2011). Restoration of the blood supply (i.e., reperfusion) by thrombolytic therapy or percutaneous coronary intervention can reduce cardiac damage. However, the process of reperfusion can also induce or exacerbate cardiomyocyte death in a process known as ischemia/reperfusion (I/R) injury (Hausenloy and Yellon 2013). During the first few minutes of reperfusion, ROS overproduction and Ca^{2+} overload open the mitochondrial permeability transition pore, leading to cardiomyocyte apoptosis (Hausenloy et al. 2003). Ischemia/reperfusion strongly increases ROS generation in various mitochondrial sites including the Krebs cycle (e.g., aconitase) and electron transfer chain complexes I, II, III, and IV via site-specific mechanisms (Chen and Zweier 2014). Detailed information on the targets, roles, and mechanisms of mitochondrial ROS generation during I/R injury were well documented in the recent review by Chen and Zweier (2014).

In 1986, Murry et al. demonstrated that brief (<5 min) and repeated (four times) ischemic episodes before prolonged ischemia significantly attenuate myocardial infarction in dogs (Murry et al. 1986). This ischemic preconditioning is an endogenous cardioprotective response against I/R injury mediated through the activation of G-protein-coupled receptors, ATP-dependent potassium channel (K_{ATP}), and various protein kinases including protein kinase C, tyrosine kinase, and the mitogen-activated protein kinase (MAPK) family (Das and Das 2008) or

inactivation of proapoptotic p53 signaling (Mocanu and Yellon 2003). Ischemic preconditioning also inhibits opening of the mitochondrial permeability transition pore by preserving mitochondrial membrane potential and activity of NADH dehydrogenase and cytochrome c oxidase and by reducing ROS production (Halestrap et al. 2007). Despite its powerful cardioprotective effect, ischemic preconditioning is difficult to apply in patients with acute coronary disease. In 2003, Zhao et al. reported that brief ischemic episodes during early reperfusion (i.e., ischemic postconditioning) attenuated myocardial infarction in dogs, similar to the effects of ischemic preconditioning (Zhao et al. 2003). Furthermore, preconditioning and postconditioning can also protect remote regions and distant organs (i.e., remote ischemic pre- or postconditioning) (Kerendi et al. 2005; Przyklenk et al. 1993). These findings opened the possibility of clinical applications (Bousselmi et al. 2014; Hausenloy and Yellon 2009). For example, ischemic preconditioning has been used in open heart and coronary bypass surgery to preserve cardiac function and reduce tissue damage (Lu et al. 1997; Szmagala et al. 1998). Regarding ischemic postconditioning, three clinical trials in children and adults with cardiovascular disease have reported positive results (Luo et al. 2007; Luo et al. 2008a; Luo et al. 2008b). The discovery of signaling pathways underlying ischemic conditioning has provided novel pharmacological targets for the development of pharmacological agents including adenosine, GLP-1, atrial natriuretic peptide, and cyclosporine A (Hausenloy and Yellon 2009).

Bursts of ROS during reperfusion impair cellular defense mechanisms against oxidative stress. In the first stage, hydrophilic antioxidants (e.g., ascorbate and glutathione disulfide) are readily oxidized by increased ROS; further oxidative stress diminishes lipophilic antioxidants (e.g., vitamin E and ubiquinol-9) (Haramaki et al. 1998). Bursts of ROS also oxidize thiol groups and lipids, leading to membrane damage and necrosis. Severe oxidative stress inhibits the activity of mitochondrial superoxide dismutase (SOD). Results of a clinical study showed that increased oxidative stress during I/R injury is associated with transient left ventricular dysfunction or stunning (Ferrari et al. 2004). Because increased oxidative stress during I/R is a major cause of myocardial infarction, the ability of antioxidants to protect against I/R-induced cardiac damage has been tested (Marczin et al. 2003). Several studies have shown that supplementation with vitamin C, vitamin E, or the glutathione (GSH) precursor *N*-acetylcysteine limits oxidative stress and enhances cardiac function after I/R in animals and patients (Dingchao et al. 1994; Ferrari et al. 1991; Mickle et al. 1991).

Cytosolic Cu/ZnSOD and mitochondrial MnSOD are both antioxidant enzymes that convert superoxide to H_2O_2. However, the cardioprotective effect of MnSOD after I/R is significantly higher than that of Cu/ZnSOD because of its location (Asimakis et al. 2002; Jones et al. 2003). These findings suggest a site-specific role for ROS and indicate that antioxidant intervention in I/R injury should target mitochondrial ROS (Marczin et al. 2003).

5.2 Cardiac Hypertrophy and Fibrosis

Cardiac hypertrophy (CH) is a morphologic adaptation to work overload and is associated with an abnormal response to beta-adrenergic stimulation. Oxidative stress is considered a major cause of CH, which strongly increases the risk of heart failure, cardiac arrhythmia, and sudden cardiac death (Maulik and Kumar 2012). In a well-designed study by Dai et al. (2011), overexpression of mitochondria-targeted catalase, but not cytosolic catalase, was shown to protect against CH, fibrosis, and mitochondrial damage in mouse models of cardiomyopathy. Overexpression of mitochondria-targeted catalase prevented the accumulation of mitochondrial protein carbonyls, DNA deletions, increased autophagy, and activation of MAP kinase extracellular signal-regulated kinase1/2 in the heart. These findings demonstrated that mitochondrial ROS are not just involved in cellular damage but have important roles in cell signaling.

Fibrosis is caused by pathological remodeling of the extracellular matrix (ECM) mediated by matrix metalloproteinases (MMPs) and tissue inhibitor of metalloproteinases (TIMPs) (Spinale 2007). Cardiac ECM provides physical connections and enables signal transduction among cardiomyocytes, cardiac fibroblasts, and blood vessels within the myocardium. Cardiac ECM undergoes remodeling in response to diverse stimuli in pathological cardiac conditions, such as myocardial infarction and overload and dilated cardiomyopathy (Spinale 2007). The major components of ECM include collagen types I and III, IV, V, and VI and fibronectin, laminin, elastin, fibrillin, proteoglycans, and glycoproteins. These ECM proteins are produced primarily by cardiac fibroblasts (Fan et al. 2012). Cardiac fibroblasts also regulate ECM homeostasis through the production of MMPs and TIMPs, which degrade ECM and inhibit ECM degradation, respectively (Spinale 2007). Because MMP activation and overexpression are common in heart disease, the inhibition of MMP expression/activity has been investigated to attenuate maladaptive cardiac remodeling. Selective MMP inhibitors such as PG11680 have been shown to prevent myocardial remodeling after myocardial infarction (Hudson et al. 2006), and inhibition of the renin–angiotensin–aldosterone pathway decreases MMP levels and cardiac remodeling (Li et al. 2000a; Sakata et al. 2004). Together with various cytokines, ROS-mediated oxidative stress is a potential activator of MMPs in the heart (Grieve and Shah 2003). ROS activates MMPs by upregulating MMP expression (Nian et al. 2004; Siwik et al. 2001; Wainwright 2004) and through posttranslational modification and activation of pro-MMPs (Fu et al. 2001; Fu et al. 2004; Yoon et al. 2002). Antioxidants have been shown to significantly reduce MMP activity, diabetes-induced cardiac dysfunction, and hypertension-induced cardiac hypertrophy (Bilginoglu et al. 2009; Rizzi et al. 2013). These findings demonstrate the important role of ROS in ECM remodeling in patients with heart disease.

5.3 Diabetic Cardiomyopathy

Diabetes is a metabolic disease caused by abnormal energy metabolism in multiple organs including the pancreas, heart, liver, and skeletal muscle. Although the primary cause of diabetes is unknown, mitochondrial dysfunction may be a major contributor to insulin resistance in major organs (including skeletal muscle and liver) and defects in insulin secretion by pancreatic beta cells (Lowell and Shulman 2005). In particular, abnormal mitochondrial fatty acid oxidation is thought to increase the accumulation of intracellular fatty acyl coenzyme As and diacylglycerol, which activate signaling pathways inhibiting insulin-stimulated glucose transport activity. This hypothesis was supported by a clinical study demonstrating that elderly individuals with severe insulin resistance in skeletal muscle had higher triglyceride levels in muscle and liver and decreased mitochondrial oxidative phosphorylation activity (Petersen et al. 2003). In addition, the insulin-resistant subjects had fewer mitochondria in muscle cells and decreased expression of nuclear-encoded genes that regulate mitochondrial biogenesis, such as peroxisome proliferator-activated receptor gamma coactivator 1alpha and 1beta (PGC-1alpha and PGC-1beta) (St-Pierre et al. 2003; Wu et al. 1999).

The pancreas produces and releases insulin in response to blood glucose levels. In obesity, insulin deficiency is caused by beta cell mass that is insufficient to meet metabolic demands due to the inadequate proliferation or apoptosis of beta cells. Because apoptosis is regulated primarily by mitochondria, mitochondrial dysfunction is a major cause of beta cell loss. Mitochondrial dysfunction also reduces ATP levels in beta cells, which inhibits the opening of K_{ATP} channels and prevents membrane depolarization, a critical signal for the opening of voltage-gated calcium channels required for insulin secretion (Maechler and Wollheim 2001). Thus, mitochondrial dysfunction contributes to both insulin deficiency and insulin resistance in the development of diabetes.

Cardiovascular disease is the most common complication and primary cause of death in patients with diabetes mellitus. Diabetes significantly increases the risk of heart disease and vulnerability to pressure overload or ischemia. Diabetic cardiomyopathy (DCM) is ventricular dysfunction occurring in diabetic patients who do not have severe coronary artery disease or hypertension (Bell 2003; Bugger and Abel 2010). Left ventricular hypertrophy and systolic/diastolic dysfunctions are often observed in diabetes patients, along with hyperglycemia, hyperlipidemia, increased activation of protein kinase C and the renin–angiotensin system, and aldosterone-induced fibrosis (Boudina and Abel 2010; Hayat et al. 2004). Potential mechanisms underlying the development of DCM include disruptions in intracellular ion homeostasis and energy metabolism, the polyol pathway, and enhanced oxidative stress (Wold et al. 2005). In addition, mitochondrial dysfunction has been suggested as a major contributor to the development of DCM in various animal and human studies (Bugger and Abel 2010). Studies in animal models have revealed impaired state 3 mitochondrial oxygen consumption, decreased activity of respiratory chain complexes, and defects in mitochondrial ultrastructure and proliferation

in the heart (Boudina et al. 2005; Duncan et al. 2007; Kuo et al. 1983). Similarly, patients with type 2 diabetes show abnormal ATP generation, fatty acid utilization, and oxidative phosphorylation in cardiac mitochondria (Anderson et al. 2009; Peterson et al. 2004; Scheuermann-Freestone et al. 2003).

Besides mitochondrial dysfunction, factors that increase oxidative stress in diabetes include increased fatty acid oxidation, polyol pathway flux, advanced glycation end products, and activation of protein kinase C-dependent NADPH oxidase (Watanabe et al. 2010; Wold et al. 2005). As in other cardiomyopathies, increased ROS leads to mitochondrial dysfunction, cardiac cell death, increased fibrosis, and contractile dysfunction in DCM; however, these effects can be attenuated by the overexpression of MnSOD, catalase, or metallothionein (Cai et al. 2006; Ye et al. 2003; Ye et al. 2004). Interestingly, increased mitochondrial ROS generation reduces cardiac efficiency by upregulating the expression and activity of mitochondrial uncoupling proteins in DCM (Boudina et al. 2005; Echtay et al. 2002; Murray et al. 2005). Proper coupling of oxygen consumption to ATP generation is essential for cardiac contraction/relaxation. Overexpression or activation of uncoupling protein 3 promotes proton leak across the mitochondrial membrane, decreasing ATP generation and increasing oxygen consumption. This is known as cardiac inefficiency and is a major cause of cardiac contractile dysfunction in DCM (Bugger and Abel 2010). Taken together, these findings demonstrate the multiple roles of oxidative stress in the development of DCM.

5.4 Benefits of Reactive Oxygen Species During Exercise

Regular exercise has beneficial effects on the cardiovascular system, significantly decreasing the risk of cardiovascular disease. However, skeletal muscles generate ROS during exercise, which increases oxidative stress. The health consequences of exercise-induced oxidative stress remain unclear (Powers and Jackson 2008). The first direct evidence for exercise-induced ROS production and subsequent tissue damage was provided by Davies et al. (1982). This was followed by studies demonstrating that vitamin E supplementation reduces exercise-induced damage in skeletal and cardiac muscles (Jackson et al. 1985; Kumar et al. 1992). However, recent studies have shown that exercise-induced ROS exert beneficial effects (Gomez-Cabrera et al. 2005; Gomez-Cabrera et al. 2008; Kang et al. 2009; Meilhac et al. 2001; Ristow et al. 2009). Skeletal and cardiac muscles show increased antioxidant capacity after moderate oxidative stress due to acute or chronic exercise, which strengthens cellular defense mechanisms against severe oxidative stress due to I/R injury and age-related cardiac dysfunction (Bowles et al. 1992; Gomez-Cabrera et al. 2008; Kwak et al. 2006; Starnes et al. 2007). In addition, ROS signaling appears to be essential for exercise-induced enhancement of PGC1-alpha-mediated mitochondria biogenesis (Kang et al. 2009), MAPK–nuclear factor kappa B signaling (Gomez-Cabrera et al. 2005), insulin sensitivity (Ristow et al. 2009), and prevention of atherosclerosis (Meilhac et al. 2001). Thus, although

high levels of oxidative stress can damage cellular components, low-to-moderate levels of oxidative stress regulate gene expression, cell signaling pathways, and skeletal muscle force production (Powers and Jackson 2008).

5.5 *Pathophysiological Role of Mitochondrial ROS in Endothelial Cells*

Coronary blood flow is a key modulator of cardiac function. In the coronary artery, mitochondrial H_2O_2 acts as a vasodilator to increase the activity of the large-conductance (119 pS) $Ca2^+$- and voltage-activated K^+ (BKCa) channel (Barlow and White 1998). The H_2O_2 is produced in the endothelium by shear stress and is therefore considered an endothelium-derived hyperpolarizing factor (Chen and Zweier 2014). Mitochondrial-derived ROS (mtROS) also activates endothelial NOS through AMPK signaling, which modulates vascular relaxation (Quintero et al. 2006). Another mitochondria-mediated vasoregulation component, mitochondrial membrane potential depolarization, regulates vascular tone by activating nitric oxide synthase (Katakam et al. 2013). In isolated rat cerebral arteries, membrane potential depolarization was induced by activating the mitochondrial ATP-sensitive potassium channel, demonstrating its key role in vascular tone modulation through ROS-dependent or ROS-independent mechanisms. These findings indicate the importance of mtROS in vascular endothelium.

However, overproduction of mtROS in endothelial cells, smooth muscle cells, and macrophages is a major cause of atherosclerosis. ROS induces oxidative modification of phospholipids, resulting in increased transport of oxidized low-density lipoprotein into the artery wall, damaging endothelial cells, and eventually causing atherosclerosis (Madamanchi et al. 2005). Oxidative stress-mediated vascular dysfunction is frequently observed in patients with diabetes mellitus (Mackenzie et al. 2013). Although antioxidant treatment of atherosclerosis in humans has not been successful to date (Lonn et al. 2005), in vitro studies and experiments in animal models support the therapeutic potential of antioxidant therapy in atherosclerosis and metabolic disease (Mackenzie et al. 2013; Mercer et al. 2012).

6 Cardioprotective Effects of Mitochondria-Targeted Antioxidants

Various therapies for cardiomyopathy and ischemic heart disease target mitochondrial dysfunction (Walters et al. 2012). These include inhibitors of mitochondrial permeability transition pore opening, activators of mitochondrial K_{ATP} channel and respiratory chain complexes, AMPK signaling modulators, and mitochondrial

Table 1 Mitochondria-specific antioxidant agents

Agent	Remark	Clinical status	Reference
MitoQ	Coenzyme Q10 derivative	Phase II (NASH)	Jauslin et al. (2003)
MitoE	Vitamin E derivative	Not yet tested	Jauslin et al. (2003)
MitoPBN	Nitrone radical trap alpha-phenyl-tert-butylnitrone	Not yet tested	Maples et al. (2004)
MitoPeroxidase (ebselen analog)	Increases mitochondrial glutathione activity	Not yet tested	Filipovska et al. (2005)
MitoGSH	Increases mitochondrial glutathione activity	Not yet tested	Sheu et al. (2006)
MitoNAC	Increases mitochondrial glutathione activity	Not yet tested	Sheu et al. (2006)
SS31 (Bendavia)	Peptide antioxidants targeted to the inner mitochondrial membrane	Phase II (AMI)	Szeto (2006)
SS02		Preclinical	Szeto (2006)
Edaravone	Used for brain and cardiac I/R injury	In use (stroke, Japan) phase IV (AMI)	Higashi et al. (2006)
NecroX	ROS/RNS scavenger, mitochondria Ca^{2+} uniporter blocker	Phase II (STEMI)	Kim et al. (2010), Thu et al. (2012)
Phenolic antioxidant prodrugs	Mitochondria beta-oxidation-mediated drug delivery	Not yet tested	Roser et al. (2010)

I/R ischemia/reperfusion, *RNS* reactive nitrogen species, *ROS* reactive oxygen species, *STEMI* ST-segment elevation in myocardial infarction, *AMI* acute myocardial infarction, *NASH* nonalcoholic steatohepatitis

antioxidants (Armstrong 2007; Szewczyk and Wojtczak 2002; Toogood 2008; Walters et al. 2012). The primary goal of antioxidant treatments, whether mitochondria-targeting or non-mitochondria-targeting, is to decrease excessive ROS and oxidative stress in order to prevent functional loss of intracellular organelles and the cell itself. The primary reason for developing mitochondria-targeting antioxidants is the biological importance of the mitochondrion, which is the control center for energy metabolism, apoptosis, Ca^{2+} homeostasis, and cell signaling (Sheu et al. 2006). Large-scale clinical studies including the Heart Outcomes Prevention Evaluation (HOPE) study (Yusuf et al. 2000) and the Heart Protection Study (HPS) (MRC/BHF 1999) have demonstrated the ineffectiveness of conventional antioxidant therapies in patients, perhaps because these antioxidants are not efficiently taken up by mitochondria (Murphy and Smith 2007). To solve problem, a number of mitochondria-targeted antioxidants have been developed. Accumulated evidence shows that mitochondria-specific antioxidants are more effective than nonspecific antioxidants in their mitochondria protective role (Sheu et al. 2006; Smith and Murphy 2011). Here, we briefly describe a number of mitochondria-targeted antioxidants with their current clinical status (Table 1).

MitoQ and MitoE are derived from coenzyme Q10 and vitamin E, respectively. The antioxidant effects of these compounds are 100- to 350-fold more potent than their untargeted analogs (idebenone and Trolox), preventing cell death from endogenous oxidative stress in cultured fibroblasts of patients with Friedreich ataxia (Jauslin et al. 2003). The safety and effectiveness of MitoQ were demonstrated in a phase II clinical trial (Smith and Murphy 2010). MitoPBN, a mitochondria-targeted nitrone radical trap alpha-phenyl-tert-butylnitrone, provides neuroprotection against ischemic stroke by blocking oxidative stress-induced lipid peroxidation (Maples et al. 2004). MitoGSH is a choline ester of GSH, a nonprotein thiol that serves as an endogenous antioxidant. Although mitochondrial GSH comprises only 15% of total cellular GSH, MitoGSH provides cytoprotective effects (Sheu et al. 2006). Similarly, a mitochondria-targeted analog of ebselen (MitoPeroxidase) (Filipovska et al. 2005) and a choline ester of *N*-acetylcysteine (MitoNAC) were developed to increase GSH activity in mitochondria and decrease oxidative stress-induced mitochondrial depolarization and apoptosis (Sheu et al. 2006). The Szeto–Schiller peptides (SS02 and SS31) represent a novel class of cell-permeable antioxidants that target the inner mitochondrial membrane (Szeto 2006). These peptide antioxidants scavenge mitochondrial ROS and inhibit mitochondrial permeability transition, thereby suppressing oxidative stress-induced apoptosis and necrosis in isolated mitochondria, cell cultures, and ischemic tissue (Cho et al. 2007; Szeto 2006). Edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one) is a strong free radical scavenger developed by Mitsubishi-Tokyo Pharmaceuticals Inc. Because of its strong mitochondrial antioxidant effect, edaravone is widely used in patients with brain and cardiac I/R injury and may be useful for improving endothelial function in patients with cardiovascular disease (Higashi et al. 2006). NecroX compounds, developed by LG Life Science Ltd., have been shown to protect cultured cardiac cells and heart mitochondria from cardiotoxic agents (tertiary butyl hydroperoxide, sodium nitroprusside, and doxorubicin), hypoxic injury, and I/R injury (Kim et al. 2010; Lee et al. 2014; Thu et al. 2012). Our recent study demonstrated that NecroX-5 inhibits the mitochondria Ca^{2+} uniporter during hypoxia/reoxygenation to prevent mitochondrial Ca^{2+} overload-induced apoptosis (Thu et al. 2012). Finally, biotransformation of phenolic antioxidant prodrugs by the mitochondrial beta-oxidation pathway protects against I/R injury in isolated cardiomyocytes (Roser et al. 2010).

7 Conclusions and Perspectives

Accumulated evidence clearly demonstrates that ROS-induced oxidative stress in mitochondria plays an important role in the development of heart disease (Fig. 3). For that reason, mitochondria-targeted therapies represent a promising clinical strategy for the treatment of heart disease. However, despite promising results in animals (Mercer et al. 2012), the effects of antioxidant treatment in patients with cardiovascular disease have been inconsistent (Lonn et al. 2005). This discrepancy

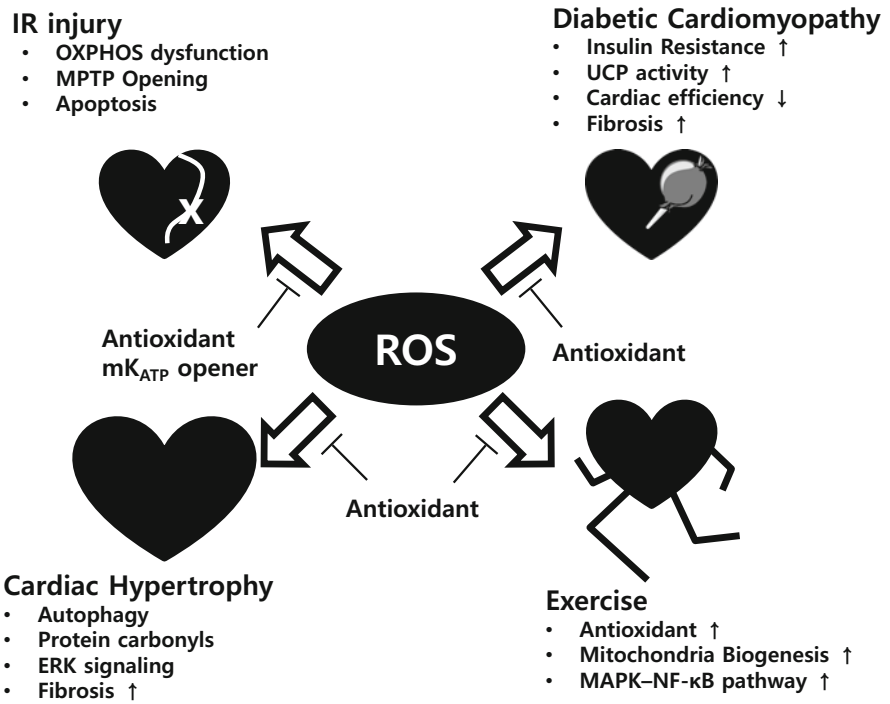

Fig. 3 Pathophysiological response of heart to reactive oxygen species (ROS). ROS mediates cardiac responses to exercise and various pathophysiological stimuli such as I/R injury, cardiac hypertrophy, and diabetic cardiomyopathy. A number of antioxidant treatments attenuate these cardiac responses, providing evidence for the mediatory role of ROS. Non-antioxidant treatments are also effective in specific conditions. For example, in I/R injury, a mitochondrial K_{ATP} channel opener also decreases oxidative stress and apoptosis in the heart. *ERK* extracellular signal-regulated kinase, *I/R* ischemia/reperfusion, *mK_{ATP}* mitochondrial ATP-dependent potassium channel, *MAPK* mitogen-activated protein kinase, *MPTP* mitochondrial permeability transition pore, *NF-kappa B* nuclear factor kappa B, *OXPHOS* oxidative phosphorylation, *UCP* uncoupling protein

may be due to the timing of treatment (before disease onset vs. after onset), antioxidant bioavailability, effects of other treatments (e.g., aspirin, angiotensin receptor blockers, statins), and, in particular, the ability to target the mitochondria (Firuzi et al. 2011; Mitra et al. 2011). An efficient antioxidant delivery system may therefore be needed to restore the function of damaged mitochondria. The ideal therapeutic agent would be selectively taken up by mitochondria within the target organs, where it can prevent oxidative damage and be recycled back to the active antioxidant form. In addition, it should be a pharmaceutically tractable and stable small molecule with acceptable oral bioavailability (Murphy and Smith 2007; Smith and Murphy 2011).

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