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Crosstalk between mitogen-activated protein kinases and mitochondria in cardiac diseases: therapeutic perspectives

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Abstract

Cardiovascular diseases cause more mortality and morbidity worldwide than any other diseases. Although many intracellular signaling pathways influence cardiac physiology and pathology, the mitogen-activated protein kinase (MAPK) family has garnered significant attention because of its vast implications in signaling and cross-talk with other signaling networks. The extensively studied MAPKs ERK1/2, p38, JNK, and ERK5, demonstrate unique intracellular signaling mechanisms, responding to a myriad of mitogens and stressors and influencing the signaling of cardiac development, metabolism, performance, and pathogenesis. Definitive relationships between MAPK signaling and cardiac dysfunction remain elusive, despite 30 years of extensive clinical studies and basic research of various animal/cell models, severities of stress, and types of stimuli. Still, several studies have proven the importance of MAPK cross-talk with mitochondria, powerhouses of the cell that provide over 80% of ATP for normal cardiomyocyte function and play a crucial role in cell death. Although many questions remain unanswered, there exists enough evidence to consider the possibility of targeting MAPK-mitochondria interactions in the prevention and treatment of heart disease. The goal of this review is to integrate previous studies into a discussion of MAPKs and MAPK-mitochondria signaling in cardiac diseases, such as myocardial infarction (ischemia), hypertrophy and heart failure. A comprehensive understanding of relevant molecular mechanisms, as well as challenges for studies in this area, will facilitate the development of new pharmacological agents and genetic manipulations for therapy of cardiovascular diseases.

Keywords

heart; MAPK; cardiac diseases; mitochondria; cell signaling

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1. Introduction

Cardiovascular diseases cause more mortality and morbidity worldwide than any other class of diseases, accounting for 31.9% of the 2.47 million deaths in the United States in 2010 (Go et al., 2014). The pathogenesis of cardiac decompensation, or heart failure (HF), can be chronic or acute in nature and is of major clinical concern. Coronary artery disease, myocardial infarction (MI), hypertension, cardiomyopathy, myocarditis, arrhythmia, hyperlipidemia, and diabetes, among other diseases, can promote the onset or progression of HF by increasing blood pressure or blood volume or reducing contractility. Indeed, myocardial ischemia is the most common cause of HF. Insufficient blood supply due to partial or complete occlusion of coronary arteries deprives the myocardium of the oxygen and substrates needed for cardiac metabolism, leading to MI and localized necrosis. The remaining cardiomyocytes must compensate for the lack of function from necrotic myocytes, so the ventricles adaptively remodel immediately after MI to maintain cardiac output (Sutton and Sharpe, 2000, Dorn, 2009). Remodeling is a complex process involving multiple signaling pathways associated with ionic regulation, reactive oxygen species (ROS) generation, substrate utilization and energy synthesis in response to cellular remodeling. Initially, cardiomyocytes can overcome the increase in workload by undergoing hypertrophic remodeling; cardiomyocytes increase heart contractility by increasing protein synthesis and adding sarcomeres. However, if the heart is too stressed, hypertrophy can become deleterious due to functional decompensation, and cause heart HF, characterized by a decreased ejection fraction, progressive chamber dilation, pro-inflammatory cytokines release, apoptosis, and fibrogenesis (Frey and Olson, 2003, Ertl and Frantz, 2005).

The heart is regulated by various intracellular signaling pathways. In particular, mitogen-activated protein kinase (MAPK) signaling has been widely implicated in cardiac pathology for several reasons. First, *in vitro* and *in vivo* stimulation of MAPK signaling promotes or suppresses cardiac pathology. Second, cardiac diseases are associated with changes in the expression and activity of MAPKs in the heart. Third, pharmacological or genetic inhibition of MAPKs affects cardiac diseases. Four classic MAPKs, including extracellular signal-regulated kinases 1/2 (ERK1/2), p38, c-Jun N-terminal kinases (JNK), and ERK5, distinctly mediate heart development, metabolism, function, and pathology. Notably, ERK1/2 and ERK5 are activated by hypertrophic stimuli, whereas JNK and p38 responded mostly to stressors, such as oxidative stress, hyperosmosis and radiation (Sugden and Clerk, 1998). MAPKs are significantly integrated in intracellular signaling and the regulation of gene expression; they target an array of cytosolic and nuclear proteins, including proteins from other signaling pathways and transcription factors (Yang et al., 2003). In addition, MAPKs directly and indirectly target mitochondria, which synthesize 80% of the ATP needed for cardiomyocyte function. Furthermore, mitochondria are the nexus of various stressors, and they initiate cell death through apoptosis, necrosis and autophagy. Previous studies revealed that MAPKs directly interact with the outer mitochondrial membrane and even translocate into mitochondria (Kharbanda et al., 2000, Baines et al., 2002, Ballard-Croft et al., 2005). Other studies demonstrated indirect effects between MAPKs and mitochondria; MAPKs affected mitochondria-mediated cell survival and cell death through their effects on ROS

and calcium signaling (Bogoyevitch et al., 2000, Zhao et al., 2001, Yue et al., 2002, Kaiser et al., 2004, Kong et al., 2005, Wall et al., 2006).

Although the precise mechanisms underlying MAPK-mitochondria signaling in cardiac diseases have not yet been established, a significant amount of evidence confirms that MAPKs profoundly influence cellular signaling underlying cardiac compensation and decompensation, in part, through interactions with the mitochondria. Since MI is the most common cause of HF, pharmacological and conditional interventions must be developed to prevent MI or otherwise delay its progression. This review integrates lessons from previous studies into a comprehensive discussion of the implications of MAPK signaling in the physiological and pathological heart. An understanding of the molecular mechanisms underlying canonical MAPK signaling and MAPK-mitochondria signaling in the heart will promote the development of new therapeutic approaches for the treatment of cardiac diseases.

2. The MAPK family in the healthy heart

To elucidate the potential therapeutic implications of targeting MAPK signaling, understanding the MAPK family in the context of a healthy heart, including genealogy, three-tiered activation cascades, the unique physiological functions of subfamilies and isoforms, and signaling regulation is important. Currently, studies on the role of MAPKs in the heart are mainly based on the following approaches: (i) analysis of the activity of MAPKs in the myocardium under physiological and pathological conditions; (ii) elucidating the effects of pharmacological inhibition/activation of MAPKs on cardiac diseases; (iii) assess the effects of gene targeted modulation of MAPKs expression on the healthy or diseased heart (Ravingerova et al., 2003). Four classical subfamilies represent the majority of the MAPK family in humans: ERK1/2, (also known as MAPK 3/1), p38 (also known as MAPKs 11-14), JNK (also known as MAPKs 8-10), and ERK5 (also known as Big MAPK 1 or MAPK 7). Atypical MAPKs, in contrast to their classical counterparts, are evolutionary primitive and apparently less implicated in cardiac physiology (Feijoo et al., 2005). MAPK enzymes are so conserved among eukaryotes that the genealogy of classical human MAPKs was traced back to evolutionary divergences in primitive eukaryotes. Indeed, studies of the yeast species *Saccharomyces cerevisiae* have directed and supplemented studies of MAPKs in mammalians including humans. ERK1/2 and ERK5 are considered pheromone response pathway-type MAPKs, or Fus3/Kss1-type MAPKs, because they are commonly activated by peptide mitogens. p38 and JNK are considered high-osmolarity growth pathway-type MAPKs, or Hog1-type MAPKs, because they respond strongly to cellular stress and inflammatory cytokines; they are appropriately dubbed stress-activated protein kinases (SAPKs) (Gustin et al., 1998, Doczi et al., 2012). Nonetheless, human MAPKs respond to an array of stimuli. ERK1/2 and ERK5 can also respond to stressors, like ROS, G-protein-coupled receptor (GPCR) agonists, and cytokines (McKay and Morrison, 2007, Raman et al., 2007). p38 and JNK can also respond to growth factors and GPCRs (Ono and Han, 2000, Raman et al., 2007).

Although some overlap exists with regard to molecular structure, substrate specificity, and signaling functions, MAPKs and their isoforms can uniquely influence cardiac physiology

based on cell type and stimulus characteristics (Gerits et al., 2007). This is, in part, due to the co-evolution of regulatory mechanisms, which impart specificity and preserve physiological signaling. Facilitated by these regulatory mechanisms, the MAPK family of serine/threonine-specific protein kinases targets a remarkable assortment of transcription factors, protein kinases, and other proteins, both in the cytosol and the nucleus, to mediate cellular adaption, growth, cellular survival, apoptosis, proliferation, differentiation, metabolism, and motility (Davis, 2000, Pearson et al., 2001, Ramos, 2008, Rincon and Davis, 2009, Wang and Tournier, 2006). MAPK signaling is like a potent molecular switch; after it prompts an appropriate cellular response, it must be deactivated by regulatory mechanisms (Ferrell, 1996). This compensatory downregulation may be illustrated in the context of physical exercise, a normal yet acute stress. Transient hypoxia and mechanical overload stimulate the MAPK signaling during exercise. Within minutes, MAPKs rectify cardiac output by increasing contractility via cardiomyocyte hypertrophy without inflammation or fibrosis (Hunter et al., 1995). If a stressor is only temporary, as in the case of normal exercise, regulatory mechanisms, such as MAPK phosphatases (MKPs) and tyrosine phosphatases, properly downregulate MAPK signaling.

Each MAPK subfamily is activated by a unique cascade; cascade intermediates exhibit exceeding substrate specificity for their associated MAPKs (Feijoo et al., 2005, Doczi et al., 2012). Yet, even before a stimulus reaches a MAPK kinase kinase (MAP3K), the first tier of a MAPK cascade, it can be influenced by an array of upstream activities (Pearson et al., 2001). Indeed, intracellular macromolecular complexes, which include docking and scaffold proteins, alter the timing and location of intracellular signaling (Whiteside and Goodbourn, 1993). Highly conserved three-tiered serial phosphorylation cascades begin when MAP3Ks phosphorylate and activate second tier MAPK kinases (MAP2Ks). MAP2Ks dually phosphorylate the activation loop of their corresponding MAPKs on a characteristic threonine-X-tyrosine motif, where X is a variable amino acid residue (glutamic acid in ERK1/2, glycine in p38, proline in JNK, aspartic acid in ERK5). This precise, highly conserved mechanism stimulates changes in MAPK global conformation and facilitates access to substrates (Pearson et al., 2001, Doczi et al., 2012). Since, removal of either phosphate from the activation loop of a cascade kinase essentially abolishes signaling, MKPs and tyrosine phosphatases, which hydrolyze two or one activating phosphate, respectively, can significantly downregulate MAPK signaling (Ferrell, 1996). Many intracellular signaling pathways, including mitochondrial signaling pathways and other MAPK signaling pathways, manipulate upstream and downstream proteins of MAPK signaling to influence dynamic myocardial growth or adaptation (Junttila et al., 2008).

2.1. ERK1/2

The ERK1/2 activation cascade, also known as the Ras-ERK pathway, has been investigated extensively. Calcium channels, RTKs, and GPCRs can internalize a stimulus. In a well-studied example, growth factor receptor-bound protein 2, a docking protein, binds to activated RTKs and, then, complexes with and activates the guanine nucleotide exchange factor, son of sevenless (SOS). Activated SOS promotes removal of GDP from Ras, which then binds GTP (McKay and Morrison, 2007). Ras is a GTPase with an extensive reach in intracellular signaling. Among its prominent signaling mechanisms, Ras phosphorylates and

activates Raf proto-oncogene serine/threonine-protein kinase (Raf-1 or c-RAF), a MAP3K. In turn, Raf activates MAPK/ERK kinase 1/2 (MEK1/2, also known as dual specificity MAPK kinase 1), a MAP2K, which activates ERK. Interestingly, ERK1/2 also is autophosphorylated via a GPCR-dependent mechanism (Lorenz et al., 2009). Within the cascade, scaffold proteins, like β-arrestin, kinase suppressor of Ras (KSR), MAPK organizer 1 (MORG1), and MEK partner 1 (MP1), interact with ERK1/2 to facilitate and modulate signaling (Dhanasekaran et al., 2007). MKPs, protein serine/threonine phosphatases and protein tyrosine phosphatases downregulate ERK1/2 signaling (Junttila et al., 2008, Owens and Keyse, 2007). Once activated, ERK1/2 can activate the proto-oncogene c-Myc and SMAD1-4, transcriptional activators implicated in heart development (MacLellan and Schneider, 2000). It also activates c-Jun and activating protein 1 (AP-1); the AP-1 transcription factor complex, which is involved in cellular proliferation and survival, can be formed by the transcription factors Fos, jun, and activating transcription factor (ATF), each of which is targeted by MAPKs (Hai and Curran, 1991, Pearson et al., 2001). Furthermore, during neonatal heart development, ERK activates transcription factor GATA4, which inhibits apoptosis and is important in the formation of the septum arteriosum (Davidson and Morange, 2000, Liang et al., 2001, Eriksson and Leppa, 2002, Naito et al., 2003). Ubiquitous expression of ERK1/2 also implicates it in signaling that influences cell death, migration, immune function, insulin signaling, cardiac hypertrophy, and cell structure including cytoskeletal properties and cell adhesion (Pearson et al., 2001, Ramos, 2008). MEK1-restricted transgenic (TG) mice demonstrated concentric hypertrophy, a phenotype similar to that observed in a weight lifter. In fact, in response to an increase in pressure from resistance training, MAPK signaling promotes parallel sarcomere addition and thickening of the left ventricular wall. This physiological phenomenon, referred to as “athlete’s heart,” improves the ability of the heart to maintain cardiac output during exercise-induced acute stress (Mihl et al., 2008). Finally, with regard to isoforms, ERK2 appears to be more important than its counterpart, ERK1, because only ERK2 null mice are nonviable. ERK2 seems to compensate for a lack of ERK1, so it is thought to be capable of fulfilling most ERK1 functions (Gerits et al., 2007).

2.2. p38

The p38 cascade exhibits more variability than the ERK1/2 cascade; unlike ERK1/2, the p38 cascade can begin with MEK kinase 1-4 (MEKK1-4), mixed lineage kinase 2/3 (MLK2/3, also known as MAPK kinase kinase 10/11), apoptosis signal-regulating kinase 1/2 (ASK1/2, also known as MAPK kinase kinase 5/6), transforming growth factor-β-activated kinase 1 (TAK1, also known as MAPK kinase kinase 7), and one amino acid protein kinases 1-3 (TAO1-3, also known as serine/threonine-protein kinases) (Raman et al., 2007). With the exception of TAO1-3, all p38 MAP3Ks activate the MAP2Ks MEK3/6 and MEK4. Finally, MEK3/6 and MEK4 activate p38 (Gerits et al., 2007). TAK1 also mediates noncanonical p38 autophosphorylation via TAB-1 (transforming growth factor-β-activated protein 1-binding protein 1), a MEK3/6-independent mechanism (Ge et al., 2002). Osmosensing scaffold for MEKK1 (OSM), JNK-interacting protein 2 (JIP2), and JNK-associated leucine-zipper protein can alter p38 signaling (Dhanasekaran et al., 2007). p38 phosphatases include MKPs 1, 2, 5, and 7, and protein serine/threonine phosphatases (PP2C) (Junttila et al., 2008, Owens and Keyse, 2007).

p38 signaling most prominently influences immune responses by affecting proinflammatory cytokine production in the cytosol and regulating immune cell proliferation, differentiation, and function. It activates c-Myc, c-Fos, GATA4, AP-1, and ATF-2 (Liang and Molkentin, 2003, Petrich et al., 2004, Rose et al., 2010). ATF-2, in particular, is activated by SAPKs, binds to cAMP response element (CRE), and, at the transcriptional level, functions as a histone acetyltransferase, activating transcription of genes important in cardiac development and cell survival (Hai and Curran, 1991, Sano et al., 1999). Moreover, p38 activates myocyte-specific enhancer factor 2A/C (MEF2A/C) and serum response factor (SRF), both of which influence cardiac differentiation and development (Sano et al., 1999). Activated p38 may also remain in the cytosol to inhibit nuclear factor of activated T-cells (NFAT), a family of calcium-regulated transcription factors, that influences immune response and cardiac development (Zarubin and Han, 2005, Macian, 2005). One study implied that p38 might be physiologically anti-hypertrophic in response to swimming (Taniike et al., 2008), but the majority of studies implies that p38 activation is associated mostly with pathological hypertrophy (Nishida et al., 2004, Watanabe et al., 2007). p38 may be negatively inotropic by modifying cardiac sarcomeric proteins and decreasing phosphorylation of α-tropomyosin (Zechner et al., 1997, Liao et al., 2001, Chen et al., 2003, Vahebi et al., 2007). The p38 MAPK subfamily has four isoforms: p38α and p38β are ubiquitously expressed, p38γ is expressed primarily in the heart and skeletal muscle, and p38δ is found in the small intestine, kidney, pancreas, and testis (Ono and Han, 2000). Knock-out of p38α in mice, but not other isoforms, caused embryonic lethal defects in erythropoiesis (Tamura et al., 2000). The p38α isoform appears to promote apoptosis via ROS production, and calcium overload (Dhingra et al., 2007). On the other hand, p38β seems to inhibit apoptosis by activating heat shock protein 27 (Hsp27), which prevents proteolysis of myofilament proteins (Li et al., 2008).

2.3. JNK

The JNK cascade mostly overlaps with the p38 cascade. It begins with the same MAP3Ks as p38, with the exception of TAO1-3 (Raman et al., 2007). After the first tier, these two signaling cascades diverge. All of the mentioned MAP3Ks can activate MEK4/7, which activates JNK. JNK can also be activated noncanonically via Wnt signaling, which involves Rac and RhoA intermediates (Zhang et al., 2009). JNK scaffold proteins include JIP1, JIP2, JNK/stress-activated protein kinase-associated protein 1 (JSAP1), JNK-associated leucine-zipper protein, and SH3 (POSH) (Dhanasekaran et al., 2007), and JNK phosphatases are MKPs 1, 2, 5, and 7 (Owens and Keyse, 2007)...

JNK, like p38, is strongly implicated in cardiac response to stress. Like other MAPKs, JNK signaling influences cell survival, apoptosis, proliferation, and differentiation, as observed from its phosphorylation of c-Myc, c-Jun, and ATF2. JNK1 and JNK2 each has four isoforms and are ubiquitously expressed. JNK3 has two isoforms and is found in the heart, brain, and testis (Davis, 2000). Confounding results reported enhanced myocyte survival as a result of both JNK activation and inhibition (Aoki et al., 2002, Dougherty et al., 2002, Engelbrecht et al., 2004). *In vivo* studies suggest that JNK impedes physiological hypertrophic growth by activating transcription factor jun-D, which mediates anti-hypertrophic and anti-apoptotic effects as part of the AP-1 transcription factor complex (Hilfiker-Kleiner et al., 2005). Lastly, JNK1 and JNK2 are connected to T cell development

and cytokine release (Gerits et al., 2007) inhibition of NFAT translocation into the nucleus (Liang et al., 2003), which blocks its regulation of thymocyte development and T cell differentiation (Macian, 2005). JNK signaling also influences heart development, metabolism, insulin signaling, cell mobility, and actin reorganization (Davis, 2000, Pearson et al., 2001, Raman et al., 2007).

2.4. ERK5

As mentioned, ERK5 is more similar to ERK1/2 than p38 and JNK. While p38 and JNK can each be activated by several MAP3Ks, ERK5, like ERK1/2, has only been shown to be activated by one MAP3K, which is MEKK2/3. MEKK2/3 activates MEK5, which activates ERK5. ERK5 scaffold proteins include Lck-associated adaptor (LAD), Grb-2-associated binder 1 (Gab1), and muscle specific A-kinase anchoring protein (Wang and Tournier, 2006). ERK5 phosphatases include MKPs 1 and 3 and the phosphotyrosine specific phosphatases PTP-SL (Buschbeck et al., 2002). ERK5 is unusual because a large COOH-terminal extension makes it more than twice the size of other MAPKs. It promotes postnatal, eccentric hypertrophic heart growth, cell survival, differentiation, growth, and proliferation by activating immediate-early response genes fos, myc, jun, and MEF2 (MacLellan and Schneider, 2000, Wang and Tournier, 2006). Ventricular volume overload promotes eccentric hypertrophy, which is characterized by serial sarcomere addition, cardiomyocyte elongation, and dilation and thinning of the left ventricle (Mihl et al., 2008). This phenotype is often observed in athletes who engage in endurance training, such as marathon runners. Unlike other MAPKs, ERK5 functions directly as a transcriptional activator, binding directly to DNA (Kasler et al., 2000, Akaike et al., 2004). Besides, numerous studies have implicated ERK5 in the inhibition of apoptosis and maintenance of vascular integrity by discovering its pro-survival role in endothelial cells and smooth muscle cells, both of which are found significantly in blood vessels (Hayashi and Lee, 2004). In fact, ERK5 is essential in the formation of a vascular system; global ERK5 deletion caused defects in vascular formation that resulted in an embryonic lethal phenotype (Regan et al., 2002, Hayashi and Lee, 2004, Hayashi et al., 2004). ERK5a is the most ubiquitously expressed isoform of the only known *erk5* gene. Other isoforms, ERK5b, ERK5c, and ERK-T appear to downregulate ERK5a (Yan et al., 2001).

Thus, despite extensive studies, the precise mechanisms of the MAPKs network in the regulation of cell differentiation, cell growth and death are not yet fully understood. Elucidating the cross-talk between the MAPKs family and other signaling pathways in the regulation of cell metabolism require further studies that can be helpful for understanding the contribution of MAPKs to myocardial damages induced by various exogenous stressors.

3. MAPKs in chronic cardiac stress (hypertrophy and heart failure)

3.1. ERK1/2

As mentioned previously, growth factors stimulate ERK1/2 signaling through RTKs and GPCRs to promote cardiac hypertrophy. Stimulation of GPCRs, such as α- and β-adrenergic, angiotensin II (AngII) and endothelin 1 (ET-1) receptors induce hypertrophy through activation of Ras-ERK cascade through Gq/G11 (*reviewed in* Liang and Molkentin, 2003,

Petrich et al., 2004, Rose et al., 2010). Interestingly, β-adrenergic ligands can activate ERK1/2 in a G protein-independent, β-arrestin-dependent manner through RTKs. The β-blockers alprenolol and carvedilol induced β_1-adrenergic receptor-mediated transactivation of epidermal growth factor receptor by arrestin, and ERK activation (Kim et al., 2008). Stimulation of both receptor complexes can mediate hypertrophic signaling through the Ras-ERK pathway. Upregulation of individual signaling molecules from the Ras-ERK pathway was associated with cardiac hypertrophy. Increased Ras expression (Kai et al., 1998) and Ras-ERK pathway activity (Eisenberg and Eisenberg, 2006) positively correlated with severity of cardiac hypertrophy in patients with hypertrophic cardiomyopathy. In animal models, TG mice with cardiac-specific expression of constitutively active (CA)-Ras (Hunter et al., 1995, Zheng et al., 2004) or CA-MEK1 (Bueno et al., 2000) developed cardiac hypertrophy, including changes in gene expression and myofibers. Targeted overexpression of RAS transgenic mice was associated with extracellular matrix remodeling, cardiac dysfunction, hypertrophic cardiomyopathy and HF (Hunter et al., 1995, Mitchell et al., 2006). Gene expression of the key regulators for energy metabolism, such as PPARα, GLUT4, and fatty acids oxidation enzymes were remarkably suppressed in these hearts.

Potential downstream targets of ERK1/2 activation in response to growth stimuli and oxidative stress are shown in Fig. 2. Numerous studies reported that the Ras-ERK pathway regulates Ca^{2+} through modulation of the activity of ion channels/exchangers and pumps. Cardiac dysfunction in Ras TG mice can occur due to changes in regulation of Ca^{2+} homeostasis in the cytoplasm. Ras upregulation in intact hearts (Zheng et al., 2004) and cultured cardiomyocytes (Ho et al., 1998) resulted in reduced expression of SERCA2 associated with low Ca^{2+} uptake by the sarcoplasmic reticulum. In addition, alterations in Ca^{2+} homeostasis can result from reduced L-type Ca^{2+}-channel (LTCC) activity and defective excitation-calcium release coupling with Ras activation in cardiomyocytes (Ho et al., 2001). Yet, recent studies revealed ET-1-induced stimulation of the LTCC via activation of ERK1/2 (Yu et al., 2013). In addition, ERK1/2 can phosphorylate and modulate the activity of Na^+/H^+ exchanger 1 (NHE-1), which is indirectly involved in Ca^{2+} regulation in the heart (Moor and Fliegel, 1999). Inhibition of ERK1/2 also significantly reduced the K^+ channels (I_K and I_{K1}) activity in hypertrophied adult cardiomyocytes (Teos et al., 2008).

Although most of studies show that the Ras-ERK cascade plays an important role in the signaling pathway leading to cardiac hypertrophy, ERK-independent mechanisms can also play a significant role in the pathogenesis of hypertrophy. In favor of the latter, genetic ablation of cardiac ERK1/2 promoted stress-induced apoptosis and HF without effect on hypertrophy in mice, suggesting that ERK1/2 signaling is not a requirement in the mediation of cardiac hypertrophy, though it does play a protective role in response to pathologic stimuli (Purcell et al., 2007). Activation of Raf-1 was not sufficient to induce cytoskeletal changes similar to those seen in hypertrophy (Thorburn et al., 1994). Notably, dominant negative (DN) mutants and pharmacological inhibitors of Raf-ERK1/2 signaling attenuated hypertrophy and increased cell death in isolated cardiomyocytes and intact hearts (Purcell et al., 2007, Lorenz et al., 2009, Cheng et al., 2011). A recent study suggested a scenario in which selective blocking of ERK-mediated hypertrophy occurs without an increase in apoptotic cardiomyocyte death. Autophosphorylation of ERK on Thr188 ($ERK2^{Thr188}$) due

to direct protein-protein interaction between ERK and Gβγ subunits was observed in mice upon stimulation of Gq-coupled receptors or after aortic banding and in failing human hearts (Lorenz et al., 2009). Notably, ERK autophosphorylation, which requires the activation and assembly of the entire Ras-ERK cascade and dimerization of ERK is a critical event in the induction of ERK-mediated cardiac hypertrophy in response to various stimuli (Lorenz et al., 2009). $ERK2^{T188A}$, which is DN for ERK^{Thr188} signaling, attenuated cardiomyocyte hypertrophic responses to phenylephrine (PE) and to chronic pressure overload in isolated cells and intact hearts without any effect on anti-apoptotic ERK1/2 signaling and physiological cardiac function (Ruppert et al., 2013). Interestingly, despite inhibition of pathological hypertrophy, $ERK2^{T188A}$ did not affect physiological cardiac growth associated with age or exercise, therefore, suggesting that interference with ERK^{Thr188} phosphorylation may be a selective therapeutic strategy in pathological ERK1/2-mediated cardiac hypertrophy.

In addition to hypertrophy, activation of the ERK cascade promotes resistance to apoptosis (Bueno et al., 2000, Yamaguchi et al., 2004), although the anti-apoptotic effects of individual components such as Raf likely do not associate with hypertrophy and can occur through a MEK-ERK- independent mechanism (Chen et al., 2001). Conversely, inhibition of Ras-ERK signaling attenuates hypertrophic response of the heart and cardiomyocytes. Anti-remodeling and anti-hypertrophic effects of mechanical unloading caused by a left ventricular assist device in patients with HF were associated with reduced cardiac ERK1/2 activity in the myocardium (Flesch et al., 2001). Likewise, hearts with DN-Raf demonstrated reduced hypertrophy in response to pressure overload (Harris et al., 2004), and DN-MEK1 inhibited ET-1- and PE-induced hypertrophy in cardiomyocytes (Ueyama et al., 2000).

Thus, activation of ERK due to stimulation of both RTKs and GPCRs promotes hypertrophy indicating a key role it plays in the pathogenesis of cardiac hypertrophy and HF. Development of hypertrophy and its progression from compensated to pathological (decompensated) state and HF is a complex process which along with Ras-ERK includes other signaling pathways and depends on exposure time, severity and nature of hypertrophic stimuli. Discrepancies between different studies are also due to variability of animal/cell models and specificity of cell metabolism in neonatal and adult cardiomyocytes used in these studies.

3.2. p38

p38, a stress-activated MAPK, is stimulated in response to various extracellular stresses including inflammatory cytokines, oxidative stress, radiation, growth factors, hyperosmolarity and others. Substantial variabilities within studies on the role of p38 in cardiac hypertrophy, ventricular remodeling and HF are due to the use of a) neonatal and adult cardiomyocytes which are metabolically different, b) various animal models or hypertrophic agonists, c) pan-p38 inhibitors or genetic upregulation/downregulation of total p38 that affect both p38α and p38β, and d) measurements of p38 activity at different time points after stimulation.

Similar to other MAPKs, p38 is rapidly activated within a few minutes of exposure to stretch, increased aortic pressure, or volume overload, although this activation is not consistent (Hoshijima and Chien, 2002). Analysis of tissue samples from the hearts with post-MI ventricular remodeling demonstrated substantial variability in p38 activity although it was higher in patients with end-stage HF compared to healthy hearts (Ng et al., 2003, Denise Martin et al., 2012). In most cases, a double-peak, transitional activation of MAPKs, including p38, suggests that MAPKs may play discrete roles throughout progression of hypertrophy, from early activation to the late hypertrophic phase (Chien, 1999, Molkentin and Dorn, 2001). Studies on isolated cardiomyocytes, predominantly, neonatal cardiomyocytes, demonstrated that stimulation of p38 promoted hypertrophy (Nemoto et al., 1998, Wang et al., 1998a, Liang and Molkentin, 2003), while pharmacological inhibition or genetic ablation of p38 prevented cell growth in response to hypertrophic stimuli (Liang and Molkentin, 2003, Nemoto et al., 1998), suggesting that p38 plays a causative role in the development of cardiac hypertrophy. Furthermore, overexpression of the upstream activators for the p38, MKK3 and MKK6 elicited pro-hypertrophic responses, including an increase in cell size, enhanced sarcomeric organization, and elevated atrial natriuretic factor expression in neonatal cardiomyocytes (Wang et al., 1998a). However, *in vivo* studies provided contradictory data on the role of p38 in the development of cardiac hypertrophy. Targeted activation of p38 in intact hearts by transgenic expression of MKK3 and MKK6 resulted in interstitial fibrosis and expression of fetal marker genes characteristic of HF, but no significant cardiac hypertrophy (Liao et al., 2001). Likewise, mice lacking PKCε exhibited enhanced activation of p38 associated with increased collagen deposition and diastolic dysfunction but preserved pressure overload-induced myocardial hypertrophy (Klein et al., 2005). Conversely, TG mice with cardiac-specific expression of DN-p38 developed cardiac hypertrophy but were resistant to cardiac fibrosis in response to pressure overload (Zhang et al., 2003). Inhibition of p38 protected post-infarction remodeling and HF in mice (Liu et al, 2005) and rats (See et al, 2004). Studies of cardiac-specific p38 knock-out mice demonstrated that p38 plays a significant role in the regulation of survival mechanisms in response to pressure overload through modulation of apoptosis and fibrosis, while cardiac hypertrophic growth is unaffected despite a dramatic down-regulation of the kinase (Nishida et al., 2004). These studies provide strong evidence that p38 activation is not the only causative factor in cardiac hypertrophy.

Notably, stimulation of different isoforms of p38 can exert distinct, even, opposite effects. Upregulation of p38α enhanced apoptosis, whereas p38β overexpression promoted hypertrophy in cultured isolated cardiomyocytes (Wang et al., 1998b). *In vivo* studies on intact hearts provided results different from those seen during *in vitro* studies, although they confirm diverse downstream targets and functional roles of p38α and p38β in the regulation of hypertrophy-associated signaling pathways. Direct injections of adenoviruses expressing p38α or p38β into the left ventricular wall of adult rats demonstrated that p38α stimulates fibrosis-related factors whereas p38β attenuated the ET-1-induced expression of the B-type natriuretic peptide. These findings indicate that p38α participates in the regulation of fibrotic remodeling process, and p38β stimulates the agonist-induced activation of the B-type natriuretic peptide and, thereby, elicits inhibitory effects on growth factors (Koivisto et al., 2011). DN-p38α transgenic mice exhibited cardiac hypertrophy despite the reduced p38α

activity (Braz et al., 2003, Zhang et al., 2003). Interestingly, a negative feedback mechanism exists between p38 and calcineurin in which upregulation of the latter enhances the activity of MAPK phosphatase-1, negatively regulating the hypertrophic response in cardiomyocytes by downregulating p38 (Lim et al., 2001). Cardiac-specific DN-p38α, and MKK3 and MKK6 TG mice exhibited enhanced cardiac hypertrophy in response to pressure overload or infusion of hypertrophic agonists, and this was associated with augmented activity and nuclear translocation of NFAT (Braz et al., 2003). These observations indicate that reduced p38 signaling promotes cardiomyocyte growth through a mechanism involving enhanced calcineurin-NFAT signaling (Molkentin, 2004, Yang et al., 2002). It should be noted that p38 exerts a negative inotropic effect on isolated cardiomyocytes by decreasing myofilament response to Ca^{2+} (Liao et al., 2002), and p38α activation directly suppresses sarcomeric function in the heart associated with decreased phosphorylation of α-tropomyosin (Vahebi et al., 2007). In contrast to downregulation of the calcineurin-NFAT pathway, activation of the MKK6-p38 MAPK signaling in neonatal cardiomyocytes prolonged the contractile Ca^{2+} transient by downregulating SERCA2 and increasing diastolic $[Ca^{2+}]_i$ and NFAT activity (Andrews et al., 2003). Downstream targets of p38 activation during cardiac and oxidative stress are summarized in Fig. 3.

Although *in vivo* studies revealed no consistent activation of p38 in cardiac hypertrophy and ventricular remodeling following MI, inhibition of p38 mostly exerted anti-remodeling effects and improved cardiac function (*reviewed in* Marber et al., 2011). DN-p38 mice had reduced infarct size which was associated with improved ventricular systolic function after MI (Ren et al., 2005). In addition to the anti-remodeling action, inhibition of p38 activity decreased tumor necrosis factor alpha (TNFα) expression and reduced inflammation-induced fibrosis in post-MI myocardium (Yin et al., 2008). There exists a feed-back mechanism, in which TNFα activated p38 in the intact heart and isolated cardiomyocytes through MKK3 (Bellahcene et al., 2006). Activation of p38 promoted apoptosis via the regulation of apoptotic protein activity. In response to TNFα, p38 induced phosphorylation (inactivation) and downregulation of the anti-apoptotic protein Bcl-xL, eventually leading to apoptosis in endothelial cells (Grethe et al., 2004). In addition, p38 stimulated cardiomyocyte apoptosis through Bcl-xL deamidation (Ren et al., 2005), attenuated phosphorylation of the pro-apoptotic protein Bad, and stimulated TNFα-induced apoptosis in endothelial cells (Grethe and Porn-Ares, 2006). Likewise, p38 inhibition up-regulated Bcl-2, whereas its activation down-regulated Bcl-2 in p38 transgenic mice hearts and neonatal cardiomyocytes, thereby, indicating that p38 functions as a pro-apoptotic signaling effector (Kaiser et al., 2004).

A diversity of basic science and preclinical studies obscures understanding of the precise role of p38 MAPK in cardiac diseases. Still, collectively, both *in vitro* and *in vivo* studies of various cells, animals, and human heart models show that p38, concurrently with other signaling pathways, plays a significant role in the pathogenesis of hypertrophy and its progression to HF. Acute activation of p38 signaling in early phases of hypertrophy may serve as an adaptive response to extracellular stresses while chronic activation of the kinase apparently exerts detrimental effects, including adverse cardiac remodeling and HF.

3.3. JNK

Studies using both animal models and cultured cells provide strong evidence that JNK is involved in pathogenesis of hypertrophy and HF. This conclusion comes from studies that demonstrated that i) cardiac hypertrophy and HF change JNK activity and ii) upregulation or inhibition of JNK using gain- and loss-of-function approaches influences cardiac hypertrophy and HF. However many questions on the cause-and-effect relationship between JNK activation and cardiac dysfunction induced by hypertrophy and HF still remain unanswered. Similar to p38, activation of JNK is transient, cyclic, and it varies depending on timing, models, severity of stress, and types of stimuli. Early studies demonstrated that hypertrophic agents, such as α_1-adrenergic receptor agonists (Ramirez et al., 1997), AngII (Kudoh et al., 1997), and ET-1 (Bogoyevitch et al., 1995) cause transient activation of JNK in cultured cardiomyocytes isolated from neonatal rats.

In vivo studies demonstrated that pressure-overload hypertrophy induced by transverse aortic constriction in rats resulted in rapid activation of JNK and its target transcription factors c-Jun and ATF-2 (Fischer et al., 2001, Nadruz et al., 2004). However, there was no difference between control hearts and hearts with pressure- or volume-overload hypertrophy induced by aortic banding for 24h (Miyamoto et al., 2004). Mechanical stress induced by hemodynamic overload plays an important role in the development of cardiac hypertrophy and ventricular remodeling associated with early activation of the hypertrophic genetic program. Mechanical stress induced by cyclic stretch in neonatal cardiomyocytes activated the JNK/c-Jun pathway (Nadruz et al., 2005). Specific activation of the MKK7/JNK pathway by CA-MKK7 induced hypertrophy in cultured cardiomyocytes (Wang et al., 1998b). Resistin promoted cardiac hypertrophy via activation of the JNK/insulin receptor substrate pathway in neonatal cardiomyocytes and adult rat hearts *in vivo* (Kang et al., 2011). Conversely, targeted inhibition of JNK using DN-MKK4, an upstream kinase of JNK, prevented JNK activation and ET-1-induced hypertrophy in cardiomyocytes (Choukroun et al., 1998) and pressure-overload in intact hearts (Choukroun et al., 1999). Importantly, studies using cultured cardiomyocytes, particularly from neonatal hearts, revealed pro-hypertrophic action of JNK activation, however, the majority of *in vivo* studies demonstrated no positive correlation between JNK activation and hypertrophy.

Transgenic animals with targeted expression of MKK7 developed congestive HF with extracellular matrix remodeling in the absence of ventricular hypertrophy, although the hearts exhibited increased levels of the hypertrophy marker genes α-skeletal actin and atrial natriuretic factor (Petrich et al., 2004). Inhibition of MEKK1-JNK signaling attenuated cardiac hypertrophy induced by heart-restricted overexpression of $G_{\alpha q}$ in mice (Miyamoto et al., 2004) whereas it had no effect on pressure overload hypertrophy (Sadoshima et al., 2002). Genetic ablation of three JNK isoforms (JNK1, JNK2 and JNK3) individually in the heart did not promote greater cardiac hypertrophy compared to wild type mice, although hearts with JNK1 deletion exhibited increased fibrosis in response to pressure overload (Tachibana et al., 2006). On the other hand, downregulation of the ASK1-JNK pathway was associated with reduced fibrosis and myocardial remodeling during AngII-induced cardiac hypertrophy (Izumiya et al., 2003). These studies support implications of JNK signaling in specific aspects of myocardial remodeling associated with cardiac pathology, while they

exclude a causative role of JNK in hypertrophy. Furthermore, TG mice expressing DN-JNK1/2 showed enhanced cardiac hypertrophy following transverse aortic constriction and spontaneous cardiac hypertrophy with aging, suggesting an anti-hypertrophic role, rather than pro-hypertrophic role, for this signaling pathway in the heart (Liang et al., 2003). Mice lacking JunD, a downstream target of JNK, exhibited enhanced pressure overload-induced hypertrophy, increased mortality, and enhanced cardiomyocyte apoptosis and fibrosis compared to wild type animals (Hilfiker-Kleiner et al., 2005, Ricci et al., 2005), suggesting that JunD limits cardiomyocyte hypertrophy. Moreover, JunD KO mice developed low adaptive pressure overload cardiac hypertrophy, while cardiac-specific overexpression of JunD resulted in spontaneous ventricular dilation and decreased contractility (Ricci et al., 2005). These data indicate that JunD, promotes both adaptive-protective and maladaptive hypertrophy in the heart depending on its expression levels.

JNK-induced activation of downstream targets in response to growth stimuli and oxidative stress are given in Fig. 4. The anti-hypertrophic action of JNK is mediated, at least partially, through inhibition of calcineurin-NFAT signaling, which plays a critical role in regulating cardiac hypertrophic growth (Molkentin et al., 1998). JNK was originally shown to phosphorylate NFATc2 (Porter et al., 2000) and NFATc3 (Chow et al., 1997) but not NFATc4 (Yang et al., 2002). In cultured cardiomyocytes, DN-JNK1/2 significantly enhanced activity of NFATc1, NFATc2 and NFATc3, indicating that JNK signaling can inhibit calcineurin-mediated translocation of NFAT isoforms to the nucleus (Liang et al., 2003), (Ricci et al., 2005). Conversely, activation of NFAT during HF may be due to downregulation of JNK, as well as Ca^{2+} overload. Activation of JNK can result in cardiac dysfunction through modulation of gap junctions. TG hearts with chronic JNK activation exhibited impaired intercellular communication associated with significant downregulation of connexin-43 expression and loss of gap junctions in myocardium (Petrich et al., 2002). The extent of reduction in Cx43 mRNA expression (40% of normal) in JNK-activated cardiomyocytes shown in these studies was similar to that found in end-stage human HF (Dupont et al., 2001). Another mechanism underlying JNK-mediated detrimental, cardiac remodeling is JNK association with extracellular matrix proteins, such as matrix metalloproteinase-2. Upregulation of matrix metalloproteinase-2 was associated with its activation in both cultured cardiomyocytes (Shimizu et al., 1998) and intact hearts (Krishnamurthy et al., 2007). Finally, as will be discussed below (see 6.3), adverse effects of JNK are mediated, at least partially, through mitochondria.

Thus, JNK plays play an important role in cardiac hypertrophy, remodeling and HF. Contradictory data obtained *in vitro* and *in vivo* studies show that the activation of JNK contributes differently to cardiac hypertrophy depending on the duration and severity of stimuli. During early-stage hypertrophy, JNK apparently involves in compensatory mechanisms in response to extracellular stimuli, however, sustained JNK activation concurrently with other signaling pathways promotes pathological hypertrophy. However, it still remains unclear why JNK activation has a dual nature, when Dr. Jekyll becomes Mr. Hyde, and *vice versa*.

3.4. ERK5

The ERK5 kinase cascade begins with activation of MEKK2/3, which activates MEK5. MEK5, then, activates ERK5 (Pearson et al., 2001). As discussed earlier, ERK5 is highly specific, and its overexpression in cultured cells does not activate other MAPKs (English et al., 1995). Many studies demonstrated that MEK5-ERK5 signaling is activated by growth stimuli via RTKs and GPCRs (Kato et al., 1997, Kamakura et al., 1999, Garcia-Hoz et al., 2012), as well as by oxidative and osmotic stresses (Abe et al., 1996). Epidermal growth factor receptors have been shown to mediate hypertrophic signaling through an MEK5-ERK5-MEF2A pathway in H9c2 cardiomyocytes (Lee et al., 2011). ERK5 signaling may be regulated differently from ERK1/2 in cardiac cells (Takeishi et al., 1999), although MEK1 inhibitors were able to inhibit ERK5, suggesting that the growth stimuli previously attributed to ERK1/2 may also be mediated via ERK5 (Kamakura et al., 1999). Gain- and loss-of-function studies demonstrated that ERK5 regulated many transcription factors responsible for postnatal cardiac growth and hypertrophy, suggesting an essential role for ERK5 signaling during cardiac development and pathogenesis (MacLellan and Schneider, 2000). Similar to other MAPKs, *in vivo* and *in vitro* studies demonstrated that various hypertrophic stimuli and growth factors rapidly and transiently enhanced ERK5 activity in cultured cardiomyocytes (Ikeda et al., 2005, Nicol et al., 2001) and intact hearts (Takeishi et al., 2001, Kacimi and Gerdes, 2003). Recent studies in dogs demonstrated that volume overload-induced eccentric hypertrophy increased the localization of p-ERK5 in caveolae and selectively activated ERK5 signaling (Liu et al., 2013). However, the progression of hypertrophy to HF reduced ERK5 activity to normal levels (Kacimi and Gerdes, 2003), or even lower levels (Takeishi et al., 2002).

ERK5 has been shown to play an essential role in the regulation of the cardiovascular network, including vascular metabolism, heart contractility and cell growth (Deng et al., 2007, Roberts et al., 2010, Wang et al., 2005). Targeted deletion of ERK5 in adult mice was associated with altered vascular integrity and endothelial failure (Hayashi et al., 2004). Deletion of the *erk5* gene in mice caused defects in the development of the heart and its blood vessels, which were severe enough to result in embryonic lethality (Regan et al., 2002). Likewise, inhibition of ERK5 activity by the overexpression of DN-ERK5 stimulated apoptosis in microvascular endothelial cells of the lung (Pi et al., 2004). In contrast, CA-MEK5 overexpression inhibited growth factor deprivation-induced apoptosis in these cells. The anti-apoptotic effects were associated with the ability of ERK5 to phosphorylate Bad, independent of Akt, PKA, or $p90^{RSK}$ kinase activity (Pi et al., 2004). The MEK5-ERK5 pathway can also modulate cardiac metabolism and hypertrophy by regulating cAMP, an important second messenger in physiological and pathological hearts. In cardiomyocytes, the muscle-specific A-kinase anchoring protein has been shown to maintain the cAMP-responsive signaling complex, which includes PKA, phosphodiesterase 4D3 (PDE4D3) and Epac1. The muscle-specific A-kinase anchoring protein-ERK5 complex suppresses PDE4D3 and facilitates cytokine-induced cardiomyocyte hypertrophy (Dodge-Kafka et al., 2005). Cardiac specific expression of CA-MEK5α reduced pressure overload-induced apoptosis and cardiac dysfunction by inhibiting a PDE3A/inducible cAMP early repressor (ICER) feedback loop (Yan et al., 2007). In addition, ERK5 interacts with the C terminus of Hsc70-interacting protein (CHIP); the ERK5-CHIP complex plays an obligatory role in the

inhibition of ICER expression, cardiac apoptosis, and pressure overload-induced dysfunction (Woo et al., 2010). Collectively, these data suggest that ERK5-induced regulation of cAMP-dependent feedback loops prevents myocardial remodeling and HF (Fig. 5).

The MEK5-ERK5 pathway also regulates myofibril contractility by influencing sarcomeric assembly and organization. Activation of MEK5 signaling in cultured cardiomyocytes resulted in serial sarcomere assembly, a process also induced by the interleukin-6 family cytokines leukemia inhibitory factor (LIF) and cardiotrophin-1 (CT-1) (Nicol et al., 2001). Expression of DN-MEK5 specifically abrogated elongation of cardiomyocytes without blocking parallel assembly of sarcomeres and reduced expression of a subset of fetal genes induced by LIF (Nicol et al., 2001, Nakaoka et al., 2003). Furthermore, activated MEK5 induced rapidly decompensating eccentric cardiac hypertrophy in TG mice, indicating a key role for MEK5 in the regulation of *in vivo* serial sarcomere assembly (Nicol et al., 2001). Likewise, eccentric cardiac hypertrophy induced by long-term, intermittent hypoxia in rats was associated with activation of the MEK5-ERK5 pathway (Chen et al., 2007). It is known that PE or ET-1 induces hypertrophy increasing cell size in all dimensions whereas LIF or CT-1 increases cell length by adding sarcomere units in a serial rather than parallel fashion in cultured myocytes (Wollert et al., 1996). Targeted inactivation of gp130 in ventricular myocytes resulted in rapid chamber dilation and myocyte apoptosis upon pressure overload (Hirota et al., 1999). These studies suggested that gp130 signaling may have a specific role in eccentric hypertrophy, which is mostly associated with volume overload. Accordingly, cell hypertrophy induced by CT-1, an activator of several signaling pathways via gp130, was suppressed by overexpression of DN-MEK5 (Takahashi et al., 2005), indicating that the MEK5-ERK5 pathway is a major pathway responsible for the hypertrophic responses to CT-1. Furthermore, activation of gp130 in cardiomyocytes mediated hypertrophic signaling through the scaffolding/docking protein Gab1-tyrosine phosphatase SHP2 complex, indicating that Gab1-SHP2 interaction plays a crucial role in gp130-dependent longitudinal elongation of cardiomyocytes through activation of ERK5 (Nakaoka et al., 2003).

It should be noted that, like other MAPKs, isoforms of MEK5, MEK5α and MEK5β, differently contribute to cardiac hypertrophy. As mentioned previously, transgenic mice with CA-MEK5β developed eccentric cardiac hypertrophy (Nicol et al., 2001) whereas mice with MEK5α overexpression demonstrated no significant difference in response to hypertrophic stimuli (Cameron et al., 2004). This difference may be due to distinct tissue-wide distribution and cellular localization of MEK5α and MEK5β. Interestingly, MEK5α, but not MEK5β, activates BMK1 (Kobayashi et al., 1997).

In conclusion, MEK5-ERK5 signaling possesses specific features, such as regulation of vascular metabolism, and assembly of sarcomeres, which significantly distinguish these kinases from other MAPKs. However, many questions related to the role of the MEK5-ERK5 axis in the pathogenesis of cardiac hypertrophy and HF still remain unclear. Lack of specific inhibitors hampers an understanding of the contribution of MEK5/ERK5 to cell metabolism.

4. MAPKs in acute cardiac stress (myocardial infarction and ischemia/reperfusion)

4.1. ERK1/2

Both *in vivo* and *in vitro* studies have yielded conflicting results on the effect of acute cardiac ischemia (infarction) on ERK1/2 activity. Global 10-min or 20-min ischemia did not activate ERK1/2 in the Langendorff-perfused rat heart (Bogoyevitch et al., 1996). Likewise, IR failed to activate cytosolic ERK1/2, however, it markedly increased phosphorylation of nuclear ERK1/2 in rabbit hearts (Ping et al., 1999). The authors suggested that the IR-induced activation of ERK1/2 occurred in the cytoplasm and was followed by translocation to the nucleus. As mentioned earlier, activation of the Ras-ERK pathway exerts anti-apoptotic effects. Genetic inhibition of cardiac ERK1/2 (Purcell et al., 2007) and Raf (Yamaguchi et al., 2004) promoted stress-induced apoptosis and HF, which suggests that the activation of ERK signaling can provide cardioprotection against oxidative stress. Notably, Raf may exert anti-apoptotic effects by downregulating the apoptotic proteins Ask1 and Mst2, independent of MEK-ERK activity (Chen and Sytkowski, 2005). TG mice hearts with activated MEK1-ERK signaling were protected from apoptosis and were resistant to ischemia-reperfusion injury (Bueno et al., 2000, Lips et al., 2004). Anti-apoptotic effects of ERK1/2 may be explained by its activation of multiple downstream effectors that diminish apoptotic pathways and stimulate pro-survival mechanisms. For example, ERK1/2 can phosphorylate $p90^{RSK}$, which in turn induces phosphorylation and inactivation of multiple pro-apoptotic proteins, including the Bcl-2 family member Bad, eventually resulting in cellular protection (Bonni et al., 1999) (Fig. 2). Activation of ERK1/2 increased expression of iNOS and eNOS, and enhanced the Bcl-2/Bax ratio associated with cardioprotection against IR (Das et al., 2008). NOS-derived NO may trigger pro-survival mechanisms through the activation of guanylate cyclase leading to cGMP production, PKG activation, and opening of mitochondrial ATP-sensitive potassium ($mitoK_{ATP}$) channels. ERK1/2 can interact with PKCε in the mitochondria to facilitate cardioprotection (Baines et al., 2002) (see 5.1.). ERK1/2 can phosphorylate GATA4, a transcription factor that promotes the expression of anti-apoptotic Bcl-2 proteins (Liang et al., 2001, Kobayashi et al., 2006). Thus, there is growing evidence that activation of the Ras-ERK pathway exerts cardioprotective effects against MI and IR through a number of downstream targets. Cardioprotective effects of ERK signaling involve a complex interplay of various regulatory mechanisms which are still being unraveled.

4.2. p38

Studies of both isolated cell cultures and intact hearts reported early transient activation of p38 in response to oxidative stress induced by ischemia or reperfusion (Bogoyevitch et al., 1996, Ma et al., 1999, Abe et al., 2000, Ping and Murphy, 2000). Activation of p38 does not always correlate with its detrimental or beneficial actions due to cyclicity of p38 activation and variability of oxidative stress. Using different p38 inhibitors, a large number of studies demonstrated that activation of p38 promotes cardiac dysfunction (Nagarkatti and Sha'afi, 1998, Ma et al., 1999, Mackay and Mochly-Rosen, 1999, Barancik et al., 2000, Clark et al., 2007, Martin et al., 2001), whereas others revealed cardioprotective effects of p38 activation

(Weinbrenner et al., 1997, Maulik et al., 1998, Mocanu et al., 2000, Bell et al., 2008). Interestingly, cardioprotective effects of p38 activation are mostly induced by ischemic preconditioning (IPC); brief repeated periods of IR prior to sustained ischemia protected hearts against oxidative stress, in part, by rapidly activating p38 (Weinbrenner et al., 1997, Maulik et al., 1998, Mocanu et al., 2000, Steenbergen, 2002, Bell et al., 2008).

The use of non-specific inhibitors along with variability in models, timing, and severity of stresses complicates understanding downstream targets of p38 signaling and its contribution to cardiac IR injury. Genetic studies discovered differential contributions of p38 isoforms, predominantly p38α and p38β, to cardiac dysfunction during ischemia. The use of the chemical-genetic approach and p38 inhibitors revealed that p38α is the dominant-active p38 isoform (Kumphune et al., 2010). It is activated by autophosphorylation and contributes to infarction, which is prevented by the direct binding of SB203580, a p38 inhibitor. Neonatal rat cardiomyocytes infected with adenoviruses encoding p38α or p38β showed isoform-selective activation during sustained, simulated ischemia; p38α remained activated but p38β did not. Moreover, cells expressing DN-p38α were resistant to lethal simulated ischemia, which suggests that inhibition of p38α reduces ischemic injury in this model (Saurin et al., 2000). Likewise, both cultured cardiomyocytes and intact hearts with inactive p38α were resistant against IR injury (Kaiser et al., 2004). Selective inhibition of p38α improved cardiac function and reduced myocardial apoptosis in a rat model of myocardial injury (Li et al, 2006). Ischemic injury was increased in hearts with DN-p38β but not DN-p38α (Cross et al., 2009), which demonstrates that loss of p38β promotes cardiac dysfunction during ischemia. It is important to note that many previous studies used pharmacological inhibitors of p38 that were not isoform-specific. Concurrent inhibition of p38α or p38β complicates the interpretation of results because activation of these isoforms in cardiac cells has different consequences. Furthermore, ATP-competitive inhibitors including the p38 type I inhibitor, SB203580, are not always specific, since they compete for the ATP binding site of all kinases (Clerk and Sugden, 1998, Hall-Jackson et al., 1999, Lali et al., 2000). For p38, this issue was partially solved by developing type II inhibitors that bind to the lower edge of the ATP-binding pocket in the C-terminal lobe. Type II inhibitors of p38 (e.g. BIRB796) selectively interact with and stabilize an inactive, ATP-binding transit pocket, thus, preventing its further activation (Pargellis et al., 2002, Kuma et al., 2005, Denise Martin et al., 2012).

Many gain- and loss-of-function studies revealed that p38 participates in induction of pro-apoptotic signals in cardiac IR (Fig. 3). p38 activation during cardiac IR was associated with TNFα-induced apoptosis, ROS generation, Ca^{2+} overload and mitochondrial dysfunction, and inhibition of p38 exerted cardioprotective effects and abrogated metabolic alterations (Dhingra et al., 2007, Schwertz et al., 2007, Sucher et al., 2009b). In addition, p38 participates in the regulation of glycogen synthesis and glycolysis in ischemic hearts (Jaswal et al., 2007).

Hearts of the MAPK activated protein kinase (MAPKAP) kinase 2 (MK2) knock-out mice were resistant to myocardial IR injury as evidenced by enhanced post-ischemic recovery of ventricular performance, reduced myocardial infarct size and apoptosis confirming that MK2, a downstream target of p38, is also involved in transmitting the death signal to the

ischemic myocardium (Shiroto et al, 2005). Activation of p38 in response to cellular stresses was associated with increased cellular resistance through enhanced actin cytoskeleton reorganization via the p38-MK2-Hsp27 pathway (Guay et al, 1997, Huot et al, 1997). Activation of the p38α-MK2 pathway stimulated phosphorylation of αB-crystallin, a heat shock protein family member, and protected cardiomyocytes against stress-induced apoptosis (Hoover et al, 2000) or myocardial infarction (Shu et al, 2005). Likewise, cardioprotective effects of MKK6 over-expression against IR and myocardial infarction was associated with increased αB-crystallin levels in the TG mice further supporting the protective role for this pathway (Degousee et al., 2003, Martindale et al, 2005).

Activation of p38 mediated cardioprotective effects of insulin against IR in rat hearts through phosphorylation of Hsp27 (Li et al., 2008). However, p38-induced phosphorylation may not be required for the cardioprotective effects of Hsp27 since overexpression of wild-type Hsp27 or a non-phosphorylatable Hsp27 mutant protein was equally capable of protecting the mouse heart from global IR. This indicates that the protection may be caused by different mechanisms or loci of action (Hollander et al., 2004). In this study, nonphosphorylatable Hsp27 mutants even reduced oxidative stress with greater efficacy than wild-type Hsp27 TG mice. Notably, inhibition of p38 with SB203580 stimulated cell necrosis but blocked contractility during reperfusion and offered cardioprotection against IR indicating a dual role of p38 activation (Sumida et al, 2005). Diminished contractility was observed in hearts of MKK3 or MK2 knock-out mice in response to TNFα (Bellahcene et al, 2006). Differential role of p38 activation was also supported by a study in which p38-mediated F-actin reorganization may stimulate apoptotic cell death and, at the same time, conversely protect against osmotic stress-induced necrosis in neonatal cardiomyocytes (Okada et al, 2005).

In conclusion, existing *in vivo* and *in vitro* studies demonstrate that oxidative stress induced by acute MI or IR causes activation of p38 in isolated cultured cardiomyocytes and hearts. Short activation of p38 in the heart, for instance, in IPC, may be cardioprotective whereas chronic activation within sustained ischemia (infarction) and reperfusion may have detrimental effects on heart function. Activation of p38 is cyclic and may have different consequences depending on models, and timing and severity of oxidative stress. Although inhibition of p38α on various animal and cell models leads to cardioprotection confirming the role of p38α in cardiac dysfunction, greater basic and preclinical research is still needed to identify appropriate targets of p38 for clinical conditions.

4.3. JNK

Similar to p38, JNK plays a dual role in IR, mediating both protective and detrimental effects depending on the timing and severity of oxidative stress. Interestingly, both genetic inhibition and activation of JNK1/2 protected the heart from IR-induced apoptosis *in vivo* (Kaiser et al., 2005). These studies suggest that cellular protection induced by sustained inhibition or activation of JNK is likely mediated through different mechanisms. Many studies using various *in vitro* and *in vivo* models revealed robust activation of JNK upon reperfusion following ischemia (Laderoute and Webster, 1997, Yin et al., 1997, Fryer et al., 2001). Conversely, pharmacological inhibition of JNK reduced IR-induced infarct size and

apoptosis in hearts (Ferrandi et al., 2004, Milano et al., 2007). Inhibition of JNK in H9c2 cardiomyocytes blocked stress-induced apoptosis (Gabai et al., 2000), and DN-JNK mutants antagonized H_2O_2-induced apoptosis in adult cardiomyocytes (Kwon et al., 2003). Mutated JNK attenuated β-adrenergic-stimulated apoptosis in cardiomyocytes through a mitochondria-dependent mechanism (Aoki et al., 2002, Remondino et al., 2003). Interestingly, inhibition of JNK1 protected cardiomyocytes from ischemia-induced apoptosis, whereas JNK2 inhibition had no effect (Hreniuk et al., 2001). On the other hand, deletion of MEKK1, a direct upstream activator of MKK4 and MKK7, induced more cardiac apoptosis in mouse hearts following pressure overload stimulation (Sadoshima et al., 2002). This is consistent with the observation that JNK inhibitory mutants increased the rates of apoptosis in cultured neonatal cardiomyocytes subjected to hypoxia and reoxygenation by almost 2-fold compared with control cultures (Dougherty et al., 2002). Likewise, cultured cardiomyocytes with DN-JNK1 or DN-MKK4 exhibited enhanced nitric oxide-induced apoptosis (Andreka et al., 2001). In conclusion, confounding experimental results suggest that JNK may simultaneously and distinctly modulate both pro-and anti-apoptotic signaling pathways in the heart. The effects of JNK on apoptosis are mediated, at least in part, by stimulation of caspase-dependent (Aoki et al., 2002) and caspase-independent pathways (Song et al., 2008, Zhang et al., 2009) in the mitochondria (see 6.3). Thus, in response to oxidative stress in cardiomyocytes, complex JNK signaling may be simultaneously protective and detrimental. Ultimate effects apparently depend on crosstalk between JNK and other signaling pathways.

4.4. ERK5

Few studies discuss the role of ERK5 in cardiac IR. Initial studies in perfused guinea pig hearts revealed maximal activation of BMK1 within 30 min of ischemia (Takeishi et al., 1999). Reperfusion of the hearts reduced ERK5 activity to normal values, but, interestingly, activated ERK1/2. These results suggest that ERK5 and ERK1/2 mediate different signaling during reperfusion. Furthermore, maximal ERK5 activation by ischemia was significantly enhanced by IPC (Takeishi et al., 2001). Cardiac-specific CA-MEK5α TG mice exhibited a 3–4-fold increase in ERK5 activation and were highly resistant to IR, as evidenced by their greater cardiac recovery after IR compared to wild-type mice (Cameron et al., 2004). However, cardiac function did not improve after MI induced by permanent ligation in CA-MEK5α TG mice (Shishido et al., 2008). Cardioprotection from MI was enhanced in hyperglycemic CA-MEK5α TG mice. These data suggest that ERK5 activation does not have a significant cardioprotective role in the permanent ligation-induced MI model *per se*, although it has a significant role in diabetes after MI, at least during the acute (1-week) phase of post-ligation (Shishido et al., 2008). We have previously discussed the role of ERK5 to prevent pressure overload-induced apoptosis and cardiac dysfunction via interaction with ICER and CHIP (see 3.4)(Yan et al., 2007, Woo et al., 2010). ICER and CHIP influence apoptosis by regulating cAMP levels. Interestingly, diabetic mice after MI demonstrated significantly high levels of ICER, which was blunted in CA-MEK5α TG mice. This suggests that ERK5 exerts cardioprotective effects against MI in diabetic mice via downregulation of ICER (Shishido et al., 2008). ERK5 can protect diabetic hearts against MI by receiving posttranslational SUMOylation. SUMOylation of ERK5 was found to inhibit its transcriptional activity in cardiomyocytes (Woo et al., 2008). Diabetes

complicated by MI, but not MI alone, increased ERK5-SUMOylation. Furthermore, CA-MEK5α TG mice inhibited ERK5-SUMOylation, thereby preventing cardiac dysfunction and apoptosis (Shishido et al., 2008). This study demonstrates that ERK5 activity can be downregulated by diabetes-dependent SUMOylation leading to post-MI cardiac dysfunction. Furthermore, the ERK5-CHIP complex is targeted by $p90^{RSK}$ in diabetic hearts, and $p90^{RSK}$ prevents ERK5-mediated CHIP activation and promotes apoptosis and cardiac dysfunction in post-MI diabetic mice. Activation of $p90^{RSK}$ disrupts ERK5-CHIP interaction by phosphorylation of ERK5 at S496 and binding of $p90^{RSK}$ to ERK5, causing dislocation of CHIP from ERK5 (Le et al., 2012). In conclusion, many questions with regard to the cause-and-effect relationship between ERK5 activation and attenuation of cardiac dysfunction and cell death remain unanswered. ERK5 participates in MI- and IR-induced cardiac response to oxidative stress. However, the precise mechanisms underlying ERK5 regulation of IR and permanent (non-reperfused) MI signaling are still unknown.

5. Mitochondrial localization of MAPKs

Mitochondria are subcellular organelles that serve as the targets and end-effectors for a myriad of cellular metabolic pathways, including cell signaling, redox control, ion homeostasis, lipid metabolism, cell growth, and cell death. Indeed, they provide approximately 90% of the ATP required for cell metabolism in the heart and represent the major source of cellular physiological and pathological ROS. In response to various extra- and intracellular stimuli, the dynamic mitochondria exhibit bidirectional motility and undergo extensive shape changes via fission-fusion (Hom and Sheu, 2009). Furthermore, mitochondria have their own genome which involves over 1,000 genes. Mitochondrial DNA encodes for 13 proteins of the electron transport chain (ETC) and oxidative phosphorylation, and the RNA genes for their translation in mitochondria. Mitochondrial DNA is not protected by histones and, therefore, has a very high (~1000 times) mutation rate compared to nuclear DNA (Wallace, 2010).

Adult cardiomyocytes contain about 5000 mitochondria, which occupy 30–35% of the cell volume. Moreover, cardiomyocytes contain two functionally distinct mitochondrial subpopulations, which differ with regard to oxygen consumption rates, Ca^{2+} sensitivity and ROS production; subsarcolemmal mitochondria (SSM) reside beneath the plasma membrane, and interfibrillar mitochondria (IFM) are located between myofibrils (Lesnefsky and Hoppel, 2003, Marzetti et al., 2013). Structurally, mitochondria consist of two membranes, the outer mitochondrial membrane (OMM) and the inner mitochondrial membrane (IMM), and the intermembrane space (IMS) between them. The OMM is permeable to molecules with a molecular mass less than 6 kDa, which pass through the membrane using voltage-dependent anion channel pores. The IMS contains over 100 proteins, including apoptotic proteins such as cytochrome c, apoptosis-inducing factor, the second mitochondrial activator of caspases (Smac)/direct IAP-binding protein with low pI (DIABLO), mammalian serine protease Omi/high-temperature requirement protein A2 (Omi/HtrA2), and endonuclease G. The release of such proteins from mitochondria into the cytoplasm stimulates both caspase-dependent and caspase-independent apoptosis. In contrast, the IMM is impermeable and uses distinct channels, exchangers and pumps to transport ions and other compounds to and from the matrix. A major part of ~500 proteins

localized in the matrix are encoded by nuclear genome and transported into the matrix through the transporter outer membrane and transporter inner membrane (TOM/TIM) protein translocation machinery (Muro et al., 2003).

Mitochondrial regulation of MAPK cascades, in particular, is especially intriguing because mitochondria-MAPK interactions are, perhaps, potent regulators in the pathogenesis of cardiac diseases. Several studies revealed direct interactions between MAPKs and mitochondria. Major lines of evidence are derived from studies using isolated mitochondria and/or morphological observations. However, the claim of translocation of MAPKs to the mitochondrial matrix was questioned by studies that reported interactions between MAPKs and OMM, as well as MAPK translocation to the IMS, but did not observe translocation to the matrix. Growing evidence suggests that not only MAPKs, but also their interacting kinases interact with mitochondria (Aoki et al., 2002, Ferreira et al., 2014). In the following sections, mitochondrial localization of MAPKs, as well as the role of MAPKs in the modulation of mitochondrial metabolism and, *vice versa*, the impact of mitochondria on MAPK signaling, will be discussed.

5.1. ERK1/2

In addition to the cytoplasm and the nucleus, ERK1/2 is also found in mitochondria of the heart (Baines et al., 2002), brain (Alonso et al., 2004, Rumora et al., 2007), renal cells (Nowak et al., 2006, Zhuang et al., 2008), human alveolar macrophages (Monick et al., 2008) and different cell lines, such as B65 cells (Kulich et al., 2007) and SHSY5Y cells (Dagda et al., 2008). Active (phosphorylated) ERK1/2 was found mostly at the OMM and in the IMS of brain mitochondria. ERK1/2 translocation to brain mitochondria followed a brain developmental pattern in rats (Alonso et al., 2004). In the same study, MEK1/2 was detected in brain mitochondria. Severe oxidative stress induced by H_2O_2 or antimycin decreased ERK1/2 activity significantly in mitochondria. Initial studies using double label confocal microscopy and immuno-electron microscopy reported localization of phospho-ERK1/2 at high labeling densities in mitochondria and autophagosomes of brain tissue in subjects with Parkinson's disease and Lewy body dementia (Zhu et al., 2003). Phospho-ERK1/2 immunoreactivity in these studies was often associated with mitochondrial proteins, mitochondrial superoxide dismutase and mitochondrial antigens. Transmission electron microscopy of immunolabeled LP07 cells detected ERK1/2 in mitochondria. In these cells, increased ERK1/2 activity in mitochondria and nuclei was observed within 1h of oxidative stress, after which the activity returned to basal levels in mitochondria but remained elevated in nuclei (Galli et al., 2008). Cardiac mitochondria of exercised rats exhibited elevated levels of RAF, an upstream mediator of ERK1/2 (Ferreira et al., 2014). Cardiac-targeted PKCε TG mice demonstrated that transgenic activation of PKCε greatly increased mitochondrial PKCε and its interaction with mitochondrial ERK1/2. Interestingly, both active and inactive PKCε bound to ERK1/2, however, increased phosphorylation of mitochondrial ERK1/2 was observed only in mice expressing active PKCε (Baines et al., 2002). Pre-ischemic increases in phospho-ERK1/2 induced by the adenosine A1/A2a receptor agonist AMP-579 were blunted by the ERK1/2 inhibitor U-0126, though only in cardiac mitochondrial and membrane fractions (Reid et al., 2005).

5.2. p38

Few studies demonstrated direct interactions between p38 and mitochondria in the heart in response to oxidative stress (Ballard-Croft et al., 2005, Sharma et al., 2010). In one study, p38 bound to and stimulated carnitine palmitoyltransferase-1 in mitochondria isolated from rat hearts, thus suggesting a novel regulatory mechanism of mitochondrial fatty acid metabolism (Sharma et al., 2010). Ischemia only induced activation of p38 in the mitochondria, whereas reperfusion increased p38 activity in cytosolic, mitochondrial and membrane fractions. Treatment with the adenosine receptor agonist AMP-579 before ischemia significantly increased p38 activity in the nuclear/myofilament fraction, whereas no activation occurred during ischemia or reperfusion (Ballard-Croft et al., 2005).

5.3. JNK

Previous *in vitro* and *in vivo* studies demonstrated the existence of mitochondrial JNK signaling in different cell types (Kharbanda et al., 2000, Ito et al., 2001, Hanawa et al., 2008, Zhou et al., 2008, Zhou et al., 2009, Zhao and Herdegen, 2009), including adult cardiomyocytes (Aoki et al., 2002). Active recombinant JNK1 was found in isolated mitochondria, but its presence was proteinase-sensitive, implying that JNK interacted with mitochondria and did not cross OMM (Zhou et al., 2008). Activation of JNK by upstream MAP2Ks stimulated translocation of a small population of JNKs to mitochondria (Weston and Davis, 2007), and inhibition of JNK activation by N-acetylcysteine, an antioxidant that prevents JNK activation during stress, blocked JNK translocation to the mitochondria in HeLa cells. Active JNK can bind to mitochondria via the mitochondria-related JNK interacting protein, Sab (Wiltshire et al., 2002, Wiltshire et al., 2004). Two kinase interaction motifs (KIMs), KIM1 and KIM2, have been shown to facilitate the interaction between JNK and Sab, although, only KIM1 was necessary for JNK binding and JNK-mediated Sab phosphorylation (Wiltshire et al., 2002). Interestingly, Sab is associated with the mitochondria and co-localizes with activated JNK in response to oxidative stress (Wiltshire et al., 2004). Furthermore, inhibition not only of JNK, but also of Sab reduced infarct size in rat hearts after heart IR (Chambers et al., 2013). Inhibition of Sab also prevented 6-hydroxydopamine (6-OHDA)-induced oxidative stress, mitochondrial dysfunction, and neurotoxicity *in vitro* and *in vivo* (Chambers et al., 2013). Apparently, inhibition of JNK-Sab interactions prevents cell death by inhibiting the detrimental mitochondrial ROS amplification loop. Currently, a peptide form of the JNK-Sab inhibitor is used as a specific inhibitor (Chambers et al., 2011). Interestingly, only JNK2 translocated to mitochondria in response to 6-OHDA-induced stress in PC12 cells (Eminel et al., 2004), indicating that JNK1 and JNK2 may play different roles in cardiomyocytes. In addition, upstream kinases of JNK also can interact with mitochondria. Oxidative stress induced translocation of activated JNK and its upstream kinase SEK1 (MKK4) to mitochondria in adult rat cardiomyocytes. The subcellular distribution of total JNK1 and SEK1 (MKK4) did not change significantly upon oxidative stress, however, mitochondrial JNK was phosphorylated, whereas cytosolic JNK remained non-phosphorylated in response to oxidative stress (Aoki et al., 2002). Notably, inhibition of mitochondrial JNK signaling also blocked activation of MKK4, an upstream activator of JNK (Win et al., 2011).

6. MAPKs regulate mitochondrial metabolism

Many studies report that the pro-survival and pro-death effects of MAPKs converge on mitochondria. MAPKs can modulate mitochondrial metabolism directly, through the interaction of individual MAPK members with mitochondria, or indirectly, by activation/inhibition of MAPK-dependent downstream signaling molecules that modulate metabolism and function of mitochondria. The roles of mitochondria in the mediation of MAPK signaling are summarized in Table 1 and shown in Fig. 6. An analysis of existing studies on MAPKs revealed little information with regard to the role of ERK5 in the regulation of mitochondrial metabolism and function. Therefore, bidirectional interactions between ERK5 and mitochondria will not be discussed in following sections.

6.1. ERK1/2

ERK1/2 MAPK participates in regulating processes like cell differentiation, proliferation, growth, adaptation, survival, and death. The role of the Ras-Raf-MEK-ERK1/2 pathway in the regulation of metabolism and function of mitochondria still remains unclear. Individual members of this pathway can mediate pro- and anti-apoptotic signals depending on their intracellular localization and types of stimuli (Majewski M et al., 1999, Alavi et al., 2003,Chu et al., 2004 Hetman et al., 2004). Activation of ERK1/2 can improve mitochondrial function, and inhibition of the Ras-ERK1/2 pathway is associated with cell death. Both MEK1 and ERK1/2 inhibitors diminished F_1F_0-ATPase activity and induced necrosis in glucose-deprived astrocytes (Yung et al., 2004). In response to toxic stress, inhibition of ERK1/2 with PD98059 induced collapse of $\Delta\Psi_{mit}$ and promoted cytochrome c release from mitochondria into the cytosol that was associated with enhanced neuronal cell death (Lee et al., 2004). Blocking of CB2 receptors exerted cardioprotective effects against IR and increased ERK1/2 phosphorylation associated with reduced cytochrome c release, high $\Delta\Psi_{mit}$ and low PTP opening (Li et al., 2014). In alveolar macrophages, ERK1/2 has been shown to regulate mitochondrial integrity and ATP production. DN-MEK cells treated with U0126 exhibited ATP depletion in a time-dependent manner. Also, ERK inhibition resulted in a rapid loss of $\Delta\Psi_{mit}$ and induced cell death (Monick et al., 2008). PKCα and ERK1/2 mediated cisplatin-induced mitochondrial dysfunction and apoptosis through cytochrome c release from mitochondria in renal cells.

Mitochondrial dysfunction and depolarization of IMM was associated with increased activation and protein expression of ERK1/2 in mitochondria. Inhibition of PKCα did not prevent cisplatin-induced ERK1/2 activation, indicating that activation of ERK1/2 by cisplatin was independent of the PKCα pathway (Nowak, 2002). Oxidant-induced activation of ERK1/2, but not p38 or JNK, attenuated mitochondrial respiration and ATP production, which was associated with decreased complex I activity and substrate oxidation (Nowak et al., 2006). ERK1/2 and PKCε mediated oxidant-induced mitochondrial dysfunction through independent pathways, and protective effects of ERK1/2 inhibition were independent of Akt activation. Interestingly, the ERK1/2 pathway had no effect on the activity of Krebs cycle dehydrogenases in renal proximal tubular cells (Nowak et al., 2006).

Activated ERK1/2 colocalized with mitochondria and phosphorylated Bcl-2 (Deng et al., 2000) and Bad (Kang et al., 2003) through direct interactions with Bcl-2 family members,

thereby confirming the contribution of ERK1/2 to the stimulation of anti-apoptotic signaling. Inhibition of the MEK1/2-ERK1/2 pathway reduced phospho-inactivation of the proapoptotic protein Bad in hypoxic cultures of neurons, suggesting that a cell-survival program involving activation of MEK1/2-ERK1/2 signaling is involved in cell survival via inactivation of Bad (Jin et al., 2002). Active Raf-1, fused with OMM targeting sequences, protected cells from apoptosis, a phenomenon associated with phosphorylation of pro-apoptotic Bad, whereas plasma membrane-targeted Raf-1 had no effect on apoptosis and resulted in phosphorylation of ERK1/2 (Wang et al., 1996). These data suggest that Bcl-2 can target Raf-1 to mitochondria to induce phosphorylation of Bad or possibly other protein substrates involved in apoptosis regulation. Also, this study demonstrates divergent signaling roles of plasma membrane-targeted and mitochondria-targeted Raf proteins in apoptosis.

The adapter protein Grb10 interacted with both Raf-1 and MEK1 and regulated signal transduction between plasma membrane receptors and the apoptosis-inducing complex on OMM by modulating the anti-apoptotic activity of mitochondrial Raf-1 (Nantel et al., 1999). Interestingly, the addition of cytochrome c to the cytosol of cells overexpressing B-Raf in fibroblasts failed to induce caspase activation, which indicates that the B-Raf/MEK/ERK pathway apparently confers protection against apoptosis at the level of cytosolic caspase activation, downstream of the release of cytochrome c from mitochondria (Erhardt et al., 1999). On the other hand, mitochondrial Raf-1 in myeloid cells exerted anti-apoptotic effects independent of ERK1/2 activity (Majewski et al., 1999). In endothelial cells, p21-activated protein kinase-1 (PAK-1)-induced phosphorylation of Raf1 at Ser338 and Ser339, promoted mitochondrial translocation of the protein kinase and protected the cells from the intrinsic pathway of apoptosis, independent of MEK1. However, VEGF induced activation of Raf-1 via Src kinase, leading to phosphorylation of Tyr340 and Tyr341 and MEK1-dependent protection from extrinsic-mediated apoptosis (Alavi et al., 2003). These findings demonstrate that Raf-1 regulates both cell survival and death through the modulation of mitochondrial signaling and death receptors

In addition to initiating survival signaling, the MEK-ERK pathway also stimulates cell death, as demonstrated by several studies. In rat astrocytes, toxic stress induced mitochondrial swelling and vacuolation, though this phenomenon was attenuated by ERK1/2 inhibition, indicating that the ERK signaling cascade is involved in the induction of mitochondrial vacuolation (Isobe et al., 2003). Treatment of B65 cells with 6-OHDA resulted in significant phosphorylation of ERK1/2 within mitochondrial fractions and mitochondrial ROS generation. Antioxidants inhibited ERK1/2 activation and protected the cells (Kulich et al., 2007). Insulin-like growth factor I receptor (IGFIR)-induced paraptosis, nonapoptotic cell death, was abrogated by inhibition of MEK2. Although mitochondria were not investigated in this study, the results implicate MEK activation in the induction of paraptosis (Sperandio et al., 2004). Doxorubicin-induced apoptosis in H9c2 cells and neonatal cardiomyocytes was associated with $\Delta\Psi_{mit}$ collapse and activation of ERK1/2 and p53 with no significant changes in p38 and JNK phosphorylation. Specific inhibitors of ERK1/2 and p53 attenuated the increased phosphorylation of ERK1/2 and p53 and prevented the toxic effects of doxorubicin (Liu et al., 2008). The ERK1/2 inhibitor U0126 effectively abrogated the anti-apoptotic effects of lovastatin, a cholesterol-lowering drug, on

the mitochondrial apoptotic pathway during hypoxia in mesenchymal stem cells, confirming that ERK1/2 activation can initiate pro-death signaling (Xu et al., 2008). Since activation of mitochondrial ERK1/2 was sufficient to induce autophagy and mitophagy, ERK1/2 could act as a downstream target for different stressors and promote cell death (Dagda et al., 2008). Notably, detrimental effects of ERK1/2 activation are dependent on subcellular compartmentalization of the MAPK (Reviewed in Chu et al., 2004, Dagda et al., 2009). In various models of toxicity in neuronal cells, a major fraction of activated ERK1/2 was found in the cytoplasm and mitochondria, but only a small amount translocated to the nucleus (Zhu et al., 2002, Dagda et al., 2008). Pro-death effects of ERK1/2 can also be mediated through different downstream targets, independent of direct mitochondrial targeting.

Thus, subcellular distribution/activation of ERK1/2 could decisively disrupt the balance between pro-survival and pro-death signals in the cell. Translocation and activation of ERK1/2 within the individual compartments of the cell, including the cytoplasm, nucleus and mitochondria, as well as the temporal and spatial coincidence with other signaling pathways, can distinctly direct survival and death pathways.

6.2. p38

Ischemia induced Bax translocation from the cytoplasm to mitochondria in neonatal cardiomyocytes, and inhibition of p38 with SB203580 blocked the translocation completely. These data link ischemia-induced p38 activation to mitochondria-mediated cell death, indicating that Bax translocation to mitochondria, a hallmark of apoptosis, occurs in response to activation of p38 (Capano, Crompton, 2006). Likewise, activation of p38 attenuated phosphorylation of Bad, another pro-apoptotic protein, and stimulated its mitochondrial translocation, inducing apoptosis in endothelial cells (Grethe, Porn-Ares, 2006). In addition, the pro-apoptotic effects of p38 may be due to its capacity to downregulate expression of Bcl-2, an anti-apoptotic protein that antagonizes interactions of Bax and Bad with mitochondria. In neonatal cardiomyocytes, genetic inhibition of p38 up-regulated Bcl-2, whereas overexpression of the active p38 mutant reduced Bcl-2 protein levels (Kaiser et al., 2004). These studies are consistent with *in vivo* observations, in which the hearts of mice expressing DN-p38 and MKK6 were protected from IR injury, and inhibition of p38 signaling resulted in up-regulation of Bcl-2 (Kaiser et al., 2004). MKK6 TG mice exhibited reduced expression of oxidative phosphorylation and fatty acid oxidation proteins, along with reductions in several proteins involved in apoptosis (Wall et al., 2006). p38 inhibition reduced IR-induced apoptosis in perfused rabbit hearts (Ma et al., 1999), and expression of DN-p38α reduced deamidation (inactivation) of the antiapoptotic protein Bcl-xL and prevented apoptosis in the mouse heart (Ren et al., 2005). Conversely, in response to TNFα, p38 phosphorylated Bcl-xL and reduced its expression due to its degradation, inducing apoptosis in endothelial cells. Inhibition of p38 by SB203580 significantly attenuated TNFα-induced apoptosis and prevented Bcl-xL phosphorylation and degradation in proteasomes, suggesting that p38 is essential for apoptosis. Interestingly, a time-dependent increase of active p38 was observed in mitochondria of cells exposed to TNFα (Grethe et al., 2004).

6.3. JNK

In addition to phosphorylating several transcriptional growth factors in the nucleus and cytoskeletal proteins in the cytoplasm, activation of JNK signaling affects many aspects of mitochondrial function related to apoptosis and bioenergetics. The spatiotemporal activation of JNK is differently regulated in distinct intracellular compartments, including the cytoplasm, the nucleus and mitochondria (Bonny et al., 2005). Many studies using a variety of animal and cell models of stress demonstrated that activated JNK can be translocated to mitochondria or otherwise activated in mitochondria (Baines et al., 2002, Chauhan et al., 2003, Brichese et al., 2004, Rumora et al., 2007, Hanawa et al., 2008, Zhou et al., 2008).

Apoptosis in multiple myeloma cells was associated with translocation of activated JNK to mitochondria and the mitochondrial release of Smac into the cytosol. DN-JNK, or blocking of JNK with a specific JNK inhibitor SP600125, abrogated stress-induced release of Smac and induction of apoptosis, indicating that JNK activation is a requirement for the release of Smac during stress-induced apoptosis in multiple myeloma cells (Chauhan et al., 2003). Likewise, DN-JNK2, but not DN-JNK1, protected PC12 cells against 6-OHDA-induced cell death, which is associated with reduced translocation of JNK2 to the mitochondria, release of cytochrome c and cleavage of caspase-3 (Eminel et al., 2004). Mitochondrial JNK inactivated Bcl-2 and Bcl-xL through phosphorylation, thereby promoting apoptosis (Kharbanda et al., 2000, Lei et al., 2002, Brichese et al., 2004 Dhanasekaran and Reddy, 2008). Furthermore, translocation of JNK to mitochondria and subsequent interaction with anti-apoptotic Bcl-xL indicates that the JNK-Bcl-xL complex is a functionally important event in the initiation of apoptosis in response to gamma radiation-induced genotoxic stress of myeloid lymphoma cells (Kharbanda et al., 2000). Likewise, β-adrenergic receptor-stimulated apoptosis in cardiomyocytes was mediated through ROS/JNK-dependent activation of the mitochondrial death pathway (Remondino et al., 2003). Activation of mitochondrial JNK in MI was associated with release of cytochrome c from heart mitochondria (Aoki et al., 2002). The molecular mechanisms underlying JNK translocation to mitochondria and JNK-induced mitochondrial dysfunction remain to be fully determined.

It seems that mitochondrial JNK signaling leads to ROS generation. JNK, but not p38 or NADPH oxidase, was responsible for mitochondrial ROS generation in response to anisomycin-induced stress in HeLa cells (Chambers and LoGrasso, 2011). JNK activation, associated with increased mitochondrial ROS generation, has been found to be involved in myocardial cell death induced by hypoxia-reoxygenation (Cicconi et al., 2003, Sucher et al., 2009a). Mitochondrial ROS, in addition to Ca^{2+} overload and ATP depletion, is a main factor leading to the mitochondrial permeability transition. Therefore, mechanisms involved in permeability transition pore (PTP) opening may also link JNK activation to mitochondrial dysfunction.

Mitochondrial PTP are non-specific channels that allow ions, water and solutes with a molecular mass of 1.5 kDa to enter the matrix, leading to amplification of ROS production, mitochondrial swelling and cell death. The molecular identity of the mitochondrial PTP remains unknown. Although initial studies implicated VDAC and ANT as essential components of the PTP complex, subsequent genetic loss- and gain-of-function studies have

questioned this conclusion (*reviewed in* Javadov et al., 2009, Bernardi, 2013). The regulatory roles of cyclophilin D, ANT and phosphate carrier, in addition to the peripheral benzodiazepine receptor, creatine kinase, hexokinase, and Bcl-2 proteins, in the promotion of PTP opening have been established. Nonetheless, the precise mechanisms underlying the permeability transition still need to be elucidated. Most recently, F_1F_0-ATPase (complex V) has shown promise as a potential structural protein of the PTP complex (Giorgio et al., 2013). The role of mitochondrial PTP opening in cardiac diseases, especially in IR, has been well reviewed elsewhere (Weiss et al., 2003, Halestrap et al., 2004, Di Lisa and Bernardi, 2006). The mitochondrial PTP has been proposed to be a promising target in the treatment of cardiac diseases, such as IR and HF (Javadov et al., 2009). Direct interaction of activated JNK with proteins of the PTP complex may stimulate pore formation and promote mitochondria-mediated cell dysfunction in response to oxidative stress. However, the lack of knowledge with regard to the molecular composition of the PTP complex limits examination of the possible interactions between JNK and PTP components under pathological conditions.

In addition, mitochondrial JNK also appears to have a role in the regulation of mitochondrial bioenergetics. Mitochondrial JNK decreased respiration rates and ATP production during acetaminophen-induced liver injury (Hanawa et al., 2008). Oxidative stress induced by H_2O_2 in primary cortical neurons increased phosphorylation of JNK at OMM which was associated with the reduced activity of pyruvate dehydrogenase (PDH) due to its phosphorylation (Zhou et al., 2008). Similar observations were reported using anisomycin in aging brain mitochondria in which activation of JNK attenuated PDH activity (Zhou et al., 2009). PDH is a matrix-localized enzyme complex that is vital to energy metabolism, linking glycolysis in the cytoplasm to the Krebs cycle in mitochondria. Inhibition of PDH by JNK enhances a shift from aerobic toward anaerobic metabolism. As a result, JNK-induced mitochondrial dysfunction and reduced ATP production can initiate cell death. These studies confirm a key role of JNK in the regulation of mitochondrial energy metabolism.

Although most studies implicate JNK in stimulating cell death signaling, activation, rather than inhibition of JNK, has been shown to offer protective effects in cultured cardiomyocytes (Dougherty et al., 2002, Dougherty et al., 2004). Transfection/infection with JNK inhibitory mutants increased apoptosis in cardiomyocytes subjected to hypoxia/reoxygenation. The p38 inhibitor SB203580 provided only partial protection against apoptosis in neonatal rat cardiomyocytes, suggesting that JNK activation is protective and that the pathway is largely independent of p38 (Dougherty et al., 2002). However, our studies using the isolated Langendorff-perfused heart model revealed that inhibition of JNK leads to further compensatory activation of p38. SU3327, a JNK inhibitor, decreased IR-induced JNK phosphorylation and, interestingly, seemed to indirectly activate p38. IR greatly increased mitochondrial p38, while treatment with the JNK inhibitor increased the accumulation of both activated p38 and JNK in the mitochondrial fraction. This could, in part, account for the absence of the expected protective effect of JNK inhibition (Jang and Javadov, *submitted for publication*). MEKK1 knock-out mice demonstrated that activation of the MEKK1-JNK pathway prevented apoptosis and inflammation, thereby protecting the heart against HF and sudden death following cardiac pressure overload (Sadoshima et al.,

2002). Oxidative stress induced by IR initiated JNK activation in mitochondria and required coupled electron transport, ROS generation, and calcium flux. These factors caused the selective and sequential activation of the calcium-dependent, proline-rich kinase Pyk2 and the small GTP binding factors Rac-1 and Cdc42. Interruption of these interactions prevented JNK activation and led to a pro-apoptotic phenotype during IR (Dougherty et al., 2004). In addition, JNK activation can play a role in preconditioning, which imparts resistance to sustained oxidative stress by various internal and external factors, such as IR, inflammation, xenobiotics, and UV radiation, among others.

Collectively, most *in vivo* and *in vitro* studies revealed the role of JNK activation in promoting mitochondria-mediated cell death in response to oxidative stress. Activity of JNK in subcellular compartments as well as type and severity of stimulus presumably play a decisive role in initiating pro-death and pro-survival.

7. Mitochondria modulate MAPK signaling

Mitochondria mediate pro-survival and pro-death pathways by modulating MAPK activity. A widely accepted model of mitochondria-mediated activation of MAPKs involves mild stress-induced opening of mitoK$_{ATP}$ channels during IPC and pharmacological preconditioning. All three major MAPKs, ERK1/2, p38 and JNK, have been shown to be activated by IPC, although the precise mechanisms underlying MAPK activation during IPC still remain elusive (Fryer et al., 2001). mitoK$_{ATP}$ channels are located in IMM and widely accepted as redox sensors and effectors of many survival signaling pathways implicated in IPC and pharmacological preconditioning (Hide et al., 1996, Gross, Fryer, 1999, Broadhead et al., 2004). Activation of protein kinases in the cytoplasm induced by short-term stress triggers the opening of mitoK$_{ATP}$ channels, which in turn causes the loss of $\Delta\Psi_{mit}$ and inhibition of ETC. Depolarization of IMM reduces Ca^{2+} overload, thereby protecting the heart from subsequent, sustained IR. One of the key regulators of mitoK$_{ATP}$ channels is PKC, which is activated in response to various cellular stresses, including hypertrophic stimuli and oxidative stress (Sato et al., 1998). There are no data on the direct stimulation of mitoK$_{ATP}$ channels by MAPKs. Importantly, the opening of mitoK$_{ATP}$ channels in response to various cellular stresses induces a short mitochondrial ROS burst, which activates down-stream survival signaling molecules, including cytoplasmic MAPKs, to protect the heart. Oxidative phosphorylation accounts for ~90% of total cellular oxygen consumption, indicating that mitochondrial metabolism could significantly affect cellular ROS signaling (Marchi et al., 2012). Complexes I and III of the mitochondrial ETC generate superoxide anion (O_2^-) in the univalent reduction of O_2 (Brand et al., 2004). Although ROS are frequently thought of as harmful byproducts of cellular metabolism that damage the cell, in fact, they are important second messengers that modulate cell signaling and can be involved in cell protection. Indeed, the latter partially explains rather unsuccessful clinical trials with antioxidants (Becker, 2004).

In addition, mitoK$_{ATP}$ channels can also be activated by ROS produced in the cytoplasm and mitochondria. Non-mitochondrial ROS induced a significant increase in the activity of reconstituted myocardial mitoK$_{ATP}$ channels *in vitro*, indicating that non-mitochondrial ROS can affect mitochondria through mitoK$_{ATP}$ channels (Zhang et al., 2001). Interestingly,

mitochondrial permeability transitions induced by exogenous ROS coincide with mitochondrial ROS generation, which leads to ROS accumulation in individual mitochondrion of isolated cardiomyocytes, a phenomenon known as “ROS-induced ROS release” (Zorov et al., 2000). This constitutes a ROS-amplification loop (Hänninen et al., 2010). If an increase in ROS reaches a threshold, it results in further ROS generation. ROS can be released into the cytosol and trigger ROS-induced ROS release in the cytoplasm and neighboring mitochondria. This signaling constitutes a positive feedback mechanism and can lead to mitochondrial dysfunction and cellular injury (Zorov et al., 2000, Zorov et al., 2006). In addition, mitochondrial Ca^{2+} uptake can stimulate ROS emission through the activation of the membrane permeability transition, implying that calcium could be a part of the mitochondrial ROS-amplification loop. Notably, ROS-induced ROS release can also occur through a PTP-independent mechanism in which increased ROS triggers the opening of the inner mitochondrial membrane anion channel (IMAC), thereby resulting in a brief increase in ETC-derived ROS (Brady et al., 2006).

The p38/JNK activator anisomycin reduced infarct size, an effect that was abolished by 5-hydroxydecanoate, an inhibitor of mitoK_{ATP} channels (Baines et al., 1999). AngII induced depolarization of $\Delta\Psi_m$ within short-time periods following the increase in O_2^- generation in vascular smooth muscle cells (Kimura et al., 2005). Furthermore, cardioprotective effects of Ang II preconditioning against cardiac IR injury in vivo were eliminated by pretreatment with 5-hydroxydecanoate or apocynin, an NAD(P)H oxidase inhibitor. Both inhibitors suppressed AngII-induced activation of p38 and JNK, suggesting that preconditioning effects of Ang II against cardiac IR may be mediated through JNK and p38 activation by NAD(P)H oxidase-derived ROS-induced mitochondrial ROS (Kimura et al., 2005). Thus, ROS generation due to a short-time activation of NAD(P)H oxidase may serve as a trigger to induce the opening of mitoK_{ATP} channels and the subsequent mitochondrial ROS burst, which in turn can mediate the preconditioning effects of Ang II (Zhang et al., 2007). p38 and mitoK_{ATP} channels play important roles during adenosine-induced late preconditioning in mouse hearts. Adenosine A1 receptor-triggered delayed cardioprotection was mediated by p38 phosphorylation in Langendorff-mode perfused hearts (Zhao et al., 2001), and mitochondrial ROS initiated phosphorylation of p38 during hypoxia in embryonic chick cardiomyocytes (Kulisz et al., 2002). Activation of p38α and hypoxia-inducible factor 1 was dependent on the production of mitochondrial ROS. p38$\alpha^{-/-}$ cells failed to activate hypoxia-inducible factor 1 under hypoxic conditions. Hypoxic activation of p38α and hypoxia-inducible factor 1 was abolished by the mitochondrial complex III inhibitor myxothiazol and the antioxidant protein glutathione peroxidase 1 (Emerling et al., 2005). Interestingly, p38 is part of a ROS-induced positive-feedback loop during heart development. Sustained activation of p38 soon after birth may contribute to the loss of cell division and binucleation in mammalian cardiomyocytes (Matsuyama and Kawahara, 2011).

Inhibition of the MEK-ERK1/2 pathway by PD98059 eliminated the cardioprotective effects of IPC (da Silva R et al., 2004). Likewise, the p38 antagonist SB203580 abolished IPC-induced cardioprotection and attenuated IPC when it was administered before the IPC stimulus (Fryer et al., 2001) or prior to and during the first 15 min of the lethal ischemia (Mocanu et al., 2000). Both short and prolonged activation of MAPKs in response to oxidative stress seem to be redox-sensitive. The extent of activation of the stress-regulated

MAPKs p38 and JNK by hydrogen peroxide was similar to that induced by IR in isolated perfused hearts (Clerk et al., 1998). IPC stimulated p38 activation through mitochondrial ROS production (Zhao et al., 2001, Kulisz et al., 2002). ROS scavengers inhibited the activation of MAPKs, indicating that MAPKs are regulated by their redox states. Moreover, activation of MAPKs by mitochondrial ROS plays a central role in mediating cardioprotective signaling of IPC. Short-time increases of ROS generated by ETC act as a trigger to resist sustained IR injury through the posttranslational modification of redox-sensitive proteins, including MAPKs. Mitochondria-generated ROS activated p38α in cultured rat cardiomyocytes that had undergone prolonged hypoxia followed by reoxygenation (Kim et al., 2006).

In addition to IPC, ERK1/2 activation induced by temperature preconditioning was shown to be a downstream process of ROS generation. Both inhibition of ERK1/2 and scavenging ROS abolished the protective effect of temperature preconditioning in adult rat cardiomyocytes (Bhagatte et al., 2012). Opening of the mitoK$_{ATP}$ channel stimulated the ERK1/2 pathway and exerted cell protection by regulating mitochondrial ROS. mitoK$_{ATP}$ channel openers triggered ERK1/2 activation via mitochondria-derived ROS in THP-1 cells. Overexpression of manganese superoxide dismutase reduced ROS production and prevented ERK activation (Samavati et al., 2002). Ang II-induced activation of MAPK in the myocardium cardiovascular tissues (Zhang et al., 2004) and rat vascular smooth muscle cells (Kimura et al., 2005a) was sensitive to the ROS scavenger tempol, suggesting that activation of MAPK was redox-sensitive. In addition, AngII-induced activation of p38 and JNK was prevented by 5-hydroxydecanoate (Kimura et al., 2005b), indicating the important role of mitoK$_{ATP}$ channels in the activation of p38 and JNK. Mitochondria-generated ROS stimulated hypoxia-induced activation of p38 in cardiomyocytes (Kulisz A et al., 2002) and ERK1/2 in endothelial cells (Schafer et al., 2003). Activation of p38 and ERK1/2 induced by PE in cultured neonatal cardiomyocytes was dependent on mitochondrial ROS (Javadov et al., 2006). Electron transport-coupled calcium flux and ROS produced in mitochondria stimulated JNK activation, which enhanced resistance of neonatal cardiomyocytes to hypoxia/reoxygenation-induced apoptosis (Dougherty et al., 2004).

Acute ROS production can promote low-conductance (reversible) mitochondrial PTP opening. In contrast to high-conductance (pathological, irreversible) mode pores, the low-conductance PTP opening has a physiological role in the generation of mitochondrial depolarization spikes and the conveyance of calcium signals between individual mitochondria (Ichas et al., 1997). The low-conductance mode PTPs are permeable to small ions and molecules with a molecular mass less than 300 Da, and pore flickering does not induce detectable matrix swelling. Alternatively, acute oxidative stress may trigger irreversible PTP opening in stress-sensitive mitochondria of certain cell compartments, such as interfibrillar mitochondria, leading to ROS burst and activation of survival protein kinases in the cell. Cyclophilin D, a major regulator of the mitochondrial PTP was required by IPC to generate mitochondrial ROS and phosphorylate Akt and Erk1/2 in mouse cardiomyocytes (Hausenloy et al., 2010). In rat cardiomyocytes, inhibition of PTP by cyclosporine A, an inhibitor of cyclophilin D, prevented PE-induced activation of p38 and ERK1/2, as well as mitochondrial dysfunction (Javadov et al., 2006). These studies indicate the existence of a feedback mechanism in which mitochondrial stimuli initiate MAPK activation. Thus,

mitochondrial ROS activate MAPK to mediate survival signaling pathways implicated in IPC and pharmacological preconditioning in the heart. However further studies are needed to elucidate the role of the mitoK_{ATP}-mitochondrial ROS-MAPK pathway in the pathogenesis of IR, hypertrophy and HF.

Altogether, current studies provide evidence of both direct and indirect interactions between MAPKs and mitochondria in response to different cellular stresses. However, the contributions of MAPKs to mitochondria-mediated cell survival and cell death mechanisms in healthy and diseased hearts remain to be elucidated. Along with extracellular stressors, mitochondrial dysfunction *per se* can initiate activation of MAPKs, although precise mechanisms of the activation loop are not clear. Importantly, spatiotemporal activation and regulation of MAPK signaling in subcellular compartments, especially in mitochondria, can stimulate pro-survival and pro-death pathways depending on the severity and type of stimuli. Considered together, these direct and indirect interactions provide evidence that a thorough understanding of mitochondria-MAPK interactions may provide novel insights into the pathogenesis of cardiac diseases. Also, interactions may be exploited to develop mitochondria-targeted therapy and improve the prognosis of heart disease.

8. Conclusions and perspectives

Many signaling networks, including the MAPKs family are involved in the pathogenesis of stress-related cardiac diseases such as MI, hypertrophy and HF. MAPKs respond transiently or permanently during myocardial stresses depending on timing, severity of stress, and types of stimuli, to mediate some of the most important signaling networks in the heart. Due to the complex interplay of regulatory mechanisms, current studies suggest multiple roles for MAPKs; in some cases, individual MAPKs foster cardioprotection, in other cases they mediate damage to the cell and cause cardiac dysfunction in response to oxidative stress. Mitochondria are powerhouses and important gate-keepers of cell life and death, and regulation of mitochondrial metabolism by MAPKs is critical for cardiac cells. Molecular mechanisms of activation of individual MAPKs and the cause-and-effect relationship between MAPK activation and cardiac diseases are not entirely clear. Understanding precise mechanisms of the role of MAPKs in cardiac diseases are obscured due to absence of highly specific inhibitors. Numerous studies revealed that the effects of MAPKs activation converge on mitochondria and modulate their metabolism. Though many questions remain unanswered, there exists enough evidence to consider the possibility of targeting MAPK-mitochondria interactions in the prevention and treatment of heart disease. A comprehensive understanding of relevant molecular mechanisms, as well as challenges in this area, will promote the development of new pharmacological agents and genetic manipulations for the treatment of cardiovascular diseases by targeting the MAPKs/mitochondria pathway.

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Abbreviations

AngII	angiotensin II
CA	constitutively active
CHIP	C terminus of Hsc70-interacting protein
CT-1	cardiotrophin-1
$\Delta\Psi_{mit}$	mitochondrial membrane potential
DN	dominant negative
ERK1/2	extracellular signal-regulated kinases 1 and 2
ET-1	endothelin-1
ETC	electron transport chain
GPCR	G-protein-coupled receptor
HF	heart failure
Hsp27	heat shock protein 27
ICER	inducible cAMP early repressor
IMM	inner mitochondrial membrane
IMS	intermembrane space
IPC	ischemic preconditioning
IR	ischemia-reperfusion
JIP	JNK-interacting protein
JNK	c-Jun NH2-terminal kinase
LIF	leukemia inhibitory factor
LTCC	L-type calcium channel
MAPK	mitogen-activated protein kinase
MAPKAP	MAPK activated protein kinase
MEF	myocyte-specific enhancer factor
MEK	MAPK/ERK kinase
MEKK	MEK kinase
MI	myocardial infarction
mitoK$_{ATP}$ channel	mitochondrial ATP-sensitive potassium channel
MK2	MAPKAP kinase-2
MKP	MAPK phosphatase
NFAT	nuclear factor of activated T-cells

NHE-1	sodium-hydrogen exchanger 1
6-OHDA	6-hydroxydopamine
OMM	outer mitochondrial membrane
PDE	phosphodiesterase
PDH	pyruvate dehydrogenase
PE	phenylephrine
PKG	protein kinase G
PTP	permeability transition pore
ROS	reactive oxygen species
RTK	receptor tyrosine kinase
SAPK	stress-activated protein kinase
Smac	second mitochondria-derived activator of caspase
TG	transgenic
TNFα	tumor necrosis factor alpha

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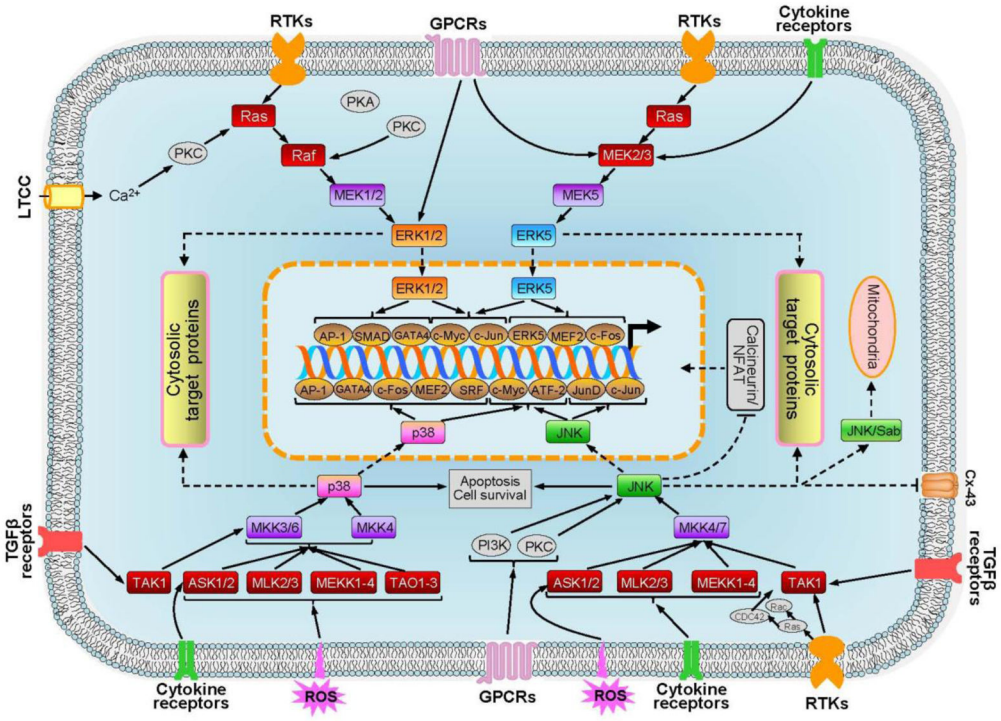

Figure 1.
Main MAPK signaling pathways in the heart.

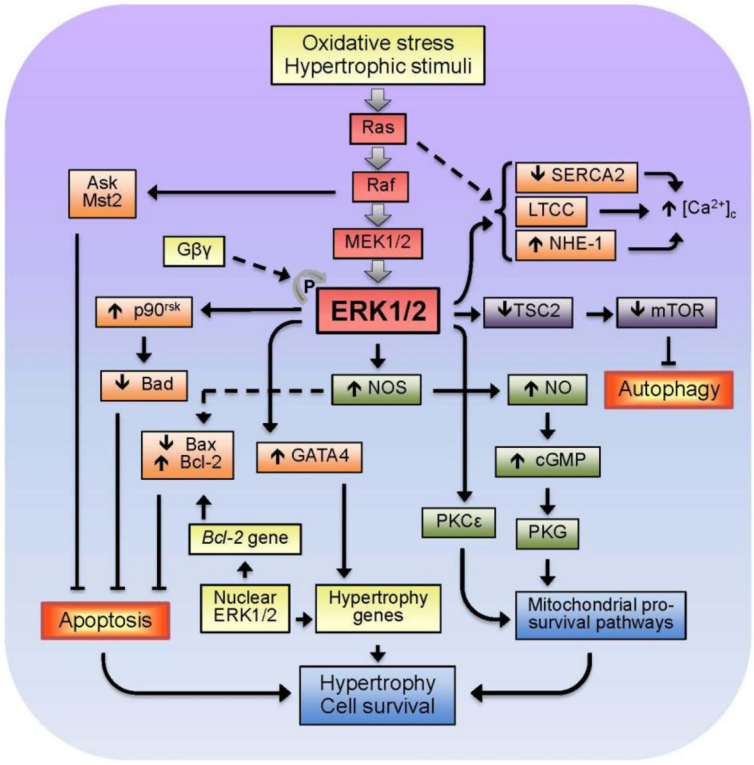

Figure 2.

Major downstream targets of ERK1/2 MAPK in response to oxidative stress and growth stimuli in the heart.

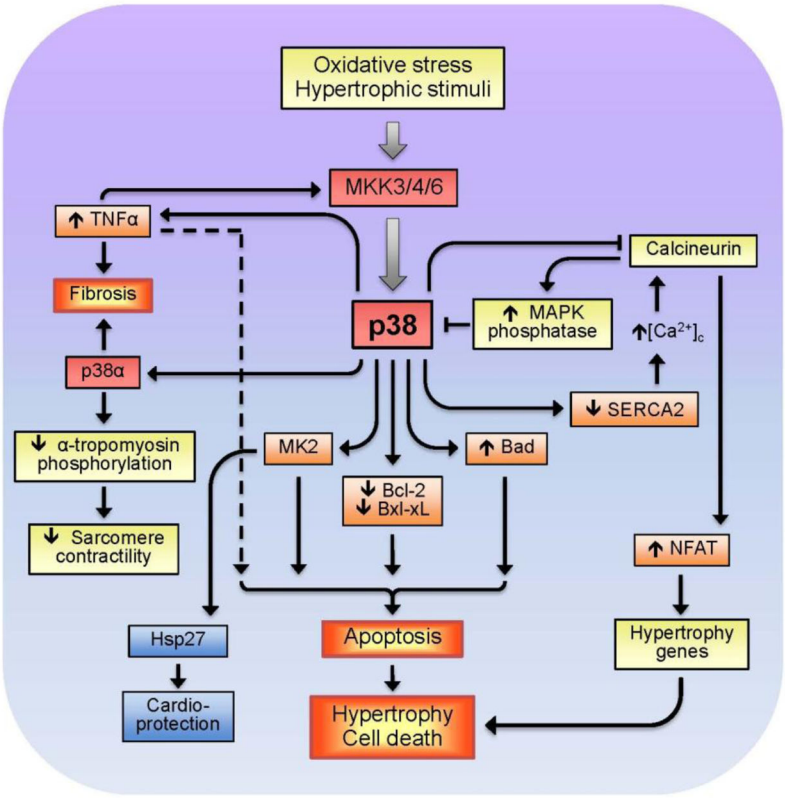

Figure 3.

p38-induced stimulation of death signaling pathways in response to oxidative stress and hypertrophic stimuli.

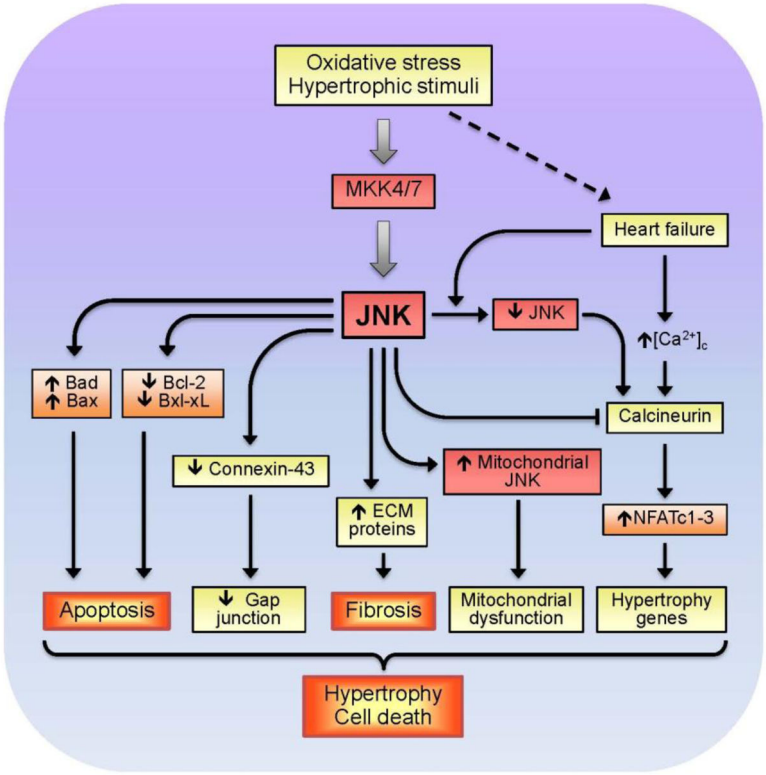

Figure 4.

Major downstream targets of JNK MAPK in response to oxidative stress and growth stimuli in the heart.

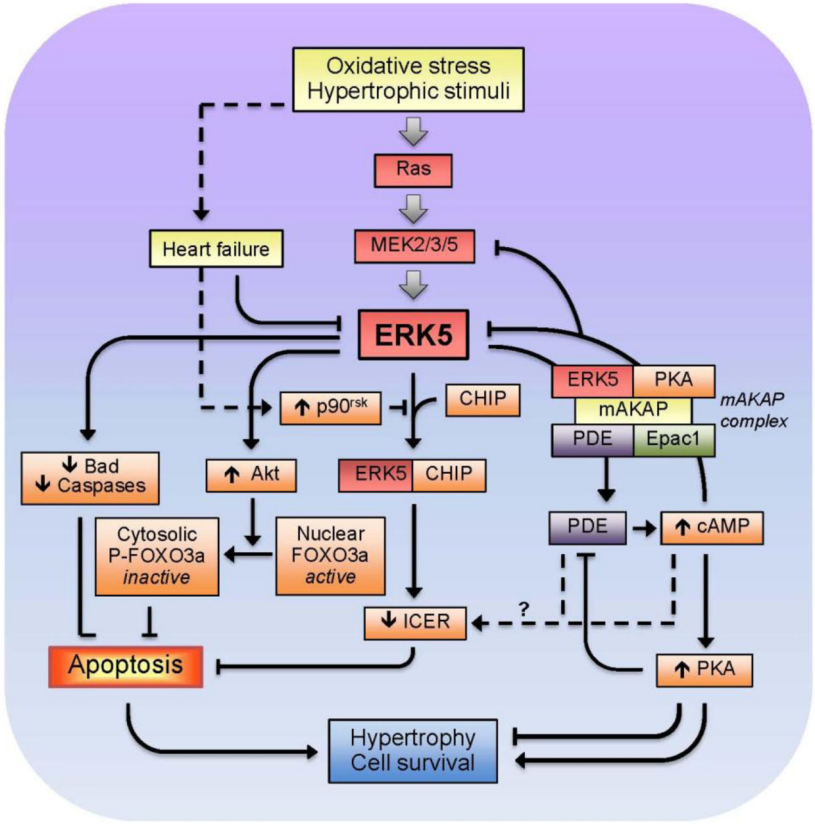

Figure 5.
Proposed role of ERK5 MAPK during oxidative stress and cardiac hypertrophy.

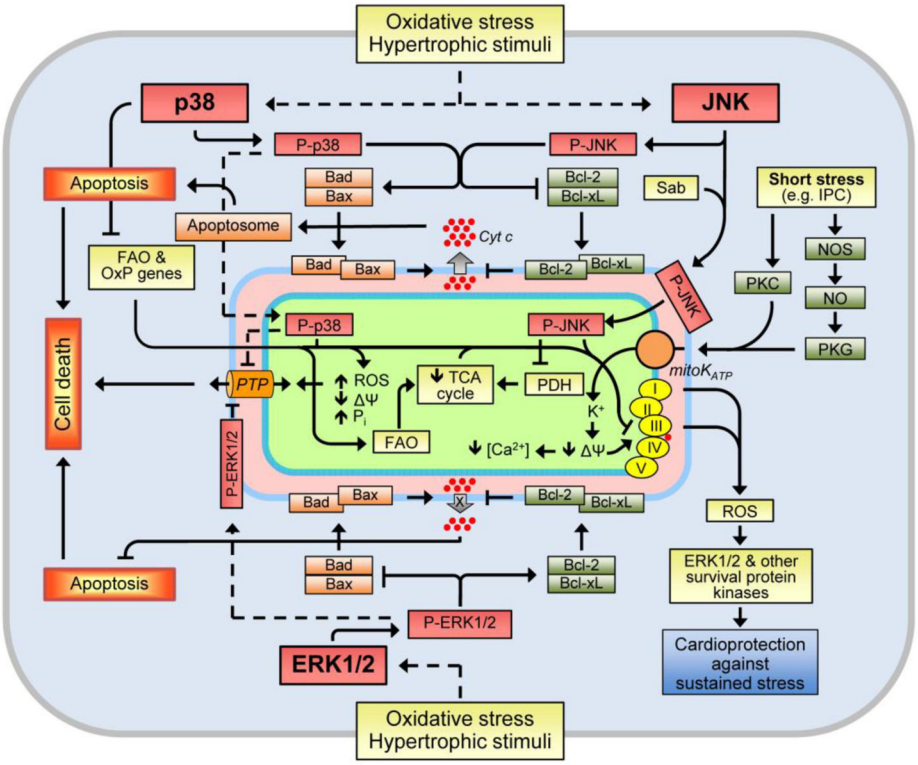

Figure 6.
Bidirectional interactions between MAPKs and mitochondria.

Table 1

The role of mitochondria in MAPK signaling

Model	Role of mitochondria	Reference
ERK		
Neonatal rat cardiomyocytes	ERK signaling required normal mitochondrial function during H_2O_2-induced oxidative stress	(Bogoyevitch et al., 2000)
TG mice	All MAPKs colocalized in cardiac mitochondria, but PKCε overexpression increased mitochondrial translocation of ERK and Bad	(Baines et al., 2002)
THP-1 cells	MitK_{ATP} channel openers activated ERK by oxidant-dependent mechanism	(Samavati et al., 2002)
Primary pig aorta endothelial cells	Mitochondria-generated ROS stimulated hypoxia-induced activation of ERK1/2	(Schafer et al., 2003)
Neonatal mouse astrocytes	MEK1/ERK pathway may modulate F_1F_0-ATPase activity	(Yung et al., 2004)
SK-N-SH cells	Inhibition of ERK leads to disruption of mitochondrial membrane potential, and resulting in enhanced cell death	(Lee et al., 2004)
Rat heart IR	Adenosine receptor preconditioning-activated ERK was found in all subcellular fractions. Loss of activated ERK was observed in mitochondrial and membrane fractions upon blocking of preconditioning	(Reid et al., 2005)
Neonatal rat cardiomyocytes	Inhibition of mitochondrial PTP resulted in decreased activation of ERK from phenylephrine-induced hypertrophy	(Javadov et al. 2006)
Adult rat cardiomyocytes	Protective effects of PKG-Iα were associated with mitoK_{ATP} channel and enhanced phosphorylation of ERK	(Das et al., 2006)
SH-SY5Y cells	Mitochondrial ERK2 regulates stress-induced mitophagy and autophagy	(Dagda et al., 2008)
Alveolar macrophages	ERK maintained mitochondrial integrity and inhibition of ERK led to cell death through both apoptosis and necrosis	(Monick et al., 2008)
Adult rat cardiomyocytes	Mitochondrial ROS production and subsequent ERK phosphorylation are necessary for temperature preconditioning of isolated ventricular myocytes	(Bhagatte et al., 2012)
Rat heart mitochondria	Raf levels in mitochondria were elevated by sustained exercise	(Ferreia et al., 2014)
p38		
Mouse heart IR	Inhibition of p38/mitK_{ATP} channel abolished adenosine receptor-induced preconditioning	(Zhao et al., 2001)
Embryonic chick cardiomyocytes	Mitochondrial ROS stimulated activation of p38 during hypoxia	(Kulisz et al., 2002)
Rat heart IR	Ischemic preconditioning induced by opening of the mitK_{ATP} channel was the upstream of p38/ROS	(Yue et al., 2002)
Mouse heart IR	DN-p38α and MKK6 showed reduced IR-induced injury and enhanced Bcl-2 associated with activation of mitochondrial death signaling	(Kaiser et al., 2004)
Rat heart IR	AMP-579 blocked the activation of mitochondrial p38 MAPK during ischemia and reperfusion.	(Ballard-Croft et al., 2005)
Mouse embryonic fibroblasts	Activation of p38α and HIF-1 was dependent on the production of mitochondrial ROS. p38 signaling was essential for HIF-1 activation	(Emerling et al., 2005)
Rat heart	AngII-induced activation of p38 was prevented by 5-hydroxydecanoate, an inhibitor of mitoK_{ATP} channels	(Kimura et al., 2005b)
Embryonic chick heart	Inhibition of p38 blocked mitochondrial apoptosis pathway	(Kong et al., 2005)
Neonatal rat cardiomyocytes	The AMPK-p38 pathway activated Bax translocation to mitochondria, and inhibition of p38 blocked the process from simulated ischemia	(Capano and Crompton, 2006)

Model	Role of mitochondria	Reference
Neonatal rat cardiomyocytes	Inhibition of PTP resulted in decreased activation of p38 in phenylephrine-induced hypertrophy dependent on mitochondrial ROS	(Javadov et al., 2006)
Neonatal rat cardiomyocytes	Hypoxia/reoxygenation-induced mitochondrial ROS activated p38α	(Kim et al., 2006)
TG mice	MKK6 overexpression reduced ETC proteins in heart mitochondria	(Wall et al., 2006)
Mouse embryonic cardiomyocytes	Inhibiting p38 reduced mitochondrial ROS, Ca^{2+} overload, and cell death	(Sucher et al, 2009)
Rat heart mitochondria	p38 bound to carnitine palmitoyltransferase-1B and activated its activity in isolated mitochondria	(Sharma et al., 2010)
Neonatal rat cardiomyocytes	p38 was a part of ROS-induced formation of a positive-feedback loop during development	(Matsuyama and Kawahara, 2011)
JNK		
U-937, Ionizing radiation	Translocation of SAPK to mitochondria was functionally important for apoptosis	(Kharbanda et al., 2000)
Adult rat cardiomyocytes	JNK activated mitochondrial apoptosis machinery induced by hydrogen peroxide	(Aoki et al., 2002)
Adult rat cardiomyocytes	DN-JNK reduced mitochondria-mediated cell death	(Remondino et al., 2003)
Neonatal rat cardiomyocytes	Hypoxia/reoxygenation-induced JNK activation was initiated by mitochondria. Blocking calcium flux and ETC prevented activation of JNK	(Dougherty et al., 2004)
PC12 cells	JNK2, not JNK1 was responsible for cytochrome c release. DN-JNK2, but not DN-JNK1 prevented cell death	(Eminel et al., 2004)
Rat heart	AngII-induced activation of JNK was prevented by the inhibitor of mitoK_{ATP} channels, 5-hydroxydecanoate	(Kimura et al., 2005b)
Adult rat cardiomyocytes	Protective effects of PKG-Iα were associated with mitK_{ATP} channel and enhanced phosphorylation of JNK	(Das et al., 2006)
HeLa cells	Activation of JNK, but not p38 or NAD(P)H oxidase induced mitochondrial ROS generation	(Chambers and LoGrasso, 2011)
H9C2 cells, Rat heart IR	Inhibition of mitochondrial JNK signaling reduced ROS, mitochondrial dysfunction, and attenuated MI following IR	(Chambers et al., 2013)