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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 crosstalk 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 crosstalk 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.

Contents

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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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 that the ventricles adaptively remodel immediately after MI to maintain cardiac output (Sutton & 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 HF, characterized by a decreased ejection fraction, progressive chamber dilation, pro-inflammatory cytokines release, apoptosis, and fibrogenesis (Frey & Olson, 2003; Ertl & 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 & 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 & Morrison, 2007; Raman et al., 2007). p38 and JNK can also respond to growth factors and GPCRs (Ono & 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; Wang & Tournier, 2006; Ramos, 2008; Rincon & Davis, 2009). MAPK signaling is like a potent molecular switch; after it prompts an appropriate cellular response, it must be deactivated by regulatory

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