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The Stress-Response MAP Kinase Signaling in Cardiac Arrhythmias

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Abstract

Stress-response kinases, the mitogen-activated protein kinases (MAPKs) are activated in response to the challenge of a myriad of stressors. c-Jun N-terminal kinase (JNK), extracellular signal-regulated kinases (ERKs), and p38 MAPKs are the predominant members of the MAPK family in the heart. Extensive studies have revealed critical roles of activated MAPKs in the processes of cardiac injury and heart failure and many other cardiovascular diseases. Recently, emerging evidence suggests that MAPKs also promote the development of cardiac arrhythmias. Thus, understanding the functional impact of MAPKs in the heart could shed new light on the development of novel therapeutic approaches to improve cardiac function and prevent arrhythmia development in the patients. This review will summarize the recent findings on the role of MAPKs in cardiac remodeling and arrhythmia development and point to the critical need of future studies to further elucidate the fundamental mechanisms of MAPK activation and arrhythmia development in the heart.

Keywords

Aging; Arrhythmia; Cardiovascular diseases; Heart; Mitogen-activated protein kinases; Stress

1 Introduction

Accumulating evidence suggests that intrinsic stress (e.g., oxidative stress and chronic inflammatory stress) are markedly enhanced in aging and cardiovascular diseases (CVDs), while the aged and pathologically altered hearts (such as by ischemia and heart failure) have also been shown to exhibit a higher susceptibility to extrinsic stress stimuli (Beckman and Ames 1998; Belmin et al. 1995; He et al. 2011; Ismahil et al. 2014; Juhaszova et al. 2005; Neuman et al. 2007). Mitogen activated protein kinase (MAPK) cascades act as critical regulators of cell survival and growth in response to both intrinsic and extrinsic stress challenges. The MAPK family is composed of c-Jun N-terminal kinase (JNK), extracellular signal-regulated kinases (ERKs), and p38 MAPKs. These three subfamilies have been the focus of extensive studies to uncover their roles in cardiac disease development (Davis 2000; Karin and Gallagher 2005; Ramos 2008; Rose et al. 2010). Recently, the impacts of these

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stress-response MAPKs on cardiac arrhythmic remodeling have begun to be revealed (Hagiwara et al. 2007; Ho et al. 1998, 2001; Huang et al. 2014; Scharf et al. 2013; Takahashi et al. 2004; Yan et al. 2013).

Cardiac arrhythmias, a disturbance in the regular rhythm of the heartbeat, are commonly associated with aging and CVDs. While ventricular arrhythmias can be life-threatening arrhythmias, atrial arrhythmia, especially atrial fibrillation (AF) is the most common arrhythmias and a significant health problem, AF is associated with significant morbidity and mortality including a 5-fold increased risk for stroke (Krahn et al. 1995; Wolf et al. 1978), tripled risk for heart failure (HF), and 40–90% increased all-cause mortality (Benjamin et al. 1998, 2009; Krahn et al. 1995). In the Framingham Cohort Study, the risk of stroke is 5.6 times higher in AF patients compared to those with sinus rhythm (Kannel et al. 1983) and AF patients present a poorer prognosis and higher mortality (Lip 2013). The comorbidity of AF aggravates existing CVDs such as HF and accelerates the progression of ventricular dysfunction, all-cause hospitalization, and increased mortality (Aleong et al. 2014; Carson et al. 1993; Clark et al. 1997; Dries et al. 1998). To date, nearly 15 million people worldwide and 5 million people in the USA are affected by HF (Cowie et al. 1997; Hershberger et al. 2003; January et al. 2014). It has been shown that CVDs and aging are also the independent risk factors for cardiac arrhythmias (Benjamin et al. 1994; Ehrlich et al. 2002; Kannel et al. 1998; Neuberger et al. 2007). By 2050, the prevalence of both AF and HF will more than double as the population ages (Di Lenarda et al. 2003; Kannel and Benjamin 2008; Linne et al. 2000). This accounts for more than 350,000 hospital admissions annually and costs the health care system approximately \$26 billion each year (Calkins et al. 2012; Kannel et al. 1982; Kannel and Benjamin 2008; Wattigney et al. 2003). Thus, this review focuses on the recent progress in understanding the role of stress-response MAP kinases in the development of cardiac arrhythmias, especially atrial arrhythmias.

2 Electrical Remodeling and Arrhythmia Development

It is generally believed that abnormal triggers initiate arrhythmias. Reentry circuits form and are sustained by an arrhythmogenic substrate, due to both molecular and structural remodeling (Allessie et al. 1976; Mandapati et al. 2000; Nattel et al. 2008). Studies suggest that electrical remodeling of membrane ion channels (e.g., Ca^{2+} and potassium channels) leads to altered action potential duration (APD) and atrial effective refractory period (AERP); both have been found to be associated with the development of AF (Christ et al. 2004; Marx et al. 2000; Nattel et al. 2007). Before the onset of AF, shorter AERPs have been associated with a higher inducibility of AF, while longer AERPs and slowing atrial conduction velocity, which may cause a pro-arrhythmogenic shortening of the conduction wavelength (Rensma et al. 1988), have been found to be linked to AF development in HF patients and animals (Huang et al. 2003; Sanders et al. 2003). In aged rabbit left atrium, we found that a slight reduction in AERP and unchanged APD were associated with slowed conduction velocity and a markedly increased pacing-induced AF compared to that of young controls (Yan et al. 2013). Although similar results of slightly altered APD and AERP were also reported in aged canine and rat atria (Anyukhovskiy et al. 2005; Huang et al. 2006), studies from coronary artery bypass graft (CABG) surgery patients suggest that AERP was positively correlated with age (Sakabe et al. 2003). However, the molecular and

electrophysiological properties of human hearts are varied and complicated, especially when co-existing pathological conditions (such as HF or myocardial infarction) are present.

Extensive studies in ventricular myocytes have shown that ectopic activities can occur by prolonged APD causing early afterdepolarizations (EADs) and by spontaneous SR Ca^{2+} releases leading to delayed afterdepolarizations (DADs) (Bers 2000; Nattel et al. 2008; Venetucci et al. 2008). EADs normally occur with abnormal depolarization during phase 2 or phase 3 of the action potential. While ventricular myocytes can only develop phase 2 EADs, atrial myocytes do not produce phase 2 EADs but may produce late phase 3 EADs with an abbreviation of the atrial APD (Burashnikov and Antzelevitch 2003). These late phase 3 EADs have only been shown to be responsible for the immediate initiation of AF following termination of paroxysmal AF, but not in the case of new-onset AF or recurrence of AF that has been terminated for a long time (Oral et al. 2003; Timmermans et al. 1998). Thus, other features of the arrhythmogenic substrate such as sarcoplasmic reticulum (SR) Ca^{2+} handling dysfunction, a generally acknowledged arrhythmogenic factor of generating DADs, could play an important role in heart failure or age-related enhancement of atrial arrhythmogenicity.

3 Excitation–Contraction Coupling

An action potential is essential for triggering myocyte contraction. Excitation-contraction coupling is the link between myocyte excitation (depolarization of the action potential) and Ca^{2+} release from the SR for myocyte contraction. Ca^{2+} entry via L-type Ca^{2+} channels along with a much smaller amount of Ca^{2+} influx via Na^{+} and Ca^{2+} exchanger (NCX) activates SR Ca^{2+} release via Ca^{2+} triggered Ca^{2+} release channel (RyR) in ventricular myocytes. During systole, this Ca^{2+} triggered SR Ca^{2+} release produces a large intracellular Ca^{2+} ($[\text{Ca}]_i$) transient that drives cell contraction (Bers 2000). During diastole, RyRs usually remain closed and excess cytosolic Ca^{2+} ions are removed from cytosol either by pumping Ca^{2+} back to SR (via SERCA2 function) or extruding Ca^{2+} from the cell (mostly via NCX function) (Bers 2000). However, RyRs can (albeit rarely) spontaneously open during diastole. Individual diastolic RyR openings represent non-spark SR Ca^{2+} leak. Diastolic RyR openings that drive local inter-RyR Ca^{2+} induced Ca^{2+} release (CICR) may produce a Ca^{2+} spark (i.e., spark-mediated SR Ca^{2+} leak). Unusually large/frequent sparks may trigger propagating diastolic Ca^{2+} waves. Abnormally high SR Ca^{2+} leak will reduce SR Ca^{2+} content and consequently reduce systolic fractional SR Ca^{2+} release ($[\text{Ca}]_{\text{FR}}$) for a given L-type voltage-gated Ca^{2+} current (I_{Ca}) trigger (Ai et al. 2005; Bers 2014; Respress et al. 2012). Propagating Ca^{2+} waves will result in excess diastolic NCX function, which is electrogenic (three Na^{+} in, one Ca^{2+} out), and thus may produce abnormal triggered activities (e.g., DADs) and initiate arrhythmias (Bers 2000, 2014).

Although Ca^{2+} handling in atrial myocytes is similar to that of ventricular myocytes, there are some important structural and cellular signal differences between atrial and ventricular myocytes. Atrial myocytes are thinner and longer (Walden et al. 2009), which may lead to a longer delay between APs and Ca^{2+} transients at the center of the cells. This property of the atrial cell can increase the instability of Ca^{2+} propagation, which is pro-arrhythmogenic. Compared to the ventricles, atria have a smaller Ca^{2+} transient amplitude and a higher rate

of intracellular Ca^{2+} decay (Freestone et al. 2000; Walden et al. 2009). This is due to an increased SERCA uptake and enhanced function of NCX to remove cytosolic Ca^{2+} during the diastolic phase (Walden et al. 2009). The increased SERCA-dependent intracellular Ca^{2+} removal is attributed to the greater amount of SERCA2 and decreased expression of SERCA inhibitory protein phospholamban (PLB) (Freestone et al. 2000; Walden et al. 2009). Also, atrial myocytes have higher SR Ca^{2+} content compared to ventricular myocytes (Walden et al. 2009). The greater SR Ca^{2+} content makes atrial myocytes prone to spontaneous diastolic SR Ca^{2+} release when RyRs are pathologically sensitized, such as during AF (Bers 2014; Chelu et al. 2009; Neef et al. 2010; Venetucci et al. 2008).

In addition, atrial myocytes exhibit a different structural pattern of the Transverse tubules (T-tubules) compared to ventricular myocytes. T-tubules are an important subcellular network involved in SR Ca^{2+} dynamics in ventricular myocytes (Brette and Orchard 2003; Franzini-Armstrong et al. 2005; Ibrahim et al. 2010; Wang et al. 2001). T-tubules are located at the z-line of the myocyte and provide close coupling of L-type Ca^{2+} channels to ryanodine receptors (RyRs) on the SR membrane. This structure allows rapid intracellular Ca^{2+} triggered SR Ca^{2+} release in response to electrical excitation (Franzini-Armstrong et al. 2005). Emerging evidence suggests that an atrial T-tubule network is present in large mammalian species including humans, sheep, dogs, cows, and horses although atrial T-tubular networks are less abundant and less organized compared to that in the ventricles (Dibb et al. 2009; Lenaerts et al. 2009; Richards et al. 2011; Wakili et al. 2010). While it was previously believed that atrial T-tubules were virtually absent in the small rodents (Berlin 1995; Forbes et al. 1990), a recent report by Frisk et al. (2014) showed similar structural organization and density of the T-tubules in pig and rat atria. A disorganized T-tubule network has been found to contribute to SR Ca^{2+} release dysfunction in failing ventricular myocytes from both human and HF animal models (Balijepalli et al. 2003; Heinzel et al. 2008; Louch et al. 2006; Lyon et al. 2009). In rapid pacing-induced failing dog atria, reduced T-tubular abundance was also found to be linked to altered subcellular Ca^{2+} dynamics and AF development (Dibb et al. 2009; Lenaerts et al. 2009; Yeh et al. 2008). While accumulating evidence suggests that atrial T-tubular structure is present in most mammalian species, its functional role in arrhythmia development requires further investigation.

4 Arrhythmia Initiation and Abnormal Ca^{2+} Triggered Activities

Arrhythmia initiation stems from DADs that are caused by SR Ca^{2+} handling dysfunction. Others and we have previously discovered that increased diastolic SR Ca^{2+} release causes abnormal ectopic activities, which lead to ventricular arrhythmogenesis in the failing heart (Ai et al. 2005; Respress et al. 2012; Yeh et al. 2008). During the diastolic phase, SR Ca^{2+} release normally shuts off almost completely (~99%). However, increased diastolic RyR Ca^{2+} release could be responsible for increased diastolic SR Ca^{2+} leak and reduced systolic $[\text{Ca}]_{\text{FR}}$ for a given L-type voltage-gated Ca^{2+} current (I_{Ca}) as the release trigger (Bassani et al. 1995; Bers 2014; Shannon et al. 2000). The increased diastolic SR Ca^{2+} leakage along with an impaired function of Ca^{2+} uptake due to altered SERCA2 elevates the amount of $[\text{Ca}]_{\text{i}}$ and prolongs the $[\text{Ca}]_{\text{i}}$ decay phase in HF (Bers 2000, 2014). Then, increased Na influx via NCX for $[\text{Ca}]_{\text{i}}$ removal can produce abnormal triggered activities (e.g., DADs)

and initiate atrial arrhythmias (Bers 2000, 2014). Studies suggest that alterations of Ca^{2+} handling proteins including RyR2, PLB, and Cav1.2 contribute to changed intracellular Ca^{2+} transients and diastolic SR Ca^{2+} release (DeSantiago et al. 2002; Schulman et al. 1992; Wu et al. 1999).

Others and we have previously demonstrated that activated CaMKII, a pro-arrhythmic signaling molecule, is critically involved in phosphorylation of RyR2–2815 and PLB–Thr17 (RyR2815-P, PLB17-P), which results in sensitized RyR channels that in turn leads to triggered activities and arrhythmia initiation due to diastolic SR Ca^{2+} leak in pathologically altered ventricles (Ai et al. 2005; Greiser et al. 2009; Hoch et al. 1999; Maier et al. 2003; Respress et al. 2012; Sossalla et al. 2010; Yeh et al. 2008; Zhang et al. 2003). Recent studies indicate that alterations of CaMKII-dependent RyR phosphorylation are also exhibited in the atrium of chronic AF patients (Chelu et al. 2009; Neef et al. 2010). Results from several animal models have shown that these altered SR Ca^{2+} handling proteins contribute to enhanced SR Ca^{2+} leak and AF development (Chelu et al. 2009; Chiang et al. 2014). Alteration of I_{Ca} could also contribute to abnormal SR Ca^{2+} release, and studies indicate that reduced I_{Ca} is a hallmark of AF-induced electrical remodeling (Christ et al. 2004; Van Wagoner et al. 1999). These results indicate that SR Ca^{2+} mishandling could be the major cause of arrhythmias in HF and chronic AF (Ai et al. 2005; Respress et al. 2012; Yeh et al. 2008). CaMKII inhibition has been shown to improve the function of L-type Ca^{2+} channel in mouse ventricular myocytes and cultured HL-1 atrial myocytes, which could be due to up-regulated expression of L-type Ca^{2+} channel proteins (Ronkainen et al. 2011; Zhang et al. 2005). However other studies have reported inconsistent results of increased, reduced, or unchanged I_{Ca} preceding the onset of AF in postoperative patients compared to that of patients at low risk for AF (Christ et al. 2004; Dinanian et al. 2008; Van Wagoner et al. 1999; Workman et al. 2009). Thus, the underlying mechanisms of abnormal Ca^{2+} handling in AF onset and maintenance in the pathologically altered heart require further investigation.

5 Arrhythmia Stabilization

Under normal conditions, the initiation of the cardiac impulse (generated from the sinus node) and impulse propagation (through gap junctional channels – specialized membrane structures that directly connect adjacent cells by providing chemical and electrical communication) across the cardiac tissue are critical for maintaining normal heart rhythm and impulse conduction.

AF is a heart rhythm disorder (termed an arrhythmia) with fast and irregular beats in the upper chambers (atria) of the heart. Abnormal triggered activities initiate AF, while arrhythmogenic substrates sustain it. The area of the pulmonary veins located adjacent to the left atrium (LA) has been shown to be the most common place for AF initiation, but the arrhythmogenic substrates include the structural and electrical remodeling of the atrium and are required for the maintenance of AF (Burstein and Nattel 2008). Both shortened atrial effective refractory period and reduced conduction velocity have been linked to the maintenance of AF (Wijffels et al. 1995). Although electrical remodeling of cardiac membrane ion channels (such as calcium and potassium channels) leads to shortened duration of action potentials and shortened refractory periods during AF, these alterations

alone might not be sufficient to provide a substrate for sustained reentry in single or multiple circuits (Nattel et al. 2007). As such, AF has been considered as a reentrant arrhythmia (Janse and Wit 1989). There is accumulated evidence suggesting that ischemia and HF as well as elderly myocardium, all undergo slowed conduction of the cardiac action potential, and this is likely due to the electrical and structural remodeling correlating with increased age (Anyukhovsky et al. 2005). Although cardiac conduction is determined by the active membrane properties of each cell (largely a function of sodium channels) and tissue resistivity (gap junction channels) (Walton and Fozzard 1983), expression and activity of sodium channels have been shown to be unchanged in aging LA (Baba et al. 2006). This disruption of electrical coupling has been associated with the age-related increase in fibrosis and the remodeling of the gap junctions in aging sinus node and aortic endothelium (Jones et al. 2004; Yeh et al. 2000). Thus, gap junction proteins could also play a critical role in slowed conduction in diseased and aging hearts.

6 MAPKs and Arrhythmia Development

Studies suggest that aged and diseased hearts exhibit increased intrinsic stress and higher susceptibility to extrinsic stress stimuli (Beckman and Ames 1998; Belmin et al. 1995; He et al. 2011; Ismahil et al. 2014; Judge and Leeuwenburgh 2007; Juhaszova et al. 2005; Li et al. 2005a; Neuman et al. 2007; Yang et al. 2005). In response to stress stimuli, the mitogen-activated protein kinases (MAPKs) are activated (Rose et al. 2010). The MAPK family is composed of three major members, c-Jun NH2-terminal kinases (JNK), extracellular signal-regulated kinases (ERK1/2), and p38 kinase. MAPK activation has been found to be critical in the development of various diseases such as diabetes (Brozzi and Eizirik 2016), cancer (Xiao et al. 2016), Alzheimer's disease (Yarza et al. 2015) as well as various cardiac diseases such as cardiac hypertrophy and heart failure (Rose et al. 2010).

Our laboratory recently discovered and reported for the first time (Yan et al. 2013) that activated JNK leads to enhanced atrial arrhythmogenicity. In aged animals, JNK activation leads to reduced gap junction channels and impaired action potential conduction velocity. Young animals subjected to an *in vivo* JNK activator (anisomycin) (Hazzalin et al. 1998; Petrich et al. 2004) challenge results in a dramatically increased incidence and duration of pacing-induced atrial arrhythmias, which is consistent with that found in aged hearts. While a significantly increased propensity for AF in aged humans has been well recognized (Benjamin et al. 1994; Go et al. 2001; Rich 2009), our recent observations (Wu et al. 2014) suggest an increase in activated JNK in aging human atrium from healthy donor hearts (which were rejected for heart transplant due to technical reasons). Moreover, we demonstrated that JNK-induced gap junction remodeling impairs atrial conduction and causes formation of reentrant circuits in cultured atrial myocytes (Yan et al. 2013, 2014). However, previous studies have suggested that gap junction remodeling was most likely to contribute to stabilization and maintenance of AF (Dupont et al. 2001; Elvan et al. 1997; Kanagaratnam et al. 2004; Kostin et al. 2002; Nao et al. 2003; Nattel et al. 2008; Polontchouk et al. 2001; Sakabe et al. 2004; van der Velden et al. 1998, 2000; Wetzel et al. 2005). Therefore, other mechanisms such as SR Ca^{2+} handling dysfunction could be responsible for the initiation of atrial arrhythmias in aged hearts. A computer simulation study (Xie et al. 2010) suggested that generating an ectopic beat in heart tissue with poorly

coupled neighboring myocytes (slowed action potential conduction) requires much fewer EAD or DAD-producing myocytes than in normal tissue composed of well-coupled cells. In another words, impaired intercellular coupling could make cardiac tissue more vulnerable to generating ectopic triggers that may initiate arrhythmias. Therefore, JNK-induced slowed conduction may create a favorable environment for JNK-induced abnormal Ca^{2+} activities to form ectopic beats and even to initiate AF. Many questions regarding the underlying mechanisms of JNK-induced AF genesis remain unanswered. Further investigations are clearly needed in this important research area.

Like JNK, both ERK and p38 are involved in various pathologies such as CVDs, diabetes, and cancers (Davis 2000; Karin and Gallagher 2005; Kyoi et al. 2006; Kyriakis and Avruch 2001; Rose et al. 2010; Yoon and Seger 2006). Although enhanced activity of ERK or p38 alone may or may not be required or sufficient for facilitating cardiac hypertrophy, both ERK and p38 were found to be activated in HF and these activated stress kinases are involved in pathological remodeling and AF development in the failing heart (Cardin et al. 2003; Li et al. 2001, 2005b; Nishida et al. 2004; Purcell et al. 2007; Wang et al. 1998; Zechner et al. 1997). Hypertrophic stimuli lead to an increase in I_{Ca} and down-regulation of SERCA2 expression via activated ERK (Hagiwara et al. 2007; Huang et al. 2014; Takahashi et al. 2004). Ras, a GTPase, is able to activate ERK through a Ras-Raf-MEK cascade (Avruch et al. 2001). However, Ras signaling activated ERK was found to contribute to down-regulation of L-type Ca^{2+} channels and reduced channel activity along with reduced SERCA2 protein expression in cultured myocytes (Ho et al. 1998, 2001). It was also found that Ras-ERK-modulated molecular remodeling led to decreased intracellular Ca^{2+} transients and impaired SR Ca^{2+} uptake, which could lead to enhanced arrhythmogenicity (Zheng et al. 2004). Moreover, recent work reported by Scharf et al. (2013) suggests that p38 directly regulates SERCA2 mRNA and protein expression via transcription factors Egr-1 and SP1. Taken together, emerging evidence indicates that the stress-response MAP kinases signaling cascades could be involved in cardiac Ca^{2+} handling and arrhythmia development. Further investigation is needed for understanding the underlying molecular and electrophysiological mechanisms of altered stress signaling cascades and their cross talking in arrhythmia development under pathological conditions.

7 MAPKs Activation and Pathological Remodeling in the Heart

Extensive studies suggest that pathologically remodeled hearts exhibit a higher propensity to arrhythmias (Ai et al. 2005; Ai and Pogwizd 2005; Desantiago et al. 2008; Guo et al. 2007; Packer 1985; Respress et al. 2012). MAPKs activation has been observed in various cell types and stress conditions. Although all the MAPK family members play important roles in the development of diabetes and CVDs (Davis 2000; Karin and Gallagher 2005; Kyoi et al. 2006; Kyriakis and Avruch 2001; Rose et al. 2010), their actions are dependent on cellular context and type (Maruyama et al. 2009). For instance, in cellular senescence JNK and p38 have opposite functions (activation or suppression) (Das et al. 2007; Wada et al. 2008). In a pressure-overload mouse model induced with transverse aortic constriction (TAC), all the three MAPKs members were activated, however JNK was activated at the early phase (7 h post-TAC) followed by the activation of p38 (3 days postTAC) and ERK (7 days post-TA) (Esposito et al. 2001). While this activation of JNK/p38 was confirmed by other groups

using the same TAC mouse model (Satomi-Kobayashi et al. 2009; Villar et al. 2013), JNK/p38 inhibition alleviated the cardiac remodeling (Zhang et al. 2014). In contrast, ERK null mice predisposed the hearts to decompensation after long-term pressure overload (Purcell et al. 2007).

The MAPK activation has also been intensively studied in MI animal models (Liu et al. 2013; Ren et al. 2005; Sun et al. 2015; Yeh et al. 2010). Studies suggest that the MAPK activation profile changes dramatically at different time points after the MI-injury. For instance, Ren et al. found that minutes after LAD-ligation in a mouse model of MI, JNK, p38 α , and ERK phosphorylation were all enhanced, while ablating p38 signaling with dominant negative expression of p38 α decreased infarct size. They also found that p38 α activation promoted a decrease in anti-apoptotic proteins (such as Bcl-2 and Bcl-XL) which further elucidated the role of p38 in MI injury and remodeling (Ren et al. 2005). In a rat model of acute MI (6 h post-MI), the activation of JNK and p38 was increased, while that of ERK was decreased and was accompanied by increased activity of caspase-3 which is pivotal in apoptosis. Further, a pharmacological reagent that decreased the activation of JNK and p38 and augmented the activation of ERK reduced the infarct size (Liu et al. 2013). Time-dependent MAPK activation has also been reported by Yeh et al., wherein the infarct or infarct border zone of post-MI mice, p38 phosphorylation is increased initially while JNK phosphorylation increased approximately 2 weeks post-MI; on the other hand, ERK phosphorylation increased after about 4 weeks post-MI, likely contributing to the post-MI ventricular remodeling (Yeh et al. 2010). In a rat model of ischemia-reperfusion (I/R) model, p38 was increased while ERK remained unchanged, during the ischemia phase, while during the reperfusion phase JNK was increased (Bogoyevitch et al. 1996). Similar findings were reported in a rat model of I/R injury (Li et al. 2011; Zhang et al. 2015). The enhanced phosphorylation of p38 and JNK after ischemia/reperfusion injury further decreased the cell viability and promoted cardiac cell apoptosis (Song et al. 2016) via decreasing Bcl-2 and increasing Bax (Li et al. 2016). Moreover, it has been recently discovered that inhibiting JNK/p38 while enhancing ERK alleviates ischemic injury-related cardiac function loss and infarct formation (Jeong et al. 2012; Milano et al. 2007). Finally, activation of JNK, p38, and ERK was also elevated in ischemic failing human hearts, while the expression level of JNK, p38, and ERK proteins remained unaltered (Cook et al. 1999; Haq et al. 2001). All these findings suggest that MAPKs are critically involved in cardiac pathological remodeling. Although this activation of MAPKs has been found in the ischemic and failing hearts, the contribution of MAPKs in the development of cardiac arrhythmias in these pathological settings requires further investigation. Modulation of MAPK activity could be a novel therapeutic strategy to promote post-MI recovery and prevent the development of cardiac arrhythmias.

8 MAPK Family

MAPKs are serine/threonine kinases that phosphorylate serine or threonine residues in a consensus sequence of Pro-X-Thr/Ser-Pro on the target protein (Bogoyevitch and Kobe 2006). The MAPKs cascade controls the activity of numerous transcription factors and enzymes, through regulating binding partners, conformational changes, subcellular localization, and protein stability (Widmann et al. 1999).

JNK, a family member of the MAPKs, was discovered by Davis in the early 1990s (Davis 2000). JNK has three major isoforms (JNK1, JNK2, and JNK3), while the major cardiac isoforms are JNK1 and JNK2. JNK is activated by dual phosphorylation of a specific threonine-X-tyrosine motif by upstream kinases MKK4 and MKK7 (Bogoyevitch and Kobe 2006; Davis 2000). In response to stress challenges, it was found that JNK was activated to regulate cell proliferation, differentiation, apoptosis, cell survival, cell mobility, and cytokine production (Bogoyevitch and Kobe 2006; Davis 2000; Raman et al. 2007). Evidence suggests that the JNK signaling pathway is critical in the development of cancer, diabetes, and cardiovascular diseases (CVD; e.g. HF, myocardial infarction, atherosclerosis) (Davis 2000; Karin and Gallagher 2005; Rose et al. 2010). Enhanced JNK activation is also linked to significantly elevated intrinsic stress (e.g., oxidative stress or inflammatory stress) (Liu et al. 2014; Sun et al. 2014). Studies have also shown that rapid transient JNK activation appears in cultured myocytes and animals that are subjected to exercise or severe pressure overload (Boluyt et al. 2003; Nadruz et al. 2004, 2005; Pan et al. 2005), while 24 h mechanically stretched myocytes or exercise trained animals showed reduced or unchanged JNK activity (Boluyt et al. 2003; Miyamoto et al. 2004; Roussel et al. 2008). These results support the hypothesis that JNK activation could be a dynamic response to the stress stimuli.

ERKs and p38 MAPKs are the other two important stress-response signaling pathways in cellular biology (Ramos 2008; Rose et al. 2010). Through investigating the effect of mutated Thr-Gly-Tyr motif of p38 on its phosphorylation status, it is now understood that canonical activation of p38 MAPK is achieved through dualphosphorylation of the Thr-Gly-Tyr motif in the activation loop (Raingeaud et al. 1995). Phosphorylation of the Threonine-Tyrosine motif is mediated by upstream MAPK kinases specific to p38, MKK3 and MKK6 (Kyriakis and Avruch 2001; Moriguchi et al. 1996; Whitmarsh and Davis 1996). More upstream MAPK regulators include low molecular weight GTP-binding proteins in the Rho family (i.e., Rac-1, cdc42, Rho and Rif) and heterotrimeric G-protein coupled receptors (Marinissen et al. 1999; Zarubin and Han 2005; Zhang et al. 1995). There are four identified genes of the p38 MAPK: p38 α , p38 β , p38 γ , and p38 δ . Studies suggest that the isoforms present in the heart are p38 α - γ (Court et al. 2002; Dingar et al. 2010; Seta and Sadoshima 2002), however Dingar et al. demonstrated that p38 δ is also expressed in the heart at a protein level comparable to p38 β , while p38 α is the most abundant, followed by p38 γ (Dingar et al. 2010). P38 α shares sequence homology with p38 β (~75%), p38 γ (~62%), and p38 δ (~61%), while p38 γ and p38 δ are ~70% identical (Cuenda and Rousseau 2007; Remy et al. 2010). Some studies suggest that the different isoforms require differential activation of MAPK kinases for full activation, one such example is p38 α , which needs both MKK6 and MKK3 activation to be phosphorylated in response to cytokines, as p38 δ is activated by MKK6, but negatively regulated by MKK3 (Remy et al. 2010).

ERK is also a Thr/Ser kinase that is normally located in the cytoplasm and translocated into the nucleus when activated (Chen et al. 2001; Widmann et al. 1999). Among the discovered eight ERK isoforms to date, ERK1/2 (44 kDa and 42 kDa, respectively) are the most extensively investigated isoforms within the ERK family (Kohn and Pouyssegur 1986; Sturgill et al. 1988). ERK also can be activated by tyrosine kinase receptors and Gi/o-, Gq-, and Gs-coupled receptors via a range of different signaling pathways (Lowe et al. 2002). The most characterized MKKK to activate ERK is Raf-1, a Ser/Thr protein kinase

(Wellbrock et al. 2004), which binds directly to activated GTP-bound Ras leading to full kinase activation (Muslin 2005). Activated ERK1/2 (phosphorylated ERK1/2) undergoes nuclear translocation to regulate cell proliferation, differentiation, adhesion, migration, and survival (Blasco et al. 2011; Hatano et al. 2003; Saba-El-Leil et al. 2003; Yao et al. 2003). Once fully activated, Raf-1 phosphorylates and activates MKK1 or MKK2. MKK $\frac{1}{2}$, which in turn phosphorylates ERK1 or ERK2 (ERK1/2) on a Threonine and a Tyrosine residue in its activation loop, thus leading to kinase activation. Fully activated ERK1/2 has a variety of substrates at the plasma membrane, in the cytosol and in the nucleus that regulates important aspects of cell physiology and are involved in the cellular pathological remodeling process.

9 Conclusions and Implications

The stress-response MAPK family serves an integral role in cardiac development, function, pathological remodeling, and arrhythmia development in the heart. Emerging evidence suggests a link between altered stress signaling cascades and cardiac pathological alteration and arrhythmic remodeling in pathologically altered hearts. The activation of the different MAPK members is dependent on cellular context, time, and pathological conditions. Thus, the functional impact of these MAPKs in the heart under stress conditions is likely complex and dynamic during the progression of CVDs and the development of cardiac arrhythmias. Further understanding of the underlying mechanisms of stress-induced cardiac remodeling and arrhythmia development could reveal potential effective therapeutic strategies for improving cardiac function and prevention and treatment of cardiac arrhythmias in the elderly and in patients with cardiovascular diseases.

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Non-standard Abbreviations and Acronyms

AERP	Atrial effective refractory period
AF	Atrial fibrillation
APD	Action potential duration
Ca²⁺	Calcium
CABG	Coronary artery bypass graft
CaMKII	Calcium/calmodulin dependent protein kinase II
CDC42	Cell division protein 42 homolog
CL	Cycle length
CVD	Cardiovascular disease
DAD	Delayed afterdepolarizations
EAD	Early afterdepolarizations

Egr-1	Early growth response protein
ERK	Extracellular signal regulated kinase
HF	Heart failure
HL-1	Mouse atrial myocyte line from Louisiana State University
I/R	Ischemia reperfusion
Ica	L-type calcium channel
JNK	c-Jun N-terminal kinase
LA	Left atrium
LAD	Left anterior descending
MAPK	Mitogen-activated protein kinase
MI	Myocardial infarction
MKK	Mitogen-activated protein kinase kinase
NCX	Sodium calcium exchange channel
p38	Member of MAPK family
PLB	Phospholamban
Pro	Proline amino acid residue
Rac1	Ras-related C3 botulinum toxin substance 1
RyR	Calcium-triggered calcium release channel
Ser	Serine amino acid residue
SERCA	Sarcoplasmic reticulum calcium ion-ATPase
SP-1	Transcription factor SP-1
SR	Sarcoplasmic reticulum
TAC	Transverse aortic constriction
Thr-Gly-Tyr	Threonine, glycine, tyrosine amino acid sequence

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