# Stress Kinase Signaling in Cardiac Myocytes

Xun Ai, Jiajie Yan, and Dan J. Bare

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 kinase (ERK), and MAPK p38 are the important members of the MAPK family in the heart. Extensive studies have revealed critical roles of activated MAPKs in the processes of cardiac injury, cardiac arrhythmias, heart failure, and other cardiovascular diseases. Advancing our understanding regarding the functional impacts of MAPKs in the development of heart diseases could shed new light on developing novel therapeutic approaches to improve cardiac function and prevent arrhythmia development in patients. This chapter summarizes relevant current knowledge on the pivotal roles of MAPKs in physiopathological and molecular remodeling in cardiac myocytes during the disease development and for the therapeutic potentials of developing MAPK inhibitors and/or activators.
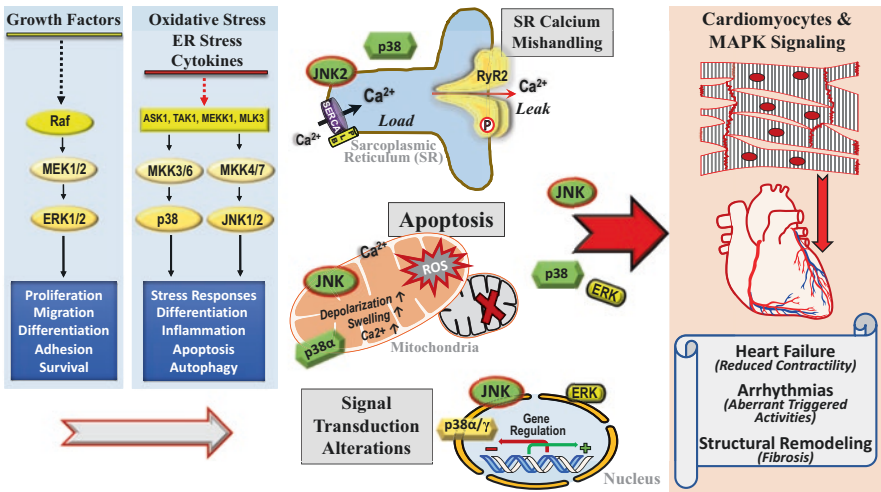
X. Ai (✉) · J. Yan · D. J. Bare
The Ohio State Univeristy, Physiology and Cell Biology, Columbus, OH, USA
e-mail: Xun.Ai@osumc.edu

Abbreviations

ASK1-2	Apoptosis signal-regulating kinases-1/2
AF	Atrial fibrillation
BAMBI	BMP and activin membrane-bound inhibitor
Ca^{2+}-ATPase	Plasma membrane calcium/calmodulin-dependent ATPase or PMCA
CICR	Ca^{2+} induced Ca^{2+} release
I_{Ca}	Ca^{2+} influx
CaMKIIδ	Calcium calmodulin kinase IIδ
Ca^{2+}	Calcium
CVDs	Cardiovascular diseases
CHOP	C/EBP homologous protein
JNK	c-jun N-terminal kinase
Cx43	Connexin43
CSBP	Cytokinin-specific binding protein
DAD	Delayed afterdepolarization
DNMT1	DNA methyltransferase-1
DOC-1	Downstream-of-CHOP gene1
DWORF	Dwarf open reading frame
ECC	Excitation-contraction coupling
ERK	Extracellular signal-regulated kinase
GSK-3	Glycogen synthase kinase-3
HF	Heart failure
HMGB1	High mobility group box 1 protein
CRP	C-reactive protein
$[Ca^{2+}]_i$	Intracellular Ca^{2+}
I/R	Ischemia-reperfusion
LTCCs	L-type Ca^{2+} channels
MK2	MAPKAP kinase-2
V_{max}	Maximal rate
MAPKs	Mitogen-activated protein kinases
MNK	Mitogen-activated protein kinase interacting protein kinase
MSK1/2	Mitogen and stress-activated protein kinase1/2
MEKK4	Mitogen-kinase protein kinase kinase kinase-4
MI	Myocardial infarction
MyBP-C	Myosin-binding protein C
NCX	Na^+/Ca^{2+} exchanger
I_k	Outward potassium current
PKCε	Protein kinase Cε
PP1	Protein phosphatase 1

PLB   Phospholamban
PAF   Platelet-activating factor
p70^{RSK} p70 ribosomal S6
p90^{RSK} p90 ribosomal S6
I_{Na} Rapid sodium influx
RISK   Reperfusion injury salvage kinase
RyR2   Ryanodine receptor channel-2
SR   Sarcoplasmic reticulum
SERCA2a   Sarcoplasmic reticulum Ca^{2+}-ATPase 2a
SPEG   Striated muscle enriched protein kinase
PTEN   Tensin homolog on chromosome 10
TNFα-R1   Tumor necrosis factor alpha receptor1
TnT   Troponin T
TGF-β   Transforming growth factor beta
TAC   Transverse aortic constriction
T-tubules   Transverse tubules
TPY   Threonine-proline-tyrosine phosphorylation motif

Introduction

The heart exhibits enhanced cellular stressors given its high level of energy consumption and output (i.e., oxidative stress, inflammatory stress, senescence stress) and with increasing age and cardiovascular diseases (CVDs), which leads to a higher susceptibility to additional extrinsic stress stimuli (i.e., ischemia, inflammation, excessive alcohol exposure, obesity) [1–9]. The mitogen-activated protein kinases (MAPKs) are stress kinases that are activated in response to both intrinsic and extrinsic stress challenges and critically regulate cell survival and growth. Over the years, MAPK activation has been found to be critical in the development of various diseases such as diabetes, cancer, Alzheimer's disease, as well as various cardiac diseases such as cardiac hypertrophy, heart failure, and atrial fibrillation [10–27]. Among ~500 recognized protein kinase genes in the human genome, the MAPK family is composed of three major members, c-jun NH2-terminal kinases (JNK), p38 mitogen-activated protein (MAP) kinase (p38), and extracellular signal-regulated kinases (ERK1/2). These three subfamilies have been the focus of extensive studies to uncover their contributions to pathological cardiac remodeling and disease development [10, 14–27].

Stress Kinase MAPK Signaling in the Heart

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 [28]. The canonical pathways leading to MAPK activation require a kinase cascade in which MAP kinase kinases phosphorylate MAPKs that in turn activate MAPKs. The MAPK cascade controls the activity of downstream target proteins including numerous transcription factors, through the regulation of binding partners, protein conformational changes, protein stability, and subcellular localization [29].

JNK

JNK is an important member of the MAPK family that is activated in response to various stress challenges and regulates cell proliferation, differentiation, apoptosis, autophagy, cell survival, cell mobility, and cytokine production [10, 21, 28, 30–32]. The JNK kinase family was discovered in the early 1990s by Kyriakis and Avruch and reported as a novel protein named as pp54 MAP-2 kinase, which is activated by phosphorylation of the amino acid residues of threonine-183 and tyrosine-185 [33, 34]. Next, two isoforms were identified with molecular weights of 46 and 56 kDa and were named JNK1 and JNK2, respectively [35]. Later, it was revealed that these JNK kinases could be activated by various extracellular stimuli. Given that these JNKs contained a threonine-proline-tyrosine phosphorylation motif (TPY), they were characterized as a member of the MAPK family. Finally, JNK3 was discovered in 1995 as the last member of this MAPK subfamily and is mainly expressed in neurons [10, 22, 36, 37]. In the heart, JNK1 and JNK2 are the major isoforms, while JNK3 is expressed at a much lower level [24, 38].

JNKs function within a protein kinase cascade and are activated by dual phosphorylation of on the specific threonine-X-tyrosine motif by the upstream kinases MKK4 and MKK7 in response to stress challenges [21, 28, 31, 39]. JNK itself is a Ser/Thr kinase that phosphorylates its substrates on serine or threonine residues in a consensus sequence of Pro-X-Thr/Ser-Pro [28]. Numerous JNK substrates have been identified and include but are not limited to Ca^{2+}/calmodulin-dependent protein kinase II δ (CaMKIIδ), c-jun, Jun-B, ATF2, c-Myc, and p53 [28, 40]. JNK activation has been observed with aging, excessive binge alcohol-triggered "holiday heart syndrome," and with CVDs such as myocardial ischemic injury and heart failure. Accumulating evidence suggests that JNK signaling is critically involved in the development of diabetes, atrial fibrillation, and other CVDs such as heart failure (HF), ischemic myocardial infarction (MI), and atherosclerosis [9, 10, 20–22, 30, 41–44].

P38

p38 MAP kinase, also referred to as RK, p40, or CSBP2 (cytokinin-specific-binding protein 2), is also a member of the MAPK family and is ubiquitously expressed in all somatic cell types [45]. Although p38 participates in signaling cascades controlling cellular responses to cytokines and other stress stimuli, the function of the p38 kinases appears to be both protective and deleterious in the stressed heart [46]. The p38 was initially found as an unidentified 38-kDa protein, which exhibited increased phosphorylation of tyrosine residues by lipopolysaccharide [47]. Later, it was discovered that there are four identified genes of the p38 MAPK: p38α, p38β, p38γ, and p38δ. P38α shares sequence homology with p38β (~75%), p38γ (~62%), and p38δ (~61%), while p38γ and p38δ are ~70% identical [48, 49]. While the heart expresses all the sub-isoforms, p38α is the most abundant, followed by p38γ [50–52]. The canonical activation of p38 MAPK was found to be achieved through dual phosphorylation of the threonine (Thr)-glycine (Gly)-tyrosine(Tyr) motif in its activation loop [53]. The phosphorylation of this threonine-X-tyrosine motif of p38 in vivo is predominantly mediated by upstream MAPK kinases, MKK3 and MKK6, which are activated by MAPK kinase kinases such as TAK1, ASK1, DLK, and mitogen-kinase protein kinase kinase kinase 4 (MEKK4) [54–57]. This cascade can be instigated by one of multiple MKK-activating MAP3Ks in a stimulus-/stress-dependent manner relevant for specific cell type. Studies suggest that the different isoforms require differential activation of MAPK kinases for full activation, one such example being p38α which requires both MKK6 and MKK3 activation to be phosphorylated in response to cytokines, while p38δ is activated by MKK6, but negatively regulated by MKK3 [49]. In addition, low-molecular-weight GTP-binding proteins in the Rho family (i.e., Rac1, Cdc42, RhoA, and RhoF (Rif)) and heterotrimeric G-protein-coupled receptors could activate p38 [58–60]. Furthermore, the activity of p38 can also be modulated by dual-specificity phosphatases, such as PAC-1 and MKP-1 [53]. Finally, the autoactivation of p38, as a non-canonical mode of p38 activation, was observed through the activation of scaffolding proteins such as TAB1 along with the "priming" phosphorylation of Tyr-323 by a tyrosine kinase of the SYK family [61–63].

ERK

The ERK family, another MAPK member group, can be divided into five subfamilies named ERK1–ERK5. ERK1 and ERK2 share 90% homology and thus are usually referred to as ERK1/2 [64, 65]. And ERK1 and ERK2 (44kDa and 42kDa, respectively [66, 67]) are the most thoroughly investigated isoforms in the ERK family. The basic ERK signal transduction cascade has been shown to follow the typical MAPK cascade reaction (Ras-Raf-MEK-ERK pathway). ERK1/2 is activated by MEK1/2-mediated phosphorylation at Thr-183 and Tyr-185 [68]. This

dual-site phosphorylation enhances the ERK1/2 activity by >1000 folds [68, 69]. ERK can also be activated by tyrosine kinase receptors and Gi/o-, Gq-, and Gs-coupled receptors via a range of different signaling pathways [70–75]. One of the best characterized MKKKs to activate ERK is Raf-1, a Ser/Thr protein kinase [76], which binds directly to activated GTP-bound Ras leading to a full activation of MKKK [77]. Once it is fully activated, Raf-1 phosphorylates and activates MKK1 or MKK2. MKK1/2, which in turn phosphorylates ERK1 or ERK2 (ERK1/2) on the Thr-X-Tyr motif in its activation loop, leads to ERK activation. Like JNK and p38, ERK is a Thr/serine (Ser) kinase that is normally located in the cytoplasm and translocates into the nucleus when it is activated [29, 78]. Fully activated ERKs phosphorylate a wide spectrum of substrates with a general amino acid consensus sequence of proline (Pro)-X-Ser/Thr-Pro that can be localized at the plasma membrane, in the cytosol and the nucleus that regulate important aspects of cell physiology including cell proliferation, differentiation, adhesion, migration, and survival [79–83].

MAPKs and Calcium Homeostasis in Myocytes

One of the hallmarks of a diseased heart is an altered protein phosphorylation state that critically contributes to ion transporter and channel dysfunctions leading to the disruption of Ca2+ homeostasis in response to both intrinsic and extrinsic stress stimuli in the heart [10, 20, 21, 22, 28, 31, 131, 132]. Calcium (Ca^{2+}) is an important cation in the conversion of an electrical signal to mechanical function (termed as excitation-contraction coupling) during each heartbeat to maintain normal cardiac function and is also important in the cellular signal transduction pathways that control myocyte survival and growth [84–91]. Excitation-contraction coupling (ECC) is an essential link between myocyte excitation (membrane depolarization of the action potential) and Ca^{2+} release from the sarcoplasmic reticulum (SR) for myocyte contraction, and this series of events is critical in the beat-to-beat cardiac muscle contraction and relaxation.

Normal and Abnormal Calcium (Ca^{2+}) Signaling in Myocytes

The cardiac action potential occurs when myocyte membrane potential is depolarized upon the initiation of a rapid sodium influx (I_{Na}) followed by Ca^{2+} influx (I_{Ca}), while repolarization occurs by the outward potassium current (I_k). During systole in normal cardiomyocytes, the Ca^{2+} entry via L-type Ca^{2+} channels (LTCCs) along with a much smaller amount of Ca^{2+} influx via the Na^+ /Ca^{2+} exchanger (NCX) activates ryanodine receptor channels (RyR2) on the SR membrane to release a large amount of SR stored Ca^{2+}. The LTCCs located in the plasma membrane are activated by the rapid sodium influx (I_{Na}) and depolarization of the myocyte membrane

[92–97]. A small amount of inward Ca^{2+} flux (I_{Ca}) through activated LTCCs triggers large quantities of Ca^{2+} to be released from the SR via cardiac ryanodine receptor type 2 (RyR2; also called Ca^{2+}-triggered SR Ca^{2+} release channels) to produce a large intracellular Ca^{2+} ($[Ca^{2+}]_i$) transient, driving myocyte contraction [89, 98–100]. This Ca^{2+}-induced Ca^{2+} release (CICR) event occurs locally within the clusters of RyR2 channels on the SR membrane that are in close proximity to LTCCs located on the plasma membrane [101, 102]. CICR is further facilitated by dyads, which are the structures consisting of terminal cisternae of SR, composed of clusters of RyR2 channels, paired with transverse tubules (T-tubules), and LTCCs [103]. Upon action potential arrival at the T-tubule, Ca^{2+} influx via LTCCs activates RyR2 channels on the cytosolic side of SR allowing for the occurrence of CICR, which activates neighboring RyR2 channels, resulting in a rapidly increased cytosolic Ca^{2+} [104, 105]. CICR is also the trigger for Ca^{2+}-troponin C binding, leading to myofilament activation and cardiac muscle contraction [106, 107]. During cardiac muscle relaxation, LTCCs close and terminate the influx of Ca^{2+}, and RyR2 channels usually are also closed. Meanwhile, the excess amount of cytosolic Ca^{2+} is removed mainly through cardiac sarcoplasmic reticulum Ca^{2+}-ATPase 2 (SERCA2) Ca^{2+} uptake back to the SR and Ca^{2+} extrusion from the myocyte to the extracellular space through NCX, while another small portion of Ca^{2+} is taken up by mitochondria via mitochondrial Ca^{2+} uniporters as well as a small Ca^{2+} efflux via the plasma membrane Ca^{2+}-ATPase (also known as plasma membrane calcium-/calmodulin-dependent ATPase or PMCA) [93, 98, 108–110]. Normal contraction of the heart requires high Ca^{2+} levels in systole and low levels in diastole [111, 112]. Therefore, SR Ca^{2+} release via RyR2 channels and reuptake via the predominating Ca^{2+} pump SERCA2a isoform (SERCA2a) and, to a much lesser extent SERCA2b isoform, critically mediate the cytoplasmic Ca^{2+} concentration, which is essential in cardiac contraction and relaxation of each heartbeat [87, 90].

Given the tightly regulated role of Ca^{2+} in ECC, even a small amount of aberrant Ca^{2+} release resulting from slowly developed pathological changes of the intracellular Ca^{2+} homeostasis can potentially have escalating negative consequences for the myocyte and ultimately the entire heart. With increasing age and abnormal stressed conditions (e.g., heart failure (HF), ischemia-reperfusion (I/R) injury, myocardial infarction (MI), post-MI, and excessive alcohol exposure), impaired Ca^{2+} homeostasis causes myocardial molecular remodeling, including aberrant gene expression, myocyte death, electrical and mechanical dysfunctions, contractile dysfunction, and triggered arrhythmic activities [24, 25, 113–122]. Abnormal Ca^{2+} dynamics such as reduced SR Ca^{2+} content via decreased uptake by SERCA2 and increased diastolic SR calcium leak via RyR2 channels are involved in the development of maladaptive cardiac remodeling. The abnormal diastolic SR Ca^{2+} leak via RyR2 openings may produce large/frequent Ca^{2+} sparks that may trigger propagating diastolic Ca^{2+} waves [113, 121, 123]. These aberrant Ca^{2+} waves result in an excess outward NCX current, which is electrogenic (3 Na^+ in, 1 Ca^{2+} out), and, thus, may produce triggered arrhythmic activities such as delayed afterdepolarization (DAD) that may initiate cardiac arrhythmias [98, 123]. Under certain pathological conditions such as HF, decreased SR Ca^{2+} refill during the SR Ca^{2+} cycling in myocytes due to reduced Ca^{2+} uptake by SERCA2a leads to a reduced Ca^{2+} transient

amplitude and consequently decreased cardiac contractility as seen in the failing heart [124–127]. In the normal diastolic phase, CICR-mediated SR Ca^{2+} release shuts off almost completely (∼99%). However, increased diastolic RyR2 channel activity leads to increased diastolic SR Ca^{2+} leak and further reduced SR Ca content, which results in a reduced systolic fractional Ca^{2+} release for a given I_{Ca} as the release trigger [123, 128, 129]. Meanwhile, this increased diastolic SR Ca^{2+} leakage along with an impaired SR Ca^{2+} uptake in HF slows down the intracellular Ca^{2+} decline and then elevates the amount of diastolic intracellular Ca^{2+} concentration, which leads to increased Na^+ influx via NCX for removing the elevated intracellular Ca^{2+} outside of the cell membrane. As a result, increased diastolic SR Ca^{2+} leak promotes aberrant Ca^{2+} events (Ca^{2+} sparks and waves), and the inward NCX current produces abnormal triggered activities, DADs, to initiate atrial arrhythmias such as atrial fibrillation (AF) and ventricular arrhythmias including ventricular tachycardia and ventricular fibrillation; fatal types of cardiac arrhythmias [94, 98, 99, 123, 130].

MAPKs in Stress-Evoked Ca²⁺ Mishandling in Myocytes

JNK is a key member of the MAPK family, which plays a critical role in maladaptive cardiac remodeling [10, 20, 21, 30, 31, 43, 133–135]. Although the contributions of JNK1 in cellular apoptosis and proliferation as well as cardiac contractile function have been well studied, the function of JNK2, one of the two major cardiac isoforms, has received significantly less attention [10, 20, 133]. Recently, a causal role of JNK2 in abnormal Ca^{2+} handling was discovered for the first time in animal models and humans with both binge alcohol exposure and increasing age with preserved cardiac function and no history of cardiac arrhythmias or any major CVDs [20, 24–26]. JNK2, but not JNK1, drives a significant diastolic SR Ca^{2+} leak and a higher SR Ca^{2+} load at the same time in the stressed myocytes. This JNK2-enhanced SR Ca^{2+} uptake partially compensates for the greater diastolic SR Ca^{2+} leak and maintains a normal level of Ca^{2+} transients and normal cardiac function, while the greater JNK2-driven diastolic SR Ca^{2+} leak acts as a key contributor to enhanced atrial arrhythmic Ca^{2+} events and arrhythmia susceptibility [24, 25].

Very recently, JNK2 was identified as a previously unrecognized enhancer of SERCA2 function via the elevation of the maximal rate (V_{max}) of SERCA2 activity by phosphorylating SERCA2 protein [24]. The SERCA2 pump activity is known to be regulated by phospholamban (PLB), sarcolipin, myoregulin, striated muscle enriched protein kinase (SPEG) and DWORF (dwarf open reading frame) micropeptide [136–139]. All those regulators that are known to increase SERCA2 Ca^{2+} affinity (K_m) do not change the V_{max}, whereas, JNK2 significantly enhances the V_{max} of SERCA2-ATPase activity but not the K_m [24, 136–139]. Intriguingly, JNK2-enhanced SR Ca^{2+}($[Ca^{2+}]_{SR}$) load by itself (in the absence of CaMKII-dependent RyR2 channel sensitization) may not be sufficient to cause significant diastolic leak, a combined higher load and CaMKII-sensitized RyR2 channels may promote the diastolic leak as previously demonstrated [24, 113, 120, 122, 123]. Thus, JNK2 is

an important stress-induced regulator driving to maintain a high SR Ca^{2+} uptake and load in order to preserve cardiac function, while JNK2 also drives a greater CaMKII-dependent SR Ca^{2+} leak to promote abnormal triggered activities (discussed in detail below), as seen in both humans and animal models.

The atrial action potential morphology differs from that of the ventricle, where the atrial action potential is generally shorter with a triangular shape due to a smaller Ca^{2+} influx and a more gradual repolarization period [140, 141]. Ca^{2+} handling in atrial myocytes while similar to that of ventricular myocytes has some important structural and molecular differences. Atrial myocytes are thinner and longer and exhibit a longer lag time between APs and Ca^{2+} transients at the center of the cell. This property of the atrial cell contributes to a higher instability of Ca^{2+} propagation, which is pro-arrhythmogenic [142]. Notably, atrial Ca^{2+} transient amplitude is smaller, and the rate of intracellular Ca^{2+} decay is higher than in ventricular myocytes due to a greater SERCA2 uptake and a stronger NCX removal of cytosolic Ca^{2+} during the diastolic phase [142, 143]. The increased SERCA2-dependent intracellular Ca^{2+} removal is attributed to a greater amount of SERCA2 protein and lower level of SERCA2 inhibitory protein PLB [142, 143]. This stronger cytosolic Ca^{2+} removal machinery in the atria leads to a higher SR Ca^{2+} content than that of ventricular myocytes, which makes atrial myocytes prone to diastolic SR Ca^{2+} leak when RyR2 is pathologically sensitized and SR Ca^{2+} overload is increased due to the dual functional impact of stress-activated JNK2 [24, 120, 123, 142, 144–146]. Thus, markedly increased JNK2 in atria exposed to stress stimuli (i.e., aging, binge alcohol) is a major contributor to continued pathological remodeling and enhanced AF risk [20, 24–26, 120]. T-tubules are a subcellular network involved in SR Ca^{2+} dynamics by the coupling of LTCCs to RyR2 channels on the SR membrane to allow a rapid intracellular Ca^{2+}-triggered SR Ca^{2+} release in response to electrical excitation [147–150]. Previously it was believed that atrial T-tubules were virtually absent in isolated myocytes from small rodents; [151, 152] however, accumulating evidence suggests that the T-tubule network is present in intact atrial myocytes and plays a functional role in atrial myocytes from both large mammalian species and small rodents (including humans, sheep, dogs, cows, and horses, rats, mice) [153–157]. These inconsistent research findings may likely be due to the nature of fast T-tubule structural deformation during myocyte isolation and preparation. However, atrial T-tubular networks are clearly less abundant and less well-organized compared to ventricular. In fact, rapid pacing-induced HF dogs showed reduced atrial T-tubular abundance that was linked to altered subcellular Ca^{2+} dynamics and AF development [122, 154, 155]. However, the involvement of the stress-response MAPKs in T-tubular remodeling remains unknown to date.

Like JNK, other MAPK members ERK and p38 are also involved in various types of stress-caused cardiac pathogenesis [10, 21, 22, 131, 132, 158]. 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 involved in pathological remodeling and AF development in the failing heart [159–165]. Hypertrophic stimuli lead to an increase in I_{Ca} and downregulation of SERCA2 expression via activated ERK [17–19]. While Ras, a GTPase, is able to activate

ERK through a Ras-Raf-MEK cascade [166], Ras signaling-activated ERK was found to contribute to downregulation of L-type Ca^{2+} channels and reduced channel activity along with reduced SERCA2 protein expression in cultured myocytes [15, 16]. Thus, Ras-ERK-modulated molecular remodeling led to decreased intracellular Ca^{2+} transients and impaired SR Ca^{2+} uptake, which could lead to enhanced arrhythmogenicity [167]. In both isolated cardiomyocytes and Langendorff-perfused intact hearts, activation of p38 MAPK signaling was found to induce SR Ca^{2+} overload through enhanced SERCA2 activity and increased SR Ca^{2+} uptake during cardiac I/R injury, which in turn prompted myocardial apoptosis [168]. Overall, the stress-response MAPK signaling cascades are critically involved in cardiac Ca^{2+} handling and stress-caused maladaptive cardiac remodeling. However, many questions remain unanswered such as the extent and detailed mechanisms of how the three MAPK members interact and functionally overlap with regards to Ca^{2+} handling in cardiac myocytes under physiological and stressed conditions.

MAPKs and Ca Handling Proteins in Myocytes

JNK2 was recently recognized as a critical activator and transcriptional regulator of CaMKIIδ, a highly validated pro-arrhythmic signal [25, 40, 120]. CaMKIIδ is a well-recognized regulator of Ca^{2+} dysregulation in cardiomyocytes through its critical contribution in phosphorylation of the Ca^{2+} handling proteins RyR2-Ser2815 (sensitizing RyR2 channels to increase diastolic SR Ca^{2+} leak) and PLB-Thr17 (elevating the SERCA activity to enhance the SR Ca^{2+} uptake), which results in triggered activities and arrhythmia pathogenesis in humans and animal models [25, 145, 146, 169–171]. In addition, CaMKIIδ also regulates other ion channels such as Ca^{2+}, Na^+, K^+ channels as well as NCX and myofilament proteins including troponin T (TnT) and myosin-binding protein C (MyBP-C) via phosphorylation [172–191]. Thus, hyper-activated CaMKIIδ drives RyR2 channel-mediated diastolic Ca^{2+} dysfunction that causes and triggers arrhythmic activities but also contributes to cardiac contractile function. Intriguingly, recent studies revealed that JNK2 has specific actions in regulating both expression and activation of CaMKIIδ, which consequently drives CaMKIIδ-dependent SR Ca^{2+} mishandling in the stressed heart. Specifically, JNK2 and CaMKIIδ were found to be tethered with each other, and JNK2 increases phosphorylation of CaMKIIδ at the autophosphorylation site Thr286 to activate CaMKIIδ in a JNK2 dose-dependent manner [25]. Protein phosphatase 1 (PP1) is known to target this specific Thr286 site to dephosphorylate CaMKIIδ [192]. Thus, a possible interrelationship between PP1 and JNK2 might exist in regulating the CaMKIIδ activity, and this is worthy of further investigation.

Although CaMKIIδ is essential in regulating a large number of cellular substrates including ion channels, pumps, transporters, and transcription factors [25, 120, 172–191, 193], exactly how the CaMKIIδ gene and protein expression is controlled remains surprisingly understudied. A recent study reported for the first time

that JNK2 downstream transcription factors c-jun and activating transcription factor 2 (ATF2) both bind to the CaMKIIδ gene promoter and regulate CaMKIIδ expression [40]. Surprisingly, c-jun was found to be a key transcription factor for the basal level expression of CaMKIIδ mRNAs and proteins. This was evidenced by the suppression of CaMKIIδ promoter baseline activity when c-jun was knocked out in the cells or the binding consensus sequence for c-jun was mutated to alter binding. Moreover, robustly activated JNK2, mimicking a stressed condition, significantly increases the binding of c-jun, but did not change the binding of ATF2, to the CaMKIIδ promoter, while JNK2 inhibition alleviated this enhanced c-jun binding activity. In addition, the JNK2 specific action in c-jun-regulated CaMKIIδ promoter activity was strongly supported by the suppressed CaMKIIδ promoter activity from JNK2 knockdown or suppressed activity [40]. These findings take on special translational importance given that the development of drugs that target CaMKIIδ activity has been considered as an appealing anti-arrhythmic intervention point; however, specificity issues driving off-target effects greatly hinder the clinical applications. Additionally, upstream or downstream components of the CaMKII signaling cascades are then considered as new potential therapeutic targets. Stress-driven JNK2 activation and the JNK2-CaMKII cross talk are likely critical mechanisms that couple stressors and maladaptive cardiac responses. Therefore, modulating JNK2 activity could be a likely therapeutic approach to prevent and treat cardiac arrhythmias.

An extensive number of studies have demonstrated that JNK1 activation is critically involved in preservation of cardiac function and promoting apoptosis after myocardial I/R, MI, and HF via the regulation of signaling pathways that modulate gene expression [10, 21, 165, 194–200]. Also, emerging evidence suggests that p38 regulates SERCA2 mRNA and protein expression via the transcription factors Egr-1 and SP1 [14]. However, the functional role of all three MAPK members and subisoforms of each kinase in Ca^{2+} handling proteins in cardiomyocytes under physiological conditions or stress challenges requires further investigation. Our advancement of understanding the functional role of MAPKs will likely aid the effort of developing novel preventive and therapeutic strategies for CVDs.

MAPKs and Molecular Remodeling in Myocytes

The MAPK signaling pathway transduces and integrates diverse stress stimuli into complex cytoplasmatic and nuclear processes and finally leads to altered cellular function including proliferation, gene expression, differentiation, and apoptosis. MAPKs regulate cellular processes via direct phosphorylation of downstream targets and/or indirectly regulate gene expression in maintaining normal cell function and cellular responses under stress stimuli challenges. Generally, the JNKs and p38 kinases regulate the stress or injury responses, while the ERKs are more specialized for mitogenic and growth factor stimulations [201, 202].

MAPKs and Gene Regulation in Myocytes

Gene regulation is one of the important functions of the MAPK family via the downstream transcription factors such as c-jun, ATF2, JunD, c-Fos, SRF, AP-1, c-Myc, MEF2, GATA, SMAD, STAT-1, and NFκB. The JNKs directly phosphorylate a number of their downstream transcription factors such as c-jun, ATF2, AP-1, JunD, Sp1, Elk1, and c-Myc [26, 40, 203–206]. The AP-1 complex is composed of homodimers of c-jun or heterodimers of c-jun/ATF2 or other combinations of transcription factors, which induce target gene expression by binding the AP-1 consensus site(s) in the promoter region of the gene or dissociating from the promoter region to upregulate or suppress the specific gene expression [40]. These activated transcription factors critically contribute to the transcriptional regulation of proteins that are involved in I/R caused myocardial injury and ATP depletion. JNK1 is also known to regulate several important genes (i.e., Notch1, SOD-3) in response to inflammation, oxidative stress, and heat stress through phosphorylation of several transcription factors (i.e., c-jun, Sp1, DAF-16) [207–209]. Under long-term stress challenges (i.e., aging, repeated binge alcohol exposure), JNK2, but not JNK1, is activated, which leads to reduced AP-1 activity but increased binding of c-jun and unchanged binding of ATF2 to the promoters of JNK2 target genes such as the "cell-to-cell communicator" gap junction protein connexin43(Cx43), "pro-arrhythmic kinase" CaMKIIδ, and "epigenetic regulatory molecule" DNA methyltransferase1 (DNMT1) to either suppress or enhance their transcriptional activities and gene expression. Consequently, this JNK2-mediated gene regulation leads to impaired cellular function including intercellular uncoupling between cardiac myocytes along with the slowing of electrical conduction or enhanced cardiac Ca^{2+}-mediated arrhythmic triggered activities or increases DNA methylation [20, 24–26, 40, 210].

Like the JNKs, p38 also directly phosphorylates transcription factors including ATF1/2/6, c-Myc, c-Fos, GATA4, MEF2A/C, SRF, STAT-1, and CHOP [53, 211–213]. Upon activation, p38 translocates into the nucleus and reenters the cytosol when inactivated which is essential for its function across all cell types [58]. The phosphorylation status and the interaction of p38 with other proteins determine its subcellular location and activities of its downstream targets [214]. For instance, activated p38/MAPKAP kinase-2 (MK2) can form a complex with activated p38 in the nucleus leading to the export of MK2 from the nucleus to phosphorylate its cytosolic substrates [215, 216]. The mitogen and stress-activated protein kinase 1/2 (MSK1/2) is a downstream target of p38 but also regulates the subcellular location of p38 and the p38/MSK complex in regulating the transcriptional activity of CREB, STAT3, and NFκB [217–221]. Moreover, p38-regulated transcription factors contribute to the upregulation of several important stress-response genes including phosphatase and tensin homolog on chromosome 10 (PTEN) that acts to limit the phosphorylation and activation of Akt as well as the transforming growth factor beta (TGF-β) signaling pathway in regulating cell growth/differentiation/apoptosis and other cellular functions [222, 223].

Activated ERK1/2, another MAPK family member, has been found to undergo nucleus-translocation and directly phosphorylate transcription factors and bind to chromatin inside the nuclei [224–226]. A recent discovery shows that autophosphorylation of ERK2 at the site of Thr188 (Thr208 in ERK1) promotes the nucleotide binding but attenuates ERK kinase activities, while inhibiting the upstream regulator MEK1/2 also abolishes the nucleotide binding and reduces the activity of ERK [227, 228]. ERK has diverse cytoplasmic targets such as the p90 ribosomal S6 (p90^{RSK}) family with isoforms 1–4, p70 ribosomal S6 (p70^{RSK}) [229], MNK [230], and glycogen synthase kinase-3 (GSK-3) [231], which consequently phosphorylate a wide range of substrates involved in gene transcription, translation, cell cycle regulation, and cell survival [232, 233]. Moreover, ERK can phosphorylate a complex family of transcription factors, the ternary complex factors (TCFs; SAP-1, Elk-1, Net, etc.), which are vertebrate ETS-domain proteins that link transcription to MAPK signaling in order to regulate the expression of c-Fos, c-Myc, and c-jun and in turn contribute to transcriptional regulation of various late-response genes that promote cell survival, cell division, and mobility, which are opposite to the regulatory role of JNK and p38 on those cellular responses as discussed above [158, 234–237]. In addition, several key transcription factors including FOXO, BETA2/NeurD1 (the basic helix-loop-helix protein partner), E4, and PDX-1 were found to be related to glucose regulation and insulin gene transcription, which also underlie the anti-apoptosis effect in myocytes and cardiac protective effect of ERK1/2 [238–241].

In summary, MAPK signaling pathways are key mediators of cell transcriptional responses to stress-induced extracellular signals. These pathways critically control gene expression in a number of ways including the phosphorylation of cytosolic proteins and regulation of transcription factors and co-regulatory proteins.

MAPKs and Apoptotic Signaling Pathways in Stress-Exposed Myocytes

Apoptosis is a highly regulated process in the cell composed of a balance between pro-death and pro-survival cell signals, and apoptotic cell death plays a pivotal role in myocyte survival in response to stress stimuli such as ischemic cardiac injury and heart failure. Apoptosis can be roughly divided into extrinsic apoptosis, meaning the apoptosis signaling coming from the environment, and intrinsic apoptosis, meaning the apoptosis signaling coming from the cell itself. The main route of apoptosis in the heart is intrinsic apoptosis, and the key initiator of intrinsic apoptosis is the mitochondrial release of cytochrome c [242]. Cytochrome c released from mitochondria forms a complex from pro-caspase 9 and its cofactor APAF-1 and eventually leads to the activation of caspase 9 and apoptosome formation in the cytosol followed by the activation of caspase 3 leading to apoptosis [242]. Various adverse conditions can lead to intrinsic apoptosis in cardiac myocytes including but not limited to redox stress, energy deprivation, and activation of Gα_q signaling

[243–245]. On the other hand, activation of the extrinsic apoptotic signaling pathway is a common phenomenon in stressed hearts such as seen with myocardial ischemic I/R, postinfarction remodeling, end-stage heart failure, and diabetes [246–249]. Two families of independent receptors that mediate the extrinsic apoptosis signaling are mainly regulated by the Fas receptor (receptor for Fas ligand, FasL) and TNFα receptor 1 (TNFα-R1). Activation of Fas receptor and TNFα-R1 by their specific ligands leads to cleavage of pro-caspase 8 into caspase 8 which further activates caspase 3 to promote apoptosis. In both extrinsic and intrinsic apoptosis, the Bcl-2 family of proteins with Bcl-homology domains plays important roles. To date, this Bcl-2 family is known to contain two subgroups, anti-apoptotic proteins including Bcl-2, Bcl-X(L), Bcl-W, Bfl-1, and Mcf-1 and pro-apoptotic proteins including Bad, Bac, Bak, Bix, Box, Bid, Bim, Bnip3, and Nix [250, 251]. Phosphorylation of Bcl-2 family members plays a key role in regulating mitochondrial membrane integrity, and MAPK has been shown to regulate the Bcl-2 family by phosphorylation [250, 251]. While anti-apoptotic Bcl-2 proteins bind to the proteins forming mitochondrial pores, controlling their opening and closure, some pro-apoptotic Bcl-2 proteins including Bax and Bak can insert into mitochondrial outer membrane upon activation via phosphorylation and form pores into the mitochondria [252–255]. The Bcl-2 family achieve the anti-apoptotic effect through the inhibition of pro-apoptotic proteins (i.e., Bad, Bax, and Bim) [256–260].

JNK and Apoptotic Signaling Pathways in Myocytes

In the heart, JNK is activated in response to various stimuli signals including mechanical stretch [261, 262], pressure overload [263–265], I/R [266, 267], and catecholamine stimulation [263], which are known to activate apoptotic signaling pathways [262, 268, 269]. Apoptosis signal-regulating kinases (ASK, including ASK1 and ASK2) promote the activation of MKK4 and MKK7, which are the upstream activators of JNK [21]. However, mixed findings regarding the role of JNK in apoptosis have been reported, suggesting complicated stress responses of JNK signaling in different cell types and potentially different isoform activation at different time frames following various stress challenges. In ROS-challenged myocyte models (H_2O_2-treated or norepinephrine-treated adult rat ventricular myocytes), JNK activation is involved in ROS-induced apoptosis, evidenced by alleviated ROS production and reduced apoptosis through JNK-specific inhibiton [270, 271]. In addition, JNK has been localized to the mitochondria in cardiac myocytes and is known to promote the mitochondrial cytochrome c release in a capase-9-dependent but capase-8-independent manner, suggesting a direct functional role of JNK in mitochondria-associated appotosis [272]. This pro-apoptotic effect of JNK was also found in noncardiac mammalian cells via enhanced phosphorylation and degradation of anti-apoptotic proteins Bcl-2 and Bcl-X(L), which removes the inhibitory regulation of Bcl-2 and consequently activates the pro-apoptotic proteins Bad, Bax, and Bim [256–260]. Furthermore, suppressing JNK1 or the MKK4 pathway from overexpression of dominant negative proteins enhances apoptosis during NO

treatment and I/R injuries, further supporting the anti-apoptotic effect of cardiac JNK in response to ischemic stress [273–275]. While JNK inhibition reduces apoptosis during numerous stress conditions including transient energy deprivation (glucose deprivation and mitochondria inhibition), I/R, and hyperglycemia in cultured H9c2 cells and myocytes, JNK-deficiency in fibroblasts activates mitochondrial apoptotic signaling [276–280]. Thus, the functional role of JNKs in cellular apoptotic pathways of the heart may vary depending on the cell type and context in response to different types of stress stimuli. While the findings discussed above are predominantly regarding the contributions of JNK1 in cellular apoptosis and proliferation that have been well studied [10, 20, 133], the functional roles of cardiac JNK2 and JNK3 (with less expression in the heart) in the apoptotic pathway under different stressed conditions remain largely unknown. Further investigations are clearly needed to enhance our understanding regarding the functional role of JNK in myocardial remodeling and maladaptive development.

p38 and Apoptotic Signaling Pathways in Myocytes

p38 is critically involved in cardiac apoptosis in various animal models of cardiac disease such as cardiac injury and HF [281–285]. p38 was found to activate p53 and promote apoptosis by enhancing the expression and translocation of Bax in mitochondria [286]. p38 can also phosphorylate Bcl-2 via translocation into mitochondria to suppress the anti-apoptotic effect of cytosolic Bcl-2 [287]. In platelet-activating factor (PAF)-treated H2c2 cardiac myocytes with elevated cytosolic Ca^{2+}, caspase 3 activity and mitochondria release of cytochrome c increase in a p38-dependent manner, further supporting the pivotal role of p38 in promoting myocyte apoptosis [288]. Also, a reduced level of Bcl-2 and enhanced apoptosis was found in cardiac myocytes with overexpression of wild-type p38 but not in the myocytes with overexpression of an inactive dominant negative form of p38α [283]. This pro-apoptotic function of p38α was further demonstrated in a mouse myocardial infarction model where overexpression of p38α alleviates the inhibition of apoptosis guard Bcl-X(L) and Bcl-2 reduces the Bcl-X(L) deamination consequently activating the pro-apoptotic signaling cascades [282]. The I/R injury response is crucially determined by mitochondrial function and activity and p38 inhibition during I/R decreases mitochondrial swelling and ultrastructural alterations and mitigates mitochondrial membrane depolarization [289]. There is also evidence that p38 activation during I/R contributes to cardiac damage by triggering intracellular Ca^{2+} overload [290]. While the pro-apoptotic role of p38α in myocytes has been well-recognized, the pro-apoptotic role of p38δ in deteriorating cardiac function was recently reported with chemotherapeutic doxorubicin-induced cardiomyopathy [291]. Moreover, p38 is a key player in α1-adrenoreceptor blocker doxazosin-induced apoptosis in cardiac myocytes that increases the risk of HF development [292, 293]. Although the overwhelming evidence suggests a pro-apoptotic role of p38, an anti-apoptosis role of p38 has also been described under certain stressed conditions. For instance, with specific β-adrenergic receptor signaling mediated through Gi-dependent receptors,

p38 could exert anti-apoptotic roles, while osmotic stress also showed anti-apoptotic function of p38 via phosphorylation of small heat shock protein αB-crystallin [294–296]. Therefore, p38 may have a differential functional impact on myocyte apoptotic signaling pathways in response to different stress stimuli. In addition, the distinct functional roles of the different sub-isoforms of p38 under different stress stimuli require further investigation.

Other than a direct regulation of p38 in the apoptotic signaling cascade proteins, p38 can also promote apoptosis in cardiac myocytes by regulating apoptotic genes via a wide panel of transcription factors including but not limited to ATF2, AP-1, GATA, SMAD, STAT-1, and NFκB [297]. For instance, in I/R injury and hypoxia animal and cell models, p38-dependent phosphorylation of ATF2 leads to enhanced expression of phosphatase PTEN which limits the phosphorylation and activation of Akt, a powerful survival pathway regulator [222]. Suppressing p38 by overexpressing dominant negative p38 or PTEN both attenuated myocyte death, cardiac injury, and functional loss after the I/R injury [222]. Enhanced expression of FasL is a well-established route toward DNA fragmentation and apoptosis [298, 299]. p38 has been shown to upregulate Fas/FasL expression via increased phosphorylation of the downstream transcription factor STAT-1 at the Ser727 site to enhance its transcriptional activity in myocytes treated with angiotensin II, norepinephrine, and hypoxia [300, 301]. Moreover, p38-dependent AP-1 and GATA transcriptional regulation were also found to upregulate TGF-β expression, which triggers the activation of transcription factor SMAD-mediated apoptosis in angiotensin II-treated myocytes [223]. GADD153 (growth-arrest-and-DNA-damage-inducible protein 153 also known as C/EBP homologous protein (CHOP)) is one of the pro-apoptotic transcription factors engaged in response to enhanced ER stress. p38-dependent activation of GADD153 has been shown to promote the expression of downstream-of-CHOP gene 1(DOC-1), which encodes for a stress-induced form of carbonic anhydrase VI that catalyzes the formation of H_2CO_3 to increase cellular stress-induced apoptosis [302, 303]. In addition, p38-activated GADD153 enhances NFκB phosphorylation and nuclear translocation, which was found in doxorubicin-induced inflammation and apoptosis in cardiac myocytes [304]. Furthermore, inhibition of p38/NFκB signaling alleviates isoproterenol-induced cardiac dysfunction in a rat model [297]. Thus far, the evidence supports a key role for p38 in myocyte apoptosis and the development of cardiac maladaptive function.

ERK and Apoptotic Signaling Pathways in Myocytes

ERK activation is largely anti-apoptotic in the heart under various stressed conditions such as I/R injury, oxidative stress, hypoxia stimulation, and β-adrenergic stimulation [305, 306]. ERK inhibition enhanced the oxidative stress-induced cell injury and apoptosis, while also pharmacologically potentiated ERK activation showed a protective effect against apoptosis induced with a chemotherapy reagent doxorubicin in cardiac myocytes [307–309]. In contrast, activated ERK1/2 attenuates I/R injury in both cell and animal models [268, 310–313]. Another interesting

finding is that the cell survival signaling through β2-adrenergic receptor activation has been shown to be regulated through activated ERK [314].

The cardiac protective roles of ERK1/2 during a stress challenge are multidimensional. ERK substrates include nuclear substrates (transcription factors) and cytosolic substrates promote apoptosis through activity and transcriptional regulation of certain key apoptosis-related proteins in the cytosol or nucleus. For example, activated cardiac ERK1/2 can phosphorylate cytosolic proteins such as phospholipase A2 and transcription-regulating kinases p90^{SRK}, GSK3, which are critically involved in cellular apoptosis under stressed conditions [315–322]. ERK1/2 also inhibits a key pro-apoptotic protein Bad by facilitating the protein kinase Cε (PKCε)-mediated phosphorylation of Bad in mitochondria and downregulates the expression of Bax, another pro-apoptotic protein in the Bcl-2 family, resulting in the inhibition of cytochrome c release from mitochondria in cardiac myocytes [312, 316–318]. Moreover, ERK-GATA4 signaling was shown to be involved in the anti-apoptosis function of ERK by upregulated expression of anti-apoptotic protein Bcl-X(L) via enhanced phosphorylation of the transcription factor GATA4 at the Ser105 site to enhance the promoter activity of Bcl-X(L) [312, 323]. It is known that activating ERK promotes the activation and nuclear translocation of transcription factor Nrf2 which promotes the expression of genes that potentiate the glutathione antioxidant response, while ERK also upregulates COX-2 via enhanced AP-1 and NFκB-2 transcriptional activity to sustain the cardiac myocyte survival and metabolism in response to an oxidative stress challenge [213, 324]. This convincing evidence suggests that ERK1/2 fulfills an anti-apoptotic role to promote cell survival and growth in response to stress stimuli to protect cardiac function. However, ERK was also found to be pro-apoptotic in certain disease models. For instance, in a diabetic rat model with upregulated HMGB1 (high mobility group box 1 protein), ERK was found to promote apoptosis via the activation of Ets-1, which eventually leads to enhanced Bax protein and caspase 3 activation [325].

Taken together, the three MAPK members fulfill unique but overlapping intracellular signaling mechanisms in responding to a myriad of mitogens and stressors mediating the signaling networks of cell survival and death as well as cardiac metabolism and pathogenesis in a cell type and context dependent manner.

Dynamic Relationships of MAPKs in Pathological Cardiac Remodeling in Stressed Hearts

Accumulating evidence suggests that the three MAPK family members play important roles in the development of pathological remodeling and maladaptive cardiac function during disease progression in a cellular context- and time-dependent manner [10, 21, 22, 131, 132, 326]. Cardiac remodeling encompasses the molecular and structural changes accompanying the electrical physiological and pathological changes in stress-exposed hearts. Those changes are manifested clinically in the progression of HF including increased heart size, deteriorated cardiac contractile function, and reduced cardiac output along with a series of clinical symptoms of

HF. Cardiomyocytes are the major cardiac cells involved in the remodeling process, although other components are also involved including the interstitium, fibroblasts, and coronary vasculature. Being terminally differentiated cells, cardiac myocytes respond to stress stimuli by adaptive growth, also known as hypertrophy, as the adaptive response in stress-exposed hearts [327]. Cardiac hypertrophy can be roughly divided into physiological (or adaptive) hypertrophy and pathological (or maladaptive) hypertrophy [328]. Physiological hypertrophy is reversible and occurs in response to continuously increased demand for cardiac function, which bears the main characteristics of increased cell size, increased fatty acid oxidation and protein synthesis, sarcomeric reorganization, and increased gene transcription related to cell growth [329, 330]. Pathological hypertrophy may also occur after myocardial ischemic injury, inflammatory heart muscle diseases (i.e., myocarditis), idiopathic dilated cardiomyopathy, or unfavorable cardiac volume loading such as hypertension, aortic stenosis, or valvular regurgitation. Pathological hypertrophy is usually accompanied by enhanced inflammation signaling, fetal gene expression, interstitial fibrosis, and risks of decompensation and progression toward to HF [329–332].

Regardless of cardiomyocyte MAPK activation under different stress conditions, a different temporal response to various stress stimuli clearly plays a role [161, 333–336]. Cardiac ERK1/2 plays an essential role in promoting myocyte survival and growth during the progression of adaptive hypertrophy and pathological maladaptive remodeling [337–339]. In response to stress stimuli, ERK1/2 can be activated by either G protein-coupled receptor (altered angiotensin II, endothelin-1, phenylephrine, catecholamines, etc.) [331, 332, 340–343], receptor tyrosine kinases (altered fibroblast growth factor, TGF-β1, growth differentiation factor 15, etc.) [344–346], or mechanical stretch [347]. Activated ERK drives a wide network of intricate pathways which activate secondary signaling to regulate cardiac myocyte cytosolic activity and gene regulation leading to cardiac hypertrophy without premature death or impaired cardiac function [84, 348–350]. While suppression of ERK1/2 signaling by inhibition of ERK1/2 or MEK1/2 with pharmacological agents and dominant negative protein overexpression abolishes hypertrophic response in myocytes during pathological insults (e.g., pressure overload, I/R injury, oxidative stress), this ERK inhibition however leads to aggravated cardiac function and exacerbated myocyte death [161, 324, 351–354]. Thus, ERK-mediated hypertrophic remodeling appears to be a beneficial early response to maintain a normal cardiac function under stress challenges.

A dynamic relationship between the three MAPKs was found in various cardiac disease models. While some studies observed only transient ERK activation in a pressure-overload mouse model induced with transverse aortic constriction (TAC), other reports suggest that ERK remained activated for 2- to 4-week post-TAC [333, 335, 336]. However, JNK and p38 were found to be constantly activated over the course of pressure overload [161, 333–336]. On the other hand, severity of the pressure overload and HF status likely plays a key role in the differential activation status of the three MAPK members [333, 335, 336]. For instance, JNK and p38 activation in the heart and in white blood cells were in positive correlation with the severity of pressure overload measured with trans-stenotic systolic pressure

gradient and the severity of hypertrophy (left ventricular weight/body weight ratio) [355]. This was supported by another study in animals showing that JNK is significantly increased with a mild to severe pressure overload (35–85% aortic constriction), while p38 is activated in HF with a more severe pressure overload (85% aortic constriction), but ERK was only transiently activated [356]. In human hypertensive patients with uncontrolled blood pressure, p38 and JNK activation is significantly higher in white blood cells compared to patients with controlled blood pressure [355]. Myocardial I/R is another common and complicated pathophysiological stressor that can lead to myocardial stunning, arrhythmias, and eventually HF [357]. Different time scales of MAPK activation have been shown in the infarct or infarct border zone of post-MI mouse, and p38 phosphorylation is increased initially, while JNK phosphorylation increased approximately 2 weeks after MI; on the other hand, ERK phosphorylation increased after about 4 weeks after MI, likely contributing to the post-MI myocardial remodeling [358]. In a rat model of I/R injury, increased p38 and unchanged ERK occurred during the acute ischemia phase, while JNK was only increased during the reperfusion phase [359]. Similarly, in a long-term ischemia porcine model of coronary embolism, JNK, p38, and ERK activations were all enhanced, contributing to the postischemic remodeling from the microinfarction and apoptosis [360]. The enhanced phosphorylation of p38 and JNK after I/R injury further decreased the cell viability and promoted cardiac cell apoptosis [361] via decreased anti-apoptotic Bcl-2 and increased pro-apoptotic Bax [280]. Moreover, acute MI (6 hours after LAD ligation) could activate both JNK and p38, yet ERK was decreased, accompanied by increased activity of pro-apoptotic protein caspase-3 [362–364]. ROS has been shown to be critical in activating MAPKs in response to I/R injury. Suppression of ROS production alleviates MAPK activation and attenuates the loss of cardiac function and decreased infarct size [365]. This is supported by the findings of ROS-dependent JNK and p38 activation in post-MI ventricular tissues [366]. In animal models of diabetes and post-MI diabetes, increased ROS was found to be responsible for intensified myocardial injury and loss of cardiac function along with increased activation of JNK and p38, and the contribution of ROS-activated JNK and p38 was confirmed by the striking rescue effect of ROS suppression and stress kinase inhibiton [367, 368]. Moreover, antioxidant/anti-inflammatory agents also prove to enhance ERK1/2 activation and preserve the cardiac function along with suppressed activities of JNK and p38 [369, 370].

Overall, dynamic changes of the three MAPKs appear to occur at different time points during the pathological cardiac remodeling process in response to a myriad of mitogens and stressors. In general, the end result of this temporally dynamic activation of p38 and JNK leads to the aggravation of cardiac injury, promotes maladaptive cardiac remodeling, and impairs cardiac function, while the activation of ERK promotes cell survival and preserves cardiac function. To date, the MAPK family has received extensive interest due to the far-reaching implications its members manifest in signaling and cross talk with other signaling networks. Further understanding regarding the dynamic relationship between the three MAPK members under different stress conditions will be required for the development of

effective therapeutic strategies and the discovery of novel therapeutic targets for early intervention and treatment of cardiac diseases.

MAPKs and Therapeutic Potentials

MAPKs are critically involved in cardiac pathological remodeling, and disease development (i.e., hypertrophy, ischemic injury, HF, and cardiac arrhythmias) positioning the modulation of MAPK activity as a novel point for therapeutic intervention. Pharmacological inhibition and genetic deletion of the three MAPK kinases has proven to change the course of stress-induced cardiac adaptive and maladaptive remodeling [333, 371]. Inhibition of JNK and p38 activities has been shown to reduce cardiac injury and preserve cardiac function in the stressed heart, and this was supported by manipulating upstream regulators of JNK and/or p38 to suppress their activities. The knockdown of Grb2 adaptor protein suppressed JNK and p38 activities (no effect on ERK), which effectively alleviated cardiac hypertrophy and apoptosis in pressure-overload hearts [334, 372]. Another example is that deletion/suppression of multiple upstream regulatory genes (i.e., BAMBI, NECTIN2, DKK3, and the 14-3-3 family) inhibits JNK and p38 activity along with exacerbated apoptosis, fibrosis, and cardiac function loss [373–376].

However, selective inhibition of each MAPK often offers different outcomes, which is in line with the evidence of differential involvement of the three MAPKs and their downstream signaling pathways at different stages during the progression of cardiac remodeling and disease development under different stress conditions. While some studies have shown a beneficial effect of competitive inhibition of the p38 signaling alone by overexpression of dominant negative p38 or pharmacological inhibition in promoting cardiac hypertrophy by preventing apoptosis and fibrosis and preserving cardiac function in response to pressure overload and I/R injury [281, 283, 372, 375, 377–379], other studies suggest that inhibiting p38 alone promotes hypertrophy but aggravates the deterioration of cardiac function in both pressure overload and I/R injury models and even abolishing the protective effects of ischemia preconditioning [380–383]. There are current clinical trials testing the safety and efficacy of p38 inhibition in myocardial infarction [384, 385]. The p38 inhibitor SB-681323 decreased the circulating inflammatory marker high-sensitivity C-reactive protein (hs-CRP) in statin-receiving patients undergoing elective percutaneous coronary intervention [386]. A phase 2 clinical trial suggests treating patients with non-ST-segment elevation myocardial infarction with the p38 inhibitor losmapimod (GW856553X) decreased circulating levels of inflammatory markers including IL-6 and hs-CRP short term (72 hour); however, no differences in inflammatory markers or risk of cardiovascular events were shown in a longer term trial (12 weeks) [384, 387, 388]. Similarly, JNK inhibition without the influence in ERK and p38 led to increased myocyte size; upregulated activation of pro-apoptotic

proteins including p53, Bad, and Bax; and exacerbated deterioration of cardiac function in different disease models [389–391]. Thus, therapeutic potentials of selective inhibition of either JNK or p38 for cardiac function protection under certain pathological conditions need to be further evaluated. Recently, JNK2, an understudied JNK isoform, showed therapeutical potentials in anti-arrhythmogenesis [20, 24–26, 392]. While accumulating evidence suggests that pro-arrhythmic molecule CaMKII may represent a target for therapy and provoked the development of CAMKII inhibitors [113, 393, 394], CAMKII inhibitors have off-target effects that hinder their clinical application [395]. With the discovery of a novel form of pathogenic kinase-on-kinase cross talk, JNK2 directly regulates CAMKII activity, and the development of compounds directed at JNK2 may represent an alternative drug target. More research is warranted to explore JNK2 as an anti-arrhythmic drug target in patients.

Considering the protective role of ERK and detrimental role of JNK and p38 in cardiac injury and pathological remodeling, developing specific strategies for use of selective MAPK inhibitors has a high clinical potential in preventing and treating cardiac injury and pathological remodeling and ultimately preserving or improving cardiac function. In fact, activation of the ERK1/2 pathway has been identified as a central component of the so-called Reperfusion Injury Salvage Kinase (RISK) pathway [396]. ERK1/2-specific in vitro kinase activity in adult hearts subjected to 20 minutes of ischemia followed by 15 minutes of reperfusion was doubled [362]. In addition to this study, others support a protective role for the MEK1-ERK2-signaling pathway against I/R injury [268, 397, 398]. A thorough experimental dissection of the RISK pathway revealed a combination of two parallel cascades, PI3K-Akt and MEK1-ERK1/2, that produced a protective effect when blocked with the co-administration of both PI3K and ERK inhibitors at different time points [399]. Thus, broadly the RISK pathway refers to a group of pro-survival protein kinases, which confer cardioprotection when activated specifically at the time of reperfusion [399, 400]. The RISK pathway has recently been seen as a universal signaling cascade for cardioprotection and is likely recruited not only by ischemic conditioning but also by other pharmacological agents such insulin, bradykinin adenosine, or statins [401] shared by most cardioprotective therapies [402]. Therefore, the cardiac protective effect of activated ERK shed new light on drug development studies. Intriguingly, pharmacological reagents that are suppressive to JNK and p38 activities while augmenting the activation of ERK lead to attenuated scar formation and improved cardiac outcome, underscoring the functional cross talk between the MAPKs [282, 362–364]. As it has been discussed in this chapter, differential changes of the three MAPKs occur during the development of adaptive and maladaptive cardiac remodeling and cardiac disease progression in cellular context and time-dependent manners. Further investigation is urgently needed to enhance our understanding of the dynamic relationships between the three MAPK members under different stress conditions, which is essential for the development of effective therapeutic strategies and the discovery of novel therapeutic targets for early intervention and treatment of cardiac diseases.

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