Basic Science for Clinicians

Mitogen-Activated Protein Kinases in Heart Development and Diseases

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Abstract—Mitogen-activated protein (MAP) kinases belong to a highly conserved family of Ser-Thr protein kinases in the human kinome and have diverse roles in broad physiological functions. The 4 best-characterized MAP kinase pathways, ERK1/2, JNK, p38, and ERK5, have been implicated in different aspects of cardiac regulation, from development to pathological remodeling. Recent advancements in the development of kinase-specific inhibitors and genetically engineered animal models have revealed significant new insights about MAP kinase pathways in the heart. However, this explosive body of new information also has yielded many controversies about the functional role of specific MAP kinases as either detrimental promoters or critical protectors of the heart during cardiac pathological processes. These uncertainties have raised questions on whether/how MAP kinases can be targeted to develop effective therapies against heart diseases. In this review, recent studies examining the role of MAP kinase subfamilies in cardiac development, hypertrophy, and survival are summarized. (***Circulation***. 2007;116:1413-1423.)

Key Words: heart failure ■ molecular biology ■ signal transduction

Among the 518 recognized protein kinases in the human kinome, the mitogen-activated protein (MAP) kinase family plays a critical role in intracellular signal transduction and regulation.[1–5] Classic MAP kinases, including extracellular signal-regulated kinases (ERK1/2), c-Jun N-terminal kinases (JNK1, 2, and 3), p38 kinase (α, β, γ, δ), and big MAP kinase (BMK or ERK5), are implicated in a wide range of cellular processes, from cell growth and proliferation to apoptosis.[6–9] Other atypical MAP kinases, including ERK3/4, NLK, and ERK7, are much less studied and are not discussed in this review.[10] MAP kinases are highly regulated protein kinases that require dual phosphorylation of their T(E/P/G)Y motif in the kinase domain to become catalytically active. At the molecular level, each of the 4 classic MAP kinase subfamilies has a clearly delineated activation cascade mediated by specific upstream MAP kinase kinase kinases (MAPKKKs) and MAP kinase kinases (MAPKKs) (the Figure). This multilayered and parallel pathway organization allows both robust signal amplification and modulation while maintaining high specificity. Indeed, MAP kinases often are induced sharply after stimulation on the basis of kinase activity assay or phospho-specific immunodetection. Although the prototypic ERK1/2 pathway is found to be responsive mainly to stimulation of growth signaling (such as fibroblast growth factor),[11] JNK and p38 are collectively called stress-activated MAP kinases because of their selective responses to physical, chemical, and physiological stressors (such as ultraviolet rays, osmotic shock, infection, and cytokines).[12] In addition, the ERK5/BMK pathway is implicated in both growth and stress signaling.[13] In addition to the intrinsic specificity of MAP kinase cascades, the functional specificity of MAP kinases is contributed further by localized scaffold proteins that facilitate specific signal complex formation.[14] In living cells, however, significant overlap and cross-talk exist among different MAP kinase cascades. Besides the classic kinase phosphorylation cascades, several noncanonical mechanisms also have been identified for MAP kinase activation, adding to the molecular complexity of MAP kinase signal transduction.[15] Negative feedback regulation by ser/thr-specific and dual-specific protein phosphatases,[16] as well as other inhibitory regulators,[17] is shown to be equally important to determine the duration and the amplitude of MAP kinase activation in stimulated cells. In short, MAP kinases form complex signaling networks that can be induced by a large array of external stimuli and can achieve highly specific cellular effects through multitudes of regulatory mechanisms.

MAP kinases are ubiquitously expressed, and their specific functions in the heart have been a focus of intensive study for more than a decade and summarized in several excellent recent reviews.[9,18–26] Other than the recently recognized role in cardiac development, MAP kinase activation is observed at different stages of heart disease progression, including hypertrophic cardiomyopathy, dilated cardiomyopathy, and ischemic/reperfusion injury in human and animal models. Recent molecular studies have revealed significant insights into the regulatory mechanisms and potential downstream targets of MAP kinases in the heart. In the meantime, animal models
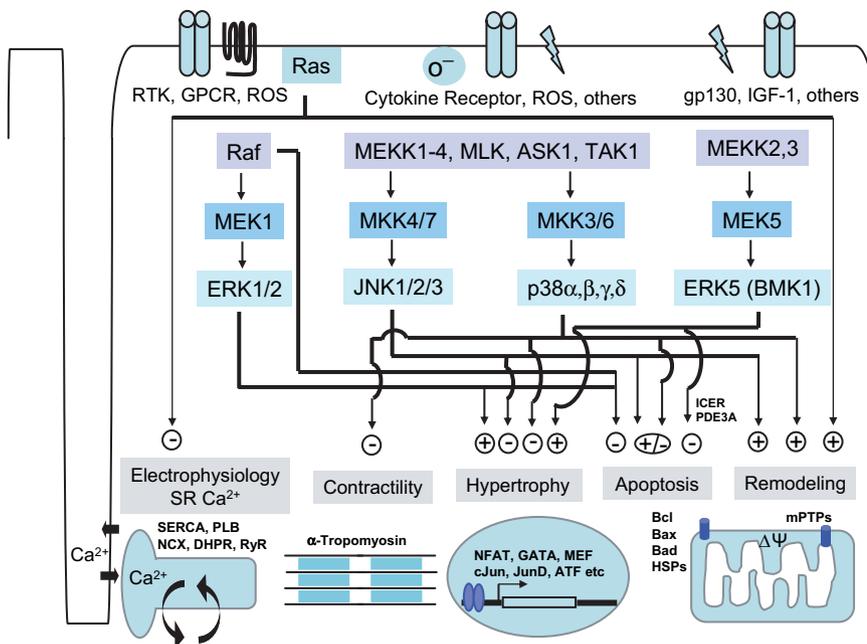

MAP kinases and their downstream effects in the heart. RTK indicates tyrosine kinase receptor; GPCR, G-protein–coupled receptor; ROS, reactive oxygen species; MEKK, MAP kinase, kinase, kinase; MLK, mixed-lineage kinase; ASK-1, apoptosis signal-regulating kinase; TAK, TGF-β–activated kinase; MEK or MKK, MAP kinase, kinase; SERCA, sarco/endoplasmic reticulum Ca(2+) ATPase; PLB, phospholamban; NCX, sodium-calcium exchanger: RyR, ryanodine receptor; DHPR, dihydropyrodine receptor; NFAT, nuclear factor of activated T-cells; GATA, GATA binding transcription factor; MEF, myocyte-specific enhancer-binding nuclear factor; HSP, heat shock proteins; mPTP, mitochondria permeability transition pore; $\Delta\Psi$, mitochondria inner membrane potential; PDE3A, phosphodiesterase 3A; and ICER, inducible cAMP early repressor.

with genetic manipulations of MAP kinase pathways have begun to yield evidence for their in vivo function in cardiac development, physiology, and pathology. Finally, improved pharmacological agents with high potency and specificity help to establish the impact of targeting specific MAP kinase pathways on cardiac function in cellular and animal models. All these advances reinforce the notion that MAP kinases are important players in cardiac physiology and pathology. However, these intense efforts also have revealed complex roles for individual MAP kinase pathways in both cardiac protection and cardiac pathologies. Controversies in the literature complicate current efforts to target MAP kinase pathways to treat heart failure. Here, an overview of the most recent advances in the field is provided, highlighting some outstanding issues and offering some perspectives about the underlying implications and future research directions.

Ras-Raf-MEK-ERK1/2

Ras-Raf-MEK-ERK1/2 is the prototypic MAP kinase cascade. Ras is a small GTP-binding protein that functions as a molecular switch and as a link between membrane tyrosine kinase receptors and the downstream signal transduction machinery. It induces downstream Raf (an MAPKKK) activation and translocation from the membrane to cytoplasm, which in turn activates MEK1 and ERK1/2 sequentially to achieve downstream effects. As an important signal conduit of peptide growth factors, the ERK pathway has long been implicated in cell growth and proliferation through gene regulation. Mutations of Ras frequently are identified in human cancer cells, rendering its classification as a proto-oncogene.[11] In the heart, cellular growth and proliferation also are important processes in development and diseases. Therefore, it is not surprising to find that the Ras-Raf-MEK-ERK pathway is critically involved in cardiac development and hypertrophy.

Ras-ERK Pathway in Cardiac Development

Recently, several genes involved in the ERK pathway were found to be affected in human congenital heart diseases. Specifically, mutations of the tyrosine phosphatase SHP2 (an important regulator for receptor tyrosine kinase–mediated MAP kinase activation),[27–30] K-Ras,[31–33] and SOS1 (an essential Ras guanine-nucleotide exchange factor)[34] were found to cause Noonan syndrome, the most common single-gene cause of congenital heart diseases.[35,36] In addition, mutations in H-Ras, B-Raf, and MEK1/2 also were found to be responsible for the less frequent but related Costello syndrome and cardio-facio-cutaneous syndrome[33,37,38] in humans. Common features among the patients of Noonan syndrome and the related Costello or cardio-facio-cutaneous syndrome include hypertrophic cardiomyopathy, electrophysiological abnormalities, and septal defects. Although a gain-of-function mutation is believed to be the underlying mechanism for the cardiac phenotype, the specific cellular and physiological bases of Noonan syndrome and related diseases are not yet fully explored.

ERK Pathway in Cardiac Hypertrophy

Cardiac hypertrophy, at the early stage, is part of a compensatory response to external stressors, including mechanical loading and oxidative stresses. The onset of cardiac hypertrophy can be a beneficial response that maintains or augments cardiac output without adverse pathology. However, when stressors persist, the compensatory hypertrophy can evolve into a decompensated state with profound changes in gene expression program, contractile dysfunction, and extracellular remodeling.[39,40] Physiological versus pathological hypertrophy can be differentiated in both qualitative and quantitative ways. However, the signaling mechanism mediating the critical transition from compensated hypertrophy to decompensated heart failure remains elusive.[25,41]

Early evidence from Ras mRNA measurements suggested a positive correlation between Ras expression level and the

severity of hypertrophy among hypertrophic cardiomyopathy patients.[42] Activation of MAP kinase activity also has been documented in different heart diseases, including dilated and ischemic cardiomyopathies.[43,44] Furthermore, an endogenous inhibitor of ERK pathway, Sprouty-1, was reported to be induced in human hearts during hypertrophy regression after implementation of a left ventricular assist device.[45] All these findings underscore the importance of MAP kinase activity in cardiac hypertrophy and other heart diseases. Evidence from cultured cardiac myocytes using an MEK-1–specific inhibitor and comprehensive cDNA gene expression profiling demonstrated the critical contribution of the ERK pathway to hypertrophic gene expression induced by prohypertrophic agonists.[46,47] In addition to the canonical tyrosine kinase receptor–mediated activation by peptide growth factors, ERK pathway can be induced in heart muscle cells by prohypertrophic hormones such as α-adrenergic receptor agonists, through Gαq/protein kinase C pathways,[48,49] or by β-adrenergic agonists via direct interaction between ERK and β-arrestin.[50,51] Direct oxidative modification of thiol groups in Ras also is reported to be important in its activation by hypertrophic stimulation.[52,53] These findings support an important, necessary, and differential role of ERK activity in cardiac hypertrophy induced by external ligands.

The in vivo role of the ERK pathway in cardiac hypertrophy has been demonstrated in several genetically engineered animal models. Cardiac-specific expression of constitutively activated MEK1 promotes cardiac hypertrophy without compromised function or long-term animal survival,[54] suggesting that activation of ERK activity promotes a compensated form of hypertrophy. It would be interesting to compare the gene expression profile in MEK1 transgenic hearts with hearts that have undergone exercise-induced hypertrophy to see whether MEK1 induced a bona fide physiological hypertrophy phenotype. In contrast, transgenic animals expressing constitutively activated V-12-H-Ras mutants in cardiomyocytes developed pathological hypertrophy characterized by fetal-gene induction, myofilament disarray, interstitial fibrosis, diastolic dysfunction, and arrhythmic sudden death.[55] These features also are observed in hypertrophic cardiomyopathy patients, including familial hypertrophic cardiomyopathy caused by sarcomere protein mutations and Noonan syndrome caused by mutations in the Ras-ERK signal pathway (discussed earlier). These observations suggest that MEK-ERK is only part of the downstream signal from Ras and plays an important role in compensatory cardiac hypertrophy during normal development and physiological adaptation. On the other hand, other downstream targets of Ras are more likely responsible for pathological changes associated with hypertrophic cardiomyopathy. This raises an interesting question as to whether the recruitment of ERK-independent pathways in stressed myocardium contributes to the ultimate transition from compensated hypertrophy to decompensated heart failure. However, the molecular components of ERK-independent downstream pathways from Ras remain to be defined. It also is important to recognize that dissection of Ras downstream pathways in such a fashion can be oversimplified. Part of the limitation of earlier transgenic studies is the use of tissue-specific but unregulated expression systems

conferred by myosin light chain-2v or α-myosin heavy chain promoters. Chronic expression of constitutively activated Ras or MEK mutants in the heart is fundamentally different from the highly regulated transient activation pattern of MAP kinases observed in intact animals. The complications from feedback regulation and secondary changes could make it difficult to dissect primary from secondary downstream effects of Ras or MEK activation in vivo. Therefore, inducible transgenic approaches as developed in recent studies should be more desirable.[56–58]

Complimentary to these gain-of-function approaches, Harris et al[59] reported a transgenic study using dominant-negative Raf to inhibit ERK pathway in the heart and demonstrated attenuated hypertrophy and gene induction during pressure overload. Furthermore, a mouse model of cardiomyocyte-specific c-Raf-1 inactivation also was established. These mice developed heart failure without hypertrophy in the absence of external stress, again suggesting an essential role of Raf in normal cardiomyocyte development and survival.[60] These observations are in agreement with earlier reports that expression of MAP kinase phosphatase-1, a negative regulator of MAP kinase activity, inhibits cardiac hypertrophy in vitro and in vivo.[61] However, because most of these studies used pressure overload to induce pathological hypertrophy, the question of the role of Raf-MEK-ERK in physiological hypertrophy (induced by swimming or treadmill training) remains unaddressed.

The downstream molecular mechanisms involved in ERK-mediated hypertrophy include transcription factors such as nuclear factor activators of transcription and GATAs.[62,63] Despite these common downstream transcription pathways, MEK1-induced compensatory hypertrophy is qualitatively different from calcineurin-mediated pathological hypertrophy, suggesting the involvement of different downstream players. In addition to the Raf-MEK-ERK cascade, Ras activation also is known to induce the PI3K/AKT pathway, which is another well-established prohypertrophic pathway. However, the specific contribution of this pathway to Ras-induced hypertrophy is not known. Gene expression profiling from temporally regulated H-v12-Ras transgenic hearts suggests that the induction of early response genes, loss of mitochondria function, and altered ionic channel proteins also are the likely culprits of pathological changes in extracellular matrix remodeling, loss of cardiac output, and electrophysiological abnormality.[64] As discussed above, diastolic dysfunction is a major consequence of Ras activation in transgenic mouse heart associated with SR calcium defects. Recent work from our laboratory has suggested that the selective induction of Gαi in Ras transgenic heart contributes to impaired sarcoplasmic reticulum calcium cycling and action potential prolongation.[64a] In short, both ERK and ERK-independent pathways contribute to the full spectrum of downstream effects from Ras that lead to cardiac hypertrophy and dysfunction.

ERK Pathway in Cardiac Protection

Cardiomyocyte death resulting from various stressors is a major cause of functional deterioration, local inflammation, and irreversible fibrotic remodeling.[39] Preventing cardiomyo-

cyte death, from either apoptosis or necrosis, constitutes both a major challenge and a potential therapeutic opportunity.[39] In cultured myocytes, peptide growth factors and other MAP kinase–inducing agents provide protective effects against serum starvation, hypoxia, or reoxygenation-induced injury. Inhibition of MEK or ERK activity with pharmacological reagents diminishes the protective effects.[19,26] In vivo, MEK transgenic hearts are protected from ischemia/reperfusion injury and myocyte apoptosis.[65] In contrast, inhibition of Raf-1 by the expression of a dominant-negative mutant or cardiac-specific knockout promoted myocyte apoptosis and decompensated heart failure.[59,60] Similarly, genetic inactivation of ERK2 (but not ERK1) promotes cellular injury and death in response to ischemia/reperfusion.[65] Therefore, the Ras-Raf-MEK-ERK pathway has an important cardioprotective role.

The specific molecular mechanisms in ERK-mediated cardiac protection are still not completely understood. In addition to the well-established Raf-1–mediated BAD and Bcl-2 phosphorylation on mitochondrial outer membrane,[66] Raf inhibits apoptosis through stabilizing the antiapoptotic protein XIAP, suppressing the proapoptotic protein MST2, and modulating the mitochondria permeability transition pore through VDAC.[67–69] Other reported downstream targets of the Raf-MEK-ERK pathway in apoptosis regulation include caspase 9, protein kinase Cϵ, p53, and others.[70] Lastly, ERK-independent downstream pathways of Ras such as PI3K/AKT have well-established antiapoptotic activities.[71] Therefore, multiple parallel mechanisms are involved in promoting cell survival and inhibiting apoptosis by the Ras-Raf-MEK-ERK pathway in the heart.

In summary, the functional role of the ERK MAP kinases in the heart presents a potential dilemma to any heart disease therapies targeting this pathway. Although uncontrolled activation of Ras-Raf-MEK-ERK signaling may trigger hypertrophic cardiomyopathy, inhibiting the pathway also can render hearts more vulnerable to stress-induced myocyte death. Ras, Raf-1, and MEK1 inhibitors are being developed as anticancer drugs. Clearly, their potential adverse effects in hearts also should be carefully monitored as in the cases of Herceptin, Doxorubicin, and Gleevec.[72–74]

JNK Pathway

Three genes, JNK1, JNK2, and JNK3, constitute this branch of the MAP kinase family that generates 10 known variants of isoforms through alternative splicing. JNK1 and JNK2 are ubiquitously expressed, whereas JNK3 expression is more restricted to the heart, brain, and testis.[75] JNK activity was first discovered as part of cellular stress response to ultraviolet-induced DNA damage.[76] The upstream MAP kinase kinases (MKK) involved in JNK cascade include MKK4 and MKK7. The further upstream MAP kinase kinase kinases (MEKKs) that can activate JNKs are MEKK1, MEKK2, and MEKK3, as well as mixed lineage kinase 2 and 3 (MLK2 and MLK3).[75] Furthermore, the signaling modules are organized by scaffold proteins such as JNK interacting protein, MKK N-terminal extension, and MEKKs. These signaling modules are thought to contribute to different specific downstream effects of JNK in response to different stressors.[14,77] Indeed,

other than the ultraviolet response, JNKs are now implicated in gene regulation, cell migration, insulin signal regulation, and neuronal function.[75] Since the original observation that JNK activity is induced in stressed myocardium under mechanical overload or ischemia reperfusion injury,[78–80] it has been a subject of intense interest about the specific role of this pathway in the heart related to hypertrophy, cell death regulation, and remodeling.

JNK Pathway in Cardiac Hypertrophy
In early gain-of-function studies performed in cultured neonatal cardiomyocytes, JNK activation led to a hypertrophic phenotype, fetal gene expression, and cellular pathology.[80] However, in vivo JNK activation in transgenic animal models failed to induce cardiac hypertrophy.[81–84] Rather, the transgenic animals developed lethal restrictive cardiomyopathy with no myocyte hypertrophy but a significant induction of fetal gene expression. However, the direct impact (at the earliest time point) of JNK activation on cardiac gene expression and function remains unclear and should be studied by achieving inducible JNK activation in the adult heart as reported.[85] In early loss-of-function studies using dominant-negative mutants of JNKs, inactivation of the JNK pathway in the heart was reported to block pressure overload–induced cardiac hypertrophy in vivo.[86] Inactivation of MEKK1 also blunted Gq-induced cardiac hypertrophy and dysfunction.[87] However, genetic inactivation of an individual JNK1, JNK2, or JNK3 gene has no significant impact on the same process.[88] Instead, JNK1 was shown to be important in maintaining cardiac contractility and prevention of heart failure under sustained mechanical overload. One possible explanation for this observed discrepancy is that different JNK isoforms have functional redundancies. Alternatively, dominant-negative mutants of JNK can have off-target effects on other hypertrophy pathways. Other than c-Jun, a prototypic downstream target of JNK and a potent hypertrophic gene activator, recent studies also suggest that prohypertrophic AKT is activated by JNK through direct phosphorylation.[89] On the other hand, JNK can also phosphorylate and inhibit calcineurin activity, which in turn attenuates hypertrophy signaling.[82] A recent report also implicated JunD as a negative regulator of cardiac hypertrophy, thus offering yet another potential molecular mechanism for the inhibitory role of JNK in cardiac hypertrophy.[90] It remains very much unclear whether different JNK isoforms or scaffold proteins are responsible for the ambiguous roles that the JNK pathway plays in the development of cardiac hypertrophy.

JNK Pathway in Cardiomyocyte Death Regulation
As a stress-induced signaling pathway, JNK has both protective and pathological roles in different cell types. This dichotomy also was observed in cardiomyocytes. Through the use of a newly developed JNK-selective inhibitor or antisense oligoes, JNK activity was shown to play an important role in myocyte apoptosis after ischemia/reperfusion.[91,92] In contrast, a number of other studies demonstrated a critical role for JNK in myocyte survival and cardioprotection.[89,93,94,81,95] JNK is reported to interact with proapoptotic Bax and Bad on

mitochondrial membrane.[96,97] However, other prosurvival pathways, including AKT, also are targeted by JNK.[89] Therefore, it was not surprising that Kaiser et al[98] reported enhanced myocyte survival after ischemia/reperfusion injury when JNK activity was genetically activated or inhibited in the heart. These seemingly contradictory and confusing results underscore the complexity of the JNK pathway in cell death regulation in the heart.

JNK Pathway in Cardiac Remodeling

Targeted activation of the JNK pathway in the heart leads to lethal restrictive cardiomyopathy in transgenic mice, yet interstitial collagen levels are not induced.[84] At the molecular level, JNK activation results in marked induction of the TGF-β pathway molecules and the selective induction of fibronectin. This result suggests that TGF-β–mediated extracellular matrix remodeling is a likely factor contributing to the increased myocardial stiffness observed in JNK-activated hearts. Furthermore, JNK activation also diminishes mitochondrial gene expression involved in fatty acid metabolism and oxidative phosphorylation chain reaction, both of which can have a major impact on the energetic status of the heart.[64] Lastly, prolonged activation of JNK activity in the heart is associated with abnormal gap junction structure, loss of the main component connexin-43, and slowed conduction velocity in the heart.[99] Recent evidence also suggests that the loss of gap junctions in the JNK-activated heart is associated with the loss of connexin-43 protein expression and proper intracellular targeting.[100] Therefore, constitutively activated JNK activity can result in different aspects of pathological remodeling and may contribute to diastolic dysfunction and arrhythmia. However, the specific signaling mechanisms underlying JNK-induced pathological changes are still poorly understood.

Considering the multifaceted signaling mechanisms involved in the JNK pathway, it is critical to resolve some of the outstanding issues currently facing us. The specificity of JNK isoforms and splicing variants, the specific signal complex components for each isoform, and the intracellular localization and dynamic activation profile in stressed myocardium need to be established to better our understanding of the functional outcome of JNK-mediated signaling in the heart.

p38 Pathway

The p38 MAP kinases are another subfamily of stress-activated protein kinases that were originally discovered as an essential molecule in lipopolysaccharide-induced tumor necrosis factor-α expression.[101] Subsequently, 4 genes of p38 subfamily members were discovered coding for the p38α, p38β, p38δ, and p38γ isoforms. The p38α and p38β isoforms are expressed ubiquitously in adult tissues. The expression of p38γ is restricted mostly to skeletal muscle, and p38δ is enriched in lung, kidney, pancreas, placenta, and testis. As a highly conserved stress signaling pathway, activation of p38 pathway has been implicated in a variety of stress responses other than inflammation such as osmotic shock, heat, and cytokines.[6,12,102] A number of upstream kinases are implicated in the phosphorylation cascades leading to the activation of p38, including MEKK1 through MEKK4, TAK1, and ASK1 at the MAPKKK level and MKK3, MKK6, and MKK4 at the MAPKK level. Other than the MKK-dependent activation, 2 other noncanonical MKK-independent activation pathways have been reported for p38. One is TAB-1–mediated autophosphorylation,[103,104] and the other is T-cell receptor–induced activation of p38 through ZAP70.[105] In the heart, the functional role of the p38 pathway has been implicated in cardiac gene regulation, myocyte hypertrophy, inflammatory response, energetic metabolism, contractility, proliferation, and cell death regulations.[21,22,83,106–108] However, significant controversies remain as to how p38 activation leads to specific aspects of cardiac pathologies in the diseased heart and whether pharmacological manipulation of p38 is a valid approach to treat heart failure.

p38 MAP Kinase in Hypertrophy

Earlier p38 studies used constitutively activated mutants of specific upstream kinases of p38, MKK3, and MKK6 to achieve specific activation of the p38 pathway. In neonatal cardiomyocytes in culture, p38 MAP kinase activation was sufficient to induce characteristic changes in cardiac hypertrophy and cell death.[109,110] However, subsequent studies using transgenic mice revealed very different effects in vivo. Targeted activation of p38 in the mouse heart did not produce any significant degree of cardiac hypertrophy.[111] On the contrary, pressure overload–induced cardiac hypertrophy appeared to be enhanced further by dominant-negative mutants of p38, revealing an inhibitory function of p38 on cardiac hypertrophy.[112] It is reported that p38-mediated nuclear factor activator of transcription phosphorylation is inhibitory to its nuclear translocation and subsequent downstream gene activation, which conceivably underlies its antihypertrophic function in the heart.[113] Recent evidence from cardiac-specific p38α conditional knockout animals also indicates that p38α is not an essential regulator for cardiac hypertrophy under pressure overload but rather surprisingly plays a protective role against cardiac myocyte apoptosis and myocardial remodeling.[114] Our preliminary evidence also suggests that double knockout of p38α and β isoforms triggers cardiac hypertrophy without external stressors (Shuxun Ren, MD, and Y.W., unpublished results, 2007). At the gene expression level, p38 activation is sufficient to induce "hypertrophic marker genes" in vitro and in vivo, suggesting that transcriptional activation of the fetal gene expression program by p38 is independent of the myocyte hypertrophy process. Although MEF-2 is shown to be a potential downstream target of p38, it is not clear whether MEF-2 activation is indeed involved in p38-induced "hypertrophy marker" gene activation in the heart.[115]

Other than fetal genes induction, several studies using gene expression profiling and detailed biochemical analysis implicated an induction of the inflammatory response and cell cycle regulation as a major consequence of constitutive p38 activation in the heart.[64,116] The induction of inflammatory cytokines can generate a positive feedback loop, leading to sustained p38 activation in the heart.[117] This observation is in agreement with the restrictive cardiomyopathy phenotype found in the p38-activated transgenic mouse heart, including

extensive interstitial remodeling and stiffening of myocardium without chamber hypertrophy or dilatation. Indeed, inflammatory myocarditis is a major cause of restrictive cardiomyopathy in humans. Therefore, it is reasonable to speculate that the p38 MAP kinase pathway may play an important role in the pathogenesis of restrictive cardiomyopathy resulting from myocarditis.

p38 in Cardiac Function and Cell Death Regulation

In addition to gene regulation, the p38 pathway is involved in the regulation of myocyte contractility and cell death. Activation of p38 leads to suppressed contractility without affecting intracellular calcium cycling.[118] The negative inotropic effect of p38 activity appears to be an epigenomic phenomenon because it is both rapid and reversible. Indeed, secondary modification of sarcomere proteins is observed in p38-activated heart associated with reduced force generation in isolated myofilaments.[119]

It is highly controversial whether p38 pathway is cardiac protective or prodeath in the heart. In numerous studies, inhibiting p38 activity in cultured myocytes or intact heart reduced apoptotic cell death under stress stimulation such as pressure overload or ischemia/reperfusion.[18,21] Inhibition of p38 is consistently observed to improve cardiac function and to reduce remodeling in the heart after ischemia/reperfusion injury or infarction.[120–126] However, a report also showed that such beneficial effect was not observed in pig, suggesting a certain degree of species specificity.[127] On the other hand, specific activation of p38 in the heart is not sufficient to induce myocyte apoptosis.[22] Furthermore, a recent study from Martindale et al[128] demonstrated that activation of p38 in the heart led to small heat-shock protein phosphorylation associated with enhanced protection against ischemia/reperfusion injury. Lastly, cardiac-specific inactivation of p38α leads to enhanced apoptosis in response to pressure overload.[114] Therefore, p38 activity can be both protective and detrimental to myocyte survival in a stressor-specific manner. The underlying mechanism for the differential function of p38 remains a puzzle.

p38 in Cardiomyocyte Differentiation and Proliferation

p38 activity has been implicated in skeletal muscle differentiation and myoblast proliferation.[129,130] Recently, several studies also suggested a new and interesting role for p38 in regulating proliferation in terminally differentiated cardiomyocytes.[131] By combining p38 inhibition and stimulation with growth factors (fibroblast growth factors), Engel et al[132] showed an increased cardiomyocyte proliferation in vitro and in vivo. These reports open the possibility of promoting myocyte regeneration as a feasible way to achieve cardiac protection and wound healing. However, it remains to be proven that the postmitotic adult cardiomyocyte can indeed complete the full cycle of cytokinesis and generate new functional myocytes in intact heart. Furthermore, it is uncertain whether the beneficial effect observed in the combination treatment of p38 inhibitor and fibroblast growth factor in the heart is contributed by regenerated new myocytes rather than the combined protective effects on the existing myocytes.

In summary, like the JNK pathway, the p38 MAP kinase pathway has conflicting roles in both cardiac protection and pathological remodeling in the heart because of its intricate regulation of gene expression, contractility, inflammatory cytokine induction, and myocyte death and proliferation. The underlying mechanisms for the diverse function of p38 in the heart are still underexplored. Clearly, the magnitude and duration of p38 activation should have a major impact on the signaling outcome as revealed by studies from manipulating MAP kinase phosphatase expression.[61] Recent reports from our laboratory and Fiedler et al[133] also demonstrate that the noncanonical activation of p38 by TAB-1 can have antagonistic or perhaps even more proapoptotic downstream effect than the canonical MKK-mediated mechanism. It is therefore likely that the ultimate outcome of p38 activation is dictated by the nature and duration of the stressors, as well as the activation pathways, amplitudes, and isoforms involved. Clearly, more studies are critically needed to dissect the specific contribution of p38 activity under specific stress conditions and the underlying molecular mechanisms.

ERK 5 Pathway

ERK 5, also known as BMK pathway, is a more recently identified branch of the MAP kinase family with a conserved N-terminal kinase domain and a unique C-terminus.[8] Activation of ERK5 involves MEKK2 or MEKK3 at the MAPKKK level and MEK5 at the MEK level. In cells, ERK5 activity has been implicated in cell proliferation and survival associated with stress or growth stimulations.[8,13]

ERK5 in Cardiovascular Development

In recent years, considerable progress has been made in uncovering the functional role of the ERK5 pathway in the heart. The most compelling evidence implicating such a role is provided by the MEK5 and ERK5 knockout mouse models. Both ERK5- and MEK5-null animals are embryonic lethal with major cardiovascular defects, including underdeveloped myocardium and impaired vasculature.[134,135] However, cardiac-specific inactivation of ERK5 in cardiomyocytes has a normal cardiac phenotype, suggesting that the abnormal phenotype in ERK5-null animals is mostly secondary to vascular defects.[136] Indeed, ERK5-null endothelial cells display abnormal morphology and survival, leading to dysfunctional vasculature and hemorrhage in adult animals when genetic inactivation is achieved in adult animals.[136]

ERK5 in Eccentric Hypertrophy and Death Regulation in the Heart

Reports about the role of ERK5 in cardiac hypertrophy are contradictory. Early reports indicated that ERK5 is a critical downstream pathway of cardiotrophin-1– and leukemia inhibitory factor–induced hypertrophy.[137,138] Activation of ERK5 with an activated mutant of MEK5 induced elongation of myocytes in vitro and eccentric hypertrophy in vivo, similar to the effect of leukemia inhibitory factor– or cardiotrophin-1–induced cardiac hypertrophy.[139] Activation ERK5 also was associated with eccentric hypertrophy in-

Developmental and Pathophysiological Roles of MAP Kinases in the Heart

Pathways (Inhibitors)	Development	Function and Pathophysiology
Ras-Raf-MEK-ERK	Nanoon and Nanoon-like syndromes[27–38]	Concentric hypertrophy ↑ [54,55]
(Bay 43-9006, U0126		SR Ca^{2+} defects and arrhythmia ↑ [55]
PD 98059, PD 184352		Cardiac protection ↑ [59,60,65]
PD 0325901,		ECM remodeling ↑ [55]
ARRY 142886) (143)		
ASK/MEKK-MKK4/7-JNKs	Insignificant or not known[87,88]	Restrictive cardiomyopathy ↑ [81–85]
		Cardiac protection ↑ ↓ [81,89,91–95,98]
(CEP-1347, SP600125)[146]		ECM and junctional remodeling ↑ [84,99]
		Hypertrophy ↓ ↑ [82–84,86–87]
ASK/MEKK-MKK3/6-p38s	Insignificant or not known[114,131]	Restrictive cardiomyopathy ↑ [111]
		Inflammatory remodeling ↑ [64,116]
(SB203580, AMG 548		Contractile dysfunction ↑ [118,119]
SCIO 469, VX702		Cardioprotection ↑ ↓ [114,120–126,128]
BIRB 796)[147]		Cardiomyocyte proliferation ↓ [131,132]
		Hypertrophy ↓ [112]
MEKK-MEK5-ERK5	Vascular defects[134–136]	Eccentric hypertrophy ↑ ↓ [137–139,141]
		Cardiac protection ↑ [142]
		Contractile dysfunction ↓ [142]

duced by intermittent hypoxia in rat.[140] Therefore, a specific role of ERK5 in eccentric hypertrophy as opposed to other forms of cardiac remodeling was proposed. However, a recent study showed that an activated cardiac isoform, MEK5α, failed to induce hypertrophy in transgenic mice but rather conferred strong cardiac protection against ischemia/reperfusion injury.[141] In addition, the same group demonstrated a link between ERK5 activity induced by insulin-like growth factor-1 and phosphodiesterase 3A/inducible cAMP early repressor loop to regulate myocyte apoptosis and contractile function.[142] The reason for such discrepancies is not clear, although different MEK5 isoforms used in these studies may be one of the causes. Potentially, intracellular targeting of ERK5 activity to different compartments may dictate specific functional outcome. In hypertrophic regulation, ERK5 activity regulates gene expression likely through its nuclear activity, whereas the phosphodiesterase 3A/inducible cAMP early repressor loop appears to be restricted in the cytosol. Nevertheless, these studies raised an exciting possibility of targeting ERK5 or its downstream molecules to promote myocyte survival and prevent dysfunction.

Targeting MAP Kinase Pathways for Heart Failure?

Given the importance of MAP kinase pathways, several potent and specific pharmacological inhibitors have been developed (see the Table). The Raf (Bay43 through 9006) and MEK (eg, PD98059 and U0126) inhibitors have been tested in many preclinical studies to inhibit cell growth and proliferation, mostly as a cancer therapy.[143] In the heart, pretreatment of PD98059 enhanced myocyte apoptosis and pathological remodeling after ischemia/reperfusion injury.[144] In a reconstituted rat heart tissue, treatment of U0126 prevented

endothelin-1– and isoprenaline-induced contractile defects and atrial natriuretic factor gene expression.[145] However, the specific impact of Raf/MEK inhibition on cardiac hypertrophy and remodeling has not been directly tested in vivo. So far, an ERK5-specific inhibitor has not been reported. Recently, JNK-specific inhibitors (CEP-1347 and SP600125) were developed.[146] Chronic treatment with SP600125 enhanced cardiomyocyte apoptosis and worsening pathology in a hamster model of dilated cardiomyopathy.[95] So far, neither this nor other JNK-targeted inhibitors have been tested in other hypertrophy or other heart failure models in vivo. Numerous studies use p38 inhibitors in vivo, and in most cases, a protective effect is achieved against stress-induced injury or remodeling in the heart, as summarized earlier. AMG 548, BIRB796, SCIO469, and VX702 are some of the newly developed, highly potent, and highly specific p38 inhibitors that have advanced to phase I clinical trials for inflammatory and other diseases (see elsewhere[147] for a summary). From the available preclinical studies, it appears that among all the MAP kinase pathways, p38 inhibition is the most promising choice to treat heart diseases, especially ischemic heart failure.

Although significant progress is being made in dissecting MAP kinase signaling in the heart, the basic questions about the functional roles for MAP kinases in cardiac regulation have yet to be fully addressed. With sophisticated genetic and molecular tools, it is increasingly clear that different MAP kinase family members play important but distinct roles in cardiac regulation and disease progression (the Table). However, our current understanding of MAP kinases in the heart remains very preliminary and offers only limited mechanistic guidance as to whether and how targeting MAP kinases can be used as a valid therapeutic approach for heart failure.

Conflicting results have been reported for each branch of the MAP kinase family about their role as either a protector against pathological insults or a promoter of pathological changes in the heart (the Figure). The functional complexity and ambiguity of the MAP kinases in the heart could be a result of the complexity in temporal profiles of activation, mobilized feedback networks, intracellular compartmentation, and signal complex composition under different conditions. Therefore, a better understanding of the role of MAP kinase pathways and targeting MAP kinase pathways as a potential therapy for heart failure requires major progress in many areas. First, we need to have comprehensive understanding of the interacting partners of MAP kinases in the heart under basal and different stress conditions. Recent advancement in genomic and proteomic approaches will help to make headway in this direction.[148] Second, we need to dissect primary and secondary effects of MAP kinase activity by combining sophisticated genetic tools and comprehensive physiological analyses. These 2 approaches will offer mechanistic links between the molecular network and physiological/pathological outcome and will help to identify potential signal pathways and nodules critical to the different aspects of cardiac pathogenesis. Lastly, we need to develop more potent and specific inhibitors for individual MAP kinase branches and nodules and test them in clinically relevant disease models. Clearly, more mysteries of the MAP kinase pathways in the pathogenesis of heart failure and their full potential as therapeutic targets need to be unraveled.

Disclosures

None.

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