Role of mitogen-activated protein kinase in cardiac hypertrophy and heart failure

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BACKGROUND: Mitogen-activated protein kinases (MAPKs) are involved in the regulation of various cellular responses including cell proliferation, differentiation and survival. Although MAPKs are activated by MAPK kinase and inactivated by phosphatases, different types of MAPKs, including extracellular signal-regulated kinases (ERK1 and 2), c-jun N-terminal protein kinases (JNK) and p38 kinases are known to participate in different signalling pathways. This article will review some salient features of the regulation and function of different forms of MAPKs in the heart. Furthermore, the status of cardiac MAPKs under different pathophysiological conditions will be described.

OBSERVATIONS: A wide variety of external stimuli are known to activate MAPKs, which are then translocated from the cytoplasm to the nucleus and regulate cardiac gene expression by phosphorylating various transcriptional factors. By virtue of the involvement of ERK1/2 in hypertrophic response and of the stress-activated JNKs and p38 kinases in the process of apoptosis, MAPKs are considered to be intimately involved in cardiac remodelling. Both growth factors and phorbol esters have been shown to strongly activate ERK1/2, whereas the activation of JNKs and p38 kinases by these agents is weak. Although ischemia-reperfusion activates all types of MAPKs, JNKs and p38 kinases are mainly proapoptotic, whereas ERK1/2 are antiapoptotic.

CONCLUSIONS: The activation of ERK1/2 is involved in signal transduction pathways associated with cardiac hypertrophy; however, the exact status of MAPKs in heart failure remains to be clearly defined. While both JNKs and p38 kinases appear to participate in the genesis of ischemia-reperfusion injury, ERK1/2 are considered to be cytoprotective.

Key Words: *Cardiac hypertrophy; c-jun N-terminal protein kinases; Extracellular signal-regulated kinases; Heart failure; Mitogen-activated protein kinase; p38 kinases*

Cardiac hypertrophy is characterized by an increase in the cellular mass of adult cardiomyocytes in the myocardium and involves alterations in both cell structure and protein expression which are mediated by changes at the transcriptional and translational levels (1). In contrast to immature cardiomyocytes, adult cardiomyocytes are terminally differentiated cells and, thus, undergo hypertrophic growth without cell proliferation. Although the progression of cardiac hypertrophy invariably leads to the development of congestive heart failure (CHF), the mechanisms that participate in the transition of cardiac hypertrophy to heart failure are not clearly understood. Several studies examining hypertrophied failing hearts in human and animal models have identified many signalling pathways that play crucial roles in CHF. Therefore, extensive work exploring the functional link among the activation of mediators, their intracellular responses and clinical consequence would provide valuable information.

Mitogen-activated protein kinase (MAPK) is one of the signalling pathways involved in cardiac hypertrophy and heart failure. It is activated in response to a wide variety of extracellular stimuli and induces changes in critical intracellular processes promoting cell growth, apoptosis and transformation (2-4). These extracellular stimuli include cell deformation, adhesion molecules, and some neurohormones (angiotensin II [Ang II], endothelin-1 [ET-1] and noradrenaline) that bind to heptahelical G-protein coupled receptors (5). There is increasing evidence showing that different members of the MAPK family such as extracellular signal-regulated kinases (ERKs), p38 kinase and c-jun N-terminal protein kinases (JNKs) are critically involved in the regulation of signalling pathways, ultimately leading to cardiac hypertrophy and CHF. Many studies using low cardiac output heart failure with significant fibrosis in the myocardium have revealed the involvement of MAPK in cardiac hypertrophy and heart failure. It has been suggested that MAPKs likely play an important role in ventricular remodelling in different cardiovascular diseases. This appears to be achieved by regulating the transactivation activity of a variety of transcription factors which control the rate and specificity of gene transcription factors that are considered to be the integral part of the hypertrophic response. The involvement of ERK in cardiac hypertrophy has been investigated using different models (6-9). Furthermore, the involvement of other members of the MAPK family, p38 kinase and JNK, in cardiac hypertrophy has also been reported (10). In this review, literature will be discussed implicating the regulatory role of MAPK in cardiac hypertrophy and heart failure.

CARDIAC HYPERTROPHY AND HEART FAILURE

Cardiac hypertrophy is a complex, compensatory mechanism for the heart to adapt to excessive workload (pressure or volume overload) and to dysfunction of the heart as a result of genetic mutation. In response to various extracellular stimuli such as mechanical stress and growth-promoting factors, eg, Ang II,

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ET-1 and transforming growth factor-beta, the myocardium undergoes adaptation in response to increased workload through hypertrophy of individual terminally differentiated myocytes. Many signalling transduction pathways linking the extracellular hypertrophic stimuli to nuclear transcription factors participate in this process. It is generally accepted that cardiac hypertrophy is one of the most critical risk factors of heart disease. The process of hypertrophy can be divided into three stages: the developing hypertrophy phase, the compensatory hypertrophy stage and the decompensatory stage, which refers to heart failure. Although patients with advanced heart failure can move back and forth between stages depending on their diets and appropriate therapy, the whole process during these three stages can be viewed as a progression (11).

Heart failure represents an enormous clinical problem where cardiac output is not sufficient to meet the metabolic requirements of the body (12). An increase in venous pressure is accompanied by molecular defects causing the progressive deterioration of the failing heart and premature death of cardiomyocytes (13). The available data indicate that heart failure affects some 18 million people in North America, and some five to 10 million people in Europe. Therefore, it is the major cause of death, hospitalization and poor quality of life worldwide (14). The incidence, prevalence and mortality of CHF have increased dramatically over the past few decades and thus, CHF has become a major social and economic burden. More importantly, despite the best available therapy after the onset of CHF symptoms, the survival of affected individuals is short, averaging less than five years following diagnosis (11,15); most heart failure patients die within 10 years of diagnosis (16). Therefore, much attention needs to be focused on the development of potential drug therapies for the treatment of CHF.

Immediate-early response genes and late response genes

When stimulated by pressure or volume overload, ischemia, stretch or increased developed tension, the terminally differentiated adult cardiomyocytes undergo transformation from their expression of an adult complement of genes to the phenotypic pattern that existed in the fetal heart. The first genes, the immediate-early response genes, are activated, in some cases, within minutes after the myocardium is stretched (17-21). In the overloaded heart, cell stretch or ischemia stimulates MAPK and other mitogenic pathways (22-26). There are more than 100 different genes which have been identified to be activated in the aforementioned conditions, Ras being one of those genes. Ras, the monomeric GTP-binding protein, plays an important role in the activation of the MAPK signalling pathway. The nuclear transcription factors c-myc, c-fos and c-jun encode the corresponding leucine zipper transcription factors. Activation of these genes is highly significant in cardiac hypertrophy. For example, nuclear transcription factors inhibit synthesis of adult phenotypes of protein isoforms in terminally differentiated cardiomyocytes. c-myc activates the hypertrophic process leading to the reversion from the adult to fetal phenotype in overloaded hearts (27). As a consequence of the activation of c-myc, the expression of a powerful apoptotic inducer, p53, increases, initiating programmed cell death (apoptosis). In case of sustained stress, the transcription factors stimulated by the *immediate-early response genes* will in turn stimulate the *late response genes*, encoding mitochondrial proteins, synthetic enzymes, cytoskeletal and myofibrillar proteins, cyclins and Cyclin-dependent kinases, nonhistone chromosomal proteins and additional transcriptional factors (28,29). The remarkable features in the response of the overloaded heart are many of the proteins encoded by these late response geness. In the volume overloaded heart, these proteins are fetal proteins or protein isoforms normally found in the fetal heart and therefore, represent stimulation of the cell cycle. Reversion to fetal phenotypes plays an important role in reducing both energy consumption and depression of contractility in the failing heart. These changes in cardiomyopathy of the volume overloaded heart are probably critical for determining the poor prognosis because of their efforts to push terminally differentiated cardiomyocytes out of the G0 phase which increase their susceptibility to apoptosis (30).

Remodelling, necrosis and apoptosis

Although hypertrophy of a damaged or overloaded heart is initially beneficial by allowing the generation of more contractile force, excessive and/or prolonged workload may eventually lead to the 'failing' or 'decompensating' cardiomyocytes, which shortens the life of cardiomyocytes and is observed clinically as heart failure (31). There are at least three overlapping general mechanisms which have been suggested to be involved in the progressive deterioration of the overloaded heart, including remodelling (progressive dilation), necrosis and apoptosis. The structural remodelling results in more dilation which represents a major cause of the cardiomyopathy of overload (11) in which the deleterious consequences of cardiac hypertrophy shorten cell life (32). Maladaptive growth and changing myocyte phenotype play an important role in causing the progressive dilation of the heart. The cardiomyocytes can undergo adaptive growth in response to appropriate external stimuli; however, the hypertrophic response cannot alleviate the overload on individual sarcomeres. In vivo, a variety of cellular stresses such as ischemia, ischemia-reperfusion and hypoxia may be applied to cardiomyocytes, inducing necrosis and hypertrophy of myocytes in different regions of the injured heart. Thus, the adaptive response may compensate for the lost contractile capacity in the short term, while sustained cardiac hypertrophy will lead to long term heart malfunction resulting in heart failure.

As noted by many investigators, apoptosis is another biological process that accounts for a part of the mortality due to heart failure. Apoptosis of cardiomyocytes can be activated in response to a variety of insults, including hypoxia, free radical stress, viral infection, adrenergic overstimulation and work overload. It can directly lead to cardiomyopathy and death because apoptosis is not accompanied by cell replacement in adult myocardium (33). Accordingly, it has been considered to be one of the most important reasons for the poor prognosis in ischemic heart disease or heart failure. Apoptosis normally occurs along with necrosis in several conditions of the cardiovascular system such as end stage heart failure (34), diabetic cardiomyopathy (35), infarcted and reperfused myocardium (36), postinfarction left ventricular remodelling (37) and during the regression of hypertrophy (38). Also, cardiomyocyte apoptosis is sufficient to cause heart failure in genetically manipulated mouse models (39). Although the absolute numbers of apoptotic cardiomyocytes are small, the conservative estimate about the duration of apoptosis could result in the loss of up to 5% to 10% of the myocardium annually, which represents a substantial loss of myocytes. These observations are consistent

with the progressive nature and poor survival in the final stage of the failing heart. However, the real impact of apoptosis of cardiomyocytes in heart failure seems to be overestimated because the time between the onset of symptoms of CHF and the death of a patient is longer than the assumed speed of cardiomyocytes' apoptosis (40). Because the onset of apoptosis is also considered an action of mitogen, it has attracted the attention of many investigators to study the cytoprotective and apoptotic signal transduction pathways which have revealed important new insights into the roles of the MAPKs.

FUNCTION OF MAPK

General characteristics

MAPKs are a group of ubiquitous serine and threonine protein kinases which are encoded by a multigene family. MAPKs are activated in response to a wide variety of extracellular stimuli and transduce signals for intracellular response. Thus, MAPKs are considered an essential part of the signal transduction pathway and play a critical role in cellular apoptosis and transformation (2-4,41). Three MAPKs, namely ERK, JNK, also known as stress-activated protein kinase (SAPK), and p38 kinase (also known as Mkp2/CBSP), have been identified. MAPK was initially identified as a serine/threonine protein kinase which can regulate cell growth and proliferation due to its ability to catalyze the phosphorylation of microtubule-associated proteins and promote the binding of growth factors to the tyrosine kinase receptors (42). More recently, the MAPK signalling pathway has been observed to be activated by cell deformation which induces the secretion of adhesion molecules via heptahelical G-protein coupled receptors. This system is also activated by some neurohormones, such as Ang II, ET-1 and noradrenaline (5).

In general, growth factors and stress are known to activate the MAPK pathways; however, the activation of each class of MAPKs appears to require a specific stimulus. For instance, growth factors and phorbol myristate acetate (PMA) activate ERK1/2 strongly, but their effects on JNK and p38 kinase are weak (43). Not only has the involvement of ERK in cardiac hypertrophy been assessed in different experimental models, but the participation of other members of the MAPK family, such as p38 kinase and JNK, has also been reported in cardiac hypertrophy. Since MAPKs are critically involved in the regulation of signalling pathways that ultimately lead to cardiac hypertrophy, MAPKs have been suggested to play an important role in ventricular remodelling in different cardiovascular diseases. **T**he specificity of gene transcription factors is considered to be an integral part of the hypertrophic response; thus, this function is carried out by regulating the activity of a variety of transcription factors.

The MAPK cascade consists of a three-tiered module, which are MAP kinase kinase kinase (MKKK, MAPKKK or MEKK), MAP kinase kinase (MKK, MAPKK or MEK) and MAPK. MKKK activates the downstream MKK, which in turn activates MAPK by catalyzing the phosphorylation of threonine and tyrosine residues within the catalytic domain (44,45). After activation, MAPK moves through large pores on the nuclear membrane, translocating into the nucleus where many of its primary targets, the transcription factors, are located (46). Transcription factors are proteins and phosphoproteins that activate a gene by binding to its promoter, accelerate its expression by binding to an enhancer sequence or slow its transcription by binding to a repressor sequence (30). These transcription factors control expression of targeted genes and regulate the induction of genes which largely determine the ultimate biological response of the cell, including the hypertrophic response of cardiomyocytes (47).

From the previous discussion, it is evident that the MAPK pathway is activated after the binding of various growth factors to their receptors on the cell surface. This interaction leads to the transmission of signals to the nucleus via membrane/cytoplasmic kinase cascades. Also, other parallel signal transduction pathways have been identified that are stimulated at the membrane. Each pathway proceeds via two sequential protein kinases: one is serine/threonine kinase, Raf-1 or MEKK1, and the other is serine/threonine and tyrosine kinase, MEK or JNK kinase (JNKK). These pathways activate MAPKs, such as ERK or JNK, which directly regulate nuclear transcription factors (48). The MKKK for activating p38 kinase has yet to be identified.

ERK signal cascade

The first subgroup of MAPK (ERK1/2) was identified in a cell extract by Sturgill and Wu in 1991 (49). Extensive studies have revealed that ERK is related to a 42 kDa protein that is transiently phosphorylated at tyrosine after stimulation by a variety of mitogens, including platelet-derived growth factor, phorbol ester and insulin-like growth factor II. It has been suggested that MAPK may play an important role in the signalling pathway responsible for the G0 to G1 transition in the cell cycle (50). The ERK pathway is coupled by a GTP-binding protein which is activated by G_{α}- and $G_{\beta\gamma}$-protein complex. The most important isoform of G_{α} in the heart which activates ERK is $G_{\alpha q}$-protein (51-57). Once stimulated by Ang II, ET-1 or α-adrenergic agonists, $G_{\alpha q}$-protein activates phospholipase C to catalyze the hydrolysis of phospholipids on the cytoplasmic side of the membrane to produce diacylglycerol (DAG) and inositol-3,4,5-triphosphate ($InsP_3$). DAG then stimulates the lipid-dependent serine/threonine kinase protein kinase C (PKC) and $G_{\beta\gamma}$-protein to activate the ERK signalling cascade (58-61). $InsP_3$ instead stimulates the release of calcium from the sarcoplasmic reticulum and thus, activates the ERK pathway via both Ras-dependent and -independent mechanisms (62,63). Activation of β-adrenergic receptors results in the production of cyclic AMP which in turn activates protein kinase A which catalyzes the phosphorylation of many transcriptional factors via the MAPK pathway and thus, stimulates protein synthesis and cell growth (64-67). By using three-dimensional digital imaging microscopy, Gonzalez et al (68) found that the majority of subcellular ERKs in quiescent cells surround the nucleus and are also present within the lumen of the nucleus. Following the activation of cells by serum, ERKs are translocated into the nucleus, supporting the concept that MAPK transmits a signal from the cytoplasm into the nucleus of a cell (68). The phosphorylated ERKs in turn catalyze the phosphorylation of Elk1, which appears to play an important role in regulating atrial natriuretic factor (ANF) expression (46,69-72). The MAPK signalling transduction cascade undergoes inactivation by specific phosphatases, such as PAC-1 and 3CH134 (73).

The ERK cascade is composed of Ha-Ras, Raf-1, MEK, ERK and Rsk, and spans from the plasma membrane to the nucleus and transduces the mitogenic signals downstream from the tyrosine kinase membrane receptor (50). The activity of ERK is stimulated by multiple extracellular stimuli and oncogenes. This

signalling transduction cascade is triggered by binding of a ligand to its receptor, stimulating Ras which plays the central role in the activation of ERK1/2. The activation of MAPK will in turn activate several cellular protein kinases, such as the ribosomal S6 kinase and MAPK-activated protein kinase 2, and catalyze the phosphorylation of some nuclear transcription factors such as Elk/p62^{TCF}, c-myc and C/EBPβ (31,50,70,74,75).

Because Ras plays a critical role in the MAPK pathway, it is important to understand the underlying mechanism for the activation of Ras. A signalling transduction cascade triggered by binding of a ligand to its receptor will activate Ras following the activation of MAPK. This, in turn, phosphorylates transcription factors, either directly or through the activation of another serine/threonine kinase, Rsk, and promotes the transcription of genes required for the growth response (76). These results further demonstrate a role for MAPK in the molecular mechanisms of cardiac hypertrophy. Ras has four isoforms which include Ha-Ras, Ki-Ras4A, Ki-Ras4B and N-Ras. Ras is a 21 kDa guanine nucleotide binding protein (77,78) localized in the plasma membrane by virtue of a number of post-translocational modifications such as farnesylation or, in the case of Ha-Ras, palmitoylation and C-terminal carboxymethylation. Ras cycles between an inactivated, GDP-bound and an activated GTP-bound state, and thus, acts as a molecular switch. Guanine nucleotide exchange factors activate Ras by increasing the exchange of GDP for GTP, while GTPase-activating proteins can potentially downregulate Ras activity by promoting the conversion of bound GTP to GDP. Activation of MAPK-mediated signals are generally initiated by ligand binding to tyrosine kinase receptors and activating their latent tyrosine kinase activity to form a series of aggregates of signalling proteins binding to one another. Son-of-Sevenless (Sos) is a guanine nucleotide exchange factor which contains proline-rich sequences that bind to the SH3 domains of the adapter protein growth receptor binding protein 2. Growth receptor binding protein 2 associates with activated receptor tyrosine kinases or with tyrosine-phosphorylated Shc via its SH2 domain. Shc will, in turn, associate with receptor tyrosine kinases, nonreceptor tyrosine kinases (eg, Src) and other, yet unidentified, proteins through its SH2 and PTB domains. When growth stimuli trigger the autophosphorylation of the tyrosine kinase receptors, the signal is transmitted to Ras, in part, by redistributing Sos in the plasma membrane where Ras is located, and thus, Sos exchanges Ras-bound GDP for GTP. Once Ras is activated, several targets of Ras will in turn be stimulated. Activation of Ras engages the phosphorylation cascade starting from Raf-1 (MKKK) to MEK, and then to the MAPK family. Although the association with Ras, per se, does not activate Raf-1, their complex formation can serve to localize Raf-1 to the plasma membrane, which is sufficient for its activation. Raf-1 was found to be an activator of MEK in mammalian cells and was found to form a stable complex with MEK and phosphorylate MEK on serine residues in vitro.

ERK in cardiac hypertrophy and heart failure

Investigations of hypertrophic responses induced by phenylephrine have indicated that Ras is biochemically activated by phenylephrine and other hypertrophic stimuli (79-83). In fact, Ras activation is required for phenylephrine-induced hypertrophy and is sufficient to induce both morphological and genetic markers of cardiac hypertrophy (84). Furthermore, Ras is involved in the increase in gene expression associated with cardiac muscle cell growth (85). One of the Ras effectors, c-Raf, is important in the hypertrophic response because its activation is sufficient for inducing this response. In addition, the activation of c-Raf is increased by hypertrophic stimulation (79,86). Inhibition of MAPK or Raf-1 by transfection or microinjection of a dominant negative form of MAPK or Raf-1 showed inhibitory effects on phenylephrine-induced transcriptional activation of ANF and myosin light chain-2, but did not suppress the organization of actin filaments by phenylephrine (69,79,87). Therefore, the activation of the Raf-mitogen-activated/ERK kinase (MEK)-ERK protein kinase cascade appears to be very important in cardiac hypertrophy.

The Ras-Raf-MEK-ERKs signalling pathway is also activated by phosphatidylinositol-3-kinase (PI3K). Introduction of constitutively activated PI3K into cells activates Ras and induces c-fos transcription, Raf-1 and MAPK activation, and other cellular responses such as Xenopus oocyte maturation and membrane ruffling in a Ras-dependent manner (34,88). However, recent research suggests that PI3K may also represent a downstream target of active Ras because labelling of phospholipid products is elevated with coexpression of active Ras and PI3K, while their production is reduced in response to a ligand when cellular Ras is inhibited (89). As previously discussed, both DAG and InsP3 promote growth in cardiomyocytes through different signalling pathways, although both ultimately include the ERK cascade (90). Because PKC is another activator of Ras (50), both Ras and PKC may regulate Ca^{2+} concentration in cardiomyocytes via the Raf-MEK-ERK cascade and thus, this pathway may represent a critical determinant of cardiac physiological function (91). However, the results from Schluter and colleagues (92) have suggested that ERK2- and PI3K-dependent pathways represent two mutually exclusive ways of signalling that lead to different aspects of the hypertrophic response to α-adrenoceptor stimulation. Pretreatment with PMA to downregulate PMA-sensitive isoforms of PKC attenuates ET-1 stimulation of A-Raf, implicating the activation of PKC in this pathway (10).

As a part of the Ras-Raf-MEK-ERK cascade, activation of MEK-1 activates the downstream targets, ERK1/2, which phosphorylate and stimulate transcription factors–such as c-myc, c-jun, activating transcription factor-2 (ATF-2), Rsk, TCF, c-fos, Elk1, UBF, Ets1, Sap1a, STAT factors and GATA4–that form some of the final targets of the cascade (93,94). ERK also triggers the phosphorylation and activation of Rsk (p90^{s6k}), an enzyme which contributes to the phosphorylation of ribosomal protein S6 and goes on to phosphorylate other transcription factors. Ribosomal protein S6 primes the protein translation machinery in the cell to meet the impending wave of gene expression events (95). ERKs also phosphorylate upstream components in the signalling cascade that lead to their activation, thus, demonstrating feedback regulation (96). Multiple extracellular hormones and peptides such as growth factors, platelet-derived growth factor, epidermal growth factor, insulin and tumour promoters (12-O-tetradecanoylphorbol-13-acetate) can also activate signals from effectors acting at the plasma membrane (50,97,98).

It has been reported that ERKs phosphorylate and activate the product of the protooncogene c-jun, which is a component of activator protein 1 (AP-1). This increases DNA binding, as well as ternary complex formation, and results in transcriptional activation for integration of MAPK signalling pathways and coordination of biological responses to different extracellular

stimuli (74). Increased activities of ERK1/2 have been observed in isolated perfused heart upon stimulation with phenylephrine (99). Although ERK1/2 were not activated in patients with cardiac hypertrophy, they were activated in the failing heart (100). To demonstrate that the activation of the renin-angiotensin system is one of the important upstream signalling events that is critically involved in the regulation of the MAPK signalling transduction pathway, Ang II was infused and was found to increase the activities of both ERKs in the heart; the activition of ERK1 was greater than that of ERK2 (101). It was also shown that high dose Ang II infusion induced differential activation of ERKs between the left and right ventricles (101). Therefore, it was suggested that ERK1 and ERK2 may play different roles in cardiac tissue through the renin-angiotensin system cascade (101). In a study examining the relationship between Ang II and MAPKs in hypertrophied neonatal rat cardiomyocytes, Aoki and colleagues (8) found that Ang II activated ERKs, while PD98059, a specific inhibitor of MEK, inhibited Ang II-induced expression of ANF at both the mRNA and polypeptide levels. Dominant negative Ras inhibited both ERK activation and ANF upregulation by Ang II, whereas constitutively active forms of Ras and MEK were sufficient to activate the ANF promoter. These results suggest that Ang II regulates ANF expression through ERK pathways and that the ERK pathway mediates an agonist-specific and phenotype-specific response in cardiac hypertrophy (8). From an experimental study carried out using mechanically stretched neonatal rat cardiomyocytes, Yamazaki et al (102) have reported that CV-11974, an angiotensin type 1 receptor antagonist, completely blocked the activation of MAPKs due to stretch. These results demonstrate that Ang II, the mediator secreted from stretched cardiomyocytes, was likely involved in the activation of Raf-1-MKK-MAPK signalling pathways (102). Mechanical stress, which normally initiates the secretion of Ang II, had also been suggested to be the possible activator for MAPK (103-105). In another study carried out on neonatal rat cardiomyocytes, Zou et al (87) observed that PKC and Raf-1, but not tyrosine kinases or Ras, are critical for Ang II-stimulated ERKs activities. In addition, Takemoto et al (106) also reported the activation of myocardial MAPK in the in vivo rat heart after applying Ang II or α- or β-adrenergic agonists.

ERKS in ischemia/reperfusion and apoptosis

Controversial results regarding the activation of ERKs in ischemia have been reported. Using an in vivo rat model, Yoshida et al (107) investigated changes in MAPK activities in an acute myocardial infarction in either ischemic or non-ischemic myocardium. The results indicated that p44 kinase (ERK1) was significantly activated, although variation was observed in the activation patterns for each group of MAPKs in different regions, including ischemic myocardium, nonischemic septal wall and right ventricular wall. The echocardiographic results suggested that MAPKs activation might be partially induced by acceleration of workload and/or stretch. Behrends and colleagues (108) also reported the activation of ERKs during ischemia in an in vivo pig model. Activation of ERKs has also been found in the ischemic human heart (109) or in cultured neonatal rat cardiomyocytes (110). During ischemia/reperfusion, most investigators have reported activation of ERKs (111-113). However, Bogoyevitch et al (114,115) suggested that ERKs' activation is not observed following either ischemia or ischemia/reperfusion. It would thus appear that the activation of ERKs was probably coupled preferentially to the activation of Gq protein receptors tyrosine protein kinase, but not to stress receptors such as JNK/SAPK and p38 kinase. These results suggest that the activation of multiple parallel MAPK signalling transduction cascades may be involved in response to different cellular stresses in the heart (116).

The activation of ERKs in cardiomyocytes may be cytoprotective for apoptosis. Yue and colleagues (117) reported that the activation of ERKs by ischemia or redox stress attenuated the number of subsequent cardiomyocytes undergoing apoptosis in the intact heart. Furthermore, inhibition of ERKs sensitized neonatal rat cardiomyocytes to daunomycin-induced apoptosis. However, activation of ERKs has been observed to exert no effect on β-adrenoceptor-mediated apoptosis or hypoxia-associated apoptosis (43,118). α1-adrenoceptor agonists and ET have been shown to inhibit cardiomyocyte apoptosis, primarily through the activation of ERKs (85,119-122). Moreover, Horiuchi et al (123) reported that ERK plays a critical antiapoptotic role in PC12W cells through the Ang II activated angiotensin II type 1 receptor signalling cascade. For these reasons, the activation of ERK signalling may play an important role in providing cytoprotection.

Signalling cascade of JNK/SAPK

The cellular stress-activated protein kinase, JNK/SAPK, was first identified as a 54 kDa protein and activated serine/threonine kinase in necrotic livers of cycloheximid-treated rats (124). JNKs are represented by more than 10 different isozymes encoded by three genes (JNK1, JNK2 and JNK3). JNK1 and JNK2 are two distant relatives of MAPK; JNK1 (46 kDa) and JNK2 (54 kDa) bind to and phosphorylate the transactivation domains of c-jun, which is a component of the AP-1 transcription factor (44,125) and Elk1 (74). Transcription factor ATF-2 has been identified as another target for JNK. The phosphorylation of ATF-2 by JNK has been shown to increase transcriptional activity and gene expression (31,75,126). However, unlike ERKs, JNK/SAPK is activated weekly by growth factors, phorbol esters and activated Ras. In addition, JNK/SAPK is strongly activated by inflammatory cytokines and cellular stresses such as viral infection, toxin, tumour necrosis factor (TNF), interleukin-1, ultraviolet (UV) radiation, heat shock, osmotic shock or low concentrations of protein synthesis inhibitors (44,45,80,127,128). The activation of the JNKs requires phosphorylation of both threonine and tyrosine in subdomain VIII of the catalytic domain which is different from the activation of ERK1/2. Because UV irradiation, hyperosmolarity and inflammatory cytokines, such as TNF, stimulate the activity of JNK, it is proposed that the JNK pathway is involved in cellular responses to stress.

The JNK pathway consists of Ha-Ras, Rac/Cdc42Hs, MEKK-1, MKK4/7 and JNKK. Rac, a monomeric G-protein related to Ras, connects the stress-activated receptor to downstream phosphorylations. Analogous to ERKs, once phosphorylated, JNK will cross into the nucleus and activate several transcription factors including c-jun, ATF-2 and Sap-1 (34-39,50,71,72,76,117,129). The earliest known target of the JNK pathway, c-jun, is part of the AP-1 transcription factor that regulates the genes involved in cell proliferation. However, the biological function of JNK remains to be elucidated. Most evidence has shown that the immediate effects of mitogenic signals, such as growth factors and phorbol esters,

stimulate the ERK pathway but not the JNK pathway. In some cases, the JNK pathway functions downstream of the ERK pathway to activate c-jun. Thus, activation of the JNK pathway may be a relatively slow process and involve autocrine factors resulting from activation of the ERK pathway or crosstalk between pathways in an unidentified fashion (50). JNKs regulate a partially overlapping set of transcription factors compared with those governed by ERK1/2. JNKs are unable to phosphorylate and activate p90RSK, the target of ERKs. However, the activity of JNKs in phosphorylating and activating the N-terminal region of c-jun family members is higher than that of ERKs (125). Overexpressed wild type and constitutively active forms of MKK7, the upstream kinase of JNK2, in neonatal rat cardiomyocytes lead to specific activation of the JNK pathway followed by cardiac hypertrophy and amplified expression of ANF and alterations in sarcomeric organization (130,131). JNK/SAPK has also been reported to be activated in failing human heart but not in the hypertrophied heart (100). Using transgenic mice, Buena et al (132) have reported that expression of physiological levels of MAPK phosphatases blocked the activation of JNK1/2, and attenuated aortic banding or catecholamine infusion-induced cardiac hypertrophy (132).

As reported by many investigators, SAPK/JNK is activated in ischemia/reperfusion but not during the ischemic phase (113,116). However, Yoshida et al (107) investigated changes in MAPK activities in an acute myocardial infarction in rats in either ischemic or nonischemic myocardium. The results indicated that JNKs were significantly activated, although variation was observed in the activation patterns in each group of MAPKs in different regions, as mentioned previously. Therefore, the role of JNK/SAPK in ischemia or ischemia/reperfusion remains to be clarified. In cardiomyocytes, SAPKs are activated by ET-1 and phenylephrine, and are markedly activated by cytotoxic cellular stresses including osmotic or oxidative stress (133,134). Because SAPKs are frequently found to be associated with apoptotis in nonmyocytic cells (135,136), it is likely they are involved in decompensated hypertrophy; however, some evidence discounting this effect has also been presented (137-140). SAPK has also been found to produce either proapoptotic or antiapoptotic effects in many cell types and the activation of JNK/SAPK in response to mechanical stress, cytokines and oxidative stress showed correlations with cardiomyocyte apoptosis (131,141-143). As reported previously, when the upstream activator of JNK, MEKK1, was deleted, apoptosis was enhanced in response to hypoxia-reoxygenation in cardiomyocytes derived from embryonic stem cells (83). Also, the activation of JNK was found to delay and attenuate cell death, but is mechanistically dissociated from apoptosis (86). Accordingly, it is proposed that the proapoptotic and antiapoptotic effects of JNK/SAPK are related to the downstream effectors of these kinases. However, the establishment of a direct cause and effect relationship between JNK activation and apoptosis is still far from clear.

Signalling cascade of p38 kinase

p38 kinase is a relatively new member of the MAPK family. It was cloned in 1994 by Han et al (79) and Rouse et al (144), separately. Similar to JNK, p38 kinase is activated by UV light and regulated by stress, such as osmotic stress and proinflammatory cytokines. However, growth factors such as phorbol ester and epidermal growth factor can only produce a modest increase in the p38 kinase activity (125). Four isoforms of p38 kinase, namely p38α, p38β, p38γ and p38δ, have been identified; p38α and p38β have been reported to exist in the myocardium (145). It has been reported that p38 kinase was required for restoring the osmotic gradient across the plasma membrane in response to increased external osmolarity; it is a mammalian homologue of the yeast osmosensing protein kinase, high osmolarity glycerol-1. It is activated by proinflammatory cytokines, such as interleukin-1 and TNF, and environmental stress such as UV irradiation. p38 kinase has a dual phosphorylation site motif which is distinct from that of ERK and JNKs. The activation loop containing these phosphorylation sites in the kinase structure is six amino acids shorter in p38 kinase than in ERKs and JNKs, suggesting that the phosphorylation of p38 kinase may occur through mechanisms distinct from those controlling the phosphorylation of ERKs and JNKs (50).

The signalling pathway that leads to p38 kinase activation is incomplete; however, several potential mediators of p38 (Ras, p21 activated kinase [146], mixed lineage kinase 3 [147] and double leucine zipper-bearing kinase [148]) have been identified. Studies have found that the MKKs for p38 kinases are JNKK1 (Sek1), MKK3 and MKK6; MKKKs may include Tak1 and Ask1 (43,118,149-151). MKK3 is specific for p38 kinase, while Sek1 phosphorylates both p38 kinase and JNKs; however, cotransfection assays in vivo have shown that Sek1 activates JNK but not p38 kinase (43). Although the biological function of p38 kinase also remains to be determined, the p38 kinase pathway is indeed involved in the regulation of inflammatory cytokine biosynthesis. The autocrine loop may be a common way of crosstalk between different MAPK pathways in mammalian cells. Like JNK, p38 kinase also phosphorylates transcription factors such as ATF2, CHOP and MEF2C, thus increasing their transactivating activities. p38 kinase/ERK phosphorylate and regulate ATF2 (149). p38 kinase has been found to be activated in the heart failure stage, but not in the hypertrophy phase (100). Activation of p38 kinase has also been reported in transgenic mice models. Buena et al (132) have reported that expression of physiological levels of MAPK phosphatases blocked the activation of p38 kinase and further attenuated cardiac hypertrophy induced by aortic banding or catecholamine infusion.

Yoshida et al (107) investigated changes in MAPKs' activities in an acute myocardial infarction in rats in either ischemic or nonischemic myocardium; the results showed that p38 kinase was significantly activated. Many other investigators have also reported that the activation of p38 kinase exacerbates the injury induced by either ischemia or ischemia/reperfusion, and therefore, inhibition of p38 kinase produces a protective effect during ischemia/reperfusion (152-154). However, other investigators have reported conflicting results, suggesting that the activation of p38 kinase may directly provide a protective effect against ischemic injury (139,155). Therefore, the precise role of p38 kinase in ischemia/reperfusion is still not clear. Likewise, both proapoptotic and antiapoptotic actions have been described for p38 kinase. The proapoptotic action of p38 kinase has been found by pretreatment of hypoxic myocytes with a selective p38 kinase inhibitor, SB242719, with reduced appearance of apoptosis (117,151). It has also been shown that oxidative stress-induced myocyte apoptosis was partially due to the activation of p38 kinase (84,150). However, antiapoptotic action of p38 kinase has also been reported due to β-adrenergic stimulation, osmotic stress and signals coupled to membrane

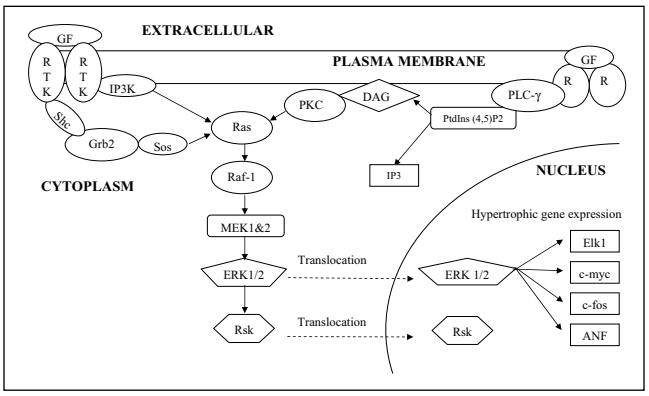

Figure 1) *The diagram of extracellular signal-regulated kinases (ERKs) pathways. ANF Atrial natriuretic factor; DAG Diacylglycerol; GF Growth factor; Grb2 Growth receptor binding protein 2; IP3K Phosphatidylinositol 3′-kinase; MEK Mitogen-activated ERK kinase; PLC-g Phospholipase C-g; PtdIns(4,5)P2 Phosphatidylinositol diphosphate; PKC Protein kinase C; R GF receptor; RTK Receptor tyrosine kinase; Sos Son-of-Sevenless*

sphingolipids which phosphorylate the small heat shock protein, αB-crystallin, activate NFκB and release antiapoptotic cytokines (156,157).

CONCLUSIONS

A great deal of work has been carried out to define the MAPK pathway (Figure 1) and its implication in different types of cardiac pathologies (Table 1). Although many investigations have focused on the roles of MAPK pathways in the development of the cardiac hypertrophy response, the evidence is still far from conclusive. Some studies have shown that the protooncogene Ha-Ras, the Gαq-containing heterotrimeric G-protein and the interleukin-6 receptor, gp130, are important mediators in the hypertrophic response both under in vitro and in vivo conditions, via activation of their downstream signalling pathways such as the MAPK cascade. ET-1, phenylephrine and phorbol esters are powerful hypertrophic agonists in cultured cardiomyocytes. Related studies have shown that the activation of ERK signal transduction cascade by these agonists may mediate the hypertrophic response, but it should be noted that it is not the sole mediator of this response. JNK and p38 kinase have also been suggested to affect cardiac hypertrophy because of their action on inhibiting cell proliferation and their promotion of apoptosis. The enormous involvement of different MAPK signalling cascades provides both the flexibility and integration of gene expression that govern normal growth. However, MAPKs probably contribute to a maladaptive growth response that is critical in patients with cardiac hypertrophy and heart failure (30).

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TABLE 1
Mitogen-activated protein kinases (MAPKs) in cardiac pathology

	MAPKs	Model (reference)
Cardiac hypertrophy	ERK	Human (100)
		Transgenic mice (119,132)
		Cardiomyocytes (158)
		Neonatal rat cardiomyocytes (159-161)
	JNK/SAPK	Human (100)
		Transgenic mice (132)
		Neonatal rat cardiomyocytes (159,162)
		Pressure overload rat (163)
	p38 kinase	Human (100)
		Transgenic mice (132)
		Neonatal rat cardiomyocytes (142,159,160,162)
Heart failure	ERK	Human (100)
	JNK/SAPK	Human (100)
	p38 kinase	Human (100)
Ang II associated cardiac hypertrophy	ERK	Transgenic mice (7)
		AT_{1a} knockout mice (164)
	JNK/SAPK	Transgenic mice (7)
	p38 kinase	Transgenic mice (7)
Hypertensive cardiac hypertrophy	ERK	Rat (101,143,165)
	JNK/SAPK	Rat (101,143)
	p38 kinase	Rat (143)
Myocardial infarction	ERK	Rat (107)
	JNK/SAPK	Rat (107,166)
	p38 kinase	Rat (107)
Cardiac apoptosis	ERK	Rat (117)
	JNK/SAPK	Mouse (131,137-140)
	p38 kinase	Rat (84,117,150,151,156,157)
Ischemia/reperfusion injury	ERK	Human (109)
		Pig (108)
		Rat (107)
		Neonatal cardiomyocytes (110)
	JNK/SAPK	Rat (107,113,116)
	p38 kinase	Rat (107,139,152-155)

Ang II Angiotensin II; AT1a Angiotensin II type 1 receptor; ERK Extracellular signal-regulated kinases; JNK c-jun N-terminal protein kinases; SAPK Stress activated protein kinase

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