

Mitogen-activated protein kinase phosphatase-1: A critical phosphatase manipulating mitogen-activated protein kinase signaling in cardiovascular disease (Review)

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Abstract. Mitogen-activated protein kinase (MAPK) cascades are important players in the overall representation of cellular signal transduction pathways, and the deregulation of MAPKs is involved in a variety of diseases. The activation of MAPK signals occurs through phosphorylation by MAPK kinases at conserved threonine and tyrosine (Thr-Xaa-Tyr) residues. The mitogen-activated protein kinase phosphatases (MKPs) are a major part of the dual-specificity family of phosphatases and specifically inactivate MAPKs by dephosphorylating both phosphotyrosine and phosphoserine/phosphothreonine residues within the one substrate. MAPKs binding to MKPs can enhance MKP stability and activity, providing an important negative-feedback control mechanism that limits the MAPK cascades. In recent years, accumulating and compelling evidence from studies mainly employing cultured cells and mouse models has suggested that the archetypal MKP family member, MKP-1, plays a pivotal role in cardiovascular disease as a major negative modulator of MAPK signaling pathways. In the present review, we summarize the current knowledge on the pathological properties and the regulation of MKP-1 in cardiovascular disease, which may provide valuable therapeutic options.

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1. Introduction

The evolutionarily conserved mitogen-activated protein kinase (MAPK) signaling cascades consist of a sequence of successively acting kinases, which are involved in a variety of physiological processes, including cellular proliferation, differentiation, metabolism, stress responses, apoptosis and survival (1). In mammalian cells, based on a signature Thr-Xaa-Tyr (TXY) motif, MAPK cascades are generally subclassified into three main branches, namely extracellular signal-regulated kinases (ERKs), c-Jun N-terminal kinases (JNKs) and p38 kinases (2). All terminal effectors are activated by the dual phosphorylation of the threonine and tyrosine residues in a conserved 'TXY' motif through a well-conserved three-tiered kinase cascade (MAPKKK-MAPKK-MAPK), and impart signal amplification, modulation and specificity in response to various stimuli (3).

Dual-specificity phosphatases (DUSPs) are an emerging and heterogeneous subgroup of protein phosphatases, which are best characterized by their ability to dephosphorylate both serine/threonine and tyrosine residues within the one substrate (4). One of the DUSP subgroups specific for MAPKs (ERKs, JNKs and p38 kinases) contains ten proteins that can dephosphorylate MAPKs at both phosphothreonine and phosphotyrosine residues within the MAPK 'TXY' activation motif, and thereby have been referred to as MAPK phosphatases (MKPs) (5,6). MKPs contain an N-terminal rhodanese or CDC25-like domain and a highly conserved C-terminal catalytic domain. Importantly, different members of the family of MKPs show distinct patterns of tissue- and cell type-specific expression, substrate specificity and subcellular localization.

The roles of ERKs, p38 kinases and JNKs has been well reported in various cardiovascular disease, the leading common cause of mortality and morbidity worldwide in humans (7,8). MKPs as major modulators of the critical signaling pathways have enjoyed the limelight in the pathogenesis of various cardiovascular. In this review, we focus on recent advances in the elucidation of the function and regulation of MKP-1, a prototypical member of the MKP family, in the pathogenesis of cardiovascular disease. The understanding of tissue- and cell type-specific functions of MKP-1 may contribute to the potential development of treatments for controlling MAPK-dependent cardiovascular disease.

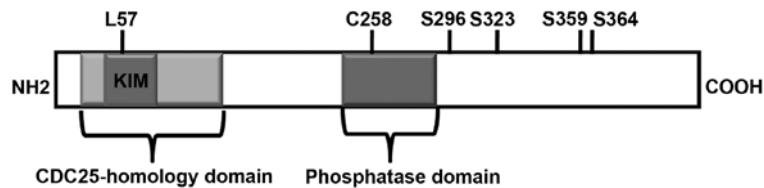


Figure 1. Schematic diagram of the structure of mitogen-activated protein kinase phosphatase-1 (MKP-1). Depicted in the NH2 terminus is the CDC25 domain containing the kinase interaction motif (KIM). The acetylation of Lys57 of KIM promotes its association with p38 MAPK. The catalytic domain is located at the carboxyl terminus. The oxidation of the catalytic Cys258 of MKP-1 protein inactivates its phosphatase activity. In C-terminal docking site for mitogen-activated protein kinases (MAPKs), the phosphorylation of Ser359 and Ser364 enhances protein stability, whereas Ser296/Ser323 phosphorylation is involved in the proteasomal degradation of MKP-1.

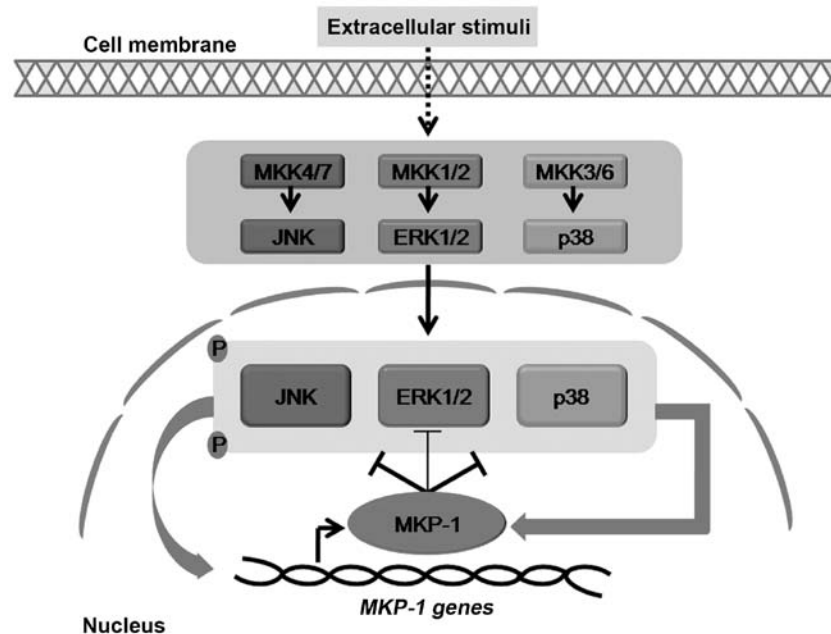


Figure 2. Diagram of the feedback loop between the mitogen-activated protein kinases (MAPKs) and mitogen-activated protein kinase phosphatase-1 (MKP-1). Activated MAPKs upon extracellular stimulation enter the nucleus to trigger transcription factor activation and lead to the altered gene transcription of MKP-1. MAPKs can phosphorylate MKP-1 protein regulating its stability and activity. By dephosphorylating MAPKs, MKP-1 terminates the MAPK signaling cascade with different substrate preference for all three terminal effectors (ERK, JNK and p38).

2. The basic structure and biological functions of MKP-1

MKP-1 is also referred to as DUSP1, which was initially identified as an immediate-early response gene (9). Structurally, MKP-1, with a molecular mass of 40 kDa, has a C-terminal phosphatase active site comprising the Asp227, Cys258 and Arg264 catalytic triad, which is highly conserved within the entire MKP family. An N-terminal rhodanese or CDC25-like domain containing critical kinase-interacting motifs (KIMs) confers specific MAPK substrates on MKP-1 (10) (Fig. 1). MKP-1 is a nuclear, inducible and ubiquitous protein with the highest expression levels observed in the heart, lungs and liver (11). As the first MAPK-selective dual-specificity protein phosphatase, it was designated as MKP-1 and was regarded as an antagonist of MAPK signaling cascades (12) (Fig. 2). Although MKP-1 was originally described as an ERK1/2-specific phosphatase, subsequent studies demonstrated that MKP-1 was also able to render both JNKs and p38 kinases inactive (13-15). To address precise substrate specificities for MKP-1, Franklin and Kraft (13) titrated the levels of MKP-1

expression in the established a U937 cell line and found that MKP-1 seemed to have a preference for JNKs and p38 kinases over ERKs. Similarly, the loss of MKP-1 has been shown to result in an increase in p38 kinase and JNK activity, but not in ERK activity in macrophages (16). By contrast, other studies have suggested that high expression levels of MKP-1 have a similar effect on the dephosphorylation of ERKs, JNKs and p38 kinases (17,18). Thus, the regulation of MAPKs by MKP-1 varies according to tissue or cell type and context.

3. Regulation of MKP-1 expression and activity

The expression of MKP-1 is subject to transcriptional and post-transcriptional levels of regulation. MKP-1 is an inducible gene with low basal levels of MKP-1 in unstressed or unstimulated cells (19). However, in response to stimuli, such as growth factors or stress, MKP-1 mRNA levels are robustly elevated in a short period of time (12). In many cases, this induction is dependent on MAPK activation, providing a well-defined negative feedback loop between MAPKs and MKP-1 (20). In

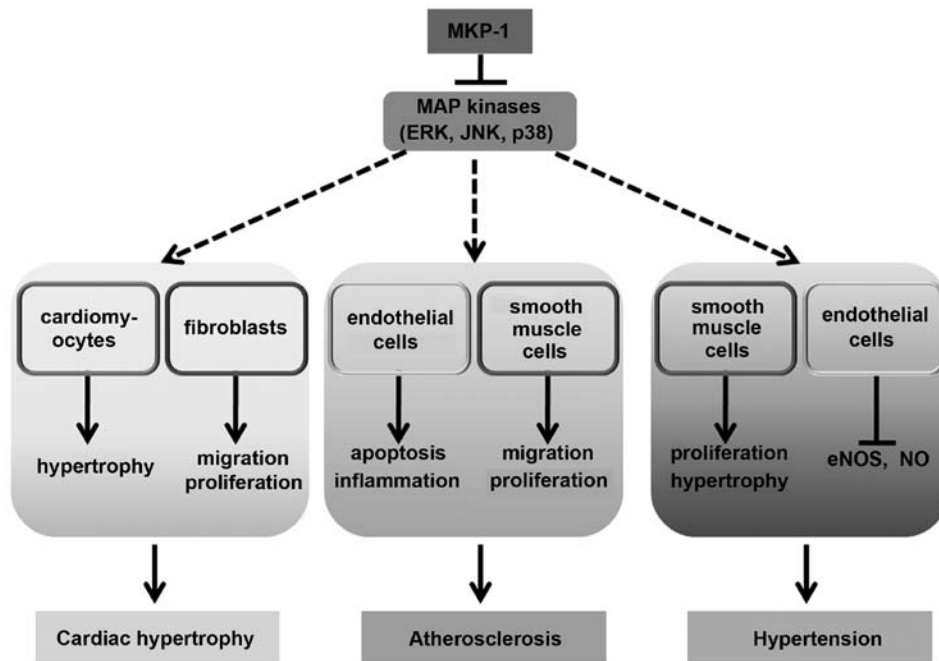


Figure 3. Mitogen-activated protein kinase phosphatase-1 (MKP-1) in the control of various cardiovascular pathogenesis. MKP-1 serves to regulate MAPK-dependent phosphorylation of responses, such as hypertrophy, proliferation, inflammation in cardiomyocytes, fibroblasts, endothelial cells and vascular smooth muscle cells. The coordinated actions of MKP-1 limit the activity of mitogen-activated protein kinases (MAPKs), establishing MKP-1 as an important player in pathologic processes, including cardiac hypertrophy, atherosclerosis and hypertension.

addition, studies have indicated that the transcriptional induction of MKP-1 also involves the transcription factor, CCAAT/enhancer binding protein- β (C/EBP β) (21), calcineurin (22) or the protein kinase C pathway (23). Albeit much effort in the past has focused on identifying the transcription factors of MKP-1 expression, the precise mechanisms underlying MKP-1 transcriptional activation are not yet fully understood. Another important mechanism through which MKP-1 may be manipulated is through mRNA stabilization. In HeLa cells under oxidative stress, HuR and NF90, two crucial RNA-binding proteins, have been shown to elevate MKP-1 mRNA stability (24). The interaction of MKP-1 RNA with the AU-rich element-binding protein, tristetraprolin, degrade MKP-1 mRNA thus decreasing the production of MKP-1 protein (25). An additional mode controlling MKP-1 expression occurs at the level of protein stability. After induction, MKP-1 is rapidly degraded with a protein half-life of approximately 1 h. As a negative-feedback mechanism, ERK1/2 can enhance the stabilization of MKP-1 by direct phosphorylation on serine 359 and serine 364 (26). Conversely, the phosphorylation of MKP-1 on serine 296 and serine 323 by ERK1/2 substantially decreases the half-life of MKP-1 through a proteolysis mechanism (27). Furthermore, MKP-1 is activated following binding to its phosphorylated substrate, ERK2, JNK1 and p38 *in vitro* (28). Acetylation on lysine 57 of MKP-1 indirectly enhances its phosphatase activity by increasing its interaction with p38 without altering the intrinsic phosphatase activity (29). Additionally, reversible oxidation of the conserved cysteine within the MKP-1 catalytic domain can inactivate the catalytic activity of MKP-1 (30). Collectively, the expression and activity of MKP-1 can be regulated at multiple levels and through complex mechanisms.

4. Role of MKP-1 in cardiovascular disease

MKP-1 has been shown to be involved in multiple physiological and pathophysiological processes, such as the immune response, energy metabolism and metabolic diseases, the development of the central nervous system and a various types of cancer (31-33). Considering the central role of MAPKs in the modulation of the pathogenesis of cardiovascular disease, it is not particularly surprising that MKP-1, a critical 'node' in MAPK signaling, plays an important role in the development and processes of various cardiovascular diseases (Fig. 3). Consistent with this, over the past 20 years, a number of studies, mostly employing animal models of cardiovascular disease, have been carried out in order to clarify the pathological properties of MKP-1.

MKP-1 in atherosclerosis. Atherosclerosis is the major cause of several cardiovascular diseases, such as acute myocardial infarction and stroke (34). MAPK signaling pathways have a prominent role in atherogenesis; however, whether MKP-1 influences atherogenesis remains unelucidated. It is well established that atherosclerosis is a chronic inflammatory disease involving the participation of multiple cells, including endothelial cells (ECs), smooth muscle cells, macrophages and T lymphocytes (35,36,38,39,42-44,46-48).

Generally, endothelial dysfunction is an important initiating step of atherosclerotic formation. Once activated by various noxious stimuli, ECs secrete a number of adhesion molecules recruiting inflammatory cytokines and cells into the vascular wall, leading to atherogenesis. Zakkar *et al* (36) found that endothelial MKP-1 expression following shear stress suppressed pro-inflammatory gene activation at atheroprotected regions

by negatively regulating p38-VCAM-1 signaling. Moreover, they further confirmed that nuclear factor erythroid 2-related factor 2 (Nrf2) as a transcription factor is required for MKP-1 expression to prevent the development of atherosclerosis (37). Similarly, MKP-1 overexpression has been shown to attenuate MAPK activation and abrogate monocyte adhesion and migration induced by monocyte chemoattractant protein-1 (38). By contrast, mice deficient in MKP-1 have shown increased levels of pro-inflammatory factors and proapoptotic proteins in ECs at atherosusceptible sites (36,39). These data are consistent with the results from other studies showing that MKP-1 is a negative regulator of inflammation by suppressing MAPKs (40,41), and suggest that MKP-1 is anti-atherogenic in the development of atherosclerotic lesions. However, these results are apparently different from those of other studies demonstrating that in apolipoprotein E null mice, MKP-1 protein expression was necessary for the promotion of the inflammatory activation of ECs and macrophage accumulation in atherogenesis (42-44), indicating that MKP-1 may be a pro-atherogenic factor for atherogenesis. Plausible explanations for this disparity include the use of different protocols, measured time points and methods, in particular experimental models, as the pathological level of oxidized lipids may be a vital inflammatory stimulus in mice.

Vascular smooth muscle cells (VSMCs) are an important component of atherosclerotic plaques. VSMCs subjected to pathological stimuli are able to proliferate, then migrate to the intima beneath the endothelium and proliferate again; this process is significantly associated with the pathology of atherosclerosis (45). Using northern blot analysis and *in situ* hybridization, Lai *et al* (46) found that MKP-1 was highly expressed in SMCs of both large and medium sized arteries *in vivo*. In cultured VSMCs, the overexpression of MKP-1 was shown to result in diminished cell growth coinciding with a decrease in MAPK activity. The proliferation and migration of smooth muscle cells following vascular injury may be attributed in part to a decrease in MKP-1 expression (46,47). Little is known about the signaling pathway modulating MKP-1 in VSMCs. It is interesting to note that LDL, a well-established risk factor for atherosclerosis, induces MKP-1 expression in SMCs through the activation of protein kinase C (48) and is associated with the intracellular free Ca²⁺ concentration (49), further supporting the critical balance between MKP-1 and MAPK levels/activities for maintaining the homeostasis of VSMCs. Of note, ginsenosides (50) and tauroursodeoxycholate (51) have been shown to reduce the viability of VSMCs in the rat carotid artery following balloon injury partly by mediating MKP-1 expression. Furthermore, probucol is able to inhibit restenosis following angioplasty by attenuating hyperplasia and the migration of VSMCs with the upregulation of MKP-1 protein expression (52). These data support the feasibility of taking measures to modulate MKP-1 expression in order to prevent atherogenesis.

Overall, the identification of the upstream molecules and mechanisms responsible for the regulation of MKP-1 expression during atherogenesis remains a major challenge for future studies. Nonetheless, to a certain extent, it is encouraging to know that the manipulation of MKP-1 expression may serve as a positive therapeutic strategy in the treatment of atherosclerosis.

MKP-1 in hypertension. As is already known, VSMCs are one of the major constituents of the blood vessel wall responsible for the maintenance of vascular contractile tone; thus, the proliferation and hypertrophy of VSMCs may participate in the pathophysiology of hypertension (45). The involvement of the MKP-1 in blood pressure has been demonstrated specifically in its role in the proliferation and hypertrophy of VSMCs. For example, Begum *et al* (53) demonstrated that due to the defective induction of MKP-1, mimicking hyperinsulinemia stimulated mitogenesis in primary cultures of VSMCs isolated from spontaneous hypertensive rats, a well-characterized animal model of essential hypertension, as opposed to Wistar-Kyoto rats (54). Mechanistically, the sustained p38 MAPK activation most likely contributes to the decrease in MKP-1 expression (54). This is somewhat similar to the results of a previous study in which the phosphorylation of MKP-1 on serine 296 and serine 323 by ERK1/2 sensitized MKP-1 protein to proteolysis (27). Subsequently, other studies also demonstrated that insulin increased MKP-1 expression through the nitric oxide (NO)/cGMP/cGMP-dependent protein kinase I α pathway, which contributed to the inactivation of MAPKs and blocked VSMC migration (55,56). Likewise, the suppression of the proliferation of pulmonary artery smooth muscle cells was explained by an MKP-1-associated increase in ERK dephosphorylation (57). Importantly, when compared with wild-type littermates, MKP-1^{-/-} mice developed considerably higher pulmonary hypertension with cellular proliferation in response to chronic hypoxia (58). Therefore, MKP-1 may be important in maintaining VSMCs in a quiescent, non-proliferative state, preventing the development and progression of hypertension.

Apart from their role in vascular remodeling, MAPKs also directly regulate vasoconstriction (59,60). Correspondingly, evidence from several studies also underscores the integral role of MKP-1, and hence MAPKs, in the regulation of vascular tone (61-64). However, the mechanisms involved regarding this aspect have yet to be clarified. Three described isoforms of NO synthase (NOS), including inducible NOS (iNOS), endothelial NOS (eNOS) and neuronal NOS (nNOS) generate NO, a free radical gas and the most important factor triggering vascular relaxation, whose essential role in the cardiovascular system is has been best demonstrated in NOS knockout mice with hypertension (65). In previous studies, mice deficient in MKP-1 following LPS challenge exhibited an increased induction of NOS and lower tail-cuff systolic blood pressure or mean arterial blood pressure than wild-type mice (66,67). Notably, the p38 MAPK inhibitor, SB203580, has been shown to prevent the induction of iNOS mRNA in the lungs of mice following LPS stimulation (68). eNOS protein expression is positively associated with the activation of the MAPK signaling pathway (69,70). Potentially, MKP-1, a clearly primary phosphatase responsible for the attenuation of MAPKs, may upregulate blood pressure by preventing the induction of NOS. Provocatively, several lines of evidence have suggested that the increased MAPK activation decreases eNOS protein levels (71-73). This role is further supported by data showing that decreased eNOS production resulting from the dysregulation of MAPKs leads to severe pulmonary hypertension in mice deficient in MKP-1 exposed to chronic hypoxia (58). The regulation of the consti-

tutive expression of NOS is a complex process, and further studies are required to elucidate the exact role of MKP-1 in NOS induction.

Taken together, although the functions and mechanisms of action of MKP-1 in vascular remodeling and vasoconstriction remain an area of ongoing investigation, once substantial data for these aspects of MKP-1 are provided, the targeted regulation of MKP-1 using certain approaches may have therapeutic value in the treatment of hypertension.

MKP-1 in cardiac hypertrophy. Cardiac hypertrophy characterized by an enlargement of the size and mass of individual cardiomyocytes and interstitial fibrosis is a key risk factor for progressive heart disease generally associated with an adverse prognosis (74). Although definitive causality between MAPK activity and cardiac hypertrophy remains disputable, studies have suggested a sufficient role for the MAPK signaling pathway in promoting cardiac hypertrophy (75-86). Likewise, a plethora of cell culture-based reports have indicated that MKP-1 can influence the hypertrophic response (76-80). The constitutive expression of MKP-1 has been shown to inhibit the stimulation of gene expression, such as atrial natriuretic factor, β -myosin heavy chain and skeletal muscle α -actin by hypertrophic agonists in cultured neonatal rat ventricular myocytes (76). In addition, it has been reported that apart from being a canonical marker of hypertrophy, the atrial natriuretic peptide can directly ameliorate the cardiomyocyte hypertrophic response induced by angiotensin II or endothelin-1. This is associated with the concomitant induction of MKP-1 expression and the suppression of MAPK activation, as the overexpression of MKP-1 also eliminates a 'sick' phenotype (77). Cardiac fibroblast (CFB) proliferation and migration is a major characteristic of cardiac hypertrophy, with the secretion of redundant growth factors and extracellular matrix components which can modify cardiomyocyte hypertrophy, accentuate cardiac dysfunction and induce fatal arrhythmia (78). Notably, MKP-1 overexpression can prevent CFB proliferation and migration through the inhibition of the MAPK pathway (79,80). Similar results were also observed in vascular fibroblast proliferation (81). These data further indicate that MKP-1, as an endogenous inhibitor of MAPKs, is crucial for cardiac hypertrophy. Using animal models of cardiac hypertrophy, studies have evaluated the role that MKP-1 may play *in vivo*. Transgenic mice of constitutive MKP-1 expression displayed significantly smaller hearts than their wild-type littermates, associated by the inhibition of p38, JNK1/2 and ERK1/2 phosphorylations (82). Similarly, pressure-overload or elevated catecholamines failed to induce hypertrophy in MKP-1 transgenic mouse hearts (82). Complimentary to these gain-of-function approaches, MKP-1/2 double knockout (DKO) mice have been shown to have a hypertrophic cardiomyopathic phenotype with aging; moreover, with pressure overload, this DKO model exhibited unrestrained p38 MAPK activation and exaggerated hypertrophic enlargement compared with a normal hypertrophic response in wild-type mice (83). These findings are similar to those observed in investigations of the overexpression of MEK1 (84), MEK6 (85), MEK7 (86), the upstream activators of three MAPK terminal effectors. It is tempting to speculate that MKP-1 can serve as a repressor of maladaptive cardiac hypertrophy of multifactorial etiology. Remarkably, several studies

have provided evidence that ginsenosides (87), estrogen (88), heptapeptide angiotensin-(1-7) (89) and all-trans retinoic acid (90) can protect the heart against ventricular hypertrophy by increasing MKP-1 expression in an animal model of cardiac hypertrophy, suggesting that it is more likely to identify pharmacological and molecular agents acting on MKP-1 to rescue this disease phenotype. Despite the fact that the MKP-1 promoter is partly responsive to calcineurin signaling independent of NFAT factors in cardiomyocytes (22), there is need for further research to determine definitive transcriptional factors targeting MKP-1.

In addition to animal models of cardiac hypertrophy, few studies have directly connected the effects of MKP-1 to heart failure. The gene or protein expression of MKP-1 has been shown to be significantly upregulated in the hearts of patients with pressure-overloaded cardiomyopathy or end-stage heart failure, respectively (91,92). Given that the MAPK signaling pathway is required to maintain cardiac contractility and mediate cardiomyocyte apoptosis, it is important to better understand the role that MKP-1 may play in heart failure.

MKP-1 in myocardial cell ischemia/reperfusion (I/R) injury. Similar to its role in hypertrophy, the role of the MAPK signaling pathway in cardiomyocyte I/R injury still eludes investigators. Some observations have pointed toward a detrimental role, whereas other studies have indicated a protective role. To date, only a few studies have investigated the effects of MKP-1 in this area. In response to I/R injury, MKP-1 transgenic hearts have been shown to be partially protected from p38-dependent injury and apoptosis (93). The induction of MKP-1 through glucocorticoid dexamethasone (94) or long-chain polyunsaturated fatty acids (95) has been shown to result in the inactivation of p38 and to exert cardioprotective effects. Accordingly, a sustained activation of JNK and an increase in cleaved caspase-9 and caspase-3 have been shown to attribute to the degradation of MKP-1 targeted by atrogin-1 (96). As discussed above, much less is known regarding the exact upstream signalings of MKP-1 which impart this protection. Antithetically, in another study, in the context of ischemic post-conditioning, the age-associated increase in MKP-1 expression failed to play a cardioprotective role (97). Indeed, studies have indicated that the activation of MAPKs during I/R injury contributes to the protective effects (98-100). In short, these contradictions reflect that I/R injury is a complex process involving multistage and multitargeted signaling networks. Dissecting the advantageous as opposed to the disadvantageous aspects of MKP-1 in this process will be a major issue in future studies.

5. Conclusions and perspectives

Over the past several decades, studies have demonstrated that the MAPK signaling plays a crucial role in cardiovascular system homeostasis and disease (8); therefore, it is not at all surprising that MKPs as a necessary brake for MAPKs are involved in cardiovascular physiological and pathophysiological processes. What is surprising is the fact that an alteration in MKP-1 expression is a key factor in numerous animal cardiovascular disease models, even though MLP-1 is one of ten MKP family members.

MKP-1 clearly plays a profound role in the regulation of MAPKs in the cardiovascular system. Moreover, by mediating the expression of MPK-1, some endogenous factors and agents can govern the pathogenesis of cardiovascular disease, underscoring the fact that MKP-1 represents an exciting new drug target for the treatment of cardiovascular disease characterized by MAPK activation. Although growing interest and research has focused on MKP-1, important unknown facts remain unknown that may be of value for the development of novel therapies, for instance MKP-1 specific substrate cell type and context dependence, upstream factors of MKP-1 in the cytoplasm or nucleus, compensatory capabilities among MKPs, and the role of MKP-1 in other cardiovascular diseases, such as myocardial infarction.

Looking ahead, further studies on the role and regulation of MKP-1 are required, presenting an important challenge and opportunity for basic and clinical scientists and may help promote the development of MKP-1 selective inhibitors or activators and may pave the way for developing novel therapeutic approaches for controlling MAPK-dependent cardiovascular disease.

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