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Mitogen-Activated Protein Kinase Phosphatase 1 (MKP-1) in Macrophage Biology and Cardiovascular Disease. A Redox-Regulated Master Controller of Monocyte Function and Macrophage Phenotype

Hong Seok Kim^{1,2} and Reto Asmis^{3,4}

¹Department of Molecular Medicine, College of Medicine, Inha University, Incheon 22212, Republic of Korea

²Hypoxia-related Disease Research Center, College of Medicine, Inha University, Incheon 22212, Republic of Korea

³Department of Clinical Laboratory Sciences, University of Texas Health Science Center at San Antonio, San Antonio, TX 78229

⁴Department of Biochemistry, University of Texas Health Science Center at San Antonio, San Antonio, TX 78229

Abstract

MAPK pathways play a critical role in the activation of monocytes and macrophages by pathogens, signaling molecules and environmental cues and in the regulation of macrophage function and plasticity. MAPK phosphatase 1 (MKP-1) has emerged as the main counter-regulator of MAPK signaling in monocytes and macrophages. Loss of MKP-1 in monocytes and macrophages in response to metabolic stress leads to dysregulation of monocyte adhesion and migration, and gives rise to dysfunctional, proatherogenic monocyte-derived macrophages. Here we review the properties of this redox-regulated dual-specificity MAPK phosphatase and the role of MKP-1 in monocyte and macrophage biology and cardiovascular diseases.

Keywords

monocyte; macrophage; redox signaling; MAPK; atherosclerosis

*Correspondence should be addressed to: Reto Asmis, PhD, Clinical Laboratory Sciences, School of Health Professions, University of Texas Health Science Center at San Antonio, 8403 Floyd Curl Drive, MC 8254, San Antonio, TX 78229-3904; Tel.: (210) 562-4054, FAX: (210) 562-4121; asmis@uthscsa.edu.

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I. INTRODUCTION

The mitogen-activated protein kinase (MAPK) signaling pathways are evolutionally highly conserved [1] and involved in diverse cellular functions, including cell proliferation, differentiation and stress responses. A wide variety of extracellular stimuli induce phosphorylation and activation of MAPKs [2, 3]. For immune cells, these stimuli commonly include cytokines, chemoattractants, reactive oxygen species, antigen–antibody complexes, and pathogen-associated molecules that engage toll-like receptors. MAPKs are serine/threonine kinase activated via phosphorylation of both the threonine and tyrosine residues within the conserved TXY sequence. The three main arms of the MAPK pathway cascade are ERK (extracellular signal-regulated kinase), JNK (c-Jun N-terminal kinase) and p38. They mediate immune cell functional responses to a wide array of stimuli [4, 5]. Activated MAPKs are inactivated through dephosphorylation of threonine and/or tyrosine residues within the activation loop [6]. MAPK dephosphorylation can be mediated by serine/threonine phosphatases, tyrosine phosphatases, and/or dual-specificity phosphatases [7]. However, by far the largest group of protein phosphatases dedicated to the specific regulation of MAPK activity in mammalian cells and tissues are the dual-specificity MAPK phosphatases (MKPs). These phosphatases dephosphorylate both threonine and tyrosine residues within the substrates they target [8].

MAPK pathways play a critical role in the activation of monocytes and macrophages by pathogens, signaling molecules and environmental cues [9–11]. Human and murine monocytes and macrophages express six MKPs (MKP-1, MKP-2, MKP-3, MKP-5, MKP-6 and MKP-7), although MKP-6 has only been reported in murine macrophages [12–20]. However, our understanding of the specific roles of these MKPs in monocyte and macrophages is still very limited. Recent evidence from our group and others suggests that MKP-1 is a central regulator of monocyte and macrophage activation, function and phenotypic fate, and loss of MKP-1 activity in these cells may play an important role in dysregulated inflammatory responses and the onset and development of metabolic and chronic inflammatory diseases, including atherosclerosis [21–25]. The focus of this review will therefore be on MKP-1 and its role in monocyte and macrophage biology in the context of cardiovascular disease.

II. MKP-1 – STRUCTURE, FUNCTIONS AND REGULATION

A. Structure

Although a three dimensional (3D) structure of MKP-1 has not been reported so far, its structure can be predicted with homology modeling using the X-ray crystal structure of MKP-2 (PDB code: 3EZZ) [26] as the template since the sequence identity between the two MKPs is 86% [27], and they have the same amino acid sequence (C–Q–A–G–I–S) in the PTP loop (residues 258–264 for MKP-1), the key component of the active site. The predicted 3D structure for MKP-1 (residues 172–314) based on calculations with ModPipe (<https://salilab.org/modpipe/>) is shown in figure 1.

B. Transcriptional Regulation

MKP-1 expression and activity can be regulated at several levels, including gene transcription, protein stability, and phosphatase activity. This multi-level regulation allows for tight control of MAPKs' activities. MKP-1, the first MKP discovered, was identified as an immediate early gene that is induced rapidly after exposure to growth factors, heat shock and oxidative stress [28–30]. As MKP-1 functions to deactivate MAPKs, it was proposed that MAPKs may activate MKP-1 transcription, as part of a negative feedback mechanism [31, 32]. Indeed, in vascular smooth muscle cells, platelet-derived growth factor (PDGF), phorbol ester, and angiotensin II, which activate ERK, but not JNK or p38, and anisomycin, a potent stimulus for JNK and p38, all induced the transient expression of MKP-1 [33]. In C3H 10T1/2 murine fibroblasts, MKP-1 induction by heat shock and H₂O₂ is primarily dependent on ERK, whereas MKP-1 induction by arsenite and UVC is primarily mediated by p38 [34]. However, in NIH 3T3 fibroblasts, MKP-1 is highly induced by stress through a JNK-mediated process, while ERK has little effect on MKP-1 induction. MKP-1 induction in macrophages by LPS involves all three MAPK subfamilies [35–38]. In addition to the MAPK pathways, members of the protein kinase C (PKC) family have also been shown to regulate MKP-1 induction in a number of systems. In cardiomyocytes treated with angiotensin II, PKC inhibitors or intracellular calcium chelation decrease MKP-1 expression while calcium ionophores increase MKP-1 mRNA levels [39]. PKC ϵ plays a critical role in MKP-1 induction in macrophages [40, 41]. While it is possible that the PKC pathways cross-talk with the MAPK cascades to regulate MKP-1 induction, MAPK-independent pathways may also be involved.

C. Epigenetic Regulation

Epigenetic mechanism has been also suggested to modulate MKP-1 expression. The mRNA expression levels of MKP-1 gene are down-regulated in both prostate cancer and breast cancer, and this downregulation appears to involve DNA methylation [42, 43]. In addition, phosphorylation and acetylation of histone H3 alters the chromatin at the MKP-1 gene locus, increasing the association of RNA polymerase II to the MKP-1 gene promoter and promoting MKP-1 transcription [34].

D. Post-Transcriptional Regulation

Because of the short half-life of MKP-1 mRNA (1 – 2 h) [44], it was generally assumed that MKP-1 expression is primarily transcriptionally regulated. This variation in half-life may stem from the different mechanisms that determine the amount of MKP-1 mRNA that accumulates. Tristetraprolin (TTP), a zinc-finger-containing AU-rich elements (ARE)-binding protein, binds to and destabilizes MKP-1 mRNA [45]. Recently, other post-transcriptional regulatory mechanisms have been shown to regulate MKP-1 levels. RNA-binding proteins HuR (also known as ELAV1) [45, 46], and NF90 [47] were found to associate with the MKP-1 3' untranslated region. HuR both stabilizes the MKP-1 mRNA and promotes its translation [48, 49]. While NF90 also stabilizes the MKP-1 mRNA, binding of NF90 appears to suppress MKP-1 translation [48].

E. Post-translational regulation

A number of post-translational modifications have been identified that modulate MKP-1 activity and stability. The binding of ERK, JNK, or p38 to recombinant MKP-1 increases the activity of the phosphatase [50, 51]. This increase in activity is induced by the interaction between domains in the amino terminus of the phosphatase and an acidic domain at the carboxyl terminus of the kinases. ERK-mediated phosphorylation of the C-terminal residues Ser359 and Ser364 in MKP-1 increases protein stability, thereby reinforcing phosphatase activity and establishing autoregulatory negative feedback control [52]. By contrast, ERK-mediated phosphorylation of the distinct residues Ser296 and Ser323 within MKP-1 results in the recruitment of the ubiquitin ligase SCFskp2, and increases the rate at which MKP-1 is degraded [53, 54]. In addition, MKP-1 is acetylated by p300 on lysine residue (Lys57) within its substrate-binding domain. Acetylation of MKP-1 enhances its interaction with p38, thereby increasing its phosphatase activity and interrupting MAPK signaling [55]. Intestinally, Lys57 is located in close proximity of MKP-1's nuclear localization sequence (NLS: aa 53–55; Fig. 2), but whether acetylation of MKP-1 affects its cellular localization is not known. Little is known about the enzymes regulating MKP-1 deacetylation. However, a recent report suggests that in macrophages class I HDACs (HDAC1, 2, and 3) can deacetylate MKP-1, and that inhibition of HDAC1, -2, and -3 blocks LPS-induced expression of TNF- α , IL-1 β , iNOS (NOS2), and nitrite synthesis [56]. Like protein tyrosine phosphatases (PTPs) [57, 58], MKP-1 contains an essential cysteine residue (Cys258) in the catalytic domain. This site is identical in both murine and human MKP-1. Reactive oxygen species (ROS) have been shown to oxidize the catalytic cysteine and inactivate the enzyme activities in MKP-1 [59, 60]. In addition, MKP-1, once oxidized, undergoes rapid degradation in the proteasome [60]. Moreover, we recently reported that *S*-glutathionylation of MKP-1 catalytic cysteine residue (Cys258), inhibits phosphatase activity, and targets the protein for proteasomal degradation [22]. Interestingly, Guan et al. reported that *S*-nitrosylation of MKP-1 on Cys258 enhances MKP-1 protein stability in cancer cells [61]. Therefore, MKP-1 activity and function appear to be regulated by redox-sensitive mechanisms. Together these data show that the different domains of MKP-1 and their post-translational modifications play distinct roles in substrate affinity, stability, and the catalytic activity (Fig. 2).

F. MKP-1 Substrates

MKPs are highly specific in their ability to recognize and bind to MAPK. However, recent evidence suggests that MKPs may also dephosphorylate non-MAP kinase proteins. For example, based on anti-sense mRNA knockdown experiments, it had been suggested that MKP-1 interacts with and dephosphorylate the signal transducers and activators of transcription (STAT) 1 protein, thus potentially directly regulating transcriptional responses to interferon γ [62], angiotensin II [63] and LPS [64]. However, subsequent *in vitro* assays demonstrated that MKP-1 fails to bind to recombinant STAT1, nor is STAT1 able to stimulate the catalytic activity of MKP-1 towards the chromogenic substrate para-nitrophenyl phosphate [51]. Together, these results strongly suggest that STAT1 is not a MKP-1 substrate and that this phosphatase plays no direct role in the regulation of STAT1-dependent transcriptional regulation in response to interferon γ . Instead, MKP-1 was found to inhibit miR155 expression thereby inducing SOCS-1, which in turn attenuates STAT1

activation [65]. How MKP-1 regulates miR-155 levels remains to be elucidated. More recently, it was reported that histone H3 also interacts with and is dephosphorylated by MKP-1 to mediate epigenetic regulation on vascular endothelial growth factor (VEGF)-induced gene transcription [66]. In agreement with this report, we found that histone H3 phosphorylation (Ser10) was increased in the MKP-1-deficient macrophage exposed to metabolic stress [21], making H3 the only known bona fide non-MAPK substrate candidate for MKP-1.

G. MKP-1 Inhibitors and Inducers

The search for MKP-1 selective inhibitors with cellular activity has been challenging because the X-ray structure of MKP-1 has not been solved, but a number of MKP-1 inhibitors have been identified. The benzo[c]phenanthridine alkaloid, Sanguinarine, was identified as a MKP-1 inhibitor from a cell-based high content screen of a collection of 720 pure natural products and their derivatives [67]. The benzofuran NU-126 was also identified as a MKP-1 inhibitor and showed some selectivity for MKP-1 over MKP-3. However, with an IC₅₀ value for MKP-1 of almost 30 μ M, NU-126 is not very potent [68]. Both PSI2106 and MDF2085 were identified from a pyrrole-2-carboxamide library, and have IC₅₀ values for MKP-1 below 10 μ M, showed greater than 5-fold selectivity for human MKP-1 over MKP-3, and a much greater preference for MKP-1 over Cdc25B, PTP1B, or VHR [69].

Increased MKP-1 expression has been reported in response to a variety of extracellular signals, including growth factors, cytokines, bacterial products such as LPS, as well as micronutrients and phytochemicals (Table 1). Note that in some instances the apparent induction of MKP-1 may be due to mRNA stabilization or reduced MKP-1 degradation [70, 71].

A better understanding of the physiological roles of the MKP-1, particularly in monocytes and macrophages, will pave the way for developing new immunomodulatory therapies for cancer and (chronic) inflammatory diseases. In cancer, MKP-1 inhibitors may prove beneficial, as MKP-1 is overexpressed in tumor cells and is considered responsible for the resistance of JNK-driven apoptotic pathways to activation by chemotherapeutics. Conversely, in inflammatory diseases such as asthma and arthritis, MKP-1 counter-regulates pro-inflammatory MAPK-mediated signaling. Developing novel ligands to upregulate MKP-1 levels and activity would make for a therapeutically attractive anti-inflammatory strategy.

III. MKP-1 – ROLE IN MONOCYTES AND MACROPHAGES

Monocytes and macrophages are essential for tissue and metabolic homeostasis, but in the context of metabolic disorders become dysfunctional and promote chronic inflammatory diseases, including vascular inflammation and atherosclerosis [87–89]. However, the underlying mechanisms are not well-understood. These cells belong to the mononuclear phagocyte system and function as part of the innate immunity to detect and clear invading pathogens as well as dying cells and tissue debris [90]. Macrophages are extremely diverse and adaptive to their microenvironment. They are potent secretory cells of various cytokines in response to “activation” by infectious agents, danger signals and other environmental

cues, and these cytokines have paracrine and autocrine effects within the tissue [91]. Macrophages originate from at least two different sources and the majority of tissue-resident macrophage populations, including splenic red pulp and alveolar macrophages, microglia, Kupffer cells, osteoclasts, Langerhans cells and large peritoneal macrophages, originate from embryonic yolk-sac-derived progenitor cells [92–96]. However, in response to tissue injury there is a vast infiltration of monocyte-derived macrophages that originate from bone marrow hematopoietic stem cells [97–99]. This recruitment of blood monocytes to discrete anatomical locations followed by their differentiation into mature macrophages is a rate-limiting step in multiple physiological processes, including wound repair, pathogen clearance, and replacement of tissue-resident macrophages [100, 101], as well as pathophysiological processes such as atherosclerosis [102].

We and others showed that maintaining protein thiol redox homeostasis is critical for the accurate programming and proper functioning of monocytes and macrophages [99, 103, 104]. Our data demonstrate that chronic exposure of monocytes to metabolic stress disrupts thiol redox homeostasis, resulting in monocyte dysfunction and the conversion of blood monocytes into a pro-inflammatory, pro-atherogenic phenotype, hyper-sensitive to chemoattractant [105, 106]. MKP-1 appears to play a critical role in preventing monocyte and macrophage dysfunction.

A. Monocyte Adhesion and Migration

Recruitment of monocyte-derived macrophages to sites of tissue injury is a hallmark of acute inflammation [107]. The extent of monocyte recruitment and macrophage accumulation is generally believed to be controlled by local inflammatory processes within that tissue [108, 109]. Monocyte recruitment, adhesion and chemotaxis, is regulated by MAPK pathways [110–113]. We previously reported that MKP-1 deficiency induced by metabolic stress results in the hyperactivation of ERK and p38 MAPK and increased monocyte adhesion and migration in response to monocyte chemoattractant protein-1 (MCP-1) and other chemokines, a process we coined “metabolic priming” [22]. With our discovery that chronic metabolic stress primes monocytes for dramatically enhanced responsiveness to chemoattractants and increased monocyte recruitment [22, 105, 106], we identified a completely novel mechanism by which metabolic disorders promote atherosclerosis, and possibly other chronic inflammatory diseases associated with metabolic disorders such as obesity, liver steatosis, kidney diseases and possibly cancer. A report by Grimshaw et al. suggests that early induction (< 90 min) of MKP-1 during monocyte migration by hypoxia or TNF- α treatment, decreases MAPK activation and inhibits monocyte chemotaxis [114]. This mechanism may result in the trapping of newly recruited monocyte-derived macrophages at sites of inflammation or hypoxia. Together, these data suggest that MKP-1 plays a crucial role in monocyte transmigration and the recruitment monocyte-derived macrophages to sites of tissue injury and inflammation.

B. Macrophage Activation and Inflammatory Responses

Macrophage activation and polarization plays a critical role in both inflammation and subsequent inflammation resolution. Dysregulation of macrophage activation and plasticity has been proposed to play a major role in impaired inflammation resolution and the

conversion of local acute inflammation into a chronic process [115]. The classification of macrophage activation states into classical (M1) polarization and alternative (M2) polarization is to a large extent based on the *ex vivo* response of macrophages to Th1 (e.g., IFN- γ and TNF- α) and Th2 (e.g., IL-4, IL-10, and IL-13) cytokines and inadequate to capture the complexity and diversity of macrophage activation states [116]. However, it continues to be broadly utilized to characterize *in vivo* macrophage phenotypes [117]. We reported that MKP-1 deficient macrophages exhibit severally skewed activation profiles, demonstrating an exaggerated pro-inflammatory “M1-like” phenotype in response to INF γ +TNF α and a severely suppressed “M2-like” inflammation resolving phenotype after IL-4 stimulation [21].

MKP-1 was originally described as a stress and growth factor-inducible non-receptor phosphatase able to dephosphorylate all three MAPKs ERK, p38 and JNK [29, 31, 32, 118]. Subsequent studies established that MKP-1 preferentially dephosphorylates p38 and JNK [119, 120]. Consistent with these findings, studies using macrophages from MKP-1 knockout mice and MKP-1 silencing by siRNA in cell lines have shown that impaired MKP-1 leads to increased and prolonged p38 and JNK phosphorylation [24, 121–123]. Despite MKP-1's substrate preference for p38 and JNK, in macrophages activation of ERK is also regulated by MKP-1. For example, in mouse macrophages, inhibition of MKP-1 expression using siRNA prolongs ERK phosphorylation and blocks of M-CSF-dependent proliferation [124]. And as mentioned above, MKP-1 deficiency results in the hyperactivation ERK and increased adhesion in in MCP-1-stimulated monocytes [22].

Given the crucial role of p38 and JNK in the regulation of cytokine biosynthesis and the substrate preference of MKP-1 for these two MAPKs, it was long suspected that MKP-1 may play an important role in the control of cytokine biosynthesis [36]. Compared with wild-type mice, MKP-1-deficient mice produced substantially greater amounts of TNF, IL-1 β , CC-chemokine ligand 2 (CCL2; also known as MCP1), granulocyte/macrophage colony-stimulating factor (GM-CSF), IL-6, IL-10 and IL-12p70 and showed a considerably higher incidence of multi-organ failure and mortality after LPS challenge *in vivo* compared with wild-type mice [25, 121, 122]. These findings are consistent with our report mentioned above that MKP-1 deficiency induced by metabolic stress predisposing macrophages to a hyper-inflammatory M1-like polarization state [21].

Overall, these studies support the concept that MKP-1 is a critical negative regulator of the innate immune response. By modulating the activities of both p38 and JNK as well as ERK, MKP-1 limits both strength and duration of signals triggering the production of inflammatory cytokines. Interestingly, the half-life of the mRNA of several cytokines, including IL-6, IL-10, and TNF, also appears to be controlled by MKP-1 by promoting the translocation of RNA binding proteins from the nucleus to the cytosol [125]. More recent data shows that MKP-1 also modulates the activity of the cytokine mRNA by destabilizing the phosphorylation status of tristetraprolin (TTP), an RNA-destabilizing protein [126].

In addition to regulating macrophage cytokine, chemokine and growth factor synthesis and release, accumulating evidence suggests that MAPKs also regulate autophagy and apoptosis in macrophages [127–129]. We recently reported that both processes are regulated by

MKP-1 and that both genetic and metabolic stress-induced MKP-1 deficiency impairs macrophage autophagy and sensitizes macrophages to oxysterol-induced caspase 3/7 activation and programmed cell death [21]. Moreover, it is known that cigarette smoke decreases MKP-1 activity in the lung [130]. Correspondingly, alveolar macrophages of smokers accumulate both autophagosomes and p62, a marker of autophagic flux acute cigarette smoke exposure was shown to induce apoptosis of alveolar macrophages [131, 132]. Interestingly, MKP-1 induction with Malvidin, a major red wine polyphenol, attenuates PARP activation by LPS in RAW 264.7 macrophages further supporting the notion that MKP-1 plays a critical role in regulating macrophage autophagy and cell death.

IV. MKP-1 – ROLE IN CARDIOVASCULAR DISEASES

A. Atherosclerosis

Atherosclerosis is a chronic inflammatory disease characterized by the infiltration and accumulation of monocyte-derived macrophages and lipid-laden foam cells in the vessel wall [108, 133, 134]. The dysregulation of macrophage activation and functions appears to be a major contributor to the conversion of acute inflammation into a chronic process and to the development and progression of atherosclerotic lesions [87]. Macrophage numbers and functionalities within atherosclerotic lesions and their removal from plaques are controlled by four key processes: recruitment, autophagy, apoptosis, and macrophage polarization. As we have reviewed above, macrophage chemotaxis [110, 111], autophagy [129], apoptosis [127, 128] and activation [135–137] are mediated by mitogen-activated protein kinase (MAPK) pathways, which in turn are counter-regulated by MKP-1 [21, 22]. Two earlier reports had suggested that complete MKP-1 deficiency in apolipoprotein E-null (apoE^{-/-}) mice is atheroprotective [138, 139]. While it is possible that these partial atheroprotective properties of complete MKP-1 deficiency reported in apoE^{-/-} mice are related specifically to apoE deficiency, a more likely explanation is that MKP-1 plays different roles in different cell types. While MKP-1 deficiency in vascular cells may protect against the formation of atherosclerotic lesions, loss of MKP-1 activity in monocytes and macrophages clearly promotes inflammatory responses, macrophage dysfunction and accelerates atherogenesis.

B. Heart failure

Monocytes and macrophages are known to be the major drivers of inflammatory and fibrotic processes in heart failure [140, 141]. However, to date no study has addressed the role of macrophage MKP-1 in heart failure. However, cardiomyocyte apoptosis triggered by RAFTK/pyk2 via p38 was shown to be blocked by MKP-1 overexpression [142]. Heart failure induced by alpha(1B)-adrenergic receptor (alpha(1B)-AR) overexpression was accompanied by reduced MKP-1 expression [143]. Human cardiac tissues from patients with heart failure secondary to rheumatic heart disease show a marked increase p38 activity, and MKP-1 levels are reduced [144]. In contrast, increased MKP-1 levels and reduced JNK and p38 activities were reported in heart tissue from end-stage heart failure patients with idiopathic dilated cardiomyopathy [145]. The reason for these diverging observations is not yet clear.

C. Myocardial infarction

Macrophages are also critical players in the pathophysiological processes induced by myocardial infarction (MI). Shortly after initial MI, a large number of macrophages exhibiting a pro-inflammatory M1-like profile are rapidly recruited to the cardiac tissue, where they contribute to cardiac remodeling [146]. After this initial period, inflammation resolution is initiated in the wound, with the infiltrated macrophages display a predominant anti-inflammatory/pro-resolution M2-like activation profile, promoting cardiac repair by mediating pro-fibrotic responses [141, 147]. Since macrophages in myocardial infarction play a similar role as they do in wound healing, we can speculate the role of macrophage MKP-1 will be similar too. By restricting p38 MAPK activation, in the early phase of tissue repair MKP-1 facilitates the transition of macrophages from a pro- to an inflammation resolving state, and during later stages the progression of macrophages into an “exhaustion-like state” characterized by cytokine silencing, thereby permitting full resolution of inflammation and tissue recovery [148]. In the absence of MKP-1, p38-induced AKT activity suppresses the acquisition of an anti-inflammatory gene program and final cytokine silencing in macrophages, resulting in impaired tissue healing [148].

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ABBREVIATIONS

ANP	Atrial natriuretic peptide
ARE	AU-rich elements
CS	catalytic sequence
DUSP	dual-specificity phosphatases
ERK	extracellular signal-regulated kinase
Grx	glutaredoxin
HA	hyaluronic acid
IFN	Interferon
IL	Interleukin
JNK	c-Jun N-terminal kinase
KBD	kinase binding domain
LPS	Lipopolysaccharides
MAPK	mitogen-activated protein kinase

MCP-1	monocyte chemoattractant protein-1
MI	myocardial infarction
MKP-1	MAPK phosphatase 1
M-CSF	macrophage-colony stimulating factor
NLS	nuclear targeting sequence
PDGF	platelet-derived growth factor
PPAR	peroxisome proliferator-activated receptor
PTP	protein tyrosine phosphatase
ROS	Reactive oxygen species
SOCS	Suppressor of cytokine signaling
STAT	signal transducers and activators of transcription
TNF	Tumor necrosis factor
TTP	Tristetraprolin
VEGF	vascular endothelial growth factor

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HIGHLIGHTS

MKP-1 is a critical counter-regulator of MAPK signaling in monocytes and macrophages

MKP-1 regulates monocyte adhesion and migration

MKP-1 regulates macrophage activation, inflammatory responses and survival.

MKP-1 activity is regulated at the level of transcription, translation and by posttranslational modifications

Figure 1. Calculated 3D Structure of MKP-1 (residues 172–314)

The position of the catalytic residue Cys258 is indicated. This figure was adopted from ModBase. (<https://modbase.compbio.ucsf.edu>, Database ID: P28562).

Figure 2. Structural Features and Sites of Post-Translational Regulation of the Human MKP-1 Protein

The N-terminal domain of MKP-1 is responsible for both nuclear localization, driven by a leucine-rich nuclear localization sequence (NLS), and for binding of MAPK through its specific arginine-rich kinase binding domain (KBD). The highly-conserved C-terminal domain of MKP-1 contains the catalytic domain and its active site sequence (CS) that catalyzes the dephosphorylation of tyrosine/threonine residues of target substrates.

Figure 3. Role of MKP-1 in Monocyte Adhesions, Chemotaxis and The Molecular Mechanisms of Monocyte Priming by Metabolic Stress

Chemoattractants, such as MCP-1 released by the vessel wall activate monocytes (blue) in the blood stream and initiate monocyte recruitment in response to vascular injury. Monocyte transmigration involves adhesion to and chemotaxis through the endothelial layer (pink). Both processes are initiated by protein kinase-dependent signaling pathways and counter-regulated by protein phosphatases (MKP-1). MKP-1 is sensitive to *S*-glutathionylation (●) of the catalytic cysteine residue which is reversed by the thiol transferase glutaredoxin (Grx). Metabolic disorders induce the expression of Nox4 in monocytes, an enzyme that generates reactive oxygen species (ROS) capable of catalyzing the *S*-glutathionylation of MKP-1. In the absence of adequate antioxidant protection, *S*-glutathionylated MKP-1 is rapidly degraded, promoting MKP-1 deficiency, hyper-activation of monocyte adhesion and migration and subsequently the increased accumulation of monocyte-derived macrophages in the injured vessel wall.

Figure 4. Role of MKP-1 in Macrophage Dysfunction induced by Metabolic Stress

Metabolic stress induces MKP-1 *S*-glutathionylation and the subsequent degradation of the phosphatase, and the overall loss of MKP-1 activity. Loss of MKP-1 activity leads to the hyper-responsiveness to chemokines, accelerated chemotaxis and increase recruitment and accumulation of dysfunction monocyte-derived macrophages, characterized by dysregulated activation profiles (M1 versus M2), impaired autophagy and increased sensitivity to oxysterol induced programmed cell death.

Table 1**Inducers of MKP-1 Expression**

Inducer	Cell Type/Tissue	mRNA/Protein	Effect/Function	References
Glucocorticoid	Endothelial cell, macrophages	mRNA	Inflammation ↓	[72–74]
Vitamin D	Monocytes, macrophages	mRNA	Inflammation ↓	[75, 76]
Curcumin	Hippocampal cells	Protein	Ethanol-induced toxicity ↓	[71]
Ursolic acid	Monocytes	Protein	Metabolic stress-induced priming ↓	[70]
Nitroalkenes	Macrophages	mRNA	Inflammation ↓	[64]
VEGF	Endothelial cell	mRNA	Migration ↓	[77]
Thrombin	Endothelial cell	mRNA	Activation ↓	[78]
Atrial natriuretic peptide (ANP)	Endothelial cell	mRNA	Activation ↓	[78, 79]
Retinoids	Mesangial cells	mRNA	Apoptosis ↓	[80]
Trichostatin A, HDAC inhibitor	Macrophages	Protein	Osteoclastogenesis ↓	[81]
Rapamycin, mTOR inhibitor	Macrophages	mRNA	Inflammation ↓	[82]
Clozapine	Frontal cortex (rat)	mRNA	Psychotic action ↓	[83]
High molecular weight hyaluronic acid (HA)	Chondrocytes	Protein	MMP production ↓	[84]
ETYA, peroxisome proliferator-activated receptor (PPAR)-α activator	Astrocytes	mRNA	Inflammation ↓	[85]
Rolipram (PDE4 inhibitor)	Macrophages	mRNA	Inflammation ↓	[86]