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Review Article

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

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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.

1. 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 (DUSP) [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 cardiovas-

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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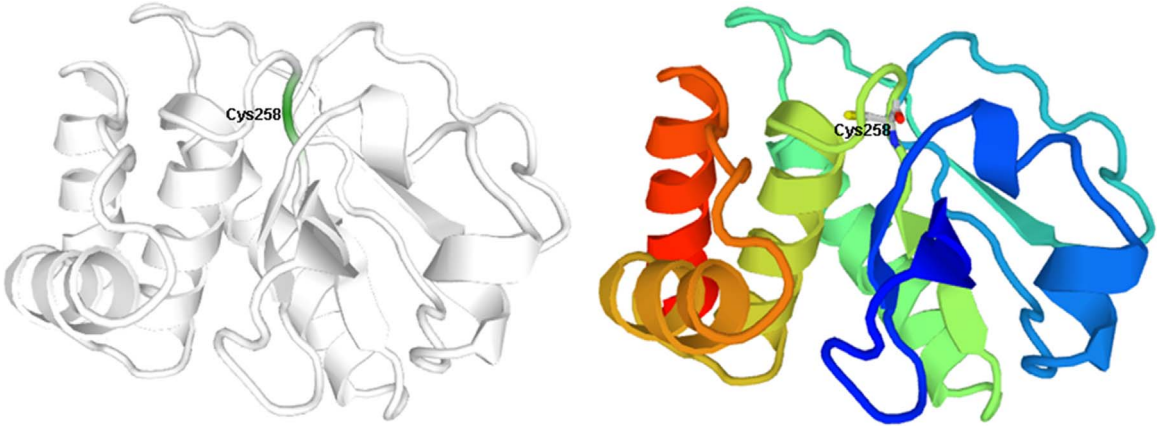

Fig. 1. Calculated 3D Structure of MKP-1 (residues 172–314). The position of the catalytic residue Cys258 is indicated. This figure was adopted from ModBase. (https://modbase.compbio.ucsf.edu, Database ID: P28562).

cular disease.

2. MKP-1 – structure, functions and regulation

2.1. 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 Fig. 1.

2.2. 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 H_2O_2 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]. PKCε 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.

2.3. 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 down-regulation 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].

2.4. 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].

2.5. 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] (Fig. 2). 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]. Interestingly, 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