Published in final edited form as:

Cell Mol Life Sci. 2013 January ; 70(2): 223–237. doi:10.1007/s00018-012-1041-2.

Diversity and specificity of the mitogen-activated protein kinase phosphatase-1 functions

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Abstract

The balance of protein phosphorylation is achieved through the actions of a family of protein serine/threonine kinases called the mitogen-activated protein kinases (MAPKs). The propagation of MAPK signals is attenuated through the actions of the MAPK phosphatases (MKPs). The MKPs specifically inactivate the MAPKs by direct dephosphorylation. The archetypal MKP family member, MKP-1 has garnered much of the attention amongst its ten other MKP family members. Initially viewed to play a redundant role in the control of MAPK signaling, it is now clear that MKP-1 exerts profound regulatory functions on the immune, metabolic, musculoskeletal and nervous systems. This review focuses on the physiological functions of MKP-1 that have been revealed using mouse genetic approaches. The implications from studies using MKP-1-deficient mice to uncover the role of MKP-1 in disease will be discussed.

Keywords

MAP kinase; MAP kinase phosphatase; Cell signaling; Knock-out mouse; Phosphatases; Dephosphorylation

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Introduction

Protein phosphorylation is a reversible process that is maintained in equilibrium by the actions of protein kinases and protein phosphatases. A major signaling pathway involved in the phosphorylation of proteins and transmission of signals that are initiated by extracellular stimuli is the mitogen-activated protein kinase (MAPK) pathway [1, 2]. The MAPKs are serine/threonine kinases that serve to phosphorylate substrates at a consensus motif defined by Xaa-Ser/Thr-Pro [3]. The MAPKs are activated by MAP kinase kinases that phosphorylate the MAPKs at conserved threonine and tyrosine (Thr-Xaa-Tyr) residues within their activation motif [1]. Mammalian MAPKs are widely expressed and consist of three major groups that are classified based upon sequence similarity, differential activation by agonists and substrate specificity. These MAPKs include the extracellular signal-regulated kinases 1 and 2 (ERK1/2), c-Jun NH_2-terminal kinases 1, 2 and 3 (JNK1/2/3), and p38α, β, δ and γ MAPKs [1, 4–6]. When activated, the MAPKs phosphorylate downstream substrates that regulate vital activities in the control of physiological processes including growth, differentiation, apoptosis, immune function, development and metabolism [1].

Since both the magnitude and duration of MAPK activity plays an important role in transducing downstream signals in the control of cellular physiology [7], the inactivation of the MAPKs is as important as its activation. MAPKs are inactivated by dephosphorylation of their conserved regulatory tyrosine and/or threonine residues within the activation loop. Given the dynamic spatio-temporal kinetics of MAPK signaling [8] the most efficient mechanism of MAPK inactivation is mediated through the rapid and direct dephosphorylation of one or both of the regulatory threonine and tyrosine residues [9]. Several phosphatases have been found to dephosphorylate one or both of the conserved threonine and tyrosine residues in the activation loop of the MAPKs to control the magnitude and duration of MAPK activity [9, 10]. The major group of enzymes that mediate MAPK dephosphorylation are those that are members of the protein tyrosine phosphatase superfamily termed the dual-specificity protein phosphatases (DUSPs) [11] (Fig. 1). The DUSPs contain a subgroup of protein tyrosine phosphatases known as the MAPK phosphatases (MKPs) that directly dephosphorylate the MAPKs specifically on both regulatory threonine and tyrosine residues [12, 13]. In mammals, there are ten active MKP family members all of which dephosphorylate the MAPKs with varying degrees of efficiency [14] (Fig. 1). MKPs are generally composed of two domains, the MAPK-binding (MKB) domain in the NH_2-terminus and the dual-specificity phosphatase domain located in the COOH-terminus [12]. The COOH-terminus domain is homologous to the prototypic DUSP VH-1 of vaccinia virus [15]. The NH_2-terminus domain, which is homologous to the rhodanase family of sulphotransferases contains two regions of sequence homology with the catalytic domain of the cdc25 phosphatase (Fig. 1). Much of the diversity amongst the MKPs stems from sequences that extend beyond either the PTP or CH2 domains in the COOH- and NH_2-termini, respectively (Figs. 1, 2).

MKPs are highly specific for the MAPKs and much structural information is now available that provides strong mechanistic insight into the molecular basis for their specificity [16–20]. Based on their sequence similarity, substrate specificity and sub-cellular localization, the MKPs can be divided into three groups; Type I, Type II, and Type III [14, 21]. Type I

MKPs consist of MKP-1/DUSP1, MKP-2/DUSP4, PAC-1/DUSP2, and hVH3/DUSP5 [22–25]. This group of MKPs localizes to the nucleus and is induced by many stimuli that activate the MAPKs. These MKPs play vital roles in the feedback control of MAPK signaling in the nucleus [26–28]. Type II MKPs selectively dephosphorylate ERK1/2 and include MKP-3/DUSP6, PYST2/DUSP7 and MKP-4/DUSP9 and they are localized to the cytoplasm [29–31]. Type III consists of MKP-5/DUSP10, MKP-7/DUSP16 and M3/6/DUSP8 that shuttle between the cytoplasm and nucleus [24, 32, 33]. Despite the fact that the MKPs all have the ability to dephosphorylate the MAPKs, these enzymes show remarkable signaling specificity [11, 34].

In this review, we will focus on the archetypal member of the MKP family, MKP-1. The physiological roles of MKP-1 and the pathophysiological implications of dys-regulated MKP-1 signaling will be reviewed. The function and regulation of MKP-1 will be discussed briefly. However, the reader is directed to more extensive reviews on the structure and regulation of the entire MKP family, which has been discussed comprehensively elsewhere [11]. Much of the data implicating MKP-1 in physiological as well as pathophysiological signaling has been derived from mice lacking the expression of MKP-1. MKP-1-deficient (*mkp-1*$^{-/-}$) mice, which were originally generated by Dorfman et al. [35], have provided an invaluable model system to study the function of MKP-1 in vivo. Here, we will discuss the current view of the physiological functions of MKP-1 and the implications of MKP-1 dysregulation in disease using animal models.

MKP-1 structure and regulation

MKP-1 is also referred to as DUSP1 and is the archetypal member of the MKP family, which was first identified as an immediate-early response gene [23, 36–38] (Fig. 1). MKP-1 is expressed in a wide variety of tissues with the highest levels observed in the heart, lungs and liver [36]. MKP-1 is localized exclusively to the nucleus through a discrete NH_2-terminus LXXLL motif [39]. The catalytic activity of MKP-1 is subject to regulation through its direct interaction with MAPK. Direct binding of ERK1/2, JNK, or p38 MAPK, enhances MKP-1 catalytic activity [40, 41]. MKP-1 mediates its interaction with the MAPKs through a MAPK binding domain or kinase interaction motif [40]. Numerous studies using both in vitro approaches and cultured cells have demonstrated that MKP-1 preferentially dephosphorylates p38 MAPK and JNK and to a much lesser extent ERK1/2 [15, 27, 42, 43].

The expression, activity, and function of MKP-1 are subject to diverse levels of regulation by extracellular stimuli. The basal expression of MKP-1 in many cell types is relatively low. However, in response to stimuli such as growth factors or stress MKP-1 is rapidly induced as an immediate-early gene [43]. The MAPKs themselves have been shown to be potent inducers of MKP-1 transcriptional activation thereby providing a well-defined negative feedback loop between the MAPKs and MKP-1. In addition to the MAPKs as inducers of MKP-1 expression, it was found that the transcription factor CCAAT/enhancer binding protein-β (C/EBPβ) is essential for the induction of MKP-1 in macrophages [44]. Following its transcriptional activation, MKP-1 is dynamically controlled at the level of mRNA stability. It was demonstrated that in response to oxidative stress MKP-1 mRNA stability

was enhanced, which, was partly mediated by the RNA binding proteins HuR and NF90 [45, 46]. In contrast, the AU-rich element binding protein tristetraprolin has been found to degrade MKP-1 mRNA [47, 48]. Other second messengers such as calcium also regulate the expression of MKP-1. Fibroblasts treated with the Ca^{2+} chelating agent BAPTA are significantly impaired in their ability to induce the expression of MKP-1 in response to serum [49]. Zhu et al. found that MKP-1 expression was inhibited by miR-101, which enhanced p38 MAPK and JNK activation in macrophages [50]. Collectively, these and other studies highlight the complex regulatory mechanisms that are engaged in order to regulate MKP-1 expression.

Additional modes of MKP-1 control occur at the level of protein stability. It has been reported that the stability of MKP-1 is enhanced upon ERK1/2 phosphorylation on serine 359 and serine 364 of MKP-1 [51]. Other studies showed that ERK1/2 phosphorylation on serine 296 of MKP-1 decreased its stability through a proteolysis mechanism involving the ubiquitin ligase SCF^{Skp2}, thereby prolonging ERK1/2 activity [52, 53]. Although it is clear that ERK1/2 phosphorylates MKP-1 at multiple residues the physiological significance of this phosphorylation on MKP-1-directed feedback on to the MAPKs remains to be fully resolved. More recently, it was shown that MKP-1 was acetylated in response to LPS treatment in macrophages by p300/CBP on lysine 57 within its substrate-binding domain [54]. Acetylation of MKP-1 increases its interaction with p38 MAPK thereby enhancing its phosphatase activity leading to decreased p38 MAPK phosphorylation. Also Kassel et al. showed that glucocorticoids enhanced the expression of MKP-1 transcription and decreased the proteosomal degradation of MKP-1 that was triggered by activation of mast cells [55]. These findings show that MKP-1 is regulated at both the transcriptional and post-translational levels to control MAPK activity.

MKP-1: a critical signaling node in the MAPK pathway

Within the intact organism the MAPKs act simultaneously and in many cases on the same substrate to exert either a positive or negative biological outcome. The complexity of downstream MAPK substrate phosphorylation likely explains, at least in part, how the MAPKs are involved in such a multitude of signaling pathways. Since MKP-1 has the capacity to dephosphorylate multiple MAPKs, within the nucleus, it serves as an important conduit through which the transmission of both positive and negative signals conveyed by the MAPKs is controlled. Therefore, MKP-1 represents a convergence point or what can be referred to as a “critical node” in the MAPK pathway. For this reason, it is seemingly more difficult than it appears to predict whether MKP-1 plays a positive or negative role in a particular pathway given its capacity to regulate multiple MAPK pathways that convey different signals on their downstream substrates. Hence, predicting the phenotypic response of mice lacking MKP-1 is not always a simple reflection of the actions of a single MAPK effect. As we will discuss, there are several cases where MKP-1 deficiency has revealed a positive, rather than a negative effect on downstream signaling.

Physiological and pathophysiological roles of MKP-1

MKP-1 is one of ten MKP family members, and it was not particularly surprising that when deleted in mice neither developmental nor post-developmental phenotypes were observed

[35]. To some extent the absence of a phenotype in mice lacking the expression of MKP-1 was generally consistent with the early view that the MKPs would likely play redundant physiological roles since they all were capable of dephosphorylating the MAPKs. Although ERK1/2 signaling was unaltered in fibroblasts derived from MKP-1-deficient mice [35, 56], work from this laboratory demonstrated that the stress-responsive MAPKs, JNK and p38 MAPK, were enhanced in their levels of activation in these cells [56]. These experiments were the first to demonstrate using genetic approaches an essential role for MKP-1 in the inactivation of the stress-responsive MAPKs.

MKP-1 in the immune system

The MAPKs are responsible for a variety of processes in the immune system including the transcriptional activation of cytokines, chemokines and other inflammatory mediators that are involved in combating infections [57]. Given the longstanding appreciation for the importance of the MAPKs in the immunological system the role that the MKPs played remained unclear until four studies published at around the same time showed that MKP-1 is a critical negative regulator of immunological signaling in macrophages [27, 58–60] (Fig. 3).

One of the major immunological functions is the defense of the body against pathogens, and that task is charged to the innate immune system. A complex assortment of cell surface receptors, known as the Toll-like receptors (TLRs), signal via pathways leading to the expression of anti- and pro-inflammatory cytokines and chemokines. The MAPK pathway is robustly activated in response to TLR-4 engagement. Using *mkp-1*$^{-/-}$ mice as a model system, work form this laboratory [27] along with three others [58–60], demonstrated that MKP-1 is a negative regulator of MAPK-mediated inflammatory responses in macrophages and dendritic cells. Importantly, all of these groups demonstrated that in *mkp-1*$^{-/-}$ mice MAPK activation was enhanced [27, 58–60]. We showed that the induction of MKP-1 in response to TLR-4 stimulation is mediated by both myeloid differentiation factor 88 (MyD88) and the TIR domain-containing adaptor-inducing IFN-β (TRIF) [27]. In response to low doses of LPS-induced toxicity, *mkp-1*$^{-/-}$ mice displayed substantially higher levels of pro-inflammatory cytokines such as TNF-α, IL-6, IL-12, MCP-1, and IFN-γ whereas later on the anti-inflammatory cytokine IL-10 was elevated [27, 59]. These results suggested that MKP-1 was involved in a temporal mode of cytokine regulation where it is initially high enough to suppress p38 MAPK and JNK activities in order to limit pro-inflammatory cytokine production, and then later on, its levels are sufficiently depressed to permit the expression of IL-10, an anti-inflammatory cytokine [27]. This mode of temporal MKP-1 regulation highlights the dynamic involvement for MKP-1 regulation of the MAPKs in the immune system (Fig. 3).

Using a global microarray analysis of approximately 14,000 mouse genes Hammer et al. reported that 608 genes were upregulated in spleen derived from *mkp-1*$^{-/-}$ mice compared with wild-type mice following LPS stimulation. These included IL-6 and IL-10 in addition to some chemokines [58] although IFN-γ and IL-12 were unchanged in *mkp-1*$^{-/-}$ mice [58]. Consistent with the phenotype of enhanced pro-inflammatory cytokines, *mkp-1*$^{-/-}$ mice exhibited kidney failure, severe hypotension, inflammatory infiltrates in the lung and other

tissues and impaired circulation compared with wild-type mice [61]. These responses are hallmarks of septic shock, which likely accounts for the increased mortality of *mkp-1*$^{-/-}$ mice when exposed to LPS [27].

The role of MKP-1 in protecting against endotoxic insult has been demonstrated in other animal models. In the animal model of periodontitis, which represents a chronic oral inflammation that involves the bone, injection of LPS locally in the palatal region of the oral cavity of *mkp-1*$^{-/-}$mice exacerbates bone loss and induces an enhanced inflammatory response [62]. In addition, osteoclastogenesis was enhanced in *mkp-1*$^{-/-}$ mice in local regions associated with increased levels of inflammation. These results suggest that MKP-1 is protective in periodontitis-associated inflammation and bone loss. Similar results where *mkp-1*$^{-/-}$ mice have been found to be hypersensitive to challenges with peptidoglycan, lipoteichoic acid, live, or heat-killed *Staphylococcus aureus* bacteria have been observed [63].

MKP-1 regulates both pro- and anti-inflammatory cytokines at multiple stages of their biosynthesis. Recently, it was shown that overexpression of MKP-1 decreased the half-lives of IL-6, IL-10 and TNF-α mRNAs in LPS-stimulated rat macrophages [64]. However, in bone marrow-derived macrophages from *mkp-1*$^{-/-}$ mice the half-lives of IL-6, IL-10, and TNF-α mRNAs were enhanced in comparison with cells from wild-type mice. Interestingly, it was suggested that MKP-1 promoted the translocation of RNA binding proteins from the nucleus to the cytosol in response to LPS [64]. This suggests that MKP-1 may also mediate cytokine mRNA stability by engaging the localization machinery of RNA binding proteins.

Although there has been much work towards understanding the role of MKP-1 in the innate immune response, other hematopoietic cells participate. Mast cells are distributed in many tissues throughout the body and are among the key effector cells in inflammatory reactions and in the innate immune response. Several studies have examined the role of MKP-1 in these cells. It was reported that both dexamethasone and p38 MAPK inhibition repressed stem cell factor-induced migration of rat peritoneal mast cells [65]. Dexamethasone also induced robust expression of MKP-1 and blocked stem cell factor-induced p38 MAPK activation. The study further demonstrated that stem cell factor-induced secretion of inflammatory cytokines was significantly blocked in response to dexamethasone or p38 MAPK inhibition [65]. Another study demonstrated that *mkp-1*$^{-/-}$ mice enhanced mast cell degranulation and were highly susceptible to anaphylaxis compared with wild-type mice, although glucocorticoids inhibited these effects [66]. This study also showed that glucocorticoid-mediated inactivation of ERK1/2 by IgE receptor cross-linking was unaffected in bone marrow-derived mast cells from *mkp-1*$^{-/-}$ mice. Collectively, these observations suggest that glucocorticoid-induced expression of MKP-1 partly regulates the inflammatory response by inhibiting cytokine secretion.

MKP-1 in adaptive immunity

A considerable amount of evidence has established a role for MKP-1 as a negative regulator of innate immunity. Similar to the innate immune response, adaptive immunity is also regulated by the MAPKs and hence the implication for a role of MKP-1. The thymus is important for the development of functional T cells which is mediated by T cell receptor

specificity [67]. It has been demonstrated that the expression of MKP-1 was significantly enhanced during the progression of cells from CD4/CD8-double positive T cells to the CD4 single positive stage [68]. T cells isolated from *mkp-1*$^{-/-}$ mice exhibited decreased activation, growth, and *Th1* and *Th17* function as measured by anti-CD3-induced IL-2 production in vitro, which correlated with increased JNK activation and decreased translocation of NFATc1 into the nucleus [69]. Consistent with this finding the study also showed that *mkp-1*$^{-/-}$ mice were deficient in anti-influenza immunity but were unaffected in a model of auto-immune encephalomyelitis [69]. Zhang and co-workers also examined the kinetics of MAPK signaling in response to PMA and ionomycin and found that JNK and ERK1/2 phosphorylation was increased in CD4^{+} T-cells derived from *mkp-1*$^{-/-}$ mice as compared with wild-type mice [69]. In contrast to ERK1/2 and JNK signaling, p38 MAPK activation was unaltered in CD4^{+} T-cells in *mkp-1*$^{-/-}$ mice as compared with wild-type mice. This suggests that MKP-1 negatively regulates JNK and ERK1/2 signaling in T-cells but not p38 MAPK. This finding is in contrast to the regulation of MAPK by MKP-1 in macrophages further highlighting cell type specific functions of MKP-1.

In a model of severe combined immunodeficiency with endotoxemia in mice Luo et al. found decreased MKP-1 and increased TNF-α mRNA expression in peritoneal macrophages derived from SCID mice in comparison with cells from wild-type littermates prior to and following treatment with LPS [70]. Interestingly, when thioglycollate-treated macrophages were co-cultured with pan-T-cells, the expression of MKP-1 mRNA and protein increased and the expression levels of TNF-α and IL-6 were reduced as compared with wild-type macrophages. This suggests that pan-T-cells could indirectly increase the expression of MKP-1 in macrophages thereby regulating the secretion of pro-inflammatory cytokines through an adaptive immune response. Further evidence for a role for MKP-1 in adaptive immunity was provided by Srivastava et al. who reported that the expression of MKP-1 was considerably increased following *L. major* infection in macrophages whereas, high doses of anti-CD40 reduced the expression of MKP-1 which was associated with increased phosphorylation of p38 MAPK [71]. Also inhibition of MKP-1 expression using triptolide and lentivirally expressed MKP-1 shRNA improved CD40-induced anti-leishmanial functions and was beneficial to mice prone to *L. major* infection. These findings suggest that MKP-1 acts a negative regulator of p38 MAPK in *L. major* microbial pathogenesis.

Dendritic cells (DCs) are the main cells responsible for transforming innate signals into adaptive immune responses. However, the mechanisms governing how DCs serve as a conduit between the intrinsic T-cell pathways and the innate immune system remain unclear. Recently, this question was examined by Huang and co-workers who showed a role for MKP-1 in mediating cross-talk between the innate response and the effector T-cell response [72]. These studies demonstrated that MKP-1 expression and activity in DCs were increased in response to signals that mainly elicit the Th1 response, and this correlated with p38 MAPK dephosphorylation in DCs. DCs from *mkp-1*$^{-/-}$mice had a decreased capacity to induce IFN-γ production from T cells and the Th1 response, but an increased activity to drive the Th17 response, in comparison with DCs from wild-type mice. Moreover, MKP-1 signaling in DCs regulated the reciprocal induction of Th1 versus Th17 CD4^{+} T-cells by modulating p38 MAPK activity and the production of IL-12 and IL-6. Collectively, these

studies show a novel role for MKP-1 as an integrator of signals from DCs to the Th1 and Th17 lineages by p38 MAPK dephosphorylation.

MKP-1 in metabolism

Metabolic syndrome is a worldwide problem that constitutes a constellation of pathophysiological syndromes that together increase the risk of developing cardiovascular disease, diabetes and stroke [73]. Although the precise cause for the development of metabolic syndrome is unclear the central associating factors are obesity and insulin resistance [73]. Other risk factors include increasing age, genetic susceptibility, hormonal changes and diet. Because of the growing obesity problem and associated metabolic syndrome there is a substantial amount of effort being made towards identifying the molecules that participate in the regulation of metabolic homeostasis with the long-term goal of identifying potential therapeutic targets. Whether the MKPs influence metabolic homeostasis had remained an open question.

The MAPKs have previously been implicated in the regulation of metabolic homeostasis mainly through targeting the phosphorylation of transcription factors that control processes such as adipogenesis, insulin signaling, glucose uptake, fatty acid metabolism, lipogenesis, and energy expenditure [74–81]. Although a role for the MKPs in the regulation of metabolic homeostasis seemed likely, it was work from this laboratory that demonstrated that MKP-1 plays an important physiological role in metabolism and potentially a pathophysiological role in the progression of obesity and metabolic syndrome [82–84]. It is also noteworthy that other MKPs are emerging as important players in metabolic signaling [85, 86].

We reported that *mkp-1*$^{-/-}$ mice on the original C57BL6/Balbc background generated by Dorfman et al. [35] were resistant to weight gain [84]. Even when bred to a pure C57BL/6 background *mkp-1*$^{-/-}$ mice remain resistant to weight gain when placed on a high-fat diet arguing against this metabolic phenotype being a result of modifier alleles and/or strain-specific differences [83, 84]. By analyzing the metabolism of these mice we were able to determine that *mkp-1*$^{-/-}$ mice expended significantly more energy than wild-type mice despite having equivalent levels of activity. Remarkably, even though *mkp–1*$^{-/-}$mice were lean on a high-fat diet these mice developed glucose intolerance yet remained resistant to the development of hepatic steatosis [84]. Hence, the surprising findings from these studies was that MKP-1 negatively regulates energy expenditure and body mass. How MKP-1 is evoking this effect still remains to be fully resolved. However, several targets of MKP-1-mediated MAPK phosphorylation have been identified [82, 83] that provide, at least in part, some level of an explanation for this phenotype.

Consistent with a role for MKP-1 as a negative regulator of the MAPKs, JNK, and p38 MAPK were found to be enhanced in the liver, white adipose and skeletal muscle tissues of *mkp-1*$^{-/-}$ whereas ERK1/2 was enhanced only in the liver [84]. The observation that JNK phosphorylation was enhanced in *mkp-1*$^{-/-}$ mice was somewhat at odds with data demonstrating that JNK activation promoted both obesity and insulin resistance [76]. However, we reconciled this by demonstrating that JNK and p38 MAPK activities were enhanced in the nucleus, but not in the cytosol, consistent with the nuclear localization of

MKP-1 [39, 84]. Thus, enhanced JNK signaling in the nucleus of the livers of MKP-1-deficient mice occurred independently to that of JNK signaling in the cytosol which was presumably subject to dysfunctional signaling leading to insulin resistance in obese mice (Fig. 4). These data provided genetic evidence for the concept of compartmentalized MAPK/MKP-1 nuclear signaling and supported the idea that MKP-1 regulates the nuclear pool of MAPKs in a spatially and functionally distinct manner in order to control metabolic homeostasis.

Our lab has also examined the role of MKP-1 in the regulation of skeletal muscle myofiber composition in obesity. An assessment of the oxidative capacity in skeletal muscle revealed that following 16 weeks on a high fat diet, muscle derived from *mkp-1*$^{-/-}$ mice had increased oxidative capacity in comparison with wild-type mice [83]. It has been suggested that the switch from oxidative to glycolytic myofibers contributes to obesity, presumably because glycolytic myofibers consume less energy [87]. In *mkp-1*$^{-/-}$ mice oxidative myofiber composition is maintained whereas wild-type mice exhibit a significant loss of oxidative myofibers, hence shifting energy balance [83]. We found that during high fat diet-feeding MKP-1 expression is upregulated suggesting that it promotes the loss of oxidative myofiber content an event that could promote susceptibility to metabolic dysfunction. Mechanistically, overexpression of MKP-1 inhibited the expression of PGC-1α, a master regulator of mitochondrial biogenesis and energy expenditure by impairing p38 MAPK-mediated PGC-1α phosphorylation, which reduced both its stability and co-activating activity [83]. Hence, MKP-1 coordinates energy sensing pathways by controlling the ability of p38 MAPK to modulate mitochondrial function through PGC-1α phosphorylation (Fig. 4).

Studies from this lab have also utilized *mkp-1*$^{-/-}$ mice that were intercrossed with the leptin receptor-deficient (*db/db*) mice to demonstrate that MKP-1 plays an important role in attenuating lipogenesis. When *mkp-1*$^{-/-}$ mice were intercrossed with leptin receptor-deficient mice the livers of these mice were markedly less steatotic in comparison with wild-type mice [88]. The resistance to the development of hepatic steatosis was partly due to enhanced hepatic *β*-oxidation in the livers of *db/db;mkp-1*$^{-/-}$ [88]. Interestingly, it was found following a genome-wide microarray analysis that the livers of *db/db;mkp-1*$^{-/-}$were enriched for a sub-set of peroxisome proliferator-activated receptor-*γ* (PPAR*γ*) target genes that were highly repressed [88]. In the liver, PPAR*γ* expression is relatively low as compared with other tissues in the body [89]. However, PPAR*γ*1, which plays an important role in lipid metabolism, is overexpressed in obesity and promotes the development of hepatic steatosis [90–92]. Hence, the observation that the livers of *db/db;mkp-1*$^{-/-}$ mice were resistant to hepatic steatosis is consistent with the idea that MKP-1 regulates lipogenesis through PPAR*γ*. The two most highly repressed PPAR*γ* target genes identified in *db/db;mkp-1*$^{-/-}$ mice were the cell death-inducing DFFA-like effector A (CIDEA) and CIDEC/fat-specific protein 27 (FSP27) [82]. Interestingly, FSP27 is overexpressed in obesity and promotes the accumulation of fat in the liver [92, 93]. Further mechanistic analyses, revealed that MKP-1 attenuated lipogenesis by limiting MAPK phosphorylation of the inhibitory Ser112 residue on PPAR*γ* [88]. These data argue for a mechanism whereby MKP-1 is required for PPAR*γ* activation (Fig. 4). Consistent with this, hepatocytes derived

from *mkp-1*$^{-/-}$ mice when treated with the PPARγ agonist, rosiglitazone, are impaired in PPARγ activation and lipid droplet formation [88]. These results demonstrate an important role for MKP-1 in promoting hepatic lipid metabolism. It is noteworthy that in our studies and those of others [94] that MKP-1 expression is upregulated in the livers of both diet-induced obese and genetically obese mice suggesting that MKP-1 plays an important role in the progression of fatty liver disease.

Collectively, the studies conducted in our lab [82–84] imply that inhibition of MKP-1 may provide a novel therapeutic strategy for the treatment of metabolic syndrome. Targeted inhibition of hepatic MKP-1 in obese patients using anti-sense approaches may have therapeutic value in the treatment of hepatic steatosis. Intuitively, MKP-1 inhibition, resulting in enhanced MAPK signaling would be anticipated to be deleterious rather than beneficial in the treatment of metabolic disorders. However, it is important to note that MKP-1 inhibition would result in the enhancement of the nuclear-restricted pool of MAPKs rather than the total cellular MAPK pool, an important distinction that is likely to be one reason that *mkp-1*$^{-/-}$mice exhibit little apparent phenotype under unchallenged conditions [35]. It still needs to be determined whether MKP-1 is overexpressed in obesity and type II diabetes in humans. Provocatively, MKP-1 expression levels are repressed in humans following bariatric surgery [95], suggesting a correlation between MKP-1 expression and fat mass. It is also unclear which tissue represents the major site through which MKP-1 influences its effect on metabolism. Future work will require metabolic analysis of MKP-1 tissue-specific deleted mice.

MKP-1 in other tissue systems

Cardiovascular system

Atherosclerosis is the major cause of several cardiovascular-related diseases including coronary syndrome and stroke [96]. The MAPK signaling pathway has been implicated in atherogenesis. For example, Ricci et al. demonstrated the involvement of JNK in the formation of foam cells during atherogenesis [97]. It has been shown that in response to an atherogenic diet the expression of MKP-1 mRNA was enhanced in atherosclerotic lesions of ApoE$^{-/-}$ mice [94]. Other studies have shown that *mkp-1*$^{-/-}$ mice displayed considerably less aortic root athero-sclerotic lesion formation compared with *mkp-1*$^{+/+}$ mice [98]. The reduction in atherosclerosis correlates with reduced plasma levels of IL-1α and TNFα, and enhanced expression levels of the anti-inflammatory cytokine IL-10. In addition, *mkp-1*$^{-/-}$ mice have higher levels of plasma SDF-1α that is negatively correlated with atherosclerotic lesion size. Importantly, transplantation of wild-type bone marrow rescued the decreased atherosclerotic lesion observed in *mkp-1*$^{-/-}$ mice [98]. This study highlights the involvement of MKP-1 in the pathogenesis of atherosclerosis, which appears to be dependent upon macrophage-mediated responses.

In a separate study, *mkp-1*$^{-/-}$/ApoE$^{-/-}$ mice were generated, and this group found that the area of atherosclerotic and *en face* lesions along the aorta were significantly lower in *mkp-1*$^{-/-}$/ApoE$^{-/-}$ mice when compared with ApoE$^{-/-}$ mice [99]. The lipid profile showed that total cholesterol and very low-density lipoprotein/low-density lipoprotein levels were reduced in comparison with ApoE$^{-/-}$ mice. The authors further showed that MCP-1 serum

levels from *mkp-1*$^{-/-}$/ApoE$^{-/-}$mice was reduced and was associated with a decreased ability to promote monocyte migration in vitro [99]. This suggests that MKP-1 deletion in ApoE$^{-/-}$ mice reduces atherogenesis, which is mediated by decreased macrophage accumulation. Intuitively, one would have anticipated that given the role of MKP-1 in limiting macrophage activation that loss of MKP-1 in ApoE$^{-/-}$ mice would have exacerbated rather than reduced the development of atherosclerotic lesions. This observation exemplifies the difficulty in attempting to ascribe the functional role of MKP-1 in any given system or disease process based either upon its actions in other tissues and/or its propensity to dephosphorylate a particular MAPK. However, the encouraging message here is that inhibition of MKP-1 would be expected to provide a positive therapeutic value in the area of treating atherosclerosis.

Atherosclerotic plaques are generated as a result of the accumulation of different cell types including endothelial cells, macrophages and fibroblasts. Different sites within the blood vessel appear to exhibit either susceptibility or resistance to the development of atherosclerotic plaques. Mice deficient in MKP-1 express increased levels of caspase 3 in endothelial cells at athero-protected sites [100]. Based on these observations, it is suggested that endothelial cells in athero-protected sites exhibit reduced apoptosis as a result of MKP-1-mediated inhibition of JNK. It is not clear why MKP-1 appears to differentially exert its effect on JNK in athero-protected as compared with athero-susceptible sites in the blood vessel. However, one might speculate that it could be related to local environmental stresses exerted on endothelial cells in certain regions of the blood vessel.

Since the MAPKs play a role in cardiac pathophysiology, it is certainly possible that the MKPs are likely to be involved in cardiac disease. However, connecting the effects of MKP-1 in animal model systems to heart disease has proved difficult and few studies have investigated this area. It has been shown that in response to chronic hypoxia, *mkp-1*$^{-/-}$ mice had higher right ventricular pressures, right ventricular hypertrophy and enhanced vascular remodeling [101]. Conversely, the right ventricular systolic pressures and the medial wall thickness of vessels were considerably higher in the *mkp-1*$^{-/-}$ mice compared with wild-type littermates after 4 weeks of hypobaric hypoxia. In addition, *mkp-1*$^{-/-}$ mice displayed decreased levels of eNOS and NO production in the lungs in comparison with wild-type mice following chronic hypoxic exposure. The protein levels of both arginase I and arginase II were increased in the lungs of hypoxic *mkp-1*$^{-/-}$ mice compared with wild-type mice [101]. These results suggest that MKP-1 negatively influences the process of vascular remodeling during hypoxia.

MKP-1 in the musculoskeletal system

The musculoskeletal system provides the structural components required for support, structural integrity and locomotion in the body. The musculoskeletal system comprises the skeleton, muscle, tendons, cartilage, ligaments and other connective tissue. The involvement of the MKPs in the musculoskeletal system has been demonstrated specifically in its role in the skeletal muscle system and bone. Skeletal myogenesis occurs during embryogenesis and in adult skeletal muscle after injury [102]. Myogenesis is a finely coordinated and tightly regulated process in which myoblasts, after cycles of replication, fuse into multinucleated

myotubes [103]. Adult skeletal muscle fibers are post-mitotic with quiescent satellite cells called muscle stem cells localizing between the sarcolemma and basal lamina. Upon damage, muscle stem cells are activated, undergo cycles of replication and enter into the process of differentiation [102, 103]. Among the many cascades of signaling pathways that regulate myogenesis, the MAPKs, especially p38 MAPK, have been established as critical players [104–112]. Yet, how the MKPs function during myogenic progression remains to be fully determined.

The first report on the role of the MKPs in skeletal myogenesis was described in studies investigating the actions of MKP-1. We found that when overexpressed in myoblasts MKP-1 induced precocious differentiation in the presence of growth factors that normally suppress differentiation [113]. In contrast, overexpression of MKP-1 during differentiation prevents the formation of multinucleated myotubes [113]. These early findings suggested that MKP-1, and hence the MAPKs, plays distinct roles in myogenic progression. More recently, using *mkp-1*$^{-/-}$mice we showed that MKP-1 is required for regenerative myogenesis [114]. In response to injury, skeletal muscles from *mkp-1*$^{-/-}$ mice failed to undergo normal regenerative myogenesis [114]. We noted that muscle stem cells derived from *mkp-1*$^{-/-}$ mice were impaired in their ability to proliferate. In addition, within the damaged regenerating area the inflammatory response was enhanced [114]. These results suggested that both the inability of satellite cells to proliferate, in addition to the enhanced inflammatory response, contributed to the failure of *mkp-1*$^{-/-}$ mice to respond to injury and repair muscle. The role of the MKPs in skeletal muscle disease has not been well defined. We intercrossed *mkp-1*$^{-/-}$ mice with a mouse model of Duchenne muscular dystrophy (*mdx* mouse) in order to examine the effects of MKP-1 on the dystrophic phenotype. We found that the dystrophic phenotype of the MKP-1-deficient *mdx* mouse was dramatically exacerbated [114]. These results suggest that MKP-1, and hence the MAPKs, are involved in the progression of dystrophic muscle diseases. However, it is not yet known what the status of MKP-1 expression is in dystrophic muscle and the activities of the MAPKs in dystrophic muscle remains controversial. Further studies examining the expression of MKP-1 and MAPKs in humans with dystrophic muscle disease as well as tissue-specific deletion of MKP-1 in both the macrophage and muscle stem cell lineages will be required to fully understand the role of MKP-1 in muscle wasting diseases.

The maintenance of bone mass occurs through the balance between the activities of bone forming osteoblasts and bone destroying osteoclasts. Using a bone marrow ablation model to study the role of MKP-1 Carlson et al. discovered that MKP-1 negatively regulates bone formation [115]. They showed that following bone marrow ablation, *mkp-1*$^{-/-}$ mice exhibited increased total bone content and subcortical bone content [115]. Prior to bone marrow ablation, the basal total bone content between male *mkp-1*$^{+/+}$ and *mkp-1*$^{-/-}$ mice were equivalent [116]. In *mkp-1*$^{-/-}$ female ovariectomized mice bone mass is reduced suggesting that MKP-1 participates in a positive manner to influence bone mass in females [116]. Finally, osteoclasts derived from *mkp-1*$^{-/-}$ mice exhibit enhanced MAPK activation in response to receptor activator of nuclear factor-kappaβ stimulation demonstrating that MKP-1 plays an essential role in attenuating MAPK activation in osteoclasts [116].

Osteoblasts are bone-forming cells and these cells are in an intimate balance with the actions of the osteoclasts to maintain bone homeostasis. Mahalingam et al. demonstrated that MKP-1-deficient osteoblasts are delayed in their ability to differentiate likely due to the hyperproliferation of MKP-1-deficient osteoblasts [117]. Although these authors suggested a role for MKP-1 in dephosphorylating ERK1/2 in osteoblasts, the involvement of MKP-1 dephosphorylating either p38 MAPK and/or JNK was not excluded. Nevertheless, these studies are supportive of an important role for MKP-1 in bone homeostasis.

MKP-1 in nervous system

There is an overwhelming amount of evidence for the involvement of the MAPKs in the brain [118]. The MAPKs have been implicated in functions such as memory and learning, neuronal plasticity and development. However, the role of MKP-1 in the brain had not been investigated. Two recent studies have shed light on the role of MKP-1 in the brain. Jeannetau et al. [119] showed that the expression of MKP-1 in cultured developing inhibitory and excitatory neurons is low but can be rapidly increased following treatment with brain-derived neurotrophic factor (BDNF) [119]. Furthermore, in response to BDNF, neurons derived from *mkp-1*$^{-/-}$ mice displayed reduced primary branch formation compared with wild-type neurons. Importantly, JNK activity is prolonged in MKP-1-deficient neurons compared with wild-type cells in response to BDNF suggesting that JNK is a major target of MKP-1 in neurons and that MKP-1 is a downstream target of BDNF signaling that is essential for axonal branching [119].

MKP-1 has also been implicated in pathophysiological processes that occur in the brain. In the hippocampal region of post-mortem human brain taken from patients with major depressive disorders MKP-1 expression is significantly increased [120]. MKP-1 was also enhanced in the hippocampus in a rat model of chronic unpredictable stress, which is a model of depressive behavior [120]. Treatment with anti-depressants stabilizes stress-induced expression of MKP-1 and behavior, and *mkp-1*$^{-/-}$ mice developed resistance to stress. In response to chronic unpredictable stress the consumption of sucrose in *mkp-1*$^{-/-}$ mice was considerably higher as compared with wild-type littermates [120]. In addition, the phosphorylation of ERK1/2 was substantially increased in the hippocampus of *mkp-1*$^{-/-}$mice in comparison with wild-type mice following chronic unpredictable stress. These studies demonstrated that MKP-1 plays a vital role in the pathophysiology of depressive disorders. Kristiansen et al., found that MKP-1 expression was significantly enhanced after NGF withdrawal in sympathetic neurons [121]. Moreover, overexpression of MKP-1 blocked JNK-mediated phosphorylation of c-Jun and inhibited cell death in sympathetic neurons. In contrast, knockdown of MKP-1 increased NGF withdrawal-induced apoptosis. Kristiansen et al. also demonstrated that at P1, superior cervical ganglia derived from *mkp-1*$^{-/-}$ mice displayed significantly increased cell death compared with wild-type mice [121]. These results were argued to explain the reduced sympathetic neuron number in the superior cervical ganglion in *mkp-1*$^{-/-}$ mice. This indicates that in sympathetic neurons MKP-1 inhibits JNK-mediated cell death.

MKP-1 in cancer

The MAPK pathway has figured prominently in the mechanisms of cancer pathogenesis [122]. For this reason, it was suspected that mice lacking MKP-1 expression would exhibit evidence of increased susceptibility to tumorigenesis. However, to date there are no such reports demonstrating that *mkp-1*$^{-/-}$ mice display any signs of increased tumorigenesis. Moreover, there is little compelling evidence that altered MKP-1 expression is causal to tumorigenesis in either humans or mouse models of cancer. Nevertheless, there are a plethora of reports citing changes in the expression levels of MKP-1 in various types of human cancers (Table 1). A survey of the literature reveals that MKP-1 expression is generally increased in a number of human tumors such as gastric adenocarcinoma, breast cancer, non-small cell carcinoma, prostate carcinoma and pancreatic carcinoma (Table 1). In contrast, there appear to be few studies citing decreased levels of MKP-1 and in some of these cases, conflicting data also cite increased MKP-1 levels in the same type of cancer. For example, both increased and decreased levels of MKP-1 have been reported in invasive ovarian cancer. In prostate cancer where MKP-1 had been suggested to be overexpressed [123], others have found MKP-1 expression levels to be initially high in dysplastic prostate lesions and then later to decline in response to increasing levels of estradiol-17β and testosterone which are known to induce prostatic dysplasia [124]. In contrast, Rauhala et al. showed that MKP-1 is downregulated in prostate cancer and that this was linked to reduced cell death [125].

Studies have shown that MKP-1 expression levels can influence tumor growth and survival. Overexpression of MKP-1 decreases the growth rate of non-small cell lung cancer (NSCLC) cells, in addition to cell invasive and migratory abilities that correlated with inhibition of MMP-2 and CXCR4 expression [126]. Xenograft studies in mice using MKP-1 overexpressing H441 cells prevented the development of NSCLC and bone metastasis. Furthermore, following daily oral rosiglitazone treatment, in H441GL-transplanted mice, bone metastasis was inhibited. Treatment with rosiglitazone blocked cell migration and invasion in vitro. MKP-1 has been identified to be a transcriptional target of p53. p53 bound to a consensus p53 binding site located in the second intron of the MKP-1 gene and transactivated MKP-1 [127]. MKP-1 mRNA and protein levels were enhanced in response to p53 activation suggesting that p53 is involved in suppressing MAPK activity. This could potentially play a role in aberrant MAPK activation in tumors with p53 mutations.

Due to the observation that MKP-1 may play a protective role in chemoresistance several studies suggest that MKP-1 inactivation may provide a novel chemotherapeutic strategy to sensitize cancer cell death. Small et al., showed that MKP-1 overexpression decreased caspase activation and DNA fragmentation and increased viability in response to treatment with mechlorethamine, doxorubicin, and paclitaxel which was mediated by JNK inhibition [128]. Sensitivity to these drugs was increased following knockdown of MKP-1 using siRNA. Overexpression of MKP-1 in osteosarcoma cells caused these cells to be more resistant to cisplatin-induced apoptosis and inhibition of MKP-1 expression reversed this effect. A recent study found that in response to luteolin MKP-1 protein expression was reduced in A549 and H460 cells which correlated with increased activation of JNK [129]. The study also showed that overexpression of a degradation-resistant MKP-1 mutant

inhibited luteolin-induced cytotoxicity in lung cancer cells [129]. These data suggest that MKP-1 inhibition plays an important role in luteolin-induced JNK phosphorylation and could partly mediate the apoptosis observed in lung cancer cells.

The role of MKP-1 in cancer still remains controversial. Identification of MKP-1-dependent MAPK targets that are altered in their levels of phosphorylation under conditions in which MKP-1 is overexpressed or under expressed in different cancers could provide a molecular road map towards dissecting the mechanism underlying the involvement of MKP-1 in cancer. Presumably, depending upon the nature and stage of the cancer distinct sets of MKP-1-dependent MAPK substrates are being phosphorylated/dephosphorylated which in turn will likely dictate tumor cell fate. More comprehensive analyses of MKP-1-dependent target proteins obtained through proteomic approaches should be performed in order to gather this information. In the absence of these and other types of analyses using genome and proteome-wide approaches much of the information on MKP-1 is cancer will remain correlative. Finally, given the robust role of MKP-1 in the immune system how MKP-1 in this system affects cancer progression should also be investigated. These studies and others once completed should provide a more substantive case for the role of MKP-1 in cancer.

Concluding remarks

Given the central role of the MAPKs in physiological and pathophysiological signaling it is not at all surprising that MKPs figure prominently in these pathways. However, what is surprising is the fact that MKP-1 seems to play such an essential role in MAPK-dependent signaling despite the fact that it is one of ten other MKP family members. This observation highlights the importance of MKP-1 in serving as a critical signaling node for the MAPKs in the nucleus.

MKP-1 clearly plays a profound role in the regulation of the MAPKs in the immune, metabolic, musculoskeletal and nervous systems. Since the role of MKP-1 in the immune system is so critical it will be important to understand how the regulation of MKP-1 in the immune system influences, if at all, the progression of other diseases such as metabolic disease, musculoskeletal diseases, and cancer progression. The progression of these diseases has been linked to the influence of chronic inflammation. Therefore, it will be important to understand the contribution of MKP-1 in the inflammatory system relative to other diseases. Finally, there is growing evidence that targeting MKP-1 pharmacologically may be of value for the treatment of metabolic disease, neurological disorders such as depression and possibly cancer. Future progress in these areas may open up new avenues of therapeutic approaches for these types of diseases.

Acknowledgments

This work was supported by grants to A.M.B. from the National Institutes of Health and from the Muscular Dystrophy Association to H.S.

References

1. Raman M, Chen W, Cobb MH. Differential regulation and properties of MAPKs. Oncogene. 2007; 26(22):3100–3112. [PubMed: 17496909]

2. Chen Z, Gibson TB, Robinson F, Silvestro L, Pearson G, Xu B-E, Wright A, Vanderbilt C, Cobb MH. MAP kinases. Chem Rev. 2001; 101(8):2449–2476. [PubMed: 11749383]
3. Cobb MH, Goldsmith EJ. How MAP kinases are regulated. J Biol Chem. 1995; 270(25):14843–14846. [PubMed: 7797459]
4. Weston CR, Davis RJ. The JNK signal transduction pathway. Curr Opin Cell Biol. 2007; 19(2):142–149. [PubMed: 17303404]
5. Karin M, Gallagher E. From JNK to pay dirt: jun kinases, their biochemistry. Physiol Clin Import IUBMB Life. 2005; 57(4–5):283–295.
6. Cuenda A, Rousseau S. p38 MAP-Kinases pathway regulation, function and role in human diseases. Biochim Biophys Acta (BBA) Mol Cell Res. 2007; 1773(8):1358–1375.
7. Bhalla US, Iyengar R. Emergent properties of networks of biological signaling pathways. Science. 1999; 283(5400):381–387. [PubMed: 9888852]
8. Pouyssegur J, Volmat V, Lenormand P. Fidelity and spatio-temporal control in MAP kinase (ERKs) signalling. Biochem Pharmacol. 2002; 64(5–6):755–763. [PubMed: 12213567]
9. Karlsson M, Mandl M, Keyse SM. Spatio-temporal regulation of mitogen-activated protein kinase (MAPK) signalling by protein phosphatases. Biochem Soc Trans. 2006; 34(Pt 5):842–845. [PubMed: 17052211]
10. Keyse SM. Protein phosphatases and the regulation of mitogen-activated protein kinase signalling. Curr Opin Cell Biol. 2000; 12(2):186–192. [PubMed: 10712927]
11. Boutros T, Chevet E, Metrakos P. Mitogen-activated protein (MAP) kinase/MAP kinase phosphatase regulation: roles in cell growth, death, and cancer. Pharmacol Rev. 2008; 60(3):261–310. [PubMed: 18922965]
12. Camps M, Nichols A, Arkinstall S. Dual specificity phosphatases: a gene family for control of MAP kinase function. Faseb J. 2000; 14(1):6–16. [PubMed: 10627275]
13. Alonso A, Sasin J, Bottini N, Friedberg I, Osterman A, Godzik A, Hunter T, Dixon J, Mustelin T. Protein tyrosine phosphatases in the human genome. Cell. 2004; 117(6):699–711. [PubMed: 15186772]
14. Theodosiou A, Ashworth A. MAP kinase phosphatases. Genome Biol. 2002; 3(7):REVIEWS3009. [PubMed: 12184814]
15. Guan K-L, Butch E. Isolation of a novel dual specific phosphatase, HVH2 which selectively dephosphorylates the mitogen-activated protein kinase. J Biol Chem. 1995; 270(13):7197–7203. [PubMed: 7535768]
16. Farooq A, Chaturvedi G, Mujtaba S, Plotnikova O, Zeng L, Dhalluin C, Ashton R, Zhou MM. Solution structure of ERK2 binding domain of MAPK phosphatase MKP-3: structural insights into MKP-3 activation by ERK2. Mol Cell. 2001; 7(2):387–399. [PubMed: 11239467]
17. Farooq A, Plotnikova O, Chaturvedi G, Yan S, Zeng L, Zhang Q, Zhou MM. Solution structure of the MAPK phosphatase PAC-1 catalytic domain. Insights into substrate-induced enzymatic activation of MKP. Structure (Camb). 2003; 11(2):155–164. [PubMed: 12575935]
18. Jeong DG, Yoon T-S, Kim JH, Shim MY, Jung S-K, Son JH, Ryu SE, Kim SJ. Crystal structure of the catalytic domain of human MAP kinase phosphatase 5: structural insight into constitutively active phosphatase. J Mol Biol. 2006; 360(5):946–955. [PubMed: 16806267]
19. Jeong DG, Jung SK, Yoon TS, Woo EJ, Kim JH, Park BC, Ryu SE, Kim SJ. Crystal structure of the catalytic domain of human MKP-2 reveals a 24-mer assembly. Proteins. 2009; 76(3):763–767. [PubMed: 19415758]
20. Zhang YY, Wu JW, Wang ZX. A distinct interaction mode revealed by the crystal structure of the kinase p38alpha with the MAPK binding domain of the phosphatase MKP5. Sci Signal. 2011; 4(204):ra88. [PubMed: 22375048]
21. Farooq A, Zhou MM. Structure and regulation of MAPK phosphatases. Cell Signal. 2004; 16(7):769–779. [PubMed: 15115656]
22. Noguchi T, Metz R, Chen L, Mattei M-G, Carrsaco D, Bravo R. Structure, mapping, and expression of *erp*, a growth factor-inducible gene encoding a nontransmembrane protein tyrosine phosphatase, and effect of ERP on cell growth. Mol Cell Biol. 1993; 13:5195–5205. [PubMed: 8355678]

23. Keyse SM, Emslie EA. Oxidative stress and heat shock induce a human gene encoding a protein-tyrosine phosphatase. Nature. 1992; 359:644–647. [PubMed: 1406996]
24. Tanoue T, Moriguchi T, Nishida E. Molecular cloning and characterization of a novel dual specificity phosphatase, MKP-5. J Biol Chem. 1999; 274(28):19949–19956. [PubMed: 10391943]
25. Mandl M, Slack DN, Keyse SM. Specific inactivation and nuclear anchoring of extracellular signal-regulated kinase 2 by the inducible dual-specificity protein phosphatase DUSP5. Mol Cell Biol. 2005; 25(5):1830–1845. [PubMed: 15713638]
26. Al-Mutairi M, Al-Harthi S, Cadalbert L, Plevin R. Over-expression of mitogen-activated protein kinase phosphatase-2 enhances adhesion molecule expression and protects against apoptosis in human endothelial cells. Br J Pharmacol. 2010; 161(4):782–798. [PubMed: 20860659]
27. Chi H, Barry SP, Roth RJ, Wu JJ, Jones EA, Bennett AM, Flavell RA. Dynamic regulation of pro- and anti-inflammatory cytokines by MAPK phosphatase 1 (MKP-1) in innate immune responses. PNAS. 2006; 103(7):2274–2279. [PubMed: 16461893]
28. Reffas S, Schlegel W. Compartment-specific regulation of extracellular signal-regulated kinase (ERK) and c-Jun N-terminal kinase (JNK) mitogen-activated protein kinases (MAPKs) by ERK-dependent and non-ERK-dependent inductions of MAPK phosphatase (MKP)-3 and MKP-1 in differentiating P19 cells. Bi Biochem J. 2000; 352(Pt 3):701–708. [PubMed: 11104676]
29. Dowd S, Sneddon AA, Keyse SM. Isolation of the human genes encoding the pyst1 and Pyst2 phosphatases: characterisation of Pyst2 as a cytosolic dual-specificity MAP kinase phosphatase and its catalytic activation by both MAP and SAP kinases. J Cell Sci. 1998; 111(Pt 22):3389–3399. [PubMed: 9788880]
30. Muda M, Boschert U, Dickinson R, Martinou J-C, Martinou I, Camps M, Schlegel W, Arkinstall S. MKP-3, a novel cytosolic protein-tyrosine phosphatase that exemplifies a new class of mitogen-activated protein kinase phosphatase. J Biol Chem. 1996; 271(8):4319–4326. [PubMed: 8626780]
31. Muda M, Boschert U, Smith A, Antonsson B, Gillieron C, Chabert C, Camps M, Martinou I, Ashworth A, Arkinstall S. Molecular cloning and functional characterization of a novel mitogen-activated protein kinase phosphatase, MKP-4. J Biol Chem. 1997; 272(8):8.
32. Muda M, Theodosiou A, Rodrigues N, Boschert U, Camps M, Gillieron C, Davies K, Ashworth A, Arkinstall S. The dual specificity phosphatases M3/6 and MKP-3 are highly selective for inactivation of distinct mitogen-activated protein kinases. J Biol Chem. 1996; 271(44):27205–27208. [PubMed: 8910287]
33. Masuda K, Shima H, Watanabe M, Kikuchi K. MKP-7, a novel mitogen-activated protein kinase phosphatase, functions as a shuttle protein. J Biol Chem. 2001; 276(42):39002–39011. [PubMed: 11489891]
34. Owens DM, Keyse SM. Differential regulation of MAP kinase signalling by dual-specificity protein phosphatases. Oncogene. 2007; 26(22):3203–3213. [PubMed: 17496916]
35. Dorfman K, Carrasco D, Gruda M, Ryan C, Lira SA, Bravo R. Disruption of the *erp/mkp-1* gene does not affect mouse development: normal MAP kinase activity in ERP/MKP-1-deficient fibroblasts. Oncogene. 1996; 13:925–931. [PubMed: 8806681]
36. Charles CH, Abler AS, Lau LF. cDNA sequence of a growth-inducible immediate early gene and characterization of its encoded protein. Oncogene. 1992; 7:187–190. [PubMed: 1741163]
37. Mohn KL, Laz TM, Hsu J-C, Melby AE, Bravo R, Taub R. The immediate-early growth response in regenerating liver and insulin- stimulated H-35 cells: comparison with serum-stimulated 3T3 cells and identification of 41 novel immediate-early genes. Mol Cell Biol. 1991; 11(1):381–390. [PubMed: 1986233]
38. Lau LF, Nathans D. Identification of a set of genes expressed during the G0/G1 transition of cultured mouse cells. EMBO J. 1985; 4(12):3145–3151. [PubMed: 3841511]
39. Wu JJ, Zhang L, Bennett AM. The noncatalytic amino terminus of mitogen-activated protein kinase phosphatase 1 directs nuclear targeting and serum response element transcriptional regulation. Mol Cell Biol. 2005; 25(11):4792–4803. [PubMed: 15899879]
40. Slack DN, Seternes OM, Gabrielsen M, Keyse SM. Distinct binding determinants for erk2/p38alpha and jnk map kinases mediate catalytic activation and substrate selectivity of map kinase phosphatase-1. J Biol Chem. 2001; 276(19):16491–16500. [PubMed: 11278799]

41. Hutter D, Chen P, Barnes J, Liu Y. Catalytic activation of mitogen-activated protein (MAP) kinase phosphatase-1 by binding to p38 MAP kinase: critical role of the p38 C-terminal domain in its negative regulation. Biochem J. 2000; 352(Pt 1):155–163. [PubMed: 11062068]
42. Franklin CC, Kraft AS. Conditional expression of the mitogen-activated protein kinase (MAPK) phosphatase MKP-1 preferentially inhibits p38 MAPK and stress-activated protein kinase in U397 cells. J Biol Chem. 1997; 272:16917–16923. [PubMed: 9202001]
43. Sun H, Charles CH, Lau LF, Tonks NK. MKP-1 (3CH134), an intermediate early gene product, is a dual specificity phosphatase that dephosphorylates MAP kinase in vivo. Cell. 1993; 75:487–493. [PubMed: 8221888]
44. Cho IJ, Woo NR, Kim SG. The identification of C/EB-Pbeta as a transcription factor necessary for the induction of MAPK phosphatase-1 by toll-like receptor-4 ligand. Arch Biochem Biophys. 2008; 479(1):88–96. [PubMed: 18761321]
45. Kuwano Y, Kim HH, Abdelmohsen K, Pullmann R Jr, Martindale JL, Yang X, Gorospe M. MKP-1 mRNA stabilization and translational control by RNA-binding proteins HuR and NF90. Mol Cell Biol. 2008; 28(14):4562–4575. [PubMed: 18490444]
46. Kuwano Y, Pullmann R Jr, Marasa BS, Abdelmohsen K, Lee EK, Yang X, Martindale JL, Zhan M, Gorospe M. NF90 selectively represses the translation of target mRNAs bearing an AU-rich signature motif. Nucleic Acids Res. 2010; 38(1):225–238. [PubMed: 19850717]
47. Emmons J, Townley-Tilson WHD, Deleault KM, Skinner SJ, Gross RH, Whitfield ML, Brooks SA. Identification of TTP mRNA targets in human dendritic cells reveals TTP as a critical regulator of dendritic cell maturation. RNA. 2008; 14(5):888–902. [PubMed: 18367721]
48. Lin N-Y, Lin C-T, Chang C-J. Modulation of immediate early gene expression by tristetraprolin in the differentiation of 3T3-L1 cells. Biochem Biophys Res Commun. 2008; 365(1):69–74. [PubMed: 17971298]
49. Scimeca JC, Servant MJ, Dyer JO, Meloche S. Essential role of calcium in the regulation of MAP kinase phosphatase-1 expression. Oncogene. 1997; 15(6):717–725. [PubMed: 9264412]
50. Zhu QY, Liu Q, Chen JX, Lan K, Ge BX. MicroRNA-101 targets MAPK phosphatase-1 to regulate the activation of MAPKs in macrophages. J Immunol. 2010; 185(12):7435–7442. [PubMed: 21068409]
51. Brondello JM, Pouyssegur J, McKenzie FR. Reduced MAP kinase phosphatase-1 degradation after p42/p44MAPK-dependent phosphorylation. Science. 1999; 286(5449):2514–2517. [PubMed: 10617468]
52. Lin YW, Yang JL. Cooperation of ERK and SCFSkp2 for MKP-1 destruction provides a positive feedback regulation of proliferating signaling. J Biol Chem. 2006; 281(2):915–926. [PubMed: 16286470]
53. Lin YW, Chuang SM, Yang JL. ERK1/2 achieves sustained activation by stimulating MAPK phosphatase-1 degradation via the ubiquitin-proteasome pathway. J Biol Chem. 2003; 278(24): 21534–21541. [PubMed: 12676937]
54. Cao W, Bao C, Padalko E, Lowenstein CJ. Acetylation of mitogen-activated protein kinase phosphatase-1 inhibits Toll-like receptor signaling. J Exp Med. 2008; 205(6):1491–1503. [PubMed: 18504304]
55. Kassel O, Sancono A, Kratzschmar J, Kreft B, Stassen M, Cato AC. Glucocorticoids inhibit MAP kinase via increased expression and decreased degradation of MKP-1. EMBO J. 2001; 20(24): 7108–7116. [PubMed: 11742987]
56. Wu JJ, Bennett AM. Essential role for mitogen-activated protein (MAP) kinase phosphatase-1 in stress-responsive MAP kinase and cell survival signaling. J Biol Chem. 2005; 280(16):16461–16466. [PubMed: 15722358]
57. Murray PJ, Wynn TA. Protective and pathogenic functions of macrophage subsets. Nat Rev Immunol. 2011; 11(11):723–737. [PubMed: 21997792]
58. Hammer M, Mages J, Dietrich H, Servatius A, Howells N, Cato ACB, Lang R. Dual specificity phosphatase 1 (DUSP1) regulates a subset of LPS-induced genes and protects mice from lethal endotoxin shock. J Exp Med. 2006; 203(1):15–20. [PubMed: 16380512]

59. Salojin KV, Owusu IB, Millerchip KA, Potter M, Platt KA, Oravecz T. Essential role of MAPK phosphatase-1 in the negative control of innate immune responses. J Immunol. 2006; 176(3):1899–1907. [PubMed: 16424221]
60. Zhao Q, Wang X, Nelin LD, Yao Y, Matta R, Manson ME, Baliga RS, Meng X, Smith CV, Bauer JA, Chang C-H, Liu Y. MAP kinase phosphatase 1 controls innate immune responses and suppresses endotoxic shock. J Exp Med. 2006; 203(1):131–140. [PubMed: 16380513]
61. Calvert TJ, Chicoine LG, Liu Y, Nelin LD. Deficiency of mitogen-activated protein kinase phosphatase-1 results in iNOS-mediated hypotension in response to low-dose endotoxin. Am J Physiol Heart Circ Physiol. 2008; 294(4):H1621–H1629. [PubMed: 18281381]
62. Sartori R, Li F, Kirkwood KL. MAP kinase phosphatase-1 protects against inflammatory bone loss. J Dent Res. 2009; 88(12):1125–1130. [PubMed: 19864641]
63. Wang X, Meng X, Kuhlman JR, Nelin LD, Nicol KK, English BK, Liu Y. Knockout of Mkp-1 enhances the host inflammatory responses to gram-positive bacteria. J Immunol. 2007; 178(8): 5312–5320. [PubMed: 17404316]
64. Yu H, Sun Y, Haycraft C, Palanisamy V, Kirkwood KL. MKP-1 regulates cytokine mRNA stability through selectively modulation subcellular translocation of AUF1. Cytokine. 2011; 56(2): 245–255. [PubMed: 21733716]
65. Jeong HJ, Na HJ, Hong SH, Kim HM. Inhibition of the stem cell factor-induced migration of mast cells by dexamethasone. Endocrinology. 2003; 144(9):4080–4086. [PubMed: 12933682]
66. Maier JV, Brema S, Tuckermann J, Herzer U, Klein M, Stassen M, Moorthy A, Cato AC. Dual specificity phosphatase 1 knockout mice show enhanced susceptibility to anaphylaxis but are sensitive to glucocorticoids. Mol Endocrinol. 2007; 21(11):2663–2671. [PubMed: 17636038]
67. Stritesky GL, Jameson SC, Hogquist KA. Selection of self-reactive T cells in the thymus. Annu Rev Immunol. 2012; 30:95–114. [PubMed: 22149933]
68. Tanzola MB, Kersh GJ. The dual specificity phosphatase transcriptome of the murine thymus. Mol Immunol. 2006; 43(6):754–762. [PubMed: 16360020]
69. Zhang Y, Reynolds JM, Chang SH, Martin-Orozco N, Chung Y, Nurieva RI, Dong C. MKP-1 is necessary for T cell activation and function. J Biol Chem. 2009; 284(45):30815–30824. [PubMed: 19748894]
70. Luo C, Yang X, Yao L, Jiang L, Liu W, Li X, Wang L. Mitogen-activated protein kinase phosphatase-1 expression in macrophages is controlled by lymphocytes during macrophage activation. Int J Mol Med. 2012; 29(1):25–31. [PubMed: 21956667]
71. Srivastava N, Sudan R, Saha B. CD40-modulated dual-specificity phosphatases MAPK phosphatase (MKP)-1 and MKP-3 reciprocally regulate *Leishmania* major infection. J Immunol. 2011; 186(10):5863–5872. [PubMed: 21471446]
72. Huang G, Wang Y, Shi LZ, Kanneganti TD, Chi H. Signaling by the phosphatase MKP-1 in dendritic cells imprints distinct effector and regulatory T cell fates. Immunity. 2011; 35(1):45–58. [PubMed: 21723158]
73. Lewis CE, McTigue KM, Burke LE, Poirier P, Eckel RH, Howard BV, Allison DB, Kumanyika S, Pi-Sunyer FX. Mortality, health outcomes, and body mass index in the overweight range: a science advisory from the American Heart Association. Circulation. 2009; 119(25):3263–3271. [PubMed: 19506107]
74. Bost F, Aouadi M, Caron L, Binetruy B. The role of MAPKs in adipocyte differentiation and obesity. Biochimie. 2005; 87(1):51–56. [PubMed: 15733737]
75. Bost F, Aouadi M, Caron L, Even P, Belmonte N, Prot M, Dani C, Hofman P, Pages G, Pouyssegur J, Le Marchand-Brustel Y, Binetruy B. The extracellular signal-regulated kinase isoform ERK1 is specifically required for in vitro and in vivo adipogenesis. Diabetes. 2005; 54(2): 402–411. [PubMed: 15677498]
76. Hirosumi J, Tuncman G, Chang L, Gorgun CZ, Uysal KT, Maeda K, Karin M, Hotamisligil GS. A central role for JNK in obesity and insulin resistance. Nature. 2002; 420(6913):333–336. [PubMed: 12447443]
77. Puigserver P, Rhee J, Lin J, Wu Z, Yoon JC, Zhang CY, Krauss S, Mootha VK, Lowell BB, Spiegelman BM. Cytokine stimulation of energy expenditure through p38 MAP kinase activation of PPARgamma coactivator-1. Mol Cell. 2001; 8(5):971–982. [PubMed: 11741533]

78. Xiong Y, Collins QF, An J, Lupo E Jr, Liu H-Y, Liu D, Robidoux J, Liu Z, Cao W. p38 Mitogen-activated protein kinase plays an inhibitory role in hepatic lipogenesis. J Biol Chem. 2007; 282(7): 4975–4982. [PubMed: 17172644]

79. Burns KA, Vanden Heuvel JP. Modulation of PPAR activity via phosphorylation. Biochim Biophys Acta. 2007; 1771(8):952–960. [PubMed: 17560826]

80. Somwar R, Koterski S, Sweeney G, Sciotti R, Djuric S, Berg C, Trevillyan J, Scherer PE, Rondinone CM, Klip A. A dominant-negative p38 MAPK mutant and novel selective inhibitors of p38 MAPK reduce insulin-stimulated glucose uptake in 3T3-L1 adipocytes without affecting GLUT4 translocation. J Biol Chem. 2002; 277(52):50386–50395. [PubMed: 12393894]

81. Barger PM, Browning AC, Garner AN, Kelly DP. p38 mitogen-activated protein kinase activates peroxisome proliferator-activated receptor alpha: a potential role in the cardiac metabolic stress response. J Biol Chem. 2001; 276(48):44495–44501. [PubMed: 11577087]

82. Flach RJR, Qin H, Zhang L, Bennett AM. Loss of mitogen-activated protein kinase phosphatase-1 protects from hepatic steatosis by repression of cell death-inducing DNA fragmentation factor A (DFFA)-like effector C (CIDEC)/fat-specific protein 27. J Biol Chem. 2011; 286(25):22195–22202. [PubMed: 21521693]

83. Roth RJ, Le AM, Zhang L, Kahn M, Samuel VT, Shulman GI, Bennett AM. MAPK phosphatase-1 facilitates the loss of oxidative myofibers associated with obesity in mice. J Clin Invest. 2009; 119:3817–3829. [PubMed: 19920356]

84. Wu JJ, Roth RJ, Anderson EJ, Hong E-G, Lee M-K, Choi CS, Neufer PD, Shulman GI, Kim JK, Bennett AM. Mice lacking MAP kinase phosphatase-1 have enhanced MAP kinase activity and resistance to diet-induced obesity. Cell Metab. 2006; 4(1):61–73. [PubMed: 16814733]

85. Emanuelli B, Eberle D, Suzuki R, Kahn CR. Overexpression of the dual-specificity phosphatase MKP-4/DUSP-9 protects against stress-induced insulin resistance. Proc Natl Acad Sci USA. 2008; 105(9):3545–3550. [PubMed: 18296638]

86. Wu Z, Jiao P, Huang X, Feng B, Feng Y, Yang S, Hwang P, Du J, Nie Y, Xiao G, Xu H. MAPK phosphatase-3 promotes hepatic gluconeogenesis through dephosphorylation of forkhead box O1 in mice. J Clin Invest. 2010; 120(11):3901–3911. [PubMed: 20921625]

87. Zierath JR, Hawley JA. Skeletal muscle fiber type: influence on contractile and metabolic properties. PLoS Biol. 2004; 2(10):e348. [PubMed: 15486583]

88. Flach RJ, Qin H, Zhang L, Bennett AM. Loss of mitogen-activated protein kinase phosphatase-1 protects from hepatic steatosis by repression of cell death-inducing DNA fragmentation factor A (DFFA)-like effector C (CIDEC)/fat-specific protein 27. J Biol Chem. 2011; 286(25):22195–22202. [PubMed: 21521693]

89. Lehrke M, Lazar MA. The many faces of PPARgamma. Cell. 2005; 123(6):993–999. [PubMed: 16360030]

90. Gavrilova O, Haluzik M, Matsusue K, Cutson JJ, Johnson L, Dietz KR, Nicol CJ, Vinson C, Gonzalez FJ, Reitman ML. Liver peroxisome proliferator-activated receptor gamma contributes to hepatic steatosis, triglyceride clearance, and regulation of body fat mass. J Biol Chem. 2003; 278(36):34268–34276. [PubMed: 12805374]

91. Matsusue K, Haluzik M, Lambert G, Yim SH, Gavrilova O, Ward JM, Brewer B Jr, Reitman ML, Gonzalez FJ. Liver-specific disruption of PPARgamma in leptin-deficient mice improves fatty liver but aggravates diabetic phenotypes. J Clin Invest. 2003; 111(5):737–747. [PubMed: 12618528]

92. Matsusue K, Kusakabe T, Noguchi T, Takiguchi S, Suzuki T, Yamano S, Gonzalez FJ. Hepatic steatosis in leptin-deficient mice is promoted by the PPARgamma target gene Fsp27. Cell Metab. 2008; 7(4):302–311. [PubMed: 18396136]

93. Traini M, Jessup W. Lipid droplets and adipose metabolism: a novel role for FSP27/CIDEC. Curr Opin Lipidol. 2009; 20(2):147–149. [PubMed: 19276894]

94. Reddy ST, Nguyen JT, Grijalva V, Hough G, Hama S, Navab M, Fogelman AM. Potential role for mitogen-activated protein kinase phosphatase-1 in the development of atherosclerotic lesions in mouse models. Arterioscler Thromb Vasc Biol. 2004; 24(9):1676–1681. [PubMed: 15242861]

95. Dankel SN, Fadnes DJ, Stavrum AK, Stansberg C, Holdhus R, Hoang T, Veum VL, Christensen BJ, Vage V, Sagen JV, Steen VM, Mellgren G. Switch from stress response to homeobox

transcription factors in adipose tissue after profound fat loss. PLoS ONE. 2010; 5(6):e11033. [PubMed: 20543949]

96. Weber C, Noels H. Atherosclerosis: current pathogenesis and therapeutic options. Nat Med. 2011; 17(11):1410–1422. [PubMed: 22064431]
97. Ricci R, Sumara G, Sumara I, Rozenberg I, Kurrer M, Akhmedov A, Hersberger M, Eriksson U, Eberli FR, Becher B, Boren J, Chen M, Cybulsky MI, Moore KJ, Freeman MW, Wagner EF, Matter CM, Luscher TF. Requirement of JNK2 for scavenger receptor A-mediated foam cell formation in atherogenesis. Science. 2004; 306(5701):1558–1561. [PubMed: 15567863]
98. Shen J, Chandrasekharan UM, Ashraf MZ, Long E, Morton RE, Liu Y, Smith JD, DiCorleto PE. Lack of mitogen-activated protein kinase phosphatase-1 protects ApoE-null mice against atherosclerosis. Circ Res. 2010; 106(5):902–910. [PubMed: 20093631]
99. Imaizumi S, Grijalva V, Priceman S, Wu L, Su F, Farias-Eisner R, Hama S, Navab M, Fogelman AM, Reddy ST. Mitogen-activated protein kinase phosphatase-1 deficiency decreases atherosclerosis in apolipoprotein E null mice by reducing monocyte chemoattractant protein-1 levels. Mol Genet Metab. 2010; 101(1):66–75. [PubMed: 20619710]
100. Chaudhury H, Zakkar M, Boyle J, Cuhlmann S, van der Heiden K, le Luong A, Davis J, Platt A, Mason JC, Krams R, Haskard DO, Clark AR, Evans PC. c-Jun N-terminal kinase primes endothelial cells at atheroprone sites for apoptosis. Arterioscler Thromb Vasc Biol. 2010; 30(3): 546–553. [PubMed: 20056910]
101. Jin Y, Calvert TJ, Chen B, Chicoine LG, Joshi M, Bauer JA, Liu Y, Nelin LD. Mice deficient in Mkp-1 develop more severe pulmonary hypertension and greater lung protein levels of arginase in response to chronic hypoxia. Am J Physiol Heart Circ Physiol. 2010; 298(5):H1518–H1528. [PubMed: 20173047]
102. Rudnicki MA, Le Grand F, McKinnell I, Kuang S. The molecular regulation of muscle stem cell function. Cold Spring Harb Symp Quant Biol. 2008; 73:323–331. [PubMed: 19329572]
103. Cerletti M, Shadrach JL, Jurga S, Sherwood R, Wagers AJ. Regulation and function of skeletal muscle stem cells. Cold Spring Harb Symp Quant Biol. 2008; 73:317–322. [PubMed: 19204065]
104. Gallo R, Serafini M, Castellani L, Falcone G, Alema S. Distinct effects of rac1 on differentiation of primary avian myoblasts. Mol Biol Cell. 1999; 10(10):3137–3150. [PubMed: 10512856]
105. Khurana A, Dey CS. p38 MAPK interacts with actin and modulates filament assembly during skeletal muscle differentiation. Differentiation. 2003; 71(1):42–50. [PubMed: 12558602]
106. Khurana A, Dey CS. Involvement of c-Jun N-terminal kinase activities in skeletal muscle differentiation. J Muscle Res Cell Motil. 2004; 25(8):645–655. [PubMed: 15750849]
107. Charrasse S, Meriane M, Comunale F, Blangy A, Gauthier-Rouviere C. N-cadherin-dependent cell–cell contact regulates Rho GTPases and beta-catenin localization in mouse C2C12 myoblasts. J Cell Biol. 2002; 158(5):953–965. [PubMed: 12213839]
108. Lluis F, Perdiguero E, Nebreda AR, Munoz-Canoves P. Regulation of skeletal muscle gene expression by p38 MAP kinases. Trends Cell Biol. 2006; 16(1):36–44. [PubMed: 16325404]
109. Perdiguero E, Ruiz-Bonilla V, Gresh L, Hui L, Ballestar E, Sousa-Victor P, Baeza-Raja B, Jardi M, Bosch-Comas A, Esteller M, Caelles C, Serrano AL, Wagner EF, Munoz-Canoves P. Genetic analysis of p38 MAP kinases in myogenesis: fundamental role of p38alpha in abrogating myoblast proliferation. EMBO J. 2007; 26(5):1245–1256. [PubMed: 17304211]
110. Perdiguero E, Ruiz-Bonilla V, Serrano AL, Munoz-Canoves P. Genetic deficiency of p38alpha reveals its critical role in myoblast cell cycle exit: the p38alpha-JNK connection. Cell Cycle. 2007; 6(11):1298–1303. [PubMed: 17534150]
111. Kondoh K, Sunadome K, Nishida E. Notch signaling suppresses p38 MAPK activity via induction of MKP-1 in myogenesis. J Biol Chem. 2007; 282(5):3058–3065. [PubMed: 17158101]
112. Sunadome K, Yamamoto T, Ebisuya M, Kondoh K, Sehara-Fujisawa A, Nishida E. ERK5 regulates muscle cell fusion through Klf transcription factors. Dev Cell. 2011; 20(2):192–205. [PubMed: 21316587]
113. Bennett AM, Tonks NK. Regulation of distinct stages of skeletal muscle differentiation by mitogen-activated protein kinases. Science. 1997; 278:1288–1291. [PubMed: 9360925]

114. Shi H, Boadu E, Mercan F, Le AM, Flach RJ, Zhang L, Tyner KJ, Olwin BB, Bennett AM. MAP kinase phosphatase-1 deficiency impairs skeletal muscle regeneration and exacerbates muscular dystrophy. FASEB J. 2010; 24(8):2985–2997. [PubMed: 20371627]
115. Carlson J, Zhang Q, Bennett A, Vignery A. Deletion of mitogen-activated protein kinase phosphatase 1 modifies the response to mechanical bone marrow ablation in a mouse model. Comp Med. 2009; 59(3):221–226. [PubMed: 19619411]
116. Carlson J, Cui W, Zhang Q, Xu X, Mercan F, Bennett AM, Vignery A. Role of MKP-1 in osteoclasts and bone homeostasis. Am J Pathol. 2009; 175(4):1564–1573. [PubMed: 19762714]
117. Mahalingam CD, Datta T, Patil RV, Kreider J, Bonfil RD, Kirkwood KL, Goldstein SA, Abou-Samra AB, Datta NS. Mitogen-activated protein kinase phosphatase 1 regulates bone mass, osteoblast gene expression, and responsiveness to parathyroid hormone. J Endocrinol. 2011; 211(2):145–156. [PubMed: 21852324]
118. Valjent E, Caboche J, Vanhoutte P. Mitogen-activated protein kinase/extracellular signal-regulated kinase induced gene regulation in brain. Mol Neurobiol. 2001; 23(2):83–99. [PubMed: 11817219]
119. Jeanneteau F, Deinhardt K. Fine-tuning MAPK signaling in the brain: the role of MKP-1. Commun Integr Biol. 2011; 4(3):281–283. [PubMed: 21980558]
120. Duric V, Banasr M, Licznerski P, Schmidt HD, Stockmeier CA, Simen AA, Newton SS, Duman RS. A negative regulator of MAP kinase causes depressive behavior. Nat Med. 2010; 16(11): 1328–1332. [PubMed: 20953200]
121. Kristiansen M, Hughes R, Patel P, Jacques TS, Clark AR, Ham J. Mkp1 is a c-Jun target gene that antagonizes JNK-dependent apoptosis in sympathetic neurons. J Neurosci. 2010; 30(32):10820–10832. [PubMed: 20702711]
122. Dhillon AS, Hagan S, Rath O, Kolch W. MAP kinase signalling pathways in cancer. Oncogene. 2007; 26(22):3279–3290. [PubMed: 17496922]
123. Magi-Galluzzi C, Mishra R, Fiorentino M, Montironi R, Yao H, Capodieci P, Wishnow K, Kaplan I, Stork PJ, Loda M. Mitogen-activated protein kinase phosphatase 1 is overexpressed in prostate cancers and is inversely related to apoptosis. Lab Invest J Tech Methods Pathol. 1997; 76(1):37–51.
124. Arnoldussen YJ, Saatcioglu F. Dual specificity phosphatases in prostate cancer. Mol Cell Endocrinol. 2009; 309(1–2):1–7. [PubMed: 19501628]
125. Rauhala HE, Porkka KP, Tolonen TT, Martikainen PM, Tammela TL, Visakorpi T. Dual-specificity phosphatase 1 and serum/glucocorticoid-regulated kinase are downregulated in prostate cancer. Int J Cancer J Int cancer. 2005; 117(5):738–745.
126. Tai CJ, Wu AT, Chiou JF, Jan HJ, Wei HJ, Hsu CH, Lin CT, Chiu WT, Wu CW, Lee HM, Deng WP. The investigation of mitogen-activated protein kinase phosphatase-1 as a potential pharmacological target in non-small cell lung carcinomas, assisted by non-invasive molecular imaging. BMC cancer. 2010; 10:95. [PubMed: 20226009]
127. Li M, Zhou J-Y, Ge Y, Matherly LH, Wu GS. The phosphatase MKP1 is a transcriptional target of p53 involved in cell cycle regulation. J Biol Chem. 2003; 278(42):41059–41068. [PubMed: 12890671]
128. Small GW, Shi YY, Higgins LS, Orlowski RZ. Mitogen-activated protein kinase phosphatase-1 is a mediator of breast cancer chemoresistance. Cancer Res. 2007; 67(9):4459–4466. [PubMed: 17483361]
129. Bai L, Xu X, Wang X, Xu S, Ju W, Chen W, He W, Wang Q, Tang H, Lin Y. A superoxide-mediated MKP-1 degradation and JNK activation pathway for luteolin-induced lung cancer cytotoxicity. Mol Pharmacol. 2012; 81(4):549–555. [PubMed: 22222766]
130. Bang YJ, Kwon JH, Kang SH, Kim JW, Yang YC. Increased MAPK activity and MKP-1 overexpression in human gastric adenocarcinoma. Biochem Biophys Res Commun. 1998; 250(1):43–47. [PubMed: 9735328]
131. Colombo J, Fachel AA, De Freitas Calmon M, Cury PM, Fukuyama EE, Tajara EH, Cordeiro JA, Verjovski-Almeida S, Reis EM, Rahal P. Gene expression profiling reveals molecular marker candidates of laryngeal squamous cell carcinoma. Oncol Rep. 2009; 21(3):649–663. [PubMed: 19212623]

132. Tomioka H, Morita K, Hasegawa S, Omura K. Gene expression analysis by cDNA microarray in oral squamous cell carcinoma. J Oral Pathol Med Off Publ Int Assoc Oral Pathol Am Acad Oral Pathol. 2006; 35(4):206–211.

133. Vicent S, Garayoa M, Lopez-Picazo JM, Lozano MD, Toledo G, Thunnissen FB, Manzano RG, Montuenga LM. Mitogen-activated protein kinase phosphatase-1 is overexpressed in non-small cell lung cancer and is an independent predictor of outcome in patients. Clin Cancer Res Off J Am Assoc Cancer Res. 2004; 10(11):3639–3649.

134. Wang HY, Cheng Z, Malbon CC. Overexpression of mitogen-activated protein kinase phosphatases MKP1, MKP2 in human breast cancer. Cancer Lett. 2003; 191(2):229–237. [PubMed: 12618338]

135. Rojo F, Gonzalez-Navarrete I, Bragado R, Dalmases A, Menendez S, Cortes-Sempere M, Suarez C, Oliva C, Servitja S, Rodriguez-Fanjul V, Sanchez-Perez I, Campas C, Corominas JM, Tusquets I, Bellosillo B, Serrano S, Perona R, Rovira A, Albanell J. Mitogen-activated protein kinase phosphatase-1 in human breast cancer independently predicts prognosis and is repressed by doxorubicin. Clin Cancer Res Off J Am Assoc Cancer Res. 2009; 15(10):3530–3539.

136. Liao Q, Guo J, Kleeff J, Zimmermann A, Buchler MW, Korc M, Friess H. Down-regulation of the dual-specificity phosphatase MKP-1 suppresses tumorigenicity of pancreatic cancer cells. Gastroenterology. 2003; 124(7):1830–1845. [PubMed: 12806617]

137. Loda M, Capoodieci P, Mishra R, Yao H, Corless C, Grigioni W, Wang Y, Magi-Galluzzi C, Stork PJS. Expression of mitogen-activated protein kinase phosphatase-1 in the early phases of human epithelial carcinogenesis. Am J Pathol. 1996; 149(5):1553–1564. [PubMed: 8909245]

138. Kundu S, Fan K, Cao M, Lindner DJ, Tuthill R, Liu L, Gerson S, Borden E, Yi T. Tyrosine phosphatase inhibitor-3 sensitizes melanoma and colon cancer to biotherapeutics and chemotherapeutics. Mol Cancer Ther. 2010; 9(8):2287–2296. [PubMed: 20682647]

139. Manzano RG, Montuenga LM, Dayton M, Dent P, Kinoshita I, Vicent S, Gardner GJ, Nguyen P, Choi YH, Trepel J, Auersperg N, Birrer MJ. CL100 expression is down-regulated in advanced epithelial ovarian cancer and its re-expression decreases its malignant potential. Oncogene. 2002; 21(28):4435–4447. [PubMed: 12080474]

140. Denkert C, Schmitt WD, Berger S, Reles A, Pest S, Siegert A, Lichtenegger W, Dietel M, Hauptmann S. Expression of mitogen-activated protein kinase phosphatase-1 (MKP-1) in primary human ovarian carcinoma. Int J Cancer J Int Cancer. 2002; 102(5):507–513.

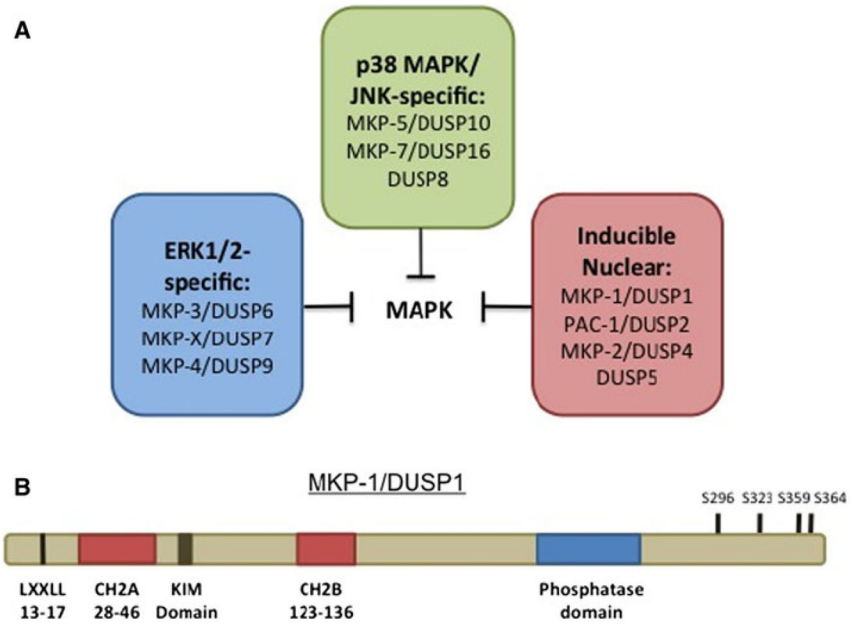

Fig. 1.

The dual-specificity protein tyrosine phosphatases. **a** Shows the family of dual-specificity protein tyrosine phosphatases (DUSPs) represented by three classes based upon their substrate specificity and sub-cellular localization. **b** Schematic representation of the domain structure of MKP-1. Depicted in the NH_2 terminus is the nuclear-targeting/retaining motif, LXXLL, the cdc25A (CH2A) and B (CHs2B) domains and the kinase interaction motif (KIM). The catalytic phosphatase domain is depicted and ERK1/2 phosphorylation sites reside within the C-terminus

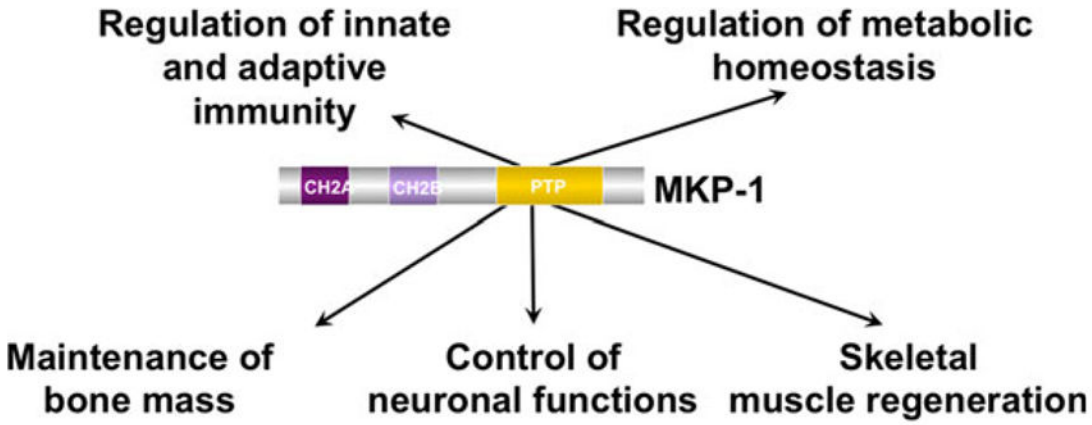

Fig. 2.

Diversity of MKP-1 signaling. The many roles of MKP-1 in physiological and pathophysiological processes have been uncovered through the use of mice lacking the expression of MKP-1. These genetic approaches have uncovered a role for MKP-1 in innate and adaptive immunity, metabolism, neuronal functions, muscle stem cell function, as well as other processes

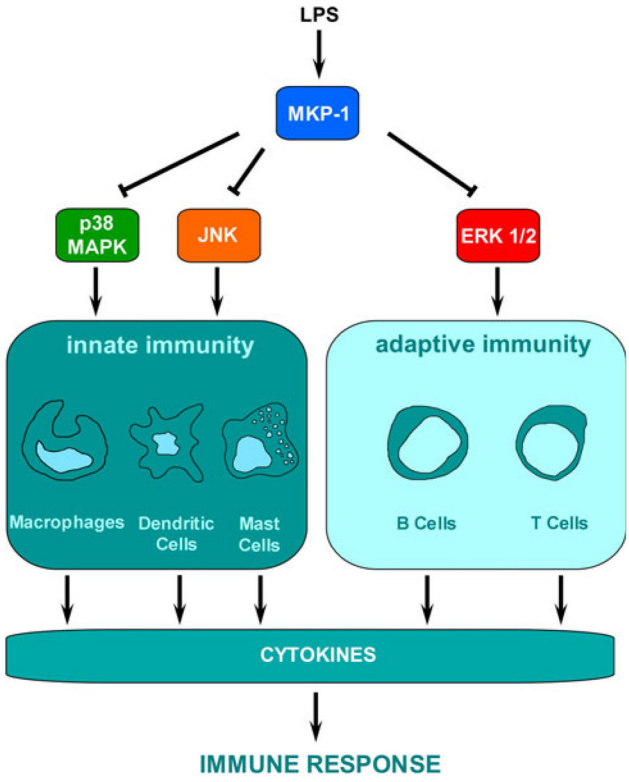

Fig. 3.

MKP-1 functions in innate and adaptive immunity. MKP-1 functions to control MAPK-mediated regulation of cytokine signaling in macrophages, B and T-cells. MKP-1 serves to limit the activity of these MAPKs thereby coordinating the responsiveness of cytokine production to mediate responses to infection and direct hematopoietic cell specification

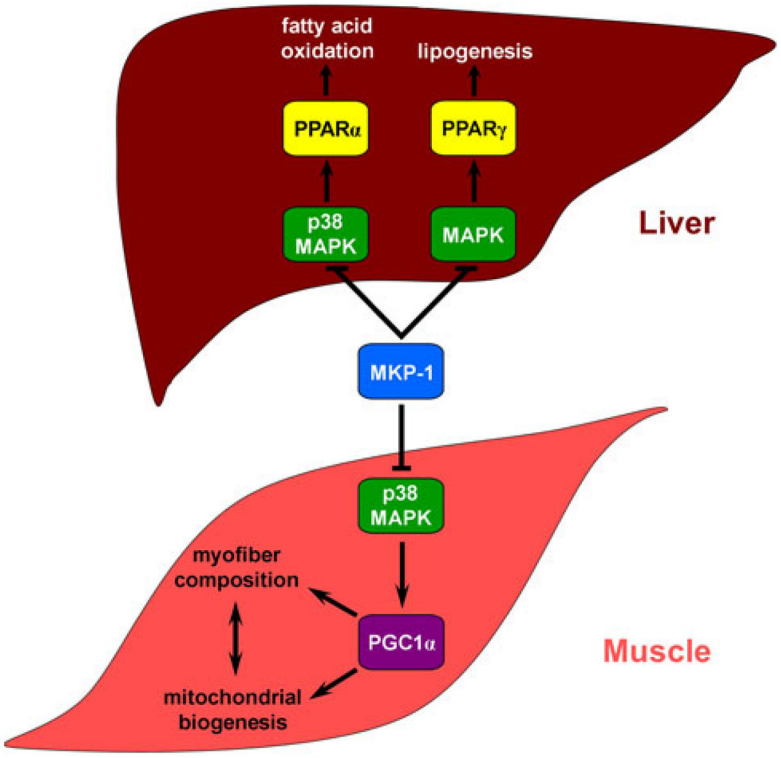

Fig. 4.

MKP-1 in the control of metabolic homeostasis. In the liver and skeletal muscle MKP-1 serves to regulate MAPK-dependent phosphorylation of the peroxisome proliferator-activated receptors (PPARs) and co-activators of the PPARs. The coordinated actions of MKP-1 on MAPK-mediated phosphorylation of targets involved in metabolic control establish MKP-1 as an important player in processes such as lipid metabolism and mitochondrial biogenesis

Table 1

MKP-1 expression in human cancers

Cancer type	Expression	References
Gastric adenocarcinoma	Increased	Bang et al. [130]
Laryngeal squamous cell carcinoma	Increased	Colombo et al. [131]
Oral squamous cell carcinoma	Decreased	Tomioka et al. [132]
Non-small cell lung carcinoma	Increased	Vicent et al. [133]
Breast cancer	Increased	Wang et al. [134]
Breast cancer	Increased	Rojo et al. [135]
Pancreatic cancer	Decreased	Liao et al. [136]
Epithelial tumors	Increased	Loda et al. [137]
Prostate cancer	Increased/decreased	Arnoldussen et al. [124]
Prostate cancer	Increased	Magi-Galluzzi et al. [123]
Melanoma	Increased	Kundu et al. [138]
Ovarian cancer (invasive)	Decreased	Manzano et al. [139]
Ovarian carcinomas (invasive)	Increased	Denkert et al. [140]