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Review

Regulation of MAP kinases by MAP kinase phosphatases

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Abstract

MAP kinase phosphatases (MKPs) catalyze dephosphorylation of activated MAP kinase (MAPK) molecules and deactivate them. Therefore, MKPs play an important role in determining the magnitude and duration of MAPK activities. MKPs constitute a structurally distinct family of dual-specificity phosphatases. The MKP family members share the sequence homology and the preference for MAPK molecules, but they are different in substrate specificity among MAPK molecules, tissue distribution, subcellular localization and inducibility by extracellular stimuli. Our understanding of their protein structure, substrate recognition mechanisms, and regulatory mechanisms of the enzymatic activity has greatly increased over the past few years. Furthermore, although there are a number of MKPs, that have similar substrate specificities, non-redundant roles of MKPs have begun to be identified. Here we focus on recent findings regarding regulation and function of the MKP family members as physiological regulators of MAPK signaling.

Keywords: MAP kinase; MAP kinase phosphatase; Dual-specificity phosphatase

1. Introduction

The MAP kinase (MAPK) signaling pathways are evolutionally highly conserved, and involved in diverse cellular functions, including cell proliferation, differentiation and stress responses. A wide variety of extracellular stimuli, such as growth factors and environmental stresses, induce sequential phosphorylation and activation of three protein kinases, MAP kinase kinase kinase (MAPKKK), MAP kinase kinase (MAPKK) and MAPK. MAPK is a serine/threonine kinase activated by MAPKK via phosphorylation on both threonine and tyrosine residues within the conserved TXY sequence. The MAPK family consists of four members, ERK1/2 (also known as classical MAPK), JNK/SAPK, p38 and ERK5/BMK1. Each molecule is activated in distinct pathways and transmits signals either independently or coordinately [1–6]. One of interesting features of MAPK signaling is that the activation of a single MAPK pathway is able to transduce multiple extracellular stimuli to their specific cellular responses. Accumulating evidence has demonstrated that differences in the duration and magnitude of MAPK activities regulate signaling specificity [7–9]. In other words, fine tuning of MAPK activity is important in determining signaling outcomes. Thus, inactivation of MAPK plays a pivotal role in various physiological processes.

Activated MAPKs are inactivated through dephosphorylation of threonine and/or tyrosine residues within the activation loop. The dephosphorylation could be achieved by serine/threonine phosphatases, tyrosine phosphatases and dual-specificity phosphatases. The serine/threonine phosphatases which dephosphorylate MAPKs include PP2A and PP2C [10]. The tyrosine phosphatases which dephosphorylate MAPKs include three MAPK-specific tyrosine phosphatases, STEP, HePTP and PTP-SL [11,12]. These serine/threonine phosphatases and tyrosine phosphatases have been covered in recent reviews [13–17]. Here we review the dual-specificity MAP kinase phosphatases (MKPs).

2. Overview of the MKP family

MKPs belong to a family of dual-specificity phosphatases and specifically dephosphorylate both threonine and tyrosine

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residues in the activation loop of MAPKs. MKPs are composed of two domains, the MAPK-binding (MKB) domain in the N-terminal half and the dual-specificity phosphatase (DSP) domain in the C-terminal half. The C-terminal DSP domain is homologous to the prototypic dual specificity protein phosphatase VH-1 of vaccinia virus, and the N-terminal MKB domain, which is homologous to the rhodanese family of sulphotransferases, contains two regions of sequence homology with the catalytic domain of the cdc25 phosphatase [18]. The DSP domains of all MKPs share strong homology with each other. Because the DSP domain alone does not show strict selectivity towards the members of MAPKs [19,20], the N-terminal MKB domain plays a major role in regulating their enzymatic specificity through docking interaction with MAPKs. The MKB domain contains a cluster of positively charged amino acids, which play a role in determining binding specificity of MKPs towards MAPKs [21,22]. In addition, a cluster of hydrophobic amino acids and another cluster of positively charged amino acids are required for the specific interaction of MKPs with MAPKs [23] (Fig. 1A). It has been shown that several MKPs are catalytically activated by substrate binding to its MKB domain [24–28]. Binding of phosphorylated MAPK to the MKB domain alters the structure of the DUSP domain. This conformational change, along with the interaction of the catalytic domain with MAPK, greatly enhances the catalytic activity of MKPs [29,30] (Fig. 1B). The details of structure, substrate binding and catalytic activation of MKPs are reviewed in a number of recent reviews [14,15,17,31,32].

3. Classification of MKPs

MKPs are highly specific for MAPKs but differ in the substrate specificity among the MAPK family members, tissue distribution, subcellular localization and inducibility by extracellular stimuli. Based on the sequence similarity, protein structure, substrate specificity and subcellular localization, the MKP family can be divided into three groups [31,32]; Type I, Type II, and Type III (Fig. 2, Table 1).

Type I MKP is a group of MKPs which localize in the nuclear compartment and are induced by many of stimuli that activate MAPKs. For this reason, it has been suggested that these MKPs play an important role in the feedback control of MAPK signaling in the nucleus. Thus, Type I MKP is an inducible nuclear MKP. Type I MKPs include MKP-1, MKP-2, PAC1, and hVH3. MKPs in this group consist of 300 to 400 amino acid residues, and contain a nuclear localization signal (NLS) sequence in their N-terminus [33].

Those MKPs that have a nuclear export signal (NES) and localize in the cytoplasm are classified as Type II MKP. Type II MKP includes MKP-3, MKP-X and MKP-4. Type II MKP is also called the Pyst subfamily of dual-specificity phosphatases. MKP-3, MKP-X and MKP-4 are thus also called Pyst-1, 2 and 3, respectively. MKPs in this group show restricted tissue distribution.

MKP-5, MKP-7 and M3/6 constitute the group of Type III MKP, and selectively dephosphorylate JNK and p38 but not ERK1/2. They have an extended region either in the N-terminus (MKP-5) or in the C-terminus (MKP-7 and M3/6) in

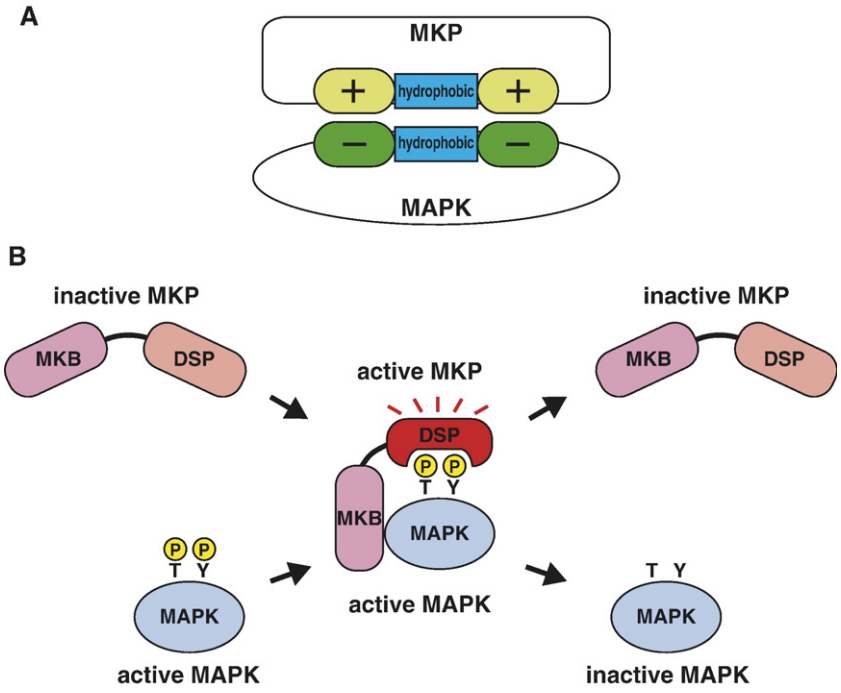

Fig. 1. Interaction of MKPs with MAPKs. (A) The docking interaction between MAPKs and MKPs. The docking surface in the MKB domain of MKPs, which can be divided into three modules, binds to the corresponding sites in MAPKs. (B) Activation of MKPs by MAPKs. The dual-specificity phosphatase (DSP) domain in MKPs is inactive without its substrate. Binding of activated MAPKs to the MKB domain induces conformational changes in the DUSP domain, which causes the increase of its catalytic activity.

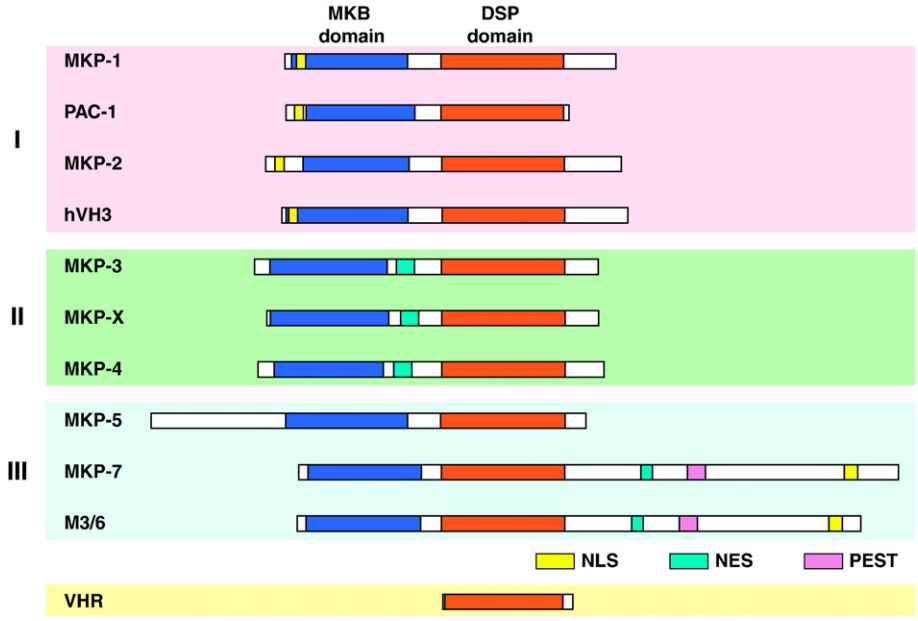

Fig. 2. Classification and domain structure of the MKP family. Domain structures of the three subgroups of MKPs are shown. VHR is an atypical "MKP". In addition to the MAPK binding (MKB) domain and dual-specificity phosphatase (DUSP) domain, nuclear localization signal (NLS), nuclear export signal (NES), and PEST sequences are indicated.

addition to the MKB and DUSP domains. While the function of this region of MKP-5 is unclear, the C-terminal region of MKP-7 and M3/6 contains NLS, NES and the PEST sequence, which is frequently found in rapidly degraded proteins [34]. Removal of the PEST sequence from these proteins results in their stabilization [35], suggesting a role for the sequence in rapid turnover. Although Type III MKPs are too large to enter the nucleus by passive diffusion, they localize both in the cytoplasm and nucleus.

There are atypical "MKPs" that consist of only a catalytic domain with no recognized targeting or docking sequence. These phosphatases consist of the DUSP domain alone and small (approximately 200 amino acids). Some of these phosphatases are able to dephosphorylate MAPKs [36–39].

Although biochemical and structural properties of MKPs have been studied extensively over the past decade, the physiological function of MKPs, including substrate specificity in vivo, has not been fully defined. Here we review the regulation and function of MKPs focusing on recent studies that used knockout mice.

4. Type I MKP

4.1. MKP-1

MKP-1, the firstly discovered MKP, was identified as an immediate early gene that is induced rapidly after exposure to growth factors, heat shock and oxidative stress [40–42]. It was reported that in fibroblasts, the time course of induction of MKP-1 after stimulation was similar to the time course of ERK1/2 inactivation. Purified recombinant MKP-1 dephosphorylates ERK1/2 in vitro, and expression of MKP-1 in cells blocks activation of ERK1/2 [43–45]. Despite these early studies, MKP-1 seems to act on JNK and p38 rather than ERK1/2 under physiological conditions, because it has been shown that MKP-1 more effectively inactivates JNK and p38 than ERK1/2 in vitro and the ERK1/2 activity is not affected in the MKP-1 deficient fibroblasts [46–48]. The catalytic activity of MKP-1 is enhanced by its binding to substrates through the MKB domain [49].

MKP-1 expression is induced by growth factors, heat shock and oxidative stress through activation of ERK1/2. Moreover, ERK1/2 phosphorylates and stabilizes MKP-1 protein [50]. More recently, it was reported that activation of p38 also

Table 1
General features of MKPs

Type	Name	Other name	DUSP No.	MAPK specificity	Subcellular localization
I	MKP-1	CL100, 3CH134, erp, hVH1	DUSP1	p38, JNK>ERK1/2	Nuclear
	PAC1		DUSP2	ERK1/2>p38	Nuclear
	MKP-2	hVH2, TYP2, STY8	DUSP4	ERK1/2, JNK	Nuclear
	hVH3	B23	DUSP5	ERK1/2	Nuclear
II	MKP-3	Pyst1, rVH6	DUSP6	ERK1/2 ERK5	Cytoplasmic
	MKP-X	Pyst2, B59	DUSP7	ERK1/2>JNK	Cytoplasmic
	MKP-4	Pyst3	DUSP9	ERL1/2, p38	Cytoplasmic
III	MKP-5		DUSP10	JNK, p38	Nuclear/ Cytoplasmic
	MKP-7	MKP-M	DUSP16	JNK, p38	Nuclear/ Cytoplasmic
	M3/6	hVH5, HB5	DUSP8	JNK, p38	Nuclear/ Cytoplasmic

stabilizes MKP-1 through MAPKAP kinase 2 [51]. Therefore, MKP-1 is involved in a negative feedback loop of MAPK signaling, and its expression level seems to be modulated at multiple stages.

MKP-1 is used as a mediator of a cross-talk between the MAPK pathway and the other signaling pathways. MKP-1 is a transcriptional target of the tumor suppressor p53 [52]. TGF-β signaling and retinoid acid signaling upregulate MKP-1 expression [53,54]. Moreover, while PKCζ induces MKP-1 expression in response to hypoxia [55], PKCδ triggers MKP-1 degradation in glutamate-induced cell death [56]. In addition, MKP-1 is induced by several hormones, such as glucocorticoids, endocannabinoid and parathyroid [57–59].

MKP-1 deficient mice appear normal and fertile, and fibroblasts derived from mice lacking MKP-1 have unaltered ERK1/2 activation, cell growth and c-*fos* expression in response to serum [47]. Therefore, the physiological role of MKP-1 was unknown. However, recent studies provided evidence for essential roles of MKP-1 in the regulation of p38 and JNK. First, primary mouse embryonic fibroblasts (MEFs) derived from mice lacking MKP-1 exhibit hyperactivation of p38 and JNK in response to serum, osmotic stress and anisomycin [60]. In addition, MKP-1 is shown to be required for attenuation of cAMP-induced p38 activation and CREB responsiveness. Interestingly, MKP-1-deficient MEFs exhibit reduced cell growth as a result of enhanced sensitivity to cell death and stress-induced apoptosis. Therefore, MKP-1 plays a critical role in the negative regulation of p38 and JNK in response to stress [60]. In a more recent study, hyperactivation of ERK1/2, p38, and JNK is seen in insulin-response tissues in MKP-1-deficient mice [61]. MKP-1-deficient mice show resistance to diet-induced obesity due to enhanced energy expenditure, which is independent of glucose homeostasis. Moreover, the activities of these three MAPKs are increased in the nucleus, but not in the cytoplasm. Thus, nuclear regulation of MAPKs by MKP-1 is essential for the management of metabolic homeostasis [61]. Macrophages from mice lacking MKP-1 also show increased JNK and p38 activities in response to lipopolysaccharide (LPS) [62]. Moreover, MKP-1-deficient macrophages are highly sensitive to endotoxic shock and produce both pro- and anti-inflammatory cytokines, including TNF, IL-6 and IL-10, more robustly and rapidly than wild-type macrophages [63–66]. The overproduction of these cytokines is dependent on p38 activity [63]. Therefore, MKP-1 plays a role in regulating inflammation during innate immune response by regulating p38 activity (see Fig. 3).

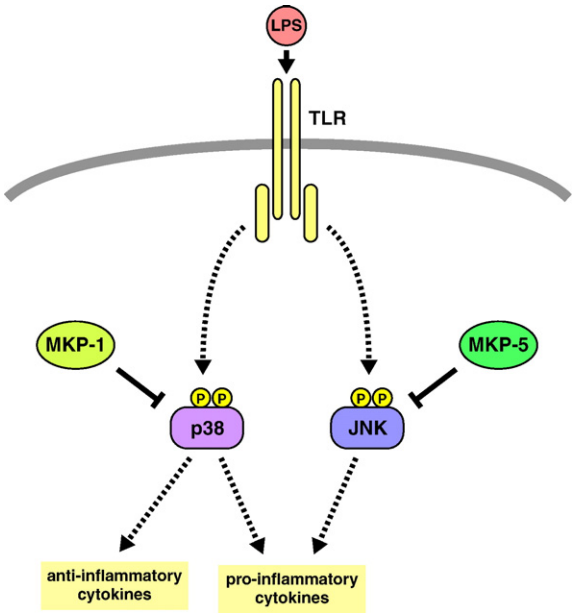

Fig. 3. Roles of MKP-1 and MKP-5 in immunity. In macrophages, LPS binding to Toll-like receptor (TLR) activates both the p38 pathway and the JNK pathway, which induce the expression of inflammatory cytokines. LPS signaling also induces both MKP-1 and MKP-5 expression, and MKP-1 and MKP-5 specifically downregulate p38 and JNK, respectively.

4.2. PAC-1

PAC-1 was originally identified as a mitogen-inducible gene in human T cells [67]. It is highly induced in T cells and B cells upon activation [68]. Activation of the ERK1/2 pathway induces PAC-1 expression [67]. PAC-1 specifically dephosphorylates ERK1/2 and p38 in vitro [46,69]. Notably, while the interaction of the PAC-1 MKB domain with ERK1/2 increases PAC-1 catalytic activity, its interaction with p38 does not [28].

Recent studies have revealed in vivo function of PAC-1. It has been shown that transcription of PAC-1 is activated by p53 through a palindromic site in the PAC-1 promoter during apoptosis [70]. Serum withdrawal and oxidative stress induce p53-dependent apoptosis and PAC-1 transcription. PAC-1 overexpression enhances sensitivity to apoptosis and suppresses tumor formation. Inhibition of PAC-1 expression by RNA interference inhibits p53-mediated apoptosis. Therefore, it is likely that PAC-1 is required for p53-mediated apoptosis. In this case, ERK1/2 activity is decreased by p53 activation, suggesting that PAC-1 specifically dephosphorylates ERK1/2 in vivo. As p38 activity is not investigated in the study, it is unclear whether PAC-1 dephosphorylates p38 in vivo. PAC-1 is identified as one of the most highly induced transcripts in activated immune effector cells as well as one of the most abundant and regulated MKPs in many activated leukocytes [71]. Thus, PAC-1 may serve as a chief regulator of MAPK activities in immunity, especially in immune effector cells associated with inflammatory reaction. Detailed analyses of recently generated PAC-1 knockout mice have identified novel function of PAC-1 in immune system [71]. PAC-1 null mice develop and age normally, and show no abnormalities in basic immune features. On the other hand, they show considerably reduced inflammatory responses in the autoimmune model of rheumatoid arthritis, in which disease pathogenesis is dependent on effector leukocytes. Therefore, although PAC-1 has no obvious function in immune cell development, it has a critical positive function in promoting inflammatory responses. Consequently, LPS-stimulated PAC-1 null macrophages produce fewer pro-inflammatory mediators, cytokines and inflammatory chemokines when compared with LPS-

stimulated normal macrophages. Notably, PAC-1 deficiency leads to increased JNK activity but unexpected impairment of ERK1/2 and p38 activities. This is surprising because it has been shown that PAC-1 dephosphorylates ERK1/2 and p38, but not JNK [28,46,69]. Pharmacological inhibition of JNK activity can rescue the reduced phosphorylation of ERK1/2 [71], suggesting that loss of PAC-1 may decrease ERK1/2 activity by upregulating JNK activity. Therefore, it is likely that there is a cross-talk between ERK1/2 and JNK. In addition, how PAC-1 targets JNK in immune system should be examined.

4.3. MKP-2

MKP-2 is the other member of type I MKP [72,73]. It has been shown that MKP-2 is induced by growth factors [73,74], gonadotropin-releasing hormone (GnRH) [75], retinoic acid [54] and the oncogene v-jun [76]. Activation of the ERK1/2 pathway induces MKP-2 expression [74]. Moreover, cellular senescence increases MKP-2 protein by blocking its degradation [77]. MKP-2 specifically dephosphorylates ERK1/2 and JNK in vitro [46], and the interaction of MKP-2 with ERK1/2 and JNK enhances its catalytic activity [25]. However, the substrate specificity of MKP-2 in vivo is still unclear. It has been reported that MKP-2 dephosphorylates JNK, but not ERK1/2 in UV-C or cisplatin treated cells [78]. In these cells, while JNK translocates to the nucleus, ERK1/2 remains in the cytoplasm. Therefore, MKP-2 may dephosphorylate nuclear JNK, but not cytoplasmic ERK1/2. Recently, MKP2 is shown to be a transcription target of p53 in mediating apoptosis [79]. MKP2 is induced by oxidative stress in a p53-dependent manner.

4.4. hVH3

hVH3 is induced by heat shock and growth factors [80,81]. In peripheral blood T lymphocytes, IL-2, IL-7 and IL-15 induce hVH3, and IL-2 induced ERK1/2 activation is inhibited by hVH3 [82], suggesting a negative feedback role for hVH3 in IL-2 signaling. Moreover, anti-CD3 stimulation of thymocytes strikingly induces hVH3 [83]. Therefore, hVH3 might play an important role in T cells. hVH3 interacts with and dephosphorylates ERK1/2 but not JNK or p38. It is possible that hVH3 is a direct transcriptional target of the tumor suppressor p53 [84].

A recent study has shown that hVH3 can regulate subcellular localization of ERK1/2 [85]. Expression of hVH3 causes both nuclear translocation and sequestration of ERK1/2. This nuclear anchoring is ERK1/2 specific and requires both the functional NLS in hVH3 and the interaction between the hVH3 MKB domain and the ERK1/2 common docking (CD) domain. Moreover, the catalytically inactive mutant of hVH3 can also anchor ERK1/2 in the nucleus. Interestingly, the inactive hVH3-anchored nuclear ERK1/2 is phosphorylated by MEK1/2 upon stimulation and the activated ERK1/2 is able to activate its nuclear target Elk-1. The results suggest that hVH3 functions as a nuclear anchor for ERK1/2.

5. Type II MKP

5.1. MKP-3

MKP-3 is specific to ERK1/2 and ERK5 [86–90]. To date, MKP-3 is the only MKP that is shown to dephosphorylate ERK5. ERK1/2 binding to the MKB domain of MKP-3 increases its phosphatase activity [19,24]. MKP-3, as well as MKP-1, is phosphorylated by ERK1/2 and this phosphorylation facilitates proteasomal degradation of MKP-3 [91]. As MKP-3 shuttles between the cytoplasm and the nucleus and is able to anchor ERK1/2 in the cytoplasm, it has been suggested that MKP-3 may play a role in determining cytoplasmic localization of ERK1/2 [92].

Regulatory mechanisms of MKP-3 expression seem to be cell type-dependent. While MKP-3 appears to be constitutively expressed in some cell types, it is induced by some growth factors, such as nerve growth factors and basic fibroblast growth factors [86,93,94]. MKP-3 is expressed in insulin-responsive tissues, and its expression in liver is markedly elevated in insulin-resistant obese mice [95]. In developing mouse embryos, MKP-3 mRNA is detected in presegmental paraxial mesoderm, limb bud and branchial arch mesenchyme, midbrain/hindbrain isthmus and nasal, dental, hair and mammary placodes [96]. As most of these have been characterized as sites of FGF/FGFR signaling, MKP-3 seems to be involved in the FGF/FGFR signaling pathway during early development. During limb development, the apical ectodermal ridge (AER)-derived FGF8 is a key factor, and its signal should be transmitted to the underlying mesenchyme [97]. It has been shown that MKP-3 is induced by FGF8 in chick, mouse and zebrafish limb/fin buds [98]. While a high level of phosphorylated ERK1/2 is detected in the AER, MKP-3 expression and Akt phosphorylation are reported to be detected only in the mesenchyme [98]. Therefore, it is likely that induction of MKP-3 expression by FGF8 is mediated through the PI3K pathway (Fig. 4). The phosphorylation status of ERK1/2 in the mesenchyme is controversial. While several studies reported that phosphorylated ERK1/2 is detected in the mesenchyme [99,100], another study failed to detect phosphorylated ERK1/2 [98]. However, mice lacking PDK1, an essential mediator of the PI3K pathway, express MKP-3 in limb buds [100]. Thus it is possible that the ERK1/2 pathway, as well as the PI3K pathway, is involved in the mechanism of MKP-3 expression (Fig. 4). While inhibition of MKP-3 expression induces apoptosis in the mesenchyme, MKP-3 overexpression causes developmental abnormalities, suggesting that MKP-3 plays a pivotal role in limb development by setting an appropriate level of ERK1/2 activity [98]. In support of this notion, both gain- and loss-of-function studies in the zebrafish embryo also have shown that MKP-3 is required for controlling the extent of ERK1/2 activity [101]. In addition, recent studies have revealed that expression of MKP-3 is also regulated by FGF in chicken neural plate, in mouse isthmic organizer during neural tube development and in developing chick somite [102–104]. Interestingly, while expression of MKP-3 is induced by FGF through the PI3K pathway in limb and isthmic organizer [98,103], it is induced

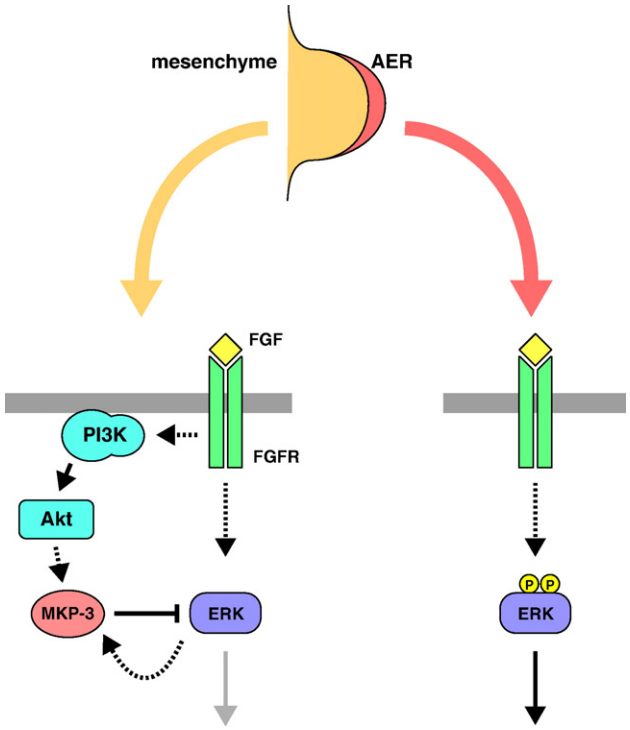

Fig. 4. Role of MKP-3 in limb bud development. In apical ectodermal ridge (AER), ERK1/2 is activated by FGF signaling. On the other hand, in mesenchyme, FGF signaling induces MKP-3 expression through activation of the PI3K-Akt and the ERK1/2 pathways. Then, ERK1/2 is inactivated by MKP-3 in mesenchyme. This MKP-3 function is important for normal limb development.

through the ERK1/2 pathway in neural plate and somite [102,104]. Expression of MKP-3 is also reported to be regulated by a maternal β-catenin signal and retinoic acid signaling [101,105].

5.2. MKP-X

It has been shown that MKP-X is able to form a complex with ERK1/2 and preferentially targets ERK1/2 protein as its substrate in vitro [86]. In addition, MKP-X binds to and dephosphorylates JNK in vitro [106]. Both MKP-X mRNA and protein are expressed in bone marrow, peripheral leukocytes from acute myeloid leukemia and several leukemia cells [107–109]. However, the biological function of MKP-X remains unclear.

5.3. MKP-4

MKP-4 specifically blocks activation of ERK1/2 when expressed in cells [110] and dephosphorylates ERK1/2 and p38 in vitro [111]. MKP-4 shows a highly restricted tissue distribution; it is expressed only in placenta, kidney, embryonic liver, migrating muscles and insulin-response tissues [110,111]. MKP-4 is identified as a candidate gene involved in the negative regulation of insulin signaling [112]. MKP-4 is expressed in the insulin-response tissues and the expression levels are up-regulated in obese, insulin-resistant rodent models. Expression of MKP-4 inhibits insulin-induced adipogenesis in preadipocytes and glucose uptake in adipocytes. It has also been reported that MKP-4 attenuates p38 activity and inhibits arsenite-induced glucose uptake in adipocytes [113]. Therefore, these studies suggest that MKP-4 negatively regulates insulin signaling via dephosphorylation of p38. The other physiological function of MKP-4 is revealed by the MKP-4 knockout mice study [114]. MKP-4 gene is on the X chromosome, and both female heterozygous and male null mice die in utero. The developmental defect is characterized by a failure to form a functional labyrinth, and this is consistent with the high expression of MKP-4 in the wild type placenta. When the placental defect was rescued, male null embryos developed to term, appeared normal and were fertile. Therefore, MKP-4 is essential for the extracellular placenta development. Surprisingly, loss of MKP-4 did not lead to significant changes in the basal phosphorylation state of any MAPKs in placental tissues. It is, however, possible that significant changes in MAPK activities were occurring in restricted compartments and/or time periods. Notably, the placental defects are caused also by the loss of MEK1, a MAPKK of ERK1/2, and p38α [115,116], suggesting that MKP-4 is involved in regulation of either or both of the ERK1/2 and p38 pathways. As MKP-4 seems to play a role in insulin signaling, it would be interesting to examine the insulin-resistance of MKP-4 knockout mice.

6. Type III MKP

6.1. MKP-5

MKP-5 binds to and dephosphorylates JNK and p38, but not ERK1/2 [20,117]. p38 is a preferred substrate. MKP-5 is expressed in heart, lung, liver, kidney and skeletal muscle. MKP-5 expression in cultured cells is elevated by stress stimuli. MKP-5 is also identified as a gene that is induced by DNA double-strand break in an ATM-dependent manner [118]. Recently, MKP-5 function in immune response has been demonstrated [119]. MKP-5 expression is strongly induced upon LPS treatment in macrophages, constitutive in naive CD4+ T cells and downregulated after T-cell activation. Then MKP-5 deficient mice were created to understand the role of MKP-5 in regulating MAPK during immune response. Deletion of MKP-5 does not cause any developmental defects, and lymphoid and myeloid cells develop normally in the absence of the MKP-5 gene, indicating that MKP-5 is not required for development of the immune system. However, T cells lacking MKP-5 exhibit markedly enhanced JNK activity but no enhancement in p38 activity. Increased JNK activity is also observed in MKP-5 deficient macrophages after LPS treatment. Thus, MKP-5 may function to decrease JNK activity in immune responses. MKP-5 null macrophages upon treatment with LPS express increased levels of the pro-inflammatory cytokines, and MKP-5 null T-cells are activated greater than wild type cells. In addition, MKP-5 deficient antigen-presenting cells (APCs) show enhanced T cell priming activity. These results suggest that MKP-5 is a negative regulator of innate immunity (see Fig. 3). On the other hand, MKP-5 deficient T-cells show reduced proliferation capability upon activation, suggesting that MKP-5

is required for proper T-cell expansion. Moreover, detailed analyses in MKP-5 deficient mice suggest that MKP-5 has a principal function in both innate and adaptive immune responses [119].

As MKP-1-deficient mice, as well as MKP-5 deficient mice, show the immune defects (see above), it seems interesting to examine the differences in their phenotypic features in detail. While MKP-1-deficient macrophages exhibit enhanced p38 activity and overproduce pro- and anti-inflammatory cytokines, MKP-5 deficient macrophages exhibit enhanced JNK activity and overproduce pro-inflammatory cytokines (see Fig. 3). Therefore, although both MKP-1 and MKP-5 dephosphorylate both p38 and JNK in vitro, they may have different substrate specificities in macrophages.

6.2. MKP-7

MKP-7, the biggest molecule in the MKP family, has a unique long C-terminal region that contains both NLS and NES, by which MKP-7 shuttles between the nucleus and the cytoplasm [120,121]. MKP-7 binds to and dephosphorylates JNK and p38 but not ERK1/2 [120,121]. MKP-7 expression is induced by JNK activation [122] and by LPS stimulation in macrophages [35]. It has been shown that MKP-7 binds to ERK1/2 through its C-terminal region, which is phosphorylated by ERK1/2 in response to several extracellular stimuli [123]. This phosphorylation of MKP-7 by ERK1/2 suppresses the proteasomal degradation of MKP-7. As MKP-7 dephosphorylates JNK and p38 but ERK1/2, it is possible that the ERK1/2 pathway inhibits JNK or p38 activity via MKP-7 stabilization. JIP-1, a scaffold protein for the JNK pathway, binds to JNK, MKK7 and MLKs, and facilitates activation of the JNK pathway [124]. MKP-7 binds to JIP-1 through its C-terminal region and inactivates JNK [125]. Moreover, MKP-7 also binds to β-arrestin 2 via the same region that interacts with JIP-1 [126]. MKP-7 dephosphorylates JNK-3, which binds to β-arrestin 2, upon activation of the JNK-pathway by ASK1 expression or the angiotensin receptor stimulation. The physiological function of MKP-7 is to be elucidated.

6.3. M3/6

M3/6 (also called hVH-5) displays specificity towards inactivation of JNK and p38 [89,127]. M3/6 has both NES and NLS sequences in its C-terminal region, which is very similar to that of MKP-7, and also shuttles between the cytoplasm and the nucleus. Like MKP-7, M3/6 binds to JIP-1 [125]. M3/6 is expressed predominantly in the adult brain, heart, and skeletal muscle [127]. M3/6 expression is induced in the brain by cocaine and odor treatment, suggesting its role in the brain [128,129]. Its expression and activity could also be regulated by those stress stimuli, that usually upregulate JNK activity. Oxidative stress decreases the expression of M3/6 [130]. M3/6 dissociates from JNK and appears in an insoluble fraction after heat shock [131]. Moreover, while phorbol ester induces JNK activation and increases the steady-state level of M3/6, to form a feedback loop [132], anisomycin and arsenite inactivate M3/6 activity [133]. It has also been suggested that M3/6 is phosphorylated in response to stress stimulation [132].

7. Atypical “MKP”

7.1. VHR

As VHR (Vaccinia H1-related) is the firstly identified dual specificity phosphatase in mammals [134], the catalytic domain of VHR has been the subject of detailed biochemical and structural analyses. VHR inactivates ERK1/2 and JNK in vivo and in vitro [36,37,135]. VHR is not acutely induced in response to MAPKs activation. Most recently, however, it has been reported that ERK1/2 positively regulates VHR phosphatase activity by inducing VRK3, a member of the Vaccinia-related kinase (VRK) family [136]. VRK3 enhances VHR activity by a mechanism independent of its kinase activity through its direct binding to VHR. Interestingly, ERK1/2 activation induces VRK3 expression. Therefore, activation of the ERK1/2 pathway induces VRK3 and enhances VHR activity, forming a feedback loop [136]. VHR is expressed in lymphoid and hematopoietic cells and is constitutively expressed in T cells, and negatively regulates T-cell receptor induced ERK1/2 and JNK activation [36]. Moreover, VHR is phosphorylated by ZAP-70, a protein tyrosine kinase which is of importance in T and NK cell signaling, and this phosphorylation is required for VHR to inhibit the ERK1/2 pathway in response to T-cell receptor activation [137]. In addition to its function in immune system, a recent study has reported that VHR plays an important role in cell cycle regulation [138]. VHR is barely detectable in cells in G1 phase, but then gradually increased during progression of the cells through S phase and is most abundant in mitotic cells. Inhibition of VHR expression by RNA interference arrests cells in the G1/S and G2/M transitions and causes the initial sign of senescence. In DNA microarray analysis, about 200 genes are downregulated and about 100 genes upregulated by VHR RNA interference. In agreement with the cell cycle arrest and senescence seen in cells lacking VHR, the most upregulated gene is p21, a CDK inhibitor, whereas the downregulated genes include cell cycle regulators, such as CDK2, CDC2, cyclinA2 and E2, general transcription factors, RNA polymerase I and II, DNA replication machinery and DNA repair proteins. Loss of VHR also causes several fold increase of serum-induced activation of ERK1/2 and JNK. Furthermore, VHR deletion-induced cell-cycle arrest is dependent on hyperphosphorylation of ERK1/2 and JNK. Therefore, VHR is required for cell-cycle progression and modulates ERK1/2 and JNK activation in a cell-cycle phase dependent manner [138].

8. Other low molecular weight dual-specificity phosphatases

MKP-6, which is not a typical MKP, is composed of its DSP domain alone, like VHR. MKP-6 can dephosphorylate ERK1/2 and JNK in vitro [139]. MKP-6 interacts with CD28 and is induced by TCR and CD28 co-stimulation in T cells, suggesting that MKP-6 functions as a negative-feedback regulator of CD28

Table 2
Low molecular weight dual-specificity phosphatases that dephosphorylate MAPKs

Name	Other name	DUSP no.	MAPK specificity	Subcellular localization
VHR		DUSP3	ERK1/2	Nuclear
MKP-6	MKP-L	DUSP14	ERK1/2, JNK	Cytoplasmic
DUSP18		DUSP18	JNK	N/D
DSP-2	JSP1, JKAP, VHX	DUSP22	JNK, p38	Cytoplasmic
MKP-8		DUSP26	p38	Nuclear

co-stimulatory signaling [139]. Besides VHR and MKP-6, there are several low molecular weight dual-specificity phosphatases that dephosphorylate MAPKs at least in vitro (see Table 2). However, function of these phosphatases is unknown.

9. Conclusion and perspectives

Modulation of MAPK activities is crucially important to regulate many biological processes. As MKPs can dephosphorylate MAPKs, it has been thought that MKPs play a pivotal role in regulation of MAPK activities. Thus, many studies have uncovered the properties and function of MKPs, although there are several members of MKPs, such as hVH-3, MKP-X and MKP-7, whose function is still unclear. Recent studies employing relevant model systems have revealed non-redundant roles of each MKP in a variety of biological processes. Knock-out of MKP-1, MKP-4, MKP-5 and PAC-1 in mice has revealed their function, such as the essential role of MKP-1, MKP-5, and PAC-1 in immune system. It is of great interest that three MKPs play different roles in the same system with their strict substrate specificity. Similarly, the study with mice lacking the other MKPs will reveal their important roles. Moreover, as MKPs seem to have redundancy in function, creating double knockout mice of MKPs will significantly increase our understanding of the function of MKPs. In chicken embryos, a variety of techniques, including tissue ablation, transplantation, RNA interference and viral injection have revealed the essential role of MKP-3 in limb development. Thus, the combination of a range of model systems and techniques will facilitate future studies.

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References

[1] L. Chang, M. Karin, Mammalian MAP kinase signalling cascades, Nature 410 (2001) 37–40.
[2] R.J. Davis, Signal transduction by the JNK group of MAP kinases, Cell 103 (2000) 239–252.
[3] E. Nishida, Y. Gotoh, The MAP kinase cascade is essential for diverse signal transduction pathways, Trends Biochem. Sci. 18 (1993) 128–131.
[4] M.J. Robinson, M.H. Cobb, Mitogen-activated protein kinase pathways, Curr. Opin. Cell Biol. 9 (1997) 180–186.
[5] T.W. Sturgill, J. Wu, Recent progress in characterization of protein kinase cascades for phosphorylation of ribosomal protein S6, Biochim. Biophys. Acta 1092 (1991) 350–357.
[6] A.J. Waskiewicz, J.A. Cooper, Mitogen and stress response pathways: MAP kinase cascades and phosphatase regulation in mammals and yeast, Curr. Opin. Cell Biol. 7 (1995) 798–805.
[7] M. Ebisuya, K. Kondoh, E. Nishida, The duration, magnitude and compartmentalization of ERK MAP kinase activity: mechanisms for providing signaling specificity, J. Cell Sci. 118 (2005) 2997–3002.
[8] L.O. Murphy, J. Blenis, MAPK signal specificity: the right place at the right time, Trends Biochem. Sci. 31 (2006) 268–275.
[9] J. Pouyssegur, P. Lenormand, Fidelity and spatio-temporal control in MAP kinase (ERKs) signalling, Eur. J. Biochem. 270 (2003) 3291–3299.
[10] D.R. Alessi, N. Gomez, G. Moorhead, T. Lewis, S.M. Keyse, P. Cohen, Inactivation of p42 MAP kinase by protein phosphatase 2A and a protein tyrosine phosphatase, but not CL100, in various cell lines, Curr. Biol. 5 (1995) 283–295.
[11] R. Pulido, A. Zuniga, A. Ullrich, PTP-SL and STEP protein tyrosine phosphatases regulate the activation of the extracellular signal-regulated kinases ERK1 and ERK2 by association through a kinase interaction motif, EMBO J. 17 (1998) 7337–7350.
[12] M. Saxena, S. Williams, J. Brockdorff, J. Gilman, T. Mustelin, Inhibition of T cell signaling by mitogen-activated protein kinase-targeted hematopoietic tyrosine phosphatase (HePTP), J. Biol. Chem. 274 (1999) 11693–11700.
[13] A.J. Barr, S. Knapp, MAPK-specific tyrosine phosphatases: new targets for drug discovery? Trends Pharmacol. Sci. (2006) 525–530.
[14] M. Camps, A. Nichols, S. Arkinstall, Dual specificity phosphatases: a gene family for control of MAP kinase function, FASEB J. 14 (2000) 6–16.
[15] S.M. Keyse, Protein phosphatases and the regulation of mitogen-activated protein kinase signalling, Curr. Opin. Cell Biol. 12 (2000) 186–192.
[16] M. Saxena, T. Mustelin, Extracellular signals and scores of phosphatases: all roads lead to MAP kinase, Semin. Immunol. 12 (2000) 387–396.
[17] X.L. Zhan, M.J. Wishart, K.L. Guan, Nonreceptor tyrosine phosphatases in cellular signaling: regulation of mitogen-activated protein kinases, Chem. Rev. 101 (2001) 2477–2496.
[18] S.M. Keyse, M. Ginsburg, Amino acid sequence similarity between CL100, a dual-specificity MAP kinase phosphatase and cdc25, Trends Biochem. Sci. 18 (1993) 377–378.
[19] M. Muda, A. Theodosiou, C. Gillieron, A. Smith, C. Chabert, M. Camps, U. Boschert, N. Rodrigues, K. Davies, A. Ashworth, S. Arkinstall, The mitogen-activated protein kinase phosphatase-3 N-terminal noncatalytic region is responsible for tight substrate binding and enzymatic specificity, J. Biol. Chem. 273 (1998) 9323–9329.
[20] T. Tanoue, T. Moriguchi, E. Nishida, Molecular cloning and characterization of a novel dual specificity phosphatase, MKP-5, J. Biol. Chem. 274 (1999) 19949–19956.
[21] T. Tanoue, M. Adachi, T. Moriguchi, E. Nishida, A conserved docking motif in MAP kinases common to substrates, activators and regulators, Nat. Cell Biol. 2 (2000) 110–116.
[22] T. Tanoue, R. Maeda, M. Adachi, E. Nishida, Identification of a docking groove on ERK and p38 MAP kinases that regulates the specificity of docking interactions, EMBO J. 20 (2001) 466–479.
[23] T. Tanoue, T. Yamamoto, E. Nishida, Modular structure of a docking surface on MAPK phosphatases, J. Biol. Chem. 277 (2002) 22942–22949.
[24] M. Camps, A. Nichols, C. Gillieron, B. Antonsson, M. Muda, C. Chabert, U. Boschert, S. Arkinstall, Catalytic activation of the phosphatase MKP-3 by ERK2 mitogen-activated protein kinase, Science 280 (1998) 1262–1265.
[25] P. Chen, D. Hutter, X. Yang, M. Gorospe, R.J. Davis, Y. Liu, Discordance between the binding affinity of mitogen-activated protein kinase subfamily members for MAP kinase phosphatase-2 and their ability to activate the phosphatase catalytically, J. Biol. Chem. 276 (2001) 29440–29449.
[26] S. Dowd, A.A. Sneddon, S.M. Keyse, 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. 111 (Pt 22) (1998) 3389–3399.
[27] D. Hutter, P. Chen, J. Barnes, Y. Liu, 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. 352 (Pt. 1) (2000) 155–163.
[28] Q. Zhang, M. Muller, C.H. Chen, L. Zeng, A. Farooq, M.M. Zhou, New insights into the catalytic activation of the MAPK phosphatase PAC-1 induced by its substrate MAPK ERK2 binding, J. Mol. Biol. 354 (2005) 777–788.
[29] A. Farooq, G. Chaturvedi, S. Mujtaba, O. Plotnikova, L. Zeng, C. Dhalluin, R. Ashton, M.M. Zhou, Solution structure of ERK2 binding domain of MAPK phosphatase MKP-3: structural insights into MKP-3 activation by ERK2, Mol. Cell 7 (2001) 387–399.
[30] A.E. Stewart, S. Dowd, S.M. Keyse, N.Q. McDonald, Crystal structure of the MAPK phosphatase Pyst1 catalytic domain and implications for regulated activation, Nat. Struct. Biol. 6 (1999) 174–181.
[31] A. Farooq, M.M. Zhou, Structure and regulation of MAPK phosphatases, Cell Signal 16 (2004) 769–779.
[32] A. Theodosiou, A. Ashworth, MAP kinase phosphatases, Genome Biol. 3 (2002) (REVIEWS3009).
[33] J.J. Wu, L. Zhang, A.M. Bennett, The noncatalytic amino terminus of mitogen-activated protein kinase phosphatase 1 directs nuclear targeting and serum response element transcriptional regulation, Mol. Cell. Biol. 25 (2005) 4792–4803.
[34] M. Rechsteiner, S.W. Rogers, PEST sequences and regulation by proteolysis, Trends Biochem. Sci. 21 (1996) 267–271.
[35] T. Matsuguchi, T. Musikacharoen, T.R. Johnson, A.S. Kraft, Y. Yoshikai, A novel mitogen-activated protein kinase phosphatase is an important negative regulator of lipopolysaccharide-mediated c-Jun N-terminal kinase activation in mouse macrophage cell lines, Mol. Cell. Biol. 21 (2001) 6999–7009.
[36] A. Alonso, M. Saxena, S. Williams, T. Mustelin, Inhibitory role for dual specificity phosphatase VHR in T cell antigen receptor and CD28-induced Erk and Jnk activation, J. Biol. Chem. 276 (2001) 4766–4771.
[37] J.L. Todd, K.G. Tanner, J.M. Denu, Extracellular regulated kinases (ERK) 1 and ERK2 are authentic substrates for the dual-specificity protein-tyrosine phosphatase VHR. A novel role in down-regulating the ERK pathway, J. Biol. Chem. 274 (1999) 13271–13280.
[38] S.A. Vasudevan, J. Skoko, K. Wang, S.M. Burlingame, P.N. Patel, J.S. Lazo, J.G. Nuchtern, J. Yang, MKP-8, a novel MAPK phosphatase that inhibits p38 kinase, Biochem. Biophys. Res. Commun. 330 (2005) 511–518.
[39] Q. Wu, S. Huang, Y. Sun, S. Gu, F. Lu, J. Dai, G. Yin, L. Sun, D. Zheng, C. Dou, C. Feng, C. Ji, Y. Xie, Y. Mao, Dual specificity phosphotase 18, interacting with SAPK, dephosphorylates SAPK and inhibits SAPK/JNK signal pathway in vivo, Front. Biosci. 11 (2006) 2714–2724.
[40] C.H. Charles, A.S. Abler, L.F. Lau, cDNA sequence of a growth factor-inducible immediate early gene and characterization of its encoded protein, Oncogene 7 (1992) 187–190.
[41] S.M. Keyse, E.A. Emslie, Oxidative stress and heat shock induce a human gene encoding a protein-tyrosine phosphatase, Nature 359 (1992) 644–647.
[42] T. Noguchi, R. Metz, L. Chen, M.G. Mattei, D. Carrasco, R. Bravo, 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. 13 (1993) 5195–5205.
[43] D.R. Alessi, C. Smythe, S.M. Keyse, The human CL100 gene encodes a Tyr/Thr-protein phosphatase which potently and specifically inactivates MAP kinase and suppresses its activation by oncogenic ras in Xenopus oocyte extracts, Oncogene 8 (1993) 2015–2020.
[44] H. Sun, C.H. Charles, L.F. Lau, N.K. Tonks, MKP-1 (3CH134), an immediate early gene product, is a dual specificity phosphatase that dephosphorylates MAP kinase in vivo, Cell 75 (1993) 487–493.
[45] C.F. Zheng, K.L. Guan, Dephosphorylation and inactivation of the mitogen-activated protein kinase by a mitogen-induced Thr/Tyr protein phosphatase, J. Biol. Chem. 268 (1993) 16116–16119.
[46] Y. Chu, P.A. Solski, R. Khosravi-Far, C.J. Der, K. Kelly, The mitogen-activated protein kinase phosphatases PAC1, MKP-1, and MKP-2 have unique substrate specificities and reduced activity in vivo toward the ERK2 sevenmaker mutation, J. Biol. Chem. 271 (1996) 6497–6501.
[47] K. Dorfman, D. Carrasco, M. Gruda, C. Ryan, S.A. Lira, R. Bravo, Disruption of the erp/mkp-1 gene does not affect mouse development: normal MAP kinase activity in ERP/MKP-1-deficient fibroblasts, Oncogene 13 (1996) 925–931.
[48] C.C. Franklin, A.S. Kraft, Conditional expression of the mitogen-activated protein kinase (MAPK) phosphatase MKP-1 preferentially inhibits p38 MAPK and stress-activated protein kinase in U937 cells, J. Biol. Chem. 272 (1997) 16917–16923.
[49] D.N. Slack, O.M. Seternes, M. Gabrielsen, S.M. Keyse, Distinct binding determinants for ERK2/p38alpha and JNK map kinases mediate catalytic activation and substrate selectivity of map kinase phosphatase-1, J. Biol. Chem. 276 (2001) 16491–16500.
[50] J.M. Brondello, J. Pouyssegur, F.R. McKenzie, Reduced MAP kinase phosphatase-1 degradation after p42/p44MAPK-dependent phosphorylation, Science 286 (1999) 2514–2517.
[51] J.H. Hu, T. Chen, Z.H. Zhuang, L. Kong, M.C. Yu, Y. Liu, J.W. Zang, B. X. Ge, Feedback control of MKP-1 expression by p38, Cell Signal (2006) (electronic publication ahead of print doi:10.1016/j.cellsig.2006.07.010).
[52] M. Li, J.Y. Zhou, Y. Ge, L.H. Matherly, G.S. Wu, The phosphatase MKP1 is a transcriptional target of p53 involved in cell cycle regulation, J. Biol. Chem. 278 (2003) 41059–41068.
[53] F. Mikami, J.H. Lim, H. Ishinaga, U.H. Ha, H. Gu, T. Koga, H. Jono, H. Kai, J.D. Li, The transforming growth factor-beta-Smad3/4 signaling pathway acts as a positive regulator for TLR2 induction by bacteria via a dual mechanism involving functional cooperation with NF-kappaB and MAPK phosphatase 1-dependent negative cross-talk with p38 MAPK, J. Biol. Chem. 281 (2006) 22397–22408.
[54] A. Palm-Leis, U.S. Singh, B.S. Herbelin, G.D. Olsovsky, K.M. Baker, J. Pan, Mitogen-activated protein kinases and mitogen-activated protein kinase phosphatases mediate the inhibitory effects of all-trans retinoic acid on the hypertrophic growth of cardiomyocytes, J. Biol. Chem. 279 (2004) 54905–54917.
[55] M.D. Short, S.M. Fox, C.F. Lam, K.R. Stenmark, M. Das, Protein kinase Czeta attenuates hypoxia-induced proliferation of fibroblasts by regulating MAP kinase phosphatase-1 expression, Mol. Biol. Cell 17 (2006) 1995–2008.
[56] B.H. Choi, E.M. Hur, J.H. Lee, D.J. Jun, K.T. Kim, Protein kinase Cdelta-mediated proteasomal degradation of MAP kinase phosphatase-1 contributes to glutamate-induced neuronal cell death, J. Cell Sci. 119 (2006) 1329–1340.
[57] T.L. Aghaloo, F.Q. Pirih, A. Shi, O. Bezouglaia, S. Tetradis, Parathyroid hormone induces mitogen-activated kinase phosphatase 1 in murine osteoblasts primarily through cAMP-protein kinase A signaling, J. Periodontol. 77 (2006) 21–30.
[58] A.R. Clark, MAP kinase phosphatase 1: a novel mediator of biological effects of glucocorticoids? J. Endocrinol. 178 (2003) 5–12.
[59] E. Eljaschewitsch, A. Witting, C. Mawrin, T. Lee, P.M. Schmidt, S. Wolf, H. Hoertnagl, C.S. Raine, R. Schneider-Stock, R. Nitsch, O. Ullrich, The endocannabinoid anandamide protects neurons during CNS inflammation by induction of MKP-1 in microglial cells, Neuron 49 (2006) 67–79.
[60] J.J. Wu, A.M. Bennett, Essential role for mitogen-activated protein (MAP) kinase phosphatase-1 in stress-responsive MAP kinase and cell survival signaling, J. Biol. Chem. 280 (2005) 16461–16466.
[61] J.J. Wu, R.J. Roth, E.J. Anderson, E.G. Hong, M.K. Lee, C.S. Choi, P.D. Neufer, G.I. Shulman, J.K. Kim, A.M. Bennett, Mice lacking MAP kinase phosphatase-1 have enhanced MAP kinase activity and resistance to diet-induced obesity, Cell Metab. 4 (2006) 61–73.
[62] Q. Zhao, E.G. Shepherd, M.E. Manson, L.D. Nelin, A. Sorokin, Y. Liu, The role of mitogen-activated protein kinase phosphatase-1 in the response of alveolar macrophages to lipopolysaccharide: attenuation of proinflammatory cytokine biosynthesis via feedback control of p38, J. Biol. Chem. 280 (2005) 8101–8108.
[63] H. Chi, S.P. Barry, R.J. Roth, J.J. Wu, E.A. Jones, A.M. Bennett, R.A. Flavell, Dynamic regulation of pro- and anti-inflammatory cytokines by

MAPK phosphatase 1 (MKP-1) in innate immune responses, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 2274–2279.
[64] M. Hammer, J. Mages, H. Dietrich, A. Servatius, N. Howells, A.C. Cato, R. Lang, Dual specificity phosphatase 1 (DUSP1) regulates a subset of LPS-induced genes and protects mice from lethal endotoxin shock, J. Exp. Med. 203 (2006) 15–20.
[65] K.V. Salojin, I.B. Owusu, K.A. Millerchip, M. Potter, K.A. Platt, T. Oravecz, Essential role of MAPK phosphatase-1 in the negative control of innate immune responses, J. Immunol. 176 (2006) 1899–1907.
[66] Q. Zhao, X. Wang, L.D. Nelin, Y. Yao, R. Matta, M.E. Manson, R.S. Baliga, X. Meng, C.V. Smith, J.A. Bauer, C.H. Chang, Y. Liu, MAP kinase phosphatase 1 controls innate immune responses and suppresses endotoxic shock, J. Exp. Med. 203 (2006) 131–140.
[67] P.J. Rohan, P. Davis, C.A. Moskaluk, M. Kearns, H. Krutzsch, U. Siebenlist, K. Kelly, PAC-1: a mitogen-induced nuclear protein tyrosine phosphatase, Science 259 (1993) 1763–1766.
[68] R.J. Grumont, J.E. Rasko, A. Strasser, S. Gerondakis, Activation of the mitogen-activated protein kinase pathway induces transcription of the PAC-1 phosphatase gene, Mol. Cell. Biol. 16 (1996) 2913–2921.
[69] Y. Ward, S. Gupta, P. Jensen, M. Wartmann, R.J. Davis, K. Kelly, Control of MAP kinase activation by the mitogen-induced threonine/tyrosine phosphatase PAC1, Nature 367 (1994) 651–654.
[70] Y. Yin, Y.X. Liu, Y.J. Jin, E.J. Hall, J.C. Barrett, PAC1 phosphatase is a transcription target of p53 in signalling apoptosis and growth suppression, Nature 422 (2003) 527–531.
[71] K.L. Jeffrey, T. Brummer, M.S. Rolph, S.M. Liu, N.A. Callejas, R.J. Grumont, C. Gillieron, F. Mackay, S. Grey, M. Camps, C. Rommel, S.D. Gerondakis, C.R. Mackay, Positive regulation of immune cell function and inflammatory responses by phosphatase PAC-1, Nat. Immunol. 7 (2006) 274–283.
[72] K.L. Guan, E. Butch, Isolation and characterization of a novel dual specific phosphatase, HVH2, which selectively dephosphorylates the mitogen-activated protein kinase, J. Biol. Chem. 270 (1995) 7197–7203.
[73] A. Misra-Press, C.S. Rim, H. Yao, M.S. Roberson, P.J. Stork, A novel mitogen-activated protein kinase phosphatase. Structure, expression, and regulation, J. Biol. Chem. 270 (1995) 14587–14596.
[74] J.M. Brondello, A. Brunet, J. Pouyssegur, F.R. McKenzie, The dual specificity mitogen-activated protein kinase phosphatase-1 and -2 are induced by the p42/p44MAPK cascade, J. Biol. Chem. 272 (1997) 1368–1376.
[75] T. Zhang, J.M. Mulvaney, M.S. Roberson, Activation of mitogen-activated protein kinase phosphatase 2 by gonadotropin-releasing hormone, Mol. Cell Endocrinol. 172 (2001) 79–89.
[76] S.L. Fu, A. Waha, P.K. Vogt, Identification and characterization of genes upregulated in cells transformed by v-Jun, Oncogene 19 (2000) 3537–3545.
[77] C. Torres, M.K. Francis, A. Lorenzini, M. Tresini, V.J. Cristofalo, Metabolic stabilization of MAP kinase phosphatase-2 in senescence of human fibroblasts, Exp. Cell Res. 290 (2003) 195–206.
[78] L. Cadalbert, C.M. Sloss, P. Cameron, R. Plevin, Conditional expression of MAP kinase phosphatase-2 protects against genotoxic stress-induced apoptosis by binding and selective dephosphorylation of nuclear activated c-*jun* N-terminal kinase, Cell Signal 17 (2005) 1254–1264.
[79] W.H. Shen, J. Wang, J. Wu, V.B. Zhurkin, Y. Yin, Mitogen-activated protein kinase phosphatase 2: a novel transcription target of p53 in apoptosis, Cancer Res. 66 (2006) 6033–6039.
[80] S.P. Kwak, J.E. Dixon, Multiple dual specificity protein tyrosine phosphatases are expressed and regulated differentially in liver cell lines, J. Biol. Chem. 270 (1995) 1156–1160.
[81] T. Ishibashi, D.P. Bottaro, P. Michieli, C.A. Kelley, S.A. Aaronson, A novel dual specificity phosphatase induced by serum stimulation and heat shock, J. Biol. Chem. 269 (1994) 29897–29902.
[82] P.E. Kovanen, A. Rosenwald, J. Fu, E.M. Hurt, L.T. Lam, J.M. Giltnane, G. Wright, L.M. Staudt, W.J. Leonard, Analysis of gamma c-family cytokine target genes. Identification of dual-specificity phosphatase 5 (DUSP5) as a regulator of mitogen-activated protein kinase activity in interleukin-2 signaling, J. Biol. Chem. 278 (2003) 5205–5213.
[83] M.B. Tanzola, G.J. Kersh, The dual specificity phosphatase transcriptome of the murine thymus, Mol. Immunol. 43 (2006) 754–762.
[84] K. Ueda, H. Arakawa, Y. Nakamura, Dual-specificity phosphatase 5 (DUSP5) as a direct transcriptional target of tumor suppressor p53, Oncogene 22 (2003) 5586–5591.
[85] M. Mandl, D.N. Slack, S.M. Keyse, Specific inactivation and nuclear anchoring of extracellular signal-regulated kinase 2 by the inducible dual-specificity protein phosphatase DUSP5, Mol. Cell Biol. 25 (2005) 1830–1845.
[86] L.A. Groom, A.A. Sneddon, D.R. Alessi, S. Dowd, S.M. Keyse, Differential regulation of the MAP, SAP and RK/p38 kinases by Pyst1, a novel cytosolic dual-specificity phosphatase, EMBO J. 15 (1996) 3621–3632.
[87] R.J. Mourey, Q.C. Vega, J.S. Campbell, M.P. Wenderoth, S.D. Hauschka, E.G. Krebs, J.E. Dixon, A novel cytoplasmic dual specificity protein tyrosine phosphatase implicated in muscle and neuronal differentiation, J. Biol. Chem. 271 (1996) 3795–3802.
[88] M. Muda, U. Boschert, R. Dickinson, J.C. Martinou, I. Martinou, M. Camps, W. Schlegel, S. Arkinstall, MKP-3, a novel cytosolic protein-tyrosine phosphatase that exemplifies a new class of mitogen-activated protein kinase phosphatase, J. Biol. Chem. 271 (1996) 4319–4326.
[89] M. Muda, A. Theodosiou, N. Rodrigues, U. Boschert, M. Camps, C. Gillieron, K. Davies, A. Ashworth, S. Arkinstall, The dual specificity phosphatases M3/6 and MKP-3 are highly selective for inactivation of distinct mitogen-activated protein kinases, J. Biol. Chem. 271 (1996) 27205–27208.
[90] S. Kamakura, T. Moriguchi, E. Nishida, Activation of the protein kinase ERK5/BMK1 by receptor tyrosine kinases. Identification and characterization of a signaling pathway to the nucleus, J. Biol. Chem. 274 (1999) 26563–26571.
[91] S. Marchetti, C. Gimond, J.C. Chambard, T. Touboul, D. Roux, J. Pouyssegur, G. Pages, Extracellular signal-regulated kinases phosphorylate mitogen-activated protein kinase phosphatase 3/DUSP6 at serines 159 and 197, two sites critical for its proteasomal degradation, Mol. Cell. Biol. 25 (2005) 854–864.
[92] M. Karlsson, J. Mathers, R.J. Dickinson, M. Mandl, S.M. Keyse, Both nuclear-cytoplasmic shuttling of the dual specificity phosphatase MKP-3 and its ability to anchor MAP kinase in the cytoplasm are mediated by a conserved nuclear export signal, J. Biol. Chem. 279 (2004) 41882–41891.
[93] M. Camps, C. Chabert, M. Muda, U. Boschert, C. Gillieron, S. Arkinstall, Induction of the mitogen-activated protein kinase phosphatase MKP3 by nerve growth factor in differentiating PC12, FEBS Lett. 425 (1998) 271–276.
[94] S. Reffas, W. Schlegel, 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, Biochem. J. 352 (Pt 3) (2000) 701–708.
[95] H. Xu, Q. Yang, M. Shen, X. Huang, M. Dembski, R. Gimeno, L.A. Tartaglia, R. Kapeller, Z. Wu, Dual specificity MAPK phosphatase 3 activates PEPCK gene transcription and increases gluconeogenesis in rat hepatoma cells, J. Biol. Chem. 280 (2005) 36013–36018.
[96] R.J. Dickinson, M.C. Eblaghie, S.M. Keyse, G.M. Morriss-Kay, Expression of the ERK-specific MAP kinase phosphatase PYST1/MKP3 in mouse embryos during morphogenesis and early organogenesis, Mech. Dev. 113 (2002) 193–196.
[97] G.R. Martin, The roles of FGFs in the early development of vertebrate limbs, Genes Dev. 12 (1998) 1571–1586.
[98] Y. Kawakami, J. Rodriguez-Leon, C.M. Koth, D. Buscher, T. Itoh, A. Raya, J.K. Ng, C.R. Esteban, S. Takahashi, D. Henrique, M.F. Schwarz, H. Asahara, J.C. Izpisua Belmonte, MKP3 mediates the cellular response to FGF8 signalling in the vertebrate limb, Nat. Cell Biol. 5 (2003) 513–519.
[99] L.B. Corson, Y. Yamanaka, K.M. Lai, J. Rossant, Spatial and temporal patterns of ERK signaling during mouse embryogenesis, Development 130 (2003) 4527–4537.
[100] T.G. Smith, M. Karlsson, J.S. Lunn, M.C. Eblaghie, I.D. Keenan, E.R. Farrell, C. Tickle, K.G. Storey, S.M. Keyse, Negative feedback

predominates over cross-regulation to control ERK MAPK activity in response to FGF signalling in embryos, FEBS Lett. 580 (2006) 4242–4245.
[101] M. Tsang, S. Maegawa, A. Kiang, R. Habas, E. Weinberg, I.B. Dawid, A role for MKP3 in axial patterning of the zebrafish embryo, Development 131 (2004) 2769–2779.
[102] M.C. Eblaghie, J.S. Lunn, R.J. Dickinson, A.E. Munsterberg, J.J. Sanz-Ezquerro, E.R. Farrell, J. Mathers, S.M. Keyse, K. Storey, C. Tickle, Negative feedback regulation of FGF signaling levels by Pyst1/MKP3 in chick embryos, Curr. Biol. 13 (2003) 1009–1018.
[103] D. Echevarria, S. Martinez, S. Marques, V. Lucas-Teixeira, J.A. Belo, Mkp3 is a negative feedback modulator of Fgf8 signaling in the mammalian isthmic organizer, Dev. Biol. 277 (2005) 114–128.
[104] T.G. Smith, D. Sweetman, M. Patterson, S.M. Keyse, A. Munsterberg, Feedback interactions between MKP3 and ERK MAP kinase control scleraxis expression and the specification of rib progenitors in the developing chick somite, Development 132 (2005) 1305–1314.
[105] T.A. Moreno, C. Kintner, Regulation of segmental patterning by retinoic acid signaling during Xenopus somitogenesis, Dev. Cell 6 (2004) 205–218.
[106] L.N. Orlev, B. Ehud, B.G. Tamar, S.A. Orit, K. Yoel, I.P. Witz, Does the dual-specificity MAPK phosphatase Pyst2-L lead a monogamous relationship with the Erk2 protein? Immunol. Lett. 92 (2004) 149–156.
[107] O. Levy-Nissenbaum, O. Sagi-Assif, D. Kapon, S. Hantisteanu, T. Burg, P. Raanani, A. Avigdor, I. Ben-Bassat, I.P. Witz, Dual-specificity phosphatase Pyst2-L is constitutively highly expressed in myeloid leukemia and other malignant cells, Oncogene 22 (2003) 7649–7660.
[108] O. Levy-Nissenbaum, O. Sagi-Assif, P. Raanani, A. Avigdor, I. Ben-Bassat, I.P. Witz, cDNA microarray analysis reveals an overexpression of the dual-specificity MAPK phosphatase PYST2 in acute leukemia, Methods Enzymol. 366 (2003) 103–113.
[109] O. Levy-Nissenbaum, O. Sagi-Assif, P. Raanani, A. Avigdor, I. Ben-Bassat, I.P. Witz, Overexpression of the dual-specificity MAPK phosphatase PYST2 in acute leukemia, Cancer Lett. 199 (2003) 185–192.
[110] M. Muda, U. Boschert, A. Smith, B. Antonsson, C. Gillieron, C. Chabert, M. Camps, I. Martinou, A. Ashworth, S. Arkinstall, Molecular cloning and functional characterization of a novel mitogen-activated protein kinase phosphatase, MKP-4, J. Biol. Chem. 272 (1997) 5141–5151.
[111] R.J. Dickinson, D.J. Williams, D.N. Slack, J. Williamson, O.M. Seternes, S.M. Keyse, Characterization of a murine gene encoding a developmentally regulated cytoplasmic dual-specificity mitogen-activated protein kinase phosphatase, Biochem. J. 364 (2002) 145–155.
[112] H. Xu, M. Dembski, Q. Yang, D. Yang, A. Moriarty, O. Tayber, H. Chen, R. Kapeller, L.A. Tartaglia, Dual specificity mitogen-activated protein (MAP) kinase phosphatase-4 plays a potential role in insulin resistance, J. Biol. Chem. 278 (2003) 30187–30192.
[113] M. Bazuine, F. Carlotti, R.S. Tafrechi, R.C. Hoeben, J.A. Maassen, Mitogen-activated protein kinase (MAPK) phosphatase-1 and -4 attenuate p38 MAPK during dexamethasone-induced insulin resistance in 3T3-L1 adipocytes, Mol. Endocrinol. 18 (2004) 1697–1707.
[114] G.R. Christie, D.J. Williams, F. Macisaac, R.J. Dickinson, I. Rosewell, S. M. Keyse, The dual-specificity protein phosphatase DUSP9/MKP-4 is essential for placental function but is not required for normal embryonic development, Mol. Cell. Biol. 25 (2005) 8323–8333.
[115] R.H. Adams, A. Porras, G. Alonso, M. Jones, K. Vintersten, S. Panelli, A. Valladares, L. Perez, R. Klein, A.R. Nebreda, Essential role of p38alpha MAP kinase in placental but not embryonic cardiovascular development, Mol. Cell 6 (2000) 109–116.
[116] S. Giroux, M. Tremblay, D. Bernard, J.F. Cardin-Girard, S. Aubry, L. Larouche, S. Rousseau, J. Huot, J. Landry, L. Jeannotte, J. Charron, Embryonic death of Mek1-deficient mice reveals a role for this kinase in angiogenesis in the labyrinthine region of the placenta, Curr. Biol. 9 (1999) 369–372.
[117] A. Theodosiou, A. Smith, C. Gillieron, S. Arkinstall, A. Ashworth, MKP5, a new member of the MAP kinase phosphatase family, which selectively dephosphorylates stress-activated kinases, Oncogene 18 (1999) 6981–6988.
[118] A. Bar-Shira, S. Rashi-Elkeles, L. Zlochover, L. Moyal, N.I. Smorodinsky, R. Seger, Y. Shiloh, ATM-dependent activation of the gene encoding MAP kinase phosphatase 5 by radiomimetic DNA damage, Oncogene 21 (2002) 849–855.
[119] Y. Zhang, J.N. Blattman, N.J. Kennedy, J. Duong, T. Nguyen, Y. Wang, R.J. Davis, P.D. Greenberg, R.A. Flavell, C. Dong, Regulation of innate and adaptive immune responses by MAP kinase phosphatase 5, Nature 430 (2004) 793–797.
[120] K. Masuda, H. Shima, M. Watanabe, K. Kikuchi, MKP-7, a novel mitogen-activated protein kinase phosphatase, functions as a shuttle protein, J. Biol. Chem. 276 (2001) 39002–39011.
[121] T. Tanoue, T. Yamamoto, R. Maeda, E. Nishida, A Novel MAPK phosphatase MKP-7 acts preferentially on JNK/SAPK and p38 alpha and beta MAPKs, J. Biol. Chem. 276 (2001) 26629–26639.
[122] S.Y. Han, S.H. Kim, L.E. Heasley, Differential gene regulation by specific gain-of-function JNK1 proteins expressed in Swiss 3T3 fibroblasts, J. Biol. Chem. 277 (2002) 47167–47174.
[123] C. Katagiri, K. Masuda, T. Urano, K. Yamashita, Y. Araki, K. Kikuchi, H. Shima, Phosphorylation of Ser-446 determines stability of MKP-7, J. Biol. Chem. 280 (2005) 14716–14722.
[124] A.J. Whitmarsh, J. Cavanagh, C. Tournier, J. Yasuda, R.J. Davis, A mammalian scaffold complex that selectively mediates MAP kinase activation, Science 281 (1998) 1671–1674.
[125] E.A. Willoughby, G.R. Perkins, M.K. Collins, A.J. Whitmarsh, The JNK-interacting protein-1 scaffold protein targets MAPK phosphatase-7 to dephosphorylate JNK, J. Biol. Chem. 278 (2003) 10731–10736.
[126] E.A. Willoughby, M.K. Collins, Dynamic interaction between the dual specificity phosphatase MKP7 and the JNK3 scaffold protein beta-arrestin 2, J. Biol. Chem. 280 (2005) 25651–25658.
[127] K.J. Martell, A.F. Seasholtz, S.P. Kwak, K.K. Clemens, J.E. Dixon, hVH-5: a protein tyrosine phosphatase abundant in brain that inactivates mitogen-activated protein kinase, J. Neurochem. 65 (1995) 1823–1833.
[128] R. Bernabeu, G. Di Scala, J. Zwiller, Odor regulates the expression of the mitogen-activated protein kinase phosphatase gene hVH-5 in bilateral entorhinal cortex-lesioned rats, Brain Res. Mol. Brain Res. 75 (2000) 113–120.
[129] N. Thiriet, N. Humblot, C. Burgun, D. Aunis, J. Zwiller, Cocaine and fluoxetine induce the expression of the hVH-5 gene encoding a MAP kinase phosphatase, Brain Res. Mol. Brain Res. 62 (1998) 150–157.
[130] Y.R. Chen, A. Shrivastava, T.H. Tan, Down-regulation of the c-Jun N-terminal kinase (JNK) phosphatase M3/6 and activation of JNK by hydrogen peroxide and pyrrolidine dithiocarbamate, Oncogene 20 (2001) 367–374.
[131] C. Palacios, M.K. Collins, G.R. Perkins, The JNK phosphatase M3/6 is inhibited by protein-damaging stress, Curr. Biol. 11 (2001) 1439–1443.
[132] T.R. Johnson, J.R. Biggs, S.E. Winbourn, A.S. Kraft, Regulation of dual-specificity phosphatases M3/6 and hVH5 by phorbol esters. Analysis of a delta-like domain, J. Biol. Chem. 275 (2000) 31755–31762.
[133] A. Theodosiou, A. Ashworth, Differential effects of stress stimuli on a JNK-inactivating phosphatase, Oncogene 21 (2002) 2387–2397.
[134] T. Ishibashi, D.P. Bottaro, A. Chan, T. Miki, S.A. Aaronson, Expression cloning of a human dual-specificity phosphatase, Proc. Natl. Acad. Sci. U. S. A. 89 (1992) 12170–12174.
[135] J.L. Todd, J.D. Rigas, L.A. Rafty, J.M. Denu, Dual-specificity protein tyrosine phosphatase VHR down-regulates c-Jun N-terminal kinase (JNK), Oncogene 21 (2002) 2573–2583.
[136] T.H. Kang, K.T. Kim, Negative regulation of ERK activity by VRK3-mediated activation of VHR phosphatase, Nat. Cell Biol. 8 (2006) 863–869.
[137] A. Alonso, S. Rahmouni, S. Williams, M. van Stipdonk, L. Jaroszewski, A. Godzik, R.T. Abraham, S.P. Schoenberger, T. Mustelin, Tyrosine phosphorylation of VHR phosphatase by ZAP-70, Nat. Immunol. 4 (2003) 44–48.
[138] S. Rahmouni, F. Cerignoli, A. Alonso, T. Tsutji, R. Henkens, C. Zhu, C. Louis-dit-Sully, M. Moutschen, W. Jiang, T. Mustelin, Loss of the VHR dual-specific phosphatase causes cell-cycle arrest and senescence, Nat. Cell Biol. 8 (2006) 524–531.
[139] F. Marti, A. Krause, N.H. Post, C. Lyddane, B. Dupont, M. Sadelain, P.D. King, Negative-feedback regulation of CD28 costimulation by a novel mitogen-activated protein kinase phosphatase, MKP6, J. Immunol. 166 (2001) 197–206.