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MKP-2: out of the DUSP-bin and back into the limelight

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Abstract

The MKPs (mitogen-activated protein kinase phosphatases) are a family of at least ten DUSPs (dual-specificity phosphatases) which function to terminate the activity of the MAPKs (mitogen-activated protein kinases). Several members have already been demonstrated to have distinct roles in immune function, cancer, fetal development and metabolic disorders. One DUSP of renewed interest is the inducible nuclear phosphatase MKP-2, which dephosphorylates both ERK (extracellular-signal-regulated kinase) and JNK (c-Jun N-terminal kinase) *in vitro*. Recently, the understanding of MKP-2 function has been advanced due to the development of mouse knockout models, which has resulted in the discovery of novel roles for MKP-2 in the regulation of sepsis, infection and cell-cycle progression that are distinct from those of other DUSPs. However, many functions for MKP-2 still await to be characterized.

Introduction

The explosion in the delineation of intracellular kinase signalling pathways in the last 25 years has been exemplified by study of the MAPK (mitogen-activated protein kinase) pathway, including its major homologues, the ERKs (extracellular-signal-regulated kinases), JNKs (c-Jun N-terminal kinases) and p38 MAPK. One feature realized very early on was that both the magnitude and kinetics of activity played a significant role in the determination of cell fate. A corollary from that model was a role for termination of the pathway by dephosphorylation. In the early 1990s, three separate groups identified a viral [1], mouse [2] and human homologue [3] of a DUSP (dual-specificity phosphatase) which could mediate dephosphorylation and inactivation of ERK [4]. Quickly, it became appreciated that these were prototypical members of a new family of enzymes, the MKPs (mitogen-activated protein kinase phosphatases) or DUSPs [5].

To date, at least ten mammalian homologues have been identified, along with several truncated atypical isoforms [6]. They dephosphorylate major homologues of the MAPK family on both the threonine and tyrosine residues within the TXY motif of the activation loop. Characterization has largely been based on four main attributes: tissue distribution, substrate specificity, regulation of cellular expression and activity in response to extracellular stimuli and, in particular, subcellular distribution (Figure 1). The first group encompasses the type 1 nuclear inducible phosphatases DUSP1/MKP-1, DUSP2/PAC-1 (phosphatase of activated cells 1), DUSP4/MKP-2 and DUSP5/hVH (human vaccinia H1 phosphatase)-3 which express an NLS (nuclear localization sequence) within the C-terminus. The second group of DUSPs (type II), including DUSP6/MKP-3, DUSP7/MKP-x and DUSP9/MKP-4, are strictly cytoplasmic, owing to the presence of NESs (nuclear export sequences). The type III group comprising DUSP8/hVH-5, DUSP10/MKP-5 and DUSP16/MKP-7 are localized in either the nucleus or cytosolic compartments.

Other distinctive features of DUSP regulation vary across the groupings and can be exemplified by a number of key studies. The prototypical MKP-1 is an early gene induced in response to a diverse array of stimuli primarily via an ERK-dependent pathway as part of a negative-feedback loop. Binding of MKP-1 to ERK via the MKB (MAPK-binding domain) followed by catalytic activation enhances phosphatase activity [7], whereas ERK-induced phosphorylation also promotes resistance to proteasome-mediated degradation [8]. Many of the type I DUSPs, including MKP-1, dephosphorylate more than one MAPKs *in vitro* [4], although substrate profiles can vary when investigated in different cell types. Type II DUSPs are exemplified by MKP-3, which can be constitutively expressed in many cell types, but are also induced by fibroblast and nerve growth factors [9]. Similar to MKP-1, binding of ERK to the MKB of MKP-3 increases phosphatase activity [10], and specificity is restricted to ERK over the other kinases [9]. The type III DUSP MKP-7, despite being more specific for JNK and p38 over ERK [11,12], nevertheless requires C-terminal Ser^{466} phosphorylation by ERK to suppress proteasomal degradation and maintain functional integrity [13]. Therefore common and distinctive features combine to characterize each class and individual DUSP. These and other

Key words: cancer, dual-specificity phosphatase (DUSP), immunity, mitogen-activated protein kinase (MAPK), mitogen-activated protein kinase phosphatase 2 (MKP-2), phosphatase, proliferation.

Abbreviations used: DUSP, dual-specificity phosphatase; ERK, extracellular-signal-regulated kinase; hVH, human vaccinia H1 phosphatase; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; MEF, mouse embryonic fibroblast; MKB, MAPK-binding domain; MKP, mitogen-activated protein kinase phosphatase; NES, nuclear export sequence; NLS, nuclear localization sequence; PAC-1, phosphatase of activated cells 1.

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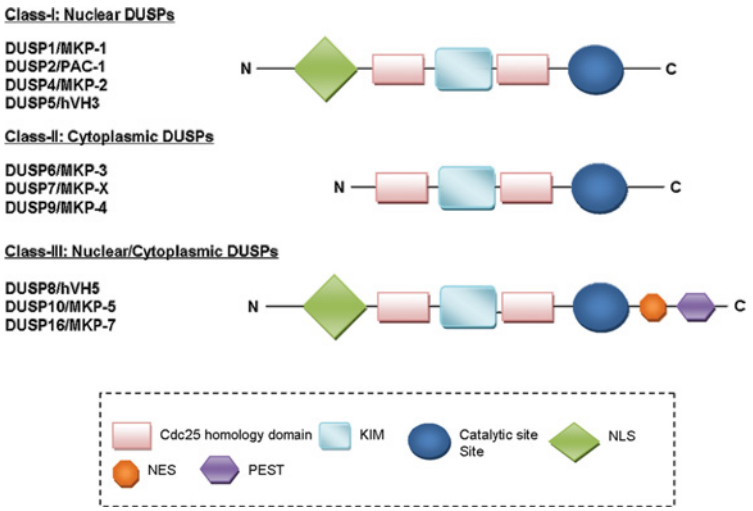
Figure 1 | Classification and domain structure of dual-specificity MAPK phosphatases

Domain structure of ten identified DUSP proteins with annotated NLSs, NESs and PEST (Pro-Glu-Ser-Thr) sequences. KIM, kinase-interaction motif. Adapted from [16]: Biochim Biophys Acta, **1773**, Kondoh, K. and Nishida, E., Regulation of MAP kinases by MAP kinase phosphatases, 1227–1237, © 2007, with permission from Elsevier.



aspects of the DUSP family are examined in more detail in several excellent reviews [5,6,14–16].

The distribution and major physiological roles of the MKPs are summarized in Table 1 and reviewed in [14]. MKP-1 has been studied to the greatest extent and shown to negatively regulate innate immune function [17–19], influence metabolic homoeostasis [20] and play a role in depression [21]. PAC-1 and MKP-5 regulate immune responses [22,23], MKP-4 is essential for placental function [24], whereas MKP-3 is linked to embryo development [25]. In addition, many of these DUSPs are implicated in dysregulation of cell proliferation and cancer [15]; however, many significant gaps in the understanding of their function remain.

DUSP4/MKP-2

One DUSP of renewed interest is MKP-2 or DUSP4. This phosphatase, a type I member, was one of the first DUSPs to be identified, but was found to have a distinct pattern of tissue distribution relative to DUSP1 [26,27]. Specificity was originally thought to be for ERK and JNK over p38, at least *in vitro*; however, studies have indicated that selectivity in cells can vary; MKP-2 can be associated with regulation of either ERK [26,27] or JNK [28–30], depending on the cell type. MKP-2 can also bind strongly to p38, but does not readily desphosphorylate this substrate *in vitro*, although one study has indicated the potential regulation of p38 in hepatocytes [31]. Whereas binding to ERK via the MKB is well established, the sites regulating interaction with JNK have not been characterized [32]. Nuclear localization is thought to be regulated by the triple arginine sequence within the MKB which functions as an NLS [32]; however, an additional more distal sequence has also been reported [33]. Furthermore, in humans, at least, there is the potential of a splice variant of MKP-2 [34], which again differs in binding to ERK and JNK relative to full-length MKP-2, possibly due to enhanced proteasome-mediated degradation.

For many years, the function of DUSP4 has been largely ignored in favour of the prototypical MKP-1. Nevertheless, the potential to play a role in aspects of cancer is a consistent feature of MKP-2 function. Indirect evidence links MKP-2 to the development of ovarian cancers [35], oesophagogastric rib metastasis [36] and pancreatic tumours. Indeed, MKP-2 expression is also dramatically increased in liver carcinoma [37] and by the homeobox gene of the HoxA10 family, which is linked to acute myeloid leukaemia [38]. These data do, however, contrast with other findings; the MKP-2 gene (*DUSP4*) is also considered to be a candidate tumour-suppressor gene, with its deletion implicated in breast cancer [39]. MKP-2 been mapped to the 8p11-p12 gene locus [40]; significantly, this locus is lost in several prostatic neoplasms [41], and allelic loss within the short arm of chromosome 8 is a frequent event in prostate cancer [42]. Consistent with these data is a recent genomic screen which correlates *DUSP4* deletion with EGFR (epidermal growth factor receptor)-mutant tumours in lung cancer within the 8p locus [43], and a study showing hypermethylation of the *DUSP4* promoter in gliomas [44].

Cellular studies correlate with some of these observations, but are limited. Stable [29] or conditional [28] overexpression of MKP-2 negatively regulates JNK signalling and, as a consequence, reduces JNK-dependent apoptosis [28,38]. In other cells types, MKP-2 is described as a mediator of H_2O_2-induced apoptosis through inhibition of ERK activation [45,46]; expression of MKP-2 in these instances is regulated by either or p53 or E2F-1 respectively. MKP-2 can also play a role in the development of senescence by inactivating nuclear ERK signalling [47], which correlates with enhanced stabilization of MKP-2 [48].

Table 1 | **Characteristics of the major mammalian DUSPs**

Group	Name	Alternative name(s)	Primary Subcellular location	MAPK substrate specificity	Tissue distribution	Physiological relevance
I	MKP-1	DUSP1, hVH-1, CL100, erp	Nuclear	p38∼JNK≫ERK	Ubiquitous	Regulator of innate immunity, management of metabolic homoeostasis and depression
	PAC-1	DUSP2	Nuclear	ERK≫p38∼JNK	Thymus, spleen, kidney and lung	Regulator of immunity, particularly with reference to immune effector cells
	MKP-2	DUSP4, hVH-2, TYP2, STY8	Nuclear	ERK∼JNK>p38	Ubiquitous	Positive role in sepsis, required for G_2/M cell-cycle progression
	hVH-3	DUSP5, B23	Nuclear	ERK≫JNK∼p38	Bone marrow, brain, lung	Modulator of T-cell development and function
II	MKP-3	DUSP6, rVH-6, Pyst1	Cytosolic	ERK≫JNK∼p38	Brain, nasal, dental, hair and mammary placodes	Required for embryo development
	MKP-x	DUSP7, Pyst2, B59	Cytosolic	ERK>p38≫JNK	Skeletal muscle, brain, heart, kidney, pancreas	Linked to leukaemic leucocytes
	MKP-4	DUSP9, Pyst3	Nuclear and cytosolic	ERK≫p38>JNK	Placenta, kidney	Required for placental development, role in insulin signalling
III	MKP-5	DUSP10	Nuclear and cytosolic	p38>JNK≫ERK	Liver, skeletal muscle, heart, lung, kidney	Principal function in both innate and adaptive immunity
	MKP-7	DUSP16, MKP-M	Cytosolic	JNK∼p38≫ERK	Heart, kidney, testis	Regulator of helper T-cell differentiation
	M3/6	DUSP8, hVH-5, HB5	Nuclear and cytosolic	JNK∼p38≫ERK	Heart, skeletal muscle, brain	N/A

Dusp4-knockout mice models

Understanding the physiological function of MKP-2 has recently been advanced by the generation of a number of *Dusp4*-knockout mice models, which has sparked renewed interest. Using one such model, it has been shown that systemic infection of the pathogen *Leishmania mexicana* is enhanced due to enhanced uptake of the parasite and reduced Th1 responses, facilitated by high levels of macrophage arginase-1 and low levels of NO production [49]. Another recent study has demonstrated a positive role for MKP-2 in septic shock [50], opposite to that previously described for MKP-1 [18]. Furthermore, our laboratory has also revealed a novel effect on the cell cycle. MEFs (mouse embryonic fibroblasts) derived from *Dusp4*-knockout mice show decreased proliferation rates and enhanced apoptosis associated with a minor up-regulation of ERK activation [51]. In addition, we have elucidated a G_2/M-phase arrest in a proportion of cells associated with enhanced cyclin B1 expression. This finding is consistent with a recent study in mice mammary tumour cells using *Dusp4* siRNA (small interfering RNA) [37]; however, in these cells the G_2/M-phase arrest is associated with a loss of cyclin B1. This effect within a late stage of the cycle is a potentially important novel feature of MKP-2 function and again distinct from that observed for MKP-1, which is usually associated with cell-cycle entry. These findings are similar to that observed for the atypical MKP VHR (vaccinia H1-related) [52], although this DUSP has additional effects at G_1/S-phase. Furthermore, another study in mice shows that *Dusp4* deletion protects again TGFβ (transforming growth factor β)-induced apoptosis in B-cells, and this is associated with enhanced ERK activation [53], suggesting that the potential for cell-specific differences in cellular outcomes might be based on a similar enhancement of ERK signalling.

This recent work raises several important questions that may be applied not only to DUSP4, but also to other MKPs. The first issue is the question of substrate specificity *in vivo* relative to that established *in vitro*. Our current studies in MEFs demonstrate a small potentitation of ERK signalling in fibroblasts, but enhanced JNK in macrophages [49]; however, another group has revealed enhanced ERK and decreased JNK and p38 MAPK due to cross-talk via MKP-1 [50]. This type of anomaly is a feature of other DUSP knockouts, in particular PAC-1, where enhanced ERK activation is observed following deletion, despite PAC-1

being selective for ERK *in vitro* [22]. The second related issue is one of redundancy: at least in relation to MAPK signalling, it is likely that MKP-2 regulatory effects may be further masked by compensatory changes in DUSP1. Another question relates to the potential for MKP-2 to act independently of effects upon MAPK phosphorylation. For example, DUSP1 is linked to the dephosphorylation of histone-1 [54]. In addition, the atypical DUSP19 functions as scaffold protein in the regulation of the MKK7 (MAPK kinase 7)/JNK activation cascade [55], thus MKP-2 may behave in a similar manner.

These possibilities make the future study of DUSP function an exciting and key area. Recently, a chemical screen has identified an inhibitor of DUSP6, indicating that this and other DUSPs may be targeted therapeutically [56]. DUSPs may be used in other therapeutic applications; for example, we have utilized adenoviral MKP-2 to abrogate JNK-mediated apoptosis in endothelial cells [57] with a view to limiting endothelial cell damage in cardiovascular conditions such as restenosis. This approach was based on a recent study showing a role for MKP-1 expression in arthero-protection through inhibition of JNK at the site of the arterial tree resistant to damage [58].

Conclusions and future perspectives

Overall, there is considerable scope for further investigation to clarify the cellular role of MKP-2 and appreciate its physiological function. The development of inducible models and double or treble knockouts to offset redundancy may be of benefit. Other possible novel roles include regulation of brain function, metabolic regulation and embryo development. Indeed, zebrafish endoderm specification is regulated by a *dusp4* homologue through regulation of *sox17* [59], which, in turn, can be linked to cardiac specification in embryonic stem cells [60]. Thus regulation of differentiation may also be a feature of MKP-2 function yet to be discovered. For MKP-2, it is time to come out of the DUSP-bin and reveal what its true function might be.

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