

Protein family review

MAP kinase phosphatases

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Summary

Mitogen-activated protein MAP kinases are key signal-transducing enzymes that are activated by a wide range of extracellular stimuli. They are responsible for the induction of a number of cellular responses, such as changes in gene expression, proliferation, differentiation, cell cycle arrest and apoptosis. Although regulation of MAP kinases by a phosphorylation cascade has long been recognized as significant, their inactivation through the action of specific phosphatases has been less studied. An emerging family of structurally distinct dual-specificity serine, threonine and tyrosine phosphatases that act on MAP kinases consists of ten members in mammals, and members have been found in animals, plants and yeast. Three subgroups have been identified that differ in exon structure, sequence and substrate specificity.

The mitogen-activated protein (MAP) kinases are evolutionarily conserved enzymes that play an important role in orchestrating a variety of cellular processes, including proliferation, differentiation and apoptosis [1,2]. To date, four major discrete groups of MAP kinases have been identified in mammalian cells, known as the extracellular signal-regulated kinases (ERK1 and ERK2), the c-Jun amino-terminal kinases (JNK1, JNK2 and JNK3), the p38 kinases (p38 α , p38 β , p38 γ and p38 δ) and ERK5/Big MAP kinase 1 (BMK1). MAP kinases are part of a three-tiered cascade consisting of a MAP kinase, a MAP kinase kinase (MAPKK, MKK or MEK) and a MAP kinase kinase kinase (MAPKKK or MEKK). Phosphorylation of the threonine and tyrosine residues in the T-loop of the MAP kinase, by its upstream kinase, results in activation. The activation of MAP kinases is not a simple switch, however, as both the duration and magnitude of activation is crucial in determining the physiological outcome in cells [3]. Thus, it seems likely that dephosphorylation of the MAP kinases is vital for their control. This is achieved by removal of phosphate groups from either the threonine residue or the tyrosine residue, or both. Both protein serine/threonine phosphatases and protein tyrosine phosphatases have been reported to dephosphorylate MAP kinases. In the past decade, however, some dual-specificity

phosphatases (DSPs) have been recognized as key players for inactivating different MAP kinase isoforms; this class of phosphatases has been designated MAP kinase phosphatases (MKPs).

Although the MKPs form a structurally and functionally distinct subclass among the large number of protein phosphatases present in eukaryotic genomes, there is a great deal of confusion regarding their classification. In this article we discuss the family of 'classical' MKPs that have been definitively shown to play a role in the de-activation of MAP kinases. Where relevant, we also mention the closely related low-molecular-weight phosphatases, whose role in MAP kinase regulation is controversial. Other more distantly related DSP families, including members of the FYVE family, which have high sequence similarity to myotubularin, and of the Cdc25 family, which dephosphorylate cyclin-dependent kinases, are beyond the scope of this review.

Gene organization and evolutionary history

Gene organization

To date, 10 genes encoding members of the classical MKP family have been isolated and characterized from mammalian

genomes (see Table 1). They all share some common features, including an extended active-site motif with significant sequence similarity to the corresponding region of the VH-1 protein tyrosine phosphatase that was isolated from vaccinia virus [4]. In addition, their amino termini contain two short regions that are homologous to sequences that flank the Cdc25 phosphatase catalytic site [5] and a cluster of basic amino-acid residues that play an important role in binding to the MAP kinases [6]. The MKPs can be further subdivided into groups depending on their substrate specificity for the MAP kinases, subcellular localization (nuclear, cytoplasmic or both) and the structural organization of their genes.

A gene closely related to the MKP family is *STYX*. The protein encoded by *STYX* contains many of the hallmarks of the MKPs but lacks a critically important catalytically active cysteine residue, having a glycine instead [7]. Interestingly, alteration of this glycine residue to cysteine renders the *STYX* protein catalytically active, suggesting that other critical residues have been retained. *STYX* appears to function as a phosphotyrosine/phosphoserine/phosphothreonine-binding protein analogous to the SH2 and PTB domains. It is unclear whether it plays any role in signaling through the MAP kinase pathways, however.

Evolutionary history

On the basis of structures predicted from genomic sequence, the MKPs can readily be divided into the following subgroups: subgroup I, *DUSP1*, *DUSP2*, *DUSP4* and *DUSP5*; subgroup II, *DUSP6*, *DUSP7*, *DUSP9* and *DUSP10*; and subgroup III, *DUSP8* and *DUSP16* (Figure 1, Table 1). Division into these three subgroups is also supported by phylogenetic

analysis (Figure 2), and to a considerable extent by substrate preference.

The genes of subgroup I consist of four exons [8-11], and the exact positions of the introns are highly conserved. The first exon encodes the amino terminus of each of the three proteins and ends within the second of the Cdc25 homology (CH2) domains. The active-site motif of all four proteins is encoded within exon 4, and the length of exon 3 is identical for all these DUSPs, suggesting that they arose from a common ancestral gene.

Subgroup II genes (*DUSP6*, 7 and 9, and provisionally 10) consist of three exons [12]. As with subgroup I, exon 1 encodes the amino terminus and the 3'-most exon encodes the active site. Unlike subgroup I, however, the central portion of the protein is encoded by a single exon. *DUSP10* has an intron/exon structure consistent with a placement within subgroup II, but it shares some features with members of subgroup III, such as a similar MAP kinase docking-site motif and similar substrate specificity. In addition, it has an extended amino-terminal region that is not present in any of the other DUSPs. Assignment of *DUSP10* to subgroup II or III or to its own subgroup may need re-evaluation in the future.

The genes of subgroup III (*DUSP8* and *DUSP16*) consist of six exons [13-15]. The lengths of exons 2, 3, 4 and 5 are identical in the two genes. Unlike the two previous subgroups, however, exon 1 encodes only the first of the CH2 domains. Exon 2 ends within the same region of the second CH2 domain as does exon 1 of subgroups I and II, however. The

Table 1

Classification and chromosomal and subcellular localization of DUSP genes

DUSP	Subgroup	Human protein	Species ortholog	Chromosomal localization	Subcellular localization	References
<i>DUSP1</i>	I	hVH1/CL100	MKP-1/3CH134 (m)	5q35	Nuclear	[8,60-62]
<i>DUSP2</i>	I	hPAC-1	—	2p11.2-2q11	Nuclear	[10,42,62]
<i>DUSP4</i>	I	hVH2/TYP1	MKP-2 (r)	8p12-p11	Nuclear	[42,63-65]
<i>DUSP5</i>	I	hVH3/B23	Cpg21 (r)	10q25	Nuclear	[48,62,66]
<i>DUSP6</i>	II	PYST1	MKP-3/rVH6 (r)	12q22-q23	Cytosolic	[49-51,65]
<i>DUSP7</i>	II	PYST2/B59	MKP-X (r)	3p21	Cytosolic	[49,51,65,67]
<i>DUSP8</i>	III	hVH5	M3/6 (m)	11p15.5	Nuclear /cytosolic	[13,43,44]
<i>DUSP9</i>	II	MKP-4	—	Xq28	Nuclear /cytosolic	[45]
<i>DUSP10</i>	II(?)	MKP-5	—	1q32	Nuclear /cytosolic	[46,52]
<i>DUSP16</i>	III	MKP-7	MKP-M (m)	12p12	Cytosolic	[14,15,36]

Compilation of DUSP genes identified in the human and other mammalian genomes. The DUSPs are classified into subgroups I, II or III (see text for details). The various alternative names for each gene in human (h) or rat (r) or mouse (m) are given. The chromosomal location of each gene and the subcellular localization of the protein product of each gene are also indicated. Multiple names are used in the literature for each member of the MAP kinase phosphatase gene family. To avoid confusion in this article, we have used the gene names recommended by the human gene nomenclature committee, which uses the root DUSP (for dual specificity phosphatase). Note that the designation of *DUSP16* is provisional.

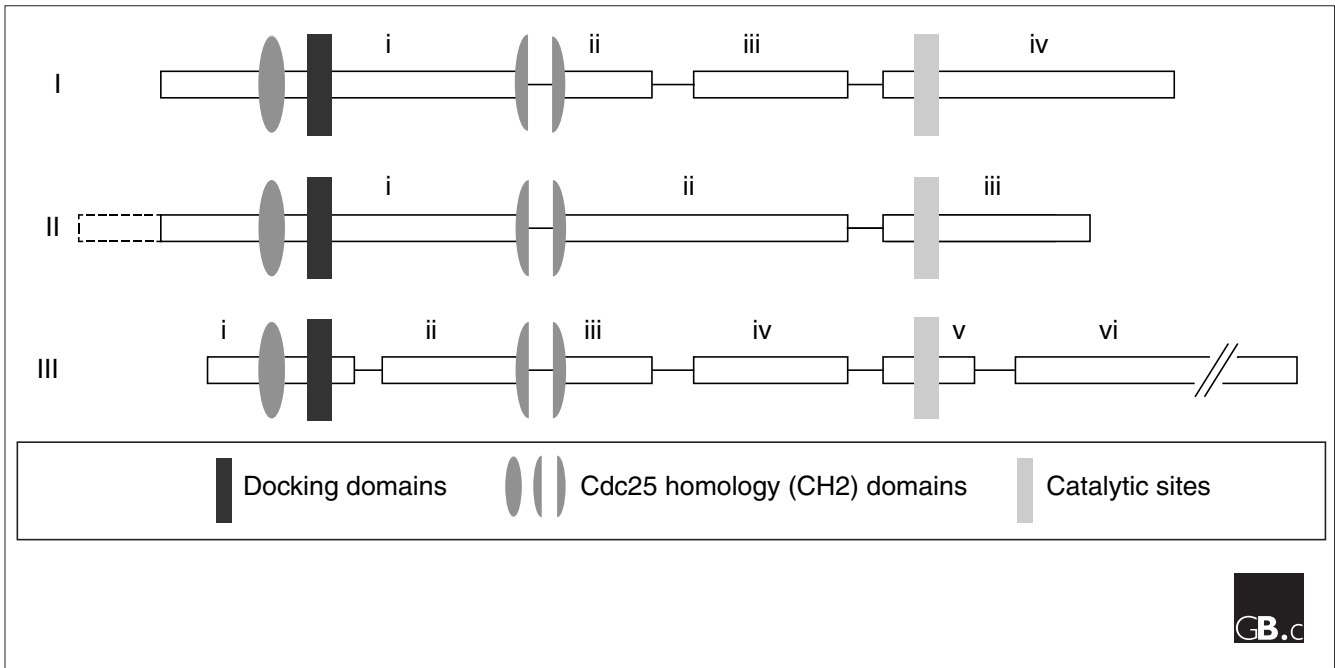


Figure 1

Gene structure of the DUSPs. Three distinct gene structures have been described for the DUSPs, allowing their classification into subgroups I, II and III. Structural motifs (CH2 domains, docking domain and catalytic domain) in the encoded proteins are indicated by shaded shapes and exons by boxes and roman numerals. The dashed box in subgroup II is an alternatively spliced exon.

central portion of the protein is encoded by two exons, as in subgroup I, rather than the single exon of subgroup II. This suggests that subgroup II genes may have diverged earlier and that subgroup I and III genes may be more closely related to each other. Exon 5 encodes the catalytic site of these DUSPs but not the carboxyl terminus; the sixth exon encodes the large extended carboxyl terminus, with the intron between the catalytic domain and the carboxyl terminus of the protein being diagnostic of this subgroup.

Overall, the high conservation of some intron/exon boundaries within all three subgroups of DUSPs indicates a common ancestral gene for each subgroup. The similarities of substrate specificity among subgroup members suggest that these ancestral genes are themselves likely to have shown some substrate preference.

Dual specificity phosphatases have been found in a wide variety of phylogenetically distinct eukaryotes, including yeasts, worms, flies and plants, as well as mammals. Although budding yeast does not encode any predicted protein tyrosine kinases, it has 16 dual specificity and low-molecular-weight phosphatases and five phosphatase-like *STYX* genes. A direct role has been demonstrated for the budding yeast dual specificity phosphatase gene *MSG5* in the regulation of the MAP kinase *Fus3* [16]. Six MKPs have been noted in the *Drosophila melanogaster* genome sequence [17]. Of these, two have been characterized: *puckered*

has been shown to encode a MKP that inactivates *basket*, the *Drosophila* equivalent of mammalian JNK [18]; in addition, a *Drosophila DUSP6*-like gene has recently been identified [19]. The sequence of the *Caenorhabditis elegans* genome includes 26 predicted DSPs, including some MKPs [20]. One of these, LIP-1, has been suggested to inactivate MAP kinase, mediating inhibition by the ligand Notch of a signaling pathway involving the GTPase Ras, during *C. elegans* vulval

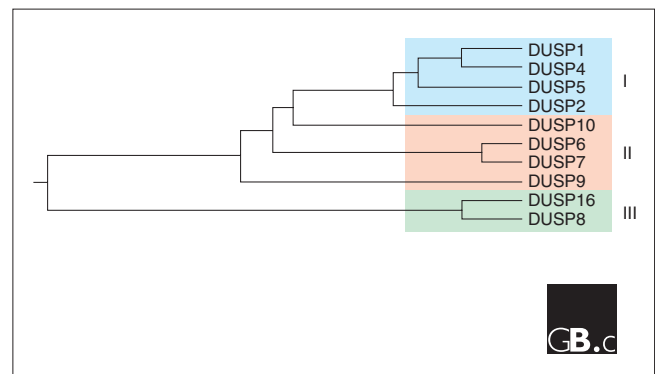


Figure 2

Phylogenetic analysis of DUSP sequences. Human DUSP amino-acid sequences were aligned and a phylogenetic tree derived using Clustal W [68] on DNASTAR. The length of the branches is proportional to sequence divergence between proteins. Subgroups I, II, and III are shaded (see text for further details).

development [21]. Moreover, at least two MKPs have been identified in *Arabidopsis thaliana*, one of which is required for relief from genotoxic stress [22].

Characteristic structural features

The catalytic domain is strongly conserved and adopts a shallow cleft conformation [24,25] that can accommodate both phosphotyrosine and phosphothreonine side chains. Upon binding of the substrate, the active-site residues are rearranged, adopting a catalytically active conformation [24] and enabling dephosphorylation (Figure 3b, available with the complete version of this article, online). The amino terminus is much less conserved, but contains two conserved CH2 domains, which have been suggested to play a role in substrate binding. All DUSPs have, near to their amino termini, a MAP kinase docking site, which consists of a cluster of positively charged amino acids [6]. The number of consecutive positively charged residues in the docking site may play a role in determining binding specificity (Figure 4, available with the complete version of this article, online) [14].

Further regions that are potentially important for docking to and activation by MAPKs have been defined in certain subsets of MKPs. The FXFP motif, and variants of this sequence (present in DUSP1, DUSP4, DUSP6, DUSP7 and DUSP9) has been shown to mediate ERK binding [30-32]. The D-domain (or D-box) comprises a cluster of basic residues amino-terminal to an L/I-X-L/I motif [30,32,33] and is present in all MKPs [34]; it is thought to mediate binding to both JNK and ERK MAP kinases [30,32]. The affinity of the MKPs for their substrates may be governed by the number, type and accessibility of docking sites. DUSP8 and DUSP16 also have an extended carboxyl terminus containing PEST sequences (abundant in proline, glutamate, serine and threonine residues) that are frequently found in rapidly degraded proteins [35]. Further details of the domains present in MKPs, including Figure 3 (showing the structure of DUSP6) and Figure 4 (showing a classification of DUSPs on the basis of docking site sequences) are available with the complete version of this article, online.

Regulation of MKPs

In 1998, Arkinstall's group [27] demonstrated that binding of DUSP6 to purified ERK2 enhances the catalytic activity of the phosphatase. Since then, several papers have attempted to elucidate the mechanism of catalytic activation of DUSP6 [37,38] and to define the regions of interaction between DUSP6 and ERK2. The derivation of the solution structure of the ERK2-binding (EB) domain of DUSP6 [38] has provided considerable insight into this issue (Figure 3a, available with the complete version of this article, online). The EB domain of DUSP6 contains a positively charged cluster of arginine residues that binds to a highly negatively charged region of ERK2. This binding causes a conformational change in DUSP6, affecting the association of its EB domain with its catalytic

domain, which results in the re-positioning of the conserved aspartate residue (Asp262 in DUSP6). These conformational effects, in conjunction with the catalytic domain binding to phosphorylated ERK2, allosterically trigger the rearrangement of DUSP6 active-site residues, resulting in a high-activity state of the phosphatase (Figure 5). This mechanism of activation of DUSP6 by its substrate may be generally applicable to the DUSPs; recent data support a similar model for both DUSP4 and DUSP9 [27,39], and binding of DUSP1 to p38 results in the catalytic activation of the phosphatase [40].

An alternative regulatory mechanism is exemplified by the binding of DUSP1 to ERK1, which results in phosphorylation of the phosphatase [41]. This phosphorylation does not directly affect the phosphatase activity of DUSP1, but instead leads to its stabilization, by reducing the rate of proteasome-mediated degradation of this rather labile protein [41].

Localization and function

Most DUSPs display wide tissue distribution but some show a rather restricted expression pattern. These include: DUSP2, which is predominantly expressed in hematopoietic tissues [42]; DUSP8, which is expressed mainly in brain, as well as in heart and lung [43,44]; DUSP9, which is detected in placenta, kidney and fetal liver [45]; and DUSP10, which appears to be restricted to liver and skeletal muscle [46]. Detailed information on expression patterns during development is not available for most DUSPs.

The DUSPs vary in their subcellular locations and can be subdivided into three major groups on the basis of location. One group consists of members expressed exclusively in the nucleus, including DUSP1, DUSP2, DUSP4 and DUSP5 [42,47,48] whereas another group includes DUSP6, DUSP7 and DUSP16, which are predominantly expressed in the cytoplasm [12,14,15,49-51]. Some DUSPs (DUSP8, DUSP9 and DUSP10) show both cytoplasmic and nuclear localizations [44-46,52]. It is of interest that DUSP9 shows punctate nuclear staining, which is reminiscent of the pattern displayed by promyelocytic leukemia (PML) protein [45]. Moreover, DUSP9 and PML co-localize in a significant proportion of cells, suggesting a potential role for DUSP9 as a regulator of kinases that phosphorylate PML. The recently identified DUSP16 has been shown to act as a shuttle protein [15]; it has both an active nuclear localization signal (NLS) and a nuclear export signal (NES), and it has been suggested to function by translocating into the nucleus, where it interacts with and dephosphorylates its substrates (JNK and/or p38) and then subsequently transports them to the cytoplasm. The sequence of the NES region of DUSP8 is very similar to that of DUSP16, and it therefore seems possible that DUSP8 also shuttles between cytoplasm and nucleus.

Despite the wealth of data supporting the role of MKPs in the regulation of MAP kinases in cell-culture systems, there

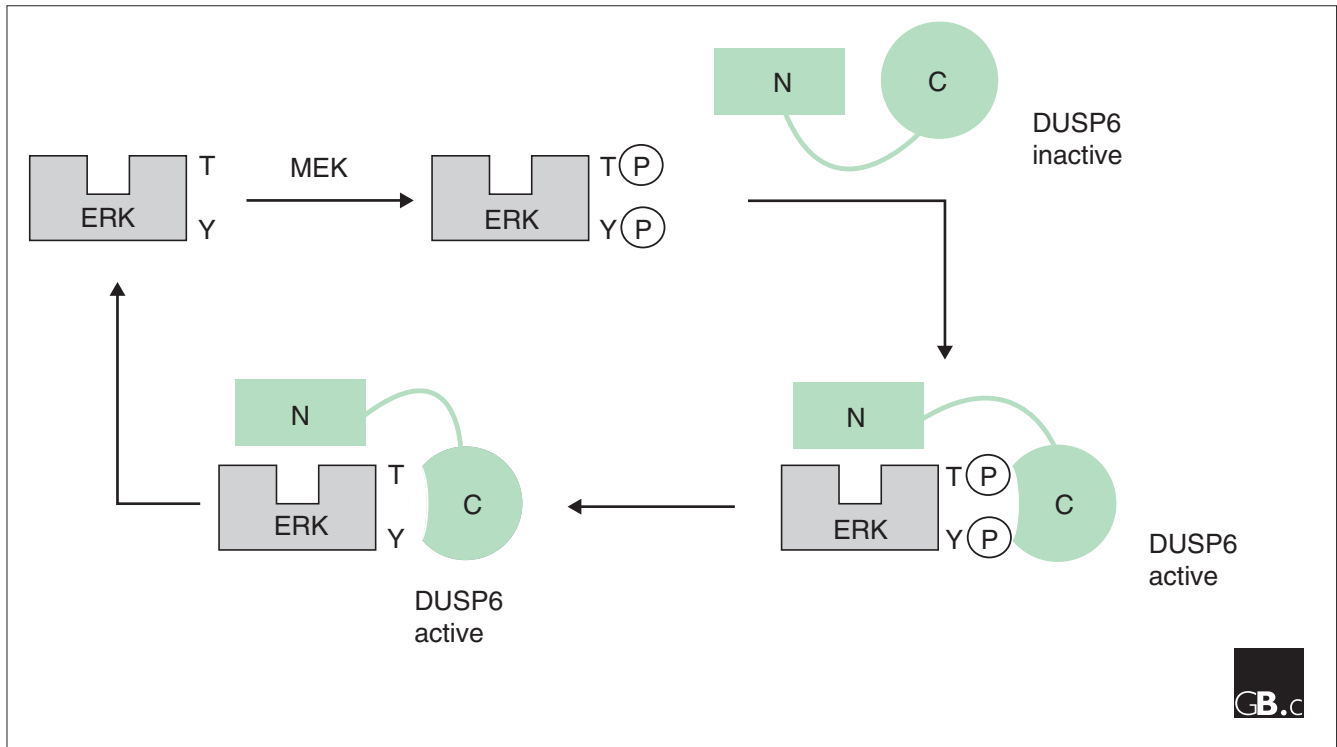


Figure 5

Activation of DUSP6 phosphatase by interaction with substrate ERK. This is a simplified schematic representation of ERK binding to DUSP6, resulting in catalytic activation. The carboxy-terminal catalytic domain is represented by a circle and the amino terminus containing the ERK binding (EB) domain by a rectangle. DUSP6 appears to exist in a low-activity state until binding to ERK through the EB domain results in a conformational change, triggering activation of the phosphatase. This results in ERK dephosphorylation and subsequent dissociation of the complex.

is as yet no direct *in vivo* evidence confirming this in mammals. Disruption of the *DUSP1* gene in mice causes no obvious phenotype [53]. Moreover, *DUSP1*-deficient embryonic fibroblasts and stem cells display no abnormalities in the regulation of MAP kinases. Genetic studies in yeasts, *Drosophila* and *Arabidopsis* have provided evidence for a role for MKPs in the regulation of MAP kinases *in vivo*, however. In *Drosophila*, mutations in *puckered* (encoding an MKP) cause severe developmental defects, resulting in embryonic lethality due to hyperactivation of *Drosophila* JNK and failure of dorsal closure [18]. Moreover, a mutant has been identified in *Arabidopsis* that develops normally but is hypersensitive to genotoxic stress as a result of disruption of a gene that encodes a MKP, *AtMKP1*. *AtMKP1* is required for maintaining the MAP kinase activity at levels that contribute to genotoxic stress resistance rather than those that trigger cell death [22].

Substrate specificity

Assessment of substrate specificity for the DUSPs has proved problematic because many of the assays used do not reflect the situation *in vivo*. From data published so far, however, it seems that many of the DUSPs have preferred substrates. For example, after transfection into mammalian cells, DUSP6 completely inactivates ERK1 and ERK2, even at low

concentrations, but not JNK or p38 kinases [49,54]; similarly, DUSP9 also displays some specificity towards ERK [45]. In contrast, DUSP8 and DUSP16 appear highly specific for the inactivation of JNK and p38 kinases but fail to inhibit ERK activation [14,15,54]; similarly, DUSP10 displays specificity for p38 and JNK kinases [46,52]. These ‘specificities’ should be treated with caution, as they may be specific to a certain cell type or physiological status [26,55,56]. Some of the specificity may reside in the docking sites present on the various MKPs, but it must be emphasized that access to substrate may be an equally important factor in regulating specificity *in vivo*.

Frontiers

MAP kinase activation has been implicated in oncogenic transformation, tumor formation and metastasis [57-59]. This suggests that the MKPs could have a role in tumorigenesis, perhaps as tumor suppressors. Several MKPs have been mapped to regions of the human genome altered in human cancer, but direct evidence for such a role is at present lacking. It will be interesting to see whether this family of genes plays a part in the development of cancer or other diseases.

The lack of relevant mammalian models makes it difficult to assign a physiological role to these phosphatases. Given the

overlapping substrate specificity displayed by members of the various subgroups, in addition to the similar tissue distributions, it seems likely that there will be a certain degree of redundancy. This issue could be addressed by combined gene targeting of the members of each subgroup. Such an approach, in conjunction with further genetic biochemical and cell biological analyses of other model organisms should result in the elucidation of the precise biological roles of these enzymes in controlling key signaling pathways. Further insight into the regulation of these phosphatases by their substrates will be gained by determining the three-dimensional structures of representative members of each subgroup, both free and in complex with their targets.

Finally, the adoption by the community of a common nomenclature (such as the DUSP system used here and recommended by the Human Gene Nomenclature committee) will considerably facilitate progress in this important area.

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References

- Schaeffer HJ, Weber MJ: **Mitogen-activated protein kinases: specific messages from ubiquitous messengers.** *Mol Cell Biol* 1999, **19**:2435-3444.
- Chang L, Karin M: **Mammalian MAP kinase signalling cascades.** *Nature* 2001, **410**:37-40.
- Marshall CJ: **Specificity of receptor tyrosine kinase signalling: transient versus sustained extracellular signal regulated kinase activation.** *Cell* 1995, **80**:179-185.
- Guan K, Broyles SS, Dixon JE: **A Tyr/Ser protein phosphatase encoded by vaccinia virus.** *Nature* 1991, **350**:359-362.
- Keyse SM, Ginsburg M: **Amino acid sequence similarity between CL100, a dual-specificity MAP kinase phosphatase, and cdc25.** *Trends Biochem Sci* 1993, **18**:377-378.
- Tanoue T, Adachi M, Moriguchi T, Nishida E: **A conserved docking motif in MAP kinases common to substrates, activators and regulators.** *Nat Cell Biol* 2000, **2**:110-116.
- Wishart MJ, Dixon JE: **Gathering STYX: phosphatase-like form predicts functions for unique protein-interaction domains.** *Trends Biochem Sci* 1998, **23**:301-306.
- Noguchi T, Metz R, Chen L, Mattei M-G, Carrasco 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.
- Kwak S, Hakes D, Martell K, Dixon JE: **Isolation and characterization of a human dual specificity protein-tyrosine phosphatase gene.** *J Biol Chem* 1994, **269**:3596-3604.
- Yi H, Morton CC, Weronowicz S, McBride OV, Kelly K: **Genomic organization and chromosomal localization of the DUSP2 gene, encoding a MAP kinase phosphatase, to human 2p11.2-q11.** *Genomics* 1995, **28**:92-96.
- Zhang T, Choy M, Jo M, Roberson MS: **Structural organization of the rat mitogen-activated protein kinase phosphatase 2 gene.** *Gene* 2001, **273**:71-79.
- Dowd S, Sneddon AA, Keyse SM: **Isolation of the human genes encoding the Pyst1 and Pyst2 phosphatases: characterization 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**:3389-3399.
- Nesbit MA, Hodges MD, Campbell L, de Meulemeester TM, Alders M, Rodrigues NR, Talbot K, Theodosiou AM, Mannens MA, Nakamura Y, et al.: **Genomic organization and chromosomal localization of a member of the MAP kinase phosphatase gene family to human chromosome 11p15.5 and a pseudogene to 10q11.2.** *Genomics* 1997, **42**:284-294.
- Tanoue T, Yamamoto T, Maeda R, Nishida E: **A novel MAPK phosphatase MKP-7 acts preferentially on JNK/SAPK and p38 α and β MAPKs.** *J Biol Chem* 2001, **276**:26629-26639.
- 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**:39002-39011.
- Doi K, Gartner A, Ammerer G, Errede B, Shinkawa H, Sugimoto K, Matsumoto K: **MSG5, a novel protein phosphatase promotes adaptation to pheromone.** *EMBO J* 1994, **13**:61-70.
- Morrison DK, Murakami MS, Clephon V: **Protein kinases and phosphatases in the Drosophila genome.** *J Cell Biol* 2000, **150**:F57-F62.
- Martin-Blanco E, Gampel A, Ring J, Virdee K, Kirov N, Tolkovsky AM, Martinez-Arias A: **puckered encodes a phosphatase that mediates a feedback loop regulating JNK activity during dorsal closure in Drosophila.** *Genes Dev* 1998, **12**:557-570.
- Kim S-H, Kwon H-B, Kim Y-S, Ryu J-H, Kim K-S, Ahn Y, Lee W-J, Choi K-Y: **Isolation and characterization of a Drosophila homologue of mitogen-activated protein kinase phosphatase-3 which has a high substrate specificity towards extracellular-signal-regulated kinase.** *Biochem J* 2002, **361**:143-151.
- Plowman GD, Sudarsanam S, Bingham J, Whyte D, Hunter T: **The protein kinases of Caenorhabditis elegans: a model for signal transduction in multicellular organisms.** *Proc Natl Acad Sci USA* 1999, **96**:13603-13610.
- Berset T, Hoier EF, Battu G, Canevascini S, Hajnal A: **Notch inhibition of RAS signaling through MAP kinase phosphatase LIP-1 during C. elegans vulval development.** *Science* 2001, **291**:1055-1058.
- Ulm R, Revenkova E, di Sansebastiano G-P, Bechtold N, Paszkowski J: **Mitogen-activated protein kinase phosphatase is required for genotoxic stress relief in Arabidopsis.** *Genes Dev* 2001, **15**:699-709.
- Denu JM, Dixon JE: **Protein tyrosine phosphatases: mechanisms of catalysis and regulation.** *Curr Opin Chem Biol* 1998, **2**:633-641.
- Stewart AE, Dowd S, Keyse SM, McDonald NQ: **Crystal structure of the MAPK phosphatase Pyst1 catalytic domain and implications for regulated activation.** *Nat Struct Biol* 1999, **6**:174-181.
- Yuvaniyama J, Denu JM, Dixon JE, Saper MA: **Crystal structure of the dual-specificity protein phosphatase VHR.** *Science* 1996, **272**:1328-1331.
- Chu Y, Solski PA, Khosravi-Far R, Der CJ, Kelly K: **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* 1996, **271**:6497-6501.
- Camps M, Nichols A, Gillieron C, Antonsson B, Muda M, Chabert C, Boschert U, Arkinstall S: **Catalytic activation of the phosphatase MKP-3 by ERK2 mitogen-activated protein kinase.** *Science* 1998, **280**:1262-1265.
- Todd JL, Tanner KG, Denu JM: **Extracellular regulated kinases (ERK) 1 and ERK2 are authentic substrates for the dual-specificity protein-tyrosine phosphatase VHR.** *J Biol Chem* 1999, **274**:13271-13280.
- Alonso A, Saxena S, Williams S, Mustelin T: **Inhibitory role for dual specificity phosphatase VHR in T cell antigen receptor and CD28-induced Erk and Jnk activation.** *J Biol Chem* 2001, **276**:4766-4771.
- Jacobs D, Glossip D, Xing H, Muslin AJ, Kornfeld K: **Multiple docking sites on substrate proteins form a modular system that mediates recognition by ERK MAP kinase.** *Genes Dev* 1999, **13**:163-175.
- Zhou B, Wu L, Shen K, Zhang J, Lawrence DS, Zhang Z-Y: **Multiple regions of MAP kinase phosphatase 3 are involved in its recognition and activation by ERK2.** *J Biol Chem* 2001, **276**:6506-6515.
- Fantz DA, Jacobs D, Glossip D, Kornfeld K: **Docking sites on substrate proteins direct extracellular signal-regulated kinase to phosphorylate specific residues.** *J Biol Chem* 2001, **276**:27256-27265.
- Yang S-H, Whitmarsh AJ, Davis RJ, Sharrocks AD: **Differential targeting of MAP kinases to the ETS-domain transcription factor Elk-1.** *EMBO J* 1998, **17**:1740-1749.

34. Johnson TR, Biggs JR, Winbourn SE, Kraft AS: **Regulation of dual-specificity phosphatases M3/6 and hVH5 by phorbol esters.** *J Biol Chem* 2000, **275**:31755-31762.
35. Rechsteiner M, Rogers SV: **PEST sequences and regulation by proteolysis.** *Trends Biochem Sci* 1996, **21**:267-271.
36. Matsuguchi T, Musikacharoen T, Johnson TR, Kraft AS, Yoshikai Y: **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* 2001, **21**:6999-7009.
37. Fjeld CC, Rice AE, Kim Y, Gee KR, Denu JM: **Mechanistic basis for catalytic activation of mitogen-activated protein kinase phosphatase-3 by extracellular signal-regulated kinase.** *J Biol Chem* 2000, **275**:6749-6757.
38. Farooq A, Chaturvedi G, Mujtaba S, Plotnikova O, Zeng L, Dhalluin C, Ashton R, Zhou M-M: **Solution structure of ERK2 binding domain of MAPK phosphatase MKP-3: structural insights into MKP-3 activation by ERK2.** *Mol Cell* 2001, **7**:387-399.
39. Chen P, Hutter D, Yang X, Gorospe M, Davis RJ, Liu Y: **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* 2001, **276**:29440-29449.
40. 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**:155-163.
41. Brondello J-M, Pouyssegur J, McKenzie FR: **Reduced MAP kinase phosphatase-1 degradation after p42/p44^{MAPK}-dependent phosphorylation.** *Science* 1999, **286**:2514-2517.
42. Rohan PJ, Davis P, Moskaluk CA, Kearns M, Krutzsch H, Siebenlist U, Kelly K: **PAC-1: a mitogen-induced protein nuclear tyrosine phosphatase.** *Science* 1993, **259**:1763-1766.
43. Martell KJ, Seasholtz AF, Kwak SP, Clemens KK, Dixon JE: **hVH-5: a protein tyrosine phosphatase abundant in brain that inactivates mitogen-activated protein kinase.** *J Neurochem* 1995, **65**:1823-1833.
44. Theodosiou AM, Rodrigues NR, Nesbit MA, Ambrose HJ, Paterson H, McLellan-Arnold E, Boyd Y, Leversha MA, Owen N, Blake DJ et al: **A member of the MAP kinase phosphatase gene family in mouse containing a complex trinucleotide repeat in the coding region.** *Hum Mol Genet* 1996, **5**:675-684.
45. 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**:5141-5151.
46. Theodosiou A, Smith A, Gillieron C, Arkinstall S, Ashworth A: **MKP5, a new member of the MAP kinase phosphatase family, which selectively dephosphorylates stress-activated kinases.** *Oncogene* 1999, **18**:6981-6988.
47. Guan K-L, Butch E: **Isolation and characterization of a novel dual specific phosphatase, HVH2, which selectively dephosphorylates the mitogen-activated protein kinase.** *J Biol Chem* 1995, **270**:7197-7203.
48. Kwak SP, Dixon JE: **Multiple dual specificity protein tyrosine phosphatases are expressed and regulated differentially in liver cell lines.** *J Biol Chem* 1995, **270**:1156-1160.
49. Groom LA, Sneddon AA, Alessi DR, Dowd S, Keyse SM: **Differential regulation of the MAP, SAP and RK/p38 kinases by Pyst1, a novel cytosolic dual-specificity phosphatase.** *EMBO J* 1996, **15**:3621-3632.
50. Mourey RJ, Vega QC, Campbell JS, Wenderoth MP, Hauschka SD, Krebs EG, Dixon JE: **A novel cytoplasmic dual specificity protein tyrosine phosphatase implicated in muscle and neuronal differentiation.** *J Biol Chem* 1996, **271**:3795-3802.
51. 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**:4319-4326.
52. Tanoue T, Moriguchi T, Nishida E: **Molecular cloning and characterization of a novel dual specificity phosphatase, MKP-5.** *J Biol Chem* 1999, **274**:19949-19956.
53. 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.
54. 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**:27205-27208.
55. Hirsch DD, Stork PJS: **Mitogen-activated protein kinase phosphatases inactivate stress-activated protein kinase pathways in vivo.** *J Biol Chem* 1997, **272**:4568-4575.
56. Refas 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.** *Biochem J* 2000, **352**:701-708.
57. Mansour SJ, Matten WT, Hermann AS, Candia JM, Rong S, Fukasawa K, Vande Woude GF, Ahn NG: **Transformation of mammalian cells by constitutively active MAP kinase kinase.** *Science* 1994, **265**:966-970.
58. Cowley S, Paterson H, Kemp P, Marshall CJ: **Activation of MAP kinase kinase is necessary and sufficient for PC12 differentiation and for transformation of NIH 3T3 cells.** *Cell* 1994, **77**:841-852.
59. Webb CP, Van Aelst L, Wigler MH, Vande Woude GF: **Signaling pathways in Ras mediated tumorigenicity and metastasis.** *Proc Natl Acad Sci USA* 1998, **95**:8773-8778.
60. Keyse SM, Emslie EA: **Oxidative stress and heat shock induce a human gene encoding a protein-tyrosine phosphatase.** *Nature* 1992, **359**:644-647.
61. Charles CH, Abler AS, Lau LF: **cDNA sequence of a growth factor-inducible immediate early gene and characterization of its encoded protein.** *Oncogene* 1992, **7**:187-190.
62. Martell KJ, Kwak S, Hakes DJ, Dixon JE, Trent JM: **Chromosomal localization of four human VH1-like protein-tyrosine phosphatases.** *Genomics* 1994, **22**:462-464.
63. King AG, Ozanne BW, Smythe C, Ashworth A: **Isolation and characterization of a uniquely regulated threonine, tyrosine phosphatase (TYP 1) which inactivates ERK2 and p54^{inK}.** *Oncogene* 1995, **11**:2553-2563.
64. Misra-Press A, Rim CS, Roberson MS, Stork PJS: **A novel mitogen-activated protein kinase phosphatase.** *J Biol Chem* 1995, **270**:14587-14596.
65. Smith A, Price C, Cullen M, Muda M, King A, Ozanne B, Arkinstall S, Ashworth A: **Chromosomal localization of three human dual specificity phosphatase genes (DUSP4, DUSP6, and DUSP7).** *Genomics* 1997, **42**:524-527.
66. Ishibashi T, Bottaro DP, Michieli P, Kelley CA, Aaronson SA: **A novel dual specificity phosphatase induced by serum stimulation and heat shock.** *J Biol Chem* 1994, **269**:29897-29902.
67. Shin D-Y, Ishibashi T, Choi TS, Chung E, Chung IY, Aaronson SA, Bottaro DP: **A novel human ERK phosphatase regulates H-ras and v-raf signal transduction.** *Oncogene* 1997, **14**:2633-2639.
68. Thompson JD, Higgins DG, Gibson TJ: **CLUSTAL W: improving the sensitivity of progressive multiple sequence alignment through sequence weighting, position-specific gap penalties and weight matrix choice.** *Nucleic Acids Res* 1994, **22**:4673-4680.

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The complete version of this article, available online at <http://genomebiology.com/2002/3/7/reviews/3009>, includes the following additional information:

- Additional discussion** of the gene organization.
- Further details** of the structural features of MKPs.
- Figure 3**, showing the structure of DUSP6.
- Figure 4**, showing a classification of DUSPs on the basis of MAP kinase docking site.
- Reference annotations.

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