Targeting dual-specificity phosphatases: manipulating MAP kinase signalling and immune responses

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Abstract | Dual-specificity phosphatases (DUSPs) are a subset of protein tyrosine phosphatases, many of which dephosphorylate threonine and tyrosine residues on mitogen-activated protein kinases (MAPKs), and hence are also referred to as MAPK phosphatases (MKPs). The regulated expression and activity of DUSP family members in different cells and tissues controls MAPK intensity and duration to determine the type of physiological response. For immune cells, DUSPs regulate responses in both positive and negative ways, and DUSP-deficient mice have been used to identify individual DUSPs as key regulators of immune responses. From a drug discovery perspective, DUSP family members are promising drug targets for manipulating MAPK-dependent immune responses in a cell-type and disease-context-dependent manner, to either boost or subdue immune responses in cancers, infectious diseases or inflammatory disorders.

Rheumatoid arthritis
A chronic, inflammatory autoimmune disorder in which leukocyte invasion of the synovial lining and hyperplasia of resident synoviocytes occurs. The ensuing overproduction of cytokines and other soluble mediators results in neovascularization, cartilage destruction, bone erosion and anarchic remodelling of joint structures.

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Signal-transduction pathways relay signals within cells through a cascade of phosphorylation and dephosphorylation events executed by kinases and phosphatases, which leads to gene transcription programmes that are appropriate for the stimulus encountered. For immune cells, these stimuli commonly include cytokines, chemoattractants, reactive oxygen species, antigen–antibody complexes, and pathogen-associated molecules that engage toll-like receptors. Signal-transduction pathways facilitate appropriate immune responses to infectious agents, but also operate during inappropriate inflammatory responses, such as in rheumatoid arthritis and asthma. Therefore, pharmacological interruption of certain signal-transduction molecules could prove effective for modifying inappropriate cellular immune responses. Indeed, numerous MAPK (mitogen-activated protein kinase) pathway inhibitors, particularly p38 (also known as MAPK14) MAPK inhibitors, are currently in clinical trials for chronic inflammatory diseases[1]. Inhibitors of other pathways, such as the nuclear factor-κB (NF-κB) pathway, are also showing promise in clinical trials[2]. Also noteworthy is the calcineurin phosphatase inhibitor cyclosporin — which regulates NFAT (nuclear factor of activated T cells) signalling and has proved to be a highly successful immunosuppressant for allo-graft rejection and inflammatory disorders, particularly psoriasis[2,3] — and of course blockbuster drugs such as the tyrosine kinase inhibitor imatinib (Gleevec; Novartis). Finally, glucocorticoids that are used widely to treat various inflammatory conditions have anti-inflammatory effects that are due in part to the induction of dual-specificity phosphatase 1 (DUSP1), a regulator of the MAPK pathway that negatively regulates pro-inflammatory gene expression in macrophages[4,5]. New ways of thinking about signalling pathway dynamics and the elements that regulate them, such as phosphatases, will offer opportunities for the manipulation of immune responses.

Until recently, the protein kinases rather than the phosphatases have enjoyed the limelight as important regulators of signalling cascades in immune cells, and hence as drug targets. This can be explained partly by the discovery of kinases around 10 years before the phosphatases. However, the phosphatases are now recognized as powerful and even dominant controllers of many biological processes. The DUSPs, a subclass of protein tyrosine phosphatases that specifically dephosporylate threonine and tyrosine residues on MAPKs and render them inactive, represent exciting new drug targets for both positive and negative regulation of immune responses. By virtue of their dual dephosphorylating capabilities, DUSPs are now recognized as key players in inactivating different MAPK isoforms, and understanding their precise physiological roles presents an important challenge and opportunity for drug development.

In this Review, we will discuss the role of DUSPs in regulating MAPKs and immune responses and suggest that targeting DUSPs may provide a more tissue-specific and controlled therapeutic approach for controlling MAPK-dependent cellular responses.

MAPKs and immune responses

The evolutionarily conserved MAPK pathway is present in yeast and all other eukaryotes and is a major signalling pathway in many cell types, particularly in immune cells[6–9]. MAPKs are fundamental regulators of most immune cell functions, including proliferation, differentiation, survival and apoptosis, chemoattraction, and production of inflammatory mediators[6,9] (BOX 1). Disruption of one or more of these cellular processes is a viable strategy for combating inflammation and other immune disorders. The roles of extracellular signal-regulated kinase (ERK), p38 and c-Jun N-terminal kinase (JNK) isoforms of MAPKs have been studied extensively in T cells, in particular for T-cell development in the thymus[10–13], $CD4^+$ T-cell differentiation to T helper 1 (T_H1) and T_H2 cells[14–16], and T-cell proliferation. ERK has a proposed role in T-cell anergy, promotes T_H2-cell differentiation and is needed for thymocyte maturation[6,15]. p38 MAPKs control production of interferon-γ (IFNG)[14] and apoptosis of certain T-cell subsets[17]. JNK1 (also known as MAPK8) and JNK2 (also known as MAPK9) cooperatively control T-helper-cell differentiation and cytokine production. JNK2 is important for thymocyte negative selection, JNK1 has a negative effect on T_H2-cell differentiation, whereas JNK2 promotes T_H1-cell differentiation[6,15].

MAPKs are pivotal for processes that are central to inflammatory responses such as cytokine production by immune cells. This is achieved through the activation of nuclear transcription factors, and through the stabilization of inflammatory cytokine mRNA using adenosine-uridine-rich elements (AREs)[18,19]. The MAP3K (MAPK kinase kinase) TPL2 (also known as MAP3K8) and ERK promote the transport of mRNA for tumour-necrosis factor (TNF) from the nucleus to the cytoplasm but have no effect on transcription of the *TNF* gene or on the stabilization of TNF mRNA following toll-like receptor 4 (TLR4) activation in macrophages[19]. p38 is probably involved in the initiation of TNF translation by the ARE region[20]. p38 also promotes transcriptional activation of the interleukin genes *IL1A* and *IL1B* in lipopolysaccharide-stimulated macrophages[21], and specifically regulates IL-12 (REF. 6) and IFNG[14] production in certain cells. JNK is also required for the production of many cytokines, including type I IFNs and IL-6, following its activation by lipopolysaccharide or inflammatory cytokines[6].

MAPKs are also important signalling elements for cell migration after chemoattractant receptor activation. JNK regulates paxillin, a cytoskeletal protein involved in cell motility, to control cell migration[22]; p38 mediates signalling through both C5AR1 (the complement component C5a receptor 1) and CXCR4 (CXC-chemokine receptor 4)[23] and controls cell directionality through its downstream substrate MAPK-activated protein kinase 2/3 (MAPKAPK2/3)[24]. Similarly, ERK governs cell motility through its ability to control both cell adhesion and detachment at the trailing end[25]. Therefore, MAPKs participate in one of the essential processes of the inflammatory response: the recruitment of leukocytes to the inflammatory lesion.

Finally, the survival and lifespan of leukocytes are carefully controlled by signals that are regulated by MAPKs to ensure that the effects of inflammatory mediators do not harm the host. In general, ERK1/2 promotes cell survival whereas p38 and JNK promote apoptosis. However, this dichotomy is not absolute given that the actual role of each MAPK is highly cell-type and context dependent[7]. p38 specifically promotes cell death of $CD8^+$ T cells but not $CD4^+$ cells through suppressing B-cell CLL/lymphoma 2 (BCL-2). JNK is involved in Fas-mediated cell death as well as Bax-mediated apoptosis by releasing Bim to suppress the pro-survival factors BCL-2 and BCL-X_L, while ERK-mediated phosphorylation of Bim inhibits its pro-apoptotic function and marks it for proteasomal degradation[7,26].

The physiological role of MAPKs in immune responses is unravelling with the aid of kinase-specific inhibitors and through genetic manipulations, and some of the phenotypes of various MAPK-deficient mice are listed in TABLE 1. These phenotypes have led numerous companies to develop inhibitors of various MAPK pathway members[1,2] (Supplementary information S1 (table)). However the roles of MAPKs in different leukocyte cell types still need to be clearly established. For instance, less information is available on the role of MAPKs in mast cells, dendritic cells, neutrophils and B cells, as well as on the different T-cell subsets, such as T-follicular helper cells and the inflammation-related T helper 17 cells. Recently, a role for ERK was established for integrating signals in TLR4-driven plasma cell differentiation[27], but B-cell phenotypes have yet to be reported in MAPK-deficient mice.

The complex web of MAPK signalling

MAPK signalling was initially viewed as a relatively simple linear receptor-to-nucleus pathway, but new knowledge from the last 5 years demonstrates a reversible phosphorylation of kinases in multiple cascades controlled by many feedback loops and much crosstalk with other pathways[28–31]. Therefore, the many kinases form a complex and sophisticated web to finely control cellular functions (FIG. 1). This may raise unexpected complications for single-kinase inhibition and may be a valid explanation for why many kinase inhibitors have failed in clinical trials (Supplementary information S1).

The intensity, duration and subcellular localization of the MAPK signal, as well as redundancy, feedback and crosstalk with other signalling molecules, cooperate to determine the specific cellular response. Hence there are multiple control points for MAPK activation that need to be considered. The distinct biological outcomes are often achieved purely because of the duration of MAPK activity, as immediate early genes act as sensors to the MAPK signal[32]. Spatial arrangement and compartmentalization are also important aspects, whereby the nucleus acts as an essential site for signal termination by sequestering

T-cell anergy
A state of T-cell unresponsiveness to stimulation with antigen. T-cell anergy can be induced by stimulation with a large amount of specific antigen in the absence of the engagement of co-stimulatory molecules.

Thymocyte negative selection
The deletion of self-reactive thymocytes in the thymus. Thymocytes expressing T-cell receptors that strongly recognize self peptide bound to self MHC molecules undergo apoptosis in response to the signalling generated by high-affinity binding.

Box 1 | **DUSPs, MAPKs and the immune response**

Generating mutant mouse strains through genetic deletion has helped to determine individual roles for mitogen-activated protein kinases (MAPKs) and some dual-specificity phosphatases (DUSPs) in both health and disease. Many of these *in vivo* studies have revealed surprising complexities. The use of unconditional, global knockouts, while instructive, is often complicated, for instance by compensatory signalling elements or embryonic lethality. Conditional knockouts that are temporally and spatially controlled should be more informative. In addition, limitations of the immune cell types that are studied or reported in MAPK and DUSP knockout systems also leave holes in our understanding of the role of individual DUSPs and MAPK isoforms in all immune cells. It is likely that DUSP and MAPK members have differing influences in various cells and generalizations that are made from data in one cell type should be avoided. Nevertheless, much information has been gleaned from global knockouts of the various MAPKs and DUSPs, which supports *in vitro* data on MAPKs and DUSPs in immune responses. However, in some cases, surprising and unpredicted roles for MAPKs and DUSPs in a whole physiological setting have been revealed. A summary of MAPKs and their associated DUSPs and immune responses are shown in the accompanying table. For phenotypes of DUSP knockouts in the immune system refer to TABLE 2.

MAPK	MAPK role	Substrate for	References
ERK1 and ERK2	Cytokine production (TNF MØ), thymic selection, T_H2 differentiation, prevention of plasma cell differentiation, survival, cell-cycle control	DUSP1–DUSP8, DUSP9, DUSP14	10,27,31,70,96, 97,110,111, 123–126
p38α	IFNG production (T_H1 cells), TNF translation, *Il1a* and *Il1b* transcription (MØ), IL-12 production (MØ and DCs), chemotaxis to C5a and CXCL12, apoptosis ($CD8^+$ cells)	DUSP1, DUSP2, DUSP4, DUSP6–DUSP8, DUSP10, DUSP16, DUSP26	14,23,31,97, 110,127–129
p38β	No major role in the immune system		129
p38γ/δ	Knockout viable, no immune investigation		130
JNK1	$CD8^+$ proliferation, thymocyte survival, IL-2 production, inhibits T_H2 differentiation	DUSP1–DUSP3, DUSP6–DUSP8, DUSP10, DUSP16, DUSP18, DUSP22	61,131–133
JNK2	Negative to $CD8^+$, proliferation, negative to IL-2, promotes T_H1 differentiation		133–136

CXCL12, chemokine (C-X-C) motif ligand 12; DC, dendritic cell; ERK, extracellular signal-regulated kinase; IL, interleukin; IFNG, interferon-γ; JNK, c-Jun N-terminal kinase; LPS, lipopolysaccharide; MØ, macrophage; T_H2, T helper 2; TNF, tumour-necrosis factor.

the MAPKs away from their cytoplasmic activators and aligning them with nuclear phosphatases[33,34]. In addition, spatial localization of MAPKs also determines the sensitivity of the MAPK module to various stimuli[34,35], as well as the specific cellular outputs by subcellular-specific substrates[36]. As will be discussed below, the DUSPs also have an important role in MAPK localization.

There is also now an increased understanding of the feedback loops[28,37] and crosstalk within the MAPK pathway and with other pathways that assist in the amplification, diversification and termination of the MAPK signal. Feedback and crosstalk have major implications for the development of MAPK inhibitors as anti-inflammatory agents. For example, the upstream TAK1-binding protein 1 (TAB1; also known as MAP3K7IP1) is directly phosphorylated by p38α and then downregulates TAK1. This feedback control limits the activation of p38, as well as downstream components such as JNK and IKK (inhibitor of NF-κB kinase kinase), and synchronizes the three pathways[29]. However, inhibition of p38 disrupts this feedback and causes the activation of the JNK and IKK pathways, which themselves are pro-inflammatory and may lead to unwanted side effects[29]. Examples of crosstalk include the ERK-dependent inhibition of p38 following exposure to transforming growth factor-β1 (TGFB1) to inhibit inflammatory cytokine production[38] and the sustained activation of JNK, which blocks ERK activation in response to mitogenic stimuli[30,31,39]. MAPKs also display crosstalk with other pathways, such as the JAK–STAT (Janus kinase–signal transducer and activator of transcription) and PI3K (phosphatidylinositol 3-kinase) pathways[40,41]. These all have major implications for successfully targeting individual MAPKs for therapeutic use. Inhibiting an individual kinase may disrupt critical feedback loops and crosstalk, which may have unexpected consequences. There is evidence for this in the context of p38 inhibitors and an observed liver toxicity in clinical trials (Supplementary information S1).

Phosphatases versus kinases in MAPK regulation

Although protein phosphatases have been considered by some as simply 'fuse switches' to prevent system overdrive, kinases are inactivated even in the presence of continuing stimuli, which suggests that phosphatases are pivotal in regulating the duration and strength of kinase activation to control the required cellular response. From a biochemical perspective, the enzymatic power of a phosphatase is as much as 100 to 1,000 times as great as that of a kinase, owing to the fact that kinases require ATP and therefore use a second-order reaction, whereas dephosphorylation is direct[42]. Hence it is conceivable that constrained signal transduction does not occur through kinase activation, but rather by the control of phosphatase expression and activity. In support of this, phosphatases, rather than the kinases, appear to have much more dynamic regulation, both in their expression and in their activity.

Second-order reaction
A second-order reaction depends on the concentration of one second-order reactant or two first-order reactants. A kinase acting on a MAPK is a second-order reaction as it requires the MAPK and ATP (that is, two first-order reactants).

Table 1 | **The DUSPs that regulate MAPK activity**

DUSP	Other names	Subcellular localization	Substrate specificity *in vitro*	MAPK activity in KO mice	Phenotype of KO mice	Human disease	Small-molecule inhibitors (indication; phase)
DUSP1	MKP1, CL100 (REF. 82), hVH1, 3CH134 (REF. 144), PTPN10 erp	Nuclear	p38, JNK, ERK[145,146]	No change in ERK, JNK and p38 in fibroblasts, ↑ p38 and JNK in macrophages, no change in ERK in macrophages	Normal development[108,109], ↑ cytokines (↓ IL-12), ↑ sepsis and CIA[96,97,110,111], metabolic phenotype[112]	↑ Breast cancer[99], ↓ prostate and ovarian cancer, affects growth of other tumours[98,147–149]	MX-7091 (cancer; discontinued preclinical), sanguinarine, chelerythrine, NU-126 (REFS 150,151)
DUSP2	PAC-1	Nuclear	ERK, p38 > JNK[62,63,74]	↓ ERK and p38 in macrophages and mast cells, ↑ JNK in macrophages and mast cells	↓ Cytokines, ↓ survival of mast cells, ↓ arthritis[31]	↑ Ovarian carcinoma, ↑ leukaemia[101,102]	ND
DUSP3	VHR[68]	Not determined	Inactive towards MAPKs	↑ ERK and JNK (RNAi studies) in HeLa cells	Cell-cycle arrest at G1-S and G2-M[70]	ND	NU-126 (REF. 151), 4-isoavenaciolide[152], RK-682 (REF. 153)
DUSP4	MKP2, hVH2 (REF. 154), TYP1 (REF. 155)	Nuclear	ERK > JNK > p38	ND	ND	ND	ND
DUSP5	hVH3, B23 (REF. 156)	Nuclear	ERK[157]	ND	ND	ND	ND
DUSP6	MKP3, Pyst1, rVH6 (REF. 158)	Cytosolic	ERK > JNK = p38 (REFS 85,86)	↑ ERK in embryos	Postnatal lethality, skeletal dwarfism, coronal craniosynostosis, hearing loss[159]	Hypermethylated in pancreatic cancer[100]	NSC 45382, NSC 295642, NSC 357756 (REF. 160)
DUSP7	MKP-X, Pyst2 (REF. 80), B59	Cytosolic	ERK > p38α (REF. 80)	ND	ND	↑ In acute and myeloid leukaemia[103,104]	ND
DUSP8	hVH5 (REF. 161), M3/6 (REF. 75), HB5	Nuclear and cytosolic	JNK > p38 > ERK[75,162]	ND	ND	ND	ND
DUSP9	MKP4 (REF. 77), Pyst3	Nuclear and cytosolic	ERK > JNK = p38	No change in ERK, JNK and p38 in embryo placentas and ES cells	Placental defects, embryonic lethal[78]	ND	ND
DUSP10	MKP5 (REF. 163)	Nuclear and cytosolic	JNK = p38 > ERK[93]	↑ JNK in T cells, no change in p38 in T cells	↑ Cytokines in macrophages and T cells, ↓ proliferation in T cells, ↓ EAE[61]	ND	ND
DUSP12	YVH1 (REF. 164)	Nuclear	ND	ND	ND	ND	ND
DUSP14	MKP6	Nuclear and cytosolic	ERK, JNK, p38 (REF. 165)	ND	ND	ND	ND
DUSP16	MKP7	Cytosolic	JNK2, JNK3, p38α,β (REF. 92)	ND	ND	ND	ND
DUSP18	N/A	Nuclear and cytosolic	JNK, no activity towards p38 or ERK1 (REF. 166)	ND	ND	ND	ND
DUSP22	JKAP, JSP1, VHX, MKPX	ND	JNK (activated)[136,167]	ND	DUSP22-deficient ES cells, ↓ JNK activation[136]	ND	JSP1 inhibitor produced by Ceptyr (inflammation; preclinical)
DUSP26	MKP8, SKRP3, NEAP	Nuclear and cytosolic	p38, ERK[168,169]	ND	ND	Promotes growth of certain cancer cells[105]	ND

↑, increased; ↓, decreased; CIA, collagen-induced arthritis; DUSP, dual-specificity phosphatases; EAE, experimental autoimmune encephalomyelitis; ERK, extracellular signal-regulated kinase; ES, embryonic stem; JNK, c-Jun N-terminal kinase; KO, knockout; MAPK, mitogen-activated protein kinase; MKP, mitogen-activated protein kinase phosphatase; ND, no data; RNAi, RNA interference.

Strong transcriptional induction and protein stabilization of phosphatases — both a result of MAPK activity[43–47] — as well as the control of their activity by reversible oxidation[48,49] are illustrative of this (FIG. 2). Interestingly, a computational analysis of the MAPK system suggests that DUSPs, and not the kinases, dictate the extent of MAPK phosphorylation following cellular activation[50]. Also, the influence of DUSPs extends beyond that of a dephosphorylating role, as some can shuttle or anchor MAPKs between the cytoplasm and nucleus[51,52].

The superfamily of tyrosine phosphatases

Phosphatases are enzymes that can hydrolyse the phosphoester bonds on protein, lipid or small-molecule substrates. MAPKs are inactivated completely by dephosphorylation of either the tyrosine or threonine residues, or both[53]. Many phosphatases are dedicated to dephosphorylating one or both of the phosphosites in the active site of MAPKs to control the magnitude and duration of MAPK activity (outweighing the number of activating kinases). In intact cells, dephosphorylation and inactivation of MAPKs occurs with kinetics that range from minutes to several hours depending on the cell type and activating stimulus[54]. The family of cysteine-dependent protein tyrosine phosphatases (PTPs) comprises 106 genes in humans and shares a canonical $C(X)_5R$ motif in their active sites. Based on structural homology and substrate preference, this superfamily is divided into seven categories[55,56] (FIG. 3; see also the Protein Tyrosine Phosphatases web site). The phosphatases that can inactivate MAPKs include: the PTPs that hydrolyse phosphotyrosine residues on activated MAPKs; the serine/threonine phosphatases, referred to as protein phosphatases (PPs), that dephosphorylate threonine residues; and the class I family of DUSPs (also known as MAPK phosphatases, DSPs or MKPs) that dephosphorylate phosphotyrosine and threonine residues that are located in the same MAPK[54,57–60] (FIG. 3). The class I family of DUSPs are further subcategorized into CH2 (CDC25 homology)-motif-containing MAPK phosphatases (MKPs), JSP1-like phophatases, MKP6-like, VHR-like, slingshot-like and SKPR1/hyVH1 (FIG. 3). Historically, the PPs were among the earliest to be identified (in the 1970s), followed by the PTPs (in the 1980s), and then by the DUSPs (1993 to present). Thus, an understanding of enzymatic regulation is greatest for the PPs, whereas knowledge about the mechanisms and substrates of PTPs and DUSPs is still emerging.

MAPK-directed DUSPs

The DUSPs form a structurally and functionally distinct subclass among the many protein phosphatases present in eukaryotic genomes. Of the 43 DUSPs depicted in FIG. 2 a further subclass classification can be made that is based on structural and sequence similarities. The class I DUSPs regulate MAPK activity through 'TXY-motif' dephosphorylation and represent particularly important negative regulators of MAPK signalling[54,61–63] (TABLE 1).

At least 16 mammalian DUSPs that show desphosphorylating activity towards MAPKs have been identified to date (TABLE 1). Of these 11 are 'typical' MKPs that contain a CH2 motif for MAPK docking and comprise three major subfamilies that are based on their sequence similarity, substrate specificity and subcellular localization[54,64–67] (TABLE 1). They all share common features, including an extended active-site motif with high sequence similarity to the corresponding region of the VH1 protein tyrosine phosphatase that was isolated from vaccinia virus[54]. In addition, their amino terminus contains a cluster of basic amino acids as part of the kinase interactive motif (KIM). The KIM confers substrate specificity and is the least homologous region demonstrating individual substrate preferences[54,67].

The first subfamily comprises DUSP1, DUSP2, DUSP4 and DUSP5. They localize to the nucleus, and are induced by growth factors or stress signals. The proteins consist of four exons, the positions of which are highly conserved. In addition, the active site motif of all four of these DUSPs is encoded within exon 4 and the length of their exon 3 is identical, which is suggestive of a common ancenstral gene[64,67]. The second subfamily comprises DUSP6, DUSP7 and DUSP9. They consist of 3 exons, are cytoplasmic in their subcellular localization and preferentially recognize ERK1 and ERK2 *in vitro*. DUSP8, DUSP10 and DUSP16 make up the third subgroup as they preferentially recognize JNK, p38 or both, respectively[54,64,67].

Of the 'atypical' DUSPs, many of which resemble CDC14 cell-cycle phosphatases, approximately six have activity towards MAPKs. DUSP3 (also known as VHR) is an additional mammalian homologue of VH1 (REF. 68) but lacks the required N-terminal motif for MAPK binding and indeed appears to be relatively inactive against MAPKs *in vitro*[69]. RNA interference of DUSP3 however had profound effects on the cell cycle mediated by JNK and ERK[70]. Additional members of this class I subfamily of DUSPs include stress-activated protein kinase (SAPK) pathway-regulating phosphatase 1 (SKRP1), which lacks the CDC25 domain but contains the conserved active-site sequence and can inactivate JNK through its binding to the upstream JNK-activator MKK4/7 (REFS 71,72).

Different DUSPs for different cell types

Multiple DUSPs probably act cooperatively in individual cells to control MAPK activity. For instance, activated macrophages express several DUSPs[73]. Nevertheless, because the many DUSPs show different patterns of tissue expression, transcriptional control, substrate specificity and subcellular localization, it is conceivable that individual DUSPs regulate specific cellular responses in certain cell types. Some DUSP family members show restricted expression to certain tissue types. For instance, DUSP2 is enriched in haematopoietic cells[31,63,74]; DUSP8 appears to be expressed predominantly in brain, heart and skeletal muscle[75]; DUSP10 is expressed ubiquitously, but is more abundant in cerebellum, skeletal muscle and bone marrow, and is transcriptionally regulated in macrophages[61,76]; whereas DUSP9 is found only in placenta, kidney and embryonic liver[77,78].

The diverse expression patterns of the many DUSPs in different immune cell types have been analysed recently[31,73,79]. These data correlate well with previous

expression studies, and emphasize that the immune cell expression patterns of some DUSPs are suggestive of individual roles for these DUSPs in certain immune responses. For example, DUSP1 is highly expressed in neutrophils, macrophages and B cells, but is absent from T helper cells. DUSP2 is largely absent from non-activated leukocytes, but is highly expressed in activated cells, especially mast cells, neutrophils and B cells (TABLE 1). DUSP3 transcripts are expressed abundantly in non-immune cells, which is suggestive of a role outside the immune system. DUSP9 is high in kidney (as previously described[77]) and intermediate

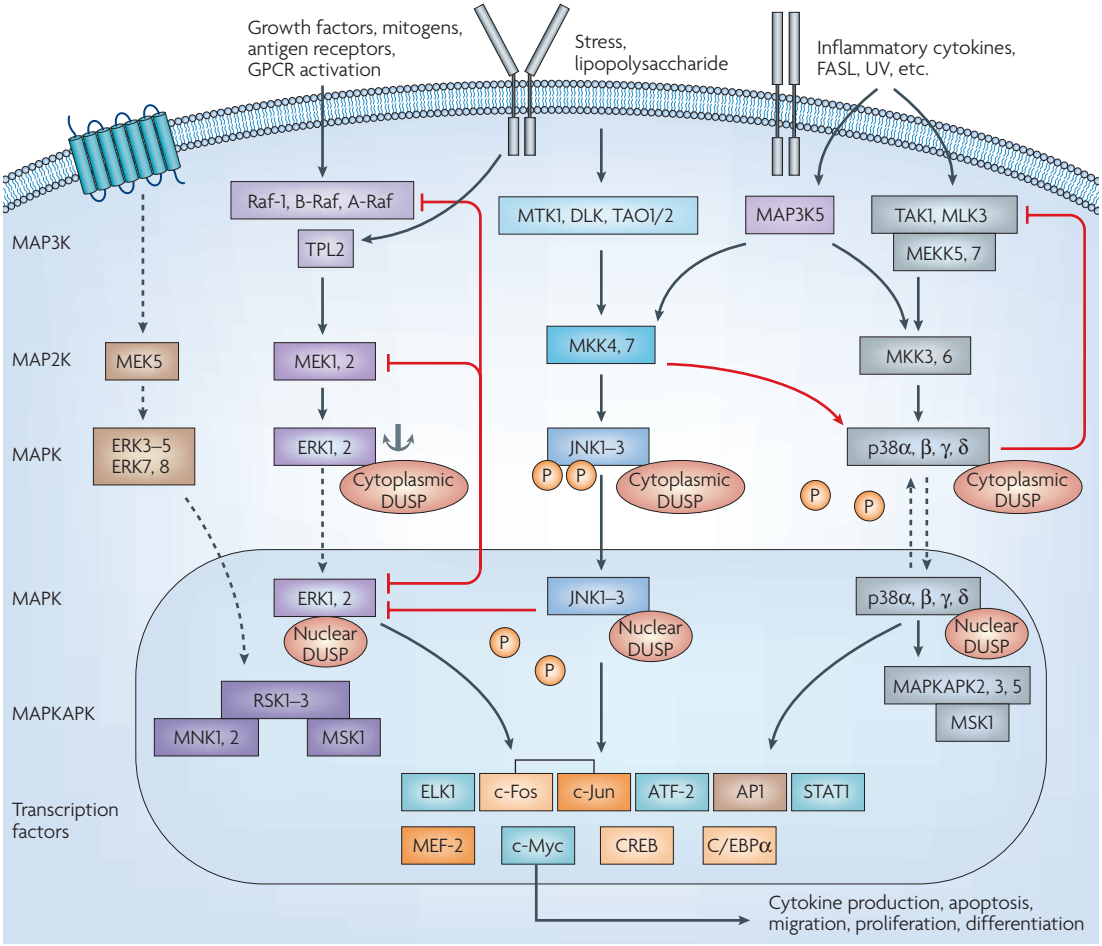

Figure 1 | **The MAPK pathway and the role of DUSPs.** The three main arms of the mitogen-activated protein kinase (MAPK) pathway, ERK (extracellular signal-regulated kinase), JNK (c-Jun N-terminal kinase) and p38, that mediate immune cell functional responses to stimuli through multiple receptors such as chemoattractant receptors, Toll-like receptors and cytokine receptors are shown. The three-tiered kinase dynamic cascade leads to activated MAPKs entering the nucleus to trigger immediate early gene and transcription factor activation for cellular responses such as cytokine production, apoptosis and migration. Approximately 18 MAPK genes encompassing four subfamilies have now been identified in mammalian cells[137]. The main classes of mammalian MAPKs consist of ERK1 and ERK2, and the more recently identified larger kinases ERK3 (α and β), ERK4 (ERK1b), ERK5, ERK7 and ERK8; p38 MAPKs (p38α, β, γ, δ); and JNKs, also known as stress-activated protein kinases (SAPK1, 2, 3) (for recent reviews see REFS 6,8,9,97,138,139). All MAPKs, except the larger ERKs that remain less well characterized[139,140], are activated by dual phosphorylation of the threonine and tyrosine residues within a conserved 'TXY' motif in their kinase domain. A general feature of MAPK pathways is the three-tiered kinase canonical cascade consisting of a MAPK, a MAPK kinase (MAP2K, MAPKK, MKK or MEK) and a MAPK kinase kinase (MAP3K or MAPKKK)[9,141]. The existence of this tier is probably essential for the amplification and tight regulation of the transmitted signal. Seven upstream MAP2Ks and 14 MAP3Ks have been identified[9,141,142]. For receptor tyrosine kinases (RTKs) and G-protein coupled receptors (GPCRs), MAPK cascade activation is initiated by small GTP-binding proteins, STE20-like kinases or by adaptor proteins that transmit the signal to MAP3Ks[9]. MAP3Ks then transfer the signal to MAP2Ks to induce MAPK activation. Thus, MAP3Ks provide some stimulus specificity, creating independent signalling modules that may function in parallel, whereas the MAPKs carry out the effector functions of each cascade, either through direct phosphorylation of effector proteins, such as transcription factors, or activation of subordinate kinases, known as MAPK-activated protein kinases (MAPKAPKs). Multiple dual-specificity phosphatases (DUSPs) specifically dephosphorylate the threonine and tyrosine residues on MAPKs, rendering them inactive either in the cytoplasm or nucleus. DUSPs also assist in shuttling or anchoring MAPKs to control their activity. Red arrows indicate feedback or crosstalk within the MAPK pathway.

in most leukocyte types. DUSP10 shows high expression in mast cells, is absent from plasmacytoid dendritic cells, is intermediate in dendritic cells and T_H1 and T_H2 cells, and is high in skeletal muscle and liver. Indeed only a limited number of DUSPs, usually only one or two, show high expression in any single immune cell type (TABLE 2). In addition to their differing patterns of tissue expression, DUSPs show differing subcellular localizations (that is, cytosolic versus nuclear), which suggests that they regulate the activity of specific pools of MAPKs[51,52].

Regulating DUSP expression and activity

An interesting feature of DUSPs is their tight and sometimes rapid transcriptional induction by growth factors or factors that induce cellular stress. Most DUSPs are inducible genes with basal levels of DUSPs being mostly low in unstressed or unstimulated cells[67]. Nuclear DUSPs (DUSP1, DUSP2, DUSP4 and DUSP5) show the most dramatic transcriptional regulation, at least in leukocytes[31]. Some DUSPs serve as immediate early genes following stimulation. DUSP1, DUSP2, DUSP4 and DUSP7 are rapidly induced in response to serum stimulation. This induction is also dependent on MAPK activation and is thought to be a mechanism for the attenuation of mitogenic signalling[43,46,80]. By contrast, DUSP6, DUSP8, DUSP9 and DUSP10 are not encoded by immediate early genes[67,81]. Different DUSPs also respond to different stimuli. For example, DUSP1 is induced by mitogens, oxidative stress, heat shock[82] and hypoxia[83,84], whereas DUSP7 is induced only moderately by serum and not by cellular stress[80]. Moreover, although DUSP6 expression is not induced by either mitogens or cellular stresses[85,86], its expression can be increased by agents that promote neuronal differentiation[81]. On the other hand, DUSP2 is highly transcriptionally regulated, but is exclusive to immune cells[31].

An additional mechanism by which DUSPs can be regulated is through their stabilization at the level of protein expression, which is controlled directly by the MAPKs. For example, DUSP1 is rapidly degraded soon after induction. However, through a negative-feedback mechanism, ERK can induce stabilization of DUSP1 by direct phosphorylation, which leads to reduced ubiquitylation and proteasomal degradation[47]. Interestingly, the reverse also occurs whereby ERK, in cooperation with the SCF^{Skp2} ubiquitin ligase, enhances polyubiquitylation and proteolysis of DUSP1 as part of a positive-feedback mechanism[45]. Furthermore, some DUSPs are activated following binding to their respective substrates. DUSP6 experiences a 25-fold increase in catalytic activity when complexed to its phosphorylated substrate, ERK2 (REF. 87). Similarly, DUSP1 catalytic activation is mediated by physical interactions with ERK2, JNK1 and p38 *in vitro*[88] and DUSP2 enzymatic activity, which is virtually inactive when alone *in vitro*, is also enhanced upon binding to ERK2 through its N-terminal domain[89,90]. Enzymatic deactivation of phosphatases also occurs by the action of reactive oxygen species that have been shown to reversibly oxidize the conserved catalytic site cysteine in PTPs and inactivate their enzymatic activity[49,91]. Indeed, TNF-induced cell death is promoted by reactive oxygen species that specifically inhibit the cysteine residue at the catalytic site of DUSPs, to increase JNK activity[48]. Thus, in a manner analogous to reversible phosphorylation, reversible oxidation provides another mode of activation or deactivation of proteins following certain cellular stimulations.

Regulating MAPK activity

Another function of DUSPs, in addition to their dephosphorylating activity, is the control of the subcellular localization of MAPKs. For instance, certain DUSPs regulate the cytoplasmic nuclear shuttling of MAPKs. DUSP16, which contains both a nuclear localization signal and a nuclear export signal, can transport both p38 and JNK from the nucleus to the cytoplasm[51]. Similarly, DUSP6, a cytoplasmic DUSP that contains a nuclear export signal, causes the cytoplasmic retention of ERK2, which is dependent on both its nuclear export signal and its KIM motif that binds the MAPK[52]. These initial discoveries may elucidate mechanisms that control MAPK subcellular localization and emphasize that DUSPs have roles other than dephosphorylating MAPKs.

Substrate specificities of DUSPs

Assessing the precise substrate specificities for the DUSPs has proved problematic, often because *in vitro* assays do not always reflect physiological roles *in vivo*. Importantly, however, DUSPs do appear to have preferred substrates. For example, DUSP6 is 100-fold more active towards ERK2 than p38 or JNK[85]. Similarly, DUSP9 seems to have a preference for ERK over other MAPKs[77]. By contrast, DUSP8, DUSP10 and DUSP16 have little activity for ERK and seem to prefer JNK and p38 kinases[51,75,76,92,93]. These reported *in vitro* substrate preferences should be treated with some caution, as different cell types and stimuli regulate different MAPKs. Thus, DUSP regulation of MAPKs may be cell-type and stimulus specific[62,94].

In addition, although all DUSPs seem to have some individual preference towards a MAPK, efficacies may differ between two DUSPs. For example, although both DUSP2 and DUSP4 have a preference for ERK *in vitro*, DUSP4 dephosphorylates ERK much more efficiently than DUSP2 (REF. 62). The substrate specificity of the various DUSPs may reside in their heterogeneous KIM docking site[95]. However, substrate availability and access in certain cells types is another important consideration. For instance, although *Dusp10*$^{-/-}$ T cells had elevated JNK activity (as predicted from *in vitro* studies), there was no change in p38 activity[61]; *Dusp1*$^{-/-}$ macrophages had elevated p38 and JNK activity but no change in ERK activity despite *in vitro* evidence that demonstrates an equal preference for all three[62,96,97]; DUSP3 had little activity towards MAPK *in vitro*, but had elevated ERK and JNK activity following RNA interference[70]; and *Dusp2*$^{-/-}$ macrophages and mast cells showed a surprising reduction in ERK and p38 activity but elevated JNK activity, highlighting the co-dependence of certain DUSPs and the strong influence of MAPK crosstalk[31] (TABLE 1).

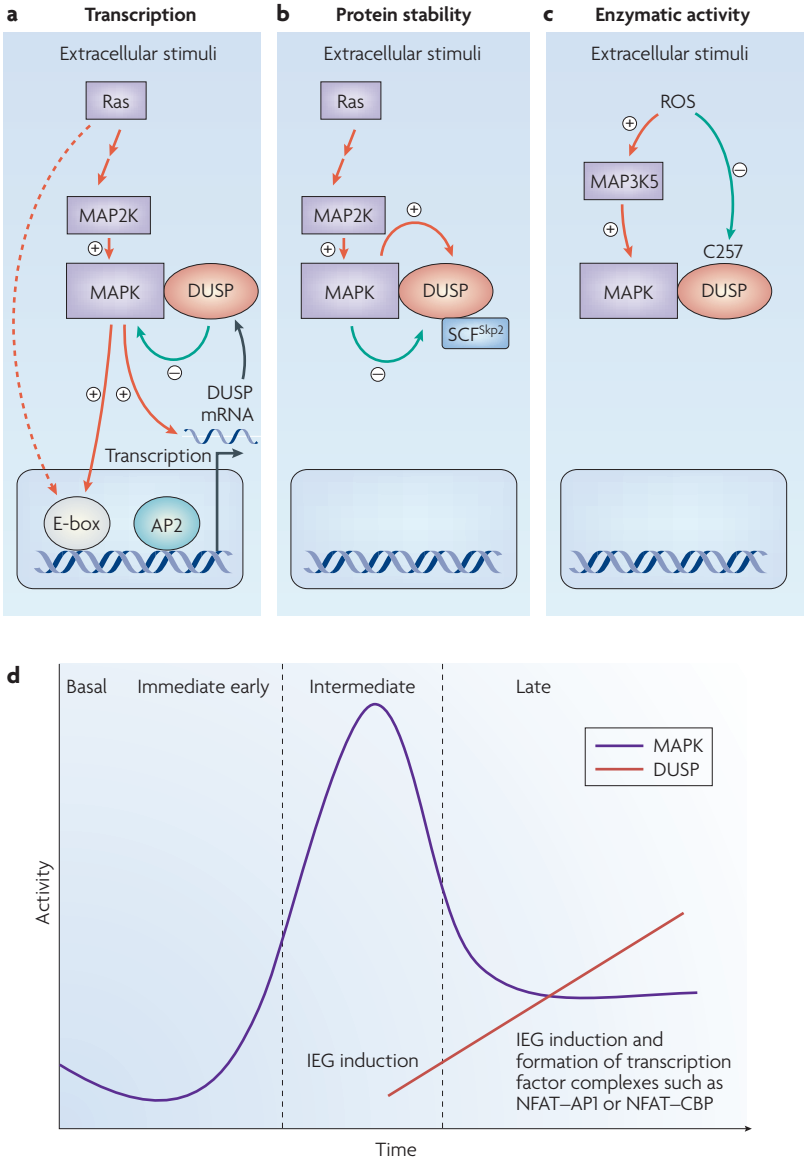

Figure 2 | **Regulation of DUSPs by MAPKs.** In contrast to mitogen-activated protein kinases (MAPKs) themselves, dual-specificity phosphatase (DUSP) expression and activity are strongly regulated by three main mechanisms as shown in panels **a**–**c**. **a** | The unique, strong, transcriptional activation of DUSPs to various stimuli either through immediate early gene (IEG) activation (DUSP1, DUSP4, DUSP7 and DUSP2), or by other transcription factors (DUSP6, DUSP9, DUSP10 and DUSP8) through activity of MAPKs themselves. MAPK-dependent activation of E-box and AP2 transcription factors leads to DUSP transcription. MAPKs also promote the stability of DUSP mRNA in the cytoplasm. **b** | Protein stability and catalytic activity of DUSPs is highly regulated through binding to MAPK substrates in both negative and positive ways. MAPK binding to DUSPs can increase protein stablility to provide feedback to MAPK activity[44]. Sometimes however, as is the case for DUSP1, MAPK binding can decrease protein stability and promote DUSP1 proteolysis through the ubiquitin ligase SCF^{Skp2}, thereby sustaining MAPK activity[45]. **c** | Reactive oxygen species (ROS) that regulate some immune responses and activate the upstream kinase MAP3K5 (also known as ASK1) directly inactivate catalytic sites (at the conserved cysteine 257) of DUSPs. **d** | The temporal control of MAPKs results in varied cellular responses. The induction of DUSP expression and activity correlates with high MAPK activity to control the sustained or late phase of MAPK activity that is crucial for inducing IEGs and forming transcription factor complexes. Red arrows indicate positive regulation and green arrows indicate negative regulation in the tight regulation loops between MAPKs and DUSPs. CBP, CREB-binding protein (also known as CREBBP); MAP2K, MAPK kinase; MAP3K, MAP2K kinase; NFAT, nuclear factor of activated T cells.

Physiological roles for DUSPs

Currently, the physiological roles of many of the DUSPs are still largely unknown *in vivo*. Many have shown correlation with multiple types of human cancers. Overexpression of the ubiquitous DUSP1, which dephosphorylates ERK, JNK and p38 (REF. 62), has been found in several malignancies, including breast and prostate[98,99]. DUSP6 is hyper-methylated in pancreatic cancer, which suggests that it could act as a tumour suppressor[100], whereas DUSP2 is increased in ovarian cancer and a splice variant was found in leukaemia[101,102]. DUSP7 shows enhanced expression in myeloid leukaemia[103,104], whereas DUSP26 is overexpressed in, and promotes growth of, anaplastic thyroid cancers[105]. DUSP1 expression is also inversely related to apoptosis[106,107], although DUSP1 deletion in mice initially yielded no obvious phenotype with normal development and MAPK activities in fibroblasts[108]. However, further studies have shown elevated p38 activity in DUSP1-deficient alveolar macrophages[109], which suggests a potential cell-type-specific activity for this DUSP.

Recently, four reports described that DUSP1 suppresses endotoxic shock *in vivo* via feedback control of p38 and JNK activity[96,97,110,111]. Interestingly, although *Dusp1*$^{-/-}$ macrophages, splenocytes and dendritic cells showed an increase in cytokine production, which demonstrates its negative control over this cellular process, IL-12 production was specifically reduced, despite similar levels in serum after lipopolysaccharide challenge, which suggests some positive regulatory activities of DUSP1 (REFS 96,97). In addition, DUSP1 regulated cytokine production in a temporally specific manner, whereby negative regulation on cytokines was seen at earlier time points following cellular activation, and positive regulation was observed at later time points[110]. A role for DUSP1 in controlling nuclear MAPKs and metabolic homeostasis has also been observed. Despite unimpaired insulin signalling and glucose homeostasis, *Dusp1*$^{-/-}$ mice were resistant to diet-induced obesity due to increased energy expenditure, but they developed glucose intolerance[112]. DUSP9 is required for placental development, but its absence appears not to influence MAPK phosphorylation[78]. Interestingly, the placental phenotype of *Dusp9*$^{-/-}$ mice highlights the need for fine-tuning the MAPK pathway for proper placental development. DUSP10 was shown to be an important regulator of innate and adaptive immune responses mediated by the attenuation of JNK activity[61]. Like DUSP1, DUSP10-deficient mice revealed a potential for both positive and negative regulation of cellular responses. *Dusp10*$^{-/-}$ mice exhibited an expected increase in cytokine production from macrophages after TLR stimulation, but also had an unexpected reduction in proliferation of T cells and protection in a model of experimental autoimmune encephalomyelitis[61]. *Dusp2*$^{-/-}$ mice also had an unexpected and complex phenotype. Activation levels of ERK and p38 actually decreased in the absence of DUSP2 in activated macrophages and mast cells, but JNK increased. This resulted in reduced inflammatory mediator production from these cells, which could be rescued through reconstitution with phosphatase-active DUSP2 (REF. 31).

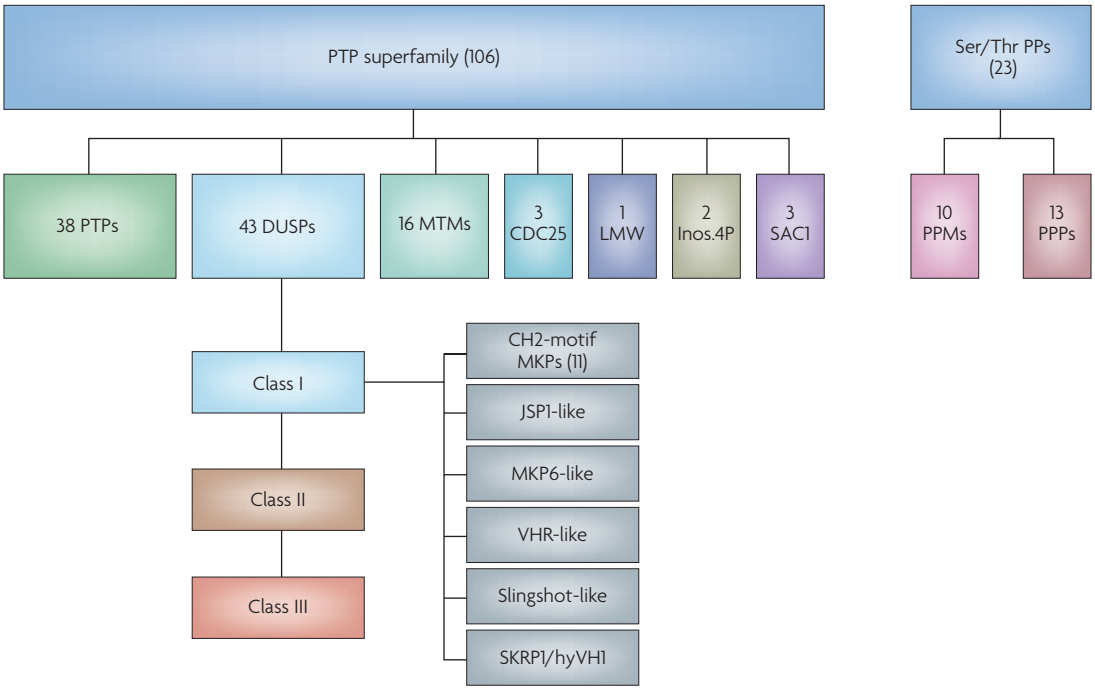

Figure 3 | **Phosphatases that regulate MAPKs.** Of the 159 phosphatases identified in the human genome that operate in signal transduction, 106 of these are considered to be protein tyrosine phosphatases (PTPs). This PTP superfamily is further subdivided into 7 categories that are based on structural homology and substrate preference. These categories are: protein tyrosine phosphatase (PTPs), dual-specificity phosphatases (DUSPs), myotuberlarin-related phosphatases (MTMs), CDC25 phosphatases, low molecular weight (LMW) phosphatases, inositol-4-phosphatases (Inos.4P) and SAC1-domain phosphatases[55,143]. PTPs and some serine/threonine phosphatases (PPs) show activity towards mitogen-activated protein kinases (MAPKs) by dephosphorylating single tyrosine or threonine residues. Class I DUSPs have activity towards MAPKs by dephosphorylating both tyrosine and threonine residues and are further subclassified into CH2-motif containing MAPK phosphatases (MKPs), JSP1-like phosphatases, MKP6-like, VHR-like, slingshot-like and SKPR1/ hyVH1. PPM, protein phosphatases, magnesium dependent; PPP, phosphoprotein phosphatases.

Dusp2$^{-/-}$ mice were protected in the KxB/N model of inflammatory arthritis, which is dependent on mast cell and macrophage activation[31].

Drug development — prospects and challenges

There is already considerable evidence that pharmacological inhibition of the MAPKs themselves can modify inflammatory responses in both animal models and in humans (see the Phase II clinical trials listed in Supplementary information S1). However, the broad expression profiles of MAPKs, as well as complex cross-talk and feedback loops, raise concerns over the potential side effects of MAPK inhibitors. Indeed, despite the enthusiasm by various companies to develop MAPK inhibitors, few have progressed to late-stage clinical trials, with many producing hepatotoxicity problems (Supplementary information S1).

Interference of DUSP activity may be an alternative strategy for manipulating MAPK pathways and immune responses in a cell-type-specific manner. Controlling DUSP activity provides opportunities for subduing immune responses in the case of chronic inflammation or autoimmunity, or boosting immune responses to fight cancers or infection. Until the mid-1990s, small-molecule inhibitors of this class of protein were limited to the broad-spectrum PTP inhibitor orthovanadate.

Recently, specific inhibitors of DUSP1, DUSP6 and DUSP22 have been identified (TABLE 1). The differences in the primary amino-acid sequence within the catalytic domain of the different subclasses of the 106 protein tyrosine phosphatases suggest that selective inhibitors might be achievable. Moreover, the X-ray crystallographic structures for DUSP2, DUSP6 and DUSP3, compared with the structures of PTEN (phosphatase and tensin homologue) or PTP1B (also known as PTPN1), reveal a different architecture within the active sites. The different widths and depths within the active sites are thought to contribute to the differential specificity for tyrosine, tyrosine/threonine or serine/threonine phosphates by the different phosphatases. Thus, the shorter serine/threonine residues may not gain access to the deeper binding pocket of the PTP and therefore may be spared from hydrolysis[113].

The active sites of PTPs are ~9 Å (REF. 114), whereas those of the DUSPs tend to be shallower at ~6 Å (REFS 89,115). The shallow pocket of VHR-like DUSPs allows both phosphotyrosine and the shorter phosphoserine/threonine substrates to reach the catalytic cysteine at the bottom, whereas the deeper PTP1B pocket permits only phosphotyrosine access. The wider opening of the PTEN pocket is consistent with its ability to dephosphorylate phosphoinositide lipids and phosphoserine/

Experimental autoimmune encephalomyelitis
An animal model of brain inflammation. It is mostly used with rodents and is a model for the human disease multiple sclerosis. It is induced with myelin oligodendrocyte glycoprotein.

Table 2 | **A summary of the expression patterns of DUSPs in immune cell types and tissues***

Immune cell/tissue	Low expression	Moderate expression	High expression
Basophils (unstimulated)	DUSP1, 2, 3, 4, 8, 9, 14, 18, 26	DUSP5, 7, 12, 16, 22	DUSP6, 10
Mast cells (IgE stimulated)	DUSP1, 3, 5, 7, 8, 9, 16, 18, 22	DUSP2, 6	DUSP4, 10, 14
Neutrophils (IL-8 or C5a stimulated)	DUSP3, 4, 7, 12, 14	DUSP5, 7, 8, 9, 10, 16, 18, 22, 26	DUSP1, 2, 6
Macrophages (LPS)	DUSP4, 5	DUSP6	DUSP1, 2, 16
DCs (LPS stimulated)	DUSP1, 3, 6, 7, 8, 9, 12, 16, 18, 26	DUSP2, 5, 7, 10, 14, 22	DUSP4
Plasmacytoid DCs (CpG stimulated)	DUSP1, 6, 8, 10, 26	DUSP2, 3, 4, 7, 9, 12, 14, 16, 18	DUSP5, 22
Naive B cells	DUSP3, 4, 14, 16, 18	DUSP6, 7, 8, 9, 10, 22, 26	DUSP1, 2, 5, 12
Plasma cells	DUSP3, 4, 6, 7, 10, 14, 16, 22	DUSP7, 8, 9, 12, 18, 26	DUSP1, 2, 5
Memory B cells	DUSP3, 4, 7, 14, 16, 18	DUSP5, 6, 8, 9, 10, 22, 26	DUSP1, 2, 12
Memory B cells (IgM)	DUSP3, 4, 6, 7, 8, 9, 10, 14, 16, 18, 26	DUSP 5, 12, 22	DUSP2
T_H1 cells	DUSP1, 3, 6, 8, 9, 18, 22, 26	DUSP2, 7, 10, 12, 14, 16	DUSP4, 5
T_H2 cells	DUSP1, 3, 8, 9, 18, 22, 26	DUSP2, 5, 6, 7, 10, 12, 14, 16	DUSP4
NK cells	DUSP3, 5, 7, 8, 9, 14, 18, 22, 26	DUSP1, 2, 6, 10, 12, 16	DUSP4
Bone marrow	DUSP4, 5, 6, 10, 12, 14, 22	DUSP2, 3, 7, 8, 9, 16, 18, 26	DUSP1
Spleen	DUSP3, 4, 8, 9, 10, 14, 16, 26	DUSP1, 5, 7, 11, 22	DUSP2, 6
Lymph node	DUSP3, 7, 8, 9, 10, 14, 26	DUSP1, 4, 5, 11, 16, 22	DUSP2, 6
Thymus	DUSP3, 8, 13, 18, 22, 26	DUSP1, 4, 7, 12, 16	DUSP2, 5, 6, 10
Tonsil	DUSP3, 4, 7, 8, 9, 14, 26	DUSP1, 6, 10, 11, 16, 22	DUSP2, 5

*Determined through transcript expression profiling[31,73,79] and Gene Expression Omnibus database sets GSE3526 and GSE3982.
DC, dendritic cell; DUSP, dual-specificity phosphatases; IL, interleukin; LPS, lipopolysaccharide; NK, natural killer; T_H, T helper.

threonine substrates in addition to phosphotyrosine[116]. Therefore, it seems feasible that compounds disrupting the catalytic region will display some specificity, at least between these two main classes. It is also possible that inhibitors may find an application, even if they do not show selectivity for individual DUSPs. Nevertheless, the shallow and hydrophilic nature of the catalytic domain of DUSPs presents challenges for drug development.

Targeting protein–protein interactions through the KIM of DUSPs may be an alternative strategy for manipulating their activity. A high degree of substrate specificity between a specific DUSP and MAPK is mediated by the KIM, which serves as a 'docking site'. KIMs are defined as short sequence motifs that lie distal to the phosphoacceptor in the linear amino-acid sequence and ensure the efficiency and specificity of substrate phosphorylation[117]. Various types of docking sites have been identified in several MAPK interacting proteins, including upstream kinases (for example, MEKs), phosphatases (DUSPs), scaffold proteins, downstream effectors (for example, MAPKAPKs) and transcription factors, and these docking sites contribute to the affinity of these molecules for specific MAPK members[118,119]. The KIM domains of multiple DUSPs have been identified, and, owing to the specificity of the protein–protein interactions at this site, disruption of KIM–MAPK interactions using small-molecule inhibitors is an intriguing area for drug discovery. For many PTPs, physical interaction via the KIM domain of the phosphatase and the target protein is required for conformational changes in the phosphatase to significantly increase enzymatic activity, which otherwise exhibits very low phosphatase activity in the absence of substrates[115,120]. This mechanism appears to be generalized across the DUSPs, but has been most studied with DUSP6 (REF. 44).

For example, ERK2 binding to DUSP6 via the conserved XXRRXXKXXLXV in the N-terminal kinase binding domain[95] stabilizes the active conformation of the active site cysteine[115] and results in an approximately 100-fold increase in enzymatic activity[44,87,99]. Interestingly, DUSP6 seems to first dephosphorylate the phosphothreonine residue within the dually phosphorylated TXY motif on ERK2, dissociate, and subsequently reassociate with monophosphorylated ERK2 phoshotyrosine[120]. Importantly, DUSP6 has been found to engage in intramolecular dephosphorylation of ERK with a binding stoichiometry of 1:1; thus ERK-binding-dependent increases in DUSP6 activity result in the dephosphorylation of the same bound ERK molecule, and not a freely soluble secondary ERK molecule. These considerations have important implications for the negative regulation of ERK, given that active ERK1 and ERK2 form dimers in solution, which may be resistant to inactivation by DUSP6. Active ERK1 and ERK2 dimers translocate into the nucleus, and ERK inactivation may be driven by dimer dissociation and subsequent binding to DUSPs. Disruption of this process by chemical inhibition of this positively charged site is therefore a viable although unproven strategy to control MAPK activation.

It is challenging to design and develop small-molecule inhibitors that exclusively target the catalytic domain of

proteins. This is due mostly to the fact that they must mimic a phosphate moiety, which will result in the molecule being highly negatively charged and so lacking drug-like properties[121]. Producing ATP mimetics seems to make targeting kinases easier. Nevertheless there are shortcomings to this approach, mainly because of a lack of specificity that is due to the conservation of the ATP-binding pockets among the many kinases[122].

Cyclosporin, a calcineurin phosphatase inhibitor, does not directly block protein–protein interactions, but rather facilitates ternary complex formation between cyclophilin A and calcineurin to affect calcineurin function. Therefore, other approaches exist for targets that are difficult to 'drug' through conventional small-molecule inhibition. Infinity Pharmaceutical's successful blocker of BCL-2 activity disrupts protein interaction rather than protein activity itself. As DUSPs become more attractive for drug development, owing to their central role in MAPK regulation, additional efforts will follow to effectively target these molecules. Other approaches that could be used for DUSP inhibition include RNA interference or anti-sense approaches as used clinically by Isis Pharmaceuticals for the phosphatase PTP1B.

Conclusions

DUSPs, a subclass of the PTPs, are emerging as attractive targets for drug discovery. DUSP inhibitors might be used to manipulate MAPK and cellular responses in both positive and negative ways. However the role of DUSPs in various cells and biological processes still needs to be determined. Further validation will come from DUSP knockout studies, as well as inducible or tissue-selective mutations of certain DUSP family members. Understanding the physiological roles of the many DUSPs should pave the way for developing new immunomodulatory therapies for inflammation or cancer, and for further understanding MAPK signalling in physiological responses. Therefore, inhibition or activation of some of these phosphatases offers an attractive means for manipulating certain MAPKs in a cell-type-restricted manner, particularly for immune-based disorders.

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