Seminars in Cell & Developmental Biology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

journal homepage: www.elsevier.com/locate/semcdb

The regulation of oncogenic Ras/ERK signalling by dual-specificity mitogen activated protein kinase phosphatases (MKPs)

Andrew M. Kidger, Stephen M. Keyse*

CR-UK Stress Response Laboratory, Division of Cancer Research, Jacqui Wood Cancer Centre, Ninewells Hospital & Medical School, Dundee DD1 9SY, UK

ARTICLE INFO

Article history:
Received 6 January 2016
Accepted 6 January 2016
Available online xxx

Keywords:
MAP kinase
Extracellular signal-regulated kinase
MAP kinase phosphatase
Dual-specificity phosphatase
DUSP5
DUSP6/MKP-3
Ras oncogene

ABSTRACT

Dual-specificity MAP kinase (MAPK) phosphatases (MKPs or DUSPs) are well-established negative regulators of MAPK signalling in mammalian cells and tissues. By virtue of their differential subcellular localisation and ability to specifically recognise, dephosphorylate and inactivate different MAPK isoforms, they are key spatiotemporal regulators of pathway activity. Furthermore, as they are transcriptionally regulated as downstream targets of MAPK signalling they can either act as classical negative feedback regulators or mediate cross talk between distinct MAPK pathways. Because MAPKs and particularly Ras/ERK signalling are implicated in cancer initiation and development, the observation that MKPs are abnormally regulated in human tumours has been interpreted as evidence that these enzymes can either suppress or promote carcinogenesis. However, definitive evidence of such roles has been lacking. Here we review recent work based on the use of mouse models, biochemical studies and clinical data that demonstrate key roles for MKPs in modulating the oncogenic potential of Ras/ERK signalling and also indicate that these enzymes may play a role in the response of tumours to certain anticancer drugs. Overall, this work reinforces the importance of negative regulatory mechanisms in modulating the activity of oncogenic MAPK signalling and indicates that MKPs may provide novel targets for therapeutic intervention in cancer.

Contents

1. Dual-specificity MAP kinase phosphatases: spatiotemporal regulators of MAP kinase signalling

A subfamily of 10 catalytically active dual-specificity protein phosphatases are dedicated to the task of negatively regulating the mammalian mitogen-activated protein kinases (MAPKs) by dephosphorylating both tyrosine and threonine residues of the signature T-X-Y motif located within the activation loop of the kinase [1–3]. These MAPK phosphatases (MKPs or DUSPs) can be broken down into three subgroups based on sequence homology, subcellular localisation and substrate specificity. There are four inducible nuclear MKPs; *DUSP1*/MKP-1, *DUSP2*, *DUSP4*/MKP-2 and *DUSP5*. Three MKPs; *DUSP6*/MKP-3, *DUSP7* and *DUSP9*/MKP-4 are both cytoplasmic and ERK selective while a further three MKPs; *DUSP8*, *DUSP10*/MKP-5 and *DUSP16*/MKP-7 preferentially inactivate the stress-activated c-Jun amino-terminal kinase (JNK) and p38 MAPKs (Fig. 1A). These enzymes share a highly conserved structure comprising of a non-catalytic N-terminal domain and a C-terminal catalytic domain. The latter contains the highly con-

* Corresponding author.
E-mail address: s.m.keyse@dundee.ac.uk (S.M. Keyse).

http://dx.doi.org/10.1016/j.semcdb.2016.01.009

A

Gene/MKP	Subcellular Localisation	Substrate Specificity	Inducible by MAPKs:
DUSP1 / MKP-1	Nuclear	JNK > p38 = ERK	ERK, p38
DUSP2	Nuclear	ERK = p38 > JNK	ERK, JNK
DUSP4 / MKP-2	Nuclear	ERK = JNK > p38	ERK
DUSP5	**Nuclear**	**ERK**	**ERK**
***DUSP6* / MKP-3**	**Cytoplasmic**	**ERK**	**ERK**
DUSP7 / MKP-X	Cytoplasmic	ERK	N/D
DUSP9 / MKP-4	Cytoplasmic	ERK > p38	N/D
DUSP8	Cytoplasmic / nuclear	JNK = p38	N/D
DUSP10 / MKP-5	Cytoplasmic / nuclear	JNK = p38	N/D
DUSP16 / MKP-7	Cytoplasmic / nuclear	JNK = p38	N/D

B

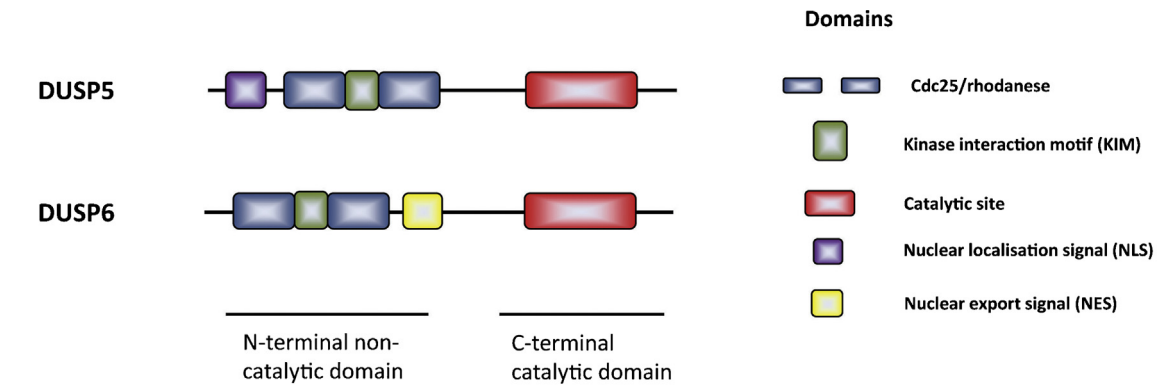

Fig. 1. (A) List of the mammalian dual specificity MAP kinase phosphatases broken down into three groups by sequence similarity, subcellular localisation and substrate specificity. The ERK-specific phosphatases *DUSP5* and *DUSP6*/MKP-3, which are the main subject of the experimental work covered in this review are highlighted in red. ND, not determined. (B) Schematics showing the domain structures of *DUSP5* and *DUSP6*/MKP-3 highlighting the disposition of the kinase interaction motif (KIM) and localisation signals located within the N-terminal non catalytic domain and the catalytic site within the C-terminal domain.

served protein tyrosine phosphatase (PTPase) active site sequence (I/V)HCXAGXXR(S/T/G). The N-terminal domain contains a conserved modular sequence known as the kinase interaction motif (KIM), which mediates differential recognition and binding of MAPK substrates and also harbours either nuclear localisation (NLS) or export (NES) signals, which determine subcellular localisation (Fig. 1B) [4]. Interestingly, in a subset of MKPs the conformation of the active site in the absence of substrate is not optimal for catalysis. However, when a MAPK substrate is engaged via the KIM, this causes an allosteric rearrangement of the active site residues within the C-terminal catalytic domain resulting in catalytic activation, a process thought to underpin greater substrate selectivity [5,6]. Finally, The observation that the KIM-mediated binding of MKPs to their cognate substrates by interaction with the conserved MAPK common docking (CD) domain does not require phosphorylation and activation of the MAPK itself has led to the idea that MKPs, by sequestering inactive MAPKs within either the nucleus or the cytoplasm, may regulate the spatial localisation as well as the duration and magnitude of signalling [7].

Many of the genes that encode MKPs are themselves highly inducible and in many cases the activity of one or more MAPK pathways is responsible for transcriptional up regulation of these enzymes. Thus, individual MKPs can act as classical negative feedback regulators of pathway activity, but can also mediate crosstalk between distinct MAPK modules. The fact that MAPK signalling and in particular the activity of the Ras–extracellular signal-regulated kinase (Ras/ERK) pathway is often abnormally activated in human cancers, suggests that MKPs may also be regulated as a result of the oncogenic activation of MAPK signalling. This idea is reinforced by several studies demonstrating that negative feedback control of Ras/ERK signalling by MKPs may play an important role in determining the biological outcome of signalling when upstream components of this pathway such as receptor tyrosine kinases (RTKs), Ras isoforms or Braf are mutated and activated [8,9]. This idea is also supported by numerous observations of either increased or decreased MKP expression in malignant disease, suggesting that these enzymes might play some role in cancer initiation and/or progression [10,11]. However, despite the large number of reported studies of MKP dysregulation the majority of both *in vitro* and tumour studies rely heavily on the overexpression of MKPs and/or correlations between MKP expression levels and clinical stage/outcome in relatively small patient cohorts. There is therefore a need for more defined genetic studies of MKP function in validated mouse models of cancer in which Ras/ERK signalling is implicated, coupled with more systematic analyses of MKP expression in large clinical cohorts before firm conclusions can be reached as to the role and significance of MKPs in malignant disease.

Here we review a number of recent studies using a variety of approaches including pharmacological and genetic manipulation of MKP expression or activity, which point towards specific roles for

Please cite this article in press as: A.M. Kidger, S.M. Keyse, The regulation of oncogenic Ras/ERK signalling by dual-specificity mitogen activated protein kinase phosphatases (MKPs), Semin Cell Dev Biol (2016), http://dx.doi.org/10.1016/j.semcdb.2016.01.009