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Role of mitogen-activated protein kinase phosphatases (MKPs) in cancer

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Abstract The mitogen-activated protein kinase (MAPK) phosphatases (MKPs) are a family of dual-specificity protein phosphatases that dephosphorylate both phospho-threonine and phospho-tyrosine residues in MAP kinases, including the c-Jun N-terminal protein kinase (JNK)/stress-activated protein kinase (SAPK), the p38 MAPK, and the extracellular signal-related kinase (ERK). Since phosphorylation is required for the activation of MAP kinases, dephosphorylation by MKPs inhibits MAPK activity, thereby negatively regulating MAPK signaling. It is known that deregulation of MAPK signaling is the most common alteration in human cancers. Recent studies have suggested that MKPs play an important role not only in the development of cancers, but also in the response of cancer cells to chemotherapy. Thus, understanding the roles of MKPs in the development of cancer and their impact on chemotherapy can be exploited for therapeutic benefits for the treatment of human cancer.

Keywords Cancer · MKP · MAPKs

1 Introduction

Mitogen-activated protein kinases (MAPKs) are major signaling transduction molecules that play an important role in regulating a variety of cellular responses, including cell proliferation, differentiation, and apoptosis. Mammalian MAPKs mainly consist of three subfamilies; the Jun N-terminal kinases (JNKs), the p38 kinases, and the extracellular signal-related kinases (ERKs) [1, 2]. MAPKs can be activated by diverse stimuli including growth factors and cellular/extracellular stresses. In response to stimuli, MAPKs are activated through the reversible phosphorylation of both threonine and tyrosine residues of the TXY motif in the catalytic domain by upstream dual-specificity kinases. These upstream kinases, namely MKK (MAP kinase kinase), include MKK1/2, MKK3/6, and MKK4/7, which are in turn activated by MAPK kinase kinases (MKKK or MEKK) [3–5]. Once activated, MAPKs phosphorylate a number of substrates and subsequently activate many signaling pathways, which lead to diverse outcomes including cell proliferation and apoptosis [4]. Since phosphorylation is required for the activation of MAPKs, it has become clear that dephosphorylation of MAPKs by members of the MAPK phosphatase (MKP) family plays a critical role in negatively regulating MAPK signaling transduction pathways. Recent studies have suggested that MKPs are involved in the development of cancer and have an important impact on the responses of cancer cells to chemotherapy. This review focuses on the role of MKPs in cancer development and discusses the progress that has been made for developing MKP inhibitors as novel anticancer agents.

2 MAPK phosphatases

The MAPK phosphatases are a family of dual-specificity protein phosphatases (DUSP) that can dephosphorylate both phospho-threonine and phospho-tyrosine residues,

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thus inactivating MAPK signaling [6]. To date, there are 11 members of MKPs identified [7]. They include MKP-1 (DUSP1), MKP-2 (DUSP4), MKP-3 (DUSP6), MKP-4 (DUSP9), MKP-5 (DUSP10), MKP-7 (DUSP16), MKP-X (DUSP7), PAC1 (DUSP2), hVH3 (DUSP5), M3/6 (DUSP8), and MK-STYX (DUSP24) [6–8]. These phosphatases structurally contain an N-terminal domain that displays homology to the catalytic domain of the Cdc25 phosphatase and a C-terminal domain that displays homology to the prototypic dual specificity protein phosphatase VH-1 of vaccinia virus [6–9]. Based on their subcellular localization, MKPs can be classified into three groups [6–8, 10]. The first group includes MKP-1, MKP-2, PAC1, and hVH3, whose expression is exclusively nuclear. The second group consists of MKP-3, MKP-4, and MKP-X, which are exclusively expressed in the cytoplasm. The third group includes MKP-5, MKP-7, and hVH5, which can be expressed in both the nucleus and cytoplasm. In addition, the MKPs can be divided into four groups based on their substrate specificity. The first group preferentially inactivates ERKs and includes MKP-3, MKP-X, and DUSP5/hVH3. The second group includes MKP-5, MKP-7, and hVH5/DUSP8, and selectively inactivates both JNK and p38. The third group includes MKP-1 and MKP-2, and can inactivate all three MAPKs including ERK, p38 and JNK. The last group includes PAC1 and MKP-4, and preferentially inactivates ERK and p38 although MKP-4 may be more potent towards ERK. It has been known that MKPs display restricted tissue distribution [8, 9]. For example, PAC1 is predominately expressed in hematopoietic cells [11] while MKP-4 is expressed in placenta, kidney and fetal liver [12]. Importantly, the nuclear MKPs including MKP-1, MKP-2, PAC1, and hVH3 can be induced by stimuli that also activate MAPKs, which suggests an important role of these MKPs in regulating MAPK signaling.

3 Role of MKPs in cancer development and progression

3.1 MKP-1 and cancer

MKP-1 is the first member of the MKP family that was identified as a MAPK phosphatase. MKP-1 was originally cloned as a growth factor inducible gene implicated in the G_0/G_1 transition [13, 14]. It has been shown that MKP-1 can be induced by stresses [15–19]. MKP-1 is able to inactivate all three major MAPKs including ERK, JNK, and p38 [16, 20–22]. Because JNK, p38, and ERK are capable of either inducing apoptosis or cell proliferation, MKP-1 is believed to be involved in regulating the cell cycle [23–26] and apoptosis [18, 19, 27–30].

Since MKP-1 is the most studied MKP, the role of MKPs in cancer stems from studies of MKP-1 expression in the different stages of various cancer types. Although MKP-1 knockout mice are developmentally normal [31], a number of studies indicated that MKP-1 expression is altered in many cancer types including breast, lung, prostate, ovarian, pancreatic, liver, and gastric adencarcinoma (Table 1). Furthermore, clinical studies showed that MKP-1 expression is correlated with cancer progression and may be useful for prognosis. For example, in human breast cancer, MKP-1 was found to be increased fivefold in malignant samples as compared to non-malignant samples [32]. Breast carcinomas expressed significantly high levels of MKP-1 even when poorly differentiated or in late stages of the disease [33]. In human lung cancer, MKP-1 expression was substantially higher in non-small cell lung cancer cells (NSCLC) than in small cell lung cancer cells [34]. NSCLC resection specimens showed high levels of MKP-1 as compared with normal lung [34]. Interestingly, high levels of MKP-1 expression independently predicted improved survival [34]. Therefore, MKP-1 can be used as a potential positive prognostic marker in NSCLC. In human ovarian cancer, the expression of MKP-1 protein was reduced in tissues from low malignant potential tumors and invasive ovarian carcinomas compared to normal ovaries and cystadenomas [35]. A moderate to strong expression of MKP-1 was detected in 57.6% of invasive ovarian carcinomas [35]. Since patients with carcinomas positive for MKP-1 had a median progression-free survival of 18.3 months compared to 40.6 months for patients with carcinomas negative for MKP-1, MKP-1 expression was a prognostic marker for shorter progression-free survival of patients with invasive ovarian carcinomas [35]. Another study showed that MKP-1 expression was down regulated in advanced epithelial ovarian cancer and its re-expression decreased its malignant potential [36]. In human prostate cancer, MKP-1 expression was lower in hormone-refractory prostate carcinomas as compared to benign prostate hyperplasia or untreated prostate carcinomas [37]. Benign prostate hyperplasia, normal prostate and high-grade pros-

Table 1 MKP family members that have been implicated in cancer development

Cancer types	MKPs	References
Breast cancer	MKP-1, MKP-2	[32, 33]
Lung cancer	MKP-1, MKP-3	[34, 49]
Ovarian cancer	MKP-1, PAC1, MKP-2	[35, 36, 50, 51]
Prostate cancer	MKP-1	[33, 37]
Pancreatic cancer	MKP-1, MKP-3	[38, 45, 46, 47]
Liver cancer	MKP-1, MKP-2	[39, 40]
Gastric cancer	MKP-1	[33, 41]
Bladder cancer	MKP-1	[33]
Leukemia	MKP-X	[52, 53]

tate intraepithelial neoplasia (PIN) expressed high levels of MKP-1 protein, and 92% of the prostate carcinomas showed almost complete loss of MKP-1 expression [37]. These data suggest that down-regulation of MKP-1 is an early event and could be important in the tumorigenesis of prostate cancer. In pancreatic cancer, MKP-1 mRNA and protein levels were increased, and down-regulation of MKP-1 expression resulted in decreased anchorage-dependent and -independent growth of pancreatic cancer cells and tumorigenicity in a nude mouse tumor model [38]. In human hepatocellular carcinoma, the expression of MKP-1 was decreased in tumor cells as compared to normal hepatocytes, and decreased MKP-1 expression significantly correlated with serum alpha-fetoprotein levels and tumor size [39]. Interestingly, the disease-free survival rates in MKP-1-negative and -positive patients were 0 and 31% at 5 years, respectively [39]. The survival rates after a surgical resection in MKP-1-negative and -positive patients were 18.2 and 65.5% at 5 years, respectively [39]. Consistent with the role of MKP-1 in liver cancer, in chemical hepatocarcinogenesis in rats, the mRNA levels of MKP-1 were increased in primary hepatomas but decreased in rat ascites hepatomas as compared with normal liver [40]. In addition, in gastric adencarcinoma. MKP-1 overexpression was associated with the development of human gastric adenocarcinoma [41]. Furthermore, a study on 164 human epithelial tumors of diverse tissue origin by *in situ* hybridization and immunohistochemistry indicated that MKP-1 was overexpressed in the early phases of prostate, colon, and bladder carcinogenesis, with progressive loss of expression with higher histological grade and in metastases [33]. Taken together, these studies strongly suggest that MKP-1 plays a critical role in cancer development and may be a useful marker for predicting the survival of patients with cancers.

3.2 MKP-3 and cancer

MKP-3 is another member of the MKP family that has been implicated in the development of cancer. MKP-3 is a cytoplasmic MKP that can inactivate ERKs [42, 43]. MKP-3 can be constitutively expressed or be induced by growth factors [8]. It has been shown that inhibition of MKP-3 causes apoptosis in the mesenchyme in the chick limb [44]. Several studies indicated that MKP-3 is a candidate tumor suppressor gene (Table 1). In pancreatic cancer, MKP-3 was slightly up-regulated in primary pancreatic cancer and dysplastic/*in situ* carcinoma cells but down-regulated in invasive carcinoma, especially in the poorly differentiated type [45]. The expression of MKP-3 was lost exclusively in the invasive carcinoma cells as compared to pancreatic intraepithelial neoplasia. In pancreata with intraductal papillary-mucinous neoplasms, lacking MKP-3 expression was observed in a relatively small fraction of intraductal adenoma/borderlines and intraductal carcinomas [46]. Most of the intraductal adenoma/borderline lesions with loss of MKP-3 harbored mutations of KRAS2 [46]. Loss of MKP-3 expression was associated exclusively with progression from pancreatic intraepithelial neoplasia to the invasive ductal carcinoma while it was potentially associated with initiation of intraductal papillary-mucinous neoplasms with mutated KRAS2 [46]. A further study showed that loss of MKP-3 expression in pancreatic cancer is partially due to hypermethylation of the expressional control region of MKP-3 in cultured human pancreatic cancer cells and in primary pancreatic cancer tissues because hypermethylation of the CpG islands in intron 1 was observed [47]. In nude mice injected with a MKP-3 inducible cell line that was transformed by Ha-ras, it was found that the treatment of mice with the tetracycline analog doxycycline resulted in a great delay in tumor emergence and growth as compared to untreated control group, indicating a role of MKP-3 in tumor suppression [48]. In addition to its role in pancreatic cancer, in human non-small-cell lung cancer, MKP-3 has been shown to be one of 6 genes whose expression is closely associated with relapse-free and overall survival [49]. Taken together, these studies suggest that MKP-3 plays an important role in cancer development in some cancers, particularly in pancreatic cancer.

3.3 Other MKP family members and cancer

In addition to MKP-1 and MKP-3, several other MKP family members that have been implicated in cancer development include PAC1, MKP-2, and MKP-X (Table 1). It has been shown that in ovarian carcinoma, the high levels of PAC1 mRNA predicted significantly worse overall survival as compared to low expression [50]. In chemical hepatocarcinogenesis in rats, MKP-2 was undetectable in normal liver but strongly expressed in hepatomas [40]. Furthermore, in human breast cancer, MKP-2 was increased 3-fold in malignant as compared to non-malignant samples [32]. MKP-2 was also down-regulated in serous carcinomas as compared with serous borderline tumors in ovarian cancers [51], which acts as a suppressor of stromal invasion. In addition, it has been reported that MKP-X was highly expressed in leukocytes obtained from acute myeloid leukemia (AML) patients [52]. High levels of MKP-X mRNA also were observed in bone marrow and peripheral leukocytes from AML and acute lymphoblastic leukemia (ALL) patients, whereas bone marrow from healthy individuals expressed very low levels of MKP-X [52, 53]. Together, these studies suggest that MKPs play an important role in cancer development and progression in a variety of cancers and could be therapeutic targets for cancer therapy.

4 MKPs and cancer therapy

An initial study on the effect of MKP-1 on UV-induced cell death showed that overexpression of MKP-1 reduces UV-induced JNK-mediated apoptosis in U937 human leukemia [27]. It is known that MKP-1 inhibits cell death induced by a number of agents including some anticancer drugs in different cancer cells. For example, overexpression of MKP-1 inhibits Fas ligand-induced apoptosis in human prostate DU145 cells [54]. It has been shown that the proteasome inhibitors Z–LLF–CHO and lactacystin inhibit MKP-1 expression by inactivating ERK activity in breast cancer cell lines A1N4-myc and MDA–MB-231 [55]. In A1N4–myc human mammary epithelial and BT-474 breast carcinoma cells, overexpression of MKP-1 decreased proteasome inhibitor-mediated apoptosis, and BT-474 cells stably expressing an MKP-1 small interfering RNA (siRNA) and MKP-1 knockout mouse embryonic fibroblasts underwent enhanced apoptosis compared with their respective controls [56]. The mechanism of MKP-1-mediated inhibition of apoptosis was associated with decreased phospho-JNK levels, whereas MKP-1 suppression or inactivation enhanced phospho-JNK [56]. Interestingly, anthracyclines repressed MKP-1 transcription, leading to enhanced proteasome inhibitor-mediated apoptosis [56]. Because proteasome inhibitors are promising new agents for the treatment of cancers, the role of MKP-1 in inhibiting proteasome inhibitor activity suggests that targeting MKP-1 could enhance proteasome inhibitor anticancer activity. In addition, several studies indicated that MKP-1 plays a critical role in cisplatin-induced cell death. It has been shown that overexpression of MKP-1 inhibits cisplatin-induced apoptosis in human embryonic kidney 293 cells [28]. Consistently, our study showed that overexpression of MKP-1 increased cell resistance to cisplatin in the human lung cancer cell H460 [19]. Furthermore, knockdown of MKP-1 by siRNA sensitized H460 cells to cisplatin-induced death [19, 30]. Importantly, tumors induced by H460 cells expressing MKP-1 siRNA grew slower in nude mice and were more susceptibility to cisplatin than parental cells, leading to the impaired growth of the tumor in mice [30]. Because cisplatin is the first line chemotherapy for several types of tumors including lung and ovarian cancers, identification of negative impact of MKP-1 on cisplatin anticancer activity suggests that targeting MKP-1 could sensitize cancer cells to cisplatin. Recently, using MKP-1 knockout mouse embryonic fibroblasts, it has been shown that loss of MKP-1 enhances cell death in response to serum starvation, anisomycin and osmotic stress [29]. Furthermore, using a large-scale oligonucleotide screen of glucocorticoid-regulated genes, MKP-1 was found to be induced after glucocorticoid activation that plays a role in cell survival signaling pathways [57]. Because dexamethasone pretreatment of breast cancer cell lines inhibited chemotherapy-induced apoptosis in a glucocorticoid-dependent manner, glucocorticoid treatment alone or glucocorticoid treatment followed by chemotherapy increased MKP-1 steady-state protein levels. Inhibition of MKP-1 induction by MKP-1 siRNA reversed the anti-apoptotic effects of glucocorticoid treatment, and induction of MKP-1 correlated with the inhibition of ERK1/2 and JNK activity, whereas p38 activity was minimally affected [57]. Blocking dexamethasone-mediated MKP-1 induction using siRNA increased ERK1/2 and JNK phosphorylation and decreased cell survival [58]. Since the widespread clinical administration of dexamethasone before chemotherapy, understanding glucocorticoid-induced survival mechanisms via MKP-1 is essential for achieving optimal therapeutic responses in these cancer patients.

In addition to MKP-1, MKP-3 is another member of the MKP family that has been recently implicated in cancer therapy. Using gene expression profiling, Cui et al. [59] found that the expression of MKP-3 was correlated with response to the antiestrogen tamoxifen in both patients and *in vitro*-derived cell line models. They showed that overexpression of MKP-3 rendered estrogen-alpha-positive breast cancer cells resistant to the growth-inhibitory effects of tamoxifen and enhanced tamoxifen agonist activity in endometrial cells [59]. Furthermore, overexpression of MKP-3 was associated with lower levels of activated ERK1/2 phosphorylation in the presence of estrogen and estrogen deprivation and tamoxifen treatment decreased MKP-3 phosphatase activity [59]. Therefore, MKP-3 may represent a novel mechanism of tamoxifen resistance, which may be targeted for enhancing tamoxifen efficacy in the treatment of breast cancer.

5 Development of MKP inhibitors for cancer treatment

Since MKPs play an important role in cancer development, progression and the responses of cancer cells to chemotherapy, MKPs are emerging as attractive targets for cancer drug discovery. Using a high-content, fluorescence-based cellular assay and the National Cancer Institute's 1990 agent Diversity Set, Vogt et al. [60] identified ten compounds that significantly increased phospho-ERK cytonuclear differences in intact cells. Three of the ten positive compounds inhibited MKP-3 *in vitro* without affecting VHR or PTP1B phosphatases [60]. The most potent inhibitor is NSC357756 that inhibited MKP-3 at IC 50 of <10 μM [60]. Based on structural information of NSC357756, Lazo et al. synthesized the compound NU-126 that was able to inhibit MKP-1 activity with an IC 50 of ~ 50 μM *in vitro* but not in cell culture [61]. In addition, Vogt et al. screened a chemical library that contains a 720-

compound collection of pure natural products and their derivatives and identified sanguinarine as a potent and selective inhibitor of MKP-1 [62]. Sanguinarine is a plant alkaloid with known antibiotic and antitumor activity but without knowing the primary cellular target. It has been shown that sanguinarine inhibits cellular MKP-1 with an IC 50 of 10 μM and showed selectivity for MKP-1 over MKP-3. In a human tumor cell line with high MKP-1 levels, sanguinarine caused enhanced ERK and JNK phosphorylation [62]. A close congener of sanguinarine, chelerythrine, also inhibited MKP-1 *in vitro* and in whole cells, and activated ERK and JNK [62]. Thus, sanguinarine analogs may represent a new class of MKP-1 inhibitors. Although sanguinarine and NU-126 are able to inhibit MKP-1, lack of selectivity and poor cellular permeability limit their utilization as therapeutics. To identity potent, selective, and cell permeable MKP-1 inhibitors, Arnold et al. screened a large chemical library and identified several uracil quinoline compounds that are potent MKP-1 inhibitors. However, the roles of these compounds in inhibiting MKP-1 in cells have not been verified yet [63].

In addition, it has been shown that triptolide, a diterpenoid triepoxide, potently blocks MKP-1 induction by lipopolysaccharide in a dose-dependent manner [64]. Blockade of MKP-1 protein accumulation by triptolide was associated with a reciprocal increase in the levels of phosphorylated/active JNK and p38 [64], indicating that triptolide may be a potential MKP-1 inhibitor. Importantly, triptolide can induce cancer cell apoptosis [65]. Thus, it is possible that triptolide kills cancer cells in part through inactivating MKP-1. Recently, Aplidin®, an antitumor agent that is in phase II clinical trials against various types of tumors, has been shown to down-regulate MKP-1, activate JNK, and induce apoptosis [66]. Furthermore, MKP-1 knockout embryonic fibroblasts were more sensitive than wild type cells to Aplidin® [66], which suggests that MKP-1 plays a role in Aplidin®-induced cell death. Because Aplidin® has been shown to kill cancer cells via several other mechanisms, down-regulation of MKP-1 may be only partially responsible for Aplidin® anticancer activity. Nevertheless, these studies suggest that MKP-1 inhibitors could be used as novel anticancer agents for cancer treatment.

Concluding remarks Accumulating evidence has provided a comprehensive picture of an important role of MKPs in cancer. On the one hand, these studies clearly indicate that the altered expression of MKPs has been detected in various types of cancers. Moreover, the levels of these MKPs are correlated with tumor prognosis. Most of these studies have been focused on MKP-1 because MKP-1 antibodies are available. However, the roles of other MKP family members in cancer are not studied at the protein level, in part due to lack of reliable antibodies. Therefore, there is a need to develop good and reliable antibodies against other members of the MKP family that can be used for immuno-staining for clinical samples. On the other hand, although recent studies have identified several compounds that can inhibit MKP-1 activity, these compounds lack selectivity or demonstrate poor cellular permeability. Therefore, a major challenge is to identify MKP small molecule inhibitors that are potent, selective and cell permeable. It is conceivable that understanding the structure and biological functions of MKPs will help develop selective pharmacological inhibitors of MKPs that can be used as novel anticancer drugs for the treatment of human cancer.

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References

1. Davis, R. J. (2000). Signal transduction by the JNK group of MAP kinases. *Cell, 103*, 239–252.
2. Johnson, G. L., & Lapadat, R. (2002). Mitogen-activated protein kinase pathways mediated by ERK, JNK, and p38 protein kinases. *Science, 298*, 1911–1912.
3. Pearson, G., Robinson, F., Beers Gibson, T., Xu, B., Karandikar, M., Berman, K., et al. (2001). Mitogen-activated protein (MAP) kinase pathways: Regulation and physiological functions. *Endocrine Reviews, 22*, 153–183.
4. Chang, L., & Karin, M. (2001). Mammalian MAP kinase signalling cascades. *Nature, 410*, 37–40.
5. Kennedy, N. J., & Davis, R. J. (2003). Role of JNK in tumor development. *Cell Cycle, 2*, 199–201.
6. Camps, M., Nichols, A., & Arkinstall, S. (2000). Dual specificity phosphatases: A gene family for control of MAP kinase function. *FASEB Journal, 14*, 6–16.
7. Dickinson, R. J., & Keyse, S. M. (2006). Diverse physiological functions for dual-specificity MAP kinase phosphatases. *Journal of Cell Science, 119*(Pt 22), 4607–4615.
8. Kondoh, K., & Nishida, E. (2006). Regulation of MAP kinases by MAP kinase phosphatases. *Biochim Biophys Acta, 1773*(8), 1227–1237.
9. Zhan, X. L., Wishart, M. J., & Guan, K. L. (2001). Nonreceptor tyrosine phosphatases in cellular signaling: Regulation of mitogen-activated protein kinases. *Chemical Reviews, 101*(8), 2477–2496.
10. Theodosiou, A., & Ashworth, A. (2002). MAP kinase phosphatases. *Genome Biology, 3*(7), REVIEWS3009.
11. Rohan, P. J., Davis, P., Moskaluk, C. A., Kearns, M., Krutzsch, H., Siebenlist, U., et al. (1993). PAC-1: A mitogen-induced nuclear protein tyrosine phosphatase. *Science, 259*(5102), 1763–1766.
12. Muda, M., Boschert, U., Smith, A., Antonsson, B., Gillieron, C., Chabert, C., et al. (1997). Molecular cloning and functional characterization of a novel mitogen-activated protein kinase phosphatase, MKP-4. *Journal of Biological Chemistry, 272*(8), 5141–5151.

13. Lau, L. F., & Nathans, D. (1985). Identification of a set of genes expressed during the G0/G1 transition of cultured mouse cells. *EMBO Journal, 4*(12), 3145–3151.
14. Charles, C. H., Abler, A. S., & Lau, L. F. (1992). cDNA sequence of a growth factor-inducible immediate early gene and characterization of its encoded protein. *Oncogene, 7*, 187–190.
15. Keyse, S. M., & Emslie, E. A. (1992). Oxidative stress and heat shock induce a human gene encoding a protein–tyrosine phosphatase. *Nature, 359*, 644–647.
16. Li, J., Gorospe, M., Hutter, D., Barnes, J., Keyse, S. M., & Liu, Y. (2001). Transcriptional induction of MKP-1 in response to stress is associated with histone H3 phosphorylation–acetylation. *Molecular and Cellular Biology, 21*, 8213–8224.
17. Liu, Y., Gorospe, M., Yang, C., & Holbrook, N. J. (1995). Role of mitogen-activated protein kinase phosphatase during the cellular response to genotoxic stress. Inhibition of c-Jun N-terminal kinase activity and AP-1-dependent gene activation. *Journal of Biological Chemistry, 270*(15), 8377–8380.
18. Zhou, J. Y., Liu, Y., & Wu, G. S. (2006). The role of mitogen-activated protein kinase phosphatase-1 in oxidative damage-induced cell death. *Cancer Research, 66*(9), 4888–4894.
19. Wang, Z., Xu, J., Zhou, J. Y., Liu, Y., & Wu, G. S. (2006). Mitogen-activated protein kinase phosphatase-1 is required for cisplatin resistance. *Cancer Research, 66*(17), 8870–8877.
20. Sun, H., Charles, C. H., Lau, L. F., & Tonks, N. K. (1993). MKP-1 (3CH134), an immediate early gene product, is a dual specificity phosphatase that dephosphorylates MAP kinase *in vivo*. *Cell, 75*, 487–493.
21. Noguchi, T., Metz, R., Chen, L., Mattei, M. G., Carrasco, D., & Bravo, R. (1993). Structure, mapping, and expression of erp, a growth factor-inducible gene encoding a nontransmembrane protein tyrosine phosphatase, and effect of ERP on cell growth. *Molecular and Cellular Biology, 13*, 5195–5205.
22. Franklin, C. C., & Kraft, A. S. (1997). Conditional expression of the mitogen-activated protein kinase (MAPK) phosphatase MKP-1 preferentially inhibits p38 MAPK and stress-activated protein kinase in U937 cells. *Journal of Biological Chemistry, 272*, 16917–16923.
23. Brondello, J. M., McKenzie, F. R., Sun, H., Tonks, N. K., Pouyssegur, J. (1995). Constitutive MAP kinase phosphatase (MKP-1) expression blocks G1 specific gene transcription and S-phase entry in fibroblasts. *Oncogene, 10*, 1895–1904.
24. Li, M., Zhou, J. Y., Ge, Y., Matherly, L. H., & Wu, G. S. (2003). The phosphatase MKP1 is a transcriptional target of p53 involved in cell cycle regulation. *Journal of Biological Chemistry, 278*, 41059–41068.
25. Yang, H., & Wu, G. S. (2004). p53 Transactivates the phosphatase MKP1 through both intronic and exonic p53 responsive elements. *Cancer Biology and Therapy, 3*(12), 1277–1282.
26. Wu, G. S. (2004). The Functional Interactions Between the p53 and MAPK Signaling Pathways. *Cancer Biology and Therapy, 3*, 156–161.
27. Franklin, C. C., Srikanth, S., & Kraft, A. S. (1998). Conditional expression of mitogen-activated protein kinase phosphatase-1, MKP-1, is cytoprotective against UV-induced apoptosis. *Proceedings of the National Academy of Sciences, U.S.A., 95*, 3014–3019.
28. Sanchez-Perez, I., Martinez-Gomariz, M., Williams, D., Keyse, S. M., & Perona, R. (2000). CL100/MKP-1 modulates JNK activation and apoptosis in response to cisplatin. *Oncogene, 19*, 5142–5152.
29. Wu, J. J., & Bennett, A. M. (2005). Essential role for MAP kinase phosphatase-1 in stress-responsive MAP kinase and cell survival signaling. *Journal of Biological Chemistry, 280*, 16461–16466.
30. Chattopadhyay, S., Machado-Pinilla, R., Manguan-Garcia, C., Belda-Iniesta, C., Moratilla, C., Cejas, P., et al. (2006). MKP1/CL100 controls tumor growth and sensitivity to cisplatin in non-small-cell lung cancer. *Oncogene, 25*(23), 3335–3345.
31. Dorfman, K., Carrasco, D., Gruda, M., Ryan, C., Lira, S. A., & Bravo, R. (1996). Disruption of the erp/mkp-1 gene does not affect mouse development: Normal MAP kinase activity in ERP/MKP-1-deficient fibroblasts. *Oncogene, 13*, 925–931.
32. Wang, H. Y., Cheng, Z., & Malbon, C. C. (2003). Overexpression of mitogen-activated protein kinase phosphatases MKP1, MKP2 in human breast cancer. *Cancer Letters, 191*(2), 229–237.
33. Loda, M., Capodieci, P., Mishra, R., Yao, H., Corless, C., Grigioni, W., et al. (1996). Expression of mitogen-activated protein kinase phosphatase-1 in the early phases of human epithelial carcinogenesis. *American Journal of Pathology, 149*(5), 1553–1564.
34. Vicent, S., Garayoa, M., Lopez-Picazo, J. M., Lozano, M. D., Toledo, G., Thunnissen, F. B., et al. (2004). Mitogen-activated protein kinase phosphatase-1 is overexpressed in non-small cell lung cancer and is an independent predictor of outcome in patients. *Clinical Cancer Research, 10*(11), 3639–3649.
35. Denkert, C., Schmitt, W. D., Berger, S., Reles, A., Pest, S., Siegert, A., et al. (2002). Expression of mitogen-activated protein kinase phosphatase-1 (MKP-1) in primary human ovarian carcinoma. *International Journal of Cancer, 102*(5), 507–513.
36. Manzano, R. G., Montuenga, L. M., Dayton, M., Dent, P., Kinoshita, I., Vicent, S., et al. (2002). CL100 expression is down-regulated in advanced epithelial ovarian cancer and its re-expression decreases its malignant potential. *Oncogene, 21*(28), 4435–4447.
37. Rauhala, H. E., Porkka, K. P., Tolonen, T. T., Martikainen, P. M., Tammela, T. L., & Visakorpi, T. (2005). Dual-specificity phosphatase 1 and serum/glucocorticoid-regulated kinase are downregulated in prostate cancer. *International Journal of Cancer, 117*(5), 738–745.
38. Liao Q., Guo J., Kleeff J., Zimmermann, A., Büchler, M. W., Korc, M., et al. (2003). Down-regulation of the dual-specificity phosphatase MKP-1 suppresses tumorigenicity of pancreatic cancer cells. *Gastroenterology, 124*(7), 1830–1845.
39. Tsujita, E., Taketomi, A., Gion, T., Kuroda, Y., Endo, K., Watanabe, A., et al. (2005). Suppressed MKP-1 is an independent predictor of outcome in patients with hepatocellular carcinoma. *Oncology, 69*(4), 342–347.
40. Yokoyama, A., Karasaki, H., Urushibara, N., Nomoto, K., Imai, Y., Nakamura, K., et al. (1997). The characteristic gene expressions of MAPK phosphatases 1 and 2 in hepatocarcinogenesis, rat ascites hepatoma cells, and regenerating rat liver. *Biochemical and Biophysical Research Communications, 239*(3), 746–751.
41. Bang, Y. J., Kwon, J. H., Kang, S. H., Kim, J. W., & Yang, Y. C. (1998). Increased MAPK activity and MKP-1 overexpression in human gastric adenocarcinoma. *BBRC, 250*(1), 43–47.
42. Groom, L. A., Sneddon, A. A., Alessi, D. R., Dowd, S., & Keyse, S. M. (1996). Differential regulation of the MAP, SAP and RK/p38 kinases by Pyst1, a novel cytosolic dual-specificity phosphatase. *EMBO Journal, 15*(14), 3621–3632.
43. Muda, M., Boschert, U., Dickinson, R., Martinou, J.-C., Martinou, I., Camps, M., et al. (1996). MKP-3, a novel cytosolic protein-tyrosine phosphatase that exemplifies a new class of mitogen-activated protein kinase phosphatase. *Journal of Biological Chemistry, 271*(8), 4319–4326.
44. Kawakami, Y., Rodriguez-Leon, J., Koth, C. M., Büscher, D., Itoh, T., Raya, A., et al. (2003). MKP3 mediates the cellular response to FGF8 signalling in the vertebrate limb. *Nature Cell Biology, 5*(6), 513–519.
45. Furukawa, T., Sunamura, M., Motoi, F., Matsuno, S., & Horii, A. (2003). Potential tumor suppressive pathway involving DUSP6/

MKP-3 in pancreatic cancer. *American Journal of Pathology, 162* (6), 1807–1815.
46. Furukawa, T., Fujisaki, R., Yoshida, Y., Kanai, N., Sunamura, M., Abe, T., et al. (2005). Distinct progression pathways involving the dysfunction of DUSP6/MKP-3 in pancreatic intraepithelial neoplasia and intraductal papillary–mucinous neoplasms of the pancreas. *Modern Pathology, 18*(8), 1034–1042.
47. Xu, S., Furukawa, T., Kanai, N., Sunamura, M., & Horii, A. (2005). Abrogation of DUSP6 by hypermethylation in human pancreatic cancer. *Journal of Human Genetics, 50*(4), 159–167.
48. Marchetti, S., Gimond, C., Roux, D., Gothie, E., Pouyssegur, J., & Pages, G. (2004). Inducible expression of a MAP kinase phosphatase-3-GFP chimera specifically blunts fibroblast growth and ras-dependent tumor formation in nude mice. *Journal of Cellular Physiology, 199*(3), 441–450.
49. Chen, H. Y., Yu, S. L., Chen, C. H., Chang, G.-C., Chen, C.-Y., Yuan, A., et al. (2007). A five-gene signature and clinical outcome in non-small-cell lung cancer. *New England Journal of Medicine, 356*(1), 11–20.
50. Givant-Horwitz, V., Davidson, B., Goderstad, J. M., Nesland, J. M., Trope, C. G., & Reich, R. (2004). The PAC-1 dual specificity phosphatase predicts poor outcome in serous ovarian carcinoma. *Gynecologic Oncology, 93*(2), 517–523.
51. Sieben, N. L., Oosting, J., Flanagan, A. M., Prat, J., Roemen, G. M. J. M., Kolkman-Uljee, S. M., et al. (2005). Differential gene expression in ovarian tumors reveals Dusp 4 and Serpina 5 as key regulators for benign behavior of serous borderline tumors. *Journal of Clinical Oncology, 23*(29), 7257–7264.
52. Levy-Nissenbaum, O., Sagi-Assif, O., Kapon, D., Hantisteanu, S., Burg, T., Raanani, P., et al. (2003). Dual-specificity phosphatase Pyst2-L is constitutively highly expressed in myeloid leukemia and other malignant cells. *Oncogene, 22*(48), 7649–7660.
53. Levy-Nissenbaum, O., Sagi-Assif, O., Raanani, P., Avigdor, A., Ben-Bassat, I., & Witz, I. P. (2003). Overexpression of the dual-specificity MAPK phosphatase PYST2 in acute leukemia. *Cancer Letters, 199*(2), 185–192.
54. Srikanth, S., Franklin, C. C., Duke, R. C., & Kraft, A. S. (1999). Human DU145 prostate cancer cells overexpressing mitogen-activated protein kinase phosphatase-1 are resistant to Fas ligand-induced mitochondrial perturbations and cellular apoptosis. *Molecular and Cellular Biochemistry, 199*, 169–178.
55. Orlowski, R. Z., Small, G. W., & Shi, Y. Y. (2002). Evidence that inhibition of p44/42 mitogen-activated protein kinase signaling is a factor in proteasome inhibitor-mediated apoptosis. *Journal of Biological Chemistry, 277*(31), 27864–27871.
56. Small, G. W., Shi, Y. Y., Edmund, N. A., Somasundaram, S., Moore, D. T., & Orlowski, R. Z. (2004). Evidence that mitogen-activated protein kinase phosphatase-1 induction by proteasome inhibitors plays an antiapoptotic role. *Molecular Pharmacology, 66*(6), 1478–1490.
57. Wu, W., Chaudhuri, S., Brickley, D. R., Pang, D., Karrison, T., & Conzen, S. D. (2004). Microarray analysis reveals glucocorticoid-regulated survival genes that are associated with inhibition of apoptosis in breast epithelial cells. *Cancer Research, 64*(5), 1757–1764.
58. Wu, W., Pew, T., Zou, M., Pang, D., & Conzen, S. D. (2005). Glucocorticoid receptor-induced MAPK phosphatase-1 (MKP-1) expression inhibits paclitaxel-associated MAPK activation and contributes to breast cancer cell survival. *Journal of Biological Chemistry, 280*(6), 4117–4124.
59. Cui, Y., Parra, I., Zhang, M., Hilsenbeck, S. G., Tsimelzon, A., Furukawa, T., et al. (2006). Elevated expression of mitogen-activated protein kinase phosphatase 3 in breast tumors: A mechanism of tamoxifen resistance. *Cancer Research, 66*(11), 5950–5959.
60. Vogt, A., Cooley, K. A., Brisson, M., Tarpley, M. G., Wipf, P., & Lazo, J. S. (2003). Cell-active dual specificity phosphatase inhibitors identified by high-content screening. *Chemistry and Biology, 10*(8), 733–742.
61. Lazo, J. S., Nunes, R., Skoko, J. J., Queiroz de Oliveira, P. E., Vogt, A., & Wipf, P. (2006). Novel benzofuran inhibitors of human mitogen-activated protein kinase phosphatase-1. *Bioorganic & Medicinal Chemistry, 14*(16), 5643–5650.
62. Vogt, A., Tamewitz, A., Skoko, J., Sikorski, R. P., Giuliano, K. A., & Lazo, J. S. (2005). The benzo[c]phenanthridine alkaloid, sanguinarine, is a selective, cell-active inhibitor of mitogen-activated protein kinase phosphatase-1. *Journal of Biological Chemistry, 280*(19), 19078–19086.
63. Arnold, D. M., Foster, C., Huryn, D. M., Lazo, J. S., Johnston, P. A., & Wipf, P. (2007). Synthesis and biological activity of a focused library of mitogen-activated protein kinase phosphatase inhibitors. *Chemical Biology and Drug Design, 69*(1), 23–30.
64. Chen, P., Li, J., Barnes, J., Kokkonen, G. C., Lee, J. C., & Liu, Y. (2002). Restraint of proinflammatory cytokine biosynthesis by mitogen-activated protein kinase phosphatase-1 in lipopolysaccharide-stimulated macrophages. *Journal of Immunology, 169*, 6408–6416.
65. Wang, X., Matta, R., Shen, G., Nelin, L. D., Pei, D., & Liu, Y. (2006). Mechanism of triptolide-induced apoptosis: Effect on caspase activation and Bid cleavage and essentiality of the hydroxyl group of triptolide. *Journal of Molecular Medicine, 84* (5), 405–415.
66. Gonzalez-Santiago, L., Suarez, Y., Zarich, N., Muñoz-Alonso, M. J., Cuadrado, A., Martínez, T., et al. (2006). Aplidin induces JNK-dependent apoptosis in human breast cancer cells via alteration of glutathione homeostasis, Rac1 GTPase activation, and MKP-1 phosphatase downregulation. *Cell Death and Differentiation, 13* (11), 1968–1981.