J. Afr. Ass. Physiol. Sci. 3 (2): 61 – 66, December, 2015

Journal of African Association of Physiological Sciences

Official Publication of the African Association of Physiological Sciences

http://www.jaaps.aapsnet.org

Review Article

Role of MAP Kinase Phosphatase-1 in health and disease

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Keywords:
Dual-specificity phosphatase (DUSP), MAP kinase phosphatases (MKPs), Knock-out mice, mitogen-activated protein kinase (MAPK), immunity, metabolism

ABSTRACT

Mitogen-activated signaling pathways (MAPK) are one of the major and evolutionary conserved signaling pathways involved in protein phosphorylation. Inactivation of MAPK activity is attained by dephosphorylation of either the tyrosine or threonine residues, or both by the actions of MAP kinase phosphatase (MKPs). The prototype member of MKP family, MKP-1 is the most extensively studied MKP compared to ten other members in the group. Several mouse genetic and *in vitro* studies have established a key role for MKP-1 in the immune and metabolic systems. However, more recently there is growing body of literature suggesting important functions in the cardiovascular, nervous and musculoskeletal systems. With the development of tissue-specific knock-out models most of these studies suggest MKP- 1 as potential therapeutic target in many disease conditions.

Abbreviations: MAPK, mitogen-activated protein kinase; DUSP, dual-specificity phosphatase; MKP, MAP kinase phosphatase; ERK, extracellular-signal-regulated kinase; JNK, c-jun N-terminal kinase; hVH, human vaccinia H1 phosphatase; PAC-1, phosphatase of activated cell 1;MKB,MAPK-binding;F .- ISSN:

INTRODUCTION

In Mammals, one of the major mechanisms used to transfer extracellular stimuli from the surface of the cell membrane to the nucleus is protein phosphorylation (Peti and Page 2013). One of the key and evolutionary conserved signaling pathways involved in protein phosphorylation is the mitogen-activated protein kinase (MAPK) signaling pathways. Many MAPK signaling pathways exist in mammals in order to regulate an integrated response to a wide range of stimuli (Kyriakis and Avruch 2001, Tomida 2015). The classic three-tiered cascade encompasses a MAPK, a MAPK kinase (MKK) and MAPK kinase kinase (MKKK). MAPK consists of three main groups; extracellular signal-regulated kinases (ERK1/2), c-Jun N terminal kinases (JNK1/2/3), and p38 MAPK. Each of these groups of MAPK is activated by dual phosphorylation on Thr and Tyr residues within the activation motif (Thr-Xaa-Tyr) of the MAPK (Kyriakis and Avruch 2012). Once activated, a MAPK can phosphorylate a number of enzymes, transcription factors and other cytoskeleton proteins (Ebisuya, Kondoh et al. 2005).

The inactivation of MAPK activity is achieved by dephosphorylation of either the tyrosine or threonine residues, or both by the actions of dual-specificity phosphatases (DUSPs) or MAP kinase phosphatases (MKPs).

There are ten family members of MKPs that dephosphorylate MAPK on the Thr and Tyr residues with variable level of specificity (Keyse 2000, Farooq and Zhou 2004). DUSPs have a common structure that comprises of the MAPK-binding (MKB) domain in the N-terminal half and the dual-specificity phosphatase domain in the C-terminal half (Camps, Nichols et al. 1998, Camps, Nichols et al. 2000). Classification of the MKPs has been established on substrate specificity, sequence similarity and subcellular distribution as shown in table 1 (Keyse 2008). There are three groups; type I which comprise of MKP-1/DUSP1, MKP-2/DUSP4, PAC1/DUSP2 and hVH3/DUSP5 are located in the nucleus (Owens and Keyse 2007). Type II encompasses MKP-3/DUSP6, MKP-X/DUSP7 and MKP-4/DUSP9 that selectively dephosphorylate ERK and they are localized in the cytosol. And type III include MKP-5/DUSP10, MKP-7/DUSP16, and hVH5/DUSP8, they dephosphorylate JNK and p38 but

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Table 1: Classification and Features of dual-specificity phosphatases

Gene name	Alternative names	Subcellular localization	Substrate specificity	Physiological roles	References
DUSP1	MKP-1, CL100, hVH-1, erp	Nuclear	p38 MAPK, JNK>>ERK	Regulator of immune function, cytokine secretion and Metabolic homeostasis	(Chi, Barry et al. 2006, Wu, Roth et al. 2006, Lawan, Zhang et al. 2015)
DUSP2	PAC-1	Nuclear	ERK>>p38 MAPK, JNK	Regulates immune effector cells	(Jeffrey, Brummer et al. 2006, Keyse 2008)
DUSP4	MKP-2, TYP2, hVH2, STY8	Nuclear	ERK, JNK>p38 MAPK	Play key role in sepsis, regulates G2/M cell-cycle progression	(Cornell, Rodenhouse et al. 2010, Lawan, Al-Harthi et al. 2011)
DUSP5	hVH-3, B23	Nuclear	ERK>>JNK, p38 MAPK	Regulates T-cell growth and function	(Kucharska, Rushworth et al. 2009)
DUSP6	MKP-3, Pst1, rVH-6	Cytosolic	ERK>>JNK, p38 MAPK	Essential for embryo development, regulates hepatic gluconeogenesis	(Owens and Keyse 2007, Jiao, Feng et al. 2012)
DUSP7	MKP-x, Pyst2, B59	Cytosolic	ERK>p38 MAPK>>JNK	Plays a role in proliferation	(Huang and Tan 2012)
DUSP9	MKP-4, Pyst3	Nuclear and cytosolic	ERK>>p38 MAPK>JNK	Role in insulin signaling and placental growth	(Bazuine, Carlotti et al. 2004, Emanuelli, Eberle et al. 2008)
DUSP10	MKP-5	Nuclear and cytosolic	p38 MAPK>JNK>>ERK	Play key role in immunity and muscle stem function and insulin resistance	(Shi, Verma et al. 2013, Zhang, Nguyen et al. 2015)
DUSP8	hVH-5, M3/6, HB5	Nuclear and cytosolic	JNK=p38 MAPK>>ERK	Unknown	
DUSP16	MKP-7, MKP-M	Cytosolic	JNK=p38 MAPK>>ERK	Regulates differentiation and cytokine production of myloid cells	(Patterson, Brummer et al. 2009, Rios, Nunes-Xavier et al. 2014)

not ERK1/2 and shuttle between the cytoplasm and nucleus (Tonks 2013).

The expression, activity and function of the MKPs are subject to various levels of regulation. For example, transcriptional activation and protein stability is mediated by MAPKs themselves in addition to reactive oxygen species that directly inactivate the catalytic site within the MKPs (Caunt and Keyse 2012). Although, there is reasonable amount of information on the biochemical properties of MKPs, the body of literature regarding their physiological function is still developing. This review will focus on the prototype family member of the MKPs, MKP-1. The current works on MKP-1 physiological functions and some of the pathophysiological implications of dysregulated MKP-1 signaling will be discussed.

MKP-1/DUSP1 in vitro and in vivo studies

MKP-1 similarly termed DUSP1, the prototype member of MKP family was identified as an immediate-early response gene (Keyse and Emslie 1992, Keyse and Ginsburg 1993). MKP-1, a type I member, is widely expressed in many tissues and cells and is selective for JNK and p38 MAPK over ERK *in vitro* and *in vivo* (Wu and Bennett 2005, Lawan, Shi et al. 2012). MKP-1 is the most studied MKP family member and important physiological function has been demonstrated both in cell type specific context and various tissue systems. Many studies have established MKP-1 as major regulator of numerous physiological and pathophysiological roles in the immune system, metabolic and cardiovascular systems. More recently

there are some studies suggesting a role for MKP-1 in the nervous and musculoskeletal systems.

Studies have established that MKP-1 is a negative regulator of MAPK-mediated inflammatory responses (Chi, Barry et al. 2006). MKP-1 plays a major role in the regulation of macrophage function and cytokine production and innate immune responses (Salojin, Owusu et al. 2006, Murray and Wynn 2011) in addition to protecting mice from lethal endotoxic shock (Hammer, Mages et al. 2006). Furthermore, some other studies suggest that MKP-1 is involved in exercise training mediated immune remodeling that could be beneficial for athletes (Rastogi, Du et al. 2011). There is a large body of evidence that implicates MAPKs in regulating metabolic signaling and contributing to metabolic syndrome (Sabio, Cavanagh-Kyros et al. 2009, Sabio, Kennedy et al. 2010, Manieri and Sabio 2015). Similarly, reports have indicated that MKP-1 plays an important role in metabolism. Findings from our lab have shown that MKP-1 deletion mice had increased ERK, JNK and p38 MAPK activities in insulin-responsive tissues in comparison to wild-type littermates (Wu, Roth et al. 2006, Roth, Le et al. 2009). Most importantly, this study established that MKP-1 whole-body knock-out (KO) mice are resistant to diet-induced obesity because of increased energy expenditure and are protected from the development of hepatic steatosis (Wu, Roth et al. 2006). In order to further investigate the mechanism by which MKP-1 regulate lipid homeostasis we utilized MKP-1 KO that were intercrossed with leptin receptor deficient mice. These studies demonstrated that *db/db;mkp-1*$^{-/-}$ hepatocytes were less steatotic in comparison with *db/db;mkp-1*$^{+/+}$ and also had a significant increase in hepatic triglyceride content (Flach, Qin et al. 2011). The resistance to the development of hepatic steatosis could be partly due to enhanced hepatic triglyceride and β-oxidation observed in the *db/db;mkp-1*$^{-/-}$ hepatocytes. Although these studies are milestone in defining the role of MKP-1 in metabolism, however, none of these previous approaches have been effective in clarifying the exact tissue contribution of MKP-1 to whole-body metabolism. More recently using tissue-specific deletion strategies we have used the *Cre-loxP* strategy to assess the contribution of MKP-1 in liver in the control of metabolism and glucose homeostasis. Our current work have demonstrated that liver-specific deletion of MKP-1 enhances gluconeogenesis and causes hepatic insulin resistance while selectively conferring protection from hepatosteatosis upon high fat feeding (Lawan, Zhang et al. 2015). These studies established that MKP-1 is a major regulator of metabolic homeostasis.

The physiological role of this phosphatase has been investigated in other tissues systems. MKP-1 has been implicated in regulating processes such as glial cell function, neuronal cell development and apoptosis (Ndong, Landry et al. 2012). Similarly, decreased MKP-1 levels have been reported in some neurological disorders such as multiple sclerosis, Huntington's disease, cerebral hypoxia and ischemia (Taylor, Moser et al. 2013), in addition to playing a role in major depressive disorder (Duric, Banasr et al. 2010). Another area that MAPK have been involved is artherosclerosis, which is one of the leading causes of cardiovascular related diseases (Ricci, Sumara et al. 2004). Equally, some studies have demonstrated a role for MKP-1 in the pathogenesis of artherosclerosis (Imaizumi, Grijalva et al. 2010). Other reports have shown that MKP-1 plays a key role in the development of dystrophic muscle diseases (Shi, Boadu et al. 2010) and regulation of bone homeostasis (Carlson, Zhang et al. 2009). The role of MKP-1 in cancer has also been explored, a review of the literature shows that MKP-1 expression is generally enhanced in a number of human tumors such as gastric adenocarcinoma, breast cancer, non-small cell carcinoma, prostate carcinoma and pancreatic carcinoma (Wang, Cheng et al. 2003, Arnoldussen and Saatcioglu 2009, Bai, Xu et al. 2012) while in some other type of cancers such as pancreatic cancer and oral squamous cell carcinoma the expression of MKP-1 is decreased (Liao, Guo et al. 2003).

CONCLUSIONS

Taken together, although MKP-1 is the most studied MKP family member there is extensive possibility for further research to elucidate the physiological and pathophysiological roles of MKP-1. Since phenotype of global knockouts are difficult to interpret and considering the development of tissue-specific knockouts, it will be interesting to examine tissue-specific contribution of MKP-1 especially in the immune and metabolic systems where MKP-1 has been established to play major role. Future works should explore the precise role of MKP-1 in other tissue systems including the cardiovascular and musculoskeletal systems, brain and cancer. These studies could unravel novel therapeutic approaches to target MKP-1 in many disease conditions.

ACKNOWLEDGEMENTS This work was supported by James Hudson Brown-Alexander B. Coxe Fellowship to A.L.

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