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doi:10.6072/H0.MP.A001718.01
Volume 2, Issue 1, 2013

Review Article Open Access

p38 beta MAP kinase

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In mammals, there are four p38 protein kinases: p38α, p38β, p38γ and p38δ. p38β was identified in 1996 as a closely related protein kinase of p38α, sharing 74% sequence identity and the Thr-Gly-Tyr dual phosphorylation motif characteristic of all p38 MAPKs. p38β is widely distributed in cells and tissues, but less so than p38α; p38β is particularly abundant in endothelial cells. p38β is activated *in vivo* by dual phosphorylation at Thr180 and Tyr182 by the MAP2K, MKK3 and MKK6 in response to a multitude of stimuli including environmental stressors, cytokines and growth factors. p38β can be dephosphorylated on both its Thr and Tyr residues by Dual-Specificity Phosphatases. p38β, like p38α, is targeted by a class of pyridinyl imidazole drugs that do not target the other two p38 MAPKs. These compounds were invaluable in discovering functions regulated by p38α and p38β. However, they do not permit to distinguish functions mediated by p38β from those regulated by p38α. This distinction has been made possible by the use of genetically engineered mice. p38β-deficient mice are not embryonic lethal such as those lacking p38α. However ectopic expression of p38β can rescue the lethality of p38α-deficiency. This suggests that p38α is the "dominant" form but that functional redundancy exists between the two related protein kinase. p38β has been shown to play specific roles in gene expression, regulation of cell death, cell differentiation and neuropathic pain. However, p38β is not involved in transducing pro-inflammatory signals, myogenesis or cell motility, when p38α is present.

KEYWORDS
Mapk11; Mitogen-activated protein kinase 11; p38 beta MAP kinase; p38 beta Map kinase; p38 beta MAPK; p38-2; p38B; p38beta; p38beta MAPK; P38BETA2; Prkm11; Protein kinase, mitogen activated kinase, 11; SAPK2; SAPK2B

IDENTIFIERS
Molecule Page ID:A001718, Species:Mouse, NCBI Gene ID: 19094, Protein Accession:NP_035291.4, Gene Symbol:Mapk11

PROTEIN FUNCTION
Background

p38β was identified in 1996 as a closely related protein kinase of p38α, sharing 74% sequence identity and the Thr-Gly-Tyr dual phosphorylation motif characteristic of all p38 MAPKs (Jiang *et al*. 1996). p38β differs most significantly from p38α in the region located between kinase domains V and VI, creating two gaps totaling eight amino acids (Jiang *et al*. 1996). A comparison between the structures of the two protein kinases showed a difference in the orientation of the N- and C-terminal domains causing a reduction in the size of the ATP-binding pocket in p38β (Patel *et al*. 2009). p38β, like p38α, is targeted by a class of pyridinyl imidazole drugs that do not target p38γ or p38δ. These compounds were invaluable in discovering functions regulated by p38α and p38β. However, they do not permit to distinguish functions mediated by p38β from those regulated by p38α. Despite efforts to design compounds that target only one of the two-related protein kinases (Patel *et al*. 2009), this distinction has been made possible by the use of genetically engineered mice. p38β-deficient mice are not embryonic lethal such as those lacking p38α (Adams *et al*. 2000, Mudgett *et al*. 2000, Beardmore *et al*. 2005). However ectopic expression of p38β can rescue the lethality of p38α-deficiency (Okada *et al*. 2007). This suggests that p38α is the "dominant" form, but that functional redundancy exists between the two related protein kinases. In order to avoid major duplications between the p38α and p38β molecule pages, only functions shown to be mediated by p38β specifically are reported in the next sections. However, the reader is referred to the p38α molecule pages to obtain a more complete overview of the functions regulated by these two protein kinases.

Transcriptional regulation

p38β phosphorylates ATF2 and increases its transcriptional activity (Jiang *et al*. 1996, Lee *et al*. 2002); this can be decreased through its interaction with histone deacetylase 3 (HDAC3) (Mahlknecht *et al*. 2004). p38β increases AP-1 transcriptional activity induced by arsenite in human breast cancer cells (Pramanik *et al*. 2003). p38β also phosphorylates ATF7 at Thr51, which prevents ATF7 sumoylation, enabling the interaction of ATF7 with TAF12, thus increasing transcription (Camuzeaux *et al*. 2008).

Cell cycle and cell death

Cell cycle Regulation

Carbon monoxide (CO)-induced activation of p38β up-regulates caveolin-1, which inhibits smooth muscle cell proliferation (Kim *et al*. 2005a). Additionally, IFNα regulates growth inhibition of Jurkat cells through p38α and p38β (Lee *et al*. 2010).

Stimulation of cell death

p38β is required for anoikis in undifferentiated intestinal epithelial cells (Vachon *et al*. 2002). Moreover, cardiomyocyte apoptosis induced by a dominant negative 14-3-3η targeted to postnatal cardiac tissue is mediated mostly by p38β, with a lesser contribution from p38α (Zhang *et al*. 2003). Furthermore, cardiomyocyte apoptosis induced by expression of Related Adhesion Focal Tyrosine Kinase (RAFTK) requires p38β (Melendez *et al*. 2004).

Protection from cell death

As is the case for p38α, p38β has also been implicated in the

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Published online: 20 Jan 2013 | doi:10.6072/H0.MP.A001718.01

protection from cell death. CO cytoprotective effects against oxidative stress in endothelial cells occur via p38β regulation of heat shock protein 70 (Otterbein *et al*. 2003, Kim *et al*. 2005b). Moreover, isoflavone Genistein induces p38β activity, which protects endothelial cells from TNFα-induced apoptosis (Si and Liu, 2009).

Cell differentiation

During keratinocyte differentiation, down regulation of the transcription factor E2F1, requires p38β (Ivanova *et al*. 2006). p38β contributes to C2C12 myogenic differentiation in conjunction with with p38α and p38γ, by selectively regulating cyclin D3, a unique target of p38β (Wang *et al*. 2008). Moreover, osteoclast differentiation requires p38β activation by TAK1 (Greenblatt *et al*. 2010).

Metabolism

p38β was found to phosphorylate glycogen synthase (GS) at Ser644, which enables subsequent phosphorylation of GS by Glycogen Synthase kinase 3 (GSK3) resulting in inhibition of GS activity (Kuma *et al*. 2004).

Nervous system

p38β binds and phosphorylates the neurotrophin receptor p75(NTR) which results in enhanced NFκB activity and decreases AP-1 activity in Schwann cells (Wang *et al*. 2000). The microtubule associated protein Tau is a good substrate of p38β, which can phosphorylate Thr181, Ser202, Thr205, Ser396, Ser404 and Ser422 (Buee-Scherrer and Goedert 2002).

Neuropathic pain

p38β expressed in the microglia of the spine and plays a role in spinal nociceptive processing (Svensson *et al*. 2005). Spinal hyperalgesia was prevented by down regulation of p38β but not p38α using antisense oligonucleotides (Fitzsimmons *et al*. 2010)

Cardiovascular system

Shear-stress mediated expression of chemokines is mediated by p38β in endothelial cells (Shaik *et al*. 2009).

Functions shown to be mediated by p38α and not p38β

Mice-lacking p38β have a slight reduction in MAPKAP-K2 activity and no reduction in MSK1 activity in response to anisomycin, demonstrating that p38α is the main isoform responsible for MAPKAP-K2 and MSK1 activation (Beardmore *et al*. 2005). Accordingly, p38α is the main form involved in mediating cytokine production, as mice lacking p38β show no defect in cytokine production or immune functions (Beardmore *et al*. 2005). Similar results were obtained through chemical genetics analysis of p38α and p38β inhibition (O'Keefe *et al*. 2007). p38α is the essential p38 isoform sustaining adult myogenesis (Ruiz-Bonilla *et al*. 2008). In cells derived from mice lacking the four different p38 MAPKs, it was found that only p38α was involved in relaying chemotactic signals (Rousseau *et al*. 2006). The activation of p38α but not p38β is required for ischemic preconditioning of the heart (Sicard *et al*. 2010).

REGULATION OF ACTIVITY

Dual phosphorylation by MKKs

The canonical activation of p38β occurs *via* dual phosphorylation of the pThr180- Gly181-pTyr182 motif, in the activation loop by MKK6 or MKK3, but not MKK3 splice variants missing the N-terminal 29 amino acids (i.e. lacking its docking site) in contrast to p38α (Jiang *et al*. 1996, Enslen *et al*. 2000). Therefore, the presence of a docking site is necessary for p38β activation by MKKs (Enslen *et al*. 2000). Thr180 and Tyr182 are exposed to the surrounding solvent on the activation loop, and in the absence of phosphorylation interfere with substrates binding (Bellon *et al*. 1999). Upon phosphorylation, p38β goes through characteristic global conformational changes that alter the alignment of the two kinase halves (N-terminal and C-terminal domains) and enhance access to substrate, which increases enzymatic activity (Bellon *et al*. 1999, Canagarajah *et al*. 1997).

Dephosphorylation

The magnitude and duration of p38β signal transduction are critical determinants of its biological effects. Therefore p38β inactivation is a crucial part of the biological responses it controls. It is believed that the same phosphatases acting on p38α are responsible for inactivating p38β. These include the members of the PP2C family, (Takekawa *et al*. 1998, Takekawa *et al*. 2000) and DUal-Specificty MAPK kinase Phosphatases (DUSP; also known as MAPK Kinase Phosphatases, MKP) (Dickinson and Keyse 2006). DUSP8 (also known as M3/6) was the first phosphatase shown to specifically target stress-activated protein kinases (Muda *et al*. 1996). The inducible nuclear DUSP, DUSP1 (also known as MKP-1) also dephosphorylates p38β (Franklin and Kraft 1997, Chu *et al*. 1996, Dickinson and Keyse 2006).

INTERACTIONS

p38β was found to interact with the neurotrophin receptor p75(NTR) (Wang *et al*. 2000). p38β was found to interact with the MAPK docking site (D-site) in the N-terminus of MKK4 (Ho *et al*. 2003) and the protein kinase MAPKAP-K5 (also known as PRAK) (New *et al*. 2003). p38β binds the phosphatase DUSP16 (Tanoue *et al*. 2001). Unphosphorylated p38β interacts with the N-terminus of HDAC3 (Mahlknecht *et al*. 2004). p38β, but not p38α, interacts with Glycogen Synthase in skeletal muscle, liver and brain (Kuma *et al*. 2004).

PHENOTYPES

p38β-deficient mice do not die due to placental defects like p38α-deficient ones (Adams *et al*., 2000, Mudgett *et al*., 2000); they are born viable and fertile (Beardmore *et al*., 2005). p38β-deficient fibroblasts did not induce caveolin-1 in response to CO, which was restored by p38β gene transfer (Kim *et al*., 2005). In mice lacking p38β, p38γ and p38δ, the regeneration and myofiber growth of adult muscle proceeded as in wild type mice, excluding a role for p38 MAPKs other than p38α in mediating muscle growth (Ruiz-Bonilla *et al*., 2008). However, mice lacking p38β were found to have reduced bone mass secondary to defective osteoclast differentiation (Greenblatt *et al*., 2010). In contrast to the other members of the p38 MAPK family, the dephosphorylation of S6K1 induced by 2-deoxy-glucose is prevented in p38β-deficient mouse embryonic fibroblasts (Zheng *et al*., 2011). This suggests a role for p38β in stress induced inhibition of cell growth.

MAJOR SITES OF EXPRESSION

p38β is widely distributed in cells and tissues, but less than p38α (Beardmore *et al*. 2005). Northern hybridization showed expression in human brain, heart, placenta, lung, liver, skeletal

muscle, kidney, and pancreas (Jiang *et al*. 1996). p38β has not been detected in monocytes, macrophages, neutrophils. However, low amounts of p38β were shown to be present in CD4+ T cells and abundantly in endothelial cells (Hale *et al*. 1999). In rheumatoid arthritis patients, p38β expression was found in synovial fibroblasts and endothelial cells, whereas the dominant p38 MAPKs found in inflamed tissue were p38α and p38γ (Korb *et al*. 2006). In the spinal dorsal horn, p38β is expressed in the microglia in contrast to p38α, which is expressed in neurons (Svensson *et al*. 2005). In the mouse brain, p38β was found to be expressed in the nucleus of neurons in contrast to p38α, which was found mostly in dendrites, cytoplasmic and nuclear regions (Lee *et al*. 2000). In the post-ischemic brain, p38β activity was biphasic; with early increase in the nuclei and dendrites of neurons and the late activation in astrocytes found in the penumbra (Piao *et al*. 2003).

SPLICE VARIANTS

No splice variants of p38β have been reported.

REGULATION OF CONCENTRATION

Diazoxide, a potassium channel activator, up-regulates p38β expression by pancreatic β-cells (Huang *et al*. 2007). p38β expression has been shown to be up-regulated in the progression of malignant astrocytoma cells (Zeng *et al*. 2008).

ANTIBODIES

To detect specifically all forms of p38β (phosphorylated and non-phosphorylated), we have previously used the R&D systems anti-p38β (cat # MAB5885). To detect phosphorylated p38β only, all p38β forms can be immuno-precipitated first with the aforementioned antibody and the phosphorylation state detected with a pan-pThr180-pTyr182 antibody, such as the Millipore anti-phospho-p38 (pThr 180/Tyr 182; cat no 09-272).

Table 1: Functional States

STATE DESCRIPTION	LOCATION	REFERENCES
p38β	Unknown	
p38β-2P	Unknown	Jiang Y *et al.* 1996
p38β(nuc)	nucleus	Jiang Y *et al.* 1996
p38β-2P(nuc)	nucleus	Jiang Y *et al.* 1996
p38β(cyto)	cytosol	Jiang Y *et al.* 1996
p38β-2P(cyto)	cytosol	Jiang Y *et al.* 1996
p38β/Hdac3(nuc)	nucleus	Mahlknecht U *et al.* 2004
p38β-2P/GS	Unknown	Kuma Y *et al.* 2004
p38β-2P/GS-1P	Unknown	Kuma Y *et al.* 2004
p38β-2P/Ngfr	Unknown	Wang JJ *et al.* 2000
p38β-2P/Ngfr-P	Unknown	Wang JJ *et al.* 2000
p38β/MK5	cytosol	New L *et al.* 2003
p38β/MKK4	Unknown	Ho DT *et al.* 2003
p38β/MK2(nuc)	nucleus	Ben-Levy R *et al.* 1998; Engel K *et al.* 1998
p38β-2P/MK2(nuc)	nucleus	Ben-Levy R *et al.* 1998; Engel K *et al.* 1998; Ronkina N *et al.* 2011
p38β-2P/MK2-2P(nuc)	nucleus	Ben-Levy R *et al.* 1998; Engel K *et al.* 1998
p38β-2P/MK2-2P(cyto)	cytosol	
p38β-2P/DUSP16	Unknown	Tanoue T *et al.* 2001

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This molecule exists in 18 states , has 18 transitions between these states and has 6 enzyme functions.(Please zoom in the pdf file to view details.)