MAPK13 (mitogen-activated protein kinase 13)

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**Identity**

Other names: MGC99536; PRKM13; SAPK4; p38delta

HGNC (Hugo): MAPK13

Location: 6p21.31

**DNA/RNA**

**Description**


**Transcription**

The MAPK13 gene encodes a 365 amino-acid protein of about 40 kDa. No splice variants have been reported.

**Pseudogene**

No human or mouse pseudogene known.

**Protein**

**Note**

p38delta (MAPK13), also known as Stress-activated protein kinase 4 (SAPK4) belongs to the p38 subfamily of MAPKs. The p38MAPK subfamily is composed by four members encoded by different genes, which share high sequence homologues and are designated as p38alpha (MAPK14, or SAPK2a), p38beta (MAPK11 or SAPK2b), p38gamma (MAPK12 or SAPK3) and p38delta (MAPK13 or SAPK4). They are about 60% identical in their amino acid sequence but differ in their expression patterns, substrate specificities and sensitivities to chemical inhibitors (Iñesta-Vaquera et al., 2008). All p38 MAPKs are strongly activated in vivo by environmental stresses and inflammatory cytokines, and less by serum and growth factors.

MAPK13 genomic context (chromosome 6, location 6p21.31).

Genomic organization of MAPK13 gene on chromosome 6p21.31. The boxes indicate coding regions (exon 1-12) of the gene.
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**Description**

p38delta (MAPK13) is a Serine/Threonine protein kinase of 365 amino acids with a predicted molecular mass of 40 kDa. It possesses the conserved amino acid domains (I-XI) characteristic of protein kinases (Goedert et al., 1997). The Thr\(^{180}\) and Tyr\(^{182}\) residues in subdomain VIII are in an equivalent position to the TXY sequence in known MAPKs. The activation of p38delta (MAPK13) occurs via dual phosphorylation of its TGY motif, in the activation loop, by MKK3 and MKK6, although it is preferentially activated by MKK3 in mouse embryonic fibroblasts (Remy et al., 2009).

**Expression**

p38delta (MAPK13) mRNA is widely expressed with high levels of expression in testes, pancreas, kidney and small intestine.

**Localisation**

p38delta (MAPK13) localizes to the cytoplasm and nucleus of cultured cells.

**Function**

p38delta (MAPK13) phosphorylates typical p38 MAPK substrates such as the transcription factors ATF2, Elk-1 or SAP1. However, it cannot phosphorylate MAPKAPK2 or MAPKAPK3, which are good substrates for other p38 MAPK isoforms (Cuenda et al., 1997; Goedert et al., 1997). p38delta possibly plays a role in cytoskeleton regulation as it has been reported to phosphorylate the cytoplasmic protein stathmin, which has been linked to regulation of microtubule dynamics (Parker et al., 1998). Microtubule-associated protein Tau is another protein substrate of p38delta (Goedert et al., 1997; Feijoo et al., 2005; Yoshida and Goedert, 2006). In addition p38delta plays a role in the regulation of protein translation by phosphorylating and inactivating the eukaryotic elongation factor 2 (eEF2) kinase (Knebel et al., 2001; Knebel et al., 2002). p38delta also plays a key role in the regulation of insulin secretion as well as in the survival of pancreatic beta cells, since p38delta catalyzes an inhibitory phosphorylation of the protein kinase D1 (PDK1), which controls insulin exocytosis in pancreatic beta cells (Sumara et al., 2009). p38delta has been suggested to play an important role in inducing keratinocyte differentiation by regulating the expression of involucrin, which is a protein expressed during keratinocyte differentiation (Eckert et al., 2003).

Activation of exogenously expressed p38delta by differentiation-inducing agents such as a bioactive green tea polyphenol (EGCG), okadaic acid (OA) or the phorbol ester TPA, correlated with increased involucrin promoter activity in keratinocytes via increased activity at AP1, Sp1 and C/EBP sites (Balasubramanian et al., 2002; Efimova et al., 2003). The mechanisms by which p38delta may regulates keratinocyte differentiation is still unknown, although it has been reported that in keratinocytes expressing exogenous p38delta this forms a complex with ERK1/ERK2 (Efimova et al., 2003; Eckert et al., 2004). Additional data supporting the idea that p38delta may play a role in keratinocyte differentiation come from a study carried out in lesional psoriasis skin (Johansen et al., 2005). It has been shown that the activity of p38alpha, p38beta and p38delta are augmented in lesional psoriasis skin compared with nonlesional psoriasis skin (Johansen et al., 2005). Alternatively, it has been also claimed that p38delta may have a dual role in keratinocytes contributing not only to the differentiation process, but also to their apoptosis in a PKCdelta dependent manner, and in response to OA or H2O2 (Efimova et al., 2004; Kraft et al., 2007).

**Homology**

p38delta (MAPK13) shows 70% identity with p38gamma (MAPK12), 60% sequence identity with p38alpha (MAPK14) and p38beta (MAPK11), 45% identity with HOG1 from S. cerevisiae, 47% identity with human SAP kinase-1 (JNK1) and 42% identity with p42 MAPkinase (ERK2).

**Implicated in**

**Skin cancer**

**Oncogenesis**

It has been suggested that p38delta functions as positive regulator of skin tumorigenesis by promoting cell proliferation and tumor development in epidermis (Schindler et al., 2009).

**Cholangiocarcinoma**

**Oncogenesis**

p38delta may serve as a diagnostic marker for expression cholangiocarcinoma (CC), since its expression is upregulated in CC relative to...
hepatocellular carcinoma (HCC) and to normal biliary tract tissue (Li-Sher et al., 2009). It has been suggested that p38delta is important for motility and invasion of CC cells (Li-Sher et al., 2009).

**Malignant Pleural Mesothelioma**

**Oncogenesis**

MAPK13 gene is hypermethylated in Malignant Pleural Mesothelioma (MPM) cell lines (Goto et al., 2009).

**Alzheimer disease**

**Note**

The protein Tau is a good in vitro substrate for the p38 isoforms p38delta and p38gamma, and its phosphorylation by these two enzymes results in a reduction in its ability to promote microtubule assembly (Goedert et al., 1997b; Feijoo et al., 2005). Moreover, overexpression of p38gamma in neuroblastoma, induces Tau phosphorylation which correlates with a decrease on Tau associated to the cytoskeleton and an increase of soluble Tau (Jenkins et al., 2000). It has been reported as well that p38delta is the major Tau kinase in neuroblastoma in response to osmotic shock (Feijoo et al., 2005) and that the p38 MAPK activator, MKK6, has also been found to be active in neurodegenerative diseases (Zhu et al., 2001). Moreover, oxidant agents implicated in Alzheimer's disease can cause hyperphosphorylation in rat brain and also induce the activation of p38delta, indicating that this kinase may be involved in Tau phosphorylation (Yin et al., 2006). On the other hand, it has been shown using phosphospecific antibodies that p38MAPKs phosphorylate Tau on residues phosphorylated in a Tau obtained from patients suffering Alzheimer's disease (Goedert et al., 1997b; Feijoo et al., 2005).

**Diabetes type 2 (diabetes mellitus)**

**Note**

p38delta plays a key role in the regulation of insulin secretion as well as in the survival of pancreatic beta cells (Sumara et al., 2009).

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