Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section
Review

MAPK12 (mitogen-activated protein kinase 12)

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Published in Atlas Database: January 2010

Online updated version : http://AtlasGeneticsOncology.org/Genes/MAPK12ID41290ch22q13.html
DOI: 10.4267/2042/44881

Identity

Other names: EC 2.7.11.24; ERK3; ERK5; ERK-6; ERK6; p38gamma; PRKM12; SAPK-3; SAPK3

HGNC (Hugo): MAPK12

Location: 22q13.33

DNA/RNA

Description

The MAPK12 entire gene spans 8.46 kb on the long arm of chromosome 22. It contains 12 exons.

Transcription

The MAPK12 gene encodes a 367 amino-acid protein of about 42 kDa. MAPK12 mRNA is 1457 bp. No splice variants have been reported.

Pseudogene

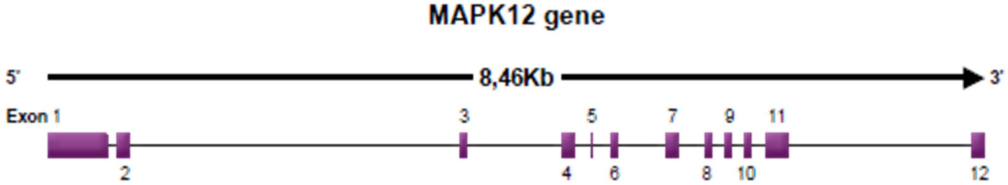
No human or mouse pseudogene known.

Protein

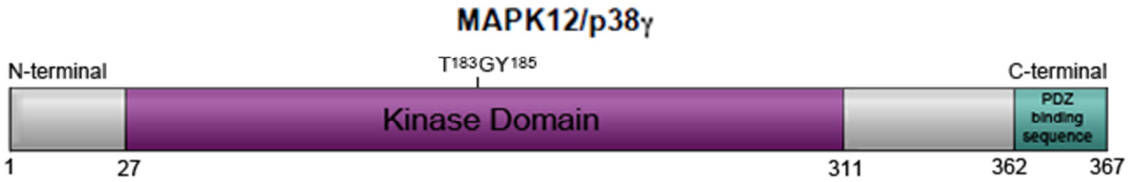
Note

p38gamma (MAPK12), also known as Stress-activated protein kinase 3 (SAPK3) belongs to the p38 subfamily of MAPKs. The p38MAPK subfamily is composed by four members encoded by different genes, which share high sequence homologies 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 expresion 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.

MAPK12 genomic context (Chromosome 22, location 22q13.33).



Genomic organization of MAPK12 gene on chromosome 22q13.33. The boxes indicate coding regions (exon 1-12) of the gene.



Schematic representation of the p38gamma (MAPK12) protein structure. Kinase Domain, catalytic kinase domain; TGY, sequence motif containing the regulatory phosphorylation residues. p38gamma (MAPK12) possesses at the C-terminal a sequence that binds to PDZ domain of several proteins.

Description

p38gamma (MAPK12) is a Serine/Threonine protein kinase of 367 amino acids with a predicted molecular mass of 42 kDa. It possesses the conserved amino acid domains (I-XI) characteristic of protein kinases (Mertens et al., 1996).
The Thr^{183} and Tyr^{185} residues in subdomain VIII are in an equivalent position to the TXY sequence in known MAPKs. The activation of p38gamma (MAPK12) occurs via dual phosphorylation of its TGY motif, in the activation loop, by MKK3 and MKK6 (Cuenda et al., 1997; Goedert et al., 1997).

Expression

p38gamma (MAPK12) mRNA is widely expressed with high levels of expression in skeletal muscle.

Localisation

p38gamma (MAPK12) localizes to the cytoplasm and nucleus of cultured cells.

Function

p38gamma (MAPK12) regulates many cellular functions by phosphorylating several proteins. A feature that makes p38gamma unique among the p38 MAPKs is its short C-terminal sequence -KETXL, an amino acid sequence ideal for binding PDZ domains in proteins. SAPK3/p38gamma binds to a variety of these proteins, such as alpha1-syntrophin, SAP90/PSD95 and SAP97/hDlg, and under stress conditions is able to phosphorylate them and modulate their activity (Hasegawa et al., 1999; Sabio et al., 2004; Sabio et al., 2005). These proteins are scaffold proteins usually targeted to the plasma membrane cytoskeleton at specialised sites such as the neuromuscular junction and gap junctions through protein-protein interactions. In the case of SAP97/hDlg its phosphorylation by SAPK3/p38gamma provided a mechanism of dissociating SAP97/hDlg from the cytoskeleton (Sabio et al., 2005). p38gamma can also phosphorylate 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). Another p38gamma substrates that do not require PDZ domain binding interactions are the mitochondrial protein Sab (Court et al., 2004) and the microtubule-associated protein Tau (Feijoo et al., 2005).

Since p38gamma expression is very high in skeletal muscle in comparison to other tissues, it is not surprising that it may play a fundamental role in skeletal muscle differentiation. Thus, p38gamma protein level increases when myoblast differentiate into myotubes endogenous (Tortorella et al., 2003; Cuenda and Cohen, 1999). Moreover, it has been shown that over-expression of p38gamma in skeletal muscle cells leads to differentiation from myoblast to myotubes, and that a dominant-negative mutant of p38gamma prevented this differentiation process (Lechner et al., 1996). Recently, Gillespie et al. (2009) reported that p38gamma phosphorylates the transciption factor MyoD, which results in a decrease in its transcriptional activity. p38gamma plays a cardinal role in blocking the premature differentiation of skeletal muscle stem cells, the satellite cells. Additionally, p38gamma regulates mitochondrial biogenesis and angiogenesis, and it is required for endurance exercise-induced skeletal muscle adaptation (Pogozelski et al., 2009).
Most of the work published on cellular transformation regulation by p38MAPK pathway has been focused on studying the role of the isoforms p38alpha and beta, but there are a number of recent publications providing evidences for the role of p38gamma (MAPK12) in cellular transformation. Overexpression of the active form of Rit, a Ras family member, in NIH3T3 cells, causes transformation and stimulates p38gamma, but not other isoforms of p38MAPKs, ERK1, ERK2 or ERK5 (Sakabe et al., 2002).
In rat intestinal epithelial cells, Ras oncogene was found to increase p38gamma RNA and protein expression with concurrently stimulated p38alpha phosphorylation and decreased p38gamma phosphorylation (Tang et al., 2005; Loesch and Chen, 2008). These results indicate that increased p38gamma gene expression is required for Ras oncogene activity but the mechanism by which p38gamma may promote Ras transformation is not clear. Recent studies show that phospho-p38alpha can down-regulate p38gamma protein expression through c-jun dependent ubiquitin/proteasome pathways (Qi et al., 2007; Loesch and Chen, 2008). On the other hand other recent study shows that whereas p38gamma mediates Ras-induced senescence at least partly by stimulating the transcriptional activity of p53 through direct phosphorylation, p38alpha appears to regulate senescence in a p53-independent, $p16^{INK4A}$ dependent manner (Kwong et al., 2009).

Homology

p38gamma (MAPK12) shows 70% identity with p38delta (MAPK13), 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 MAP kinase (ERK2).

Mutations

Note

No mutation reported yet.

Implicated in

Breast cancer

Oncogenesis

In human MCF-7 breast cancer cells, MKK6 expression inhibits DNA synthesis. This inhibitory effect is enhanced by the co-expressed p38gamma (Pramanik et al., 2003; Loesch and Chen, 2008). Ras also increases p38gamma protein expression in human breast cancer (Qi et al., 2006).

Skin cancer

Oncogenesis

p38gamma isoform is specifically implicated in melanoma death induced by UV radiation, cisplatin treatment (Pillaire et al., 2000). Moreover, melanoma cells overexpressing PDGF-Ralpha show a marked increase of p38gamma (Faraone et al., 2009).

Hepatoma

Oncogenesis

p38gamma expression is increased in hepatoma cell line HLE (Liu et al., 2003).

Ovarian cancer

Oncogenesis

p38gamma expression is regulated by the TNF-related apoptosis inducing ligand (TRIAL) and IL-8 in cellular lines from ovarian cancer (Abdollahi et al., 2003).

Pancreatic cancer

Oncogenesis

The levels of p38gamma seem to be decreased in pancreatic cancer cells (Crnogorac-Jurcevic et al., 2001).

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This article should be referenced as such:

Cerezo-Guisado MI, Cuenda A. MAPK12 (mitogen-activated protein kinase 12). Atlas Genet Cytogenet Oncol Haematol. 2010; 14(11):1007-1010.