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Gene Section
Mini Review

MAPK14 (mitogen-activated protein kinase 14)

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Identity

Other names: CSBP1; CSBP2; CSPB1; EXIP; Mxi2; PRKM14; PRKM15; RK; SAPK2A; p38; p38ALPHA

HGNC (Hugo): MAPK14

Location: 6p21.31

DNA/RNA

Description

The gene spans a region of 83.53 kb and the coding part is divided into 41 different exons.

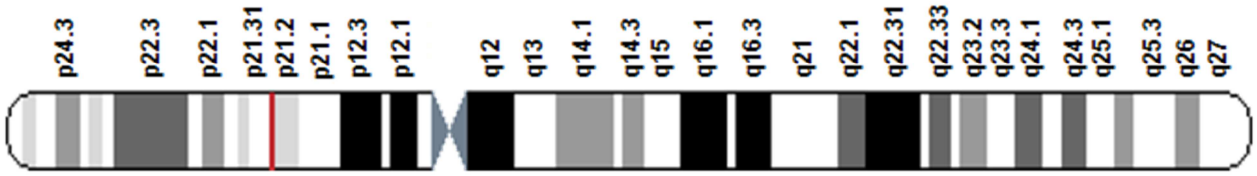
Larger transcripts contain 12 or 13 exons. (GATExplorer).

Transcription

9 types of transcripts have been described, although only 5 are protein coding transcripts. The larger 4319-nucleotide transcript encodes a protein of 360 amino acid residues. The first and last exons are partially untranslated.

Pseudogene

None described so far.



Schematic representation of human chromosome 6 indicating the position of MAPK14 locus (p21.31) (red bar).

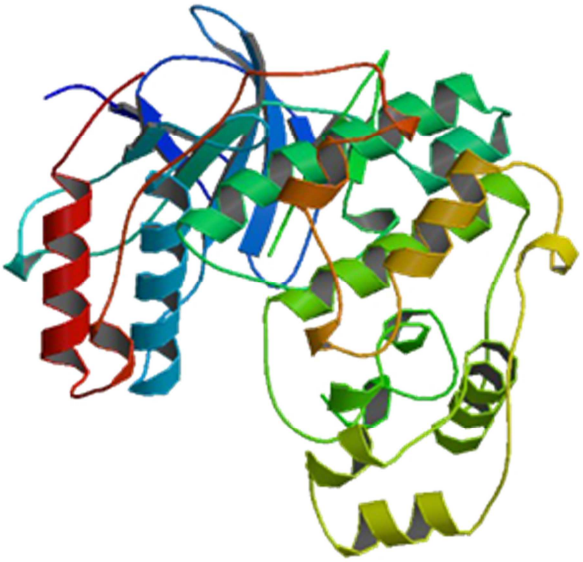
MAPK14 gene locus. Representation of the MAPK14 gene organization indicating the position of the exons (coding region) and untranslated regions.

MAPK14 protein domains. Schematic representation of MAPK14 protein indicating the position of its functional domains. 30-54: protein kinase ATP signature, ATP-binding region; 59-162: MAPK signature; 24-308: protein kinase domain.

Protein

Description

MAPK14 is a Ser/Thr kinase composed of 90 to 360 residues depending on the transcript variant.



Crystal structure of MAPK14 at 2.3 A resolution. From PDB (access number: 1WFC).

Expression

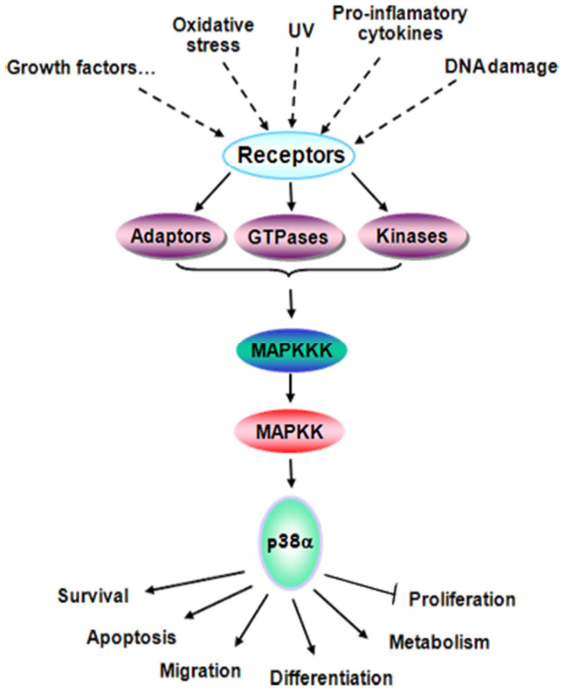
p38alpha MAPK is ubiquitously expressed, being the p38 most abundant isoform.

Localisation

p38alpha is mainly present in the cytosol, but it can translocate to the nucleus. In addition, it can be localized in the mitochondria or in other subcellular compartments.

Function

p38alpha is mainly activated by various environmental stresses and proinflammatory cytokines, but many other extracellular signals, including growth factors, also lead to p38alpha activation. The canonical activation requires its phosphorylation in threonine and tyrosine residues by dual-specificity MAP kinase kinases (MKKs), MKK3, MKK6 and MKK4. Substrates of this kinase include transcription factors, such as ATF1, ATF2, ATF6, p53, MEF2 or C/EBPbeta and protein kinases, such as MAPKAP-K2 and MAPKAP-K3 (also known as MK-2 and MK-3), MSK-1, MNK-1/MNK-2 and other proteins.
p38alpha MAPK is essential for embryonic development and it regulates different cellular functions such as proliferation, differentiation, cell death, adhesion, migration, as well as the response to stress and many metabolic pathways, among others. It does so through regulation of transcription, mRNA stability, chromatin remodelling, protein synthesis, etc.
Concerning cell death, although p38alpha plays an important role as a pro-apoptotic signal, it can play a dual role, acting as either a mediator of cell survival or of cell death, depending on the cell type and the stimuli. Related with its function as a negative regulator of proliferation and a mediator of apoptosis, p38alpha acts as a tumor suppressor in the initial stages of a tumorigenic process, while at later stages it can promote metastasis.



Signaling through p38alphaMAPK. Signaling through MAPK14 cascade and its role in the regulation of cellular functions. MAPK14 is involved in signaling pathways triggered by a variety of stimuli such as growth factors, oxidative stress, UV, cytokines and DNA damage. Depending on the stimulus, different receptors and intermediates (adaptors, GTPases or kinases) are activated leading to the activation of the p38alpha MAPK cascade. This cascade is initiated by activation of MAPKKKs, which phosphorylate and activate MAPKKs (MKK3/6/4), which in turn lead to activation of MAPK14 through dual phosphorylation in Tyr and Thr. Once phosphorylated, MAPK14 phosphorylates a number of cytosolic and nuclear substrates, including transcription factors, which lead to the control of many cellular responses.

Mutations

Somatic

4 somatic mutations according to Ensembl: COSM21366; COSM20563; COSM35409; COSM12875.

Implicated in

Hematopoietic malignancies

Disease

p38 MAPK, mainly the p38alpha isoform, is a key player in the maintenance of hematopoiesis homeostasis, as it balances both proliferative and growth inhibitory signals triggered by the growth factors and cytokines that regulate normal hematopoiesis. Alterations in this p38 MAPK-controlled balance may result in either overproduction or depletion of myelosuppressive cytokines leading to the development of certain bone marrow failure syndromes. For example, p38alpha is responsible for the enhanced stem cell apoptosis characteristic of low grade myeolodysplastic syndromes (MDSs). On the other hand, imbalance toward the proliferative side may conduct to the development of myeloproliferative syndromes (MPSs), such as leukemia, lymphomas and myelomas. In particular, p38alpha MAPK plays a pro-apoptotic role in chronic myeloid leukemia (CML). In fact, p38alpha MAP kinase pathway mediates the growth inhibitory effects of IFNalpha and STI-571, two drugs used in the CML treatment, which underscores the importance of this pathway in the generation of antileukemic responses.

Alzheimer's disease

Disease

Alzheimer is an incurable, neurodegenerative disease characterized by a progressive deterioration of the cognitive, memory and learning ability due to the accumulation of plaques containing amyloidogenic Abeta proteins and tangles containing hyperphosphorylated tau protein. The ASK1-MKK6-p38 signaling pathway participates in amyeloid precursor protein (APP) and tau phosphorylation in response to oxidative stress and contributes to the expression of the beta-secretase gene and the induction of neuronal apoptosis triggered by ROS.

Parkinson disease

Disease

Parkinson is a degenerative disorder of the central nervous system characterized by muscle rigidity, tremor and loss of physical movement caused by a progressive loss of dopaminergic neurons. Mutations in alpha-synuclein are one of the main causes of Parkinson. alpha-synuclein activates p38alpha MAPK in human microglia promoting a potent inflammatory stimulation of microglial cells. Additionally, the p38alpha MAPK plays a role in dopaminergic neural apoptosis through the phosphorylation of p53 and expression of the pro-apoptotic protein Bax.

Amyotrophic lateral sclerosis

Disease

ALS is a progressive, lethal, degenerative disorder of motor neurons leading to paralysis of voluntary muscles. Numerous evidences point to a role of p38 MAPK in the development and progression of ALS induced by mutations in SOD1 (superoxide dismutase 1) gene. Mutant SOD1 provokes aberrant oxyradical reactions that increase the activation of p38 MAPK in motor neurons and glial cells. This increase in active p38 MAPK may phosphorylate cytoskeletal proteins and activate cytokines and nitric oxide, thus contributing to neurodegeneration through different mechanisms including apoptosis.

To be noted

Note

See also the Deep Insight: "Role of p38alpha in apoptosis: implication in cancer development and therapy".

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