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Gene Section

Mini Review

MAPKAPK2 (mitogen-activated protein kinase-activated protein kinase 2)

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Identity

Other names: MAPKAPK-2, MK2
HGNC (Hugo): MAPKAPK2
Location: 1q32.1
Note: MAPKAPK2 is involved in many cellular processes including: stress and inflammatory response, nuclear export, gene expression regulation and cell proliferation, acting with p38 MAP gene.

DNA/RNA

Note
MAPKAPK2 encodes a member of the Ser/Thr protein kinase regulated through direct phosphorylation by p38 MAP kinase. Inhibition of the p38 MAPK pathway could be a possible target to inflammatory diseases therapy. Unfortunately, blocking p38 MAPK activation "in vivo" implies in high toxicity and it does not have oral bioavailability. MAPKAPK2/MK2 inhibitors acting downstream of p38 could be reasonable solutions to overcome this problem (Duraisamy et al., 2008).

Description

Size 49,338 bases, starts at 204924912 and ends at 204974256 bp from pter with plus strand orientation.

Transcription

We found some discordant information regarding MAPKAPK2 splice variants. Kervinen et al. 2006, described that the human MAPKAPK2 gene encodes two alternatively spliced transcripts and also that this gene contains 14 different introns (13 gt-ag, 1 gc-ag). Transcription produces 9 different mRNAs, 8 alternatively spliced variants and 1 unspliced form. There are 5 probable alternative promoters and 3 validated alternative polyadenylation sites. The mRNAs appear to differ by truncation of the 5' end, presence or absence of 7 cassette exons, overlapping exons with different boundaries, alternative splicing or retention of 3 introns.

Pseudogene

ATF4C - Cyclic AMP-dependent transcription factor ATF-4, localized at chromosome 17, location: 17q25.1.

Protein

Description

MAPKAPK2 has two alternatively spliced transcripts, encoding 400 and 370 amino acids, with sequence heterogeneity from Lys-353 to the C-terminus. Crystal structure shows: 1) an autoinhibitory domain, consisting of 328-370 residues; 2) a helix-turn-helix structure that occupies the substrate-binding cleft of the kinase domain and inhibits kinase function (ter Haar et al., 2007).

Localisation

The 400-residue MAPKAPK2 (isoform 1) consists of an N-terminal Pro-rich region, a kinase domain, an autoinhibitory domains, and C-terminal nuclear export (NES) and nuclear localization (NLS) signals. The 1-370 isoform (isoform 2) lacks NES and NLS, consistent with its presence only in the cytoplasm. MAPKAPK2 also phosphorylates proteins found in both the nucleus (cAMP-response element-binding protein, or CREB) and cytoplasm (HSP25/27 and LSP-1) (Kervinen et al., 2006).

Function

MAPKAPK2 is required for both cytokines production and cell migration (Kotlyarov et al., 2002).

MAPKAPK2 is activated upon stress by p38 MAPK, which binds C terminus of MAPKAPK2, leading to subsequently phosphorylation of its regulatory sites. After activation, MAPKAPK2 is transferred from nucleus to cytoplasm, and cotransport p38 to the new localization. In murine knockout model, MAPKAPK2 blockage leads to a dramatic reduction of tumor necrosis factor (TNF) production in response to lipopolysaccharide (Kotlyarov et al., 2002). One of the major substrates of MAPKAPK2 is the heat shock protein HSP27, which stimulates actin polymerization in order to facilitate recovery from destruction of cytoskeleton during cellular stresses.

Homology

Isoform 1 and 2 see figure below.

Isoform 1

```
        10         20         30         40         50         60
MLSNSQGQSP PVPFPAPAPP PQPPTPALPH PPAQPPPPPP QQFPQFHVKS GLQIKKNAII

        70         80         90        100        110        120
DDYKVTSQVL GLGINGKVLQ IFNKRTQEKF ALKMLQDCPK ARREVELHWR ASQCPHIVRI

       130        140        150        160        170        180
VDVYENLYAG RKCLLIVMEC LDGGELFSRI QDRGDQAFTE REASEIMKSI GEAIQYLHSI

       190        200        210        220        230        240
NIAHRDVKPE NLLYTSKRPN AILKLTDFGF AKETTSHNSL TTPCYTPYYV APEVLGPEKY

       250        260        270        280        290        300
DKSCDMWSLG VIMYILLCGY PPFYSNHGLA ISPGMKTRIR MGQYEFPNPE WSEVSEEVKM

       310        320        330        340        350        360
LIRNLLKTEP TQRMTITEFM NHPWIMQSTK VPQTPLHTSR VLKEDKERWE DVKEEMTSAL

       370        380        390        400
ATMRVDYEQI KIKKIEDASN PLLLKRRKKA RALEAAALAH
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Isoform 2

```
        10         20         30         40         50         60
MLSNSQGQSP PVPFPAPAPP PQPPTPALPH PPAQPPPPPP QQFPQFHVKS GLQIKKNAII

        70         80         90        100        110        120
DDYKVTSQVL GLGINGKVLQ IFNKRTQEKF ALKMLQDCPK ARREVELHWR ASQCPHIVRI

       130        140        150        160        170        180
VDVYENLYAG RKCLLIVMEC LDGGELFSRI QDRGDQAFTE REASEIMKSI GEAIQYLHSI

       190        200        210        220        230        240
NIAHRDVKPE NLLYTSKRPN AILKLTDFGF AKETTSHNSL TTPCYTPYYV APEVLGPEKY

       250        260        270        280        290        300
DKSCDMWSLG VIMYILLCGY PPFYSNHGLA ISPGMKTRIR MGQYEFPNPE WSEVSEEVKM

       310        320        330        340        350        360
LIRNLLKTEP TQRMTITEFM NHPWIMQSTK VPQTPLHTSR VLKEDKERWE DVKGCLHDKN

       370
SDQATWLTRL
```

Mutations

Note

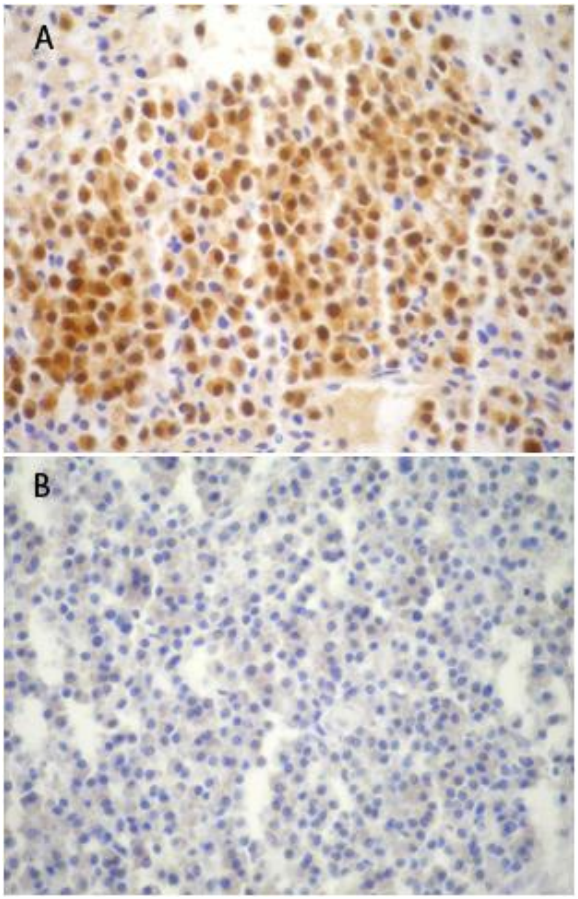
There is one described mutation: position 804 of mRNA, allele change GCC to GGC. At protein level, residue change A [Ala] to G [Gly].

Implicated in

Multiple myeloma (MM)

Note

Hideshima et al. 2004 have shown that overexpression of HSP27 confers resistance to bortezomib, a proteasome inhibitor currently used as front line MM therapy, combined with corticosteroids and immunomodulatory drugs, such as thalidomide and lenalidomide. Therefore, overexpression of MAPKAPK2 could be related to MM resistance to chemotherapy. They hypothesized that inhibition of MAPKAPK2 activity could augment bortezomib cytotoxicity by down regulating HSP27. Felix et al. 2009, at their gene expression studies, supported further exploitation of this pathway as therapeutic target in MM, although immunohistochemistry did not show high frequency of protein expression in MM (21%) (Felix et al., 2009).



Panel showing bone marrow samples of MM cases: A - plasma cells nuclear and cytoplasmatic positivity for MAPKAPK2; B - sample negative for MAPKAPK2 (400X).

Bladder cancer

Note

Kumar et al. 2010, showed that overexpression of the matrix metalloproteinases MMP-2 and MMP-9 have prognostic value in transitional cell carcinoma of bladder. p38 MAPK modulated MMP-2/9 mRNA expression and MMP-2/9 activity as mediators of tumor cells invasive capacity. Therefore, p38 MAPK inhibition blocks MMP-2/9 activities mediated by MAPKAPK2 (Kumar et al., 2010).

Skin tumor

Note

Using the two-stage chemical carcinogenesis model, Johansen et al. 2009 studied the effect of MAPKAPK2-deficiency and TNF-alpha-deficiency on skin tumor development in mice. Their findings demonstrate a dual role of MAPKAPK2 in the early stages of tumor promotion through regulation of both the inflammatory response and apoptosis of DNA-damaged cells. These results also identify MAPKAPK2 as a possible target for skin carcinoma therapy (Johansen et al., 2009).

Prostate cancer

Note

TGFbeta is an important regulator of cell adhesion and motility in a variety of cell types. p38 MAP kinase is necessary for TGFbeta -mediated up-regulation of matrix metalloproteinase type 2 (MMP-2), as well as TGFbeta -dependent increases in prostate cell invasion. Xu et al. 2006 demonstrated, after transient transfection, that both MAPKAPK2 and HSP27 are necessary for TGFbeta -mediated increases in MMP-2 activity in any cell type, as well as prostate cancer cells (Xu et al., 2006).

Alzheimer's disease (AD)

Note

Culbert et al. 2006 suggested that MAPKAPK2 plays a role in neuroinflammatory and neurodegenerative diseases, such as AD. The MAPKAPK2 activation and expression were increased in lipopolysaccharide (LPS) + interferon gamma-stimulated microglial cells, demonstrating MAPKAPK2 ability in eliciting a pro-inflammatory response. Again, MAPKAPK2 pathway can be considered a target for control of this degenerative brain disease.

Psoriatic skin

Note

Alterations in this specific signal transduction pathway may be involved in increased expression of proinflammatory cytokines in inflammatory diseases (Johansen et al., 2006). The increased activation of MAPKAPK2 is responsible for the elevated TNFalpha protein expression in psoriatic skin, making this pathway a potential target in the treatment of psoriasis (Johansen et al., 2006).

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