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Gene Section
Review

MAP3K7 (mitogen-activated protein kinase kinase kinase 7)

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Identity

Other names: TAK1; TGF1a

HGNC (Hugo): MAP3K7

Location: 6q15

DNA/RNA

Description

MAP3K7/TAK1 gene spans 71 kb of DNA and contains 17 exons and 16 introns. Exon 1 contains the 5' UTR of the mRNA and encodes 40 amino acid of N-terminal of the protein. Exons 2 to 8 encode the kinase domain. Exon 17 encodes the carboxyl end of the TAK1 protein and contains the 3'UTR. Exon 12 and exon 16 are alternative exons.

The promoter is located between 799 bp and 1215 bp upsteam of the exon 1. The promoter has the character of housekeeping genes: the absence of TATA box, the presence of CpG island and SP1 binding sites.

Transcription

Four alternatively spliced transcripts encoding 4 distinct isoforms because of the presence or absence of alternative exons 12 or/and 16 are detected.

Variant A: It lacks an in-frame coding segment, exon 12.

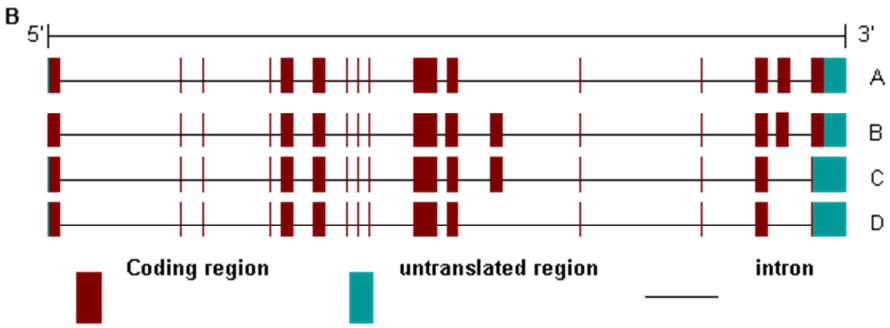
Variant B: This variant contains both alternative exons 12 and 16 and encodes the longest isoform.

Variant C: Variant C lacks the exon 16 resulting in a frame shift in exon 17. The resulting isoform C has a distinct and shorter C terminus when compared with variants A and B.

Variant D: Variant D lacks both exons 12 and 16.

The regulation of the TAK1 mRNA alternative splicing is tissue specific. The different variants of TAK1 may have specialized functions.

A: The 17 exons are shown as black vertical bars. The exon numbers are shown on top of each exon. The CpG island is shown as a white box. The positions of exons in the cDNA are 1-282, 283-393, 394-459, 460-505, 506-644, 645-768, 770-898, 899-1029, 1030-1111, 1112-1242, 1243-1372, 1373-1453, 1454-1518, 1519-1624, 1625-1686, 1687-1802, and 1803-2850. The sizes (in base pairs) of intron 1 to 16 are 14956, 3073, 6891, 1407, 3451, 2913, 1278, 1499, 2290, 659, 2625, 8150, 12553, 4358, 695, and 1765, respectively.



B: MAP3K7 transcripts.

Pseudogene

No pseudogene of MAP3K7/TAK1 was reported in human.

Protein

Note

MAP3K7/TAK1 isoform B contains 606 amino acids (aa) and has a predicted molecular weight of 67 kDa, isoform D contains 491 aa and has a predicted molecular weight of 53.7 kDa, isoform C contains 518 aa and has a predicted molecular weight of 56.7 kDa, and isoform A contains 579 aa and has a predicted molecular weight of 64 kDa.

Description

MAP3K7/TAK1 was first identified by screening a mouse cDNA library for clones that could act as MAPKKKs. The mouse TAK1 cDNA encodes a 579-amino acid protein. The mouse TAK1 protein contains a 300-residue COOH-terminal domain and a putative NH2-terminal protein kinase catalytic domain. The kinase domain has approximately 30% identity to the catalytic domains of Raf-1 and MEKK1. Kondo et al. (1998) cloned human TAK1 from lung cDNA library by screening with mouse TAK1 sequence. Human TAK1 gene encodes a 579-amino-acid protein. The hTAK1 gene has 91.8% identity with the mTAK1 gene at the nucleotide level and has 99.3% to that at the amino acid level. Human TAK1 mRNA with a size of 3.0 kb was observed to express in all the tissues examined by Northern blotting. Kondo et al. (1998) found 2 isoforms of TAK1. Isoform 2 had an insertion of 27 amino acids between amino acids 403 and 404 of isoform 1 which corresponded to the mTAK1 sequence previously identified by Yamaguchi et al. (1995). The two isoforms were expressed at different ratios. Isoform 1 (Variant A) was predominantly expressed in brain, heart and spleen while the isoform 2 (Variant B) was preferentially in the kidney.

Independently, Sakurai et al. (1998) cloned hTAK1 as well as two alternatively spliced isoforms. Human TAK1a (Variant A) has 99.3% identity to murine TAK1. TAK1b (Variant B) had an insertion of 27 amino acids and TAK1c had a deletion of 39 amino acids in the carboxyl-terminal region. The catalytic domains of these three isoforms were 100% identical to that of murine TAK1. The mRNA for TAK1a and TAK1b were expressed in Hela, Jurkat and THP1 cells and TAK1a mRNA expessed predominantly in these cell lines. TAK1c mRNA (Variant C) was expressed only in Hela cells. Northern blot analysis revealed the expression of TAK1 mRNA in all the human tissues examined with the size of 3.2 and 5.7 kb. Dempsey et al. (2000) identified a fourth splice variant of TAK1 called TAK1d (Variant D). TAK1d lacked the two alternative exons and encoded a 491 amino acid protein. TAK1a and b were the most abundant forms in most tissues examined. The carboxyl-end variant TAK1 proteins were unlikely to interfere with the catalytic activity of TAK1 or its interaction with TAB1 since both of which involve the N terminus, but may affect its interaction with TAB2 which associates with the carboxyl-ends of the TAK1 proteins.

Expression

TAK1 was ubiquitously expressed in all tissues. TAK1a (variant A) was the most abundant form in heart, liver, skeletal muscle, ovary, spleen and peripheral blood mononuclear cells; TAK1b (Variant B) was more abundant in brain, kidney, prostate and small intestine; TAK1c (Variant C) is ubiquitously expressed and predominantly in prostate; and TAK1d (Variant D) existed in most tested tissues as a minor variant.

Localisation

TAK1 is mostly localized in cytoplasm.

Function

TAK1 is a member of the serine/threonine protein kinase family. It can be activated by transforming growth factor-beta (TGF-b) and TAK1 deletion mutant missing the N-terminal 22 amino acid is constitutively active. In response to TGF-b, TAK1 can phosphorylate and activate MAP kinase kinases MKK3, MKK4 and MKK6. TAK1 can activate NF-kB in the presence of TAB1. TAK1 is also involved in pro-inflammatory cytokines signaling by activa-ting two kinase pathways. One is a MAPK cascade that leads to the activation of JNK and the other is IkB kinase cascade that causes the activation of NF-kB. It was shown that TRAF6 is a signal mediator that activates IKK and JNK in response

to pro-inflammatory cytokine interleukin 1. The activation of IKK by TRAF6 requires two intermediary factors, TRAF6-regulated IKK activator 1 (TRIKA1) and TRIKA2. TRIKA1 is an ubiquitin-conjugating enzyme complex consisted of Ubc13 and Uev1A. TRIKA1, together with TRAF6, catalyze the formation of a Lys63-linked polyubi-quitin chain that mediates IKK activation. TRIKA2 is composed of TAK1, TAB1 and TAB2. The activation of TAK1 kinase complex is dependent on its polyubiquitination by the TRAF6-Ubc complex and phosphorylation of several residues within the kinase activation loop by yet-to-be identified kinases. The ubiquitinated TAK1 can phosphorylate IKKbeta specifically at S177 and S181. Mutation analysis revealed that a point mutation in the ATP-binding domain of TAK1 (K63W), which abolished its kinase activity, was unable to activate IKK. TAK1 was activated by auto-phosphorylation on Ser192 and dual phosphorylation of Thr-178 and Thr-184 residues within the activation loop. Mutation of a conserved serine residue (Ser192) in the activation loop between kinase domain VII and VIII abrogated the phosphorylation and activation of TAK1. TAK1 is linked to TRAFs by two adaptor proteins TAB2 and TAB3. The interaction of TAB2/TAB3 with TAK1 is essential for the activation of signaling pathway mediated by IL-1.

It was shown that protein phosphatase 2Cepsilon (PP2Cepsilon) inhibited the IL-1 and TAK1 induced activation of MKK4-JNK or MKK3-p38 signaling pathway. PP2Cepsilon inactivated TAK1 by associating with and dephosphorylating TAK1. A type-2A phosphatase, protein phosphatase 6 (PP6), was also identified as a TAK1-binding protein. PP6 repressed TAK1 activity by dephos-phorylating Thr187.

Homology

Human TAK1-like (TAKL) gene encoded a 242 amino acid protein which shared a homology with human TAK1. The amino acid sequences of TAK1 were highly conserved between human and mouse.

Mutations

Note

No mutation of human MAP3K7 was reported.

Implicated in

Breast cancer

Note

TGF-b1 signaling is involved in tumor angiogenesis and metastasis by regulating matrix proteosis. MMP-9 is an important component of these TGF-b1 responses. TAK1 is important for TGF-b1 regulation of MMP9 and metastatic potential of breast cancer cell line MDA-MB231. Suppression of TAK1 reduces the expression of MMP9 and tumor cell invasion. TAK1 and NFkB are required for the human MCF10A-CA1a breast cancer cells to undergo invasion in response to TGF-b. A novel TAB1:TAK1: IKKb: NFkB signaling axis forms aberrantly in breast cancer cells and enables oncogenic signaling by TGF-b.

Lung cancer

Note

Mutation analysis: Study on 39 lung cancer specimens and 16 lung cancer cell lines indicated that hTAK1 was not a frequent target for genetic alternations in lung cancer.

TAK1 variant D activated by siRNAs of specific sequences leads to down stream activation of p38 MAPK and JNK but not NFkB pathway. In human lung cancer cell line NCI-H460 the activation of these pathway cause cell cycle arrest and apoptosis. It suggests that TAK1 D may be a new and promising therapeutic target for the treatment of non-small cell lung cancer. Telomeres are essential elements at the ends of chromosomes that contribute to chromosomal stability. The length of the telomere is maintained by the telomerase holoenzyme, which contains the reverse trans-criptase hTERT as a major enzymatic subunit. The activity of telomerase is absent in most normal human cells because of the downregulation of the hTERT transcript resulting in the shortening of telomeres after each replicative cycle. However, in immortalized cells and cancer cells, the telomere lengths are maintained through an increase in hTERT expression. TAK1 can repress the transcription of hTERT in A549 human lung adenocarcinoma cell line and this repression is caused by recruitment of HDAC to the hTERT promoter.

Cervical carcinoma

Note

Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL), a member of TNFa ligand family, induces apoptosis in a variety of tumor cells. TRAIL induced the delayed phospho-rylation of TAK1 in human cervical carcinoma HeLa cells. TRAIL induced apoptosis was enhanced by downregulation of TAK1.

Head and neck squamous cell carcinoma

Note

NFkB was constitutively activated in head and neck squamous cell carcinoma (HNSCC). Constitutive activation of NFkB in HNSCC was caused by constitutive activation of IKK. Constitutive activa-tion of NFkB is mediated through the TRADD-TRAF2-RIP-TAK1-IKK pathway.

Arthritis

Note

Exercise/joint mobility has therapeutic potency for inflammatory joint diseases such as rheumatoid and osteoarthritis. The biomechanical signals at

physiological magnitudes are potent inhibitors of inflammation induced by NFkB activation in fibrochondrocytes. The biomechanical signals exert anti-inflammatory effects by inhibiting phosphorylation of TAK1.
JNK is essential for metalloproteinase (MMP) gene expression and joint destruction in inflammatory arthritis. TAK1 is an upstream kinase of JNK. TAK1 play an important role for the IL1b induced JNK activation and the JNK induced gene expression in fibroblast-like synoviocytes (FLSs). It suggests that TAK1 is a potential therapeutic target to modulate synoviocyte activation in rheumatoid arthritis (RA).

Inflammation

Note

Pro-inflammatory molecules lipopolysaccharide and Interleukin 1 trigger the activation of TAK1, which in turn activates multiple kinase JNK, p38, IKK and PKB/Akt which are important components of kinase cascades involved in inflammation. Thus TAK1 plays an important role in inflammation.

Human airway epithelial cells

Note

Act1/TRAF6/TAK1-mediated NF-kB activation stimulated by IL-17A regulates gene induction in human airway epithelial cells. Dominant negative TAK1 reduces IL-17A induced gene expression.

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