

Gene Section

Review

BAX (BCL2-associated X protein)

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Identity

Other names: BCL2L4

HGNC (Hugo): BAX

Location: 19q13.33

Local order: Orientation: Plus Strand.

DNA/RNA

Description

The BAX gene, with 6.939 bases in length, consists of 6 exons and 5 intervening introns.

Transcription

The BAX gene is characterized by 5 protein coding transcripts (alpha/psi, beta, delta, epsilon, sigma). Bax-beta encodes the longest isoform (891 bp) of the gene. BAX-alpha/Bax-psi variant is 888 bp in length and codes for a protein isoform that possesses a shorter and different C terminus, as compared with the isoform BAX-beta. The third variant (BAX-delta), which is 741 bp in length, lacks exon 3, whereas it retains the functionally critical C-terminal membrane anchorage region, as well as the BCL2 homology 1 and 2 (BH1 and BH2) domains, although it has a shorter and different C terminus, in comparison with BAX-beta. The fourth identified variant of BAX, which is designated as BAX-epsilon, is 986 bp in length because it contains an extra fragment within the coding region, as well as a distinct 3' coding region and 3' UTR, resulting in a distinct BAX isoform with a shorter and distinct C terminus, as compared with BAX-beta. The fifth identified variant of BAX, BAX-sigma, is 849 bp in length and has also a shorter and different C terminus, when compared with the isoform beta.

Pseudogene

Not identified so far.

Protein

Note

The BAX gene encodes for a 21 kDa protein, named BAX-alpha. It was the first death-inducing member of the BCL2 family to be identified, and it was detected as a protein co-purified with BCL2 in immunoprecipitation studies. The BH3 domain of BAX is essential for its homodimerization and its heterodimerization with BCL2 and BCL-XL. Furthermore, the protein contains a hydrophobic C-terminal region essential for membrane targeting, while BH1 and BH2 domains show homology to pore-forming proteins that contribute to apoptosis. In addition to BAX-alpha, which is the major protein product of the whole gene, BAX undergoes alternative splicing, resulting in the production of distinct protein isoforms. The tumour suppressor p53 is a transcriptional regulator of BAX, since the promoter of the BAX gene possesses four regions with high homology to the consensus p53 binding sites.

Description

The BAX belongs to the BCL2 family of proteins. It is composed of 192 amino acids (21184 kDa), with a calculated molecular mass of 21.184 kDa. The BAX protein exists as a monomer, a homodimer, or as a heterodimer with BCL2, E1B 19K protein, BCL2L1 isoform Bcl-X(L), MCL1 and BCL2A1/A1. It also interacts with SH3GLB1 and HN. It contains one BH3 homology domain.

Localisation

BAX protein has been reported to be localized in the

mitochondria, mitochondrial permeability transition pore complex, mitochondrial outer membrane, endoplasmic reticulum membrane and cytoplasm.

Function

BAX protein heterodimerizes either with members of the BCL2 family of proteins or with tyrosine kinases enabling them to display its proapoptotic function within the cell. It is also implicated in the loss of mitochondrial membrane potential and the release of cytochrome c.

Homology

Human BAX shares 99.5% amino acid identity with Pan troglodytes, 97.4% identity with *Canis lupus familiaris*, 96.4% identity with *Bos Taurus*, 92.2% identity with *Mus musculus*, 91.2% identity with *Rattus norvegicus* and 52.7% identity with *Danio rerio*. In addition, BAX protein presents high homology to the BCL2 protein, containing the conserved regions BH1, BH2 and BH3.

Mutations

Note

One regulatory type of mutation has been identified according to which a guanine substituting adenosine substitution at position 125 (G125A) in the BAX promoter is associated with higher stage of chronic lymphocytic leukemia (CLL) and failure to respond to treatment in CLL patients. Additionally, 110 SNPs, with known clinical association and the following IDs, have been reported in Entrez SNP database: rs62125987, rs62125961, rs61473366, rs61415800, rs60900019, rs59878749, rs59152877, rs57453473, rs57028628, rs56251427, rs56251427, rs55692456, rs55692456, rs36101119, rs36096807, rs36017265, rs35946201, rs35630245, rs35475300, rs35258702, rs34873472, rs34124134, rs34043541, rs28624947, rs28450536, rs12983717, rs12976339, rs12976283, rs12975003, rs11671610, rs11669164, rs11669162, rs11668424, rs11668008, rs11667351, rs11400412, rs11358529, rs11302449, rs10644606, rs7508566, rs7259013, rs7255991, rs7255559, rs4645904, rs4645903, rs4645902, rs4645903, rs4645902, rs4645901, rs4645900, rs4645899, rs4645898, rs4645897, rs4645896, rs4645895, rs4645894, rs4645893, rs4645891, rs4645890, rs4645889, rs4645888, rs4645887, rs4645886, rs4645885, rs4645884, rs4645883, rs4645882, rs4645881, rs4645880, rs4645879, rs4645878, rs4309503, rs3817074, rs3817073, rs2387583, rs1985882, rs1974820, rs1805419, rs1805418, rs1805417, rs1805416, rs1075531, rs1057369, rs1010104, rs1010103, rs1009316, rs1009315, rs905238, rs704243.

Implicated in

Various cancers and diseases

Disease

Colorectal cancer, T-cell acute lymphoblastic leukemia, chronic lymphocytic leukemia (CLL), B cell chronic lymphocytic leukemia, osteomyelitis.

Prognosis

BAX mutations have been found to be associated with positive prognosis in Dukes B2 patients, concerning survival.

The G(-248)A polymorphism in the promoter region of the BAX gene has been associated with reduced BAX expression, advanced disease stage, reduced treatment response and short overall survival in B-cell chronic lymphocytic leukemia (CLL).

Polymorphisms were found for BAX, caused by variation in nucleotide A repeat number at position 360 in the 5'-region of BAX gene. These allelic frequencies of BAX polymorphism were significantly different between males and females and therefore associated with gender-based hematocrite (HCT) differences

Substitution of the nucleotide G-->A at position -248 in the BAX gene was more frequent in patients with osteomyelitis and was associated with a longer lifespan of their peripheral blood neutrophils, probably possessing a significant role in the pathogenesis of osteomyelitis.

In cases of malignancies, the concentration of BAX protein in cancer cells is reduced. In addition, p53-deficient mice show reduced BAX levels, ultimately developing T-cell lymphoma.

Reduction of BAX expression levels is negatively associated with many cancers outcome. It is associated with a variety of adverse prognostic factors such as poor response to radio- and chemotherapy, advanced stage, lymph node metastasis, and reduced disease-free and overall survival in variety cancer types, such as colorectal, pancreatic, breast, head and neck, prostate, small cell lung cancer and gynecological (ovarian) malignancies. More specifically, the enhanced expression of BAX protein is a positive prognostic factor for pancreatic cancer and sensitizes human pancreatic cancer cells to apoptosis induced by chemotherapeutic agents. In the case of stage II colon cancer, treated only with surgery, BAX protein expression may be a predictor for prognosis. In ovarian cancer, BAX protein may have a predictive potential in taxane-platinum-treated patients. Moreover, in resected non-small cell lung cancer, low expression of BAX implies poor prognosis. In addition, in patients with advanced esophageal cancer, treated with

chemoradiotherapy, reduced expression levels of BAX predict poor prognosis. Low expression of BAX was also

significantly associated with poor PFS and OS in nasopharyngeal cancer patients.

In lung cancer, BAX is translocated to the nucleus, enhancing tumour development. Furthermore, mutational analysis of the gene in cases of lung cancer patients revealed the presence of a silent point mutation in codon 184 (TCG>TCA), as well as intronic mutations.

In T cells and endometrium of patients with acute lymphoblastic leukaemia, frameshift mutations have been detected in the BAX gene.

It is a common observation in cases of gastrointestinal cancer, the detection of two specific missense mutations of the BAX gene in codon 169 (Thr > Ala or Thr > Met), which cause inhibition of the proapoptotic activity of the protein and enhance the development of cancer.

Various chemotherapeutic treatments act via up-regulation of the BAX gene to block tumour progression.

BAX is highly expressed in HL-60 but it was found to be hardly expressed in HL-CR cells, a C2-ceramide-resistant HL-60 subline, which has been recently established. These cells showed reduced response to a variety of anticancer drugs including ceramide, doxorubicin, etoposide and cytosine arabinoside.

Hybrid/Mutated gene

Not identified so far.

Abnormal protein

Not identified so far.

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