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Gene Section
Mini Review

BCL2L11 (BCL2-like 11 (apoptosis facilitator))

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Identity

Other names: BAM, BIM, BIM-alpha6, BIM-beta6, BIM-beta7, BOD, BimEL, BimL
HGNC (Hugo): BCL2L11
Location: 2q13
Local order: According to GeneLoc and NCBI Map Viewer, genes flanking BCL2L11 in plus strand direction are: ACOXL 2q13 (acyl-Coenzyme A oxidase-like); PAFAH1P2 2q13 (platelet-activating factor acetylhydrolase, isoform Ib, pseudogene 2).
Note: BCL2L11/BIM is a BH3-only protein from the Bcl-2 family. Bcl-2 family members are the main regulators of programmed cell death via the mitochondrial (intrinsic) apoptotic pathway. Interactions between pro- and anti-apoptotic proteins of the Bcl-2 family decide the fate of cells after a stress signals. BH3-only proteins are activated in response to cellular stresses such as DNA damage. BCL2L11/BIM is one of the most potent BH3-only proteins, shown to mediate apoptosis in response to stimuli such as cytokine deprivation, deregulated calcium flux and microtubule perturbation. In vivo, BCL2L11/BIM is essential for hematopoietic homeostasis, thymocyte negative selection and as a barrier against autoimmunity.

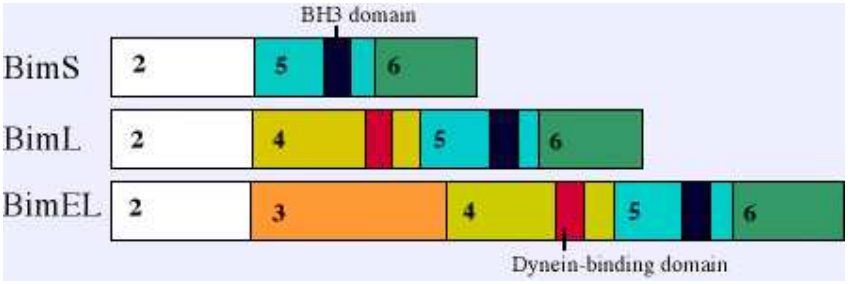
DNA/RNA

Description

The BIM gene spans 47,532 bases, centromere to telomere orientation. Three major isoforms are produced by alternative splicing of 6 exons. These isoforms differ in size and have different apoptotic activity. The three major BIM isoforms are BIMEL (BCL2L11 isoform 1), BIML (BCL2L11 isoform 6) and BIMS (BCL2L11 isoform 9). More than 12 minor BIM isoforms have been cloned from human tissues, and involve exons contained within the large introns. The physiological relevance of these minor isoforms is undetermined.

Transcription

Based on studies using the mouse BIM gene, it was found that the 800-bp region immediately upstream of exon 1 contains the important elements for control of BIM expression. The BIM promoter does not contain a TATA or CAAT box and has the characteristics of a 'TATA-less' promoter.



Schematic diagram of the three major BIM isoforms encoded by the human BIM gene. All three isoforms contain exon 5 (contains the BH3 domain) while only BIML and BIMEL possess the dynein light chain-binding domain encoded by exon 4.

It is very GC-rich and contains six GGGCGG motifs, the recognition site for the transcription factor SP1. There are alternative promoters located in intron 1.

Pseudogene

There are no known pseudogenes for BIM.

Protein

Description

There are three major isoforms of BIM. BIMEL is the longest (198 amino acids and 22.0kDa), followed by BIML (138 amino acids long and 15.8kDa), and BIMS (112 amino acids and 12.3kDa). All three isoforms contain a BH3 domain (but not the BH1, BH2 and BH4 domains found in other members of the family). They have different pro-apoptotic potencies suspected to be due at least in part to differences in interaction with the dynein motor complex.

Expression

BIM is found in many organs and cell types including brain, heart, kidney, liver, lung, ovary, testis, spleen, thymus and trachea. It is also present in hematopoietic, epithelial, neuronal, and germ cells. BIML and BIMEL were found to be co-expressed at similar levels in many cell types, but BIMS is sometimes not detected.

Localisation

In healthy cells, most BIM molecules (BIML and BIMEL) are either bound to DLC1 cytoplasmic dynein light chain and sequestered to the microtubule-associated dynein motor complex or associated with the pro-survival proteins on the mitochondria. A C-terminal hydrophobic domain present in all three major isoforms of BIM localizes the protein to intracytoplasmic membranes.

Function

BIM is a pro-apoptotic member of the Bcl-2 family important in mediating apoptosis in response to various intrinsic stimuli. Studies using BIM knockout mice showed that it plays a large part in maintaining hematopoietic homeostasis. BIM-deficient mice have high numbers of B cells, CD4 and CD8 single-positive T cells, macrophages and granulocytes in their periphery. BIM is also needed for the deletion of auto-reactive B and T cells and on a mixed C57BL/6/129Sv genetic background, BIM-deficient mice developed a fatal systemic lupus erythematosus (SLE)-like disease. Lymphocytes lacking BIM are refractory to a number of stimuli including cytokine deprivation, deregulated calcium ion flux. BIM is also important in turning off immune responses following acute viral infection. BIM cooperates with the death ligand Fas (which triggers the extrinsic pathway) to shut down immune responses following chronic viral infection and to prevent autoimmunity. Experiments using mice deficient for both BIM and pro-survival Bcl-2 demonstrated that Bcl-2 is an essential guardian of BIM. Indeed, removal of just one allele of BIM prevented polycystic kidney disease and restored normal growth of Bcl-2-deficient mice. Loss of both alleles restored a robust hematopoietic system and prevented graying.

Regulation

BIM is regulated by transcriptional control which differs with cell types by transcription factors including FOXO-3a and c-JUN. BIM is also controlled via alternative splicing that produces many different isoforms. BIM is regulated as well by post-translational modifications such as phosphorylation by ERK1, ERK2 and JNK. Phosphorylation-dependant ubiquitylation is thought to regulates BIM's half life.

Interactions

Unlike some BH3-only proteins, BIM is a promiscuous binder of pro-survival proteins and can bind BCL2, BCLX, BCLW, MCL1 and BCL2A1 with high affinity. There are also some reports that BIMS is able to bind BAX (multidomain pro-apoptotic effector of the pathway) and activate it directly, but whether this binding occurs physiologically is unclear.

Homology

BIM belongs to the Bcl-2 family of proteins and contains the BH3 domain which is homologous to the BH3 domains of:

The pro-survival proteins: BCL2, BCLX, BCLW, MCL1, BCL2A1/BFL1, Bcl-B/BOO.

The multidomain pro-apoptotic proteins: BAX, BAK, BOK.

The other BH3-only proteins: PUMA, NOXA, BAD, HRK, BMF, BIK, BID.

Mutations

Note

The BIM gene is located at chromosome 2q13, a region where alterations (mainly deletions) have been reported for 14 cases of human malignancy, mostly hematopoietic in origin. Although loss of Bim by itself does not elevate tumor incidence in mice within the first 12 months of life, it was found that deletion of even a single allele of BIM dramatically accelerates tumor formation in mice expressing the Eμ-myc transgene (which causes myc over-expression in the B cell compartment). These results suggest that, at least in B cells, BIM is an important tumor suppressor.

Implicated in

Mantle cell lymphoma

Note

Down-regulation of BIM expression was discovered in 5 of 7 mantle cell lymphoma cell lines tested while normal expression was found in two MCL cell lines without deletion of 2q13. These results suggest that BIM is the most likely candidate target gene of 2q13 loss/deletion and that its down-regulation may

contribute to tumorigenesis of MCL (Tagawa et al., 2005; Mestre-Escorihuela et al., 2007).

Disease

Mantle cell lymphoma (MCL) is a subtype of B-cell lymphoma characterized by the t(11;14)(q13;q32) translocation that results in the overexpression of the cell cycle regulator CCND1 (cyclin D1). However, experiments with transgenic mice have shown that over-expression of CCND1 is not sufficient to induce lymphomas. Comparative genomic hybridization (CGH) and chromosome banding analyses have been used to identify additional mutations that help CCND1 inducing tumours. Several genomic imbalances have been associated with MCL, and show both gains or losses of genomic DNA. In particular, homozygous deletion at chromosome 2q13, the region that contains the BIM gene, has been observed in several MCL cell lines.

For more information on mantle cell lymphoma, see: www.leukemia-lymphoma.org/attachments/National/br_1172589724.pdf

Alzheimer's disease

Disease

Alzheimer's disease (AD) is a progressive disorder characterized by selective neuron loss and formation of neurofibrillary tangles and of plaques containing amyloid-Beta peptide (ABeta). It results in dementia, a term used to describe a progressive decline in mental functioning. BIM has been implicated in the death of neurons caused by the accumulation of Ab (Biswas et al., 2007).

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