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Gene Section
Review

BAK1 (BCL2-antagonist/killer 1)

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Identity

Other names: BAK; BAK-LIKE; BCL2L7; Bcl2-L-7; CDN1; MGC117255; MGC3887

HGNC (Hugo): BAK1

Location: 6p21.31

Local order: Orientation: minus strand.

Located approximately 380 kb centromeric to the human major histocompatibility complex (MHC) class II region.

Note

The BAK1 gene produces the Bak protein, a pro-apoptotic protein from the Bcl-2 protein family. Either Bak or Bax is required to permeabilize the mitochondrial outer membrane during the mitochondrial (intrinsic) pathway of apoptotic cell death. Bak is a single-pass membrane protein that localises to the mitochondrial outer membrane in healthy cells, while Bax moves to mitochondria during apoptosis. Both Bak and Bax convert to the activated, pro-apoptotic form by undergoing a large conformational change before oligomerising to form apoptotic pores in the mitochondrial outer membrane. Pore formation allows the release of cytochrome c, Smac and other proteins that promote protease (caspase) activity to kill the cell. Thus, Bak/Bax pore formation is a major point of no return in cell death. The activation of Bak (and Bax) is initiated when the cell up-regulates the pro-apoptotic BH3-only members of the Bcl-2 family. Bak activation is blocked if sufficient prosurvival (anti-apoptotic) Bcl-2 family members (e.g. Bcl-xL, Mcl-1, Bcl-2 and A1) are present to sequester the BH3-only proteins and also perhaps the activated Bak and Bax proteins. As cancer cells often express high levels of these prosurvival proteins, several agents that target the prosurvival proteins are being developed as novel cancer therapeutics.

DNA/RNA

Description

The BAK1 gene, with 7748 bases in length, and contains 6 exons. The first exon is non-coding, and most of the largest, final exon is untranslated.

Transcription

The BAK1 gene transcribes a 211 aa protein Bak. A possible 101 aa splice variant, called BAK-like, contains BH1, BH2 and TM domains, but no BH3 domain, with a 2.4 kb transcript of BAK-like detected in most human tissues and exhibiting pro-apoptotic activity. Two other human BAK1 mRNA variants are present in GenBak but may not be expressed: the BakM variant would be 190 aa and lack 21 amino acids in the linker region between alpha-helices 1 and 2; another would be 153 aa with the stop codon upstream of a splice junction and therefore predicted to be subject to nonsense-mediated mRNA decay. However in mice, a similar 151 aa N-Bak that contains only the BH3 domain is reportedly expressed in neurons.

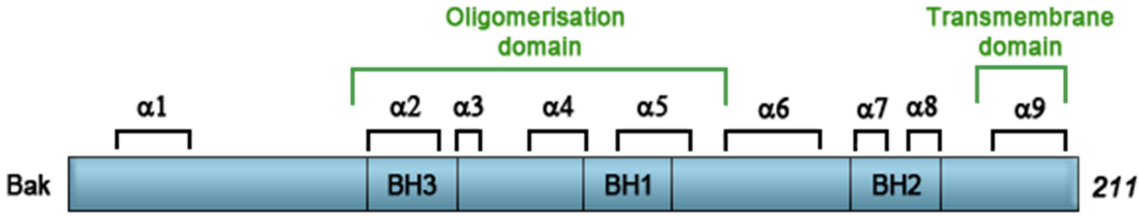
Pseudogene

There are two pseudogenes: Bak2 (chromosome 20) and Bak3 (chromosome 11).

Protein

Note

The BAK1 gene encodes for a 23409 Da protein, named Bak. The Bak cDNA was isolated by three groups by virtue of its protein product interacting with the adenovirus E1B 19K protein, or its homo-



The human Bak protein is 211 aa in length. Bcl-2 homology (BH) domains indicate regions of sequence homology with other Bcl-2 family members, with the BH3 domain being present in all members. The structure of non-activated Bak is similar to that of the prosurvival Bcl-2 family members, with alpha helices 1-9 indicated. The oligomerization domain is important for homo-oligomerization and pore formation, while the transmembrane domain anchors Bak in the mitochondrial outer membrane.

logy to the BH1 and BH2 domains of Bcl-2. The BH3 domain of Bak is essential for its binding to a hydrophobic surface groove on the prosurvival proteins Bcl-xL and Mcl-1. The Bak BH3 domain is also important for binding to a similar hydrophobic groove in another activated Bak molecule to form Bak oligomers and the formation of pores.

Expression

BAK1 mRNA is expressed widely in different tissues as an approximately 2.4 kb transcript. Highest mRNA levels are in the heart and skeletal muscle.

Localisation

The Bak protein is inserted in the mitochondrial outer membrane in healthy cells, while its close homologue Bax translocates to mitochondria after an apoptotic stimulus. A small proportion of Bak has also been detected at the endoplasmic reticulum membrane.

Function

Bak (or Bax) is required to form pores in the mitochondrial outer membrane during apoptotic cell death. The killing activity of Bak is regulated by other members of the Bcl-2 family. For example, certain BH3-only proteins (Bim and Bid) are reported to directly bind Bak to convert it into the activated conformation, while the prosurvival proteins (e.g. Bcl-xL and Mcl-1) can sequester activated Bak and so prevent Bak homo-oligomerization and pore formation. The role of Bak at the ER membrane is unclear.

Homology

Human Bak shares 99.5% amino acid identity with Pan troglodytes, 91.9% identity with Canis lupus familiaris, 86.2% with Bos taurus, 77.2% with Rattus norvegicus. BAK1 is not found in the Danio rerio genome. Human Bak has 53% amino-acid sequence identity with the BH1 and BH2 domains of Bcl-2. Over the full sequence, Bak is 25, 33 and 19% identical to Bcl-2, Bcl-xL and Bax, respectively.

Mutations

Note

Several Bak single point mutations have been associated with autoimmune diseases, aortic aneurysms, and cervical, colorectal and gastric cancers, although the causal relationship is not clear. In addition, around 200 SNPs, with unknown clinical association have been reported in Entrez SNP database.

Somatic

Somatic mutations were increased in uterine cervical carcinoma (6 from 42) compared with non-neoplastic tissue (0 from 32). While an early study reported somatic mutations in 17% of samples of colorectal and gastric cancers in Korean patients, a later study reported no somatic mutations in 192 colorectal and gastric cancers.

Implicated in

Lymphoma and leukemia

Note

Lymphomas and leukemias have high levels of Bcl-2 prosurvival proteins that prevent Bak (and Bax) from inducing apoptosis. New anti-cancer therapies that target prosurvival proteins can activate Bak (or Bax) to re-instate apoptotic cell death. In one example, a new drug, GX15-070, was found to induce apoptosis in mantle cell lymphoma cell lines by binding to Mcl-1 and assist in Bak activation (Pérez-Galán et al., 2007). This drug is in clinical trials for refractory chronic lymphocytic leukemia (Storey, 2008), and is presumably acting by indirectly activating Bak (or Bax).

Gastric and colorectal cancer

Note

The first report of Bak mutations being associated with gastrointestinal cancers was of missense BAK1 mutations in 3 of 24 gastric cancers and 2 of 20 colorectal cancers, with mutations observed only in advanced-stage cancers (Kondo et al., 2000). In another study, BAK1 mutations were also rare (3/107) in patients with gastric adenocarcinomas, and were each associated with late stage disease (Kim et al., 2003). However, no somatic mutations were found in 192 patients with colorectal and gastric cancers, and the rare single-nucleotide substitutions (4/129) were also found in the corresponding normal tissue samples (Sakamoto et al., 2004).

Uterine cervical carcinoma

Note

Possible role for Bak mutation in uterine cervical carcinoma was reported (Wani et al., 2003). In a study of 42 patients, 6 missense (M60V, D30N, D57N, V74M, I80T and V191A) and one silent mutations in the coding region of BAK1 were found, with no mutations detected in 32 non-neoplastic cervix tissue samples. Mutations were associated with late-stage disease and with resistance to chemotherapy, but were not statistically significant due to sample size.

Melanoma

Note

In patients with superficial-spreading melanoma high Bak levels corresponded to improved survival (10-year survival of 62%), while low Bak correlated with low survival (10-year survival of 10%) (Fecker et al., 2006). Bax levels correlated in a similar way.

Autoimmune diseases

Note

Severe autoimmune disease occurs in adult mice following deletion of both Bak and its close relative Bax (Takeuchi et al., 2005). The mice accumulate excess memory B- and T-cells in lymphoid and mesenchymal organs, leading to hepato-splenomegaly, lymphadenopathy, and thymic selection impairment. In humans, similar deletion of two copies of BAK1 (and BAX) does not occur, however less marked changes in Bak protein levels, as well as BAK1 mutations, have been associated with autoimmune disease in rare cases (see below).

Sjogren's syndrome

Note

The Bak protein and its gene mutation may participate in the pathology and susceptibility of Sjogren's syndrome, as Bak was over-expressed in patient autoimmune lesions (Anaya et al., 2005). In a later study three polymorphisms in BAK1 were associated with Sjogren's syndrome (Delgado-Vega et al., 2009).

Coeliac disease

Note

A significant increase in Bak mRNA and protein levels was found in the intestinal lesions of patients with untreated coeliac disease (Chernavsky et al., 2002). The increase in Bak and in apoptosis of enterocytes may be due to increased IFN-gamma signalling.

Graves' disease

Note

Differential expression of Bak (and Bcl-2 and Bax) was associated with apoptosis in thyrocytes and lymphoid follicles, implicating Bak in the pathology of Grave's disease (Hiromatsu et al., 2004).

Multiple sclerosis

Note

Bak mRNA levels were increased in the autoimmune lesions of patients with multiple sclerosis (Banisor and Kalman, 2004).

Ataxia telangiectasia

Note

BAK1 mutations were observed in 8 of 50 patients with ataxia telangiectasia, and were each a silent mutation in exon 2 in codon 14 (TGC>TGT), while none of the healthy controls had such an alteration (Isaian et al., 2009).

Transient platelet loss

Note

Bak can be activated to kill platelets as a side effect of new anti-cancer treatments (Mason et al., 2007; Oltersdorf et al., 2005). The small molecule ABT-737 is a BH3-mimetic that binds specifically to prosurvival proteins (Bcl-2, Bcl-xL, Bcl-w) that are commonly over-expressed in cancers. As platelets contain Bcl-xL as the predominant prosurvival protein guarding Bak, ABT-737 causes Bak activation and transient loss of platelets.

Age-related hearing loss

Note

In mice, Bak-mediated apoptosis exacerbated age-related hearing loss (Someya et al., 2009; Someya et al., 2007). Moreover, hearing loss was decreased if Bak was deleted, if mice were kept on a calorie restriction diet, or given oral supplementation with antioxidants. In keeping with oxidative stress was proposed to induce Bak expression in primary cells from cochlear cells.

Aortic aneurysms

Note

A possible role for Bak mutation in aortic aneurysms was evident in a study of 31 patients with abdominal aortic aneurysms (Gottlieb et al., 2009). Two single nucleotide polymorphisms (R42H and V52A) in the BAK1 gene were present in both diseased (31 cases) and healthy aortic tissue (5 cases), but not in matching blood samples. The authors propose that multiple variants of a gene such as BAK1 might pre-exist within disease-susceptible tissues, and can be selected for during disease progression.

To be noted

Note

The Bak protein plays a role in many diseases due to its central role in apoptotic cell death. However, most Bak dysregulation is not due to mutations in Bak, but rather to altered expression or mutation of Bak regulators (e.g. Bcl-xL and Mcl-1). If Bak (and its homologue Bax) fail

to activate and form a pore in mitochondria, the cell may survive when it was meant to die, and so contribute to cancer. In the opposite scenario, if Bak (or Bax) is activated inappropriately and mitochondria are permeabilized, excessive cell death can occur, for example, in neurodegenerative disease, autoimmune disease, and platelet loss following anti-cancer treatments. Agents that can trigger Bak-mediated apoptosis in a non-targeted way include most anti-cancer agents, while agents that may trigger Bak (and Bax) indirectly by targeting Bcl-2, Bcl-xL, Bcl-w, Mcl-1 and A1, include antisense, antibody and small molecule approaches (Storey, 2008).

References

Chittenden T, Flemington C, Houghton AB, Ebb RG, Gallo GJ, Elangovan B, Chinnadurai G, Lutz RJ. A conserved domain in Bak, distinct from BH1 and BH2, mediates cell death and protein binding functions. EMBO J. 1995 Nov 15;14(22):5589-96

Chittenden T, Harrington EA, O'Connor R, Flemington C, Lutz RJ, Evan GI, Guild BC. Induction of apoptosis by the Bcl-2 homologue Bak. Nature. 1995 Apr 20;374(6524):733-6

Kiefer MC, Brauer MJ, Powers VC, Wu JJ, Umansky SR, Tomei LD, Barr PJ. Modulation of apoptosis by the widely distributed Bcl-2 homologue Bak. Nature. 1995 Apr 20;374(6524):736-9

Herberg JA, Phillips S, Beck S, Jones T, Sheer D, Wu JJ, Prochazka V, Barr PJ, Kiefer MC, Trowsdale J. Genomic structure and domain organisation of the human Bak gene. Gene. 1998 Apr 28;211(1):87-94

Kondo S, Shinomura Y, Miyazaki Y, Kiyohara T, Tsutsui S, Kitamura S, Nagasawa Y, Nakahara M, Kanayama S, Matsuzawa Y. Mutations of the bak gene in human gastric and colorectal cancers. Cancer Res. 2000 Aug 15;60(16):4328-30

Lindsten T, Ross AJ, King A, Zong WX, Rathmell JC, Shiels HA, Ulrich E, Waymire KG, Mahar P, Frauwirth K, Chen Y, Wei M, Eng VM, Adelman DM, Simon MC, Ma A, Golden JA, Evan G, Korsmeyer SJ, MacGregor GR, Thompson CB. The combined functions of proapoptotic Bcl-2 family members bak and bax are essential for normal development of multiple tissues. Mol Cell. 2000 Dec;6(6):1389-99

Wei MC, Lindsten T, Mootha VK, Weiler S, Gross A, Ashiya M, Thompson CB, Korsmeyer SJ. tBID, a membrane-targeted death ligand, oligomerizes BAK to release cytochrome c. Genes Dev. 2000 Aug 15;14(16):2060-71

Wei MC, Zong WX, Cheng EH, Lindsten T, Panoutsakopoulou V, Ross AJ, Roth KA, MacGregor GR, Thompson CB, Korsmeyer SJ. Proapoptotic BAX and BAK: a requisite gateway to mitochondrial dysfunction and death. Science. 2001 Apr 27;292(5517):727-30

Cherñavsky AC, Rubio AE, Vanzulli S, Rubinstein N, de Rosa S, Fainboim L. Evidences of the involvement of Bak, a member of the Bcl-2 family of proteins, in active coeliac disease. Autoimmunity. 2002 Feb;35(1):29-37

Kim SP, Hwang MS, Cho YR, Kwon SY, Kang YN, Kim IH, Sohn SS, Mun KC, Kwon TK, Lee SR, Suh SI. Mutations of the BAK gene are infrequent in advanced gastric adenocarcinomas in Koreans. Cancer Lett. 2003 May 30;195(1):87-91

Wani KM, Huilgol NG, Hongyo T, Shah K, Chatterjee N, Nair CK, Nomura T. Genetic alterations in the coding region of the bak gene in uterine cervical carcinoma. Br J Cancer. 2003 May 19;88(10):1584-6

Banisor I, Kalman B. Bcl-2 and its homologues in the brain of patients with multiple sclerosis. Mult Scler. 2004 Apr;10(2):176-81

Hiromatsu Y, Kaku H, Mukai T, Miyake I, Fukutani T, Koga M, Shoji S, Toda S, Koike N. Immunohistochemical analysis of bcl-2, Bax and Bak expression in thyroid glands from patients with Graves' disease. Endocr J. 2004 Aug;51(4):399-405

Kim JK, Kim KS, Ahn JY, Kim NK, Chung HM, Yun HJ, Cha KY. Enhanced apoptosis by a novel gene, Bak-like, that lacks the BH3 domain. Biochem Biophys Res Commun. 2004 Mar 26;316(1):18-23

Sakamoto I, Yamada T, Ohwada S, Koyama T, Nakano T, Okabe T, Hamada K, Kawate S, Takeyoshi I, Iino Y, Morishita Y. Mutational analysis of the BAK gene in 192 advanced gastric and colorectal cancers. Int J Mol Med. 2004 Jan;13(1):53-5

Anaya JM, Mantilla RD, Correa PA. Immunogenetics of primary Sjögren's syndrome in Colombians. Semin Arthritis Rheum. 2005 Apr;34(5):735-43

Aouacheria A, Brunet F, Gouy M. Phylogenomics of life-or-death switches in multicellular animals: Bcl-2, BH3-Only, and BNip families of apoptotic regulators. Mol Biol Evol. 2005 Dec;22(12):2395-416

Oltersdorf T, Elmore SW, Shoemaker AR, Armstrong RC, Augeri DJ, Belli BA, Bruncko M, Deckwerth TL, Dinges J, Hajduk PJ, Joseph MK, Kitada S, Korsmeyer SJ, Kunzer AR, Letai A, Li C, Mitten MJ, Nettesheim DG, Ng S, Nimmer PM, O'Connor JM, Oleksijew A, Petros AM, Reed JC, Shen W, Tahir SK, Thompson CB, Tomaselli KJ, Wang B, Wendt MD, Zhang H, Fesik SW, Rosenberg SH. An inhibitor of Bcl-2 family proteins induces regression of solid tumours. Nature. 2005 Jun 2;435(7042):677-81

Takeuchi O, Fisher J, Suh H, Harada H, Malynn BA, Korsmeyer SJ. Essential role of BAX,BAK in B cell homeostasis and prevention of autoimmune disease. Proc Natl Acad Sci U S A. 2005 Aug 9;102(32):11272-7

Willis SN, Chen L, Dewson G, Wei A, Naik E, Fletcher JI, Adams JM, Huang DC. Proapoptotic Bak is sequestered by Mcl-1 and Bcl-xL, but not Bcl-2, until displaced by BH3-only proteins. Genes Dev. 2005 Jun 1;19(11):1294-305

Fecker LF, Geilen CC, Tchernev G, Trefzer U, Assaf C, Kurbanov BM, Schwarz C, Daniel PT, Eberle J. Loss of proapoptotic Bcl-2-related multidomain proteins in primary melanomas is associated with poor prognosis. J Invest Dermatol. 2006 Jun;126(6):1366-71

Hetz C, Bernasconi P, Fisher J, Lee AH, Bassik MC, Antonsson B, Brandt GS, Iwakoshi NN, Schinzel A, Glimcher LH, Korsmeyer SJ. Proapoptotic BAX and BAK modulate the unfolded protein response by a direct interaction with IRE1alpha. Science. 2006 Apr 28;312(5773):572-6

Karbowski M, Norris KL, Cleland MM, Jeong SY, Youle RJ. Role of Bax and Bak in mitochondrial morphogenesis. Nature. 2006 Oct 12;443(7112):658-62

Mason KD, Carpinelli MR, Fletcher JI, Collinge JE, Hilton AA, Ellis S, Kelly PN, Ekert PG, Metcalf D, Roberts AW, Huang DC, Kile BT. Programmed anuclear cell death delimits platelet life span. Cell. 2007 Mar 23;128(6):1173-86

Pérez-Galán P, Roué G, Villamor N, Campo E, Colomer D. The BH3-mimetic GX15-070 synergizes with bortezomib in mantle cell lymphoma by enhancing Noxa-mediated activation of Bak. Blood. 2007 May 15;109(10):4441-9

Someya S, Yamasoba T, Weindruch R, Prolla TA, Tanokura M. Caloric restriction suppresses apoptotic cell death in the mammalian cochlea and leads to prevention of presbycusis. Neurobiol Aging. 2007 Oct;28(10):1613-22

Willis SN, Fletcher JI, Kaufmann T, van Delft MF, Chen L, Czabotar PE, Ierino H, Lee EF, Fairlie WD, Bouillet P, Strasser A, Kluck RM, Adams JM, Huang DC. Apoptosis initiated when BH3 ligands engage multiple Bcl-2 homologs, not Bax or Bak. Science. 2007 Feb 9;315(5813):856-9

Xu JX, Hoshida Y, Hongyo T, Sasaki T, Miyazato H, Tomita Y, Aozasa K. Analysis of p53 and Bak gene mutations in lymphoproliferative disorders developing in rheumatoid arthritis. J Cancer Res Clin Oncol. 2007 Feb;133(2):125-33

Dewson G, Kratina T, Sim HW, Puthalakath H, Adams JM, Colman PM, Kluck RM. To trigger apoptosis, Bak exposes its BH3 domain and homodimerizes via BH3:groove interactions. Mol Cell. 2008 May 9;30(3):369-80

Storey S. Targeting apoptosis: selected anticancer strategies. Nat Rev Drug Discov. 2008 Dec;7(12):971-2

Dewson G, Kluck RM. Mechanisms by which Bak and Bax permeabilise mitochondria during apoptosis. J Cell Sci. 2009 Aug 15;122(Pt 16):2801-8

Dewson G, Kratina T, Czabotar P, Day CL, Adams JM, Kluck RM. Bak activation for apoptosis involves oligomerization of dimers via their alpha6 helices. Mol Cell. 2009 Nov 25;36(4):696-703

Gottlieb B, Chalifour LE, Mitmaker B, Sheiner N, Obrand D, Abraham C, Meilleur M, Sugahara T, Bkaily G, Schweitzer M. BAK1 gene variation and abdominal aortic aneurysms. Hum Mutat. 2009 Jul;30(7):1043-7

Someya S, Xu J, Kondo K, Ding D, Salvi RJ, Yamasoba T, Rabinovitch PS, Weindruch R, Leeuwenburgh C, Tanokura M, Prolla TA. Age-related hearing loss in C57BL/6J mice is mediated by Bak-dependent mitochondrial apoptosis. Proc Natl Acad Sci U S A. 2009 Nov 17;106(46):19432-7

Delgado-Vega AM, Castiblanco J, Gómez LM, Diaz-Gallo LM, Rojas-Villarraga A, Anaya JM. Bcl-2 antagonist killer 1 (BAK1) polymorphisms influence the risk of developing autoimmune rheumatic diseases in women. Ann Rheum Dis. 2010 Feb;69(2):462-5

Isaian A, Bogdanova NV, Houshmand M, Movahadi M, Aghamohammadi A, Rezaei N, Atarod L, Sadeghi-Shabestari M, Tonekaboni SH, Chavoshzadeh Z, Hassani SM, Mirfakhrai R, Cheraghi T, Kalantari N, Ataei M, Dork-Bousset T, Sanati MH. BAK, BAX, and NBK/BIK proapoptotic gene alterations in Iranian patients with ataxia telangiectasia. J Clin Immunol. 2010 Jan;30(1):132-7

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