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Gene Section
Mini Review

BAD (BCL2-antagonist of cell death)

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Identity

Other names: BAD (BCLXL/BCL2 associated death promoter homolog; BBC2; BCL2L8 (Bcl-2-like 8 protein)
HGNC (Hugo): BAD
Location: 11q13.1

DNA/RNA

Description

The gene spans 14,9 kb, on reverse strand.

Transcription

Alternate splicing encoding for the same protein.

Protein

Description

168 amino acids, 18,4 kDa.; 'BH3 only' Bcl2 family member (do not possess BH1, 2 and 4 domains). The BH3 domain is essential for proapoptotic function. There are structural similarities between the Bcl2 family proteins and bacterial toxins which form membrane pores after oligomerisation. Do not possess a transmembrane domain in COOH term, in contrast with a number of other BCL2 family members; may be phosphorylated on serine residues (see below).

Expression

Wide.

Localisation

Cytoplasm vs membrane of the mitochondria (see below).

Function

Proapoptotic. protein:

In its inactive form, Bad is phosphorylated. Proteins which phosphorylate BAD are: RAF1, ribosomal S6 kinase 1 (p90/RSK1), AKT/PKB (PI3K-AKT pathway) at Serine 136 (in murine BAD), PKA at Ser 155, PIM1 and PIM2 at Ser 112 (Ser 75, 99, and 118 in human BAD correspond to Ser 112, 136, and 155 in murine BAD respectively). Phosphorylated BAD interacts with 14-3-3 scaffold proteins in the cytoplasm (14-3-3 is a protein which can interact with a hundred other proteins).
Cleavage of the 14-3-3 protein by caspase-3 allows the release of BAD from its association with the 14-3-3 protein and facilitates BAD translocation from the cytosol to the mitochondria. Under apoptotic stimuli also, calcineurin (Ca++ activated protein phosphatase) dephosphorylates BAD, also allowing its dissociation from 14-3-3.
Once BAD is dephosphorylated (posttranslational modification), it is active; it translocates to the outer membrane of the mitochondria (like other proapototic members of the Bcl2 family), and forms heterodimers with BCL-XL (and, to a lesser extend, heterodimers with BCL2 or BCL2L2) to block BCL-XL antiapoptotic function. Dimers BCL-XL/BAD are similar to dimers BCL-XL/BAK.

Homology

Bcl2 family members:
The antiapoptotic members with BH 1 to 4 domains:
BCL2 (18q21), BCL1L1/BCLX-L (20q11), BCL2L2/BCL-W (14q11), BCL1L10/BCL-B/BOO/DIVA (15q21), BCL2A1/BFL1/A1 (15q24), BNIP1/EIB-19K (5q33), MCL1 (1q21)
The proapoptotic members with BH 1 to 3 domains:
BAK1/BCL2L7 (6p21), BAX (19q13), BCL2L13/BCL-Rambo/MIL1 (22q11), BOK/MTD/BCL2L9 (2q37).
The only-BH3 apoptotic members:

BBC3/PUMA (19q13), BCL2L11/BIM/BOD (2q13), BID (22q11), BIK/NBK/BBC1 (22q13), BLK (8p23), BMF (15q14), BNIP3/NIP3 (10q26), BMIP3L/NIX (8p21), HRK/DP5/BID3 (12q24), PMAIP1/NOXA (18q21).

References

Yang E, Zha J, Jockel J, Boise LH, Thompson CB, Korsmeyer SJ. Bad, a heterodimeric partner for Bcl-XL and Bcl-2, displaces Bax and promotes cell death. Cell. 1995 Jan 27;80(2):285-91

del Peso L, González-García M, Page C, Herrera R, Nuñez G. Interleukin-3-induced phosphorylation of BAD through the protein kinase Akt. Science. 1997 Oct 24;278(5338):687-9

Kelekar A, Chang BS, Harlan JE, Fesik SW, Thompson CB. Bad is a BH3 domain-containing protein that forms an inactivating dimer with Bcl-XL. Mol Cell Biol. 1997 Dec;17(12):7040-6

Ottilie S, Diaz JL, Horne W, Chang J, Wang Y, Wilson G, Chang S, Weeks S, Fritz LC, Oltersdorf T. Dimerization properties of human BAD. Identification of a BH-3 domain and analysis of its binding to mutant BCL-2 and BCL-XL proteins. J Biol Chem. 1997 Dec 5;272(49):30866-72

Wang HG, Pathan N, Ethell IM, Krajewski S, Yamaguchi Y, Shibasaki F, McKeon F, Bobo T, Franke TF, Reed JC. Ca2+-induced apoptosis through calcineurin dephosphorylation of BAD. Science. 1999 Apr 9;284(5412):339-43

Datta SR, Katsov A, Hu L, Petros A, Fesik SW, Yaffe MB, Greenberg ME. 14-3-3 proteins and survival kinases cooperate to inactivate BAD by BH3 domain phosphorylation. Mol Cell. 2000 Jul;6(1):41-51

Cowburn AS, Cadwallader KA, Reed BJ, Farahi N, Chilvers ER. Role of PI3-kinase-dependent Bad phosphorylation and altered transcription in cytokine-mediated neutrophil survival. Blood. 2002 Oct 1;100(7):2607-16

Moriishi K, Koura M, Matsuura Y. Induction of Bad-mediated apoptosis by Sindbis virus infection: involvement of pro-survival members of the Bcl-2 family. Virology. 2002 Jan 20;292(2):258-71

Adachi M, Zhang YB, Imai K. Mutation of BAD within the BH3 domain impairs its phosphorylation-mediated regulation. FEBS Lett. 2003 Sep 11;551(1-3):147-52

Won J, Kim DY, La M, Kim D, Meadows GG, Joe CO. Cleavage of 14-3-3 protein by caspase-3 facilitates bad interaction with Bcl-x(L) during apoptosis. J Biol Chem. 2003 May 23;278(21):19347-51

Yan B, Zemskova M, Holder S, Chin V, Kraft A, Koskinen PJ, Lilly M. The PIM-2 kinase phosphorylates BAD on serine 112 and reverses BAD-induced cell death. J Biol Chem. 2003 Nov 14;278(46):45358-67

Bonnefoy-Berard N, Aouacheria A, Verschelde C, Quemeneur L, Marçais A, Marvel J. Control of proliferation by Bcl-2 family members. Biochim Biophys Acta. 2004 Mar 1;1644(2-3):159-68

Petros AM, Olejniczak ET, Fesik SW. Structural biology of the Bcl-2 family of proteins. Biochim Biophys Acta. 2004 Mar 1;1644(2-3):83-94

Schinzel A, Kaufmann T, Borner C. Bcl-2 family members: integrators of survival and death signals in physiology and pathology [corrected]. Biochim Biophys Acta. 2004 Mar 1;1644(2-3):95-105

Sorenson CM. Bcl-2 family members and disease. Biochim Biophys Acta. 2004 Mar 1;1644(2-3):169-77

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