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 proapoptotic 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/BBCl (22q13), BLK (8p23), BMF (15q14), BNIP3/NIP3 (10q26), BMIP3L/NIX (8p21), HRK/DP5/BID3 (12q24), PMAIP1/NOXA (18q21).

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