Quick Guide

Bcl10

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What is it? Bcl10 is an intracellular signalling protein which positively regulates lymphocyte proliferation by connecting antigen receptor-induced signals of B and T cells to the activation of the transcription factor NF-κB.

It first came to prominence... as a candidate gene near the chromosomal translocation t(1;14)(p22;q32) found in B-cell lymphomas of the mucosa associated lymphoid tissue (MALT). At the same time, Bcl10 was found by database searches for novel proteins with a caspase recruitment domain (CARD). Bcl stands for B cell lymphoma or leukemia, and is used for genes found through chromosomal translocations associated with these diseases. Some other Bcl proteins include the cell cycle regulatory protein Bcl1/Cyclin D1 and the anti-apoptotic protein Bcl2.

Previously ascribed function... A pro-apoptotic function was given to Bcl10 based on overexpression studies and on the characterization of genetic mutations predicting the expression of truncated, potentially non-functional forms of Bcl10 in lymphomas and other tumors.

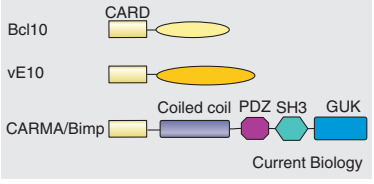

Figure 1. Bcl10 and its relatives
Bcl10, viral E10 and the three CARD-containing MAGUKs (CARMA1, 2 and 3/Bimp3, 2 and 1/CARD11, 14 and 10) contain an amino-terminal CARD motif. The viral protein has a carboxy-terminal consensus site (CysCys) for lipid modification through a geranylgeranyl moiety. The CARMA/Bimp homologues contain other protein-protein interaction domains (coiled coil, PDZ, SH3 and GUK).

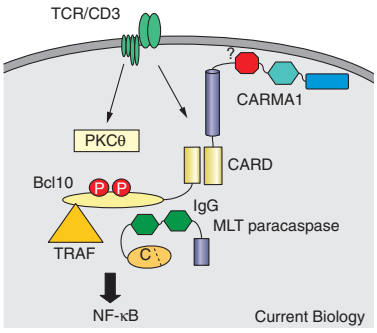

Figure 2. Working model for Bcl10.
Bcl10 is a positive regulator of antigen-receptor induced NF-κB activation. Members of the TRAF (TNF receptor associated factor) family of scaffolding proteins may relay Bcl10 to the NF-κB signalling machinery. An interaction of Bcl10 with PKCθ is suggested from the similar phenotypes of the PKCθ and Bcl10 knock-out mice — lack of NF-κB-dependent T-cell activation.

Can we live without it? Probably not, about one third of Bcl10 deficient mice embryos develop lethal exencephaly. Surviving mice are severely immunodeficient, and their B and T lymphocytes are defective in antigen receptor-induced cellular activation and proliferation.

Any related proteins? Several. Its closest homologue is the equine herpesvirus-2 protein E10, which has an amino-terminal CARD motif of about 50% sequence identity with Bcl10. Three CARD-containing proteins of the membrane-associated guanylate kinase (MAGUK) family, designated CARMA (CARD-MAGUK) or Bimp (Bcl10-interacting MAGUK protein) also have considerable CARD sequence identity with Bcl10.

How does Bcl10 work? It's not clear, but the molecular mechanism probably involves binding of Bcl10's amino-terminal portion to the CARMA proteins via a CARD–CARD interaction, and binding of its carboxy-terminal portion to MLT1, a caspase-like molecule identified from another recurrent chromosomal translocation of MALT lymphomas.

How does its herpesviral homologue work? vE10 is targeted to the plasma membrane via a covalent lipid modification where it induces phosphorylation and membrane recruitment of Bcl10, leading to the constitutive activation of the transcription factor NF-κB.

Is Bcl10 mutated in tumors? Translocation of Bcl10 to the immunoglobulin heavy chain locus in the MALT-associated chromosomal translocation t(1;14)(p22;q32) predicts its deregulated expression because of the proximity of potent B cell transcriptional enhancers or the generation of mutant forms of Bcl10 due to the action of the immunoglobulin somatic hypermutation mechanism. Mutated forms of Bcl10 encoding carboxy-terminal truncations have been found, but whether they are expressed in MALT is an ongoing debate. The phenotype of the Bcl10-deficient mice suggests that upregulation of Bcl10 or expression of an active form of Bcl10 might mimic a constitutive NF-κB signal from the antigen receptor and promote antigen independent growth and lymphoma progression.

Where can I find out more?

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