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SnapShot: BCL-2 Proteins

J. Marie Hardwick and Richard J. Youle

Johns Hopkins, Baltimore, MD 21205, USA and NIH/NINDS, Bethesda, MD 20892, USA

BCL-2 family proteins regulate apoptotic cell death. BCL-2 proteins localize to intracellular membranes such as endoplasmic reticulum and mitochondria, and some family members translocate from the cytoplasm to mitochondria following a cell death stimulus. The prototypical family member Bcl-2 was originally identified at chromosome translocation breakpoints in human follicular lymphoma and was subsequently shown to promote tumorigenesis by inhibiting cell death rather than by promoting cell-cycle progression.

BCL-2 family proteins have traditionally been classified according to their function and their BCL-2 homology (BH) motifs. The general categories include multidomain antiapoptotic proteins (BH1-BH4), multidomain proapoptotic proteins (BH1-BH3), and proapoptotic BH3-only proteins (see Table 1). In the traditional view, anti-death BCL-2 family members in healthy cells hold pro-death BCL-2 family members in check. Upon receiving a death stimulus, BH3-only proteins inactivate the protective BCL-2 proteins, forcing them to release their pro-death partners. These pro-death BCL-2 family proteins homo-oligomerize to create pores in the mitochondrial outer membrane, resulting in cytochrome *c* release into the cytoplasm, which leads to caspase activation and cell death. An alternative model suggests that anti-death BCL-2 proteins bind and inhibit a subset of BH3-only proteins (e.g., BID) that otherwise directly induce the oligomerization of BAX or BAK. However, not all available data are consistent with these models, and some family members appear to lack cell death regulatory functions. Therefore, BCL-2 family proteins can also be classified based on their amino acid similarities and three-dimensional structures (see Table 2). Growing attention is being paid to alternative mechanisms of action for BCL-2 family proteins, including the regulation of mitochondrial dynamics, autophagy, energetics, and other functions.

There are three BCL-2-related proteins in the nematode *Caenorhabditis elegans*, including CED-9, EGL-1, and CED-13. CED-9 is required for survival, inhibits CED-4-mediated activation of CED-3 (a caspase), and is inhibited by the BH3-only proteins EGL-1 and CED-13 during cell death; CED-9 can exhibit pro-death activity and may regulate mitochondrial dynamics. The fruit fly *Drosophila melanogaster* encodes two BCL-2 family proteins. The functions of these in cell death are uncertain.

Viral BCL-2-like proteins are encoded by different types of DNA viruses, including examples not listed. Many viral BCL-2-like proteins inhibit apoptotic cell death, but others may alter their animal hosts and host cells during the course of infection by alternative functions.

Protease cleavage sites have been identified in the N-terminal regions of a number of BCL-2 family proteins, including BCL-2, BCL-x_L, MCL-1, BAX, BID (cleaved to generate truncated tBID with exposed BH3 domain), and BAD. Cleavage may inactivate anti-death activity or activate pro-death activity.

Three-dimensional structures for all indicated proteins are found at the Protein Data Bank (PDB) (<http://www.rcsb.org/pdb/home/home.do>) as are additional domain structures for BAD, BNIP3L, and Beclin. Other available structures include a BH3 motif in Beclin/Atg6/Vps30 binding to the cleft of BCL-2 and a structure of the viral gHV68 BCL-2 homolog M11. BNIP3 belongs to a different protein family.

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Table 1
BCL-2 Family Proteins—Traditional Classification

Cell Death Function	BH Motifs	Overall Amino Acid Similarity	BCL-2 Fold	Example Proteins
Antiapoptotic	Multiple	+	+	BCL-2, BCL-x _L , viral BHRF1
Proapoptotic	Multiple	+	+	BAX, BAK
Proapoptotic BH3-only	BH3-only	–	+ or –	BID, BAD, BIM, PUMA, others

Table 2
BH Family Proteins—Structural Classification

Group	≥1 BH Motif	Overall Amino Acid Similarity	BCL-2 Fold	Example Proteins
BCL-2	+	+	+	BCL-2, BAX
BCL-2	+ or ±	–	+	BID, Viral FIL
BH3-only	+	–	–	BIM, Beclin