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The Bcl-2 Protein Family: Arbiters of Cell Survival

Jerry M. Adams and Suzanne Cory

REVIEW

Bcl-2 and related cytoplasmic proteins are key regulators of apoptosis, the cell suicide program critical for development, tissue homeostasis, and protection against pathogens. Those most similar to Bcl-2 promote cell survival by inhibiting adapters needed for activation of the proteases (caspases) that dismantle the cell. More distant relatives instead promote apoptosis, apparently through mechanisms that include displacing the adapters from the pro-survival proteins. Thus, for many but not all apoptotic signals, the balance between these competing activities determines cell fate. Bcl-2 family members are essential for maintenance of major organ systems, and mutations affecting them are implicated in cancer.

Life requires death. Multicellular organisms eliminate redundant, damaged, or infected cells by a stereotypic program of cell suicide termed apoptosis (*1*). Interest in the control of apoptosis has grown exponentially with the recognition of its vital roles in normal development, tissue homeostasis, and defense against pathogens (*2*), and the realization that disturbed apoptosis may contribute to cancer and to autoimmune and degenerative diseases (*3*, *4*). Penetrating genetic analysis of the nematode *Caenorhabditis elegans* revealed two loci, *ced-3* and *ced-4*, essential for programmed cell death during worm development, and a third, *ced-9*, that could prevent their action (*5*). The first mammalian regulator emerged when *bcl-2*, the gene activated by chromosome translocation in human follicular lymphoma (*6*), was unexpectedly found to permit the survival of cytokine-dependent hematopoietic cells, in a quiescent state, in the absence of cytokine (*7*). This discovery, verified in other cell lines and transgenic mice (*3*), established that cell survival and proliferation were under separate genetic control and that disturbances in both were likely to contribute to neoplasia.

The mechanism of apoptosis is remarkably conserved (Fig. 1), albeit with the expected greater complexity in mammals. CED-9 and Bcl-2 proved to be functional and structural homologs (*8*), and their survival function is opposed either by close relatives such as Bax (*9*) or by distant cousins such as mammalian Bik (also known as Nbk) (*10*) and nematode EGL-1 (*11*). The execution phase was illuminated when CED-3 proved to belong to a new family of proteases, now called caspases, whose sequential activation and cleavage of key target proteins dismantles the cell (*12*). Synthesis of caspases as minimally active precursors precludes their premature activation, and the long-mysterious CED-4 and its mammalian homolog Apaf-1 (*13*) are now recognized to be adapters for facilitating the autocatalysis that initiates the proteolytic cascade (*12*).

The growing Bcl-2 family can somehow register diverse forms of intracellular damage, gauge whether other cells have provided a positive or negative stimulus, and integrate these competing signals to determine whether the cell is "to be or not to be." Certain death signals, however, such as those from the CD95 "death receptor" (also known as Fas or APO-1) (*14*), seem largely to bypass the step controlled by Bcl-2 (Fig. 1 and below). Recent insights about the biochemical and biological functions of the Bcl-2 family and its role in neoplasia are the focus of this review. Related issues are addressed in previous reviews (*3*, *4*, *15*, *16*) and the accompanying articles (*12*, *14*, *17*, *18*).

Opposing Factions in the Family

At least 15 Bcl-2 family members have been identified in mammalian cells and several others in viruses (*3*). All members possess at least one of four conserved motifs known as Bcl-2 homology domains (BH1 to BH4) (Fig. 2). Most pro-survival members, which can inhibit apoptosis in the face of a wide variety of cytotoxic insults, contain at least BH1 and BH2, and those most similar to Bcl-2 have all four BH domains. The two pro-apoptotic subfamilies differ markedly in their relatedness to Bcl-2. Bax, Bak, and Bok (also called Mtd), which contain BH1, BH2, and BH3, resemble Bcl-2 fairly closely. In contrast, the seven other known mammalian "killers" possess only the central short (9 to 16 residue) BH3 domain; they are otherwise unrelated to any known protein, and only Bik and Blk are similar to each other. These "BH3 domain" proteins (*19*) may well represent the physiological antagonists of the pro-survival proteins, because programmed cell death in *C. elegans* requires EGL-1 (Fig. 1), which binds to and acts via CED-9 (*11*). BH3 is essential for the function of the "killers," including EGL-1 (*11*, *19*).

Pro- and anti-apoptotic family members can heterodimerize and seemingly titrate one another's function, suggesting that their relative concentration may act as a rheostat for the suicide program (*9*). Mutagenesis established that the BH1, BH2, and BH3 domains strongly influence homo- and hetero-dimerization (*19*, *20*), and the three-dimensional structure of Bcl-x_L provided the explanation (Fig. 3). Coalescence of the α helices in its BH1, BH2, and BH3 regions creates an elongated hydrophobic cleft, to which a BH3 amphipathic α helix can bind (*21*). BH3-cleft coupling, reminiscent of ligand-receptor engagement, may account for all dimerization within the family. Hence, Bax and its analogs may prove to have alternate conformations: one like Bcl-x_L and another with BH3 rotated outside to allow its insertion into the groove of a pro-survival protein (*21*).

Heterodimerization is not required for pro-survival function (*22*), contrary to early indications (*20*). For pro-apoptotic activity, heterodimerization is essential in the BH3 domain group (*19*), but less so for those of the Bax group, which may have an independent cytotoxic impact (below). Indeed whether Bax binds to Bcl-2 inside cells has become controversial, because the detergents used in cell lysis facilitate their association (*23*).

Some death agonists may preferentially target subsets of the death

The authors are at the Walter and Eliza Hall Institute of Medical Research, Post Office Royal Melbourne Hospital, Victoria 3050, Australia.

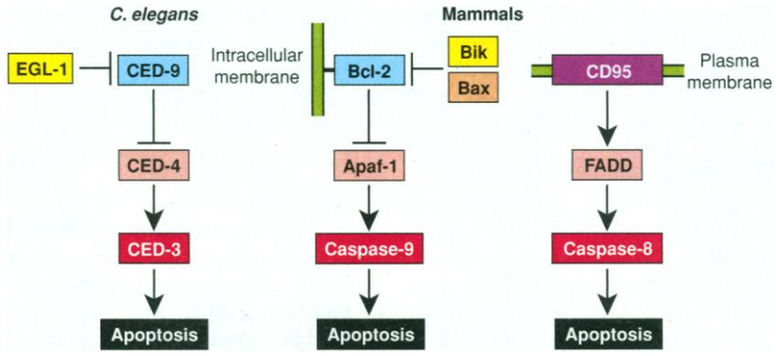


Fig. 1. Pathways to cell death in *C. elegans* and mammals. The CED-9/Bcl-2 family integrates positive and negative signals and arbitrates whether apoptosis should occur; activation of CED-4/Apaf-1 commits to apoptosis, and CED-3/caspases mediate the death process. In mammalian cells, the Bcl-2 family rules on signals from diverse cytotoxic stimuli (for example, cytokine deprivation and exposure to glucocorticoids, DNA damage, or staurosporine). However, the signal induced by engagement of the "death receptor" CD95 proceeds primarily through the adaptor FADD, which directly activates caspase-8 and largely bypasses the Bcl-2 family (see text).

repressors. Bok, for example, interacts with Mcl-1 and the Epstein-Barr viral protein BHRF1 but not with Bcl-2, Bcl-x_L, or Bcl-w (*24*). Within the BH3 group, Bid is promiscuous, binding to Bax and Bak as well as to the anti-apoptotic proteins, but the others bind only to certain of the death inhibitors (*25*).

Bcl-2 resides on the cytoplasmic face of the mitochondrial outer membrane, endoplasmic reticulum (ER), and nuclear envelope and may register damage to these compartments and affect their behavior, perhaps by modifying the flux of small molecules or proteins (*15*, *17*). Although the COOH-terminal hydrophobic domain of Bcl-2 (Fig. 2) is important in membrane docking, its deletion does not abrogate Bcl-2 survival function (*26*). Furthermore, only a fraction of Bcl-x_L resides on membranes, and Bax is cytosolic before an apoptotic stimulus (*23*), even though both, like most other family members, bear hydrophobic domains (Fig. 2). We surmise that Bcl-2 and its relatives dock on specific proteins on each organelle. Potential docking sites on the ER include the integral membrane proteins Bap31 and BI-1 (*27*).

Potential Mechanisms

In accord with *C. elegans* genetics (*5*), biochemical evidence suggests that the pro-survival proteins may function by directly inhibiting the ability of CED-4–like molecules to activate caspases (Fig. 4). CED-9 and Bcl-x_L can bind to CED-4, which also binds CED-3 and stimulates its activation (*28*, *29*). The BH4 region of Bcl-x_L is required for pro-survival activity and interaction with CED-4 and might serve as a direct binding site for CED-4 or modulate the overall Bcl-x_L structure (*30*). Bcl-x_L has recently been reported to bind also to the CED-4–like portion of Apaf-1, whereas procaspase-9 binds to its NH_2-terminal caspase recruitment domain (CARD) (*31*) (Fig. 4). Bcl-x_L may inhibit the association of Apaf-1 with procaspase-9 and thereby prevent caspase-9 activation. Pro-apoptotic relatives like Bik may free CED-4/Apaf-1 from the death inhibitor (*28*, *31*) (Fig. 4).

The pro-survival proteins also seem to maintain organelle integrity. Bcl-2 directly or indirectly prevents the release from mitochondria of cytochrome c, which [along with adenosine triphosphate (ATP)] may facilitate a change in Apaf-1 structure to allow procaspase-9 recruitment and processing (*13*, *15*, *17*) (Fig. 4). Precluding cytochrome c release is unlikely to be the sole function of Bcl-2, because Bcl-2 can protect cells after much has been released, and microinjected cytochrome c does not kill all cell types (*17*). Whether organelle damage is part of the trigger for apoptosis or an amplification step remains unclear.

The structure of Bcl-x_L (particularly its α5 and α6 helices) (Fig. 2) resembles the membrane insertion domains of bacterial toxins, prompting the hypothesis that members having the BH1 and BH2 domains function by forming pores in organelles such as mitochondria

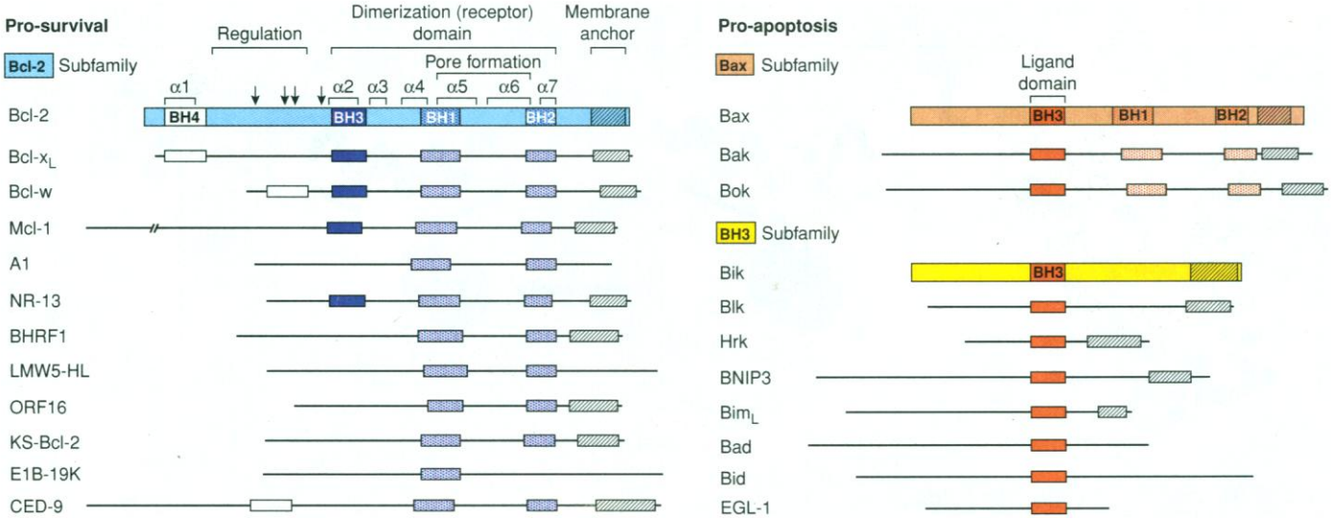


Fig. 2. The wider Bcl-2 family. Three subfamilies are indicated: The Bcl-2 cohort promotes cell survival, whereas the Bax and BH3 cohorts facilitate apoptosis. BH1 to BH4 are conserved sequence motifs. The functional domains of Bcl-2 are described in the text. The Bax subfamily resembles the Bcl-2 subfamily but lacks a functional BH4 domain. Except for the BH3 domain, the BH3 subfamily is unrelated to Bcl-2 (*19*). α1 to α7 indicate helices identified in Bcl-x_L, in which a core of two hydrophobic helices (α5 and α6) is flanked by five amphipathic helices, and a flexible (nonconserved) loop connects α1 with α2 (*21*). Arrows indicate Ser and Thr residues phosphorylated in Bcl-2 (see text). All proteins compared are mammalian (usually human), except for NR-13 (chicken), CED-9, and EGL-1 (*C. elegans*), and the viral proteins BHRF1, LMW5-HL, ORF16, KS-Bcl-2, and E1B-19K.

(*21*). Bcl-x_L, Bcl-2, and Bax do form channels in lipid bilayers in vitro, and those created by Bax and Bcl-2 have distinct characteristics, including some ion selectivity (*17*, *32*). To date little data link this ability to control of apoptosis, although a more plausible case can be made for killing by Bax (below).

Caspase-Independent Death

While most pro-apoptotic proteins probably directly antagonize pro-survival proteins via their BH3 "death ligands" (Fig. 4), the Bax group may also kill by damaging organelles. Yeast have provided tantalizing evidence. Although *Saccharomyces cerevisiae* and *Schizosaccharomyces pombe* apparently lack Bcl-2–like proteins, CED-4, and caspases, both are killed by Bax and Bak (*33*), and Bcl-2 can protect, apparently by preventing mitochondrial disruption (*17*). BH3 deletion ablates toxicity (*33*), implicating homodimerization. These findings seem to flag a form of death predating the caspases, which may well still be extant in mammals. Even in the presence of a caspase inhibitor, overexpression of Bax-like proteins, or their enforced dimerization, kills mammalian cells, provoking DNA condensation and membrane alterations without caspase activation or DNA degradation (*34*). Bax and Bax-like proteins might mediate caspase-independent death via channel-forming activity (above), which could promote the mitochondrial permeability transition or puncture the mitochondrial outer membrane (*17*). However, because the evidence for caspase-independent death relies largely on overexpression and chemical inhibitors, its physiological relevance remains uncertain.

Regulation of Family Members

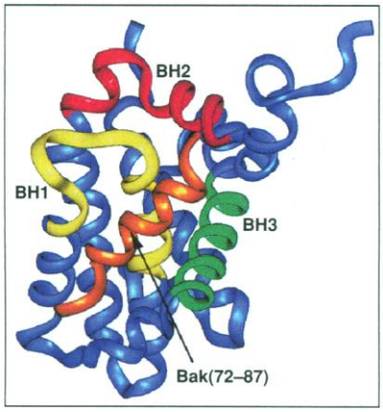
The Bcl-2 family is regulated by cytokines and other death-survival signals at different levels. Several pro-survival genes are induced transcriptionally by certain cytokines (*35*), and *bax* is induced in some cells as part of the p53-mediated damage response (*36*) (below). Cytokine-mediated cell survival, however, also involves posttranslational regulation. In hematopoietic cells stimulated by interleukin-3 (IL-3), Bad is phosphorylated and the product sequestered in the cytosol by 14-3-3 proteins, precluding its inhibition of Bcl-x_L (*37*). The signal from the receptor seems to be transduced by phosphoinositide 3-kinase through the kinase Akt to Bad. For pro-survival members, phosphorylation may both augment and suppress activity. Known sites lie in the nonconserved flexible loop (Fig. 2), thought to negatively regulate Bcl-x_L activity (*38*). Bcl-2 may be activated by Ser^{70} phosphorylation but inactivated, or otherwise altered, by phosphorylation of several loop sites, perhaps by Jun kinase (JNK) (*39*). Sustained activation of the JNK or p38 kinase pathways, perhaps after caspase activation, has been implicated in apoptosis (*40*), and Bcl-2 family members would be appealing targets.

Physiological Roles

Bcl-2 protects against diverse cytotoxic insults—for example, γ- and ultraviolet-irradiation, cytokine withdrawal, dexamethasone, staurosporine, and cytotoxic drugs (*3*). Culling of autoreactive T cells in the thymus, however, is not blocked by a *bcl-2* transgene (*41*). Furthermore, Bcl-2 protects poorly against apoptosis of lymphocytes induced by ligation of the receptor CD95 (*42*). Thus, in at least the lymphoid system, the major CD95-induced pathway, which activates caspase-8 (*12*, *17*), bypasses the Bcl-2–inhibitable step common to most stress pathways (*42*) (Fig. 1). CD95 may also trigger alternative pathways, because Bcl-2 reportedly protects against CD95-induced death in certain cell types (*43*).

Although pro-survival genes appear to have equivalent effector function, "knockout" mice have established that each maintains particular organ systems. Despite the widespread Bcl-2 expression during embryogenesis, *bcl-2*$^{-/-}$ mice develop normally, and only later exhibit marked lymphoid apoptosis, melanocyte, neuronal, and intestinal lesions, and terminal kidney disease (*44*). In contrast, *bcl-x*$^{-/-}$ mice die in utero as a result of massive death of erythroid and neuronal cells, and chimera experiments suggest that their B cell but not T cell development is impaired (*45*). Adult *bcl-w*$^{-/-}$ mice are healthy, but spermatogenesis is ablated by the death of germ cells and supporting Sertoli cells (*46*). Most likely, every cell type is protected by at least one of the guardians.

As expected for loss of a pro-apoptotic gene, *bax*$^{-/-}$ mice exhibit increases in some cell types: granulosa cells, certain neurones, lymphocytes, and immature germ cells (*47*, *48*). Their thymocytes exhibit normal sensitivity to γ-irradiation, so Bax is not essential for p53-dependent apoptosis (*48*). Crosses of knockout mice (*49*) revealed that Bax is responsible for much of the neuronal death in *bcl-x*$^{-/-}$ mice and the lymphoid in *bcl-2*$^{-/-}$ mice.



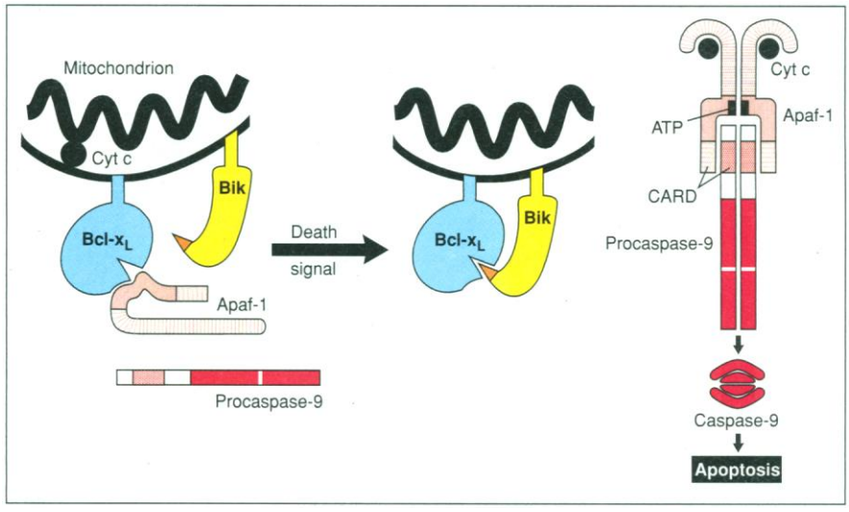


Fig. 3 (left). Structure of Bcl-x_L with a BH3 peptide bound. [Derived from studies by Sattler *et al.* (*21*)]. The BH1, BH2, and BH3 regions of Bcl-x_L are shown in yellow, red, and green, respectively. The Bak BH3 peptide (16–amino acid) binding to the groove is in orange. **Fig. 4 (right).** Model for Apaf-1 regulation by the Bcl-2 family. Bcl-x_L (or another pro-survival member) may bind Apaf-1 and prevent it from activating procaspase-9 (or another initiating procaspase). A death signal may, for example, provoke interaction of a BH3 family member (here Bik) or perhaps a Bax family member with Bcl-x_L, preventing it from neutralizing Apaf-1. In the presence of cytochrome c released from mitochondria and ATP, Apaf-1 can then bind to procaspase-9 and promote its dimerization and activation by autocatalysis (*12*, *13*). Caspase-9 subsequently activates effector caspases. CARD denotes a protein association domain. Many questions about this model remain (see text).

Cell Cycle Impact

The Bcl-2 family can modulate cell cycle progression (*48*, *50*, *51*). Under suboptimal growth conditions, Bcl-2 promotes exit into quiescence and retards reentry into cycle. This effect is genetically separable from its survival function, because cell cycle inhibition but not pro-survival function is ablated by a deletion in the nonconserved loop or mutation of tyrosine-28 (*52*). The inhibition might involve a protein that can bind that region of Bcl-2, such as the phosphatase calcineurin (*53*). T cells expressing Bcl-2 make less IL-2, the cytokine required for their progression into S phase, apparently because of reduced nuclear translocation of the transcription factor NFAT (*51*). NFAT transit requires comigrating calcineurin, which Bcl-2 may sequester on cytoplasmic membranes (*53*). Whatever the mechanism, the cell cycle–inhibitory effect may have evolved to reduce the oncogenic impact of Bcl-2 (below).

Involvement in Cancer

Apoptosis normally eliminates cells with damaged DNA or an aberrant cell cycle, that is, those most likely to engender a neoplastic clone. With the discovery of the anti-apoptotic function of the *bcl-2* oncogene (*7*), the concept emerged that a raised threshold for apoptosis represents a central step in tumorigenesis (*3*). The oncogenic impetus of *bcl-2* translocation, found in most follicular lymphomas and some cases of diffuse large cell lymphoma and chronic lymphocytic leukemia, was verified in *bcl-2* transgenic mice (*3*). These mice all accumulated excess noncycling mature B lymphocytes, and the lymphomas that eventuated often carried *myc* translocations, which can also accompany progression of follicular lymphoma. Synergy between *myc* and *bcl-2* in tumorigenesis, first noted in vitro (*7*), was demonstrated for lymphoma and for breast cancer in bi-transgenic mice (*54*). Their cooperativity may in part reflect the ability of each gene to counter an anti-oncogenic impulse of the other: Under the limiting growth conditions pertaining in vivo, Myc over-expression elicits apoptosis as well as proliferation (*18*), whereas Bcl-2 encourages cell cycle exit as well as survival (above). Bcl-2 coding changes may also relieve cell cycle inhibition: Many progressed follicular lymphomas display missense mutations in the relevant NH_2-terminal region (*52*, *55*).

All pro-survival *bcl-2*-like genes are potentially oncogenic, and some mutations probably increase their expression indirectly. In hematopoietic cells, oncoproteins such as Myb, Ras, and AML1-ETO induce *bcl-2* expression (*56*), and that of *bcl-2* and *A1* is often elevated in myeloid leukemia and stomach cancer, respectively (*57*). For solid tumors, the present variable correlation between expression of such genes and prognosis (*4*) may become clearer as more family members are analyzed.

Pro-apoptotic family members may act as tumor suppressors. Bax is mutated in human gastrointestinal cancer and some leukemias (*58*). Moreover, its expression is activated in some cell types by the p53 tumor suppressor, which can provoke apoptosis (*18*, *36*). In a transgenic model of choroid plexus brain tumors, as well as in fibroblasts, loss of *bax* did reduce apoptosis and increase tumorigenicity but only about half as much as loss of p53 (*59*). Thus, *bax* is not the only gene responsible for p53-driven apoptosis (above).

Puzzles and Prospects

Many fundamental questions about the Bcl-2 family remain. The circuitry conveying upstream death-survival signals is hazy, as are critical issues regarding commitment. Is a Bcl-x_L–Apaf-1 complex present in healthy cells or formed only after a death signal? How does this association restrict Apaf-1 activity? Are procaspases part of ternary complexes, or do they associate only with liberated Apaf-1? If there indeed prove to be multiple mammalian CED-4 homologs, will each have a specific pro-survival regulator and activate a specific procaspase? One would like to understand how family members are targeted to particular organelles, how they affect organelle functions, and the physiologic relevance of caspase-independent killing and pore-forming ability. Structural studies on Bax-like proteins may enlighten us as to why they share so many features with the pro-survival group yet have opposite function. For the newly described BH3 family, quantitative data on association with the pro-survival proteins should clarify whether each has a preferred partner or is more promiscuous. Their very divergent sequences may hint that each responds to a distinct signal—one, say, to a deranged cytoskeleton and another to damaged DNA. Whether death-survival signals alter their expression or provoke posttranslational modification needs more study.

Clarifying how the Bcl-2 family governs apoptosis might provide the ability to adjust the apoptotic threshold in clinical settings. The small interface between opposing members (Fig. 3) provides one target for pharmacological intervention, illustrated by the apoptotic action of 16-residue BH3 peptides (*60*), and the Bcl-x_L–Apaf-1 complex and organelle docking sites may offer others. Both agonists and antagonists can be envisioned. Degenerative diseases and acute ischemic episodes would clearly benefit from pharmacologic agents that retard further apoptosis. For cancer, delineating the apoptotic defects in specific tumor types may engender therapies that reestablish the normal death program. Paradoxically, oncogenic changes render certain tumors *more* susceptible to apoptosis (*18*), and it may prove feasible to exploit that vulnerability.

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