The BCL-2 protein family: opposing activities that mediate cell death

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Abstract | BCL-2 family proteins, which have either pro- or anti-apoptotic activities, have been studied intensively for the past decade owing to their importance in the regulation of apoptosis, tumorigenesis and cellular responses to anti-cancer therapy. They control the point of no return for clonogenic cell survival and thereby affect tumorigenesis and host–pathogen interactions and regulate animal development. Recent structural, phylogenetic and biological analyses, however, suggest the need for some reconsideration of the accepted organizational principles of the family and how the family members interact with one another during programmed cell death. Although these insights into interactions among BCL-2 family proteins reveal how these proteins are regulated, a unifying hypothesis for the mechanisms they use to activate caspases remains elusive.

BH3 motif
The amino-acid sequence LXXXGD, in which X represents any amino acid. This motif is conserved between most core BCL-2 family members and among BH3-only proteins.

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The *BCL-2* (B-cell lymphoma-2) gene was discovered at the t(14;18) chromosome translocation breakpoint in B-cell follicular lymphomas, where its transcription becomes excessively driven by the immunoglobulin heavy chain gene promoter and enhancer on chromosome 14 (REFS 1–3). One key early discovery that introduced a new paradigm for carcinogenesis was that overexpression of *BCL-2* does not promote cell proliferation as most previously discovered oncogenes do; rather, overexpression of *BCL-2* inhibits cell death[4]. Apoptosis has now been widely accepted as a prominent tumour-suppression mechanism. Mutations in certain oncogenes that result in the activation of cell proliferation, such as deregulated *MYC* expression, require a second mutation to inhibit the apoptosis machinery so that tumour promotion can proceed efficiently[5,6]. Thus, the combined overexpression of *BCL-2* and *MYC* synergize potently in the development of lymphomas and certain other types of cancer[7]. It has also become clear that, beyond roles in cancer, BCL-2 and other members of the family are essential for an array of apoptosis programmes, including developmentally programmed cell death, tissue turnover and host defence against pathogens.

In mammals, there are at least 12 core BCL-2 family proteins, including BCL-2 itself and proteins that have either three-dimensional (3D) structural similarity or a predicted secondary structure that is similar to BCL-2 (FIG. 1). These proteins display a range of bioactivities, from inhibition to promotion of apoptosis. Numerous so-called BH3-only proteins share homology with each other and the remainder of the BCL-2 protein family only through the short BH3 motif[8]. Other than BID, the predicted overall structures of the BH3-only proteins seem to be unrelated and appear to lack a close evolutionary relationship to the core members of the BCL-2 family[9]. But, all BH3-only proteins interact with and regulate the core BCL-2 family proteins to promote apoptosis. Several of the members of these two classes have been knocked out in mice to reveal their physiological roles, redundancy and interactions *in vivo* (TABLE 1).

This review covers recent insights into the biochemical, cellular and physiological roles of the BCL-2 family without reiterating the roles of these proteins in cancer and drug development, which have recently been expertly reviewed[5,10]. With the recent advances in understanding BCL-2 family protein interactions, we focus on how such interactions lead these proteins to change subcellular localization and conformation to regulate their bioactivities. The latest progress into the differential regulation of organ development, maintenance and tissue turnover in mice by BCL-2 family members are also reviewed.

BCL-2 family proteins in apoptosis

All pathways to apoptosis converge on the activation of caspases, which are cysteinyl aspartate proteases that coordinate the efficient dismantling and engulfment of doomed cells (FIG. 2). Two pathways of cell death can be distinguished by whether they require BCL-2 family proteins and by which caspases are crucial for their execution. The intrinsic pathway — also called the BCL-2-regulated or mitochondrial pathway (in reference to the role these organelles play) — is activated by various

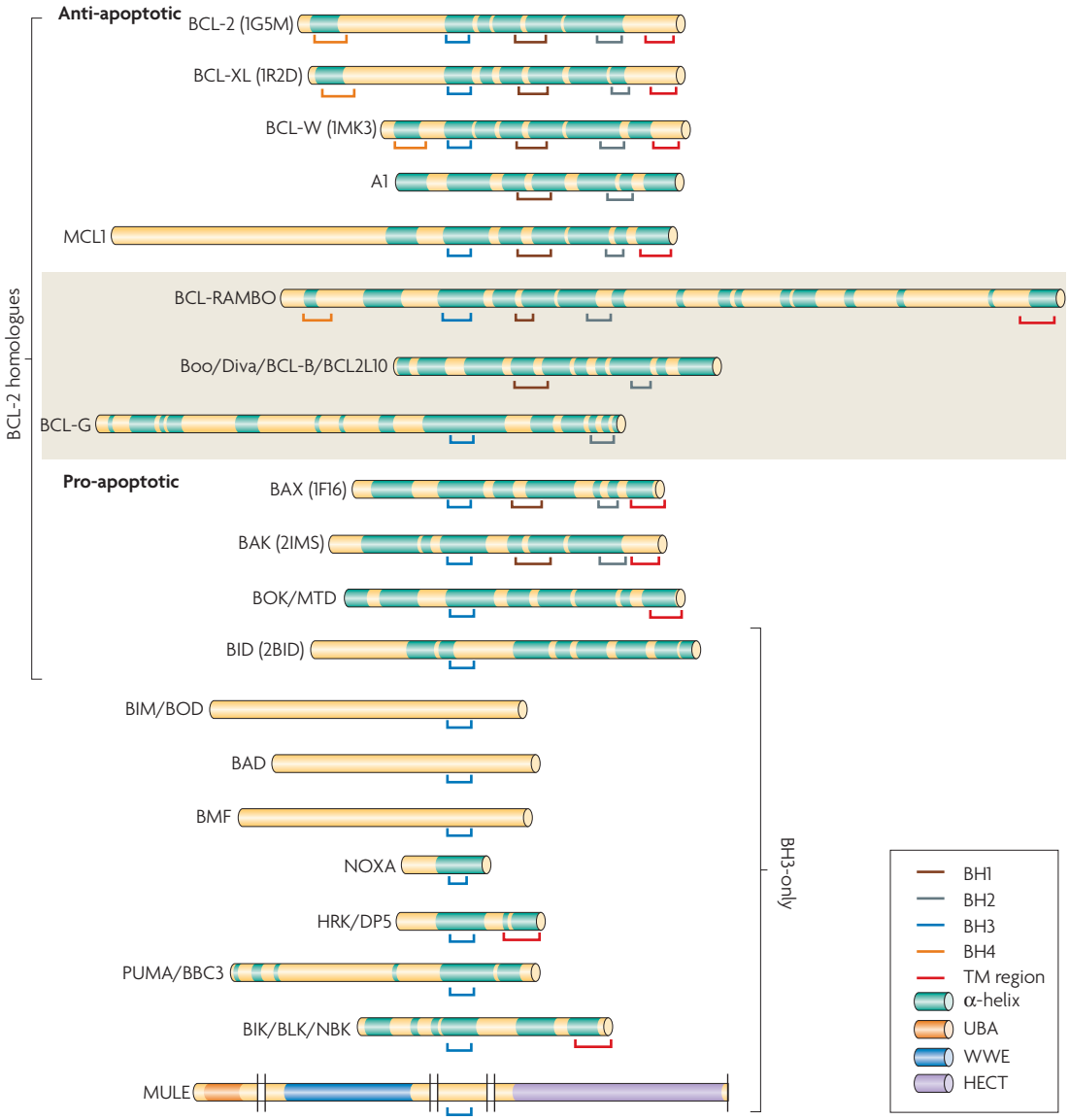


Figure 1 | **Sequence alignment of core BCL-2 family proteins and BH3-only proteins.** Green bars depict α-helical segments from the determined structures (when labelled by Protein Data Bank (PDB) identifier in parentheses) or from secondary structure prediction (as predicted using PSIPRED). Red lines label regions of predicted transmembrane (TM) domains (as predicted using TMHMM). Sequence homologies of the BH1 (brown lines), BH2 (grey lines), BH3 (blue lines) and BH4 (orange lines) regions are shown. The BH1, BH2 and BH3 domains fold to line a hydrophobic pocket that can bind BH3-only peptides. The BH3 domain, particularly among the BH3-only proteins, mediates interaction between the BH3-only proteins and core BCL-2 family proteins and thereby promotes apoptosis. The upper five proteins (BCL-2, BCL-XL, BCL-W, A1 and MCL1) are generally anti-apoptotic. The three proteins in the shaded area are less well studied and cannot be categorized at this time. The lower 12 proteins are considered to be pro-apoptotic. MULE contains a ubiquitin-associated domain (UBA), the Trp-Trp-Glu interaction module (WWE) and a HECT ubiquitin ligase domain. BID has a unique role as both a BCL-2 homologue and a BH3-only protein and links the intrinsic and extrinsic apoptosis pathways (FIG. 2). BIM (also known as BOD), BAD and BMF are unstructured proteins.

developmental cues or cytotoxic insults, such as viral infection, DNA damage and growth-factor deprivation, and is strictly controlled by the BCL-2 family of proteins. This pathway predominantly leads to the activation of caspase-9 (REF. 11) but, at least in certain cell types, the intrinsic pathway can proceed in the absence of caspase-9 or its activator, apoptotic protease-activating factor-1 (APAF1)[12].

The extrinsic or death-receptor pathway is triggered by ligation of so-called death receptors (members of the tumour necrosis factor (TNF) receptor family, such as Fas or TNF receptor-1 (TNFR1)) that contain an intracellular death domain, which can recruit and activate caspase-8 through the adaptor protein Fas-associated death domain (FADD; also known as MORT1) at the cell surface. This recruitment causes subsequent activation of

TNF receptor family
Cell-surface receptors in the tumour necrosis factor (TNF) family.

Table 1 | **Phenotypes of mice that are deficient in BCL-2 family members**

BCL-2 family member	Defects caused by its deletion*	Refs
Pro-survival family members		
BCL-2	Abnormal death of renal epithelial progenitors, melanocyte progenitors and mature B and T lymphocytes. Causes fatal polycystic kidney disease (100% mortality by 6 weeks), premature greying and lymphopoenia (but all of these effects can be rescued by concomitant loss of the BH3-only protein BIM).	130
BCL-XL	Abnormal death of fetal erythroid progenitors and neuronal cells. Causes death around embryonic day 14 (100% mortality).	129
BCL-W	Abnormal death of developing sperm cells. Causes male sterility.	132
A1A	Abnormally accelerated death of granulocytes and mast cells in culture.	133
MCL1	Failure in implantation. Conditional knockout causes premature death of immature and mature B and T lymphoid cells, as well as haemopoietic stem cells.	128
Pro-apoptotic BAX/BAK family members		
BAX	Mild lymphoid hyperplasia, male sterility due to sperm-cell differentiation defect.	135
BAK	No obvious defects detected so far.	136
Pro-apoptotic BH3-only proteins		
BIM	Lymphoid and myeloid cell hyperplasia, fatal SLE-like autoimmune disease (on mixed genetic C57BL/6x129SV background), many cell types are abnormally resistant to cytokine deprivation, deregulated calcium flux and the chemotherapeutic drug taxol; mild but significant resistance of many cell types to DNA damage and glucocorticoids.	143
BID	BID-deficient mice are resistant to Fas-activation-induced hepatocyte killing and fatal hepatitis; however, some cell types (such as lymphoid cells) are normally sensitive to Fas-induced apoptosis.	13, 14
PUMA	Many cell types are profoundly resistant to DNA damage; many are also resistant to cytokine deprivation, glucocorticoids and phorbol ester.	150,151
BAD	Mild resistance of some cell types to deprivation of epidermal growth factor or insulin growth factor.	154
HRK	Abnormal, although relatively mild, resistance of certain neuronal populations to deprivation of nerve growth factor.	155,156
BIK	No obvious defects detected so far.	158
NOXA	Relatively mild resistance of fibroblasts to γ-irradiation or etoposide, but profound resistance of these same cells and keratinocytes in the skin to ultraviolet irradiation.	150

*These are phenotypes found in mice. The roles of these proteins may differ in humans. BAD, BCL-2 antagonist of cell death; BAK, BCL-2-antagonist/killer-1; BAX, BCL-2-associated X protein; BCL-2, B-cell lymphoma-2; A1A, BCL-2-related protein A1A; BCL-W, BCL-2-like-2; BCL-XL, a BCL-2-like protein; BID, BH3-interacting domain death agonist; BIK, BCL-2-interacting killer; BIM, BCL-2-like-11; HRK, harakiri (also known as death protein-5); MCL1, myeloid cell leukaemia sequence-1; PUMA, BCL-2 binding component-3; SLE, systemic lupus erythematosus.

downstream (effector) caspases, such as caspase-3, -6 or -7, without any involvement of the BCL-2 family. In some cells, most notably hepatocytes, the extrinsic pathway can intersect the intrinsic pathway through caspase-8 cleavage-mediated activation of the pro-apoptotic BH3-only protein BID[13,14]. The C-terminal truncated form of BID (tBID) translocates to mitochondria and promotes further caspase activation (caspase-9 and the effector caspases caspase-3, -6 and -7) through the intrinsic pathway. In these situations, loss of BID or overexpression of *BCL-XL* inhibits cell death[13].

BCL-2 family proteins have opposing apoptotic activities. BCL-2 family members have classically been grouped into three classes. One class inhibits apoptosis (BCL-2, BCL-XL, BCL-W, MCL1, BCL-B (also known as BCL-2L10) and A1 (also known as BCL-2A1), whereas a second class promotes apoptosis (BAX, BAK and BOK (also known as MTD)). A third divergent class of BH3-only proteins (BAD, BIK (also known as BLK or NBK), BID, HRK (also known as death protein-5 (DP5)), BIM (also known as BOD), BMF, NOXA and PUMA (also known as BBC3)) have a conserved BH3 domain that can bind and regulate the anti-apoptotic BCL-2 proteins to promote apoptosis (FIG. 1). It appears that the pro-apoptotic family members BAX and BAK are crucial for inducing permeabilization of the outer mitochondrial membrane (OMM) and the subsequent release of apoptogenic molecules (such as cytochrome *c* and DIABLO (also known as SMAC)), which leads to caspase activation. The anti-apoptotic family members, such as BCL-2 and BCL-XL, inhibit BAX and BAK. Recent evidence indicates that BH3-only proteins de-repress BAX and BAK by direct binding and inhibition of BCL-2 and other anti-apoptotic family members[15]. By contrast, an opposing model postulates direct activation of BAX and BAK by some BH3-only proteins (specifically BIM, tBID and PUMA)[16] (FIG. 2).

Death domain
A protein-interaction module that consists of six α-helices and that is involved in apoptosis and other signalling pathways.

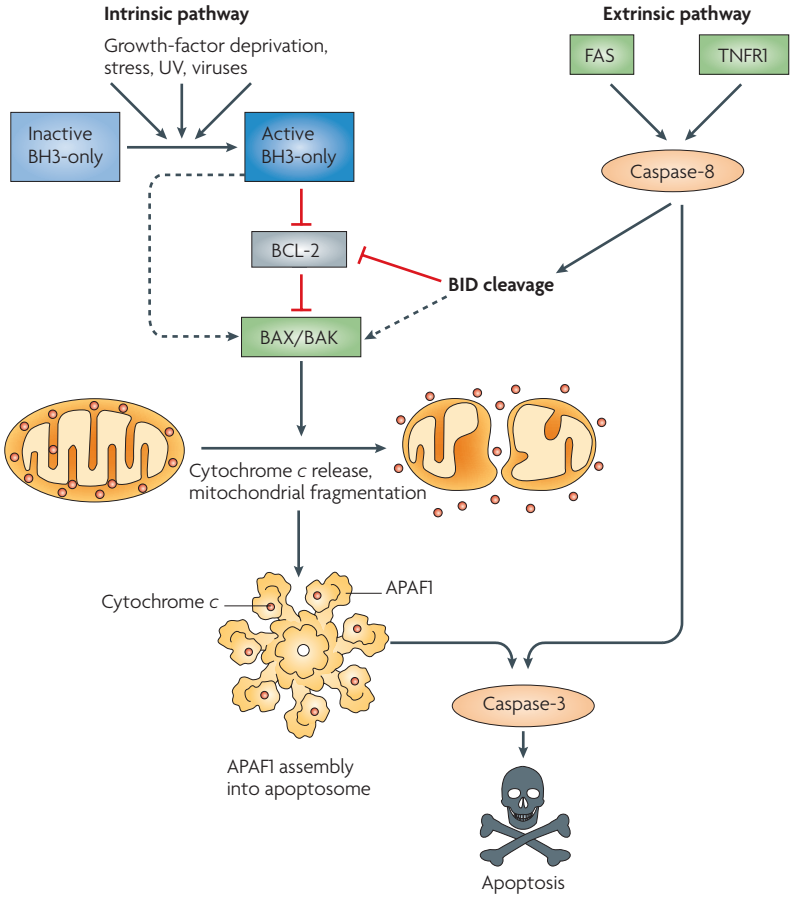


Figure 2 | **Scheme depicting intrinsic and extrinsic pathways of apoptosis.** Apoptosis can be induced by cell surface receptors, such as Fas and tumour necrosis factor receptor-1 (TNFR1) (extrinsic pathway, right), or by various genotoxic agents, metabolic insults or transcriptional cues (intrinsic pathway, left). The intrinsic pathway starts with BH3-only protein induction or post-translational activation, which results in the inactivation of some BCL-2 family members. This relieves inhibition of BAX and BAK activation, which in turn promotes apoptosis. Some BH3-only proteins, such as BIM and PUMA, may also be able to activate BAX and/or BAK (as shown by the dotted line). Once activated, BAX and BAK promote cytochrome *c* release and mitochondrial fission, which leads to the activation of APAF1 into an apoptosome and activates caspase-9 to activate caspase-3. Caspases in turn cleave a series of substrates, activate DNases and orchestrate the demolition of the cell. The extrinsic pathway can bypass the mitochondrial step and activate caspase-8 directly, which leads to caspase-3 activation and cell demolition. The BCL-2 family regulates the intrinsic pathway and can modulate the extrinsic pathway when cleavage of BID communicates between the two pathways.

Mitochondrial outer membrane permeabilization
The process by which the outer membrane of mitochondria leaks certain soluble intermembrane space proteins, such as cytochrome *c*, into the cytoplasm.

Apoptosome
The caspase-9 activation complex that is composed of APAF1 heptamers and that is assembled on binding of APAF1 monomers to cytochrome *c*.

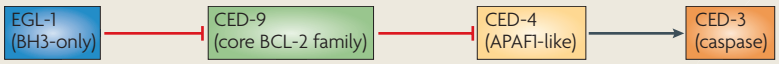
BAX and BAK promote caspase activation by their effects on mitochondria. Either directly or indirectly, these two pro-apoptotic BCL-2 family members induce the release of proteins from the space between the inner and outer mitochondrial membranes[17]. This process of mitochondrial outer membrane permeabilization (MOMP) results in the release of cytochrome *c* and other soluble proteins into the cytosol. Although it is commonly thought that BAX and BAK form pores in membranes, the biochemical nature of such pores and how anti-apoptotic BCL-2 family proteins might regulate them remains a key and controversial issue in the field of cell death[18]. At the same time as cytochrome *c* release (or immediately before), BAX and BAK induce mitochondria to fragment into more numerous and smaller units, which suggests connections between mitochondrial division processes and the functions of the BCL-2 family[19].

Once the OMM has been permeabilized, soluble proteins diffuse from the intermembrane space into the cytosol, where they promote caspase activation. The best studied of these proteins is cytochrome *c*, which binds to APAF1 and leads to the assembly of a heptameric protein ring called an apoptosome, which can bind pro-caspase-9 and induce its activation through a conformational change[20,21]. Cytochrome *c*–APAF1-dependent activation of caspase-9 is absolutely required for neuronal and fibroblast cell-death processes[22]. However, in addition to this process, lymphocytes can probably use alternative APAF1-, caspase-9- and cytochrome *c*-independent, but pro-apoptotic BCL-2-family-member-dependent, pathways for caspase activation and cell killing[12,22]. Intriguingly, caspase activation in lymphocytes can be amplified by APAF1 even when APAF1 has not been incorporated into the apoptosome[22].

One APAF1-independent pathway of caspase activation is the relief of caspase inhibition by inhibitor of apoptosis proteins (IAPs), such as XIAP, which bind and neutralize certain caspases (such as caspase-9 and caspase-3). This inhibitory action of IAPs can be antagonized by the binding of DIABLO, which is released from mitochondria after the activation of BAX and/or BAK. However, DIABLO-deficient mice[23], as well as XIAP-deficient mice[24], do not display significant apoptotic phenotypes, which suggests that novel processes of caspase activation remain to be discovered. Several APAF1 related proteins, called NOD-like receptors, regulate alternative pathways of caspase activation that occur in non-apoptotic host defence processes that are associated with innate immunity and serve as examples of pathways that can also have roles during apoptosis[25]. One of these NOD-like receptors, NALP1, can be regulated by BCL-2 and BCL-XL[26] in manner that is reminiscent of caspase activation in the worm (BOX 1).

BCL-2 and BCL-XL appear to control cell survival beyond the APAF1–caspase-9 axis. If caspase activation is inhibited by loss of APAF1 or caspase-9, or even by the combined loss of caspase-9 and caspase-2, the rate of acquisition of apoptotic morphology of myeloid progenitors and mast cells induced by growth-factor withdrawal or DNA damage can be significantly delayed. However, although the onset of apoptotic morphology can be delayed, the cells still lose clonogenic potential and thus effectively die, unlike cells that overexpress BCL-2 or BCL-XL[27,28]. Thus, the step of apoptosis regulation that is controlled by the BCL-2 family appears to be the most general final commitment step for the decision between cell life and death. The disruption of mitochondria by BAX and BAK may be one cause of eventual clonogenic cell death in the absence of apoptosome activation. Normally, caspase activation rapidly and efficiently mediates cell demolition and removal. When caspases are blocked, certain features of apoptosis can be lost (or delayed), which causes the cells to die more slowly by BCL-2-family-mediated mitochondrial disruption or by novel caspase-activation pathways that have yet to be characterized.

Box 1 | **The mechanism of CED-9, the *C. elegans* orthologue of BCL-2**



Genetic analyses of the apoptosis pathway in *Caenorhabditis elegans* and recent biochemical insights are consistent with the model shown in the figure above. EGL-1, a BH3-only protein, is transcriptionally induced by developmental cues for programmed cell death. EGL-1 binds to the BCL-2 homologue CED-9, thereby freeing CED-4, an AAA+ ATPase that is related to apoptotic protease-activating factor-1 (APAF1), which is normally sequestered by CED-9. The released CED-4 assembles into a tetrameric apoptosome and activates the protease activity of the caspase CED-3. This model differs from the cytochrome *c* release model of mammalian cells (FIG. 2). It is not anticipated that homologous proteins regulate the same process by different mechanisms, so some underlying common process among BCL-2 family members of *C. elegans* and mammals may await discovery.

Two studies indicate that CED-9 may do more than prevent CED-4 activation. In worms with mild *ced-3* loss-of-function mutations in which some excess cells survive, weak loss-of-function *ced-9* alleles actually increase cell survival, which suggests that CED-9 also has pro-apoptotic activity[163]. This might indicate that, depending on its conformation, CED-9 can have BCL-2-like (that is, anti-apoptotic) or BAX-like (that is, pro-apoptotic) activity[94]. In addition, loss of CED-9 activity inhibits cell death due to overexpression of *drp-1* (REF. 122), which further suggests that the sole core BCL-2 family protein in *C. elegans* can function in both pro- and anti-apoptotic modes. Certain mammalian BCL-2 family members have also been reported to be convertible between anti- and pro-apoptotic forms[164,165]. CED-9 resides on mitochondria, as many mammalian BCL-2 family proteins do, but how this localization relates to its biochemical action remains unclear. Similar to programmed cell death in mammals and flies, mitochondria become fragmented during apoptosis in the worm[122] upstream of caspase activation, showing that there is one common denominator involving mitochondria in all three systems.

Future studies should explore how BCL-2 family members function in sponges, echinoderms and insects. One recent study in *D. melanogaster* came to the surprising conclusion that although the two BCL-2 family members are required for certain stress-induced apoptosis pathways, they are not required for developmentally programmed cell death[166].

Structure and evolution

The core multi-BH domain BCL-2 family members and, surprisingly, the BH3-only protein BID (FIG. 1) have conserved regions of sequence homology and similar predicted secondary structure. Structures of seven of these proteins (BCL-XL[29], BCL-2 (REF. 30), BCL-W[31,32], MCL1 (REF. 33), BAX[34], BAK[35] and BID[36,37]) show remarkable similarity, which is intriguing considering that some are pro-apoptotic and others are anti-apoptotic. Ks-BCL-2, a viral homologue of BCL-2 (REF. 38), as well as two viral proteins without apparent sequence similarity to BCL-2 family proteins, M11L[39,40] and N1L[41], display a helical fold that is similar to that of BCL-XL, and these inhibit apoptosis, which indicates that several viruses use BCL-2 family members to counteract host defence.

The 3D structures of the seven core BCL-2 family proteins mentioned above have yet to reveal any distinguishing difference between anti-apoptotic members (such as BCL-XL and MCL1) and pro-apoptotic members (such as BAX and BID). All seven proteins are helical bundles with a hydrophobic helix-turn-helix hairpin that is flanked on both sides by pairs of amphipathic helices. Excluding the viral anti-apoptotic BCL-2-like proteins, BCL-2 homologues appear to have C-terminal membrane-anchoring domains. In addition, pro-apoptotic BID appears to be myristoylated to mediate membrane anchorage[42]. In three proteins, BAX, BCL-W and MCL1, the C-terminal anchor has been included in the structural analysis and fits into a hydrophobic pocket formed by the BH1, -2 and -3 regions. The same pocket that sequesters the C-terminal membrane anchor can also bind to peptides of the BH3-domain sequences of BAK, BAD and BIM[43–45], which suggests that it also functions in dimerization with BH3-only proteins and/or multi-BH-domain-containing BCL-2 family members (FIG. 3). An extended BIM BH3 peptide that is 23 amino acids in length binds along the hydrophobic groove of BCL-XL, although it is inverted in the C- to N-terminal helical direction relative to the orientation of the BAX and BCL-W C-terminal membrane anchors[45] (FIG. 3).

Classically, BH3-only proteins have been defined as having homology to the core BCL-2 family members in only the BH3 domain. Recent sequence analyses indicate that, except for BID, the BH3-only proteins have predicted secondary structures or determined 3D structures that are unrelated to the core BCL-2 family members, and, except for BID, they probably acquired BH3 motifs by convergent evolution[9]. One particular example of a BH3-motif-containing protein that is not otherwise related to the core BCL-2 family is MULE, an E3 ligase that reportedly targets MCL1 for ubiquitylation and proteasomal degradation. MULE has a BH3 domain and can loosely be considered to belong to the class of BH3-only proteins, which interact with and regulate other members of the BCL-2 family[46,47] (FIG. 4). Even the autophagy regulatory protein beclin-1 reportedly binds to BCL-2 through a BH3 domain, although further biochemical and genetic experiments are needed to establish a functional connection[48]. BAD, BMF and BIM are intrinsically unstructured[49] and, along with PUMA, these proteins are not likely to be core BCL-2 family homologues on the basis of secondary structure predictions (FIG. 1).

So, BH3-only proteins include various proteins that share a single motif that allows them to bind and regulate the core BCL-2 family members. BID, by contrast, is the one BH3-only protein with a determined structure that places it squarely in the core BCL-2 family members, which perhaps explains why BID shares certain properties with multidomain BCL-2 family members, such as the ability to oligomerize[50] and to permeabilize membranes[51]. Thorough phylogenetic analyses of the BCL-2 family have generated important insights into the origins of the core BCL-2 family members (BOX 2) and the BH3-only proteins, and suggest that many of these proteins might have biological activities beyond regulation of cell death[9,52].

BCL-2 family protein activation

BH3-only proteins are pro-apoptotic and function as initial sensors of apoptotic signals that emanate from various cellular processes. BH3-only protein expression can be induced by transcription factors. For example, NOXA and PUMA are induced by the tumour suppressor p53 in response to DNA damage[53–55], and BIM is induced by the class O forkhead box transcription factor-3A (FOXO3A) in response to growth-factor deprivation[56] and by the transcription factors CEBPα

Inhibitor of apoptosis protein
(IAP). One of a family of proteins that inhibits apoptosis by binding or degrading caspases.

NOD-like receptor
A cytosolic receptor that is homologous to NOD1 and is involved in innate immunity pathways.

E3 ligase
One of a family of proteins that facilitate the transfer of ubiquitin from a donor protein to a specific substrate protein that may signal the target for proteosomal degradation.

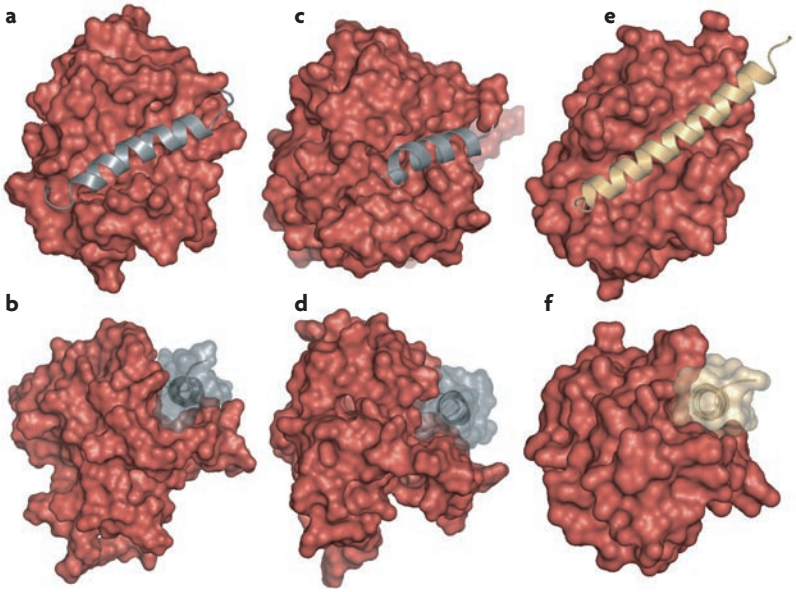


Figure 3 | **Space-filling models of the structures of BAX, BCL-W and BCL-XL bound to a BIM BH3-region peptide.** Comparing the structures of full-length BCL-2 family members with those bound to BH3 peptides from other BCL-2 family members suggests how subcellular localization might be linked to protein–protein interactions among family members. (The structures in the lower panels are rotated 90 degrees from those in the top panels.) Full-length BAX (**a**,**b**) and BCL-W (**c**,**d**) fold with the C-terminal helix (grey) sequestered in a hydrophobic pocket. This C-terminal domain is experimentally deleted in BCL-XL (**e**,**f**), which binds to an extended BH3 domain peptide of BIM (yellow) in the homologous pocket that is occupied by the membrane anchor in BAX, BCL-W and MCL1. The BIM peptide orientates in the pocket in the opposite direction to the endogenous regions of the C terminus (that is, in the C- to N-terminal direction). Because the C-terminal helix is involved in membrane binding and is thought to penetrate deeply into membranes (FIG. 5), this helix would become displaced from the hydrophobic pocket on mitochondrial translocation (see Supplementary information S1 (movie)). Emptying this pocket of the C-terminal helix would enable it to bind BH3 domains (yellow) from other BCL-2 family members, allowing hetero- or homodimer formation. Alternatively, binding of BH3-only proteins to BAX or BCL-W in the cytosol could displace the C-terminal helix from the pocket and trigger mitochondrial translocation. Non-structured amino acids in BAX (1–12) and BCL-W (1–8 and 170–178) have been excluded from the models.

(CCAAT-enhancer binding protein-α) or CHOP (CEBP homologous protein) in response to endoplasmic reticulum (ER) stress[57]. BH3-only proteins can also be activated post-translationally; for example, BAD is activated by loss of phosphorylation in response to growth-factor deprivation[58]; BID is activated by caspase-8-mediated proteolysis[59,60]; BIM is activated by release from the dynein motor complex[61] or by loss of extracellular signal-regulated kinase (ERK)-mediated phosphorylation (which targets it for ubiquitylation and proteasomal degradation in healthy cells)[62,63]; BMF is activated by release from actin–myosin motor complexes[64]; and BIK is activated by an unknown mechanism in response to inhibition of protein synthesis[65].

Regulation of the expression levels of anti-apoptotic BCL-2 family proteins is another way in which cells can regulate apoptosis. For example, BCL-XL can be transcriptionally induced by growth factors through the Janus kinase–signal transducer and activator of transcription (JAK–STAT) pathway to promote cell survival[66]. MCL1 is rapidly degraded by the ubiquitin–proteasome pathway in response to cytokine deprivation or other death stimuli (such as ultraviolet (UV) radiation) and can be upregulated post-transcriptionally to prevent apoptosis by inhibiting the rate of degradation[46,67]. Regulation of the expression levels of the pro-apoptotic proteins BAX and BAK is less apparent and the proteins appear to be constitutively expressed at more or less constant levels. BAX and BAK are primarily post-translationally regulated by other members of the BCL-2 family.

When BH3-only proteins are induced or activated, they interact with core BCL-2 family proteins to promote apoptosis. The binding of BH3-only proteins or BH3 peptides to specific anti- and pro-apoptotic BCL-2 family members has been determined by using yeast two-hybrid analysis, plasmon resonance binding assays and by cell-free mitochondria and liposome permeabilization studies[68–72,73]. Together, these assays indicate that some BH3-only proteins, such as BIM and PUMA, bind all anti-apoptotic BCL-2 family members, whereas others, such as BAD and NOXA, bind only certain anti-apoptotic BCL-2 family members (FIG. 4). In addition to interaction with anti-apoptotic BCL-2 family members, several reports show synergy of BID or BIM with BAX in cell-free membrane permeabilization assays, which suggests that some BH3-only proteins may directly bind and activate BAX and BAK[70–72]. However, it is difficult to detect binding of full-length BID, tBID or BIM to BAX or BAK[15], although a modified BH3 peptide can bind BAX and/or BAK[74]. Other models in which BH3-only proteins directly activate BAX and BAK are called into question owing to results from *Bim*/*Bid* double knockout mice and their cell lines, which show that these putative direct activators of BAX and BAK are not required for many apoptotic pathways[15]. Thus, known BH3-only proteins appear to induce apoptosis primarily by inhibiting anti-apoptotic BCL-2 family members, thereby liberating BAX and BAK to cause MOMP and activation of the caspase cascade (FIG. 2). The precise biochemical mechanisms that lead to the activation of BAX and BAK remain a mystery and constitute the 'holy grail' of apoptosis research.

Dynamics of subcellular localization

The anti-apoptotic BCL-2 protein is embedded in the ER, the nuclear envelope and the OMM by a hydrophobic C-terminal membrane-spanning domain, with most of its amino acids in the cytosol[75,76]. Although BCL-2 in any of these subcellular locations can block apoptosis, the functions of BCL-2 at the ER and the nuclear envelope are less clear than those on mitochondria and have recently been reviewed[77,78].

In contrast to BCL-2, BAX is mostly cytosolic and sequesters its hydrophobic C-terminal membrane anchor in its BH3-binding pocket (FIG. 3), with a minor fraction lightly bound to the OMM[79]. BAX appears to exist as a monomer in the cytosol of cells rather than being bound to any anti-apoptotic BCL-2 family members[80]. During apoptosis induction, BAX translocates specifically to mitochondria (see Supplementary information S1 (movie)),

ER stress
The accumulation of unfolded or incompletely glycosylated proteins in the endoplasmic reticulum (ER) results in stress that may lead to apoptosis.

Dynein motor complex
A molecular machine that transports cargo along microtubules.

JAK–STAT pathway
The Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathway is a signalling pathway that is activated by growth factors and cytokines.

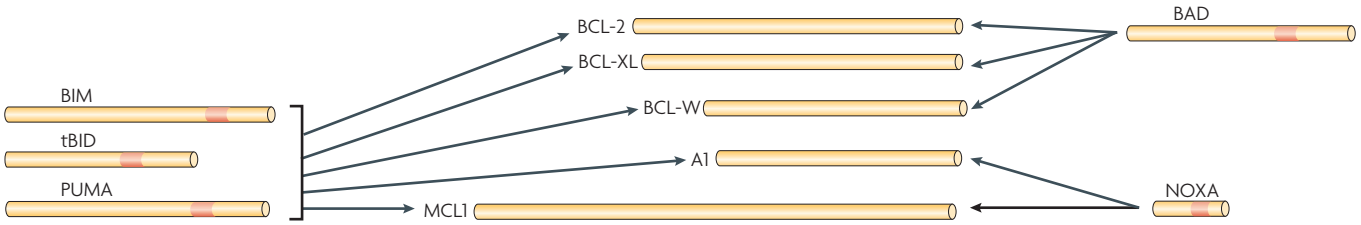


Figure 4 | **BH3-only protein binding specificity for BCL-2 homologues.** BIM and PUMA bind to all five anti-apoptotic BCL-2 family members tested. By contrast, NOXA only binds to MCL1 and A1, and BAD binds selectively to BCL-W, BCL-2 and BCL-XL. tBID binds avidly to BCL-XL, BCL-W, MCL1 and A1, but only weakly to BCL-2. BH3-only proteins do not appear to bind strongly to BAX or BAK. These binding specificities recapitulate the ability of these proteins to activate apoptosis. For example, BIM, BID or PUMA alone can induce apoptosis, whereas a combination of NOXA and BAD is required. This probably enables the fine specificity of apoptosis regulation in different tissues and during changes in cellular developmental stages. The BH3 domain is shown in red and the five anti-apoptotic BCL-2 family proteins are shown in the middle of the figure.

where it inserts into the OMM as an integral membrane protein[81] using its C-terminal membrane anchor[82], perhaps with organelle targeting specified by defined regions in the N terminus[83]. This translocation step of BAX, although reversible in certain situations, usually correlates closely with the irreversible commitment of cells to die and to the cytochrome *c* release step discussed below.

BOK also translocates from the cytosol to mitochondria during apoptosis[84], whereas BAK already resides on the OMM (see subcellular localization of BCL-2 family members in Supplementary information S2 (table)) in healthy cells, where it has been reported to be bound to MCL1 (REF. 67) and to BCL-XL[73]. Notably, BAK–MCL1 and BAK–BCL-XL interaction experiments rely on detergent extraction of membrane proteins that, in some cases, can cause artefactual interactions among BCL-2 family proteins[85]. Although the OMM channel protein VDAC2 (voltage-dependent anion channel-2) also reportedly binds to BAK[86] and is important for BAK import into the OMM[87], *Vdac1*/*Vdac2*/*Vdac3* triple knockout mice display normal apoptosis[88], indicating little or no role for VDACs in BCL-2 family protein regulation. The mitochondrial localization of BAK may be a consequence of MCL1 binding into the BH3 pocket of BAK and displacing the C-terminal membrane anchor, allowing it to interact with membranes. Although the BH3 domain is the obvious candidate domain of MCL1 for this interaction, it is not exposed in the soluble MCL1 structure[33]. The C-terminal membrane anchor of BCL-XL has been proposed to mediate binding to BAX by fitting into its BH3-binding pocket in *trans*[89], which suggests another way by which BCL-XL and MCL1 can interact with BAK. On apoptosis induction, MCL1 is degraded (at least in certain cell types in response to certain cytotoxic stimuli)[67,90] and/or the MCL1–BAK and BCL-XL–BAK interactions are disrupted by BH3-only proteins, such as NOXA, BIM[73] or BIK[65], which frees BAK to promote apoptosis.

Because the translocation of BAX to the mitochondria correlates with pro-apoptotic activity, it is curious that BCL-2 is constitutively membrane bound but BCL-XL[79,91], BCL-W[92] and MCL1 (REF. 90) exist partly in the cytosol and translocate from the cytosol to mitochondria during apoptosis. Their binding to BH3-only proteins appears to be the trigger, perhaps by displacing the C-terminal membrane anchors of BCL-XL[89] and BCL-W[92] by occupancy of the hydrophobic pockets. The intracellular translocation probably correlates with conformational changes and deep insertion of BCL-XL and BCL-W into the OMM. Whether this translocation of anti-apoptotic BCL-2 family members represents a mechanism to inhibit apoptosis, inactivation by BH3-only proteins or even conversion into pro-apoptotic effectors remains unclear[92,93]. It has, for example, been postulated that binding of a BH3-only protein changes the conformation of the pro-survival BCL-2-like protein so that it can then initiate formation of BAX and/or BAK oligomers in the mitochondrial and other intracellular membranes to cause initiator caspase activation[94].

Box 2 | **Phylogenomics of BCL-2 family proteins**

BCL-2 gene orthologues have been identified in all metozoan animals examined so far[9]. The earliest metazoan that has been analysed, the sponge[52], contains two *BCL-2* related genes that most closely resemble mammalian *BOK*[8], which has so far received little attention in mouse and human systems. Interestingly, *Monosiga brevicollis*, a single cell choanoflagellate that is closely antecedent to sponges, has no identifiable *BCL-2* family member in its recently sequenced genome (C. Wang, personal communication), which suggests that *BCL-2* family genes evolved with multicellular life forms. However, some recent viral gene products have been found with the signature helical fold of BCL-2, and these function in apoptosis regulation[39–41], which suggests that additional structural orthologues of BCL-2 might exist in eukaryotes without discernible primary sequence homology. The number of apparent BCL-2 family member genes in different orders varies widely. The sea urchin (*Strongylocentrotus purpuratus*) has ten homologous genes, significantly more than insects (*Drosophila melanogaster*; two core BCL-2 family members) and round worms (*Caenorhabditis elegans*; one core BCL-2 family member) (BOX 1). *C. elegans* also has one prominent BH3-only gene, *egl-1*, which appears to be crucial for most (and perhaps all) developmentally programmed somatic cell death[160], and another BH3-only gene, *ced-13*, which might have a role in stress-induced cell killing[161]. Zebrafish contain genes for nine versions of core BCL-2 family members and homologues of eight of the best-studied BH3-only genes[162]. Humans and mice have a similar set of 12–13 structural homologues of BCL-2 family proteins, which indicates that family member organization is stable among mammals.

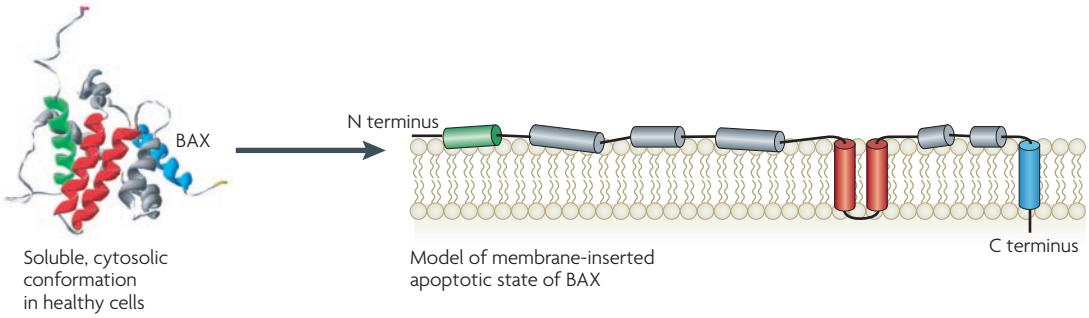


Figure 5 | **Conformational changes in BCL-2 family members during apoptosis.** BAX undergoes extensive conformational changes during the mitochondrial translocation process (see Supplementary information S1 (movie)). The protein changes from a soluble cytoplasmic protein in healthy cells to one that appears to have at least three helices inserted into the mitochondrial membrane in apoptotic cells. The C-terminal helix (blue) and the amphipathic helices (red) in the soluble, cytoplasmic form of BAX (left) are thought to insert deeply into the mitochondrial membrane (right) during early stages of apoptosis. In addition to changes in membrane topology, the N-terminal amino acids 13–27 (green) change from a conformation that is buried in the protein folds and inaccessible to the monoclonal antibody 6A7 to a conformation that is fully accessible to antibody binding during apoptosis. Immunostaining of cells with antibody 6A7 is a good marker of the conformational change[95]. However, certain steps of this conformational change, such as the N terminus exposure, may be reversible when apoptosis triggers are aborted. Other members of the BCL-2 family undergo similar changes in conformation during apoptosis, including BAK, in which an N-terminal epitope is exposed. Interestingly, even anti-apoptotic members of the BCL-2 family change conformation, and models of BCL-2 topology in the membrane that are similar to those of BAX have been proposed[103].

Conformational changes during apoptosis

Both pro- and anti-apoptotic BCL-2 family members undergo dramatic conformational changes during apoptosis to unfold and insert deeply into the lipid bilayer (FIG. 5). For example, BAX changes conformation to reveal a hidden epitope in its N terminus[80,95,96], shows increased proteolytic sensitivity[81] and forms oligomeric complexes[97–99] around the time it translocates to mitochondria.

Two steps in the activation process of BAX can be discerned: an initial translocation to mitochondria, and then the N-terminal conformational change that is likely to be coupled to membrane insertion and oligomerization. The translocational step appears to be reversible under certain conditions[100]. Amino acids 14–23 in the N terminus of BAX are hidden when the protein is in its 'healthy cell' conformation, but become exposed in the early stages of apoptosis. The monoclonal antibody 6A7 binds to these amino acids and can be used to identify the rearrangement of this specific region of BAX[80]. This BAX epitope has been crystallized bound to the 6A7 monoclonal antibody, revealing the large extent of remodelling of the BAX N terminus that occurs during apoptosis[101]. BAK also changes conformation[102] and oligomerizes[99] during apoptosis. How many units of BAX or BAK form these oligomers is still unclear, and it appears that these oligomers are distributed over a wide range of molecular weights.

BCL-2 also changes conformation during apoptosis owing to binding of BH3-only proteins. Although a model of this membrane-inserted form of BCL-2 (REF. 103) resembles that of BAX[104], the anti-apoptotic BCL-2 family proteins do not proceed to form oligomers, unlike the pro-apoptotic family members. The conformation of anti-apoptotic BCL-2 family members in solution (FIG. 3) probably represents the conformation found in healthy cells, which does not bind to pro-apoptotic BAX. However, BCL-2 and BCL-XL may bind BAX and BAK after they insert into membranes, possibly when they adopt conformations that resemble those induced by detergents[85], and may cap the BAX or BAK oligomers and inhibit chain elongation[105]. One report concluded that only the form of BCL-2 found in the early stages of apoptosis could bind BAX and BAK and further inhibit BAX or BAK oligomerization to promote cell survival[93]. However, this would yield the counter-intuitive situation in which BH3-only proteins could inhibit apoptosis by promoting a change in the conformation of BCL-2 so that it more actively inhibits BAX and BAK. Other work found that the anti-apoptotic activity of BCL-W was inactivated on insertion of BCL-W into the membrane during apoptosis[92].

Altering mitochondria

BCL-2 family members interact with mitochondria either constitutively or on induction of apoptosis and, although they might have activities in other cellular compartments, it is clear that they regulate apoptosis by their impact on the OMM.

Pro-apoptotic BCL-2 proteins induce cytochrome c release. The OMM becomes permeable to soluble intermembrane space proteins at around the same time as BAX is translocated and BAK undergoes conformational change. Cytochrome *c*, DIABLO, adenylate kinase, the Ser protease OMI, apoptosis-inducing factor (AIF), deafness dystonia protein (DDP), endonuclease G and a cleaved form of OPA1 (a mitochondrial dynamin-like GTPase) have all been reported to be released from the mitochondrial intermembrane space into the cytosol of cells undergoing apoptosis[17,106–108]. Cytochrome *c* and DIABLO release have been consistently shown to be important for caspase activation.

The initial finding that the structure of BCL-XL resembles that of the translocation domain of diphtheria toxin led to the proposal that BCL-XL might form pores in membranes[29]. In trying to understand how pore-formation activity is related to biological activity, a confusing factor is that both pro- and anti-apoptotic BCL-2 family members appear to be able to form membrane channels *in vitro*[29,109,110]. Incubation of BAX with isolated mitochondria induces cytochrome *c* release[111], and incubating BAX with liposomes allows the release of large (up to 10^6 Da) dextran molecules[112], which is consistent with the lipidic pores that were identified in lipid bilayer studies[113]. BCL-XL inhibits BAX-induced cytochrome *c* release from isolated mitochondria[111] and dextran release from liposomes[70]. Furthermore, the BH3-only protein BID can synergize with BAX to cause cytochrome *c* release in cell-free assays, either by activating BAX or by preventing anti-apoptotic BCL-2 family members from inhibiting BAX and BAK. Thus, one model for BAX and BAK activation is that they form large pores in the OMM that allow the release of proteins into the cytosol, inducing caspase activation. However, the biochemical nature of this putative BAX–BAK pore, such as the number of molecules of BAX that comprise the pore, remains unknown.

Curiously, certain cell types (such as some neuronal populations and cardiomyocytes) can survive the cytochrome *c* release step, at least for a limited amount of time[114,115]. In such cells, caspases might be stringently regulated by caspase-inhibiting IAPs. In these cases, apoptosis requires the release of DIABLO from mitochondria to relieve the IAP inhibition and thereby allow caspase activation. This might be a specialized adaptation of normally long-lived post-mitotic cells (which are essential for animal survival) to supply these cells with additional protection from cell-death activation and to prevent their accidental death.

Roles in mitochondrial fragmentation and morphology. Confocal and electron microscopy analyses of BAX translocation to mitochondria reveal that the earliest detectable form of 'activated' BAX does not localize to the entire OMM, but is found concentrated at small focal regions on the mitochondrial surface[116]. BAK also moves into these 'BAX foci' during apoptosis induction. This focal cluster form of BAX observed by microscopy has an altered N-terminal conformation and probably reflects the *in situ* state of BAX and BAK as oligomers. These sites of BAX coalescence often develop into mitochondrial division sites[117], linking BAX to the promotion of the mitochondrial fragmentation processes that occur almost simultaneously with the release of cytochrome *c*[118] (FIG. 2).

Inhibition of mitochondrial fission *in vitro* by downregulation of the mitochondrial dynamin family member DRP1 delays cytochrome *c* release and can decrease caspase activation, which suggests that the organelle division machinery somehow participates in the regulation of apoptosis[119]. Deletion or mutation of *Drp1* in *D. melanogaster*[120,121] and *drp-1* in *C. elegans*[122] also inhibits apoptosis *in vivo* (BOX 1). Conversely, inhibition of mitochondrial fusion by loss of a different mitochondrial dynamin family member, OPA1, induces spontaneous apoptosis[123].

Unexpectedly, healthy cells that lack both BAX and BAK have altered mitochondrial morphology and slower mitochondrial fusion rates, which indicates that BAX and BAK affect mitochondrial morphogenesis machineries even in the absence of apoptotic stimuli[124]. Recent work showing that OPA1 controls mitochondrial cristae formation and that tight cristae junctions can inhibit cytochrome *c* release during apoptosis suggests how mediators of mitochondrial fission and fusion might have a role in cytochrome *c* release and apoptosis[125]. In contrast to cytochrome *c* and OPA1, the release of other mitochondrial intermembrane space proteins (such as DIABLO) is not inhibited by *DRP1* knockdown[126], which underscores the suggestion that the role of the mitochondrial fission machinery in apoptosis might be indirectly linked to the cytochrome *c* release step. Ectopic expression of human *BCL-XL* and *C. elegans ced-9* in mammalian cells has been found to affect mitochondrial morphogenesis, which shows that it is possible to separate the process of organelle fusion regulation by BCL-2 family members from the regulation of apoptosis[127].

Physiological roles of BCL-2 proteins

BCL-2 family members have essential roles in the mouse from early embryogenesis through to adult tissue homeostasis. The nervous system, haematopoietic tissues and spermatogenesis are particularly dependent on BCL-2 family protein regulation (TABLE 1).

Anti-apoptotic BCL-2 proteins. MCL1 and BCL-XL are both essential for normal embryogenesis. *Mcl1*$^{-/-}$ embryos die before implantation at the blastocyst stage[128] and *Bcl-x*$^{-/-}$ mice (in which the entire *Bcl-x* locus (incorporating *Bcl-xl* and *Bcl-xs*) was knocked out) survive only until fetal day 13.5, displaying severe defects in erythropoiesis and neuronal development[129]. By contrast, although BCL-2-deficient mice survive to birth, they have defects in the immune system, hair follicles and renal epithelial cells, and all succumb to polycystic kidney disease by ~4–8 weeks of age (the age of death is influenced by genetic background)[130,131]. *Bcl-w*-knockout male mice are sterile owing to defective spermatogenesis, but otherwise both females and males are developmentally normal[132]. Analysis of the essential functions of A1 by gene targeting is complicated by the fact that, in contrast to humans, mice have four *a1* genes. Mice that lack A1A are essentially normal, but their granulocytes and mast cells undergo apoptosis abnormally rapidly in culture[133,134].

Pro-apoptotic BCL-2 proteins. *Bax*-knockout mice are viable and females are fertile, but both males and females have mild overgrowth of neurons and mild lymphoid hyperplasia, and males have a severe defect in sperm-cell differentiation, which results in sterility[135]. The *Bak*$^{-/-}$ phenotype in mice is even less pronounced than that of the *Bax*$^{-/-}$ mice: their fertility and most of their tissues are normal[136], although they do exhibit mild platelet hypertrophy owing to a requirement for BAK to mediate the turnover of these anuclear cellular fragments[137].

Erythropoiesis
The production of red blood cells.

Remarkably, however, *Bax*/*Bak* double knockout mice display various severe defects, indicating extensive redundancy in their activities[136]. A large fraction of *Bax*/*Bak* double knockout mice die during embryogenesis (particularly on an inbred C57BL/6 background; D.C.S. Huang, unpublished observations) or perinatally (on a mixed genetic background). The neonates display various developmental deficits — such as webs between their digits, imperforate vaginas and abnormally increased numbers of lymphoid and myeloid cells — that are caused by the persistent survival of cells that normally undergo developmentally programmed death[136,138]. *In vitro* experiments with cells from *Bax*/*Bak* double knockout mice have shown that BAX and BAK are required for most forms of stress-induced apoptosis[139] and that these cells are even resistant to enforced expression of BH3-only proteins[140,141]. These results demonstrate that BAX and BAK are essential for apoptosis induction downstream of the BH3-only proteins.

Importantly, the heart, liver, lungs and many other organs develop normally in *Bax*/*Bak* double knockout mice[136]. This might indicate that apoptosis, or at least BAX/BAK-dependent apoptosis, is not crucial for normal morphogenesis and normal cell turnover in these organs. However, it remains possible that the closely related (but only relatively poorly studied) protein BOK has a crucial role in these tissues. It will therefore be informative to generate *Bok*$^{-/-}$, *Bax*/*Bok* and *Bak*/*Bok* double knockout mice and, perhaps most importantly, *Bax*/*Bak*/*Bok* triple knockout mice.

BH3-only proteins. Gene-targeting experiments have also helped to define the essential functions of BH3-only proteins (reviewed in REF. 142). Loss of BIM causes abnormal accumulation of lymphoid and myeloid cells and, on a mixed (C57BL/6x129SV) genetic background, fatal SLE-like autoimmune disease[143]. BIM is crucial for the deletion of autoreactive T and B cells[144,145] during their development and for the termination of immune responses[146]. *In vitro* experiments demonstrated that BIM is essential for apoptosis that is induced by growth-factor deprivation of a surprisingly broad range of cell types, including lymphocytes[143], osteoclasts[62], mast cells[147], epithelial cells, endothelial cells[63] and neurons[148,149]. BIM-deficient lymphocytes are also less vulnerable to deregulated calcium flux and have only minor resistance to γ-irradiation or treatment with glucocorticoids[143].

Loss of BID has little effect on developmental apoptosis and, although it renders mice resistant to Fas-induced hepatocyte apoptosis and fatal hepatitis[13,14], lymphoid cells from *Bid*$^{-/-}$ mice are normally sensitive to Fas ligand[14]. PUMA, by contrast, is crucial for DNA-damage-induced apoptosis, which is mediated by p53 (REFS 150–152). Curiously, although γ-radiation and UV radiation both trigger apoptosis in a p53-dependent manner, PUMA is essential for γ-radiation-induced apoptosis and NOXA is essential for UV-radiation-induced apoptosis within the same cell type (transformed fibroblasts)[153]. This suggests that, depending on the type of DNA damage and the nature of the molecular mechanism of damage detection, p53 might be activated in subtly different ways, thereby determining which of its two pro-apoptotic BH3-only target genes is activated preferentially. Alternatively, different forms of DNA damage might activate distinct pathways that act in parallel with p53 signalling to determine whether *PUMA*, *NOXA* or both are induced. PUMA is also crucial for cell death that is induced by certain p53-independent apoptotic stimuli, including cytokine deprivation or treatment with glucocorticoids or phorbol ester[150,151].

Mice that lack the BH3-only proteins that can only bind some pro-survival proteins (BAD, BIK, HRK, BMF or NOXA) have mild phenotypic abnormalities. This is consistent with the hypothesis that these BH3-only proteins are relatively weak killers compared to BIM, PUMA or BID, which bind to anti-apoptotic BCL-2 family members more promiscuously. Mice that lack BAD, BIK, HRK, BMF or NOXA are essentially normal in appearance and are normally fertile. In BAD-deficient mice, some cell types have subtle resistance to epidermal growth factor or insulin growth factor deprivation[154]; however, although these *Bad*$^{-/-}$ mice were reportedly abnormally prone to lymphoma development, this could not be reproduced in a subsequent study (P.N. Kelly and A.S., unpublished observations). Neuronal populations from *Hrk*$^{-/-}$ mice exhibited some resistance to nerve-growth-factor deprivation[155,156], but this was less pronounced than the protection afforded by loss of BAX[157], which indicates that other BH3-only proteins are probably also involved.

Because many cells express more than one BH3-only protein and several apoptotic stimuli can activate more than one BH3-only protein, functional overlap appears to be likely, and this has indeed been confirmed in early studies on double knockout mice that lack two BH3-only proteins. Although *Bim*$^{-/-}$ and *Bik*$^{-/-}$ male mice both have normal spermatogenesis, severe defects that cause male sterility became apparent in *Bim*/*Bik* double knockout mice[158]. As in *Bax*$^{-/-}$ males[135], the failure to produce mature sperm cells in *Bim*/*Bik* double knockout mice was a result of the abnormal accumulation and persistence of immature progenitors, which prevent differentiating cells from getting access to specialized niches on stromal cells.

Analysis of mice that lack both BIM and PUMA has shown that these two BH3-only proteins are the most crucial for apoptosis initiation in response to many death stimuli in a broad range of cell types, particularly those of haemopoietic origin[159]. For example, although loss of either BIM or PUMA alone renders lymphoid and myeloid cells resistant to cytokine deprivation or treatment with glucocorticoids, only the combined loss of both proteins provided as much protection as the overexpression of BCL-2 or the combined loss of BAX and BAK[159].

BH3-only versus core BCL-2 proteins. The breeding of mice that lack both a BH3-only protein and a BCL-2 pro-survival family member has helped to clarify functional relationships between these proteins. Remarkably, loss of a single allele of *Bim* prevents the fatal polycystic kidney disease and lymphopoenia caused by loss of BCL-2 (*Bim*$^{+/-}$ *Bcl-2*$^{-/-}$ mice), and loss of both *Bim* alleles even prevents the abnormal death of melanocyte

SLE-like autoimmune disease
A rodent pathology that resembles human systemic lupus erythematosus, which is commonly known as lupus.

progenitors and premature greying[131]. These results indicate that when BCL-2 is absent in renal epithelial stem cells, lymphoid cells and melanocyte progenitors, the physiological levels of BIM are not sufficiently opposed and cause abnormal apoptosis, presumably by neutralizing the activity of other pro-survival BCL-2 family members, such as BCL-XL or MCL1.

Concluding remarks

Our understanding of the regulation of BCL-2 family members and their roles in tissue dynamics of mammals has greatly expanded in recent years. BH3-only proteins sense signals to induce apoptosis and relay this information to core BCL-2 family members to initiate cell death. BAX and BAK are induced to change conformation and permeabilize the OMM. How BAX and BAK function in this process remains unclear despite intensive study. Difficulties in defining the structure of these proteins after conformational change, oligomerization and membrane insertion, as well as in determining their intermolecular binding partners in membranes, has impeded progress. The molecular trigger that induces BAX translocation and BAK activation has so far also eluded discovery.

The difference between anti- and pro-apoptotic BCL-2 family proteins needs to be defined both on a structural and functional basis. One model to explain the difference is that anti-apoptotic members can act as dominant-negative inhibitors of the pro-apoptotic members. The functional effect of BH3-only proteins binding to the anti-apoptotic BCL-2 family members also deserves more study. Recent advances in understanding the intermolecular interactions among the family members, corroborated at the level of animal studies, along with cell biology advances offer abundant clues for deciphering the remaining mysteries of cellular commitment to apoptosis.

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DATABASES

Entrez Gene: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene
BCL-2
UniProtKB: http://beta.uniprot.org/uniprot
APAF1 | BAD | BAK | BAX | A1 | BCL-B | BCL-W | BCL-XL | BID | BIK | BIM | BMF | BOK | caspase-8 | caspase-9 | DIABLO | HRK | MCL1 | PUMA | XIAP

FURTHER INFORMATION

Richard J. Youle's homepage:
http://neuroscience.nih.gov/Lab.asp?Org_ID=81
Andreas Strasser's homepage:
http://www.wehi.edu.au/facweb/indexresearch.php?id=24

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