CHAPTER FIVE

BH3-Only Proteins in Health and Disease

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Contents

Abstract

BH3-only proteins are proapoptotic members of the broader Bcl-2 family, which promote cell death by directly or indirectly activating Bax and Bak. The expression of BH3-only proteins is regulated both transcriptionally and posttranscriptionally in a cell type-specific and a tissue-specific manner. Research over the last 20 years has provided significant insights into their roles in tissue homeostasis and various pathologies, which in turn has led to the development of novel therapeutics for numerous diseases. In this review, a snapshot of the progress over this period is given, including our current understanding of their regulation, mode of action, role in mammalian development, and pathology.

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1. INTRODUCTION

The Bcl-2 family members are the arbitrators of the mitochondrial apoptotic pathway. These include both pro- and antiapoptotic proteins, the stoichiometry of which regulates mitochondrial integrity and cellular survival. Owing to their importance in cellular homeostasis during embryonic development, immune responses, involvement in various pathophysiologies, and cellular response to chemotherapeutic drugs, this family of proteins has been studied intensively for over a decade. The seminal finding of Bcl-2 function in B-cell lymphoma (Vaux et al., 1988; Tsujimoto et al., 1985) led to the identification of a wide range of proteins broadly classified as antiapoptotic (Bcl-2), proapoptotic (BH3-only), and the adaptor or the "pore-former" (Bax/Bak) Bcl-2 family members. They form a highly selective network of functional interactions that ultimately govern the permeabilization of the mitochondrial outer membrane and subsequent release of apoptogenic factors, such as cytochrome *c* (Doerflinger et al., 2015).

The "BH3-only" proteins are considered to be the sentinels of cellular stress (Puthalakath and Strasser, 2002). They recognize a diverse array of stimuli to initiate apoptosis—including growth factor deficiency and developmental cues—for the removal of damaged, unwanted, or infected cells (Strasser et al., 2011). The Bcl-2 family members share short stretches (<20 residue) of conserved sequence referred to as BH (Bcl-2 Homology) domains (Sato et al., 1994). This multidomain family includes Bcl-2 and various pro- and antiapoptotic proteins. The folded BH domains facilitate the binding of proapoptotic BH3-only proteins with very high affinity (Czabotar et al., 2014). In mammals, 8 BH3-only proteins have been characterized (Bim, Bad, Bmf, Bid, Noxa, Bik, Puma, and Hrk) and are defined by the presence of a single, 9–13 amino acid, BH domain called BH3 (reflecting the chronology of its discovery).

The BH3-only proteins are intrinsically disordered proteins and in the absence of binding to their partner protein(s), they exist at very high entropy levels—with the exception of Bid (Kvansakul and Hinds, 2014). In the case of Bid, it must be unfolded prior to caspase cleavage and activation (Shamas-Din et al., 2013). The BH3 domain folds into an α-helical bundle only upon its interaction with the hydrophobic groove of the prosurvival Bcl-2 family proteins (Rautureau et al., 2012; Sattler et al., 1997). Mutational analyses have demonstrated that the BH3 domain is required for the binding BH3-only proteins to Bcl-2-like prosurvival proteins and, thereby, to initiate

apoptosis. In mammals the BH3-only proteins differ in their expression pattern and mode of activation. Studies in gene-targeted mice have indicated that different BH3-only proteins are required for the initiation of programmed cell death by distinct apoptotic stimuli. These studies also revealed that they are spatially and temporarily regulated (Wong and Puthalakath, 2008), allowing them to play an important role in development and ontogeny. Analyses of patient-derived tissue samples has also revealed their role in the onset and development of diseases, such as cancer (Ng et al., 2012) and sepsis (Weber et al., 2008). Thus, understanding the regulation of their expression and the structural basis of how BH3-only proteins induce apoptosis have greatly helped in the development of novel therapeutics for treatment of various diseases. In this review, we provide a brief snapshot of the present state of knowledge of the involvement of BH3-only proteins in some important diseases and some suggestions on future research direction.

2. BETWEEN THE QUICK AND THE DEAD

The stoichiometry between anti- and proapoptotic BH3-only proteins determines cellular survival, and therefore, the levels of BH3-only proteins are subject to very stringent regulation, which limits their cellular abundance. This is achieved through both transcriptional and posttranslational means (Puthalakath and Strasser, 2002; Wong and Puthalakath, 2008). BH3-only proteins interact with posttranslational modifying enzymes for processes, such as phosphorylation/dephosphorylation, ubiquitylation, and proteolysis, with the inherently disordered nature of the BH3-only proteins facilitating the access of these modifying enzymes (Rautureau et al., 2010). BH3-only proteins have a limited abundance in cells that have not been subjected to apoptotic stress. Under normal homeostasis, Noxa (Craxton et al., 2012) and Bim (Wiggins et al., 2011) can be degraded at proteasomes without ubiquitylation—a process that can be blocked by Mcl-1. However, Bim is also subject to phosphorylation and ubiquitylation-dependent degradation (Puthalakath et al., 2007). During endoplasmic reticulum stress (ER-stress), protein phosphatase 2A (PP2A)-mediated dephosphorylation of Bim results in a lack of ubiquitylation, cellular accumulation, and eventually apoptosis (Puthalakath et al., 2007). In another example, the three isoforms of Bim—BimS, BimL, and BimEL (short, long, and extra-long, respectively) show differential affinity

for dynein binding, which correlates with their apoptotic potential (Puthalakath et al., 1999). Another posttranslational modification is the proteolytic cleavage of Bid, which is required for its interaction with Bcl-2 proteins. BH3-only proteins are also subject to transcriptional regulation as detailed in Table 1. This table is not exhaustive but it gives an indication of the many ways in which BH3-only proteins may be regulated. Multiple signals and stimuli can regulate one particular protein, or one signal can regulate multiple proteins, implying a complex network of control required for specificity. For example, whereas both Puma and Bim are regulated by ER stress, Bim appears to be more critical for regulating ER stress induced apoptosis in thymocytes (Puthalakath et al., 2007). In contrast, Puma is more important in neuronal cells (Reimertz et al., 2003).

3. FIDELITY VERSUS PROMISCUITY

In simple forms of multicellular eukaryotes, such as *C. elegans*, the process of apoptosis follows (Horvitz, 1999) a simple linear pathway (i.e., EGL-1→CED-9 → CED-4 → CED-3). In a healthy cell, CED-9 remains bound to CED-4 at the mitochondria, preventing it from activating the caspase CED-3 (Chen et al., 2000). Cells destined to die produce excess EGL-1, which binds to CED-9 and displaces CED-4, which then migrates to the nuclear envelope (presumably in association with CED-3) (Chen et al., 2000; Conradt and Horvitz, 1998). However, in higher order eukaryotes (i.e., mammals) the process is much more elaborate, involving multiple family members with tissue- and time-specific expression patterns and differential affinities. Apoptosis is triggered by either directly activating Bax-like proteins, or by neutralizing antiapoptotic Bcl-2 proteins. Initially, it was believed that the BH3-only proteins trigger apoptosis through promiscuous binding with all antiapoptotic family members. This was based on the structural similarities among various antiapoptotic molecules, including viral homologs (Huang et al., 2002), where BH domains 1, 2, and 3 form a hydrophobic cleft, to which BH3-only proteins bind (Kelekar and Thompson, 1998). Structures of BH3-only proteins bound to viral Bcl-2 (vBcl-2) proteins show they interact in a similar way to complexes of mammalian family members (Kvansakul and Hinds, 2013). Signaling specificity could arise from diverse modes of regulation, such as transcriptional and posttranslational modifications (Puthalakath and Strasser, 2002). Once expression is upregulated (or activated by caspase cleavage in case of Bid), the

Table 1 Mechanisms of regulation of BH3-only proteins.

Protein	Transcriptional/posttranslational	Stimulus	Regulatory protein	References
Bim	Transcriptional	ER stress	CHOP	Puthalakath et al. (2007)
	Transcriptional	βAR stimulation	c-Myc	Lee et al. (2013)
	Transcriptional	Factor withdrawal	FOXO3A	Huntington et al. (2007)
	Posttranscriptional	Myc inactivation	miR17~92	Li et al. (2014)
	Posttranslational	ER stress	PP2A	Puthalakath et al. (2007)
	Posttranslational	UV	DLC/JNK	Puthalakath et al. (1999); Lei (2003) Moujalled et al. (2011)
	Posttranslational	cAMP	PKA	Reimertz et al. (2003)
Puma	Transcriptional	ER stress	p53	Akhter et al. (2014)
	Transcriptional	β-Amyloid	FOXO3	Ekoff et al. (2007)
	Transcriptional	Factor withdrawal	FOXO3	Whelan et al. (2010)
Bmf	Transcriptional	Anoikis	Hif (?)	Puthalakath et al. (2001)
	Posttranslational	Anoikis	Dynein light chain	Wang et al. (2009)
Noxa	Transcriptional	ER stress	Epigenetic?	Villunger et al. (2003)
	Transcriptional	Genotoxic stress	p53	Towers et al. (2009)
		NGF withdrawal	c-Jun	Sanz et al. (2001)
Hrk	Transcriptional	IL3	DREAM	Sutton et al. (2003)
Bid	Posttranslational	Fas/CD95	Caspase 8	Motobayashi et al. (2009)
Bad	Posttranslational	IGF-1	Akt	Jiang and Clark (2001)
Bik	Posttranslational	sIgM ligation	PI3K	

BH3-only proteins target all prosurvival members. However, subsequent studies using affinity measurements clearly reveal hierarchical and selective binding between various BH3-only proteins and antiapoptotic Bcl-2 family proteins (Chen et al., 2005; Willis et al., 2005). Bim and Puma appeared to be promiscuous binders, interacting with all prosurvival members with equal affinity, whereas other members displayed differential affinity (up to 1000-fold) toward various prosurvival proteins. For example, while Noxa did not bind to Bcl-2, Bcl-Xl, or Bcl-W, it bound to Mcl-1 and A1 with nanomolar affinities. Furthermore, replacement of the Bim BH3 domain with that of BAD, Noxa, or Puma did not rescue the *Bcl-2*$^{-/-}$ phenotype (Merino et al., 2009). These differential affinities are reflected in the profound phenotypes observed in both Bim and Puma knockout mice compared with limited phenotype observed in other BH3-only protein knockouts. This information is invaluable in designing tailor-made BH3 mimetic drugs against cancers overexpressing different antiapoptotic Bcl-2 members.

4. THE ACTIVATION CONUNDRUM

Intracellular steady-state levels of BH3-only proteins increase in response to an apoptotic stress stimulus. This leads to activation of the multidomain proapoptotic proteins Bax and Bak, causing the release of proapoptogenic factors, such as cytochrome *c* (Jurgensmeier et al., 1998). However, the activation process of Bax and Bak has been the subject of great debate. The original hypothesis suggested the "hit and run" model where tBid could act as a membrane-targeting death ligand for Bak, leading to cytochrome *c* release and apoptosis (Wei et al., 2000). Although tBid appeared to be required for Bak oligomerization, tBid could not be detected in the complex, prompting the authors to propose the "hit and run" model where tBid no longer binds after inducing a conformational change in Bak. Since this study, carried out using isolated mitochondria, only examined Bid an alternative model must be established to explain the mode of activation by at least seven other BH3-only proteins. The model put forth by Kuwana et al. (2005) suggested two nonmutually exclusive modes of Bax/Bak activation. On the one hand, Bid and Bim (and even Puma) could activate Bax/Bak molecules directly whereas all other BH3-only proteins act as derepressors. The derepressors act by preventing the interaction between activators and

antiapoptotic Bcl-2 family members, thereby freeing the activators to directly activate Bax/Bak molecules. This model implies that the derepressors have higher affinities for antiapoptotic molecules [which is contrary to that observed by Chen et al. (2005)] and/or the steady-state levels of this group of proteins would be higher than the activators. Direct activation also predicts that there will be an increased binding between Bax/Bak and the activators in dying cells. Consequently, mice/cells deficient in Bim, Bid, and Puma would be phenotypically similar to Bax/Bak knockout cells, however, this is not the case (Nechushtan et al., 2001; Antonsson et al., 2001; Zhu et al., 2004; Villunger et al., 2011). Furthermore, these experiments were conducted in the presence of detergents (Bax is prone to detergent-induced conformational changes) and may not reflect the physiological state of Bax/Bak. Adopting detergent-free isolation techniques similar to those used for studying tetrameric potassium channels (Dorr et al., 2014) would assist greatly to resolve these issues.

Huang's group (Chen et al., 2005; Willis et al., 2007) proposed an alternative model (the indirect activation model) where, in a situation analogous to *C. elegans*, antiapoptotic Bcl-2 family proteins bind Bax/Bak molecules preventing their activation. Cellular induction of BH3-only proteins leads to the displacement of Bax/Bak molecules from this complex, leading to their activation and eventual apoptosis. This is consistent with the observation that potent killers, such as Bim and Puma have promiscuous, high affinity binding toward antiapoptotic Bcl-2 family proteins, whereas less potent killers bind only a subset of prosurvival proteins. Additionally, degradation of Mcl-1 by Noxa also supports an indirect activation model (Czabotar et al., 2007). However, this proposition also has drawbacks. Indirect activation of Bak appears to involve sequestration by Mcl-1 and Bcl-xL (Willis et al., 2005), but this model is more problematic for Bax. Bak exists constitutively on the membrane, Bax is predominantly cytosolic (whereas the antiapoptotic Bcl-2 family members are membrane bound) and requires some form of activation before it can relocalize to the membrane. Therefore, it could be assumed that while indirect activation is more likely the mode for Bak, the balance of evidence suggests that direct activation is the probable means of Bax activation (Wang et al., 1996; Desagher et al., 1999; Wei et al., 2000). These three models of Bax/Bak activation are shown in Fig. 2. Resolving these issues (i.e., how BH3-only proteins kill) is a key step toward tailoring therapeutic agents based on BH3-mimetics.

5. BH3-ONLY PROTEINS, HOMEOSTASIS, AND DEVELOPMENT: IT'S A MATTER OF LIFE AND DEATH

In spite of the controversial views on Bax/Bak activation, the role of Bim, Bid, and Puma in this process is undisputed and therefore their role is crucial in the mitochondrial apoptotic pathway. Mitochondrial apoptosis plays a central role in cell death "from inside out" (i.e., tissue homeostasis and organ development). Therefore, its deregulation leads to a variety of diseases. In this section, we will discuss the present state of knowledge on the role of BH3-only proteins in mammalian development, diseases associated with its deregulation, and attempts to harness the potential of our understanding of BH3-only protein regulation in developing therapeutics to treat various diseases.

5.1 BH3-Only Proteins and Homeostasis

Developmental homeostasis dictates the way animals develop. These homeostatic mechanisms operate through a highly integrated network of controls, including positive and negative feedback loops, responding to a wide range of stimuli including developmental cues. Homeostatic regulation by apoptosis plays an important role in tissue development and in formation of the neural network (Bredesen, 1995). The role of programmed cell death in vertebrate ontogeny and development was appreciated in the 1950s (Glucksmann, 1951), which predates the coining of the term "apoptosis" by a couple of decades (Kerr et al., 1972). However, the advent of gene knockout technology and generation of mouse models with precise genetic ablation helped to shape our understanding of the role of apoptosis, particularly the role of BH3-only proteins, in mammalian physiology and pathophysiology.

5.1.1 If No Phenotype, Cross it With Bim$^{-/-}$

One of the earliest gene knockout models with a tangible phenotype was generated by the Strasser lab in the late 1990s (Bouillet et al., 1999). A significant number of *Bim*$^{-/-}$ mice die in utero before E9.5, suggesting that Bim plays a role in early embryonic development (Bouillet et al., 1999). The reason for this is yet to be determined, but it is tempting to speculate that this phenotype may be similar to that observed in *Bax*$^{-/-}$/*Bak*$^{-/-}$ (Wei et al., 2001), *Capase 9*$^{-/-}$ (Kuida et al., 1998; Hakem et al., 1998), and *Apaf*$^{-/-}$ (Yoshida et al., 1998) mice, which all exhibited embryonic lethality in the

absence of apoptosis. Subsequent studies have shown, unequivocally, the role of Bim in tissue homeostasis in adult mice. *Bim*$^{-/-}$ mice accumulated abnormal levels of white blood cells, including T cells, B cells (particularly the antibody secreting plasma cells), and cells of the myeloid lineage (Bouillet et al., 1999). Although the number of megakaryocytes was not elevated, surprisingly, the platelet count was abnormally low and these mice exhibited thrombocytopenia. The reason for this was not clear at the time, however, in light of the role Blc-xL-regulated apoptosis plays in the generation of platelets (Mason et al., 2007), it could be concluded that Bim acts as a rheostat in the production of platelets. In addition to regulating the immune system from a developmental perspective, Bim also plays a crucial role in modulating the immune response, for example, in thymic negative selection (Bouillet et al., 2002), in negative selection of peripheral T cells (Hildeman et al., 2002), in removal of autoreactive B cells (Enders et al., 2003), and in the shutdown of acute T-cell immune responses to viral infection (Pellegrini et al., 2003).

The role of Bcl-2, the archetypal member of the family, in developmental homeostasis is well recorded (Veis et al., 1993). Although *Bcl2*$^{-/-}$ mouse embryos develop normally, these mice display postnatal growth retardation and early mortality. The thymus showed massive apoptotic involution, mirroring the phenotype observed in *Bim*$^{-/-}$ mice. Furthermore, these mice had polycystic kidney disease and graying with the second hair follicle cycle. Initially, it was assumed that this was due to the role that Bcl-2 played in the redox-regulated melanin biosynthetic pathway. However, all these defects observed in the *Bcl-2*$^{-/-}$ mice could be completely reversed with simultaneous removal of Bim (Bouillet et al., 2001); this demonstrates the crucial role that Bim plays in homeostatic regulation in many tissues. Additionally, unpublished work from our own laboratory shows that a deficiency of Bim affects organogenesis (Fig. 1). Splenomegaly observed in *Bim*$^{-/-}$ mice was attributed to a lack of apoptosis, leading to an enlarged spleen from the accumulation of excess lymphocytes. However, this increased organ size, also seen in other tissues including heart and lung, cannot be attributed solely to lack of apoptosis. In heart tissue, the size of the average cardiomyocyte is twice that of WT under normal homeostatic conditions [Fig. 1A–B and (Lee et al., 2013)]. These cells express significantly elevated levels of beta-adrenergic receptor 2 (β_2-AR), Vascular Endothelial Growth Factor (VEGF), and B-type natriuretic peptide (BNP) and increased Protein kinase A (PKA)/Akt phosphorylation (Fig. 1C). It appears that, at least in the case of cardiomyocytes and lymphocytes (Lee et al., 2013), Bim regulates cellular growth and proliferation. It could be argued that, in the absence of Bim, lack of apoptosis

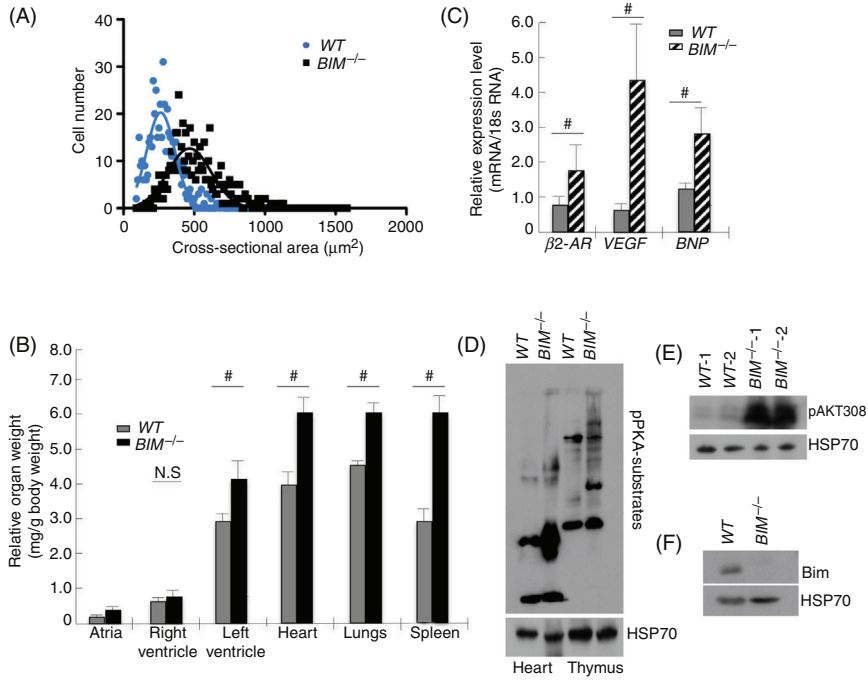

Figure 1 Bim ablation leads to selection of cells with increased proliferation potential. (A) Cross-sectional area measurement of cardiomyocytes from WT and *Bim*$^{-/-}$ mice. (B) Relative organ weight between WT and *Bim*$^{-/-}$ mice. (C) Increased gene expression in the absence of Bim. (D) Increased PKA activation in *Bim*$^{-/-}$ heart and thymus. (E) Increased Akt activation in *Bim*$^{-/-}$ heart muscle. (F) Western blot to confirm the identity of *Bim*$^{-/-}$ tissues. Error bars ± SD, $n = 3$. #$p < 0.005$–0.05.

drives selection pressure toward cells expressing increased β-ARs and/or increased PKA and PI3K/Akt signaling, leading to increased cellular growth and proliferation (Fig. 1D–F). Of note, the second messenger cyclic AMP (cAMP) is the main driver of the PKA pathway and the role of cAMP in cytolysis and ontogeny in shaping palatal development in rats was first reported in 1972 (Pratt and Martin, 1975). Yet another example of BH3-only protein involvement in the homeostatic control of tissue sculpturing is the clearing of the lumen in the terminal buds of mammary glands during puberty, which is a Bim-dependent process. However, the role of other BH3-only proteins in homeostatic control is less studied and mostly in Bim-null background where the phenotype is more apparent. This includes the role of Puma in lymphocyte development (Erlacher et al., 2006), and Bmf in B-cell homeostasis, mammary acinar morphogenesis

(Pinon et al., 2008), and utero-vaginal development (Hubner et al., 2010). Table 2 gives a list of developmental processes that are potentially regulated by BH3-only proteins. Whereas the roles of Bim, Bmf, Puma, and Bid are characterized by genetic deletion in mouse models, the roles of other members are inferred by association only.

5.1.2 Breaking Bad: Beyond Apoptosis

While most BH3-only proteins are studied in the context of apoptosis in tissue homeostasis, Bad is an exception. Initial studies reported that the apoptotic activity of Bad was regulated by Akt phosphorylation. However, subsequent studies, involving genetic knockout mice, revealed no apoptotic phenotype. This could be for many reasons, including redundancy among BH3-only proteins. However, a later study (Chattopadhyay et al., 2001) found that Bad, as a heterodimeric complex with Bcl-xL, could regulate S-phase progression. This study presented a compelling case using MEFs, although its relevance for the regulation of cellular homeostasis in vivo has not been determined. Despite this, the studies on the role of Bad in regulating mitochondrial energetics have gone beyond the realms of intellectual pursuit to a potentially significant translational outcome. Pioneering work by the Korsmeyer group (Danial et al., 2003) demonstrated that Bad can act as a sentinel for glucose levels in the pancreatic islets, thereby regulating glucokinase activity (GK), respiration, and cellular energetics. Mouse models developed subsequent to this initial finding demonstrated the potential of Bad-BH3 mimetics for restoring beta cell function and insulin production in diabetic mice (Danial et al., 2008). Furthermore, structural studies (Szlyk et al., 2014) also revealed that the Bad-BH3 phosphomimetic drug engages a previously uncharacterized region near the enzyme's active site without affecting the allosteric regulation of the enzyme. Based on studies conducted in mice (Ljubicic et al., 2015), where the phospho-Bad-BH3 mimetic protected mice from beta cell loss and diabetes, it could present itself as a new frontier in the treatment of type 2 diabetes.

Nonapoptotic roles for Bid are highly controversial. Bid was shown to have an inherent lipid transferase activity, leading to augmented lipid transfer from the ER membrane to mitochondria (Esposti et al., 2001). However, these experiments were conducted with either isolated mitochondrial and ER membranes or liposomes, and the in vivo relevance of this study is yet to be established. Moreover, an altered lipid profile in Bid knockout mouse organs has not yet been reported. Bid has also been reported to contribute to mitochondrial ROS generation, which, in turn, leads to NFκB activation

Table 2 Developmental and homeostatic roles of BH3-only proteins.

Protein	Tissue affected	References
Bim	Lymphocyte homeostasis	Bouillet et al. (1999)
	Thymic negative selection	Bouillet et al. (2002)
	Negative selection in the periphery	Hildeman et al. (2002)
	Removal of autoreactive B cells	Enders et al. (2003)
	Immune modulation after viral infection	Pellegrini et al. (2003) Huntington et al. (2007)
	NK cell homeostasis	Lee et al. (2013)
	Cardiomyocyte homeostasis	Hou and Van Parijs (2004)
	Dendritic cell homeostasis	Hakonen et al. (2014) O'Reilly et al. (2000); Hagenbuchner and Ausserlechner (2013)
	Pancreatic β-cell homeostasis	
	Neuronal cell homeostasis	
	Endothelial cell homeostasis	Naik et al. (2011)
Bmf	Mammary acinar development	Pinon et al. (2008)
	Utero-vaginal development	Hubner et al. (2010)
Puma	Lymphocyte homeostasis	Erlacher et al. (2006)
	Primordial oocyte homeostasis	Kerr et al. (2012)
Bid	Cell polarity regulation	Partanen et al. (2007)
	Terminal myeloid differentiation	Amanullah et al. (2002)
	Organization of mitochondrial cristae	Murphy et al. (2005)
Bad	Cell cycle regulation	Chattopadhyay et al. (2001)
	Hepatic energy metabolism	Gimenez-Cassina et al. (2014)
Noxa	Plasma cell precursor homeostasis	Bretz et al. (2011)
	Dendritic cell homeostasis	Vremec et al. (2015)
	Mitotic regulation	Zhong et al. (2014)
Hrk	Gonad development	Savulescu et al. (2013)
	Embryonic development	Semenova et al. (2008); Jurisicova et al. (2003)
Bik	Breast tissue remodeling	Xie et al. (2012)
	Spermatogenesis	Coultas et al. (2005)

upon exposure to low-doses of the carcinogen 5-MCDE. This has been attributed to its "antiapoptotic" activity (Luo et al., 2010). Apart from being counterintuitive, the authors failed to explain how low-dose carcinogen treatment led to Bid activation and translocation to mitochondria. Other controversial (nonapoptotic) roles for BH3-only proteins include Bid in the DNA damage response (Zinkel et al., 2007; Kamer et al., 2005; Liu et al., 2011; Kaufmann et al., 2007) and the NOD1-mediated inflammatory response (Yeretssian et al., 2011; Nachbur et al., 2012); Bim and Puma in the unfolded protein response (UPR) (Rodriguez et al., 2012; Herold et al., 2014; Puthalakath et al., 2007; Reimertz et al., 2003).

5.2 BH3-Only Proteins and Diseases

The role of BH3-only protein-mediated apoptosis in development, the immune response, and tissue homeostasis is well established. The relative abundance or the equilibrium between BH3-only proteins and antiapoptotic proteins determines a cell's susceptibility to apoptosis. Therefore, any disturbance in this equilibrium may lead to a variety of pathological conditions in humans. The prototypic member of the family, Bcl-2, was first identified in B-cell lymphoma (Vaux et al., 1988). Since then, prosurvival Bcl-2 family proteins have been implicated in a variety of cancers, including chronic lymphocytic leukemia, acute lymphoblastic leukemia, small cell lung cancer, prostate cancer, and non-Hodgkin's lymphoma. A lack of BH3-only protein function can have cellular effects similar to Bcl-2 overexpression, contributing to diseases, such as cancer and autoimmune disorders. Certain pathologies are also associated with overexpression of BH3-only proteins. In this section, we will discuss various diseases where BH3-only proteins are directly associated or implicated. Our understanding of their role as tumor suppressors comes from studies of both gene knockout mice and patient samples, whereas their role in other pathologies has been identified mostly from mouse models.

5.2.1 BH3-Only Proteins and Tumor Development

As BH3-only proteins play a central role in apoptosis following a genotoxic stress, it is highly likely that their absence allows cells to accumulate mutations that may lead to neoplasia. There is strong evidence that several BH3-only proteins function as tumor suppressors, and reduced expression level of BH3-ony proteins is a hallmark of many cancers. In mouse models, ablation of one copy of Bim accelerated c-Myc-induced B-cell lymphoma (Egle et al., 2004). This study also suggested that loss of Bim could substitute for the loss of p53. Another study from the same group found that combined loss of Puma and p21 could also accelerate c-Myc driven lymphomagenesis (Valente et al., 2015). There are many other mouse models where a role of Bim in tumor development has been reported (Merino et al., 2015; Vandenberg et al., 2014; Tan et al., 2005). Furthermore, $Bid^{-/-}$ mice developed myeloid hyperplasia that progressed to malignancy resembling chronic myelomonocytic leukemia (Zinkel et al., 2003). Similarly, Bad-deficient mice spontaneously developed diffused B-cell lymphoma (Ranger et al., 2003) and hepatocyte-specific loss of Puma diminished the incidence of toxin-induced hepatocellular carcinoma (Qiu et al., 2011). Thus, all these reports define a role for BH3-only proteins as tumor suppressors and hence

it would be counterintuitive to suggest that BH3-only proteins could act as oncogenes. However, in mouse models, there are at least two reports that suggest otherwise. A surprising finding from the Strasser group reported that loss of Puma ablated gamma-radiation-induced tumorigenesis (Michalak et al., 2010). Absence of Puma reduced the attrition rate in stem/progenitor cells or reduced the number of cycles of attrition and repopulation of stem/progenitor cells and thereby acts as a circuit breaker of lymphomagenesis. The authors also suggested that this could be one of the reasons for therapy-induced malignancies. Similarly, loss of Bid delayed tumorigenesis in chronic liver injury-mediated hepatocarcinomagenesis (Orlik et al., 2015). This report suggested that the tumor-promoting function of Bid in chronic liver injury is not related to enhanced proliferation or an impaired DNA damage response. In contrast, Bid suppresses p38 activity and facilitates malignant transformation of hepatocytes.

Additional insights about the role of BH3-only proteins in the development of tumors arise from genetic studies of human cancer samples. Bim also has been reported to be downregulated in many human cancers, such as Mantel cell lymphoma (Tagawa et al., 2005), Burkitt's, large B-cell lymphoma, multiple myeloma (Mestre-Escorihuela et al., 2007; De Bruyne et al., 2010), and myelodysplastic syndrome (Jilg et al., 2016). Deletions on chromosome 19 (19q13.3), which is linked to the Puma locus are often seen in gliomas, neuroblastomas, and in certain B-cell lymphomas (Karst and Li, 2007). Other examples of BH3-only proteins' involvement in human cancers include Bmf in colon, lung, and breast carcinoma (Schmutte et al., 1999; Wick et al., 1996); Bad in colon cancers and multiple myeloma (Lee et al., 2004b; Pompeia et al., 2004); Bid in gastric cancer (Lee et al., 2004a); Noxa in diffuse large B-cell lymphomas (Mestre-Escorihuela et al., 2007); Bik in renal cell carcinoma, glioma, colorectal cancers, head and neck cancers, B-cell lymphomas (Sturm et al., 2006; Bredel et al., 2005; Castells et al., 1999; Reis et al., 2002; Arena et al., 2003); and Hrk in gastric and colorectal cancers and glioblastoma (Nakamura et al., 2005, 2008; Obata et al., 2003). However, consistent with the observations in mice, there are examples where BH3-only proteins may not serve as tumor suppressor proteins, rather, enhance tumor formation. Elevated levels of Bid have been found in prostate, ovarian, colorectal, and brain cancers, in non-Hodgkin's lymphomas (Krajewska et al., 2002), and in hepatocellular carcinomas (Chen et al., 2001). It has been argued that initial overexpression of BH3-only proteins may facilitate selection of aggressive tumor cells during tumor progression, ultimately leading to silencing of these genes in advanced

cancers (Lomonosova and Chinnadurai, 2008). However, presence of elevated levels of Bid in metastatic epithelial hepatic carcinoma argues against such gene silencing (Chen et al., 2001). A more plausible explanation for this phenomenon is that these proteins are nonfunctional mutants similar to the p53 mutants found in many cancers (Watanabe and Sullenger, 2000). However, no sequence analyses of these overexpressed BH3-only proteins have been reported to date to substantiate this explanation. Also, in these tumors, overexpression of BH3-only protein is probably countered by simultaneous elevation of antiapoptotic Bcl-2 family proteins.

5.2.2 BH3-Only Proteins in Sepsis

Sepsis is defined as the host inflammatory response to severe, life-threatening infection with the presence of organ dysfunction. The host immune response in sepsis can be divided into two stages, a hyperinflammatory phase and a hypoinflammatory phase. During the hyperinflammatory phase, activated immune cells (mostly of the innate immune system) produce copious amounts of inflammatory cytokines, which can lead to multiple organ failure. However, improved treatment protocols have resulted in most patients surviving this stage and entering a protracted immune suppressive phase (Hotchkiss et al., 2013). This phase is characterized by extensive apoptosis of cells of the adaptive immune system (i.e., B cells and T cells) (Ayala et al., 1996; Efron et al., 2004; Hotchkiss et al., 1999), leading to prolonged lymphopenia with patients left susceptible to nosocomial infections. Therefore, lymphocyte apoptosis is a predictor of patient survival (Sherwood and Hotchkiss, 2013). The role of Bim in sepsis-induced lymphopenia is amply demonstrated by the work of Richard Hotchkiss (Chang et al., 2007; Peck-Palmer et al., 2009; Shindo et al., 2015). Others have shown that *Bim* is induced to very high levels in lymphocytes from patients with early stage severe sepsis (Weber et al., 2008). Therefore, taking into account approximately 50 failed drug trials in treating sepsis in the last three decades (all aimed at dampening the immune response during sepsis), a better understanding of apoptotic regulation by BH3-only proteins may help the development of more effective therapeutic strategies.

5.2.3 BH3-Only Proteins in Cardiomyopathy

Progressive loss of cardiomyocytes due to apoptosis is one of the main contributing factors to heart failure (HF) (Singh et al., 2000). Beta-adrenergic receptor (β-AR) stimulation increases cardiac contractility, accelerates cardiac relaxation, and increases heart rate. However, excessive

stimulation of β-ARs, by either excessive catecholamine signaling during stress (Singh et al., 2001) or autoantibodies (Jahns et al., 2004), results in apoptosis via activation of cAMP-dependent PKA (Xiao, 2001). Published reports from our laboratory have demonstrated the role of Bim (Moujalled et al., 2011; Lee et al., 2013) and Puma (Rahimi et al., 2013) in the apoptosis process regulated by the β-AR-PKA axis. The β-AR-PKA axis triggers apoptosis through the transcriptional induction of Bim in tissues, such as the thymus and heart. In these cell types, catecholamine-mediated apoptosis is abrogated by the loss of Bim. Induction of Bim is driven by the transcriptional coactivator CBP (CREB-binding protein) together with the protooncogene c-Myc. Association of CBP with c-Myc leads to an altered pattern of histone acetylation and methylation at the Bim promoter site (Lee et al., 2013). β-blockers have been extensively used to treat cardiomyopathy/heart failure for the last 50 years. Despite their common use, heart failure remains poorly controlled with a 5-year survival rate of only 50%. Apart from a subgroup of heart failure patients who do not tolerate β-blockers, their use can have serious consequences in asthma patients who suffer bronchospasm associated with β-blocker usage. Even in patients with mild-to-moderate HF, initiation of therapy and uptitration of β-blocking agents can be difficult, requiring both persistence and optimal management to allow target doses to be achieved. Patients with unstable hemodynamics usually cannot tolerate β-blockers, apparently due to blockade of sympatho-β-AR-PKA mediated functional compensation. Therefore, there is a need to develop novel therapeutics that improve the biological properties of the failing heart—that is, one that maintains the β-AR-mediated functional compensation and at the same time is capable of blocking the apoptotic arm of the β-AR pathway. Understanding the signal bifurcation between the contractile function and the apoptotic process will go a long way in achieving this.

5.2.4 BH3-Only Proteins in Diabetes

Diabetes is yet another pathology where involvement of BH3-only proteins is established. Experiments in animal models suggest that the death of pancreatic islet cells could be due to intrinsic upregulation of Bim and/or Puma, or due to defective negative selection of autoreactive T cells. Bim and Puma are upregulated in islet cells in response to proinflammatory cytokines or in hyperglycemic conditions (Barthson et al., 2011; Marroqui et al., 2014; Wali et al., 2014; McKenzie et al., 2010). In contrast, spontaneous autoimmune diabetes seen in nonobese diabetic (NOD) mice is

correlated with low levels of Bim expression and decreased thymic negative selection (Liston et al., 2004). In diabetes patients, low levels of cathepsin H were associated with a diabetes phenotype and proinflammatory cytokines dampened cathepsin H expression contributing to Bim upregulation in islets (Floyel et al., 2014). Other evidence for the involvement of BH3-only proteins in human diabetes is: increased mRNA levels of Bim and Puma in the islets of donors with type 2 diabetes (Wali et al., 2014), upregulation of Bim, and increased apoptosis of islets under diabetogenic conditions (Ardestani et al., 2014) as well as the involvement of Bid in complement activation and in the development of obesity and insulin resistance (Hillian et al., 2013). In mouse experiments, Bid has also been reported to be involved in death-receptor mediated apoptosis of pancreatic islet. However, the relevance of death receptor-mediated apoptosis in diabetes is not known to date (McKenzie et al., 2008).

5.2.5 BH3-Only Proteins in Neurodegenerative Disorders

Neurodegenerative diseases are a group of diverse disorders characterized by progressive loss of neurons and include Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD). In a study involving transgenic HD monkeys (Kocerha et al., 2014) expressing mutant HTT protein, miR-128a [a regulator of *Puma* transcript levels (Adlakha and Saini, 2013)] was found to be associated with the HD phenotype. This study also reported that miR-128a was downregulated in human HD patients. Similarly, ER-stress mediated upregulation of Bim and Puma has been reported in ALS (Matus et al., 2013). In an in vivo model, where 6-hydroxydopamine (6-OHDA) is used to induce apoptosis of dopaminergic neurons, leading to Parkinson's disease, transcriptional upregulation of both *Bim* and *Puma* was observed (Biswas et al., 2005a).

Thrombin is considered to be an inflammatory cytokine in Alzheimer's disease (Grammas and Martinez, 2014). Though thrombin prevents apoptosis in many cell types [including monocytes, osteoblasts, myoblasts, and astrocytes (Ritchie and Fragoyannis, 2000; Pagel et al., 2003; Chinni et al., 1999; Vaughan et al., 1995)], it is an apoptosis inducer in motor neurons (Turgeon et al., 1998; Smirnova et al., 1998). Consistent with these observations, Bim was upregulated in thrombin-induced apoptosis of cultured cortical neurons (Rao et al., 2007) and in postmortem brains of Alzheimer's disease patients, specifically within entorhinal cortical neurons (Biswas et al., 2005b). Finally, there was a selective induction of Bim in cerebral microvessels isolated from 18-month-old APPsw (Tg2576) mice—a model

of cerebral amyloid angiopathy—suggesting a pivotal role for Bim in β-amyloid-induced cerebrovascular degeneration in vivo (Yin et al., 2006).

5.2.6 BH3-Only Proteins in Arthritic Diseases

The role for BH3-only proteins in arthritic diseases could be twofold, as reported in diabetes. It could be either due to increased expression of BH3-only proteins resulting in excess cell death—as seen in osteoarthritis (OA)—or a lack of BH3-only protein expression, leading to excessive inflammatory responses as seen in rheumatoid arthritis (RA). OA is a chronic degenerative cartilage disorder characterized by increased apoptotic death of chondrocytes. Studies with mouse and human chondrocytes showed a c-Jun-dependent upregulation of Puma in response to IL-1β leading to apoptotic death. Consistent with this, immunohistochemical studies revealed that the Puma and c-Jun proteins were upregulated in chondrocytes from the articular cartilage of OA patients (Lu et al., 2014). In another study using chondrocytes isolated from the articular cartilage of OA patients, and in cultured mouse chondrocytes treated with IL-1β, Bim appeared to be upregulated in a c-Jun-dependent fashion (Ye et al., 2014). Furthermore, RNAi-mediated Bim knockdown reduced chondrocyte apoptosis—suggesting a role for Bim (Ye et al., 2014).

Macrophages possess widespread proinflammatory, destructive, and remodeling capabilities that can critically contribute to acute and chronic disease. Impaired apoptosis could lead to accumulation of macrophages, and activation of macrophages in the inflamed synovial membrane/pannus significantly correlates with the severity of RA (Kinne et al., 2000). Macrophages isolated from $Bim^{-/-}$ mice secreted elevated levels of inflammatory cytokines (Scatizzi et al., 2006). Similarly, mice deficient in Bid ($Bid^{-/-}$) showed a delayed resolution of K/BxN serum transfer-induced arthritis. $Bid^{-/-}$ mice also displayed increased inflammation, bone destruction, and pannus formation compared to wild-type mice (Scatizzi et al., 2007). Consistent with these observations in mice, macrophages isolated from the synovial fluid tissue of patients suffering from RA showed reduced Bim and Puma expression (Scatizzi et al., 2010)—highlighting a redundant role for BH3-only proteins in arthritic diseases.

5.2.7 BH3-Only Proteins in Hepatic Disorders

Apoptosis of hepatocytes is a universal feature of most hepatic disorders. The consequences of sustained liver cell death include hepatic fibrosis, which can culminate in cirrhosis, portal hypertension, and organ failure (Baskin-Bey and Gores, 2005). As is the case in most other tissues, a fine balance between

the anti- and pro-Bcl-2 family proteins is necessary for liver homeostasis—demonstrated by studies in mouse models. Spontaneous hepatocyte apoptosis in *Bcl-xL*$^{-/-}$ or *Mcl-1*$^{-/-}$ mice was reversed by simultaneous Bim deletion, and hepatocyte apoptosis caused by the BH3 mimetic ABT-737 was completely prevented in Bim/Bid double knockout mice (Kodama et al., 2013). Oxidative stress-induced liver damage or free fatty acid-mediated hepatocyte apoptosis is caused by increased Bim expression (Tao et al., 2013; Corazza et al., 2006; Malhi et al., 2006). Similarly, LPS-induced liver damage is abrogated in Bim/Bid double knockout mice (Kaufmann et al., 2009).

BH3-only proteins regulate the homeostasis of hepatocytes and also other resident cell types in the liver. For example, liver-activated CD8+ T cells showed increased expression of Bim and caspase 3, making the T cells prone to apoptosis following intrahepatic activation (Holz et al., 2008). HBV-specific CD8+ T cells from patients with chronic infection showed higher Bim expression, and blocking Bim-mediated apoptosis enhanced the recovery of HBV-specific CD8+ T cells (Lopes et al., 2008). Similarly, during chronic lymphocytic choriomeningitis virus (LCMV) infection, Bim played a dual role in the development of T cell-mediated apoptosis (Lauer et al., 2012). Absence of Bim in parenchymal cells attenuated liver damage, while loss of Bim in the lymphoid compartment enhanced hepatitis. In *Bim*$^{-/-}$ mice, the effect of Bim deficiency in the lymphoid compartment was counterbalanced by the reduced sensitivity of *Bim*$^{-/-}$ hepatocytes to T cell-induced apoptosis, resulting in the protection of the mice from hepatitis (Lauer et al., 2012). Other BH3-only proteins that have significant impacts on liver disease are Puma and Bid. Puma expression is a prognostic indicator of HBV-related hepatocellular carcinoma (HCC) (Peng et al., 2015). Bid is a BH3-only protein connecting TNF-receptor family-mediated apoptosis to the mitochondrial apoptotic pathway and, therefore, is involved in a wide range of hepatic disorders including, for example, alcoholic hepatitis, non-alcoholic steatohepatitis (NASH), cholestatic liver disease, hepatic fibrosis, and cirrhosis (Guicciardi and Gores, 2005, 2010).

5.2.8 BH3-Only Proteins in Autoimmune Disorders

BH3-only proteins, particularly Bim, are the key regulators of immune cell apoptosis (Bouillet et al., 1999; Enders et al., 2003). *Bim*$^{-/-}$ mice have defective negative selection in the thymus and in the periphery (Bouillet et al., 2002; Hildeman et al., 2002) suggesting that lack of Bim could lead to autoimmunity. *Bim*$^{-/-}$ mice accumulate self-reactive lymphocytes, develop autoantibodies, and—with certain genetic backgrounds—succumb

to SLE-like autoimmune disease later in life (Hughes et al., 2006), however, this does not lead to a fully manifested autoimmune state. However, experiments involving *Bim*$^{-/-}$/*lpr*/*lpr* (Fas receptor mutation) mice demonstrated the synergistic effect of these two cell death pathways in regulating autoimmunity (Hughes et al., 2008). Shutdown of an acute T-cell response to herpes simplex virus involved only Bim with no contribution by Fas (Hughes et al., 2008; Pellegrini et al., 2003), whereas both pathways synergized in killing antigen-stimulated T cells in chronic infection with murine gamma-herpesvirus (Hughes et al., 2008). *Bim*$^{-/-}$/*lpr*/*lpr* mice developed remarkably enhanced and accelerated fatal lymphadenopathy and autoimmunity compared to mice lacking only one of these apoptosis inducers. Bim and Bmf have overlapping functions during mouse development, coregulating lymphocyte homeostasis and apoptosis in a nonredundant manner. Double deficiency of Bim and Bmf caused more B lymphadenopathy than loss of a single BH3-only protein alone and this was associated with autoimmune glomerulonephritis and a range of malignancies in aged mice (Labi et al., 2014). Similarly, mice deficient in both Bim and Puma spontaneously developed autoimmunity in multiple organs, and their T cells could transfer organ-specific autoimmunity. Puma- and Bim-doubly-deficient mice had a striking accumulation of mature, single-positive thymocytes, suggesting an additional defect in thymic deletion was the basis for disease (Gray et al., 2012). Most of the studies on the role of BH3-only proteins in autoimmunity have been conducted using mice, with convincing reports of their role in human disease only emerging recently. There are clear data that low levels of Bim expression enhance macrophage survival in the synovial fluid of RA patients (Scatizzi et al., 2010). Bim-BH3 mimetic treatment enhanced apoptosis without inducing cytotoxicity, ameliorated arthritis development, reduced the number of myeloid cells in the joint, and ameliorated arthritis development enhanced apoptosis without inducing cytotoxicity (Scatizzi et al., 2010). However, in certain other diseases, such as Sjorgen's syndrome, there was no altered sensitivity to apoptosis or expression of the BH3-only protein Bim in dendritic cells ruling out the involvement of BH3-only proteins (Vogelsang et al., 2014). Another human example is autoimmune lymphoproliferative syndrome (ALPS), where lack of apoptosis causes autoimmunity as well as excessive lymphocyte accumulation, particularly of CD4$^-$, CD8$^-$ alpha-beta T cells. Mutations in ALPS typically affect CD95 (Fas/APO-1)-mediated apoptosis, one of the extrinsic death pathways involving TNF-receptor superfamily proteins, but certain ALPS individuals have no such mutations. Instead, these individuals have activating

mutations in the NRAS oncogene, which do not impair CD95-mediated apoptosis but increase RAF/MEK/ERK signaling. This markedly decreases the proapoptotic protein Bim and attenuates intrinsic, nonreceptor-mediated mitochondrial apoptosis (Oliveira et al., 2007). Overall, based on the mice studies and human data, it appears that Bim is the most critical of all BH3-only proteins in regulating immune cell survival and autoimmunity.

6. CONCLUDING REMARKS

Intense investigations into BH3-only family proteins during the past two decades have led to a greater understanding of their structure, functional interactions, and role in normal physiology and pathophysiology. Although great strides have been made in understanding their regulation (transcriptional, posttranscriptional, and posttranslational), the specific mechanisms whereby they induce apoptosis (i.e., Bax/Bak activation) remain an enigma. Most recent advances were achieved through the generation of mouse models with specific and compound gene knockouts. While gene knockout mouse models have been of great value in unraveling the function of BH3-only and other proteins, the time, effort, and associated costs in generating such mice have been constraining bottlenecks. With the advent of disruptive technologies, such as CRISPR-mediated gene editing and Next Generation Sequencing, we may now generate knockout mice, and human cell lines, with relative ease. This will greatly aid in understanding the role of BH3-only proteins in a human context.

Our understanding of the role of BH3-only proteins in development and ontogeny has come, exclusively, from studies of mouse models, whereas our understanding of their role in various pathologies has come from studies of both mouse models and patient samples. Thus, we know their role in varied diseases, such as cancer, neurodegenerative disorders, inflammatory diseases (such as sepsis and arthritis), cardiovascular diseases, diabetes, and hepatic disorder (Fig. 2). Our understanding of the role of BH3-only proteins in diseases has led to the development of new generation therapeutics, such as BH3 mimetics for treating cancer (Delbridge et al., 2016). Furthermore, understanding the function of BH3-only proteins beyond apoptosis, such as the role Bad plays in regulating glucose-mediated insulin secretion from pancreatic beta cells (Danial et al., 2008), has led to the development of novel therapeutics for treating type 2 diabetes (Ljubicic et al., 2015). Despite these success stories, the readers of this review are warned of a cautionary tale; the

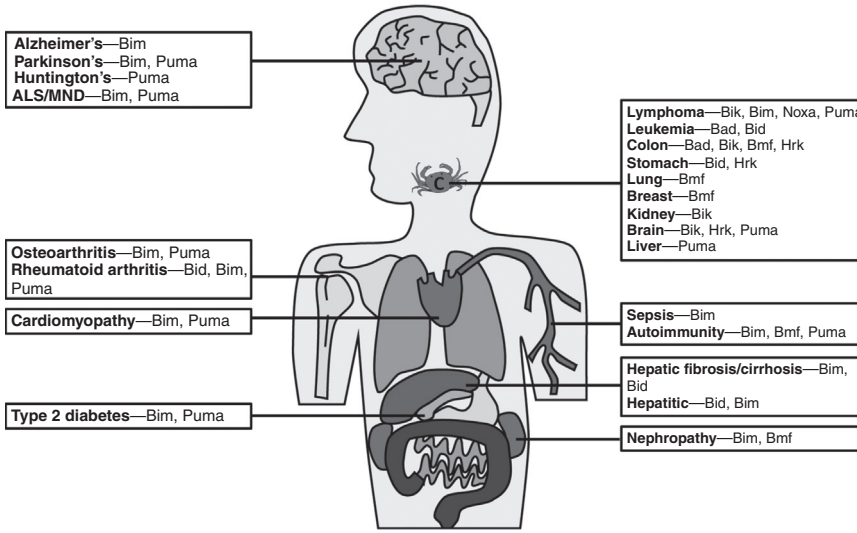

Figure 2 Role of BH3-only proteins in pathophysiology. While our understanding on the role of BH3-only protein in ontogeny exclusively came from mouse models, their role in pathology came from both mouse models and patient-derived samples. This figure is a snapshot on the role of BH3-only proteins in various human diseases (see text for details).

translational aspect of BH3-only protein research is overwhelmingly skewed toward treating cancer. BH3 mimetics could also be useful for treating other human diseases. For example, economic and health impact of cardiovascular diseases and neurodegenerative disorders are equally, if not more, significant than cancer. Sepsis alone kills more people than breast cancer, prostate cancer, and HIV/AIDS combined, with BH3-only proteins being implicated in all of these morbidities (Akhter et al., 2014; Lee et al., 2013; Chang et al., 2007). Recent reports also suggest that BH3-mimetics could be useful in treating autoimmune disorders (Mason et al., 2013; Cottier et al., 2014; Niss et al., 2015) and in treating acute childhood asthma (Tumes et al., 2008; El-Gamal et al., 2004). Further research to unravel molecular pathways involved in BH3-only protein expression (Lee et al., 2013) will undoubtedly lead to the development of therapeutics targeting these diseases.

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