Biochimica et Biophysica Acta 1813 (2011) 564–574

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbamcr

Review

Integrating stress signals at the endoplasmic reticulum: The BCL-2 protein family rheostat☆

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ARTICLE INFO

Article history:
Received 5 October 2010
Received in revised form 11 November 2010
Accepted 14 November 2010
Available online 29 November 2010

Keywords:
Endoplasmic reticulum
Unfolded protein response
BCL-2 family

ABSTRACT

The assembling of distinct signaling protein complexes at the endoplasmic reticulum (ER) membrane controls several stress responses related to calcium homeostasis, autophagy, ER morphogenesis and protein folding. Diverse pathological conditions interfere with the function of the ER altering protein folding, a condition known as "ER stress". Adaptation to ER stress depends on the activation of the unfolded protein response (UPR) and protein degradation pathways such as autophagy. Under chronic or irreversible ER stress, cells undergo apoptosis, where the BCL-2 protein family plays a crucial role at the mitochondria to trigger cytochrome *c* release and apoptosome assembly. Several BCL2 family members also regulate physiological processes at the ER through dynamic interactomes. Here we provide a comprehensive view of the roles of the BCL-2 family of proteins in mediating the molecular crosstalk between the ER and mitochondria to initiate apoptosis, in addition to their emerging functions in adaptation to stress, including autophagy, UPR, calcium homeostasis and organelle morphogenesis. We envision a model where BCL-2-containing complexes may operate as stress rheostats that, beyond their known apoptosis functions at the mitochondria, determine the amplitude and kinetics of adaptive responses against ER-related injuries. This article is part of a Special Issue entitled Mitochondria: the deadly organelle.

1. Introduction

Regulated cell death is a crucial event for development and cell physiology, and alteration of this process could result in the occurrence of severe human diseases such as inflammation, cancer, neoplasia, neurodegeneration or autoimmune disorders [1–5]. Subcellular organelle stress is observed in many pathological processes, where complex signaling responses mediate the adaptation to stress or trigger apoptosis when a critical threshold of damage is reached [6]. Execution of apoptosis depends in part on the activation of caspases, a process tightly regulated by the BCL-2 family of proteins at the mitochondria. Here, we summarize and highlight some relevant aspects of the crosstalk between the ER and mitochondria in the regulation of apoptosis. We also discuss how components of this pathway modulate signaling pathways through assembling protein complexes containing components of the BCL-2 protein family and stress regulators. Data discussed here suggest that several BCL-2 protein family members have novel functions beyond apoptosis in regulating ER calcium homeostasis and specialized stress responses such as autophagy and the unfolded protein response (UPR).

2. Regulation of apoptosis by the BCL-2 protein family

The BCL-2 family of proteins is essential for the regulation of intrinsic cell death, by controlling the release of cytochrome *c* and apoptosome assembling. The BCL-2 family of proteins is comprised by both pro- and anti-apoptotic members defined by different domains and classified by the sequence homology in up to four α-helical domains called *B*CL-2 *h*omology BH1 to BH4 [7] (Fig. 1A). The family is subdivided into pro-apoptotic members that contain BH1 to BH3 domains (i.e. BAX and BAK). The second subset is termed "BH3-only" members (i.e. BID, BIK, BIM, PUMA and NOXA) (Fig. 1A), which contain a single α-helical domain critical for activation of apoptosis

Abbreviations: ER, endoplasmic reticulum; UPR, unfolded protein response; IRE1α, inositol-requiring transmembrane kinase/endonuclease; PERK, PKR-like ER kinase; ATF6, activating transcription factor 6; XBP-1, X-Box-binding protein 1; JNK, jun N-terminal kinase; ERK, extracellular signal-regulated kinase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; AIP1, ASK1-interacting protein 1; TRAF2, TNF-receptor associated factor-2; JIK, c-Jun N-terminal inhibitory kinase; PTP-1B, protein-tyrosine phosphatase 1B; MCL-1, myeloid cell leukemia sequence 1; PP2A, serine/threonine phosphatase 2A; BI-1, Bax inhibitor 1; IP3R, inositol triphosphate receptor; RyR, ryanodine receptor; SERCA, sarcoplasmic/endoplasmic reticulum calcium ATPase; eIF2α, eukaryotic initiation factor 2; TMBIM, Transmembrane BAX Inhibitor Motif Containing; PTP, mitochondrial permeability transition pore

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doi:10.1016/j.bbamcr.2010.11.012

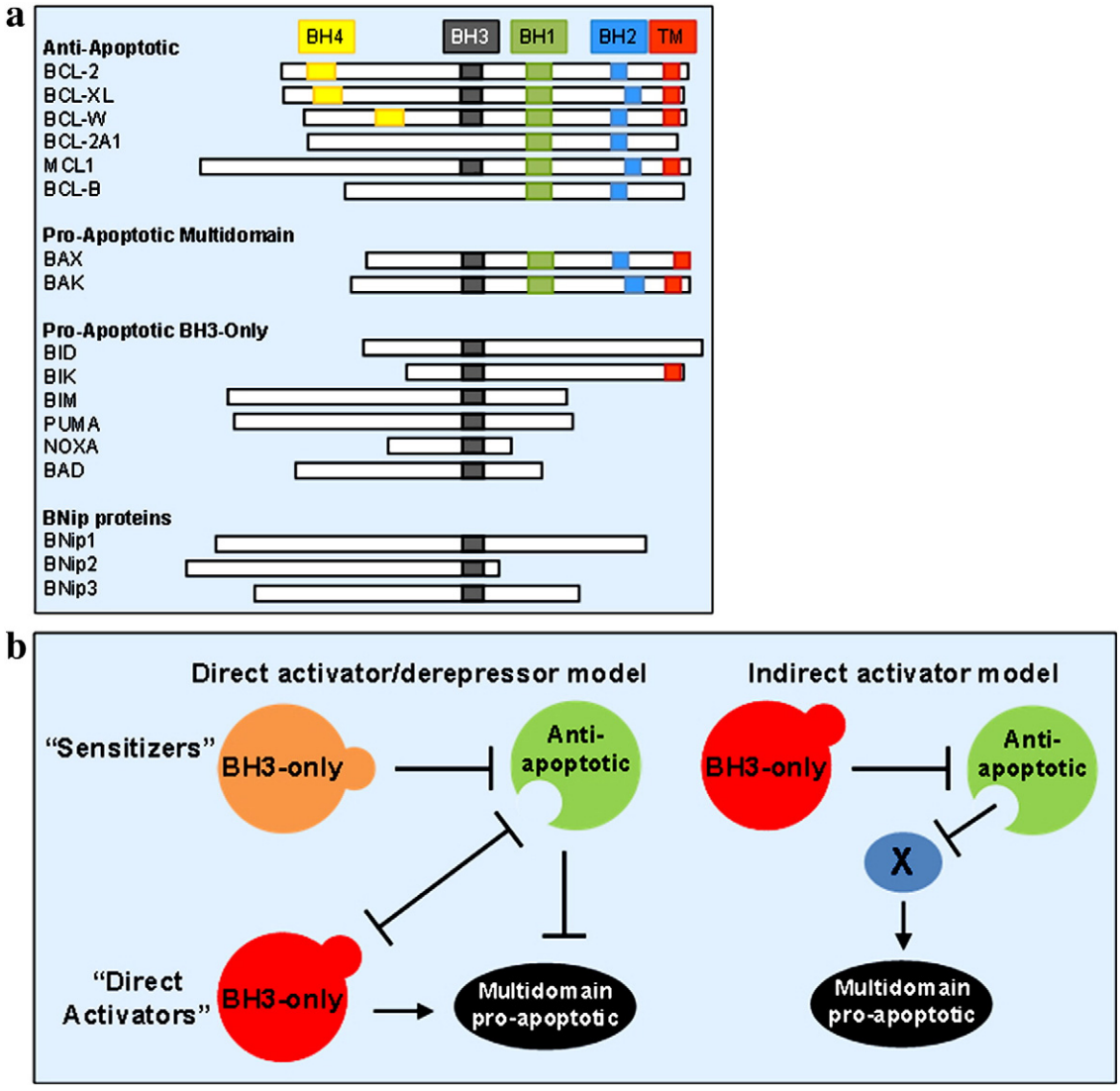

Fig. 1. The BCL-2 family of proteins. (a) The BCL-2 family of proteins is defined by the presence of up to four domains homologous to BCL-2. This group of proteins is functionally subdivided into pro- and anti-apoptotic proteins. Pro-apoptotic members can be further subdivided into more fully conserved "multidomain" members possessing BCL-2 homology domains 1, 2, and 3, or "BH3-only" members which display only about nine amino acids of sequence homology within the single death-promoting domain. (b) Left panel: One model of activation of BAX/BAK by BH3-only proteins. Some BH3-only proteins activate BAX/BAK through a direct binding (i.e. tBID, BIM, and PUMA, activator BH3-only proteins). They also bind anti-apoptotic proteins (BCL-2, BCL-XL, and MCL-1), which inhibit their pro-apoptotic activity. Other BH3-only proteins, termed de-repressors or sensitizers, antagonize and inhibit specific subsets of pro-survival BCL-2 proteins (BAD inhibits BCL-2 and BCL-XL, and NOXA inhibits MCL-1), lowering the threshold for activation of apoptosis by releasing activator BH3-only proteins bound to anti-apoptotic proteins. Right panel: Alternatively, another model proposes that differential binding of BH3-only proteins to anti-apoptotic BCL-2 family members may neutralize their anti-apoptotic activity, releasing or activating an unknown factor (here termed as X) that leads to BAX and BAK oligomerization at the mitochondria, and cytochrome *c* release.

[7–9] in addition to BNIP proteins, which contain poor conservation in the BH3-domain [10–12]. A second group of family members contains BH1, BH2, BH3, and BH4 domains, and is composed of several apoptosis-inhibitory proteins (i.e. BCL-2, BCL-X_L, MCL-1, BCL-w, BCL-2A1, BCL-B and many others) [8,13]. Several anti- and pro-apoptotic components of the BCL-2 protein family share similar three-dimensional structures, and a complex hierarchy of biochemical interactions operates to regulate apoptosis [9,14]. Genetic and biochemical studies indicate that BAX and BAK function in concert as a major core of the intrinsic apoptosis pathway in the mitochondria [15,16]. Upstream BH3-only proteins respond to particular apoptotic signals and subsequently trigger the conformational activation of BAX and BAK, inducing their intramembranous homo-oligomerization and resultant mitochondrial outer membrane permeabilization (MOMP) [17]. MOMP is a key step for the release of cytochrome *c* and the assembling of the apoptosome [9,17]. The BH3-only proteins can be functionally separated into two subtypes: (i) activators (i.e. tBID, BIM, and PUMA) that directly engage BAX and BAK to trigger cytochrome *c* release, but are sequestered by anti-apoptotic BCL-2 molecules; and (ii) sensitizers or inactivators (i.e. BAD and NOXA) that only bind to and antagonize anti-apoptotic BCL-2 members releasing activator BH3-only proteins [18–20] (Fig. 1B). Alternatively, differential binding to anti-apoptotic proteins may explain the action of activator and sensitizer/inactivator BH3-only proteins [21] (Fig. 1B), or a combination of both models [22].

Different BCL-2 family members have distinct patterns of developmental expression, subcellular localization, and differential responsiveness depending on the specific death stimuli (reviewed in [8,23]). For example, specific BH3-only proteins or combinations of them operate as sentinels of cellular damage in response to various death stimuli (i.e. oxidative stress, growth factor deprivation, DNA damage, death receptor engagement, ER stress, etc.) [8], and they can be activated either by transcriptional upregulation or through post-translational modifications [24].

3. ER stress-mediated apoptosis

3.1. The unfolded protein response

The ER has multiple complex functions, highlighting its major role in calcium storage and protein synthesis/folding. Other important functions include biosynthesis of steroids, cholesterol, and other lipids. Membrane-spanning and secreted proteins are synthesized in the ER and undergo post-translational modifications, folding, quality control and oligomerization. A physiological demand of high secretory activity, or pathologic conditions including proteasome inhibition, mutant protein expression, ER calcium depletion, or redox changes, interferes with oxidative protein folding at the ER lumen, resulting in the accumulation of unfolded or misfolded intermediates, a cellular condition referred to as "ER stress" [25,26].

To alleviate ER stress cells activate a signaling pathway known as the UPR. The UPR transmits information about the protein folding status in the ER lumen to the cytoplasm and nucleus to decrease the unfolded protein load [27]. However, if the UPR's mechanisms of adaptation and cell survival are insufficient to decrease the unfolded protein load, the UPR initiates cell death by apoptosis [28,29]. Therefore, the capacity to handle ER stress constitutes an important step in maintaining the balance between the life and death of a cell.

UPR signaling is initiated by at least three distinct transmembrane stress sensors: IRE1α (*I*nositol-*R*equiring transmembrane kinase/*E*ndonuclease), PERK (*P*KR-like *ER K*inase), and ATF6 (*A*ctivating *T*ranscription *F*actor 6). IRE1α is a Ser/Thr protein kinase and endoribonuclease that, upon activation, initiates the unconventional splicing of the mRNA encoding the transcriptional factor *X-B*ox-binding *p*rotein *1* (XBP-1) [30–32]. In mammalian cells, a 26 nucleotide intron of *xbp-1* mRNA is spliced out by activated IRE1α, leading to a shift in the coding reading frame. This splicing event promotes the expression of a more stable and potent transcriptional activator called XBP-1s that controls the upregulation of UPR-related genes involved in protein folding, redox metabolism, ER-associated degradation and protein quality control [33]. Indeed, XBP-1 expression is essential for the proper function of specialized secretory organs such as liver, pancreas, and salivary gland, as well as B-lymphocytes [34]. In addition, recent reports indicate that the RNAse activity of IRE1α mediates the rapid degradation of a subset of mRNAs, that either encode ER proteins with transmembrane domains or secreted proteins that may be difficult to fold [33,35,36], contributing to alleviation of ER stress.

Activated PERK phosphorylates the eukaryotic translation initiation factor 2α (eIF2α), inhibiting its activity [26]. eIF2α phosphorylation augments the specific translation of the mRNA encoding Activation of Transcription-4 (ATF4), a transcription factor essential for the upregulation of many UPR-associated genes that function in amino acid metabolism, redox homeostasis, autophagy, and apoptosis [26]. Finally, activation of ATF6 leads to its translocation from the ER membrane to the Golgi where it is proteolytically processed, releasing the cytosolic domain which translocates to the nucleus acting as a transcription factor that upregulates several ER chaperones and ERAD-related genes [26].

IRE1α activation also controls the activation of stress responses involving JNK (*J*un *N*-terminal *K*inase) [37,38], ERK (*E*xtracellular signal-*r*egulated *k*inase) [39], p38MAPK [40], NF-κB (*N*uclear *F*actor *k*appa-light-chain-enhancer of activated *B* cells) [41] and possibly the ER-resident caspase-12 in rodent cells [42]. Additionally, c-Jun N-terminal inhibitory kinase (JIK) was identified as a binding partner and modulator of the IRE1α/TRAF2 complex [42] (Fig. 2).

3.2. Crosstalk between the BCL-2 family of proteins and the UPR: a bi-functional role

The most conserved ER stress sensor is IRE1α. Different reports indicate that IRE1α activity is regulated by specific interactions with different pro- and anti-apoptotic proteins through a scaffold referred to as the *UPRosome* [34]. As part of this platform, we initially described a new function of BAX and BAK where they modulate the amplitude of IRE1α signaling at the ER membrane [43]. This regulation is mediated by a physical association between the cytosolic domains of IRE1α with

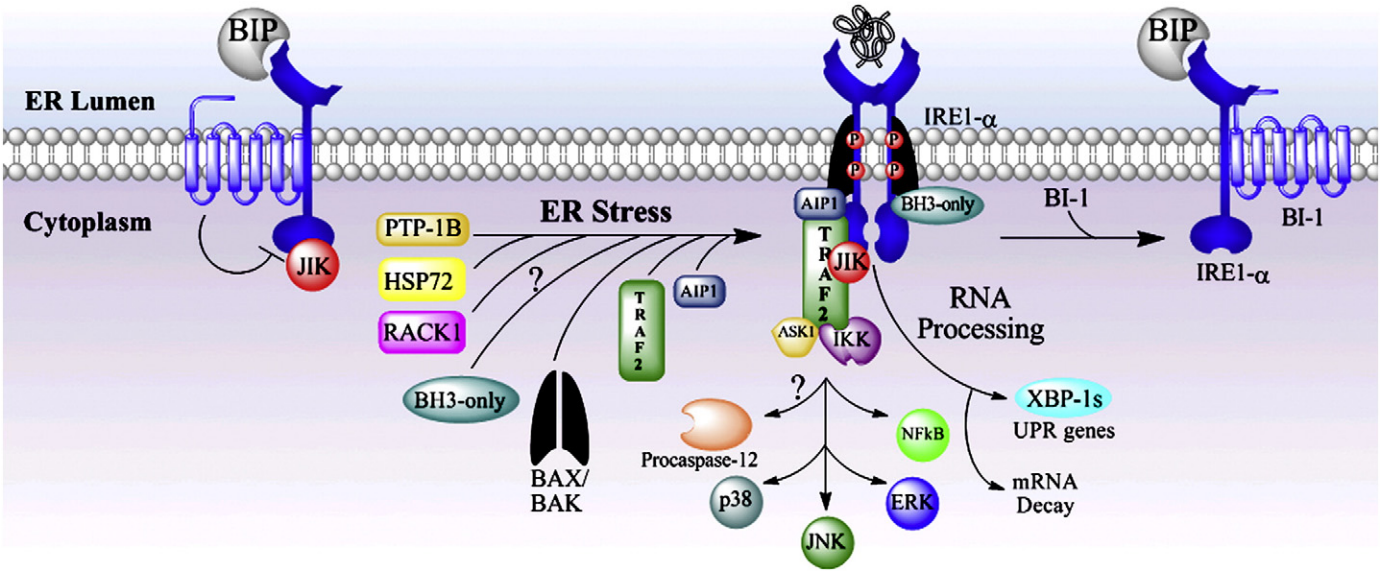

Fig. 2. Regulation of the *UPRosome* signaling platform by the BCL-2 protein family. Inactive IRE1α (monomer) binds in the luminal domain to the ER chaperone BIP and through cytosolic domain binds to BI-1, and JIK. Under ER stress conditions, accumulation of misfolded protein on the ER promotes IRE1α activation and releasing its partial inhibitory effect of BIP over IRE1α. The putative interaction between the ER luminal domain of IRE1α with unfolded proteins may also help in stabilizing its oligomeric and active state, leading to its autophosphorylation and the activation of the endoribonuclease domain. The *UPRosome* interactome is composed of several proteins that modulate the amplitude and kinetics of IRE1α activity, which may include PTP-1B, AIP1, HSP72, RACK1, BAX/BAK and presumably BH3-only proteins and other components. The active form of IRE1α interacts with AIP1 and TRAF2, initiating the activation of ASK1/JIK and the subsequent activity of alarm stress signals mediated by JNK, p38MAPK and ERK pathway. The sequestration of IKK by IRE1α/TRAF2 promotes NF-κB activation. Also, IRE1α may regulate the processing of murine pro-caspase-12, through the binding of TRAF2. In addition, IRE1α processes the mRNA of X-Box-binding protein-1 (XBP-1s), with the result of an active transcription factor termed XBP-1s. The RNAse activity of IRE1α also mediates the rapid degradation of a subset of mRNAs (mRNA decay). IRE1α can recover the inactive state by interacting with BI-1 and the chaperone BIP.

BAX/BAK [43] (Fig. 2). For example, BAX and BAK double knockout (DKO) cells display a specific deficiency in the autophosphorylation and oligomerization of IRE1α, leading to a stable association with BiP. Similarly, BAX/BAK deficient mice and cells show a decreased expression of IRE1α-downstream signals including JNK phosphorylation and XBP-1s expression under experimental ER stress conditions [43]. At the biochemical level, BAX and BAK form a protein complex with the cytosolic domain of IRE1α, possibly stabilizing its active form. The BH1 and BH3 domains were shown to be necessary for this regulatory activity [43].

Overall, these findings suggest a new role for pro-apoptotic family members to act as accessory factors for the instigation of certain UPR signaling events. In this line, during early steps of UPR response a subpopulation of BAX and BAK may instigate pro-survival effects in adaptation to ER stress through IRE1α signaling, or engage mitochondrial-mediated apoptosis when homeostasis cannot be restored (bi-functional roles).

Under prolonged ER stress IRE1α activity is turned off, suggesting the existence of components that negatively control its activity. Whereas PERK maintains its signaling, possibly sensitizing chronically damaged cells to apoptosis [32,44,45]. Accordingly, we and others recently reported that the ER located anti-apoptotic protein Transmembrane BAX Inhibitor Motif Containing (TMBIM)-6, also known as BAX inhibitor-1 (BI-1), regulates IRE1α activity [46–48], and it is required for the inactivation of IRE1α [49], possibly due to a concerted mechanism that requires a direct binding and displacement of BAX/BAK from the *UPRosome* [48,49] (Fig. 2). BI-1 is an ER-located protein that is predicted to have anti-apoptotic activities, contained within the TMBIM family of evolutionary conserved proteins [50–52]. Although BI-1 was identified on a yeast screening as a gene that blocks BAX-mediated toxicity, immunoprecipitation experiments failed to detect a physical interaction with BAX [53]. Interestingly, BI-1 physically interacts with BCL-2 and BCL-X_L [49,53]. However, it is not known what the functional impact of protein–protein interactions between BI-1 and BCL-2 family members are. It may be feasible that they form heterodimeric complexes that synergize in the inhibition of apoptosis.

Whether or not other BCL-2 family members modulate the IRE1α *UPRosome* remains unexplored. Interestingly, the specific expression of the BH3-only proteins BIM and PUMA at the ER membrane leads to the activation of IRE1α/JNK pathway on a BAK-dependent manner [54]. These findings were obtained in the absence of any ER stressor when the proteins are overexpressed and targeted to the ER, indirectly suggesting that these BH3-only proteins are potent activators of the IRE1α UPR branch. In this particular cell system, engagement of IRE1α/JNK was proposed to have a pro-apoptotic effect through an unknown signaling to the mitochondria [55]. It was explored whether or not this phenotype was related to a physical interaction between BIM/PUMA and IRE1α. The authors proposed a model where alterations of calcium homeostasis are an upstream component involved in the activation of JNK by BH3-only proteins.

IRE1α is also controlled by the expression of the ER-located protein tyrosine phosphatase 1B (PTP-1B) [40]. Similarly, the pro-apoptotic protein ASK1-interacting protein 1 (AIP1) specifically regulates and enhances IRE1α signaling under cellular ER stress, possibly through the formation of a protein complex [56]. Recently, HSP72 and RACK1 proteins were identified as new interacting proteins that instigate IRE1α activity [57,58] (Fig. 2). Interestingly, BAX, BAK, BI-1, AIP1, PTP-1B and HSP72 expression specifically affects IRE1α activation and not PERK-dependent signaling [40,43,49,58], and all of them have been linked to the regulation of apoptosis suggesting bi-functional roles [59].

TRAF2 interacts with pro-caspase-12 and promotes its clustering and activation in response to ER stress [42], which may be linked to IRE1α and apoptosis [37,42]. Since the IRE1α/TRAF2/ASK1 complex activates JNK signaling [37,38], it may also induce apoptotic cell death in an analogous fashion to what has been described for the TNF receptor [19,37,38,41,60,61], but the mechanism linking these two phenomena is not clear. In contrast to these models, IRE1α/XBP-1 signaling is traditionally linked to adaptation to ER stress and cell survival (reviewed in [27,62]).

3.3. BH3-only proteins and ER-stress-mediated apoptosis

Several reports in the literature addressed the possible role of BH3-only proteins in the modulation of apoptotic cell death under chronic or irreversible ER stress conditions and the molecular crosstalk with the mitochondria to trigger cytochrome *c* release [28,63]. Although the possible mechanisms related to the induction of apoptosis by ER stress are not fully understood, many relevant regulators have been identified in the last decade where BH3-only proteins have a crucial role in triggering BAX and BAK activation in the mitochondria (reviewed in [64–66]). Some BH3-only proteins that undergo transcriptional upregulation under ER stress include PUMA and NOXA [67]. These proteins are mostly known as genes upregulated by DNA damage, but under prolonged ER stress they are transcriptionally induced on a p53-dependent manner [68,69] (Fig. 3). However, it is not clear what the signaling events regulating p53 by ER stress are. Interestingly, a recent report suggested that CHOP may also regulate PUMA expression [70]. Another study revealed that NOXA can be induced on an ATF4-dependent manner, independent of CHOP or IRE1α expression [71]. An early cDNA microarray analysis showed that PUMA is upregulated by ER stress [67] and a global RNA interference screen for genes that regulate ER stress-mediated apoptosis corroborated the functional role of PUMA in this process [72], and identified NOXA as an additional apoptosis mediator. Additionally, MEFs cells lacking *puma* or *noxa* genes are partially resistant to ER stress-mediated apoptosis [69]. PUMA and NOXA are also upregulated under ER stress conditions in a melanoma cell context in addition to MCL-1 [73]. Anticancer agents that induce ER stress such as Eeyarestatin I, a potent inhibitor of protein translocation and inhibitor of ERAD, leads to NOXA upregulation by the ATF3 and ATF4 transcriptional factors [74].

Another BH3-only member, BIK, is primarily localized to the ER but it is neither transcriptionally nor post-translationally induced by ER stress [75]. BIK controls the release of calcium by BAK oligomerization at the ER triggering apoptosis (see below) [76]. Furthermore, BIM is transcriptionally and post-translationally upregulated by ER stress [67,77]. BIM mRNA levels are upregulated by the transcription factor CHOP [77]. In addition, BCL-2 is downregulated by CHOP [77] (Fig. 3). Moreover, BIM deficient mice are resistant to ER stress-induced apoptosis *in vivo*, similar to the phenotype described for cells and mice deficient in CHOP expression [78–80] and BAX and BAK conditional DKO mice [43]. BIM is also upregulated by post-translational mechanisms [24,81]. Under normal conditions, BIM is found in the dynein motor complex of the microtubule cytoskeleton. However, under ER stress BIM translocates to the ER where it may promote caspase activation through an unknown mechanism [82]. Dephosphorylation of BIM by the serine/threonine phosphatase 2A (PP2A) also increases its pro-apoptotic activity under ER stress condition in different cell types, preventing its ubiquitination and proteasomal degradation [77]. Correlative studies in rat primary cultures showed that BAD is also activated by dephosphorylation and produce apoptosis in cortical neurons undergoing ER stress [83]. Another BH3-only protein, BID, is post-translationally upregulated by caspase-2-dependent proteolytic activation upon ER stress, leading to BAX/BAK activation at the mitochondria [84], however a defined mechanism linking the UPR and caspase-2 is still lacking.

In addition to the mitochondria, BAX and BAK oligomerize at the ER membrane under ER stress conditions [85], a phenomena instigated by BH3-only proteins [15]. Interestingly, a new report suggest that activation of BAX and BAK proteins increases ER

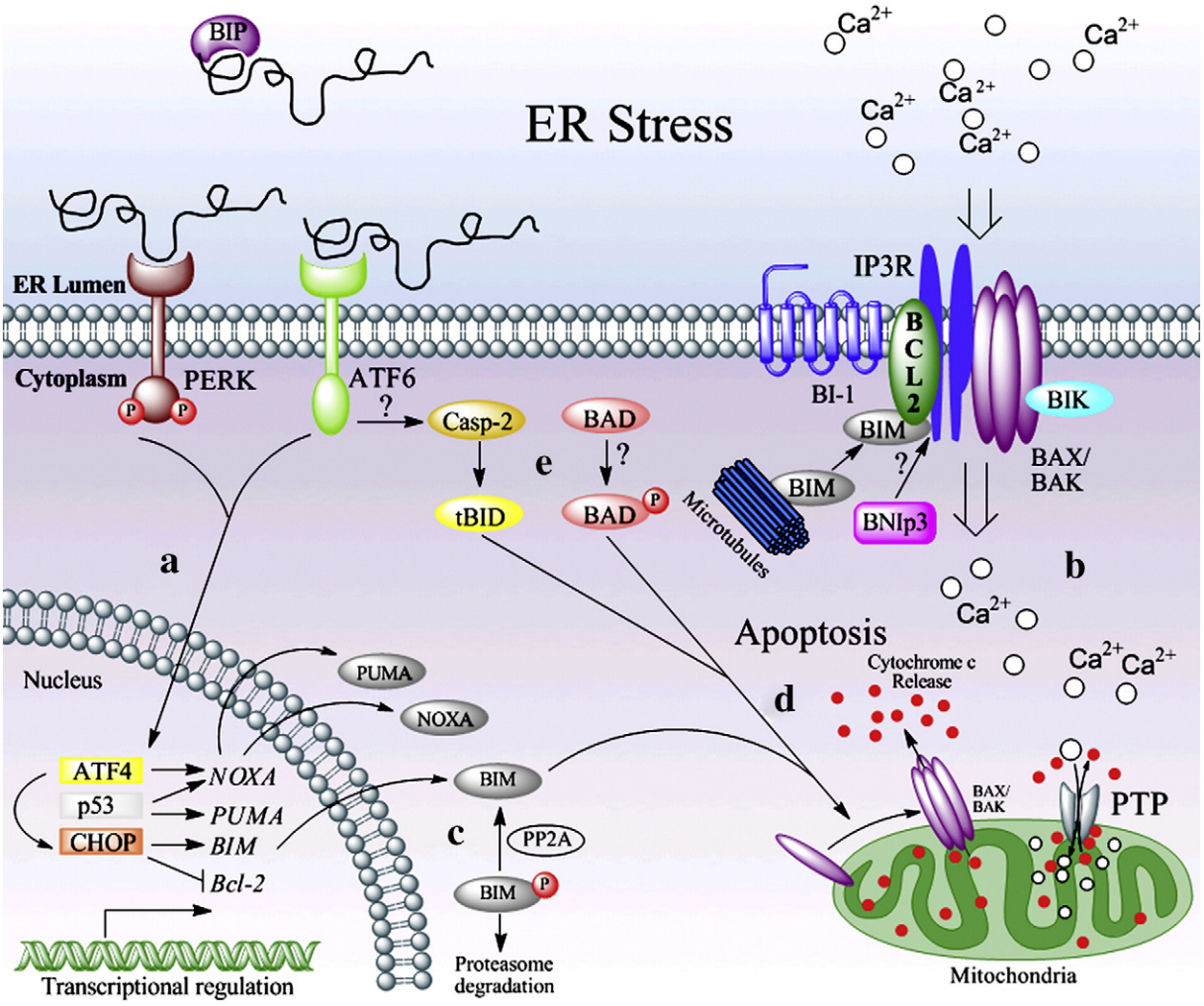

Fig. 3. Role of the BCL-2 protein family in the apoptotic crosstalk between ER and mitochondria during chronic ER stress. (a) The UPR stress sensors promote the transcriptional activity of ATF4, p53 and CHOP. PUMA and NOXA are transcriptionally induced in cells undergoing ER stress in a p53-dependent manner. BIM is also upregulated and BCL-2 is downregulated by the transcription factor CHOP. (b) BCL-2 family members also regulate ER calcium homeostasis at the ER. ER calcium release followed by mitochondrial calcium uptake may influence cytochrome *c* release by controlling the permeability transition pore (PTP). (c) BIM protein levels can be regulated by phosphorylation, ubiquitination and proteasomal degradation. BIM is desphosphorylated by PP2A increasing its pro-apoptotic activity. Under physiological conditions, BIM is found in the dynein motor complex of the microtubule cytoskeleton and could also associate with BCL-2 in the ER membrane. (d) The activation of BH3-only proteins BIM, PUMA and NOXA leads to homo-oligomerization of BAX and/or BAK at the mitochondria with the subsequent release of cytochrome *c* and caspase-dependent apoptosis. (e) BAD may also trigger apoptosis by its dephosphorylation under ER stress, and under the same conditions BID activates apoptosis when it is cleaved by caspase-2.

membrane permeability, leading to the release of luminal proteins during ER stress-induced apoptosis [86]. ER permeability may represent a new component regulating the activation of cell death. This novel observation may open the possibility of identifying new pathways in the regulation of ER stress-mediated apoptosis in an analogous fashion as the apoptosome. Interestingly, we described that BAX-channel inhibitors block apoptosis under different cell death settings, suggesting a direct role of the BAX forming pore activity on cell death [87]. It will be also interesting to explore if BAX/BAK pores at the ER directly control calcium release from the ER. The use of BAX-channel inhibitors may help address this hypothesis.

4. Relationship between the BCL-2 protein family and ER calcium homeostasis.

A large amount of evidence indicates that the expression balance between anti- and pro-apoptotic proteins at the ER membrane determines the steady state ER-calcium content, possibly by modulating a passive calcium leak (reviewed in [88–90]). This calcium-regulating activity by BCL-2-related proteins has a direct impact on the amount of calcium released after agonist stimulation (Fig. 3). For example, BAX and BAK DKO cells have decreased ER calcium content and stimulated release [85,91], similar to the phenotype of BCL-2 overexpressing cells (see examples in [92–98]). Different BH3-only proteins are located at the ER or translocate to its membrane under stress conditions and impact calcium homeostasis [76,99] (reviewed in [88–90]). Finally, BNIP3 (Bcl-2/adenovirus E1B 19-kDa interacting protein 3) is part of a BH3-only subfamily with poor conservation of the BH3 domain. Localization of BNIP3 to the ER membrane facilitated release of calcium and subsequently increased uptake of calcium into mitochondria [97]. Thus, the balance between different components of the BCL-2 family of proteins at the ER membrane may constitute a "fine tuning rheostat" for the regulation of calcium metabolism. TMBIM family members such as TMBIM6/BI-1 and its orthologue GAAP/TMBIM4 expression also alter ER calcium homeostasis possibly downstream of the BCL-2 family where they reduce ER calcium content [100–105].

At the biochemical and mechanistic level, several groups have shown that BCL-2 and BCL-X_L form a protein complex with the *i*nositol tri*p*hosphate *r*eceptor (IP3R) [106–111], possibly modulating the opening of a channel (Fig. 3). The IP3R, together with the *ry*anodine *r*eceptor (RyR), are the main channels that control ER calcium release

in cells. Phosphorylation of BCL-2 by JNK in a non-structured loop occurs at the ER membrane, negatively regulating its anti-apoptotic activity [88], in addition to its ability to control the ER calcium content [92,112]. Purification of the native protein complexes containing BCL-2 at the ER membrane identified the phosphatase PP2A [113] as an interacting partner that dephosphorylates the sites targeted by JNK. This regulation by PP2A may be also relevant to control ER calcium homeostasis.

An inactivation and destabilization of the ER Ca^{2+} importer, *s*arcoplasmic/*e*ndoplasmic *r*eticulum *ca*lcium ATPase (SERCA) is caused by its direct interaction with BCL-2 [114–116], resulting in reduced ER-calcium content. Thus, in summary, these data suggest that depending on the cellular context and the stimuli, different BCL-2 containing protein complexes may exist at the ER membrane to control calcium signaling. Hence, the balance between pro- and anti-apoptotic BCL-2 related proteins at the ER determine the ER steady state calcium content and the rate of calcium release after stimulation.

Calcium uptake by the mitochondria has a direct impact on the susceptibility of a cell to undergo apoptosis, influencing the drop in mitochondrial membrane potential, and the release of cytochrome *c* and caspase activation (Fig. 4). Interestingly, in an elegant study, Scorrano and co-workers described that the control of ER calcium by BAX and BAK has a specific effect on calcium mediated-apoptosis (i.e. arachidonic acid, ceramide or H_2O_2 treatment) and not ER stress [91]. On the other hand, reconstitution of BAX/BAK DKO cells with a mitochondrial-targeted BAX recovered the susceptibility of these cells to ER stress-induced apoptosis, without affecting the calcium phenotype. Interestingly, cytosolic calcium increases could trigger cytochrome *c* release independent of BAX and BAK through the opening of the mitochondrial permeability transition pore (PTP), a non-specific pore in the inner mitochondrial membrane (see reviews in [117,118]). Opening of the PTP leads to dissipation of the mitochondrial transmembrane potential ($\Delta\Psi_m$) and an influx of solutes. This causes expansion of the matrix, resulting in sufficient swelling to rupture the outer mitochondrial membrane and causing cytochrome *c* release. Although the molecular identity of PTP remains uncertain, different components are proposed; the best validated is Cyclophilin D, a target of cyclosporin A. Thus, the control of calcium metabolism by the BCL-2 family probably reflects a new function in cell physiology beyond the direct control of apoptosis, but it indirectly modulates mitochrondrial-mediated apoptosis through activation of the PTP.

5. Role of the BCL-2 protein family in autophagy

Autophagy refers to the global process by which intracellular components are recycled through lysosome degradation (reviewed in [119]). Autophagy acts as a critical survival response under starvation conditions in which the degradation of intracellular proteins and organelles provides a source of amino acids during poor nutritional conditions. Intracellular components can be delivered to lysosomes for degradation by three different mechanisms known as macro-autophagy, microautophagy and chaperone-mediated autophagy [119,120]. The best-studied form of autophagy is macroautophagy, hereafter referred to as autophagy. The hallmark of autophagy is the formation of double-membrane-bounded autophagosomes [121].

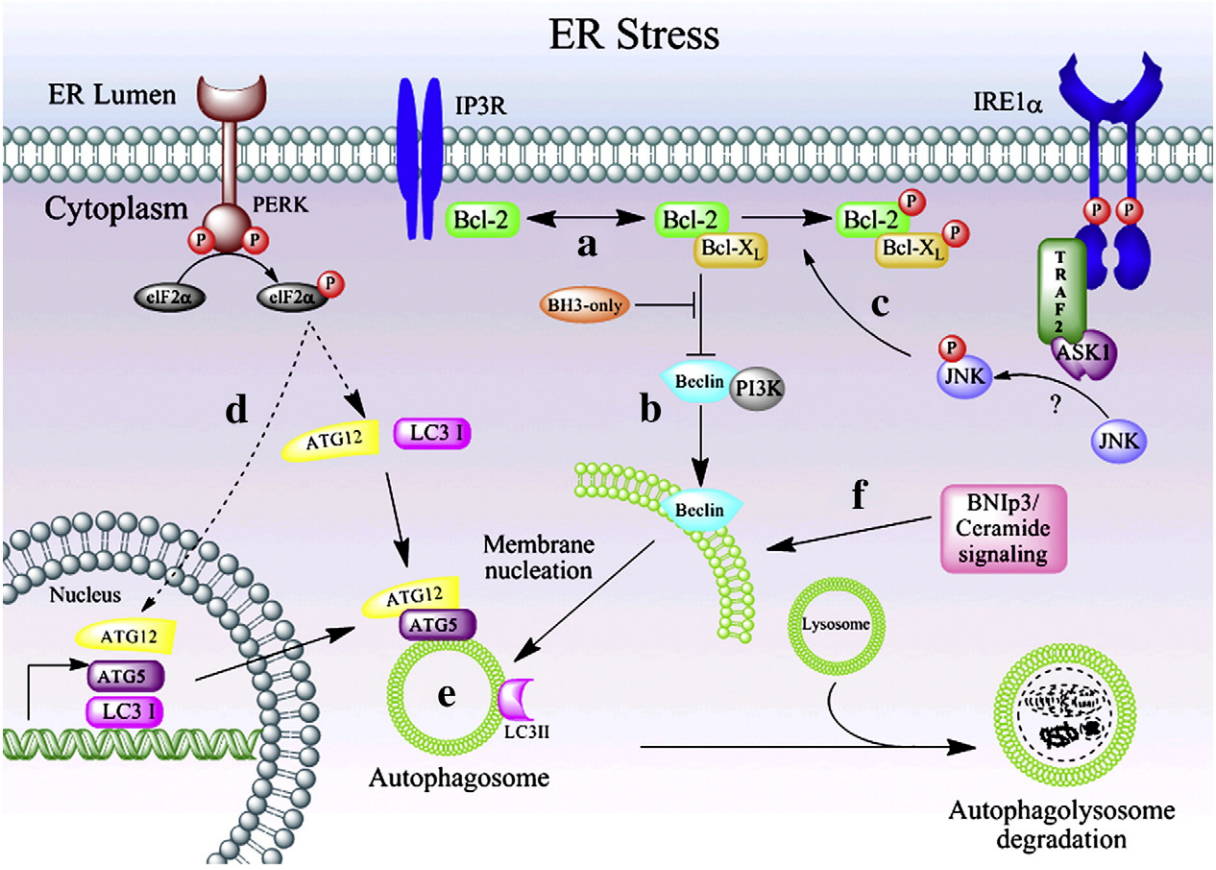

Fig. 4. Regulation of autophagy by the BCL-2 family members. (a) At the ER membrane BCL-2 and BCL-X_L are associated with the IP3R modulating BECLIN-dependent autophagy. (b) Beclin-1 is negatively regulated through an interaction with BCL-2/BCL-X_L at the ER membrane, and BH3-only proteins antagonize this interaction. (c) Upon ER stress, IRE1α and JNK get activated, where JNK may phosphorylate BCL-2/BCL-X_L, promoting autophagosome formation by releasing active Beclin-1/PI3K complex. (d) Activation of PERK may also activate autophagy through the transcriptional upregulation of ATG12, ATG5 and LC3. (e) The Beclin-1/PI3K complex initiates membrane nucleation by regulating downstream ATG12–ATG5 complex and LC3-II conversion to form autophagosomes. Lysosome fusion to the autophagosome forms the active autophagolysosome where proteins and organelles are degraded. (f) In addition, BNIP3 and ceramide signaling regulates autophagy.

Autophagosomes fuse with lysosomes to form autophagolysosomes, where intracellular components are degraded (Fig. 4). Autophagy is a highly regulated process with complex steps that are controlled by a family of *a*utophagic *r*elated *g*enes (termed *atg* genes) [119,122]. The generation of *atg* deficient mice unveiled the function of autophagy in diverse processes, including development, cell differentiation, tissue remodeling, immunity, host-to-pathogen response and cell death/survival under stress conditions [119]. Beclin-1 (also known as Atg6) is the first identified mammalian autophagy gene product [123]. Beclin-1 is a haplo-insufficient tumor suppressor that was originally isolated as a BCL-2-interacting protein [124–126]. BCL-2 negatively regulates Beclin-1 through a direct binding (Fig. 4) [127]. Surprisingly, this regulatory activity of BCL-2 on autophagy is specifically attributed to its expression at the ER membrane [127], suggesting that signaling events originating from the ER are crucial for autophagy. It is important to note that there is only a unidirectional regulation between BCL-2 and Belclin-1, since Beclin-1 binding to BCL-2 does not modify BCL-2 mediated apoptosis [128].

BCL-2/Beclin-1 complex formation also is regulated by BH3-only proteins, suggesting an extensive crosstalk between apoptosis and the autophagy regulatory components [129,130]. Most importantly, a functional BH3-like domain was identified in Beclin-1 and its mutation disrupted the interaction of Beclin-1 with BCL-X_L [129]. Expression of BAD decreased the interaction between Beclin-1 and BCL-X_L at the ER membrane, and experiments performed in *C. elegans* deficient in EGL-1, a BH3 containing protein, corroborated this model *in vivo*. Similarly, the pharmacological BH3 mimetic ABT-737 competitively inhibited the interaction between Beclin-1 and BCL-2/BCL-X_L, stimulating autophagy [129,130]. In addition, the BH3-only protein BNIP3 has been shown to regulate autophagy under different settings, possibly related to ceramide signaling [131–136]. It remains to be determined if BNIP3 affects the stability of the BCL-2/Beclin-1 complex. Finally, another report indicates that phosphorylation of BCL-2 by JNK is essential for the control of autophagy by Beclin-1 [137] (Fig. 4), a post-translational modification that affects the binding of BH3-only proteins to BCL-2 [92].

A connection between ER calcium homeostasis and autophagy occurs also through the IP3R [138–140] (reviewed in [141]). Stimuli that increase cytosolic calcium activate autophagy, which is blocked by BCL-2 [140]. Blocking the IP3R modulates autophagy that arises from specifically inhibiting BCL-2 or BCL-X_L targeting to the ER membrane. Unexpectedly, IP3R-dependent autophagy was attributed to the activation of Beclin-1 and other autophagic related genes, and this regulation was independent of calcium release, possibly due to a role of IP3R as a scaffold protein rather than a calcium channel. Finally, many laboratories have now shown that ER stress triggers autophagy, an effect that is also regulated by UPR stress sensors [138,142–147]. Autophagy may serve as a mechanism to eliminate damaged ER under stress conditions or to control the rate of ER expansion [145]. Unexpectedly, the activation of autophagy by ER stress requires IRE1α and is not inhibited by BCL-2 overexpression, a strategy that blocks autophagy mediated by IP3R, suggesting that there are at least two independent pathways controlling autophagy from the ER [138]. However, it remains to be determined if the IRE1α/JNK signaling branch regulates the BCL-2/Beclin-1 complex through phosphorylation. The direct phosphorylation of eIF2α by PERK is required for the LC3 conversion, a fundamental process for autophagy induction [142]. The PERK branch of the UPR possibly regulates autophagy at the transcriptional level [148,149].

6. Relationship between BCL-2 protein family and ER morphogenesis

Some pro-apoptotic members also have a role in the regulation of ER structure/function. Accordingly, co-expression of BAK with BCL-X_L or BAK mutant promote extensive swelling and vacuolization of ER cisternae [150]. Moreover, under similar conditions, the expression of upstream BH3-only activators recapitulates ER swelling and vacuolization just when RyR activity is inhibited. This effect is mediated by BAK, but not by BAX [150]. In addition, BAX and BAK may regulate the ER biogenesis through the interaction with IRE1α and activation of XBP-1 [43]. Moreover, experiments in non-apoptotic cells revealed a role of BAX and BAK in mitochondrial morphogenesis [151]. Interestingly, it seems that these two pro-apoptotic multidomain proteins are required for normal fusion of mitochondria into elongated tubules [151].

The BH3-only protein BNIP1 is another pro-apoptotic protein involved in the regulation of ER structure. In HeLa cells it has been shown that BNIP1 is a component of a protein complex comprising syntaxin18, an ER-located soluble *N*-ethylmaleimide-sensitive *f*actor (NSF) *a*ttachment protein *re*ceptor (SNARE) [152]. In addition, the BH3-only domain plays an important role in the binding of α-SNAP, an adaptor that serves as a link between the chaperone ATPase NSF and SNAREs. These results, together with the known apoptotic function of BNIP1, unmasked a possible crosstalk between apparently independent cellular events such as apoptosis and ER membrane fusion [152]. Interestingly, proteins linked to mitochondrial dynamics (fusion and fission) also modulate ER morphogenesis and fragmentation, related to the dynamics of ER–mitochondria contact sites [153–155]. The physiological impact of the modulation of ER morphogenesis by the BCL-2 protein family remains to be determined.

7. Concluding remarks

The BCL-2 protein family is essential to mediate the crosstalk between the ER and mitochondria to trigger apoptosis under conditions of chronic or irreversible ER stress. The complexity of mechanisms mediating this cell death process is diverse and may depend on the specific type of ER injury and the cell type/tissue affected. This review summarizes most evidence supporting an evolutionary process whereby key regulators of cell death also participate in vital cellular functions beyond apoptosis. Accordingly, BCL-2-related proteins do not only operate as upstream regulators of caspases, but they also actively perform specific cellular functions related to ER physiology. In support of this idea, there is growing evidence of non-apoptotic functions for the BCL-2 family beyond the ER including cell cycle regulation [156,157], participation in DNA damage responses (i.e. BID) [158,159], inflammation, (i.e. BCL-2) [160] and glucose/energy metabolism (i.e. BAD) [161,162]. Here we dissected the different BCL-2 family containing protein complexes at the ER membrane and discussed their function in diverse cellular processes. As a common denominator of their bi-functional activities, the BCL-2 protein family may operate as specialized stress sentinels that actively participate in crucial processes, allowing constant homeostatic quality control to respond to irreversible cellular damage activating adaptation to stress or apoptosis. Overall we propose a model where complex signaling platforms are assembled at the level of the ER membrane to determine the activation status of several stress responses such as autophagy, calcium signaling, and the UPR in terms of signaling intensity and kinetics of activation/inactivation. As a stress rheostat, BCL-2-containing complexes would involve multiple components that, beyond their anti- and pro-apoptotic effect on mitochondrial integrity, act at the level of the ER membranes to determine the capacity to adapt to ER injuries. In contrast, under chronic ER stress, the expression of specific components (i.e. BIM, PUMA, NOXA, and other factors) would induce BAX and/or BAK activation at the mitochondria to trigger cytochrome *c* release and apoptosis [36,77,82,163].

Mutations in certain genes are responsible for a variety of neurological disorders related to the misfolding and accumulation of abnormal protein aggregates in the brain. In many of these diseases alteration of ER homeostasis contributes to neuronal dysfunction.

These diseases include Parkinson's disease [164], Alzheimer's disease [165], Prion diseases [166] Amyotrophic Lateral Sclerosis (ALS) [167], Huntington's disease [168] and many others. Consequently, the first steps in the death pathways downstream of ER stress may represent important therapeutic targets. In addition, BH3-only proteins, such as BIM and PUMA, have been implicated in Alzheimer's disease [25], Huntington's disease [169,170] and ALS [171,172], in addition to brain ischemia [173–175] *in vivo*. Thus, pharmacological manipulation of BCL-2 protein family activity may be beneficial in the treatment of these fatal diseases related to ER stress. A number of small molecules and synthetic peptides are currently available with proven therapeutic applications in disease mouse models, including BCL-2 inhibitors [176,177], BAX channel inhibitors [87], BAX/BAK activator peptides [178,179] and many others (see reviews in [66,180]). These drugs may be used as pharmacological tools to manipulate the activity of stress signaling pathways regulated by the BCL-2 protein family (i.e. autophagy, calcium metabolism or the UPR) and alter their function in pathological conditions.

Acknowledgements

We thank Craig Wirth for helpful discussion. This work was supported by the FONDECYT no. 1100176, FONDAP grant no. 15010006, Millennium Nucleus No. P07-048-F and No. P07-011-F, Alzheimer's Association, High Q Foundation-CHDI, Michael J. Fox Foundation for Parkinson's Research, and ICGEB (to CH); FONDECYT no. 3100033 (to DRG); CONICYT no. 24090143 (to DRR).

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