On the antioxidant mechanisms of Bcl-2: a retrospective of NF-κB signaling and oxidative stress

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Abstract

Antioxidant and prooxidant signaling pathways are emanating as major players in, and regulators of, cell death and apoptosis. Redox conception of the critical role of oxidative stress in determining cell fate is being established—a foundation that craves deeper than the basic understanding of physiochemical interactions to extend beyond that into the realms of deciphering the molecular codes implicated with apoptosis. The proto-oncogene Bcl-2 is no stranger being a major player and decoder in controlling apoptosis, ostensibly via the regulation of redox equilibrium and disequilibrium. One of those potential mechanisms exhibited by Bcl-2 is its ability to counteract the detrimental effects of cell damage caused by free radicals, thereby gaining its well-known property of being an antioxidant. But the question is: what are the molecular mechanisms involved with the antioxidant role of Bcl-2 in the face of cell damage and apoptosis? Currently, a stance is being upheld in that the Bcl-2 antioxidant efficacy should be weighed against its ability to manipulate transcriptional control, through the regulation of specific transcription factors. NF-κB is no doubt one of the best candidates when it comes to the arena of oxidative stress, inflammation, and apoptosis. Therein, current themes in the burgeoning antioxidant role of Bcl-2 are exposed within the context of transcriptional control of NF-κB, thereby holding potential avenues for alleviating therapeutic approaches in the regulation of apoptosis.

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Reactive oxygen and nitrogen species (ROS/RNS) have the potential to induce indiscriminate damage to all biological molecules, macromolecules, and structures [1–7]. ROS/RNS and other mediators have been recognized in the regulation of many cellular responses to physical and chemical stimuli [8–13]. Apoptosis is the ultimate cell response to injury. When cell functions are fundamentally compromised, a cell can, on its own initiative, or in response to cytokine messengers from neighboring cells, commit suicide [4,14,15].

Apoptosis is a gene directed process of cellular deletion that establishes equilibrium between cell birth and cell death. This is an important defense against many types of biological damage such as radiation, viral infections, drug toxicity, and cancer [16–20]. By this process, the cell can exert a direct control on its own death, sacrificing itself to protect its host. Apoptosis features vary widely among different cell types and depend upon the nature of the apoptotic stimulus, but some characteristics are common to all. An apoptotic cell shrinks, fragments its DNA into small ladders, and activates specific endonucleases and proteases which form membrane-bounded blebs that can be engulfed and digested by neighboring tissue cells or macrophages without causing inflammation [4,21].

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Cell death and the paradigm of necrosis versus apoptosis

Since the term ‘apoptosis’ was coined [37], a vast quantity of work has been performed in search of the cause of the phenomenon it originally alluded to [4,5,38]. It became clear, however, that some cells are genetically programmed, or destined, for death during the normal development of multi-cellular organisms [39]. The general apoptotic model today is one of intercellular signaling molecules operating in intracellular effector systems that balance each individual cell’s progress to either life (survival) or death (apoptosis) [4,5,40] (Fig. 1).

Apoptosis, first identified as ‘shrinkage necrosis’ [41–44], was originally observed in mature human/vertebrate tissues as a stochastic loss of cells that showed distinctive histopathologic morphology and induced a minor inflammatory response [45]. Simply, it was argued that the key tenets of this model state that there is a universal genetic program that governs cell death at different stages of development, that a variety of stimuli can elicit or activate this program and that, even though many divergent transduction mechanisms are involved, apoptosis ultimately requires the activation of a downstream convergent and common pathway [4,5,45]. Apoptosis results from a series of tightly targeted proteolytic events (as opposed to generalized or random protein degradation). The process is initiated from the cytoplasm by constitutively present factors, and enucleated cells undergo the cytoplasmic events. Several mechanisms for the effector of apoptosis were initially proposed, including membrane damage, DNA degradation, or reactive oxygen species, but early events of the actual execution process result from activation of a set of highly specific proteases [40]. Several mechanisms exist for activation of the executioner, and some of these other effects may contribute to the protease activation. During apoptosis, cells undergo characteristic morphologic changes including condensation and fragmentation of the nucleus, shrinkage of the cytoplasm, and formation of apoptotic bodies containing self-enclosed fragments (Fig. 1). These features stand in sharp contrast with those that characterize necrosis, the prevailing form of cell death resulting from non-specific injury such as trauma, exposure to toxins or abrupt deprivation of vital resources necessary for supporting life.

The distinct forms of cell death: morphological aspects

At least two distinct forms of death are known by which cells, including airway epithelial cells, undergo death: (i) the well-characterized, and usually rapid, necrotic tissue damage induced by physical trauma or...
other injury and (ii) a more protracted and morphologically distinct form of cell death that was then termed apoptosis [4,5]. In apoptosis, cells often shrink, dissociate from surrounding cells, and undergo cytoplasmic membrane blebbing. The rapid condensation and aggregation of chromosomes and the formation of small apoptotic bodies are major manifestations of cell death. During apoptosis, even as cellular organelles retain their definition for a long time, the nucleus in particular displays a distinctive pattern of hetero-chromatization and eventual fragmentation. In many, but not all, apoptotic cells, the condensed chromosomes are acted upon by specific nuleases which cleave the DNA, thereby producing a characteristic ladder of DNA fragments [46–48].

Necrotic cell death, on the other hand, is relatively violent and is characterized by cytoplasmic swelling, rupturing of cell membranes, dilatation of the mitochondria, and disintegration of subcellular and nuclear components [4]. Conversely, apoptosis is characterized by an ordered series of events that take place over a longer period of time. Although necrosis may be more analogous to random acts of cellular violence leading to cellular murder, apoptosis is more appropriately referred to as cellular suicide. The cell initiates apoptotic death when it senses that its environment or physical state has been vigorously compromised; this is, indeed, the ultimate self-sacrifice (Fig. 1).

**The biochemistry of cell death**

If there is no simple dichotomy in the modes of cell death, perhaps there is more than one basic genetic program for death and more than one final common pathway. Perhaps some ligand-induced cell death could result from confused or inappropriate regulation of gene expression rather than from turning on pre-set genetic programs (Fig. 1). Studies of Caenorhabditis elegans development, for example, have contributed significantly to the bio-molecular understanding of cell death [49–53]. Genetic analysis has led to the identification of cellular genes required for programmed cell death during the development of C. elegans. The isolation and molecular characterization of C. elegans death (ced) genes demonstrated that the ced-3 gene was homologous to the mammalian interleukin-1β-converting enzyme (ICE; caspase-1) [49,50,54]. ICE was originally isolated from mammalian cells as an enzyme essential

<table>
<thead>
<tr>
<th>Caspase/old name</th>
<th>Size (kDa)</th>
<th>Target</th>
<th>Activation</th>
<th>Domain</th>
<th>Substrates</th>
<th>Function</th>
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<tr>
<td>Caspase-1 ICE</td>
<td>45, 20 + 10</td>
<td>WEHD</td>
<td>TPLD, FEDD</td>
<td>CARD</td>
<td>Pro-IL-1β, self</td>
<td>Inflammation</td>
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<td>DVAD</td>
<td>DQQD, EESD</td>
<td>CARD</td>
<td>Self + ?</td>
<td>Initiator?</td>
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<td>32, 17 + 12</td>
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<td>IETD, ESMD</td>
<td>PARP, PK, U1-70K, iCAD, self</td>
<td>Effector</td>
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<tr>
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<td>WVRD, LEED</td>
<td>CARD</td>
<td>Pro-IL-1β, procaspase-1, self</td>
<td>Inflammation</td>
<td></td>
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<td>CARD</td>
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<td>DVVD, TEVD</td>
<td>Lamins</td>
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<td>TEVD</td>
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<td></td>
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<td>53, 18 + 11</td>
<td>I/LETD</td>
<td>VETD, LEMD</td>
<td>DED</td>
<td>PARP, self, procaspases</td>
<td>Initiator</td>
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<td>PEPD, DQLD</td>
<td>CARD</td>
<td>PARP, self, procaspases</td>
<td>Initiator</td>
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<td>IEHD, SQTD</td>
<td>DED</td>
<td>Procaspase-3, -7</td>
<td>Initiator?</td>
</tr>
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* Adapated with modification, courtesy of [112].

Table 1

# Inflammation

# Effector

# Initiator
for the proper processing and biologic activation of pro-interleukin-1β, a cytokine involved in mediating cellular inflammatory processes [4,54]. The expression of ced-3 rapidly induces apoptosis, as does ICE, demonstrating that the ced-3 gene encodes a cysteine protease essential for programmed cell death. Many of the ICE-like proteases, henceforth referred to as caspases, were subsequently isolated by molecular cloning [54].

The term caspase refers to a universal nomenclature: c reflects a cysteine protease mechanism and aspase refers to the ability of these proteases to cleave a protein following an aspartic acid residue [4,40] (Table 1). Many of these caspases contain a conserved sequence, QAC(R/Q)G, required for the catalytic activity of these enzymes [54]. The activation of caspase proteases has been linked to the aggregation of cell surface receptors when receptor-sensitive target cells are exposed to the appropriate ligand or when the receptors self-aggregate in response to their high cell-surface density. Therefore, a functional caspase enzyme can be generated following the receptor oligomerization by autocatalysis or by the action of another alerted caspase. Recent evidence suggested that caspases regulate the process of apoptosis by controlling additional cellular processes such as the progression through the well-defined cell cycle and its various regulators [55,56].

The nature and function of Bcl-2

Multicellular organisms eliminate redundant, damaged, or infected cells by a stereotypic program of cell death. The Bcl-2 gene was discovered as the translocated locus in a B-cell leukemia; this translocation is also found in some B-cell lymphomas [57–60]. The first mammalian regulator of apoptosis, therefore, emerged when B-cell leukemia/lymphoma-2 (Bcl-2), the gene activated by chromosome translocation in human follicular lymphoma [61,62], was found to inhibit apoptosis and to permit the survival of cytokine-dependent hematopoietic cells, both in a quiescent state and in the absence of exogenous cytokines.

Bcl-2 gene is a human proto-oncogene located on chromosome 18 (Fig. 2). Its product is an integral membrane protein (called Bcl-2) located in the membranes of the endoplasmic reticulum (ER), nuclear envelope, and in the outer membranes of the mitochondria [4,62,63]. In the cancerous B cells, the portion of chromosome 18 containing the Bcl-2 locus has undergone a reciprocal translocation with the portion of chromosome 14 containing the antibody heavy chain locus. This t(14;18) translocation places the Bcl-2 gene close to the heavy chain gene enhancer. This enhancer is very active in B cells (whose job it is to synthesize large amounts of antibody) [64–66]. So it is not surprising to find that the Bcl-2 protein is expressed at high levels in these t(14;18) cells (Fig. 2). In summary, this gene encodes an integral outer mitochondrial membrane protein that blocks the apoptotic death of some cells such as lymphocytes. Constitutive expression of Bcl-2, such as in the case of translocation of Bcl-2 to Ig heavy chain locus, is thought to be the cause of follicular lymphoma. Two transcript variants, produced by alternate splicing, differ in their C-terminal ends.

Ced-9 of C. elegans and the mammalian Bcl-2 proved to be functional and structural homologues and their survival function is opposed either by close relatives such as Bax, or by distant cousins such as the mammalian Bik, or Nkb and nematode EGL-1 [51]. All members possess at least one of four conserved motifs known as Bcl-2 homology domains (BH-1–BH-4). Most pro-survival members, which can inhibit apoptosis in the face of a wide variety of cytotoxic insults, contain at least BH-1 and BH-2, and those most similar in structure to Bcl-2 have all four BH domains. Pro- and anti-apoptotic family members can heterodimerize and seemingly are capable of titrating one another’s function, suggesting that their relative concentrations may act as a rheostat for the suicide program. Bcl-2 resides on the cytoplasmic face of the mitochondrial outer membrane, ER, and nuclear envelope and may register damage to these compartments and affect their behavior, possibly by modifying the flux of small molecules and proteins [52,67,68].

On the other hand, Bax, for instance, is found in the cytosol before an apoptotic stimulus, even though it, like most other family members, bears a hydrophobic domain. Biochemical evidence suggests that the pro-survival proteins may function by directly inhibiting the activity of caspases, directly or indirectly preventing the release of cytochrome c from the mitochondria, which, along with ATP, may facilitate structural changes in the pro-caspase domain, allowing its cleavage and activation [69,70]. Bax, Bax-like proteins, and other anti-survival proteins may promote apoptosis by
cleaving and activating caspases but also can initiate caspase-independent death via channel-forming activity, which could promote the mitochondrial permeability transition or puncture the mitochondrial outer membrane (Fig. 3) [4,40].

**Bcl-2: an antioxidant perspective and the role of NF-κB**

The classic question that often poses itself is: Is Bcl-2 an antioxidant proto-oncogene and what are the mechanisms implicated? Concurrent with this perspective, the
demonstration that Bcl-2 exhibits antioxidant properties, ostensibly via the regulation of specific transcription factors [71–73] and the down-regulation of oxidative stress [74,75], thereby retarding the onset and evolution of apoptosis [28,76]. Moreover, non-toxic concentrations of reactive metabolites of oxygen and nitrogen play an important role in regulating the expression of genes involved in the inflammatory response and in modulating apoptosis [72]. Understanding the precise mechanism by which Bcl-2 inhibits NF-κB activity may provide insights into the pluripotent anti-apoptotic actions of this molecule (Fig. 4).

Bcl-2 may interfere with the nuclear migration of the NF-κB, which is oxidant-responsive. For instance, in mouse L cells, over-expression of Bcl-2 interfered with the activation of NF-κB by H2O2 [71]. However, Bcl-2 had no effect on the activation of NF-κB by TNF, even though it protected cells from TNF-induced apoptosis. Moreover, this effect of Bcl-2 over-expression was mimicked by exogenous pyrrolidine dithiocarbamate (PDTC), an antioxidant/pro-oxidant thiuram [71].

Thiol agents and Bcl-2 also identify an apoptotic pathway that requires the activation of NF-κB. Since oxidative stress has been purported as a common mediator of apoptotic death, albeit not exclusively, Lin et al. [77] investigated the effects of antioxidants on Sindbis virus (SV)-induced apoptosis in two cell lines, AT-3 (a prostate carcinoma line) and N18 (a neuroblastoma line). The thiol antioxidant, N-acetyl-L-cysteine (NAC), abrogated SV-induced apoptosis but not via the inhibition of viral entry or viral replication, changes in extracellular osmolarity or to increases in cellular glutathione levels, nor can they be mimicked by chelators of trace metals, inhibitors of lipid peroxidation or peroxide scavengers. In contrast, other thiol agents including PDTC were protective. Within hours of infection, SV induced a robust increase in nuclear NF-κB activity, mediating protection of cells from programed cell death. TNF-α and cycloheximide caused infected cells to undergo apoptosis and the inhibition of TNF-α-induced NF-κB activation by NAC resulted in increased apoptosis, while pre-activation of NF-κB by the non-apoptotic inducer IL-1β caused a relative decrease in apoptosis [78]. Furthermore, inhibition of constitutive NF-κB activity induced apoptosis, suggesting that NF-κB protects cells from a persistent apoptotic signal. Of particular interest, TNF-α and NAC treatment resulted in a marked decrease in Bcl-2 protein levels in HIV-1-infected cells, coupled with an increase in Bax protein, suggesting that the difference in susceptibility to TNF-α-induced apoptosis may relate to the differences in relative levels of Bcl-2 and Bax [78]. The protective role of NF-κB in blocking TNF-α and HIV-1-induced apoptosis was supported by studies in Jurkat T cells engineered to express IκB-α repressor mutants (TD-IκB) under the control of a tetracycline-responsive promoter. Cells, for example, underwent apoptosis in response to TNF-α only when NF-κB activation was inhibited by TD-IκB expression [78]. In addition, TNF-α treatment induced a marked decrease in Bcl-2 protein levels in TD-IκB expressing cells, suggesting an integral association between Bcl-2 and NF-κB signaling.

Bcl-2 suppresses apoptosis resulting from disruption of the NF-κB survival pathway (Fig. 4). For instance, a role has been delineated for Bcl-2 and NF-κB in mediating an adaptive survival response to the TNF-α signaling pathway for apoptosis. Over-expression of Bcl-2 protein in prostatic carcinoma cells impaired TNF-α-mediated cytotoxicity but did not impose a block to, or potentiate, TNF-α signaling of IκB-α degradation, nuclear import of the RelA p65, or NF-κB-dependent transactivation [79]. Moreover, expression of dominant-negative IκB-α mutant proteins enhanced TNF-α-induced apoptosis in control cells but not in cells expressing high levels of Bcl-2 protein. Similarly, PDTC potentiated TNF-α-stimulated apoptosis signaling through a Bcl-2-regulated mechanism, indicating that the efficacy of strategies proposed to enhance TNF-α-mediated cytotoxicity by inhibiting NF-κB will likely be influenced by context-dependent variables such as Bcl-2 expression [79]. In another model, NF-κB, AP-1, and Bcl-2 were down-regulated during PDTC-induced apoptosis, ostensibly via the up-regulation of p53 [80,81]. Using the same concept, ischemia–reperfusion and ischemic adaptation have been reported to differentially regulate the expression of Bcl-2 and NF-κB by increasing the antioxidant efficacy [82].

Agents that modulate intracellular molecules and nucleotides are also implicated in Bcl-2-mediated cytoprotection (Fig. 3). For example, cAMP increasing agents attenuate the generation of apoptosis. Specifically, the inhibition of retinoblastoma (Rb type I) phosphatase
and ICE/CED-3-like protease activities, and the abrogation of c-myc expression, are mechanisms attributed to the anti-apoptotic action of cAMP-dependent Bcl-2 [83]. Moreover, suppression of N-methyl-N’-nitro-N-nitrosoguanidine (MNNG)- and S-nitrosoglutathione (GSNO)-induced apoptosis by Bcl-2 has been reported to occur via the inhibition of glutathione-S-transferase [73]. Bcl-2-expressing cells prevented MNNG- and GSNO-induced apoptosis. This mechanism mediating the production of GSNO in cells was found capable of apoptosis initiation while the over-expression of Bcl-2 can prevent MNNG-mediated cell apoptosis through the elevation of glutathione levels [73]. Recently, a novel biphasic effect of PDTC reported on neuronal cell viability was mediated by the differential regulation of intracellular zinc and copper ion levels, NF-κB, and MAPKs [84,85]. In addition, copper can induce apoptosis via the regulation of Bax, ROS, and NF-κB in a Bcl-2-independent mechanism [86]. Protein phosphatase 2A was shown to modulate the proliferation of human multiple myeloma cells via the regulation of the production of ROS, Bcl-2, and anti-apoptotic factors [87].

The differential expression of apoptosis cofactors is redox sensitive and requires NF-κB-selective targeting (Fig. 4). Recently, we have used fetal alveolar type II (fATII) epithelial cells to evaluate the role of signaling factors involved in oxidative stress-induced programmed cell death. Bcl-2, for instance, showed maximum abundance of ROS, Bcl-2, and anti-apoptotic factors [87].

NF-κB and the Bcl family are markedly involved in the regulation of pathophysiologic conditions, in vitro and in vivo. For example, it has been reported that there is increased expression of antioxidant and anti-apoptotic genes in islets that may contribute to β-cell survival during chronic hyperglycemia [94]. The genetic program for glucose-induced mesangial cell apoptosis was characterized by an up-regulation of the Bax/Bcl-2 ratio [95]. Moreover, up-regulation of Bcl-2 through hyperbaric pressure transfection of TGF-β1 ameliorates ischemia–reperfusion injury in rat cardiac allografts [96]. Genetic redox preconditioning also differentially modulates AP-1 and NF-κB responses following cardiac ischemia–reperfusion injury and protects against necrosis and apoptosis [97].

NF-κB-dependent MnSOD expression was also shown to protect adenocarcinoma cells from TNF-α-induced apoptosis [98]. This mechanism, however, was reported to be independent of the expression of Bel-XI, a Bel-2-related gene [98]. Interestingly, the generation of ROS and activation of NF-κB by non-αβ component of Alzheimer’s disease amyloid were suppressed by Bcl-2 [99]. In jibe, β-amyloid treatment also led to decreased ΔΨm, the cleavage of poly(ADP-ribose)polymerase, an increase in the Bax/Bel-XI ratio, and activation of c-Jun N-terminal kinase [76]. In addition, constitutively active NF-κB was shown to be required for the survival of the S-type neuroblastoma [100,102]. Bcl-2 and Bel-XI are also protective in induced tumor growth and the loss of mitochondrial transmembrane potential (ΔΨm) and DNA fragmentation. Examination of initiator caspases revealed the cleavage of caspase 9 but not caspase 8 or the effector caspase 3. To determine the pathway leading to mitochondrial dysfunction, analysis of Bcl-2 family members established that only A1 mRNA levels were reduced prior to ΔΨm loss and that ectopic expression of A1 protected against cell death following inactivation of NF-κB [89]. Thus, constitutive NF-κB activation preserves macrophage viability by maintaining A1 expression and mitochondrial homeostasis. Furthermore, it has been demonstrated that inhibition of inflammatory endothelial responses involved a pathway which mediates caspase activation and NF-κB p65 cleavage [90]. Of note, oxidative stress, which is commonly associated with the evolution of a inflammatory response [10–12], is counterbalanced by antioxidant mechanisms and Bcl-2 that inhibit apoptosis essentially via interacting with mitochondrial SOD [91]. This is corroborated by the observation that endothelial apoptosis induced by oxidative stress through activation of NF-κB was suppressed by the anti-apoptotic effect of antioxidant agents and Bcl-2 [92]. In the endometrium as well, it was demonstrated that the inhibition of growth and apoptosis of human endometrial cells by RU486, an antiprogestin, involves stimulation of NF-κB binding with subsequent modulation of apoptosis regulatory genes Bax and Bel-2 [93].

NF-κB and the Bcl family were shown to have differential expression in TGF-β-regulated genes Bax and Bcl-2 [93]. The Bcl family was shown to be independent of the expression of Bel-XI, a Bel-2-related gene [98]. Interestingly, the generation of ROS and activation of NF-κB by non-αβ component of Alzheimer’s disease amyloid were suppressed by Bcl-2 [99]. In jibe, β-amyloid treatment also led to decreased ΔΨm, the cleavage of poly(ADP-ribose)polymerase, an increase in the Bax/Bel-XI ratio, and activation of c-Jun N-terminal kinase [76]. In addition, constitutively active NF-κB was shown to be required for the survival of the S-type neuroblastoma [100,102]. Bcl-2 and Bel-XI are also protective in induced tumor growth
and metastasis [101–104]. Notably, RelA over-expression reduced tumorigenicity and activated apoptosis in human cancer cells [105].

Summary and prospects

The implications of the antioxidant effects of Bcl-2 and its relationship with the regulation of NF-κB, and therefore cell destiny/apoptosis, hold promising avenues for understanding senescence, oxidative damage, cell injury, and incapacitation (Figs. 3 and 4). It is conspicuous that antioxidant/prooxidant mechanisms and redox signaling are major players in determining cell fate under physiologic and pathologic conditions [106–111]. This will fundamentally contribute to our understanding of the biochemistry of disease and the pharmacology of apoptosis and to the development of alleviating therapeutic strategies.

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