The role of Bcl-2 in controlling the transition between autophagy and apoptosis (Review)

AHMET ALPEREN PALABIYIK

Department of Nursing, Faculty of Health Sciences, Ardahan University, Çamlıçatak, Ardahan 75002, Turkey

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Abstract. The Bcl-2 protein family serves a key role in maintaining cellular homeostasis by regulating the balance between autophagy and apoptosis. The present review aimed to summarize interactions of Bcl-2 with key proteins, including Beclin 1, Bax and Bcl-2 homologous antagonist/killer, as well as its influence on cellular processes such as mitophagy, nutrient sensing and endoplasmic reticulum stress response. The impact of post-translational modifications of Bcl-2, including phosphorylation, ubiquitination and sumoylation, is discussed with respect to their regulatory roles under stress. In pathological states, Bcl-2 upregulation in cancer suppresses apoptosis and autophagy, thereby facilitating tumor survival and resistance to chemotherapy. Conversely, in neurodegenerative diseases, impaired autophagy and increased apoptosis contribute to neuronal loss. Therapeutic strategies targeting Bcl-2 (for example inhibitors such as venetoclax, navitoclax, obatoclax and combination therapies involving autophagy modulators) were evaluated for their potential efficacy. There is lack of understanding of tissue-specific functions of Bcl-2 and its interactions with non-coding RNAs. Future research should prioritize these areas and leverage advanced single-cell technologies to elucidate the real-time dynamics of Bcl-2 in cell processes. The present review highlights the key role of Bcl-2 in cell fate determination and highlights its potential as a therapeutic target, offering insight for the development of innovative treatments for cancer, neurodegenerative disorder and age-related diseases.

Contents

Correspondence to: Dr Ahmet Alperen Palabiyik, Department of Nursing, Faculty of Health Sciences, Ardahan University, Yenisey Campus, Çamlıçatak, Ardahan 75002, Turkey
E-mail: ahmetalperenpalabiyik@ardahan.edu.tr

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1. Introduction

The Bcl-2 protein family constitutes a key group of regulators that maintain cellular homeostasis by modulating both autophagy and apoptosis (1). This family is classified into anti-apoptotic proteins, including Bcl-2, Bcl-xl and myeloid cell leukemia 1 (Mcl-1), and pro-apoptotic proteins, such as Bax, Bcl-2 homologous antagonist/killer (Bak) and BH3 interacting-domain death agonist (2) (Table I). This classification underscores their opposing roles in cell survival and programmed cell death. Anti-apoptotic proteins inhibit mitochondrial outer membrane permeabilization (MOMP) and suppress caspase activation, thereby preventing apoptosis. By contrast, pro-apoptotic proteins promote MOMP and facilitate apoptotic cascades, leading to cell death. The dynamic equilibrium between these determines cellular fate under stress conditions (3-6).

Autophagy and apoptosis are key for cellular integrity. Autophagy, a catabolic pathway, degrades and recycles damaged organelles and misfolded proteins to sustain cell energy levels and homeostasis (7,8). Conversely, apoptosis eliminates irreversibly damaged or dysfunctional cells, thereby preventing harm to the organism (9,10). While these processes are distinct, they share regulatory molecules, including Bcl-2 family proteins, and their interplay is key for cell decision-making under stress conditions (11).

The role of Bcl-2 is multifaceted. Bcl-2 inhibits autophagy by binding to Beclin 1, a key autophagy regulator, thereby suppressing autophagic flux initiation. Simultaneously, it prevents apoptosis by interacting with pro-apoptotic proteins such as Bax and Bak. However, under severe or prolonged stress, post-translational modifications (PTMs), including phosphorylation, may disrupt these interactions, shifting the balance toward either autophagy or apoptosis (12-14). Dysregulation of Bcl-2-mediated pathways is implicated in various pathological conditions: In cancer, Bcl-2 upregulation enhances tumor survival by preventing apoptosis

and suppressing autophagy, contributing to chemotherapy resistance (15). Conversely, in neurodegenerative disorders, impaired regulation of autophagy and apoptosis accelerates neuronal loss. These pathological contexts highlight the key role of Bcl-2 in coordinating the transition between autophagy and apoptosis (16,17).

The present review aimed to provide a comprehensive analysis of the mechanisms by which Bcl-2 regulates autophagy and apoptosis. By examining its molecular interactions, pathological implications and potential as a therapeutic target, the present review aimed to elucidate the central role of Bcl-2 in cellular homeostasis and disease pathogenesis.

2. Database search

The present review was conducted through a systematic literature search in PubMed (pubmed.ncbi.nlm.nih.gov/), Google Scholar (scholar.google.com/) and Web of Science (https://www.webofscience.com/wos/). The search covered publications from January 2014 to December 2024. The following search terms were: 'Bcl-2 AND autophagy', 'Bcl-2 AND apoptosis', 'Bcl-2 AND Beclin 1', 'Bcl-2 AND mitophagy', 'Bcl-2 AND cancer resistance', 'Bcl-2 AND neurodegeneration', 'Bcl-2 inhibitors AND therapy' and 'Bcl-2 AND post-translational modifications'. Only peer-reviewed articles published in English were selected. Eligible studies included review articles and preclinical and clinical studies; non-peer-reviewed sources (for example, preprints, conference abstracts, editorials) and articles without a primary focus on Bcl-2 regulatory functions were excluded. Reference lists of studies were manually searched to identify additional relevant literature that may have been missed in the initial search.

3. Mechanisms of Bcl-2 in regulating autophagy

Bcl-2 and autophagy regulation. Bcl-2 regulates autophagy through its interactions with Beclin 1 and mitochondrial quality control mechanisms (18). The inhibition of autophagy by Bcl-2 primarily occurs via direct binding to the BH3 domain of Beclin 1, a key autophagy regulator (13). This interaction prevents Beclin 1 from initiating autophagosome formation, thereby restricting autophagic activity under physiological conditions (14). However, under metabolic or oxidative stress, PTMs, such as phosphorylation at serine 70 (Ser70), disrupt this interaction, enabling Beclin 1 to activate autophagy (19-21) (Fig. 1).

Bcl-2 regulates mitophagy, the selective degradation of dysfunctional mitochondria. It modulates MOMP, thereby controlling the release of mitochondrial quality control factors such as PTEN-induced kinase 1 and Parkin (22,23). These proteins coordinate mitochondrial tagging for degradation, ensuring the elimination of damaged mitochondria while preventing excessive mitophagy, which could compromise cellular bioenergetics (24).

This dual regulatory function positions Bcl-2 as a key integrator of cellular stress signals (Fig. 2). Under nutrient deprivation, AMPK activation phosphorylates Bcl-2, leading to its dissociation from Beclin 1, facilitating autophagy (25,26). Conversely, under nutrient-rich conditions, mTOR activation stabilizes the Bcl-2-Beclin 1 complex, thereby inhibiting autophagy and promoting cell survival. Furthermore, oxidative stress-induced phosphorylation of Bcl-2 determines whether the balance shifts toward autophagy or apoptosis (27,28).

PTMs of Bcl-2. PTMs of Bcl-2 serve a key role in modulating its interactions and function, allowing for precise regulation of autophagy and apoptosis. Phosphorylation at residues such as Ser70 enhances dissociation of Bcl-2 from Beclin 1, thereby promoting autophagy in response to stress, including nutrient deprivation or oxidative damage. Conversely, phosphorylation at alternative sites may stabilize interactions of Bcl-2 with pro-apoptotic proteins, further suppressing apoptosis (29,30).

Caspase-mediated cleavage of Bcl-2 during apoptosis is another key PTM, converting Bcl-2 from an anti-apoptotic protein into a pro-apoptotic fragment that amplifies apoptotic signaling (31,32). Additionally, ubiquitination regulates proteasomal degradation of Bcl-2, influencing its intracellular levels and functional activity. Sumoylation and acetylation are key PTMs that modulate interactions of Bcl-2 with mitochondrial and cytosolic targets, further underscoring the complexity and context-dependent nature of its regulation (33-35) (Fig. 3).

Role of Bcl-2 in nutrient sensing and metabolic regulation. Bcl-2 serves a key role in nutrient sensing and metabolic regulation. Through its interactions with the mTOR and AMPK pathways, Bcl-2 enables cell adaptation to nutrient deprivation by modulating autophagy (36). During starvation, AMPK activation phosphorylates Bcl-2, weakening its interaction with Beclin 1 and enhancing autophagy to sustain energy production and preserve cellular integrity (37). This phosphorylation also facilitates the redistribution of autophagic machinery components to damaged or stressed cell regions, ensuring a targeted autophagic response.

Conversely, under nutrient-rich conditions, mTOR signaling suppresses autophagy, with Bcl-2 contributing to this suppression by stabilizing Beclin 1 in an inactive state and reinforcing cell proliferation pathways (38,39). Additionally, Bcl-2 serves a role in modulating lysosomal function during autophagy, ensuring the efficient degradation and recycling of cellular components. This multifaceted regulatory function underscores the key role of Bcl-2 in maintaining metabolic homeostasis and dynamically responding to fluctuating nutrient levels (26,40,41).

Bcl-2 in endoplasmic reticulum (ER) stress and unfolded protein response (UPR). Under ER stress, Bcl-2 serves a key role in modulating the UPR, an important mechanism for cell adaptation to misfolded protein accumulation (42). At ER-mitochondria contact sites, Bcl-2 regulates calcium signaling by controlling calcium release from the ER to mitochondria, which is key for both ATP production and apoptosis regulation (43). Dysregulated calcium transfer can result in mitochondrial calcium overload, triggering pro-apoptotic pathways.

Prolonged ER stress compromises the anti-apoptotic functions of Bcl-2 by altering its interactions with proteins at contact sites. Additionally, Bcl-2 directly modulates UPR pathways through interactions with key mediators such as inositol-requiring enzyme 1 and protein kinase R-like ER kinase, thereby influencing the cell fate between adaptive recovery and apoptotic cell death. Bcl-2 also contributes to

Table I. Family members of Bcl-2.

Effect on apoptosis	Protein		Function	Key interactions
Anti-apoptotic	Bcl-2		Inhibits apoptosis, promotes cell survival	Bax, Bak, Beclin 1
	Bcl-xl		Prevents apoptosis, maintains mitochondrial integrity	Bax, Bak, Bad
	Mcl-1		Supports cell survival	Bax, Bak, BH3-only proteins
	Bcl-w		Inhibits apoptosis, supports neuronal survival	Bax, Bak
	A1/Bfl-1		Promotes cell survival, especially in immune cells	
Pro-apoptotic	Multi domain	Bax	Oligomerizes in the cytosol upon activation, translocates to mitochondria to induce MOMP and initiate apoptosis	Bcl-2, Bcl-xl, Bak
		Bak	Constitutively anchored in the mitochondrial membrane; triggers MOMP upon activation and promotes apoptosis in cooperation with Bax	Bcl-2, Bcl-xl, Bax
	BH3 only	Bid	Activates Bax and Bak, promotes apoptosis	Bcl-2, Bcl-xl
		Bim	Activates Bax and Bak, inhibits Bcl-2 and Bcl-xl	
		Bad	Interacts with anti-apoptotic proteins to promote apoptosis	
		Noxa	Targets Mcl-1 for degradation, induces apoptosis	Mcl-1
		Puma	Inhibits Bcl-2 family proteins, induces apoptosis	Bcl-2, Bcl-xl, Mcl-1
		Bnip3	Regulates autophagy and apoptosis	Beclin 1, Bcl-2
		Bik	Promotes apoptosis by interacting with anti-apoptotic proteins	Bcl-2, Bcl-xl

Mcl-1, myeloid cell leukemia 1; Bak, Bcl-2 homologous antagonist/killer; Bid, BH3-interacting domain death agonist; Bim, Bcl-2-interacting mediator of cell death; MOMP, mitochondrial outer membrane permeabilization; Bad, Bcl-2-associated death promoter; Bik, Bcl-2-interacting killer; Puma, p53 upregulated modulator of apoptosis; Bnip3, Bcl-2/adenovirus E1B 19 kDa-interacting protein 3.

stabilizing mitochondrial membrane potential during ER stress, further underscoring its multifaceted role in maintaining cell homeostasis under adverse conditions (44-46).

Bcl-2 in immune cell regulation. Bcl-2 is key for the survival and function of immune cells, including T and B lymphocytes. By inhibiting apoptosis, Bcl-2 promotes the longevity of memory T cells, which are key for maintaining immune memory and facilitating rapid secondary responses to antigens (47). Additionally, it supports the development of germinal center B cells, enabling effective antibody diversification and maturation.

Dysregulation of Bcl-2 in immune cells is associated with pathologies, including autoimmune disease, where excessive survival of autoreactive lymphocytes exacerbates immune responses, and lymphoproliferative disorders, which are characterized by uncontrolled immune cell proliferation (48,49). Beyond its role in apoptosis regulation, Bcl-2 also modulates autophagy within immune cells, aiding adaptation to metabolic and environmental stress. This dual function in apoptosis inhibition and autophagy regulation enables immune cells to sustain functionality during nutrient deprivation or infection, ensuring a robust and persistent immune response (50,51).

Bcl-2 in aging and cellular senescence. Aging and cellular senescence are associated with alterations in the regulation of autophagy and apoptosis, reflecting a decline in the efficiency of cell stress response mechanisms. The expression and activity of Bcl-2 decrease with age, which can impair mitochondrial quality control and lead to the accumulation of damaged organelles (52,53). This contributes to increased oxidative stress, as reactive oxygen species are no longer effectively neutralized, thereby exacerbating age-associated pathologies such as neurodegeneration, cardiovascular disease and metabolic disorders. In senescent cells, the altered function of Bcl-2 not only affects autophagic flux but also disrupts the balance between cell survival and programmed cell death, resulting in chronic inflammation and tissue dysfunction (54,55). Therapeutic strategies (such as BH3 mimetics, Bcl-2 inhibitors, caloric restriction mimetics, or gene therapy approaches) targeting Bcl-2 in aging aim to restore the balance between autophagy and apoptosis by enhancing mitochondrial turnover, decreasing oxidative damage and promoting tissue regenerative capacity. These interventions may mitigate age-associated functional decline and enhance cell resilience in aging populations (56,57).

4. Role of Bcl-2 in apoptosis

Inhibition of pro-apoptotic proteins. Bcl-2 inhibits apoptosis by binding pro-apoptotic proteins such as Bax and Bak, thereby preventing MOMP and the subsequent release of cytochrome

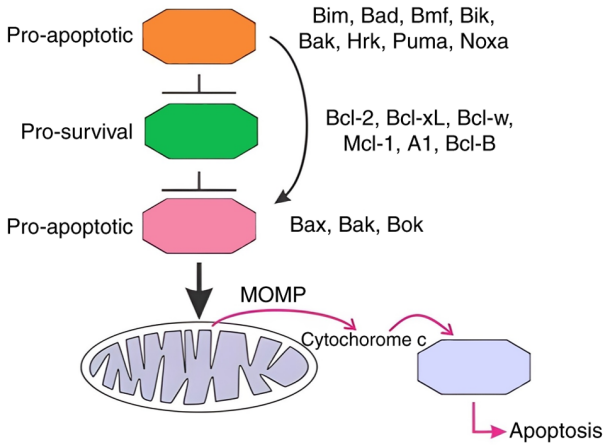

Figure 1. Role of the Bcl-2 protein family in regulating apoptosis. Bcl-2 family regulates cell survival or death. BH3-only proteins (Bim, Bad, Puma) interact with and inhibit anti-apoptotic proteins (Bcl-2, Bcl-xL), enabling activation of pro-apoptotic effector proteins (Bax and Bak). These proteins facilitate MOMP by forming pores in the mitochondrial outer membrane. This results in the release of cytochrome c, which binds apoptotic protease activating factor-1 and activates the apoptosome, ultimately leading to apoptosis. MOMP, mitochondrial outer membrane permeabilization; BH3-only, Bcl-2 homology 3-only; Bcl-w, Bcl-2-like protein W; Mcl-1, myeloid cell leukemia 1; A1, Bcl-2-related protein A1; Bok, Bcl-2-related ovarian killer; Bim, Bcl-2-like protein 11; Bad, Bmf, Bcl-2-modifying factor; Bik, Bcl-2 interacting killer; Bak, Bcl-2 homologous antagonist/killer; Hrk, harakiri. Diagram taken from the study by Banjara *et al* (6) with permission.

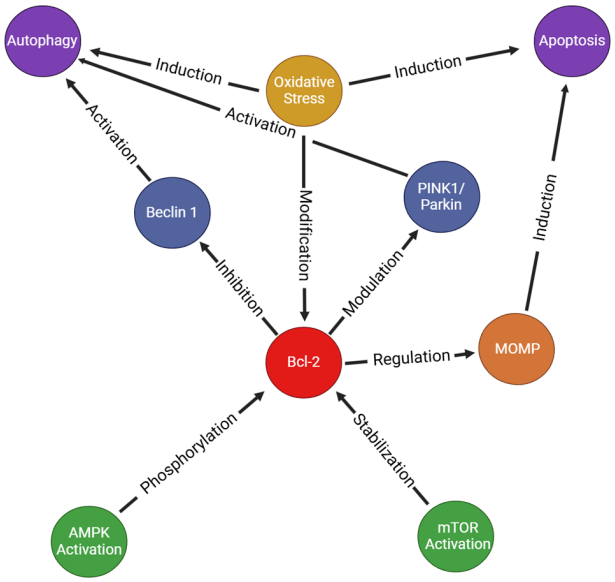

Figure 2. Bcl-2 regulation in autophagy and apoptosis. Bcl-2 regulates the balance between autophagy and apoptosis by integrating cellular signals. It inhibits autophagy by binding Beclin1, preventing autophagosome formation. Under metabolic stress, AMPK activation phosphorylates Bcl-2, inhibiting its interaction with Beclin 1 and promoting autophagy. mTOR activation stabilizes Bcl-2, suppressing autophagy. Bcl-2 modulates mitophagy by regulating PINK1 and Parkin, ensuring mitochondrial quality control. In response to severe stress, MOMP triggers apoptosis, with Bcl-2 acting as a key regulator. Oxidative stress modifies Bcl-2 via post-translational modifications, influencing the shift between autophagy and apoptosis. PINK1, PTEN-induced kinase 1; MOMP, mitochondrial outer membrane permeabilization; Parkin, E3 ubiquitin ligase. This image was created with BioRender.com.

c. This inhibition blocks the activation of caspases, the key executors of apoptosis, which cleave cellular substrates and ultimately lead to cell death (58,59). Activity of Bcl-2 is regulated by its interactions with BH3-only proteins, such as Bad and Bcl-2-like protein 11, which disrupt its anti-apoptotic function under cellular stress (60). These interactions are modulated by upstream signaling pathways, including the PI3K/AKT pathway, which phosphorylates Bcl-2 to enhance its stability and anti-apoptotic function. Furthermore, Bcl-2 serves a key role in maintaining mitochondrial dynamics by influencing the balance between fission and fusion (19,61). It interacts with dynamin-related protein 1 to limit excessive mitochondrial fragmentation, a process associated with apoptotic signaling. Moreover, Bcl-2 regulates ER-mitochondria contact sites, which are key for calcium signaling and apoptotic regulation, further reinforcing its role in cell survival (62,63).

Dual role in cell survival and death. Anti-apoptotic functions of Bcl-2 are context-dependent and associated with environmental cellular stressors. Under mild stress, Bcl-2 effectively binds and neutralizes pro-apoptotic proteins such as Bax and Bak, thereby maintaining mitochondrial integrity and promoting cell survival (64,65). However, under severe or prolonged stress, Bcl-2 undergoes PTMs, such as phosphorylation or cleavage, which alter its binding affinity and disrupt its interactions with Bax and Bak (59,66). This can trigger MOMP, leading to the release of apoptogenic factors such cytochrome c. Additionally, the function of Bcl-2 is modulated by upstream pathways, such as JNK signaling, which phosphorylate Bcl-2 at specific residues, shifting the balance from survival to apoptosis. These mechanisms highlight the dual role of Bcl-2 as a regulator of both cell survival and programmed cell death depending on cellular context and stress severity (67-69).

5. Interplay between autophagy and apoptosis

Molecular crosstalk. Interplay between autophagy and apoptosis involves shared regulatory proteins, including Bcl-2. By sequestering Beclin 1, Bcl-2 inhibits autophagy while promoting cell survival, thus ensuring cell resources are preserved under stress (70,71). This regulatory mechanism helps cells avoid autophagic overactivation, which leads to self-digestion and cellular demise. By contrast, when Bcl-2 binds to Bax or Bak, its anti-apoptotic function is compromised, tipping the balance toward apoptosis (72,73). This switch is triggered by upstream signals, such as JNK activation or oxidative stress, which alter the conformation of Bcl-2 and disrupt its interactions. The modulation of this crosstalk is key for maintaining cellular homeostasis, particularly under dynamic environmental conditions (72,74).

Pathological implications. In cancer, Bcl-2 upregulation leads to autophagy inhibition and resistance to apoptosis, facilitating tumor progression by enabling cancer cells to evade programmed cell death and adapt to metabolic stresses (75,76). This dysregulation contributes to therapy resistance, as cancer cells exploit Bcl-2-mediated survival pathways to withstand chemotherapeutic and radiological insult. In neurodegenerative diseases such as Alzheimer's and Parkinson's disease, impaired autophagy and increased apoptosis exacerbate neuronal

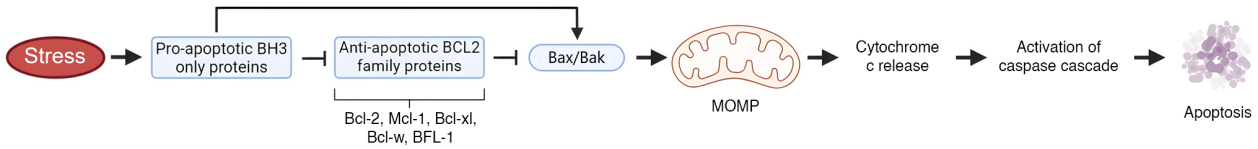

Figure 3. Regulation of Bcl-2 via PTMs. Bcl-2 is regulated by PTMs such as phosphorylation, ubiquitination and caspase cleavage. Phosphorylation at Ser70 promotes autophagy by dissociating Bcl-2 from Beclin 1, while other phosphorylation sites stabilize interactions with pro-apoptotic proteins, suppressing apoptosis. Caspase cleavage converts Bcl-2 into a pro-apoptotic fragment, amplifying apoptosis. Ubiquitination controls its degradation, influencing cellular levels. PTM, post-translational modification; MOMP, mitochondrial outer membrane permeabilization; Mcl-1, Myeloid cell leukemia 1; Bak, Bcl-2 homologous antagonist/killer; Bcl-w, Bcl-2-like protein W; BFL-1, Bcl-2-related protein A1. This image was created with BioRender.com.

loss by promoting the accumulation of damaged organelles and proteins, further destabilizing cell homeostasis (77,78). Targeting Bcl-2 to restore the balance between autophagy and apoptosis holds therapeutic potential for mitigating disease progression, enhancing cell survival and improving treatment response in these conditions (19).

6. Therapeutic implications

Cancer therapy and drug resistance. Upregulation of the anti-apoptotic protein Bcl-2 (79) contributing to chemotherapy resistance in numerous types of cancer, particularly hematological malignancies such as chronic lymphocytic and acute myeloid leukemia (80). The development of Bcl-2 inhibitors, notably venetoclax, targets this resistance mechanism. Venetoclax, a selective Bcl-2 inhibitor, has efficacy in inducing apoptosis in cancer cells by antagonizing the function of Bcl-2 (81,82). Other Bcl-2 inhibitors, such as navitoclax and obatoclax, have been developed. Navitoclax targets both Bcl-2 and Bcl-xl, making it a broader inhibitor, while obatoclax is a pan-BCL inhibitor that disrupts multiple anti-apoptotic proteins (83). However, clinical applications of these inhibitors are limited due to dose-limiting toxicity, particularly thrombocytopenia associated with navitoclax (84).

Resistance to venetoclax presents a clinical challenge. Mechanisms underlying resistance include the upregulation of alternative anti-apoptotic proteins, such as Mcl-1 and Bcl-xl, which compensates for Bcl-2 inhibition, thereby sustaining cell survival (85). Additionally, acquired mutations in the Bcl-2 gene, such as the Gly101Val mutation, decrease venetoclax binding affinity and lead to therapeutic resistance (86). Recent studies have demonstrated that pathogens manipulate host cell death pathways to promote their survival and replication, highlighting the interplay between infectious agents and cell death mechanisms (87-89). Furthermore, metabolic adaptations within cancer cells may decrease their dependence on Bcl-2-mediated survival pathways, further complicating treatment outcomes (90).

To overcome venetoclax resistance, combination therapeutic strategies are under investigation. One approach involves the concurrent inhibition of both Bcl-2 and Mcl-1 to prevent compensatory survival signaling (91). Preclinical studies have shown that combining venetoclax with Mcl-1 inhibitors enhances apoptotic responses in resistant cancer models (92,93). For example, the combination of venetoclax + Mcl-1 inhibitors, such as S63845 and AZD5991, exerts synergistic effects in preclinical leukemia models, leading to increased cancer cell apoptosis (94,95). Another promising therapeutic strategy involves the integration of venetoclax, a potent Bcl-2 inhibitor, with autophagy modulators to counteract resistance mechanisms in cancer therapy (96). Autophagy, a catabolic process responsible for degrading and recycling intracellular components, is upregulated in malignant cells as a cytoprotective response to therapeutic stress (97). This adaptive mechanism enables tumor cells to survive apoptotic triggers induced by agents such as venetoclax (98).

Furthermore, dual inhibition strategies targeting both Bcl-2 and autophagy-associated signaling pathways, including the PI3K/Akt/mTOR axis, have garnered interest (99). The combination of venetoclax with PI3K inhibitors (e.g., idelalisib) or mTOR inhibitors (e.g., everolimus) has shown synergistic cytotoxicity in hematologic malignancies by concurrently blocking parallel survival pathways and enhancing apoptotic priming (100). Autophagy, a cellular degradation process, is co-opted by cancer cells as a survival mechanism under therapeutic stress (101). Inhibiting autophagy in conjunction with Bcl-2 antagonism has shown promise in preclinical settings, suggesting a potential method to mitigate resistance (102). Additionally, the combination of venetoclax + PI3K/mTOR pathway inhibitors, such as idelalisib and everolimus, has been explored to enhance apoptotic responses by disrupting alternative survival signals (103). These combination approaches aim to address the adaptive resistance mechanisms that cancer cells employ to evade venetoclax-induced apoptosis. *Neurodegenerative disorder*. In neurodegenerative diseases such as Alzheimer's and Parkinson's disease, dysregulation of Bcl-2 family proteins is implicated in neuronal cell death (104). Alterations in the expression of Bcl-2 and associated proteins disrupt the balance between pro-apoptotic and anti-apoptotic signals, leading to increased neuronal vulnerability and degeneration (105). For example, decreased Bcl-2 expression or function may fail to counteract pro-apoptotic stimuli, resulting in enhanced neuronal apoptosis (66). Conversely, upregulation of anti-apoptotic Bcl-2 family members, such as Bcl-2, Bcl-xL, and Mcl-1, can inhibit key apoptotic processes, leading to the accumulation of damaged neurons. Therapeutic strategies targeting Bcl-2 family proteins have been explored to restore the balance between cell survival and death in neurodegenerative disorders (106). For example, small-molecule inhibitors of anti-apoptotic proteins such as Bcl-2 and Bcl-xL, promote the clearance of damaged neurons by enhancing apoptosis (107). Conversely, in diseases like Alzheimer's and Parkinson's, upregulation of pro-survival Bcl-2 has been investigated to prevent excessive neuronal loss and mitochondrial dysfunction (106). Modulating Bcl-2 activity to enhance neuronal survival while preventing the accumulation of dysfunctional

cells holds promise as a potential approach for mitigating neurodegeneration (108).

7. Research gaps and future directions

While progress has been made in elucidating the role of Bcl-2 in autophagy and apoptosis, several key gaps remain. First, the precise mechanisms by which the PTMs of Bcl-2, such as phosphorylation, ubiquitination and sumoylation, modulate its dual role in different cell contexts require further exploration. For example, specific PTMs may have contrasting effects on its interactions with Beclin 1 vs. pro-apoptotic proteins such as Bax and Bak.

Second, the tissue-specific roles of Bcl-2 in regulating the autophagy-apoptosis axis remain largely unexplored (109). Variations in Bcl-2 expression and its interactions with cellular machinery across tissues may provide insights into why certain diseases, such as neurodegeneration and cancer, exhibit distinct pathological profiles associated with this protein.

Third, the interplay between Bcl-2 and emerging regulatory pathways, such as non-coding RNAs (for example, microRNAs and long non-coding RNAs), presents a promising but underexplored area (110). These molecules may modulate activity of Bcl-2 indirectly, influencing autophagic and apoptotic responses (111).

Additionally, the potential for combination therapies that simultaneously target anti-apoptotic and autophagy-suppressive roles of Bcl-2 has yet to be fully realized. Preclinical models should evaluate the efficacy of dual inhibitors or combinations of Bcl-2 inhibitors with autophagy modulators in cancer, neurodegenerative disease and aging-associated conditions. Finally, advances in single-cell analysis and imaging technologies should be leveraged to study the real-time dynamics of Bcl-2 in coordinating autophagy and apoptosis at the cell and subcellular levels. Such approaches may uncover transient interactions and compartmentalized functions of Bcl-2 that are not apparent in bulk analyses.

Future research is key for developing precise, context-specific therapeutic strategies targeting Bcl-2. Future studies should identify additional PTMs of Bcl-2 that regulate its dual role and tissue-specific roles of Bcl-2 in different diseases and develop combination therapies targeting both autophagy and apoptosis.

8. Conclusion

Bcl-2 is a key regulator of the autophagy-apoptosis axis, orchestrating cellular responses to stress and maintaining homeostasis. Its dual role as an inhibitor of apoptosis and modulator of autophagy underscores its key importance in cellular fate determination. By interacting with Beclin 1, Bax, Bak and other molecular partners, Bcl-2 regulates autophagic flux and apoptotic pathways to adapt to dynamic cellular environments.

In pathological contexts, such as cancer and neurodegenerative disease, dysregulation of the functions of Bcl-2 contributes to disease progression, making it a valuable therapeutic target. Targeting Bcl-2 using inhibitors or combination therapies that modulate both autophagy and apoptosis is a promising avenue for innovative treatment strategies. Furthermore, research on the interactions if Bcl-2 with non-coding RNAs, PTMs and tissue-specific roles has increased understanding of its full regulatory network (112).

Future therapeutic interventions should develop precise, context-specific strategies to facilitate advancements in cancer therapy and neurodegeneration management. A deeper understanding of the regulation of Bcl-2 and its interplay with other cellular pathways is key for advancing biomedical research and improving patient outcomes.

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Authors' contributions

AAP conceived and designed the study, performed the literature review and wrote the manuscript. Data authentication is not applicable. The author has read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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