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BCL Protein and It's Intrinsic Apoptotic Pathway: A Literature Review

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Abstract:

The BCL (B-cell lymphoma) protein family is a diverse group of regulators critically involved in apoptosis, a tightly controlled process crucial for maintaining tissue homeostasis. Dysregulation of apoptosis is a common feature in cancer, emphasizing the need to comprehend the intricate mechanisms underlying the function of the BCL family. This literature review offers a comprehensive exploration of the structural domain organization of the BCL family, shedding light on how these proteins orchestrate apoptosis. The family comprises anti-apoptotic proteins, pro-apoptotic effectors, and BH3(BCL-2 homology 3)-only proteins, each with distinct structural features and functional roles in apoptotic signaling pathways. Anti-apoptotic proteins like BCL-2 serve as guardians against cell death by preserving mitochondrial integrity. Pro-apoptotic effectors, on the other hand, actively promote apoptosis by inducing mitochondrial outer membrane permeabilization. BH3-only proteins act as molecular switches, mediating the delicate balance between pro- and anti-apoptotic signals. This review delves into the specific role of BCL-2, a prominent family member, in various cancers such as lung, breast, and prostate cancers. Highlighting its significance as a potential therapeutic target, the article underscores the importance of understanding the molecular nuances of BCL-2 in cancer progression. Moreover, recent advancements in BCL-2 inhibitor development are discussed, showcasing their potential as targeted therapies for cancer treatment. These inhibitors represent a promising avenue for personalized cancer therapy, aiming to selectively induce apoptosis in cancer cells while sparing normal cells. The review emphasizes the importance of these inhibitors in addressing the specific challenges posed by BCL-2 dysregulation in diverse cancer types. By elucidating the structural and functional aspects of the BCL protein family, this literature review provides valuable insights into apoptotic signaling pathways. It not only deepens our understanding of the molecular intricacies governing cell death but also presents novel strategies to modulate apoptosis in cancer cells. Ultimately, the article highlights the significance of BCL proteins as promising therapeutic targets and the potential of BCL-2 inhibitors for personalized cancer therapy, paving the way for advancements in cancer treatment.

Key Words: BCL-2 proteins, BH3 only proteins, anti-apoptotic proteins, pro-apoptotic proteins

Introduction

The B-cell lymphoma (BCL) protein family encompasses a diverse group of regulatory proteins involved in the intricate control of apoptosis, a fundamental process in cellular

homeostasis (1). Apoptosis, or programmed cell death, plays a crucial role in embryonic development, tissue remodelling, and the elimination of damaged or infected cells(2). Dysregulation of apoptosis is strongly associated with the pathogenesis of various diseases, including cancer, Studying of BCL proteins essential for understanding and developing therapeutic strategies (2).

The BCL family can be classified (Figure 1) into three main groups based on their function and structural domains: anti-apoptotic proteins (e.g., BCL-2, BCL-XL), pro-apoptotic effectors (e.g., BAX, BAK), and BCL-2 homology-3 (BH3) only proteins (e.g., BIM, BAD)(3). These proteins dynamically interact and regulate the balance between cell survival and death by modulating mitochondrial integrity, caspase activation, and the release of pro-apoptotic factors (4).

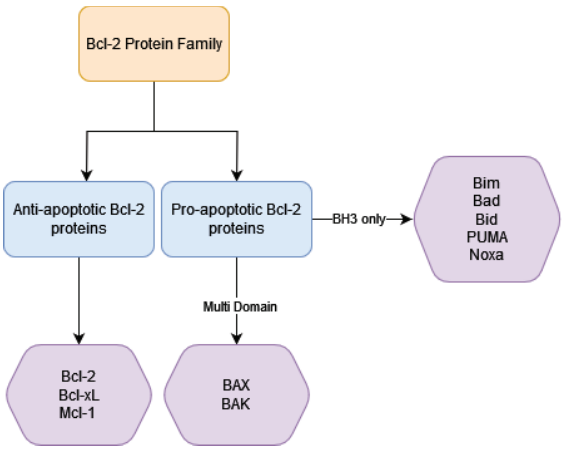

Figure 1: Classification of Bcl-2 Protein Family

Overexpression of B-cell lymphoma 2 (BCL-2) has been associated with increased resistance to apoptosis, allowing cells to evade programmed cell death and contribute to tumorigenesis and cancer progression (4). The dysregulation of BCL-2 expression or function can lead to the evasion of apoptosis, promoting cell survival, tumor growth, and resistance to therapeutic interventions. Therefore, understanding the role of apoptosis in regulating the BCL-2 protein is important in cancer research and may provide valuable insights into the development of targeted therapies (4).

Investigating the role of BCL proteins in cancer research is of paramount importance due to their central involvement in apoptosis and their dysregulation in various malignancies (5). Aberrant expression of BCL proteins, such as upregulation of anti-apoptotic proteins or loss of pro-apoptotic effectors, can confer a survival advantage to cancer cells, contributing to tumor initiation, progression, and therapy resistance (6).

Recent studies have highlighted the clinical significance of BCL proteins as diagnostic and prognostic markers in multiple cancer types (7). For instance, BCL-2 overexpression has been associated with adverse outcomes in lung cancer and breast cancer while BCL-2 downregulation has been linked to aggressive prostate cancer phenotypes (8). Understanding the structural and functional aspects of BCL proteins can uncover novel therapeutic targets and inform the development of precision medicine approaches.

One of the remarkable advancements in the field has been the development and utilization of small-molecule inhibitors and BCL-2 homology 3 (BH3) mimetics that specifically target the BCL-2 protein (9). These compounds aim to disrupt the interactions between BCL-2 and its pro-apoptotic counterparts, such as BCL-2-associated X protein (BAX) and BCL-2 homologous antagonist/killer (BAK) and restore the apoptotic signalling cascade (9,10). By inhibiting the anti-apoptotic function of BCL-2, these drugs promote apoptosis and sensitize cancer cells to cytotoxic therapies (11).

Venetoclax (ABT-199), a potent BCL-2 inhibitor, has emerged as a breakthrough therapeutic agent in the treatment of certain haematological malignancies (12). It has demonstrated remarkable efficacy as a single agent or in combination with other chemotherapeutic drugs in various haematological cancers, including

chronic lymphocytic leukaemia (CLL) and acute myeloid leukaemia (AML) (12,13). Venetoclax has been approved by regulatory authorities and is commercially available for the treatment of specific indications. Other BCL-2 inhibitors currently under investigation include navitoclax (ABT-263) and sabutoclax (BI-97C1), which target both BCL-2 and related anti-apoptotic proteins, such as B-cell lymphoma-extra-large (BCL-XL) and myeloid cell leukaemia sequence 1 (MCL-1) (13). These inhibitors have shown promising results in preclinical studies and early-phase clinical trials, demonstrating their potential as therapeutic options for various cancers (12).

Furthermore, the development of BH3 mimetics, which mimic the BH3 domain of pro-apoptotic proteins and selectively target anti-apoptotic proteins, has opened new avenues for precision medicine (14). These BH3 mimetics, such as obatoclax, ABT-737, and ABT-199, have shown efficacy in preclinical models and are being evaluated in clinical trials for the treatment of haematological and solid malignancies (15).

Moreover, the development of small-molecule inhibitors and BH3 mimetics that selectively target BCL proteins has shown promising results in preclinical and clinical studies. These targeted therapies aim to restore the delicate balance between pro- and anti-apoptotic BCL proteins, sensitizing cancer cells to cell death and overcoming treatment resistance (15). Therefore, unravelling the intricate mechanisms of BCL protein regulation and their interactions provides a foundation for the development of innovative therapeutic strategies in cancer treatment.

Structural domain of BCL family

The BCL-2 homology (BH) domains constitute a crucial structural feature of the BCL protein family. BH domains are conserved regions within the protein sequence that participate in protein-protein interactions and determine the functional properties of BCL proteins (16). The BH domains are classified into four subgroups: BH1, BH2, BH3, and BH4. Each subgroup has distinct structural and functional characteristics. BH1 and BH2 domains are primarily found in the multi-domain anti-apoptotic proteins, while BH3 domains are present in both pro-apoptotic effectors and BH3-only proteins (16). Multi-domain anti-apoptotic proteins, such as BCL-2, BCL-XL, and MCL-1, contain multiple BH domains, including BH1, BH2, and BH3 (17).

Understanding the structural organization of BCL proteins and their functional domains is important in elucidating the complex mechanisms underlying apoptosis. Dysregulation of BCL proteins can lead to abnormal cell survival, contributing to the development and progression of various diseases, including cancer (18).

Anti-apoptotic Proteins

BCL-2

BCL-2 interacts with proteins like BAX and BAK, which promote cell death. BCL-2 forms complexes with these proteins, preventing them from causing damage to the mitochondria and stopping the release of apoptotic factors (19). BH3-only proteins such as BAD, BIM, PUMA, and BID can neutralize the inhibitory effect of BCL-2, allowing other pro-death proteins to initiate apoptosis. Additionally, there are synthetic compounds called BH3 mimetics that mimic the function of BH3-only proteins. BH3 mimetics can disrupt the interaction between BCL-2 and pro-survival proteins, leading to apoptosis (19).

BCL-XL

BCL-XL (BCL2L1) protein consists of structural domains including BH1, BH2, and BH3 domains (20). These domains are important for protein-protein interactions and modulating the function of BCL-XL. BCL-XL is primarily localized in the mitochondria, where it exerts its anti-apoptotic effects (21). By residing in the outer membrane of mitochondria, BCL-XL

protects the integrity of these organelles and prevents the release of apoptotic factors. Interacting proteins of BCL-XL include Bax and Bak, which are pro-apoptotic proteins (21). BCL-XL forms heterodimers with Bax and Bak, inhibiting their pro-apoptotic activity (21). This interaction prevents the formation of pores in the mitochondrial membrane, thereby blocking the release of apoptotic factors. Key regulators of BCL-XL include BH3-only proteins like Bim, Bad, and Puma (22). These proteins can bind to BCL-XL and neutralize its anti-apoptotic function, allowing pro-apoptotic proteins to promote apoptosis (22,23). Recent studies have shed light on the importance of BCL-XL in cell survival and apoptosis regulation (23). A study presented a case of a patient with metastatic colon cancer and highlighted the role of BCL-XL in the progression of the disease. The study found that the patient had a mutation in the v-Raf murine sarcoma viral oncogene homolog B (BRAF) and a deficiency in mismatch repair, which led to the overexpression of BCL-XL and contributed to the development of metastatic lesions (23).

MCL-1

MCL-1 possesses structural domains including BH1, BH2, and BH3 domains. These domains are important for its interactions with other proteins and modulating its anti-apoptotic function (24). The protein is primarily localized in the mitochondria, where it exerts its anti-apoptotic effects (25). By residing in the outer membrane of mitochondria, MCL-1 helps maintain mitochondrial integrity and prevents the release of apoptotic factors. MCL-1 interacts with several proteins, including pro-apoptotic members of the BCL-2 family such as BIM, BAK, and NOXA (26). These interactions are crucial for determining the balance between cell survival and apoptosis. MCL-1 can form heterodimers with pro-apoptotic proteins, inhibiting their ability to promote apoptosis (27).

BCL-W

BCL-W (BCL2L2) is an anti-apoptotic protein that has been less studied compared to other members of the BCL-2 family (28). It shares structural homology with other anti-apoptotic proteins, including BCL-2 and BCL-XL. Like other BCL-2 family members, BCL-W functions to inhibit apoptosis and promote cell survival (28).

BFL-1

This protein consists of BH1, BH2, and transmembrane domains, which are essential for its interactions with other proteins and its anti-apoptotic function. BFL-1 is primarily localized to the mitochondria, particularly the outer mitochondrial membrane (29). BFL-1 has been associated with various cellular processes and interactions. One notable interaction involves its binding to Beclin-1, which enhances the proliferation of macrophages and mast cells during allergic reactions. By interacting with Beclin-1, BFL-1 supports the survival and expansion of these immune cells (30).

Pro-apoptotic Effectors

BAX (Bcl-2-associated X protein)

BAX is a pro-apoptotic protein that plays a crucial role in programmed cell death. It is activated by various apoptotic signals, such as DNA damage, endoplasmic reticulum stress, and growth factor withdrawal (31). The activation of BAX involves a series of conformational changes, oligomerization, and membrane insertion (32). These processes lead to the formation of pores in the outer mitochondrial membrane, known as mitochondrial outer membrane permeabilization (MOMP) (31). As a result, Cytochrome c, among other factors, is released into the cytoplasm, leading to the assembly of the apoptosome and subsequent activation of caspases, initiating cell death (33).

BAK (Bcl-2 antagonist/killer)

Like BAX, BAK interacts with anti-apoptotic proteins such as BCL-2 and BCL-XL. The dynamic balance between BAK and these anti-apoptotic proteins determines whether apoptosis is initiated or prevented (34).

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BOK (Bcl-2-related ovarian killer)

BOK exhibits a broader range of pro-apoptotic activities compared to BAX and BAK. It can induce apoptosis through both mitochondrial-dependent and mitochondrial-independent pathways (35). BOK interacts with Beclin-1 and other autophagy-related proteins, modulating autophagic activity (36). BOK expression is regulated by cellular stressors such as DNA damage and viral infection. Its upregulation can contribute to cell death in response to these stressors (36).

BH3- Domain only Protein

Bcl-2-interacting mediator of cell death (BIM)

The binding of BIM to anti-apoptotic proteins results in the displacement of pro-apoptotic effectors, leading to their activation and subsequent initiation of apoptosis (37). BIM can also directly activate BAX and BAK by interacting with their hydrophobic grooves, promoting their oligomerization and pore formation in the mitochondrial outer membrane (38).

BH3-interacting domain death agonist (BID)

BID serves as a critical link between the extrinsic and intrinsic apoptotic pathways (Figure 2), connecting death receptor activation to mitochondrial apoptosis (39). Upon cleavage by caspase-8, BID generates the truncated form (tBID), which translocate to the mitochondria and interacts with BAX and BAK (40). The interaction of tBID with BAX and BAK induces their conformational changes and activation, promoting MOMP and the release of apoptotic factors (41).

p53 upregulated modulator of apoptosis (PUMA)

PUMA is a potent inducer of apoptosis and functions as a critical mediator of p53-dependent and -independent apoptotic pathways (42). Its transcriptional activation occurs in response to various cellular stresses, including DNA damage, oncogenic signalling, and hypoxia (43).

Bcl-2-associated death promoter (BAD)

In its unphosphorylated state, BAD forms heterodimers with BCL-2 or BCL-XL, preventing their interactions with pro-apoptotic effectors, BAX and BAK (44). Phosphorylation of specific serine residues on BAD promotes its dissociation from BCL-2 or BCL-XL, enabling the activation of BAX and BAK (45).

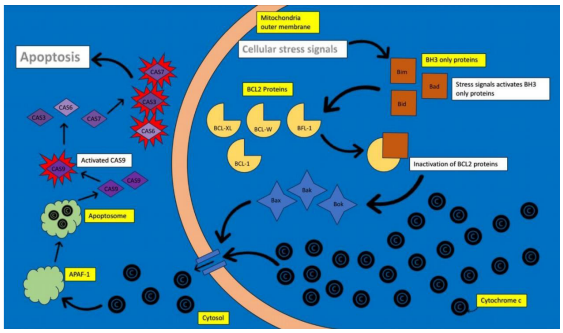

Figure 2: Intrinsic apoptotic pathway.

Table 1: BCL2 family members and their key regulators.

BCL Family Member	Structural Domains	Function	Cellular Localization	Interacting Proteins	Key Regulators
BCL-2	BH1, BH2, BH3, BH4	Anti-apoptotic	Mitochondrial membrane	BAX, BAK, BAD, BIM	BH3-only proteins, BH3 mimetics, BCL-2 homology 3 (BH3) peptides
BCL-XL	BH1, BH2, BH3, BH4	Anti-apoptotic	Mitochondrial membrane	BAX, BAK, BAD, BIM	BH3-only proteins, BH3 mimetics, BCL-2 homology 3 (BH3) peptides

MCL-1	BH1, BH2, BH, BH4	Anti-apoptotic	Mitochondrial membrane	BIM, NOXA	BH3-only proteins, BH3 mimetics, Mule, Mule-induced degradation
BCL-W	BH1, BH2, BH3, BH4	Anti-apoptotic	Mitochondria	BAX, BAK, BIM, BAD, PUMA	BH3-only proteins, BH3 mimetics (context-dependent)
BFL-1	BH1, BH3	Anti-apoptotic	Mitochondria	BAX, BAK, BIM, BAD, PUMA	BH3-only proteins, BH3 mimetics
BAX	BH1, BH2, BH3	Pro-apoptotic	Cytoplasm, Mitochondria	BCL-2, BCL-XL, MCL-1, BFL-1	BH3-only proteins, BH3 mimetics, tBID, PUMA, BIM, BAD, Bmf, Hrk, ART
BAK	BH1, BH2, BH3	Pro-apoptotic	Mitochondria	BCL-2, BCL-XL, MCL-1, BFL-1	BH3-only proteins, BH3 mimetics, tBID, PUMA, BIM, BAD, Bmf, Hrk, ART
BOK	BH1, BH2, BH3	Pro-apoptotic	Mitochondria	BCL-2, BCL-XL, MCL-1, BFL-1	BH3-only proteins, BH3 mimetics, tBID, PUMA, BIM, BAD, Bmf, Hrk, ART
BIM	BH3	BH3- domain only proteins.	Cytoplasm, Mitochondria	BCL-2, BCL-XL, MCL-1, BFL-1	JNK, p38, FOXO, ERK, Chk1
BID	BH3	BH3- domain only proteins.	Cytoplasm	BCL-2, BCL-XL, MCL-1, BCL-1	Caspase-8, caspase-3
PUMA	BH3	BH3- domain only proteins.	Cytoplasm, Mitochondria	BCL-2, BCL-XL, MCL-1, BFL-1	p53, p73, NOXA, BAX, BAK, BAD, MCL-1, BCL-XL, BCL-2
BAD	BH3	BH3- domain only proteins.	Cytoplasm	BCL-2, BCL-XL, MCL-1, BFL-1	Akt, PKA, Raf-1, ERK, JNK, Pim-1, B-Raf, PAK1, PKC, S6K, RSK, PDK1

BCL-2 and lung

Several studies have investigated the relationship between BCL-2 and lung cancer. In high-grade neuroendocrine lung cancers, BCL-2 has been identified as an acquired vulnerability and a potential therapeutic target (46). Targeted inhibition of BCL2 has shown efficacy in overcoming resistance to chemotherapy in non-small cell lung cancer (NSCLC) cell lines (47). However, the prognostic importance of BCL-2 expression in lung cancer is still debated. While some studies have shown that BCL-2-negative expression is associated with poor prognosis[47], a systematic review of studies in non-small cell lung cancer revealed conflicting results, with smaller studies showing a significant relationship between BCL-2 expression and risk of dying, while larger studies showed non-significant effects (48).

The regulation of BCL-2 expression and its impact on lung cancer progression have also been investigated. For example, nicotine

has been found to induce BCL-2 phosphorylation, leading to increased survival of lung cancer cells (49). Additionally, the transcription factor Runt-related transcription factor 2 (RUNX2) has been implicated in inhibiting the apoptosis process in lung cancer, and its knockdown has been shown to downregulate the expression of BCL-2 (50). Furthermore, the interaction between BCL-2 and other molecules has been explored. BCL-2-associated athanogene 3 (BAG3), a member of the BAG family, has been found to have a tight relationship with BCL-2 and can synergistically act with BCL-2 to induce anti-apoptotic effects in lung cancer (51). The miR-497/BCl-2 axis has also been identified as a potential therapeutic target in lung cancer, as miR-497 can decrease resistance to cisplatin by targeting BCL-2 (52).

BCL-2 plays a complex role in lung cancer, with both therapeutic and prognostic implications. Targeted inhibition of BCL-2 has shown promise in overcoming resistance to chemotherapy in NSCLC, while the prognostic significance of BCL-2 expression in lung cancer remains controversial. Further research is needed to fully understand the mechanisms underlying the relationship between BCL-2 and lung cancer and to explore its potential as a therapeutic target.

BCL-2 and breast cancer

Early studies have shown that BCL-2 expression is associated with low-grade, slowly proliferating Oestrogen positive (ER+) breast tumours, and its correlation with ER status is attributed to the improved survival observed in these tumours[53]. Recent studies have further supported the clinical validity of BCL2 as a prognostic marker for early-stage breast cancer, independent of ER, Human Epidermal Growth Factor Receptor 2 (HER2), and adjuvant therapy received (53). BCL-2 expression has been associated with favourable 5-year recurrence-free survival (RFS) and disease-specific survival (DSS) in luminal A breast cancer[54]. However, the prognostic role of BCL-2 expression in breast cancer is subtype-specific, and its significance in other subtypes remains unclear (54). In addition to its prognostic value, BCL-2 has been investigated in relation to other factors in breast cancer. High BCL-2 protein expression has been associated with a favourable outcome regardless of ER, Progesterone (PR), or HER2 status (55). On the other hand, BCL2 expression is only observed in a small proportion of triple-negative breast cancers (55). Furthermore, BCL-2 has been studied in the context of genetic polymorphisms. A study found that the BCL-2 C (-938) A gene polymorphism was associated with an increased risk of developing breast cancer (56). However, another study did not find an association between a BCL-2 promoter polymorphism (rs2279115) and BCL-2 expression or overall survival in breast cancer patients (57). The relationship between BCL-2 and breast cancer has also been explored in terms of its interaction with other molecules. miR-181a-5p has been found to downregulate BCL-2, leading to apoptosis in breast cancer cells (58). Additionally, BCL-2 expression has been correlated with p52 expression in breast carcinoma, suggesting a potential relationship between the two (59).

Breast cancer research has focused on BCL-2, whose expression has been linked to a variety of clinicopathologic traits and prognoses. When it comes to specific breast cancer subtypes, particularly luminal A tumours, BCL-2 has demonstrated prognostic relevance. Research is still being done on its importance in various subtypes of breast cancer as well as how it affects prognosis. Furthermore, studies have shown BCL-2 interacts with several other elements, including genetic polymorphisms and molecular interactions. To completely comprehend BCL-2's function in breast cancer and its potential as a therapeutic target, more research is required.

BCL-2 and prostrate cancer

Overexpression of BCL-2 has been associated with adverse prognostic factors,

disease progression, and therapy resistance in prostate cancer (60). High BCL-2 expression has been correlated with higher Gleason scores and lower biochemical recurrence-free survival in patients with advanced prostate cancer (61). Additionally, BCL-2 has been implicated in the development of castration-resistant prostate cancer (62). The regulation of BCL-2 in prostate cancer has also been investigated. The Mouse Double Minute 2 homolog (MDM2) oncogene, which has ubiquitin ligase activity, may have a direct role in BCL-2 regulation (63). The transcription factor RUNX2 has been shown to bind to the promoter region of antiapoptotic genes, including BCL-2, in prostate cancer cells (50). Furthermore, microRNA-205 has been identified as a regulator of BCL-2 in prostate cancer, with repression of BCL-2 by miR-205 being confirmed through reporter assays and western blotting (64). The relationship between BCL-2 and other factors in prostate cancer has also been explored. Down-regulation of BCL-2 has been associated with self-reported fatigue in non-metastatic prostate cancer patients receiving external beam radiation therapy (65). Additionally, a study found that a BCL-2 polymorphism (-938 C>A) showed a protective role in susceptibility to papillary thyroid carcinoma (66). BCL-2 has been studied in relation to prostate cancer, and its overexpression has been associated with adverse prognostic factors, disease progression, and therapy resistance. The regulation of BCL-2 in prostate cancer involves various mechanisms, including the involvement of the MDM2 oncogene, the transcription factor RUNX2, and microRNA-205. Further research is needed to fully understand the role of BCL-2 in prostate cancer and its potential as a therapeutic target.

BCL-2 as therapeutic targets to treat cancer

There are several types of therapeutic inhibitors that target BCL-2 in various cancers. These inhibitors include microtubule-directed agents, protein phosphatase 1/2A inhibitors, bromodomain and extra-terminal (BET) protein inhibitors, autophagy inhibitors, mitochondrial respiration inhibitors, ceramide metabolism inhibitors, epigenetic therapy, and MDM2 inhibitors. Microtubule-directed agents, such as taxol and nocodazole, have been shown to induce BCL-2 phosphorylation (67). Protein phosphatase 1/2A inhibitors, such as okadaic acid, can also induce BCL-2 phosphorylation (67). These agents target BCL-2 through different pathways, including extracellular signal-regulated kinase activation and G2/M accumulation (67). BET protein inhibitors have been investigated for their potential to increase sensitivity to BCL-2 inhibitors in chronic lymphocytic leukaemia (CLL) (68). These inhibitors work by inhibiting bromodomain and extra-terminal proteins, which can enhance the effectiveness of BCL-2 inhibitors like venetoclax (68). Autophagy inhibitors have also been explored as therapeutic agents targeting BCL-2. Inhibition of the dissociation of the Beclin1 and BCL-2 complex, a negative regulator of autophagy, has been shown to be a potential strategy for developing autophagy inhibitors (69). These inhibitors can be useful in the treatment of diseases involving autophagy dysregulation, including cancer and viral infections (69). Mitochondrial respiration inhibitors have been investigated for their potential to target BCL-2 in high-grade MYC-associated B-cell lymphoma (70). These inhibitors can disrupt mitochondrial metabolism and induce cancer cell death, potentially synergizing with BCL-2 inhibitors (70). Ceramide metabolism inhibitors have also been explored as potential therapeutics targeting BCL-2. Inhibition of ceramide metabolism can sensitize leukaemia cells to inhibition of BCL-2 like proteins, leading to enhanced apoptosis (71). Epigenetic therapy has been shown to activate endogenous retroelements, which remodel mitochondrial metabolism and sensitize cancer cells to BCL-2 inhibitors (72). This combination therapy has shown efficacy in acute myeloid leukaemia and may have potential for other cancers (72). MDM2 inhibitors, such as nutlin-3a, have been investigated for their ability to activate the p53 pathway and overcome BCL-2 overexpression in lymphoma. Combination therapy of MDM2 inhibitors with

BCL-2 inhibitors has shown synergistic effects in inducing apoptosis in leukaemia (73).

Conclusion

Apoptosis and programmed cell death are tightly regulated by the BCL-2 protein family. The family includes both proapoptotic and antiapoptotic members that, in turn, either encourage or prevent the release of cytochrome c from mitochondria. Through the creation of pores in the outer mitochondrial membrane, the proapoptotic proteins BAX and BAK directly mediate the release of cytochrome c. The antiapoptotic members, on the other hand, like BCL-2 and BCL-XL, stop the release of cytochrome c and support cell survival. BH3-only proteins are a diverse group of proteins that regulate apoptosis and autophagy. They can be classified into BH3-only proteins, sensitizers, and activators. These proteins play a critical role in promoting apoptosis by activating proapoptotic effectors or neutralizing antiapoptotic proteins. BH3-only proteins also contribute to the induction of autophagy. Understanding the structural and functional aspects of BH3-only proteins is important for developing targeted therapies for cancer and other diseases.

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