Alternative splicing of *BCL-X* and implications for treating hematological malignancies (Review)

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Abstract. *BCL-X* is a member of the BCL-2 family. It regulates apoptosis and plays a critical role in hematological malignancies. It is well-known that >90% of human genes undergo alternative splicing. A total of 10 distinct splicing transcripts of the *BCL-X* gene have been identified, including transcript variants 1-9 and ABALON. Different transcripts from the same gene have different functions. The present review discusses the progress in understanding the different alternative splicing transcripts of *BCL-X*, including their characteristics, functions and expression patterns. The potential use of *BCL-X* in targeted therapies for hematological malignancies is also discussed.

Contents

1. Introduction

BCL-X is a member of the *BCL-2* gene family (1). The proteins in this family share homology over four conserved regions referred to as the BH1-4 domains that determine dimer formation of the proteins, as well as their function in regulating apoptosis (1) Of the four domains, the BH1, BH2 and BH3 domains facilitate the formation of a hydrophobic slit, which is involved in the uptake of the BH3 domain of pro-apoptotic proteins via heterodimerization; the BH4 domain is often absent in pro-apoptotic proteins, but present in antiapoptotic activity (2,3).

BCL-X regulates apoptosis and plays a critical role in hematopoiesis, lymphopoiesis and hematological malignancies (4-6). Motoyama *et al* (6) performed experiments in which homologous recombination was applied to knockout *BCL-X*. The results demonstrated that *BCL-X* plays a pivotal role in supporting immature lymphocytes survival. In addition, several studies have reported its key role in the lifespan of mature hematopoietic cells, including terminal differentiation stages of erythropoiesis and differentiated megakaryocytes (5,7). Mice deficient in *BCL-X* are anemic and develop severe thrombocytopenia (8). Deregulated expression of *BCL-X* function may also play a role in the pathogenesis of some hematologic disorders, particularly polycythemia vera (9).

Recently, it has been suggested that >90% of human genes undergo alternative splicing (10). Different transcripts from the same gene have the same or different expression pattern and functions (11-14). Rosa *et al* (11) reported that six transcript variants of ZNF695 are co-expressed in cancer cell lines, and transcript variant one and three were predominantly expressed in leukemia. Handschuh *et al* (12) demonstrated that all three NPM1 transcripts are upregulated in leukemia compared with control samples. However, Zeilstra *et al* (13) reported that CD44 variant isoforms (CD44v), but not CD44s, have unique functions in promoting adenoma initiation in Apc (Min/+) mice. In addition, the H2AFY gene encodes H2A histone variant MacroH2A1, including two isoforms (MacroH2A1.1 and MacroH2A1.2) (15). MacroH2A1.1 is predominantly expressed in differentiated cells, while MacroH2A1.2 is preferentially expressed over 1.1 in proliferative cells (14). The MacroH2A1.1 isoform presents as pleiotropic tumor suppressor, by repressing cellular processes, including cell proliferation, migration and invasion, whereas the function of MacroH2A1.2 is mainly cancer-type dependent (14).

A total of 10 distinct splicing transcripts of the *BCL-X* gene have been identified, including transcript variants 1-9 and ABALON. The present review discusses the progress in understanding the alternative splicing transcripts of *BCL-X* in terms of their characteristics, functions and expression patterns. The potential use of *BCL-X* in targeted therapies for hematological malignancies is also discussed.

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2. Alternative splicing of *BCL-X*

BCL-X, also known as *BCL2L1*, *BCL2L* and *PPP1R52*, is located at 20q11.21 (16,17). The *BCL-X* gene was first identified through a screen of the chicken lymphoid cDNA library with a probe for the *BCL-2* gene at low stringency (1). The gene, such as other genes, including ZNF695, NPM1 and H2AFY, is associated with alternative splicing, and 10 transcripts have been identified to date (transcript variants 1-9 and ABALON; Fig. 1 and Table I).

Variant 1 (GenBank: NM_138578.3) represents the longest transcript, with 2,574 base pairs (bp) and contains an open reading frame (ORF, 702 bp) (Table I). It encodes a protein with 233 amino acids that displays 44% amino acid identity with human BCL-2 (1). Thus, this splicing variant encodes the longer isoform BCL-X_L (B cell lymphoma-extra-large; Bcl2l1), also known as BCL-xL. Variants 3 (NM_001317919.2), 4 (NM_001317920.2), 5 (NM_001317921.2), 7 (NM_001322239.2), 8 (NM_001322240.2) and 9 (NM_001322242.2) differ from variant 1 in the 5'untranslated region, whereas their ORFs are the same as that of variant 1. Therefore, they encode the same isoform as transcript variant 1 (Table I). The ORFs and amino acid sequence of BCL-X_L are presented in Table II.

Transcript variant 2 (NM_001191.4) also derives from *BCL-X*, with a length of 2,385 bp. Its sequence is different from that of variant 1 in the second exon, which is the result of differential usage of two 5' splice sites within the first coding exon (Table II). This difference results in the absence of the sequence encoding the 63 amino acids of the BCL-X_L ORF, which display the greatest homology to BCL-2 (1). This results in a shorter ORF with 513 bp compared with variant 1, and thus, the variant encodes a 170-amino acid protein named isoform BCL-X_S (Table II).

Variant 6 (NR_134257.1) contains a different internal exon from variant 1 and is considered a non-coding RNA as use of the same 5'-most supported translational start codon found in variant 1 generates the potential for nonsense-mediated mRNA decay. Another long non-coding RNA generated by alternative splicing of the primary *BCL-X* RNA transcript is INXS (also named ABALON, NR_131907.1), which is 1,903 bp in length (Table I).

BCL-X can be alternatively spliced to produce 10 transcripts. Among them, seven transcripts encode the same isoform BCL-X_L, whereas the transcript variant 2 translates the shorter isoform BCL-X_S. Besides, two long non-coding RNAs are also generated from the gene. Currently, there are no reports on the two non-coding RNAs (variant 6 and INXS) derived from *BCL-X*. Thus, the present review focuses on these two splice isoforms (BCL-X_L and BCL-X_S).

3. Function of *BCL-X* splicing variants in hematopoietic cells

BCL-X_L that inhibit apoptosis or promote compensatory proliferation. It is well-known that variants of *BCL-X* regulate apoptosis (2). While BCL-X_L inhibits apoptosis, BCL-Xs has pro-apoptotic functions via the inhibition of BCL-2 and BCL-X_L (1). BCL-X_L protein binds and sequesters pro-apoptotic Bak/Bax proteins via their BH3 domains, which inactivates them (18) and prevents caspase activation (19-21). This renders the cells resistant to apoptotic cell death (1,18-21). However, it has been reported that BCL-X_L and Bax also act independently to support cell survival, based on findings that BCL-X_L can limit apoptosis independent of Bax expression, and that BCL-X_L protects B cells from immunosuppressant-induced apoptosis (22). Furthermore, while BCL-X_L cannot stop cell damage and cell cycle arrest induced by certain drugs, it can contribute to lower rates of cell death following drug treatment (23-25).

Josefsson *et al* (26) demonstrated that deletion of BCL-X_L leads to megakaryocyte apoptosis and failure of platelet shedding. Conversely, Kaluzhny *et al* (27) reported that overexpression of BCL-X_L in megakaryocytes (MKs) increases the number of MKs and decreases apoptosis. In addition, BCL-X_L expression is necessary for the survival of reticulocytes and MKs, and the absence of functional BCL-X_L expression results in anemia and thrombocytopenia (8,28-31). Dolznig *et al* (32) interpreted the mechanism of anemia due to loss of BCL-X_L. The authors demonstrated that during erythroid maturation, erythropoietin (Epo) regulates the number of red blood cells via apoptosis inhibition arising from Epo-dependent upregulation of BCL-X_L (32). Furthermore, overexpression of erythroid progenitors BCL-X_L also can induce erythroid colonies without Epo (33).

Harb *et al* (34) reported that BCL-X_L does not inhibit leukemogenesis or affect the apoptosis of tumor cells. The authors clarified the role of BCL-X_L in Philadelphia chromosome-positive (Ph+) B-cell acute lymphoblastic leukemia using two mouse models, and the results demonstrated that loss of BCL-X_L expression does not prohibit leukemogenesis or alter the percentage of apoptotic cells, but promotes cellular proliferation. Conversely, overexpression of BCL-X_L decreases cellular proliferation. These results identified unexpected functions of BCL-X_L in cell-cycle entry and tumor cell proliferation. Studies in mice lacking *BCL-X* expression have suggested that BCL-X_L expression may be essential to the survival of proliferating hematopoietic precursor cells (6,34).

BCL-X_S that promote apoptosis and are associated with BCL-X_L. BCL-X_S expression can block resistance to apoptosis induced by overexpression of BCL-2 (1,35). Accordingly, BCL-X_S expression has been demonstrated to promote apoptosis by inhibiting the anti-apoptotic function of BCL-2 (1). Additional research demonstrating heterodimer formation between BCL-X_S and BCL-X_L, as well as heteromultimer formation of these proteins with BCL-2, suggested that BCL-X_S play a dominant role in inactivating BCL-2 or BCL-X_L (35).

Consistently, BCL-X_S was recently demonstrated to limit the protective effects of BCL-X_L in the contexts of growth factor withdrawal and chemotherapeutic drug treatment (36). Thus, relative expression of BCL-X_S and BCL-X_L may be essential in balancing cell death and survival during hematopoietic cell differentiation.

4. Expression and clinical significance of *BCL-X* splicing variants

BCL-X is differentially expressed in different differentiated hematopoietic cells and lymphoid tissues. In 1993, *BCL-X*

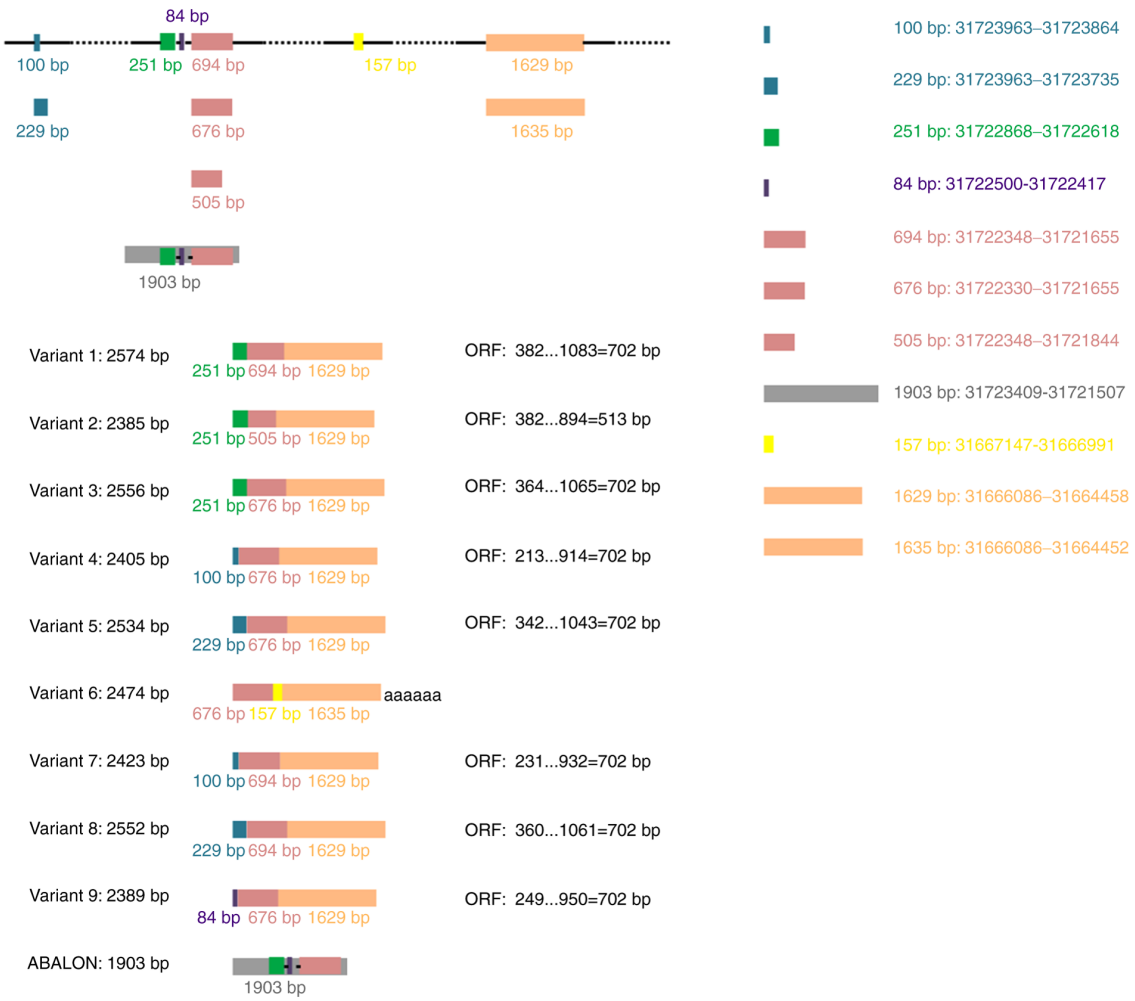

Figure 1. Alternative splicing transcripts of *BCL-X*. *BCL-X* consists of 11 exons on the same DNA strand. The size and location of each exon in the genome are depicted on the right-hand side. Colored boxes represent exons. Blue boxes represent variable exons with 100 and 229 bp. Green box represents exon with a length of 251 bp. Purple boxes represent exons which are 84 bp in length. Red boxes represent variable exons with 694, 676 and 505 bp. Yellow boxes represent exons with a length of 157 bp. Orange boxes represent variable exons with 1,629 and 1,635 bp. In addition, the grey exon with 1903 bp covers a region of exons painted green, purple and red. A total of 10 distinct splicing transcripts were produced through alternative splicing, including eight mRNAs encoding two protein isoforms and two non-coding RNAs. ORF, open reading frame; bp, base pair.

mRNA expression was observed in a variety of tissues (thymus, bursa and the central nervous system), with the highest levels observed in lymphoid and the central nervous system (1). Although *BCL-X* mRNA expression is not observed in single-positive thymocytes or mature peripheral blood T cells, rapid induction of high levels of *BCL-X* mRNA expression has been observed following mitogenic activation (1). In addition, double-positive thymocytes express higher levels of BCL-X_S compared with BCL-X_L (1). However, Ohta *et al* (37) reported that the BCL-X_L protein, but not the BCL-X_S protein, is expressed in hematolymphoid tissue.

In 1994, Krajewski *et al* (38) reported the detection of *BCL-X* immunostaining in precursors of myeloid cells and metamyelocytes. The authors demonstrated that most bone marrow polymorphonuclear cells lack *BCL-X* expression along with most spleen and peripheral blood granulocytes, in accordance with other studies (37,39,40). Subsequently, Sanz *et al* (40) demonstrated that peripheral blood monocytes and alveolar macrophages are positive for *BCL-X*. In addition, *BCL-X* expression levels are either maintained or upregulated during monocyte/macrophage differentiation but downregulated with the maturation of myeloid progenitors into polymorphonuclear cells (40,41). Furthermore, *BCL-X* expression during erythropoiesis is notably increased in terminally differentiated erythroblasts (42).

Sanz *et al* (40) demonstrated that BCL-X_L is the most highly expressed form of *BCL-X* in HL-60 and CD34+ cells differentiating into monocytes/macrophages. Furthermore, BCL-X_L is the predominant *BCL-X* form expressed in peripheral blood mononuclear cells (43). However, in hematopoietic precursors, the predominant *BCL-X* form is BCL-X_S (44). Andreeff *et al* (45) reported that in normal hematopoietic progenitor cells, BCL-X_L is highly expressed in the earliest $CD34^+/33^-/13^-$ compartment and to a lesser extent in $CD34^+/13^+$ cells, but is absent in promyelocytes (CD34-/33+). Furthermore, BCL-X_S was detectable only in the most immature $CD34^+/33^-/13^-$ compartment (45). In addition, BCL-X_L and BCL-X_S are not expressed in neutrophils (43), and the expression of BCL-X_S has not been detected in erythroid cells (42).

Different expression patterns of BCL-X_L and BCL-X_S in hematological malignancies. BCL-X_L has been detected in a variety

Table I. Alternative splicing transcripts of *BCL-X*.

Transcript variant	Accession number	Definition	Length (bp)	Exon		Open reading frame		Protein		
				No.	Location	Location	Length (bp)	Amino acid	Molecular weight, KD	Name
Variant 1	NM_138578.3	mRNA	2,574	3	31722868-31722618, 31722348-31721655, 31666086-31664458	382…1083	702	233	26	BCL-X_L
Variant 3	NM_001317919.2	mRNA	2,556	3	31722868-31722618, 31722330-31721655, 31666086-31664458	364…1065	702	233	26	BCL-X_L
Variant 4	NM_001317920.2	mRNA	2,405	3	31723963-31723864, 31722330-31721655, 31666086-31664458	213…914	702	233	26	BCL-X_L
Variant 5	NM_001317921.2	mRNA	2,534	3	31723963-31723735, 31722330-31721655, 31666086-31664458	342…1043	702	233	26	BCL-X_L
Variant 7	NM_001322239.2	mRNA	2,423	3	31723963-31723864, 31722348-31721655, 31666086-31664458	231…932	702	233	26	BCL-X_L
Variant 8	NM_001322240.2	mRNA	2,552	3	31723963-31723735, 31722348-31721655, 31666086-31664458	360…1061	702	233	26	BCL-X_L
Variant 9	NM_001322242.2	mRNA	2,389	3	31722500-31722417, 31722330-31721655, 31666086-31664458	197..898	702	233	26	BCL-X_L
Variant 2	NM_001191.4	mRNA	2,385	3	31722868-31722618, 31722348-31721844, 31666086-31664458	382…894	513	170	19	BCL-X_S
Variant 6	NR_134257.1	Non-coding RNA	2,474	3	31722330-31721655, 31667147-31666991, 31666086-31664452	No	-	No	-	-
ABALON	NR_131907.1	Non-coding RNA	1,903	1	31721507-31723409	No	-	No	-	-

NM, sequence derived from mRNA; NR, sequence derived from non-coding RNA.

Table II. ORF and encoding amino acid sequence of *BCL-X*.

	Sequence
ORF (702 nt)	ATGTCTCAGAGCAACCGGGAGCTGGTGGTTGACTTTCTCTCCTACAAGCTTTCCCAGAAAG GATACAGCT GGAGTCAGTTTAGTGATGTGGAAGAGAACAGGACTGAGGCCCCAGAAGGGACTGAATCGG AGATGGAGAC CCCCAGTGCCATCAATGGCAACCCATCCTGGCACCTGGCAGACAGCCCCGCGGTGAATGGA GCCACTGGC CACAGCAGCAGTTTGGATGCCCGGGAGGTGATCCCCATGGCAGCAGTAAAGCAAGCGCTGA GGGAGGCAG GCGACGAGTTTGAACTGCGGTACCGGCGGGCATTCAGTGACCTGACATCCCAGCTCCACATC ACCCCAGG GACAGCATATCAGAGCTTTGAACAG**GTAGTGAATGAACTCTTCCGGGATGGGGTAAACTGGG GTCGCATT** **GTGGCCTTTTTCTCCTTCGGCGGGGCACTGTGCGTGGAAAGCGTAGACAAGGAGATGCAGGT ATTGGTGA** **GTCGGATCGCAGCTTGGATGGCCACTTACCTGAATGACCACCTAGAGCCTTGGATCCAGGAGA ACGGCGG** **CTGG**GATACTTTTGTGGAACTCTATGGGAACAATGCAGCAGCCGAGAGCCGAAAGGGCCAGG AACGCTTC AACCGCTGGTTCCTGACGGGCATGACTGTGGCCGGCGTGGTTCTGCTGGGCTCACTCTTCAGT CGGAAATGA
Protein (233 aa)	MSQSNRELVVDFLSYKLSQKGYSWSQFSDVEENRTEAPEGTESEMETPSAINGNPSWHLADSPAV NGATG HSSSLDAREVIPMAAVKQALREAGDEFELRYRRAFSDLTSQLHITPGTAYQSFEQ**VVNELFRDGV NWGRI** **VAFFSFGGALCVESVDKEMQVLVSRIAAWMATYLNDHLEPWIQENGGW**DTFVELYGNNAAAES RKGQERF NRWFLTGMTVAGVVLLGSLFSRK

ORF, open reading frame; NT, nucleotide; AA, amino acid. The second coding exon of ORF are underlined. The absence of the sequence encoding the 63 amino acids of BCL-XL are indicated in bold.

of hemopoietic cell types, including lymphoid and myeloid leukemia lines, such as HL-60, K562, KG1a, ML-1, Molt3, Jurkat, Raji and CEM (46,47). However, BCL-X_S is weakly expressed in K562 and VAL lines (lymphoid lines) (48) and not expressed in AS-E2 cells (49).

Upregulated BCL-X_L expression was observed in both acute myeloid leukemia (AML) (46) and acute lymphocytic leukemia (ALL) (50). Bogenberger *et al* (51) measured BCL-X_L expression in 577 patients with primary AML using a reverse phase protein array proteomic approach. The results demonstrated that normal CD34+ progenitor cells express less BCL-X_L than most FAB classifications, and BCL-X_L expression is higher in M6 compared with other AML FAB classifications (51). BCL-X_L is highly expressed in leukemic $CD34^+/13^+$ or CD34-/13+ cells (44,45). Notably, the percentages of BCL-Xs positive cells among M2 and M3 types were higher than those in other types (48). Furthermore, significantly lower expression of BCL-X_S was observed in CD34+ vs. CD34-leukemias (48).

In addition to acute leukemia, BCL-X_L and BCL-X_S have been detected in other hemopoietic diseases. For example, Gottardi *et al* (52) observed high BCL-X_L levels during the leukemic phase in 16 of 23 B cell type chronic lymphocytic leukemia (B-CLL) cases and 8/11 mantle cell lymphoma (MCL) cases (52), while BCL-X_S was observed in only low-to-trace amounts during the leukemic phase in 13/23 B-CLL cases and 6/11 of MCL cases (52). In addition, Brousset *et al* (53) recently reported on the frequent expression of *BCL-X* in Reed-Sternberg cells of 1 Hodgkin's disease. Zhang *et al* (41) evaluated BCL-X_L expression during differentiation of megakaryocytic cells from essential thrombocythemia (ET) patients. The authors demonstrated that BCL-X_L protein expression is downregulated in ET during differentiation of megakaryocytes.

Clinical significance in hematological malignancies. Expression of apoptosis-regulating protein *BCL-X* in AML blasts at diagnosis is associated with disease-free survival (54). Recent studies have reported that overexpression of BCL-X_L leads to cellular resistance to various pharmaceutical agents, such as etoposide, doxorubicin, cisplatin, vincristine, bleomycin and paclitaxel, as well as ionizing radiation (23,50,55-59). Overexpression of BCL-X_L has also

been associated with poor clinical outcomes in patients with AML (58). However, research indicates no gain in prognostic information from BCL-X_L expression (60). Reverse transcription PCR analysis demonstrated high levels of BCL-X_L mRNA in minimal residual disease (MRD) but not in normal cells (45).

Campos *et al* (48) revealed an inverse correlation between the percentages of BCL-2- and BCL-X_S-positive cells in AML and ALL. Among the 57 patients included in the study, 37 experienced complete remission (CR), and samples from these patients contained a significantly higher percentage of BCL-X_S-expressing cells compared with samples from patients who did not achieve CR (48). Notably, BCL-X_S expression was observed with greater frequency in T-cell leukemias than in B-cell leukemias and was associated with a higher remission rate. Notably, for both AML and ALL, the remission rates were higher among patients with leukemic cells expressing BCL-X_S (48). Cell lines hyperexpressing BCL-X_S are also more sensitive to viral- or chemotherapy-induced apoptosis (61,62).

Deng *et al* (63) observed a higher ratio of BCL-X_L to BCL-X_S expression in patients with AML, with a poor prognosis (-5, -7) than those with a good prognosis [inv16, t(8;21)]. The authors reported a higher ratio of BCL-X_L to BCL-X_S expression in chemoresistant subtypes compared with chemosensitive subtypes (63). An increase in the ratio of BCL-X_L to BCL-X_S expression was also observed in MRD of AML compared with *de novo* diagnosed AML (45).

5. Therapies targeting *BCL-X* for hematological malignancies

The BH3 mimetics, such as ABT-199 (venetoclax), ABT-737 and ABT-263 (navitoclax), are small molecules that mimic the BH3 domains of BCL-2 family proapoptotic proteins (60,62). They have been used to bind and antagonize the functions of BCL-2 and/or BCL-X_L to promote cell death in hematological malignancies (64-69).

ABT-199 specifically targets BCL-2 protein and has low affinity for BCL-X_L (64). Currently, ABT199 is the only US food and drug administration-approved antitumor agent targeting the BCL-2 family of proteins, and is useful for the treatment of certain hematologic malignancies, such as AML and CLL (70-72). However, prolonged monotherapy tends to beget resistance to ABT-199, and the report indicated that targeting of myeloid cell leukemia-1 (MCL-1) and BCL-X_L can restore sensitivity to the ABT-199 among previously resistant AML cell lines, which would delay or even prevent the development of drug resistance in these cells (73). In addition, co-expression of high BCL-2 levels with low BCL-X_L levels was demonstrated to render multiple myeloma (MM) cell lines sensitive to ABT-199, whereas co-expression of BCL-2 and BCL-X_L was associated with resistance to ABT-199, but sensitivity to the BCL-X_L-selective inhibitor A-1155463 in MM cells (73,74).

The ABT-737 molecule has a high affinity for BCL-2, BCL-X_L and BCL-W, but because it is not orally bioavailable, its administration via chronic single-agent therapy or in combination regimens is difficult (65). The orally bioavailable equivalent of ABT-737 is ABT-263 (66). ABT-263 treatment of tumor cells quickly leads to apoptosis by blocking interactions between Bcl-2/Bcl-X_L and pro-death proteins, as well as by inducing Bax translocation and cytochrome c release (66). In a xenograft model of ALL, oral ABT-263 treatment alone induced complete tumor regression, and even though ABT-263 exhibited limited efficacy as a single-agent treatment in xenograft models of aggressive B-cell lymphoma and MM, it significantly enhanced the efficacies of other commonly used therapeutic regimens (63). These findings provided the necessary evidence for clinical trials of the effectiveness of ABT-263 for treating B-cell malignancies (66). Despite the promising efficacy of ABT-263 observed in preclinical studies (65,66), thrombocytopenia resulting from the inhibition of BCL-X_L (a critical pro-survival factor in megakaryocytes/platelets) (75,76) is a dose-limiting toxicity for the clinical use of ABT-263 (77).

To reduce the dose-limiting platelet toxicity of ABT263, Khan *et al* (78) converted it to DT2216, a BCL-X_L proteolysis-targeting chimera (PROTAC), that targets BCL-X_L to the Von Hippel-Lindau E3 ligase, which is minimally expressed in platelets. PZ15227 is another BCL-X_L PROTAC, which targets BCL-X_L to the cereblon E3 ligase (79). BCL-X_L PROTACs are bivalent small molecules containing a ligand that recognizes the target protein and recruit it to the E3 ligase. Target protein is polyubiquitinated and degraded in proteasome. These results confirm that BCL-X_L PROTACs have improved antitumor potency and reduced platelet toxicity compared with ABT263 (78,79).

The first selective BCL-X_L inhibitor, WEHI-539, was discovered via high-throughput screening and demonstrated to induce BAK-dependent apoptosis (68). Later research using fragment-based approaches led to the development of the BCL-X_L antagonists A1155463 and the next-generation drug A1331852 (80). Wang *et al* (81) proposed that A1155463 may effectively kill ABT-199-resistant AML cells via their high expression of BCL-X_L. Although preclinical studies of A1155463 and A1331852 have produced promising results, these compounds have not yet entered clinical trials (80-84).

The novel BH3 domain mimetic, JY-1-106, antagonizes BCL-X_L and MCL-1, and has been reported to promote cell death among HL-60 cells when administered as a single-agent treatment and in combination with retinoids (85). In addition, the greatest reduction in cell viability was observed when JY-1-106 was applied in combination with the RARγ antagonist, SR11253 (72). These findings suggest that combined administration of a dual BCL-X_L/MCL-1 inhibitor with retinoids may be a promising strategy for treating leukemia (85).

6. Conclusion

In conclusion, 10 distinct transcripts are generated from the *BCL-X* gene. It encodes proteins, including BCL-X_L and BCL-X_S, as well as non-coding RNAs, including variant 6 and INXS. The expression patterns and functions of variant 6 and INXS remain unknown; however, studies have provided valuable insights into the expression patterns and functions of BCL-X_L and BCL-X_S in hematological malignancies. Therapies based on targeting *BCL-X* have been evaluated for their potential effectiveness against hematological malignancies, but a therapy with satisfactory

clinical efficacy is yet to be discovered. Thus, continued efforts to develop better targeted therapies based on *BCL-X* are required.

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Availability of data and materials

Not applicable.

Authors' contributions

WC conceived the present study. WC prepared the original draft and the figure. JL performed the literature analysis. WC revised the manuscript . Data authentication is not applicable. All authors 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.

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