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Research Progress on the Application of the BCL6 Gene in Breast Cancer

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Abstract

Breast cancer has become one of the most common malignant tumors among women worldwide. Compared with European and American countries, the proportion of late-stage diagnoses among Chinese patients is relatively high. Although the diagnosis and treatment methods for breast cancer are constantly being updated and improved, most patients still face problems such as recurrence, metastasis, and drug resistance due to the heterogeneity of breast cancer itself. Therefore, it is urgent to find new therapeutic targets for breast cancer. B-cell lymphoma 6 protein (BCL6), as a transcriptional repressor, plays an important role in the occurrence and development of breast cancer. Studies have shown that high expression of BCL6 is closely related to the malignant characteristics, metastatic ability, and prognosis of tumors, and inhibiting its expression can enhance the sensitivity of breast cancer cells to chemotherapy drugs. This article reviews the expression and function of BCL6 in breast cancer, related molecular mechanisms, potential therapeutic targets, research progress in chemotherapy resistance, and discusses its future development and application in breast cancer.

Keywords

BCL6, Breast Cancer, Signaling Pathway, Chemotherapy Resistance, Therapeutic Target

1. Introduction

Breast cancer is the most common malignant tumor in women globally and the leading cause of cancer-related deaths in less developed countries, ranking second in more developed countries [1]. Although significant progress has been made in

breast cancer treatment in recent years, some patients still face issues such as recurrence, metastasis, and drug resistance. Therefore, it is necessary to conduct in-depth research on its molecular mechanisms to develop new treatment strategies [2]. To investigate its molecular mechanisms, we have noted a key transcriptional repressor, B-cell lymphoma 6 (BCL6), which plays a critical role in the development and progression of many tumors. Therefore, among the many molecular markers in breast cancer research, the important role of BCL6 in the occurrence and development of breast cancer should also receive widespread attention.

BCL6 is a transcriptional repressor that plays a key role mainly in B cell development and function. Its abnormal expression in various tumors, especially lymphomas, is considered an important oncogene [3]. In breast cancer, high expression of BCL6 is significantly associated with larger tumor size, higher histological grade, stronger invasive and metastatic ability, higher risk of recurrence, and poorer treatment response [4] [5]. Studies have shown that BCL6 promotes the survival and proliferation of breast cancer cells by regulating the expression of genes related to cell proliferation and survival [6]. Additionally, BCL6 interacts with Signal Transducer and Activator of Transcription 3 (STAT3) in triple-negative breast cancer, further affecting tumor cell function [7].

In recent years, there have been increasing studies on the relationship between BCL6 and breast cancer. Walker *et al.* showed that BCL6 is highly expressed in breast cancer cell lines [8], and its gene locus is amplified in about 50% of primary breast cancers, suggesting that BCL6 may play an important role in the occurrence or progression of breast cancer. Furthermore, they demonstrated that inhibiting BCL6 expression can induce apoptosis in breast cancer cells, suggesting its potential as a new therapeutic target for breast cancer [6]. Louwen *et al.* again demonstrated the important role of BCL6 in breast cancer progression and emphasized the correlation between BCL6 and tumor biological characteristics [2]. Sultan *et al.* used a genome-wide shRNA screen and found that the expression level of BCL6 is related to the sensitivity or resistance to paclitaxel [4]. Inhibiting BCL6 expression can enhance the therapeutic effect of paclitaxel, providing new insights into drug resistance, revealing the key role of BCL6 in paclitaxel resistance, and offering new potential therapeutic strategies to overcome chemotherapy resistance in breast cancer. Furthermore, Ollila and Olszewski pointed out that the expression of BCL6 in extranodal diffuse large B-cell lymphoma (DLBCL) is significantly associated with its prognosis and risk of central nervous system recurrence [9]. This finding may provide new ideas for breast cancer treatment. Meanwhile, Luo *et al.*'s research showed that the expression of BCL6 is related to the prognosis of primary breast diffuse large B-cell lymphoma [10], highlighting the broad pathological significance of BCL6 in different subtypes of breast cancer. These research results indicate that BCL6 not only plays an important role in the occurrence and development of breast cancer but may also become a key target for improving existing treatment efficacy.

In summary, BCL6 is deeply involved in multiple aspects of breast cancer, in-

cluding occurrence, metastasis, recurrence, and drug resistance, while simultaneously highlighting its significant value as a potential therapeutic target. These research advances provide important clues for in-depth analysis of its molecular mechanisms and lay the foundation for developing targeted therapy strategies. With further research on the functional regulation of BCL6, we expect it to help optimize treatment decisions for breast cancer patients.

2. Molecular Characteristics of BCL6 and Its Role in Tumors

Research has found that BCL-6 belongs to the anti-apoptosis family, located on human chromosome 3q27. The encoded Bcl6 protein is a zinc finger protein that functions as a transcriptional inhibitor [11] [12]. The essence of this gene causing most tumors is its mutations and chromosomal translocations. Abnormally expressed BCL-6 can directly regulate cell differentiation, proliferation, and apoptosis, promote tumor growth, and cause malignant transformation of germinal center-derived B cells. As a transcriptional repressor, BCL6 binds to corepressors such as BCOR and NCOR1/NCOR2 through its BTB domain, thereby recruiting enzymes like EZH2 and HDAC3. Meanwhile, its ZF domain can recognize and bind specific DNA sites with a core sequence of 5'-TTCCTAGAA, collectively mediating transcriptional repression of target genes [13]. Furthermore, BCL6, as a transcription factor with the ability to regulate the expression of multiple genes, participates in regulating the expression of genes related to cell differentiation, stemness, survival, and proliferation. It can be induced in the tumor microenvironment through the TLR4 and mTOR pathways [14]. BCL6 is highly expressed in breast cancer cell lines and tissue specimens, and its expression level is associated with disease progression and poor survival of breast cancer patients; it is a direct target gene of miR-339-5p. The expression of miR-339-5p can significantly reduce the mRNA and protein levels of BCL6, suggesting the post-transcriptional regulatory role of miRNA on BCL6 [15]. BCL6 is not only involved in the proliferation and metastasis of tumor cells but may also affect the biological characteristics of tumors by regulating related signaling pathways. One study showed [16] that BCL6 expression is significantly higher in the stem cell-like sphere culture of triple-negative breast cancer (TNBC) than in its adherent counterpart, and the loss of BCL6 function significantly reduces sphere formation, preferentially targeting CD44-positive rather than aldehyde dehydrogenase (ALDH)-positive stem-like cells. BCL6 promotes the self-renewal and maintenance of TNBC stem cells by inhibiting the transcription of the Numb gene and activating the Notch signaling pathway. Additionally, BCL6 can interact with the EZH2 and BCoR corepressors to regulate the expression of the Numb gene through epigenetic mechanisms, thereby affecting the activity of the Notch signaling pathway.

BCL6 has also been widely studied in other tumors. Fan *et al.* found that miR-10a can inhibit DLBCL cell proliferation and promote apoptosis by targeting BCL6 [17]. Researcher Zhao Dongmei *et al.* found that BCL6 is generally highly expressed in the serum and tissues of patients with endometriosis [18], suggesting

that BCL6 may also serve as a new target for the clinical diagnosis and treatment of endometriosis. Li *et al.* found that BCL6 also plays a key role in promoting KRAS-addicted lung cancer and therefore suggested that BCL6 could be used as a new therapeutic target for this difficult-to-treat condition [19]. Wu Huihua, He Xingzhen *et al.* found that BCL6 expression in ulcerative colitis intestinal tissue is lower than in normal tissue, and BCL6 expression in gastric cancer tissue is significantly lower than in normal tissue [20] [21]. Therefore, BCL6 is not an absolute oncogene, as its function exhibits "context-dependent" characteristics. Furthermore, Yang Li *et al.* analyzed the impact of BCL6 overexpression on alternative splicing in cells through high-throughput sequencing, suggesting that BCL6 may be involved in tumorigenesis by regulating gene splicing [22]. Li Ying and Zhang Xiaoyan also discussed the expression changes of BCL6 in psoriasis and other diseases [23], further emphasizing its key role in cell apoptosis. Zhang *et al.* found that BCL6 in diffuse large B-cell lymphoma is significantly correlated with tumor subtype and patient prognosis [24]. Ding Yihan *et al.* showed that the expression of BCL6 in chronic myeloid leukemia cells is closely related to cell proliferation and apoptosis, suggesting its important role in tumor cell survival [25]. Additionally, Wei Min *et al.* found that estradiol (E2) can promote the proliferation of ectopic endometrial glandular epithelial cells by upregulating BCL6 protein expression, further supporting the potential role of BCL6 in tumor growth [26].

3. Expression and Function of BCL6 in Breast Cancer

Research on the mechanism of the BCL6 gene in breast cancer has gradually increased in recent years. Numerous studies have shown that its expression in breast cancer tissues is significantly higher than in benign breast lesion tissues. Researcher Zheng L *et al.* collected 228 breast cancer patient tissue specimens and 80 benign lesion tissue specimens for immunohistochemical analysis [12]. They found that the protein and mRNA expression levels of BCL6 were significantly increased in breast cancer tissues and demonstrated a positive correlation with tumor size, lymph node metastasis, histological grade, and TNM stage. Therefore, we can consider that high expression of BCL6 is significantly associated with patients' overall survival and recurrence-free survival, suggesting that it may serve as a prognostic marker for breast cancer.

Many scholars have also studied the function of BCL6 in breast cancer. To further clarify the clinical significance of BCL6 in tumors, we further explored the relationship between BCL6 expression and the biological characteristics of tumors. Research shows that the occurrence of HER-2 positive breast cancer is closely related to the high expression of BCL6. BCL6 may promote tumor progression by influencing cell cycle and apoptosis pathways [27]. Moreover, the expression of BCL6 may be regulated by other transcription factors such as STAT3 and STAT5. The interaction between these factors may play a key role in the development of breast cancer [6]. Some research proposes that the interaction be-

tween BCL6 and ZBTB16 may play an important role in breast cancer progression. Low expression of ZBTB16 is associated with high expression of BCL6, also indicating its potential as a biomarker [28]. Meanwhile, the relationship between BCL6 and STAT4 shown in research is also noteworthy. The expression level of STAT4 in breast cancer is negatively correlated with patient prognosis. Inhibiting BCL6 can increase STAT4 expression, thereby inhibiting tumor cell proliferation [29]. Furthermore, Yang Li *et al.*, by constructing a lentiviral cell model overexpressing BCL6 [22], found that BCL6 overexpression is associated with various alternative splicing genes and related pathways, further revealing the complex role of BCL6 in tumor biology. In summary, the high expression of BCL6 in breast cancer is closely related to the biological characteristics of the tumor and may participate in the occurrence and development of breast cancer through various mechanisms.

4. Related Molecular Mechanisms and Signaling Pathways of BCL6 in Breast Cancer

The BCL6 gene, as a type of transcriptional repressor, plays a key role in the occurrence and progression of breast cancer. Current related research shows that the abnormal expression of BCL6 is closely linked to the proliferation and survival of breast cancer cells. Walke *et al.* found that BCL6 is highly expressed in breast cancer cell lines [8], and its gene locus is amplified in about half of primary breast cancers. Using ChIP-seq analysis, they identified specific genomic regions regulated by BCL6 in breast cancer cells, suggesting that BCL6 can promote cancer cell survival by inhibiting the expression of specific genes. Louwen *et al.* further proposed that elevated BCL6 levels are associated with malignant characteristics of breast cancer, such as larger tumor diameter [2], higher grade, stronger invasiveness, easier recurrence and metastasis, etc. These studies show that BCL6 promotes the proliferation and survival of breast cancer cells by regulating multiple signaling pathways. Additionally, Cardenas *et al.* found that inhibiting BCL6 expression can enhance the sensitivity of breast cancer cells to chemotherapy drugs [30], suggesting the potential targeting role of BCL6 in breast cancer treatment. BCL6 activates the Notch signaling pathway by transcriptionally inhibiting the Numb gene. The specific mechanism involves BCL6 binding to the response element in the first intron of the Numb gene (numb-1 RE), enhancing Notch signaling by inhibiting Numb expression, thereby promoting the self-renewal of breast cancer stem cells (CSCs) and tumor drug resistance. In triple-negative breast cancer (TNBC) models, the expression level of BCL6 is significantly correlated with the enrichment of the Notch signaling pathway, and its inhibition leads to decreased expression of Notch signaling pathway-related genes (such as Hes1, Hes2, Hey1, and Hey2) [16].

Existing research has found that the BCL6 molecule and the PRL → PRL receptor (PRLR) → JAK2 → STAT5 signaling pathway it mediates play a very critical role in the process of breast cancer occurrence and development. STAT5a has an

important regulatory effect on the expression of BCL6 in mammary epithelial cells and breast cancer cells. This research indicates that prolactin can inhibit the expression of BCL6 through the STAT5a mechanism. Chromatin immunoprecipitation experiments confirmed that STAT5a can physically interact with the regulatory region of the BCL6 gene, thereby downregulating its mRNA and protein levels. In T-47D and SK-BR-3 breast cancer cells, STAT5 plays a more dominant role in regulating BCL6 expression levels than its family members STAT3 and STAT4. When STAT5 expression decreases, BCL6 expression increases accordingly [31]. Conversely, BCL6 can also interfere with STAT5 function by sharing DNA target sequences with STAT5. For example, BCL6 overexpression significantly inhibits prolactin-induced Stat5 reporter gene expression. This mutual inhibitory effect between BCL6 and STAT5a is closely related to the differentiation state of breast cancer cells: BCL6 is upregulated in undifferentiated breast cancer but inhibited during lactational differentiation of mammary epithelium. Its upregulated expression is associated with the loss of differentiation in breast cancer cells [32].

Other studies have shown that BCL6 is detected to have increased expression in tumor tissues and decreased expression in normal tissues in breast cancer, and it has been found to be part of the PI3K/AKT signaling pathway, which is significantly altered in breast cancer [33]. This suggests that BCL6 may play a role in the occurrence and development of breast cancer by participating in the abnormal regulation of the PI3K/AKT signaling pathway. Its abnormal expression may be related to the overactivation of the pathway, thereby affecting malignant biological behaviors such as proliferation and survival of tumor cells, and has certain functional significance in tumor progression.

Although existing research indicates the key role of BCL6 in breast cancer, the understanding of its specific mechanism of action is still insufficient. For example, how BCL6 interacts with other transcription factors such as STAT3 and STAT5, and its functional differences in different subtypes of breast cancer, all require further investigation [6]. Moreover, the role of BCL6 in the tumor microenvironment and its interaction with immune cells also deserve in-depth study to more comprehensively understand its function in breast cancer. Specifically, high expression of Bcl-6 can modulate the chemokine network and other pathways to suppress the recruitment and infiltration of effector immune cells (such as cytotoxic T cells) that target tumor cells at the tumor site, while potentially promoting the enrichment of immunosuppressive cells. This helps tumor cells evade immune surveillance and ultimately accelerates the progression and worsening of breast cancer. Tamma *et al.* pointed out that the translocation and expression of BCL6 are closely related to the development of breast cancer [34], especially in high-grade tumors. The expression of BCL6 is related to the infiltration of macrophages and mast cells in the tumor microenvironment, further confirming the important role of BCL6 in the tumor microenvironment. Additionally, the research by Ollila [9] and Olszewski shows that the expression of BCL6 in primary breast diffuse

large B-cell lymphoma is associated with prognosis, suggesting its potential role in breast cancer drug resistance.

5. Research on BCL6 as a Therapeutic Target in Breast Cancer

Research on using BCL6 as a therapeutic target for breast cancer is increasing. Many studies have investigated the impact of BCL6 inhibition on the sensitivity and efficacy of chemotherapy drugs. Research shows that inhibiting BCL6 expression can enhance the sensitivity of breast cancer cells to chemotherapy drugs. Tang Huimin *et al.* found that inhibiting BCL6 expression can make drug-resistant cell lines more sensitive to imatinib [35], suggesting that BCL6 may play an important role in the drug resistance mechanism. Additionally, Sun Xiaomei and Zhao Yi indicated that the expression of BCL6 in diffuse large B-cell lymphoma is closely related to chemotherapy efficacy [36]. High expression of BCL6 may increase chemotherapy resistance, affecting patient prognosis. Therefore, targeting BCL6 may bring new treatment methods for breast cancer patients. Research also shows that the expression of BCL6 is related to the number of chemotherapy cycles. Patients with more than three chemotherapy cycles have a higher survival rate when BCL6 expression is high, further confirming the potential of BCL6 as a new therapeutic target [10].

However, current research on BCL6 still has some shortcomings. Although studies have shown that BCL6 inhibition can enhance the efficacy of chemotherapy drugs, the specific mechanism is still unclear, and there is relatively little clinical application research. Future research should focus on in-depth exploration of the mechanism of BCL6 in breast cancer and how to effectively target BCL6 for clinical treatment. Li Shuang and Yang Jiyuan pointed out in colon cancer research that the methylation status of BCL6 is related to the clinical characteristics of tumors [37], indicating that BCL6 indeed has potential targeting value in different types of tumors. Currently, in terms of targeted degradation strategies, various BCL6 bifunctional degraders have been developed in recent years, including tricyclic quinones, 1,8-naphthyridin-2-ones, and tricyclic quinolinones. These degraders induce BCL6 degradation through the PROTAC (Proteolysis Targeting Chimera) mechanism, leading to cancer cell apoptosis and tumor regression in BCL6-positive cancers, and have shown significant efficacy in preclinical studies [38]. The exploration of BCL6 targeted combination therapy strategies can be based on the key signaling pathways it regulates and upstream and downstream molecular interactions. In the BCL6-STAT4 signaling pathway, the BCL6 inhibitor TP-021 can increase the level of STAT4 in breast cancer cells by inhibiting BCL6, thereby inhibiting the proliferation ability of breast cancer cells in vitro [29]. Given that the expression level of STAT4 is negatively correlated with the prognosis of breast cancer patients and its expression is related to immune cell infiltration, it is suggested that on the basis of targeting BCL6 with TP-021, combining with the regulation of the STAT4-related immune microenvironment may

further enhance the anti-tumor effect. Furthermore, BCL6 is highly expressed in breast cancer cell lines and tissue specimens, and its overexpression can promote the proliferation, migration, invasion, and survival of breast cancer cells. As BCL6 is a direct target gene of miR-339-5p, its expression can induce the expression of CXCR4 and cyclinD1 proteins [15]. Therefore, combining BCL6 inhibitors with miR-339-5p mimics or CXCR4/cyclinD1 inhibitors may synergistically inhibit BCL6 and its downstream oncogenic signaling pathways, enhancing the therapeutic potential for breast cancer. Although therapeutic strategies targeting BCL6 hold broad prospects, the development of its inhibitors still faces several key challenges: On one hand, it is necessary to overcome the complexity of the BCL6 protein-protein interaction interface to achieve highly specific inhibition and avoid interfering with the functions of other proteins containing BTB domains; on the other hand, tumor cells may develop acquired resistance through mechanisms such as activating compensatory pathways or BCL6 mutations. Additionally, the physiological functions of BCL6 in normal germinal center B cells and follicular helper T cells require drugs to possess precise tumor targeting to mitigate potential adverse effects on the immune system.

In summary, BCL6 has potential application value as a therapeutic target for breast cancer, but further research is needed to verify its effectiveness and safety in clinical treatment.

6. Relationship between BCL6 and Chemotherapy Resistance in Breast Cancer

The role of BCL6 in chemotherapy resistance of breast cancer is increasingly receiving attention. Research shows that the expression of BCL6 is closely related to the resistance of breast cancer cells to chemotherapy drugs. Kim *et al.* found through analysis that the amplification of BCL6 is related to resistance to CDK4/6 inhibitors [39], suggesting that BCL6 may serve as a biomarker for drug resistance. Furthermore, Sultan *et al.* found in a genome-wide shRNA screen that knocking down BCL6 can enhance the sensitivity of breast cancer cells to paclitaxel [4], indicating the key role of BCL6 in chemotherapy resistance. Beck *et al.* proposed that BCL6 affects the survival and proliferation of breast cancer cells by regulating the expression of genes related to drug resistance [5]. These studies support the possibility of BCL6 as a biomarker for chemotherapy resistance. However, current research still has some shortcomings. For example, the specific mechanism of BCL6 in different breast cancer subtypes is not yet clear, and its interaction with other drug resistance-related genes still needs further study. Louwen F *et al.* found that the expression of BCL6 is related to the prognosis of primary breast diffuse large B-cell lymphoma [2], suggesting its potential role in breast cancer drug resistance. Therefore, future research needs to further investigate the specific role of BCL6 in chemotherapy resistance and its potential clinical application value. De Santis *et al.* emphasized the role of BCL6 in triple-negative breast cancer [16], pointing out that it may affect the tumor's treatment response by regulating the

self-renewal and drug resistance mechanisms of stem-like cells.

7. Summary and Outlook

BCL6 is an important transcriptional repressor with BTB and zinc finger domains, regulating gene expression by recruiting corepressors and binding specific DNA sequences. In breast cancer, BCL6 is involved in tumor stem cell maintenance, cell proliferation, and invasion. It can promote tumor progression by inhibiting Numb and activating the Notch signaling pathway, providing new directions for mechanistic research and targeted therapy of breast cancer. Research on BCL6 in the field of breast cancer is gradually attracting widespread attention, especially regarding its potential as a therapeutic target and biomarker. Its inhibition can not only directly induce cancer cell apoptosis but also enhance the sensitivity of cancer cells to chemotherapy drugs such as paclitaxel. BCL6 is expected to become a potential new target for breast cancer treatment. The expression level of BCL6 in breast cancer is closely related to the malignant degree, metastatic ability, and prognosis of the tumor, which also provides a basis for BCL6 in breast cancer treatment strategies.

However, the specific mechanism of BCL6 in breast cancer remains controversial. Although existing research shows that BCL6 affects tumor cell survival by regulating cell cycle and apoptosis-related genes, the specific molecular mechanisms are still unclear. Moreover, current studies lack control for potential confounding factors, such as patient age, tumor stage, and treatment regimen, all of which may affect the analysis of the association between BCL6 and clinical outcomes [40]. Additionally, the mechanism of action of BCL6 may differ in different subtypes of breast cancer, which also needs to be considered in data analysis. Not only that, the mechanism of action of BCL6 in breast cancer may involve different regulatory pathways, which also need to be explored in future research [41], thus advancing research into personalized treatment. The BioTarget tool proposed by Tham [42] *et al.* can be used to assess the activity of the BCL6 pathway, further promoting research on individualized therapy. Wei Z *et al.* proposed that the interaction between BCL6 and miRNA may play an important role in tumorigenesis and development, providing a new perspective for further research [43]. Furthermore, there are some imperfections in the existing research. For example, although the role of BCL6 in breast cancer has been confirmed by many studies, most research still focuses on the correlation between its expression level and clinical features, lacking in-depth research on its specific functions and mechanisms of action. Therefore, subsequent investigations should focus on revealing the specific pathways of BCL6 in breast cancer cells and its functional differences in different subtypes of breast cancer.

In summary, BCL6 can demonstrate its potential as a biomarker and therapeutic target in breast cancer-related research, but more studies are needed to verify its potential and safety in clinical applications, such as clinical biomarker validation studies should be advanced as soon as possible to clarify the molecular char-

acteristics associated with sensitivity or resistance to BCL6-targeted therapies, enabling precise screening of potential beneficiary populations. Secondly, early-phase clinical trials (Phase I/II) for novel BCL6 inhibitors (such as degraders based on PROTAC technology or highly selective small-molecule inhibitors) should be initiated to systematically evaluate their safety, pharmacokinetics, and preliminary efficacy, as well as to explore rational combination therapy strategies. which also lays a solid foundation for our subsequent research.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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