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REVIEW ARTICLE

FBXW7 in leukemia: A critical regulator of oncogenic stability and a potential therapeutic target

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Abstract

F-Box and WD repeat domain-containing 7 (FBXW7) is a key tumor suppressor and substrate-recognition component of the Skp1-Cullin-F-box E3 ubiquitin ligase complex, responsible for targeting several crucial oncogenic proteins for proteasomal degradation. It plays a significant role in preventing the accumulation of pro-oncogenic substrates, thereby maintaining cellular homeostasis. Mutations or inactivation of FBXW7 disrupt these processes, leading to the stabilization of oncogenic proteins such as c-Myc, Notch, myeloid cell leukemia 1, and cyclin E, which drive malignant transformation in several cancers, including hematological malignancies such as T-cell and B-cell acute lymphoblastic leukemia. These mutations contribute to resistance to apoptosis, dysregulated proliferation, and poor prognosis, highlighting FBXW7 as a critical factor in leukemia pathogenesis and a promising therapeutic target. Here, we review FBXW7's structure and function, its key substrates in leukemia, and therapeutic strategies that restore its function or target the oncogenic pathways it regulates. Advances in genome-wide CRISPR screenings and proteomics have further illuminated FBXW7's involvement in multidrug resistance, positioning it as a biomarker and therapeutic target for improving leukemia treatment outcomes.

Keywords: F-Box and WD repeat domain-containing 7; Leukemia; Ubiquitin-proteasome pathway; c-Myc; Notch; Myeloid cell leukemia 1; Tumor suppressor; Therapeutic target

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1. Introduction

1.1. Overview of leukemia

Leukemia is a highly heterogeneous hematologic malignancy, characterized by the abnormal proliferation of leukemia cells in the hematopoietic system.[1] These cells lose normal regulation of proliferation and differentiation. This condition often arises from clonal genetic mutations in hematopoietic stem or progenitor cells, which cause these cells to transform into leukemia cells under uncontrolled conditions.[2] Genetic mutations, chromosomal aberrations, and epigenetic alterations not only grant leukemia cells abnormal proliferative capacity but also lead to the loss of normal differentiation function.[3] As a result, these cells remain in an undifferentiated or poorly differentiated

state, unable to complete normal differentiation programs, and continue to proliferate in the bone marrow, peripheral blood, and other tissues. This abnormal proliferation is driven by dysregulated cell cycle control, differentiation inhibition, and enhanced self-renewal ability. For example, certain leukemia cells acquire specific mutations that disrupt negative feedback regulation of proliferation, further exacerbating uncontrolled cell division by altering cyclin expression or activating abnormal signaling pathways.[4] In addition, these leukemia cells typically lack the ability to respond to death signals, allowing them to evade apoptosis and enhance their survival within the body.[5] The unchecked proliferation of leukemia cells breaks through normal regulatory mechanisms, leading to the accumulation of large numbers of leukemia cells in the blood, disrupting hematopoiesis, and triggering a series of clinical symptoms, including anemia, thrombocytopenia, and neutropenia, which manifest as fatigue, bleeding tendencies, and increased susceptibility to infections.[6] Since normal hematopoietic cells in the bone marrow are replaced by leukemia cells, the patient's immune function is severely compromised, making them highly susceptible to bacterial, viral, and other infections, further exacerbating the condition.[7] Therefore, the treatment of leukemia requires not only controlling the proliferation of leukemia cells but also restoring the normal function of the hematopoietic system, alleviating the patient's clinical symptoms, and improving their quality of life and survival rate.

Leukemia is broadly classified based on the lineage of the affected hematopoietic cells (myeloid or lymphoid) and the degree of cellular maturity (acute or chronic).[8] The most common types of leukemia include (Figure 1):

(i) Acute myeloid leukemia (AML)[9]: Characterized by the rapid accumulation of immature myeloid blasts in the bone marrow.[10]
(ii) Acute lymphoblastic leukemia (ALL)[11]: Involves immature lymphoblasts and is more common in children.[12] ALL can be further subdivided into T-cell ALL (T-ALL)[13] and B-cell ALL (B-ALL).[14]
(iii) Chronic myeloid leukemia (CML)[15]: Typically progresses from a chronic phase with more mature myeloid cells to a more aggressive blast crisis.[16]
(iv) Chronic lymphocytic leukemia (CLL)[17]: A slow-growing leukemia of more mature lymphocytes, commonly affecting older adults.

The clinical manifestations of leukemia include fatigue, recurrent infections, easy bruising, and bleeding,[18] caused by the impaired production of normal blood cells.[19] Advances in molecular diagnostics have revealed a wide array of genetic mutations driving the various leukemia subtypes.[20] Key oncogenes and tumor suppressors, such as NOTCH1 in T-ALL[21] and Breakpoint Cluster Region–Abelson (BCR–ABL)[22] in CML, are implicated in the development and progression of these malignancies. Understanding the molecular landscape of leukemia has enabled more precise diagnostic tools and targeted therapies.

1.2. Leukemia in China: Incidence and risk factors

In China, leukemia remains a major public health issue, particularly affecting children and young adults.[23,24] The high incidence of leukemia, along with challenges in early diagnosis and treatment, poses complex health threats to this population. Due to the incomplete development of the immune system in children and young people, coupled with susceptibility to environmental pollution, genetic factors, and other influences, the incidence of leukemia is especially prominent in this group.[25] Recent epidemiological data indicate that the annual incidence of leukemia is approximately 3 – 4 cases per 100,000 people,[26] with ALL being the most common cancer among children,[27] peaking between the ages of 2 and 5.[28] In adults, the incidence of AML and CLL is relatively higher.[29] Leukemia has become one of the leading causes of cancer-related deaths among children and young adults in China. This phenomenon highlights the urgent need for improvements in early diagnosis, effective prevention, and treatment strategies for leukemia, to reduce the disease burden and improve patient survival rates.

Multiple factors are associated with the etiology of leukemia, including genetic susceptibility, environmental exposures (e.g., radiation, benzene, and pesticides), and viral infections. For instance, exposure to ionizing radiation or chemical carcinogens has been linked to increase leukemia risk.[30] Genetic predisposition also plays a role, with certain inherited disorders, such as Li–Fraumeni syndrome[31] and Fanconi anemia,[32] predisposing individuals to leukemia. In addition, viral infections such as Epstein-Barr virus[33] and human T-cell lymphotropic virus type 1[34] have been implicated in the development of leukemia.

1.3. Molecular pathogenesis of leukemia

Leukemia arises from the accumulation of genetic mutations[35] and chromosomal abnormalities[36] that disrupt normal cell signaling pathways, cell cycle checkpoints, and apoptosis. These genetic lesions often involve oncogenes, tumor suppressor genes, and epigenetic regulators, which collectively drive the clonal expansion of leukemic cells.

For example, BCR-ABL, generated by the t(9;22) chromosomal translocation, is a characteristic marker of CML.[37] The BCR-ABL fusion protein possesses

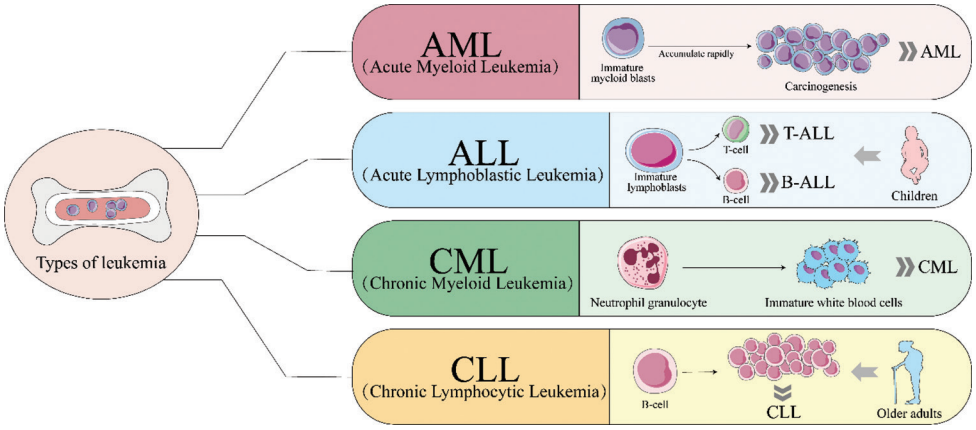


Figure 1. The most common types of leukemia
Abbreviations: B-ALL; B-cell acute lymphoblastic leukemia; T-ALL: T-cell acute lymphoblastic leukemia.

constitutively active tyrosine kinase activity,[38] which drives uncontrolled cell proliferation by activating downstream signaling pathways such as RAS/MAPK,[39] PI3K/AKT,[40] and STAT5,[41] thereby promoting leukemia development. Similarly, in AML, mutations in genes such as *FLT3*,[42] *NPM1*,[43] and *CEBPA*[44] are also common. These mutations lead to abnormal proliferation of myeloid precursor cells and inhibit their differentiation process. In T-ALL, mutations in the *NOTCH1* gene are frequently observed, resulting in continuous activation of the Notch signaling pathway, which promotes T-cell proliferation and leukemia progression.[45] Typical symptoms of T-ALL include persistent fever, lymphadenopathy, hepatosplenomegaly, anemia, bleeding tendencies (such as petechiae or epistaxis), and increased susceptibility to infections.[46] In addition, mutations in tumor suppressor genes such as F-box and WD repeat domain-containing 7 (*FBXW7*) are also common genetic alterations in T-ALL and other types of leukemia.[47] As an important regulatory factor, FBXW7 is responsible for the degradation of key oncogenic proteins. When FBXW7 function is lost, the stability of its oncogenic substrates, such as c-Myc and Notch, increases, further promoting leukemia progression and potentially leading to treatment resistance.[48] Therefore, understanding these genetic alterations is of critical importance for the diagnosis, prognostic assessment, and development of targeted therapeutic strategies for leukemia.

Treatment approaches for leukemia have evolved considerably in recent decades, with the advent of chemotherapy, targeted therapies, immunotherapy, and hematopoietic stem cell transplantation.[48] However, many patients develop resistance to therapy, relapse, or experience significant toxicity, underscoring the need for novel therapeutic approaches that target the underlying molecular mechanisms of leukemia.

2. Structure and function of FBXW7

2.1. Structural insights into FBXW7

FBXW7 (also known as hCDC4 or SEL-10)[49] is one of the best-characterized members of the F-box protein family. As part of the Skp1-Cullin-F-box (SCF) E3 ubiquitin ligase complex, FBXW7 serves as the substrate recognition subunit,[50] targeting specific proteins for ubiquitin-mediated degradation through the proteasome. The degradation of these substrates is essential for regulating critical cellular processes such as cell cycle progression, apoptosis, differentiation, and signal transduction.

Substrate specificity of FBXW7 is dictated by its WD40 repeat domain,[51] a β-propeller structure that recognizes phosphorylated degron motifs on its target proteins.[52] This interaction is dependent on the phosphorylation status of the substrate, often mediated by upstream kinases like glycogen synthase kinase 3.[53] Once a substrate is phosphorylated at specific serine or threonine residues, FBXW7 binds to the phosphorylated degron, marking the protein for ubiquitination.[54]

The F-box domain, located at the N-terminal region of FBXW7, binds to Skp1,[55] anchoring FBXW7 to the larger SCF complex. Together with Cullin1 (Cul1)[56] and Rbx1 (Roc1),[57] the SCF complex facilitates the transfer of ubiquitin from an E2-conjugating enzyme to the substrate, tagging it for proteasomal degradation. This modular structure allows FBXW7 to play a crucial role in maintaining protein homeostasis by regulating the timely turnover of key regulatory proteins involved in oncogenesis (Figure 2).

2.2. The role of FBXW7 in cellular homeostasis and tumor suppression

FBXW7 is integral to the regulation of several key cellular processes, including cell cycle progression, apoptosis,

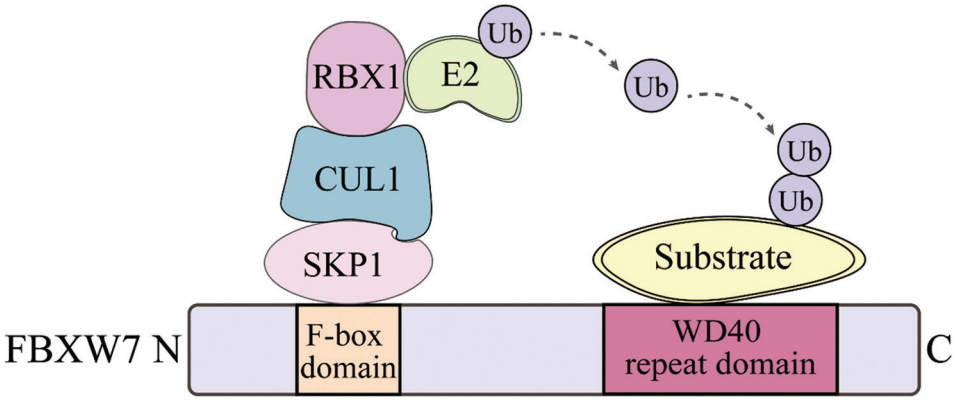


Figure 2. Structure and function of FBXW7
Abbreviations: CUL1: Cullin 1; E2: Ubiquitin-conjugating enzyme E2; FBXW7: F-box and WD repeat domain-containing 7; RBX1: RING-box protein 1; SKP1: S-phase kinase-associated protein 1; Ub: Ubiquitin.

and differentiation.[58] By targeting oncogenic proteins for degradation, FBXW7 prevents their accumulation and ensures that cells progress through the cell cycle in a controlled manner, undergo apoptosis when necessary, and maintain proper differentiation. Some of the major processes regulated by FBXW7 include (Figure 3):

(i) Cell cycle regulation: FBXW7 controls the progression of the cell cycle by degrading cyclin E,[59] a key regulator of the G1-to-S phase transition.[60] In the absence of FBXW7, cyclin E levels become dysregulated, leading to unchecked entry into S phase, excessive DNA replication stress, and genomic instability.[61]

(ii) Apoptosis: FBXW7 also regulates apoptosis by targeting the anti-apoptotic protein Myeloid cell leukemia 1 (MCL-1) for degradation.[62] By maintaining the appropriate levels of MCL-1, FBXW7 ensures that cells with significant DNA damage or other stressors undergo apoptosis. Dysregulation of MCL-1 degradation due to FBXW7 loss contributes to apoptosis resistance[63] and tumor survival.[64]

(iii) Signal transduction: FBXW7 regulates several oncogenic signaling pathways, most notably the Notch signaling pathway. The Notch intracellular domain (NICD)[65] is a transcription factor that drives the expression of genes critical for T-cell development and proliferation.[40,66] FBXW7 targets NICD for degradation, thus preventing prolonged Notch signaling that could otherwise promote leukemogenesis.

(iv) Differentiation and metabolism: FBXW7 also controls the degradation of other key proteins involved in cellular differentiation and metabolism,[67] including transcription factors like KLF5[68] and metabolic regulators like HIF1α.[69] By regulating these processes, FBXW7 helps maintain cellular quiescence and differentiation under physiological conditions.

Mutations in *FBXW7* disrupt its ability to bind and degrade these substrates, leading to their accumulation and the promotion of oncogenic signaling pathways. This loss of function is particularly significant in cancers like leukemia, where *FBXW7* mutations lead to the stabilization of proteins that drive uncontrolled proliferation, apoptosis evasion, and resistance to chemotherapy.

3. FBXW7 as a tumor suppressor in leukemia

3.1. Key substrates of FBXW7 in leukemia

FBXW7 acts as a tumor suppressor by controlling the degradation of several key oncogenic proteins. In leukemia, the loss or mutation of *FBXW7* leads to the accumulation of these substrates, promoting leukemogenesis and resistance to therapy.[70] The most critical FBXW7 substrates implicated in leukemia include (Figure 4):

(i) c-Myc: c-Myc is a master regulator of cell growth, metabolism, and proliferation. It is a transcription factor that drives the expression of genes involved in ribosome biogenesis,[71] nucleotide metabolism,[72] and cell cycle progression.[73] In normal cells, FBXW7 tightly regulates c-Myc levels by targeting it for ubiquitin-mediated degradation.[74] Mutations in *FBXW7* that prevent the degradation of c-Myc lead to its accumulation, driving oncogenic transcriptional programs that promote uncontrolled cell proliferation and metabolic reprogramming in leukemia cells.[75]

(ii) Notch: The Notch signaling pathway is crucial for normal T-cell development, but in T-ALL, mutations in *FBXW7* or in *NOTCH1* result in the stabilization of the NICD.[76] This sustained activation of Notch signaling drives the proliferation of leukemic cells and impairs their differentiation, contributing to disease progression.[77]

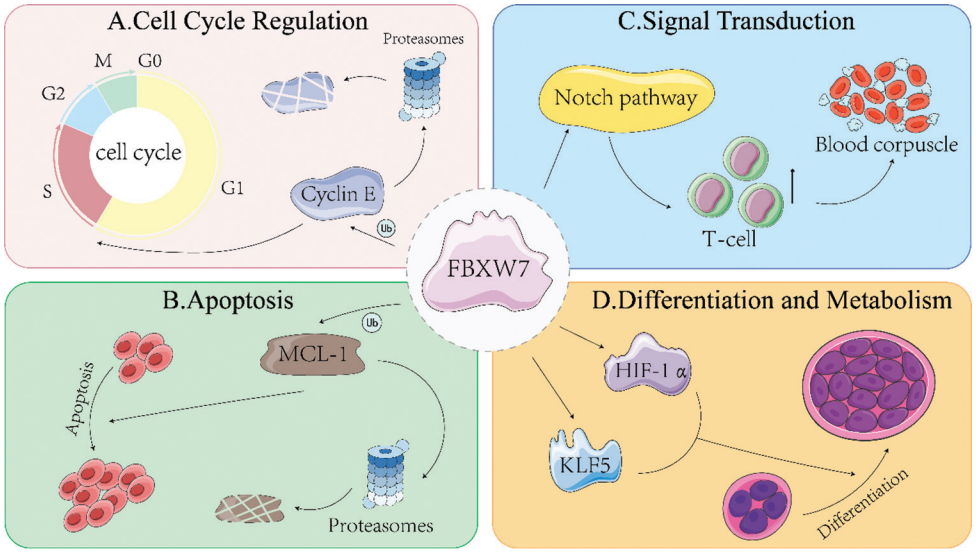


Figure 3. Major biological processes regulated by FBXW7. (A) Cell cycle regulation; (B) apoptosis; (C) signal transduction; and (D) differentiation and metabolism.

Abbreviations: Cyclin E: Cyclin E protein involved in cell cycle regulation; FBXW7: F-box and WD repeat domain-containing 7; HIF-1 α: Hypoxia-inducible factor 1 alpha; MCL-1: Myeloid cell leukemia 1; T-cell: T lymphocyte, a type of immune cell.

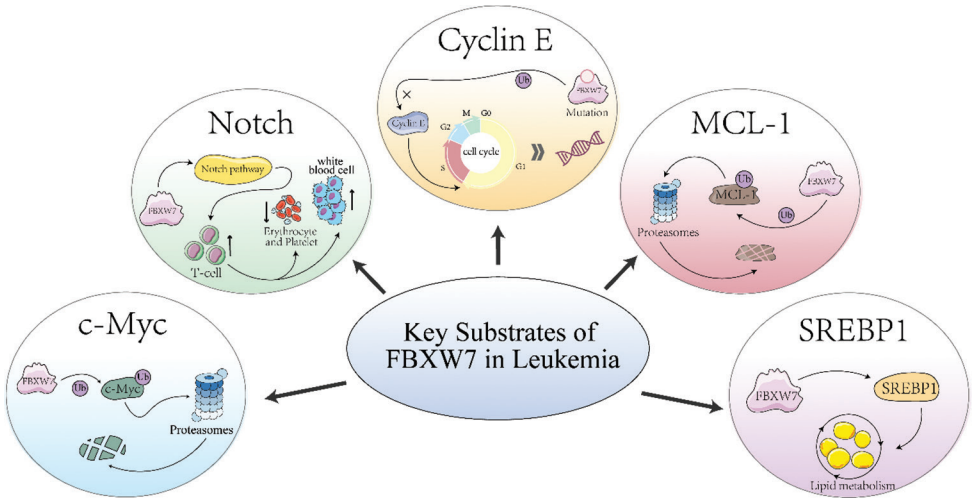


Figure 4. Key substrates of FBXW7 in leukemia

Abbreviations: c-Myc: Cellular myelocytomatosis oncogene; Cyclin E: Cyclin E protein involved in cell cycle regulation; MCL-1: Myeloid cell leukemia 1; Notch: Notch receptor protein involved in cell signaling; SREBP1: Sterol regulatory element-binding protein 1.

(iii) Cyclin E: Cyclin E is a regulator of the G1-to-S phase transition in the cell cycle, and its degradation is necessary to maintain normal cell cycle progression.[78] In FBXW7-mutant leukemia cells, cyclin E is stabilized, resulting in enhanced entry into S phase, leading to excessive DNA replication stress and genomic instability, both of which drive leukemogenesis.[79]

(iv) MCL-1: MCL-1 is a member of the BCL-2 family of anti-apoptotic proteins, and its overexpression is frequently observed in chemotherapy-resistant leukemia.[80] FBXW7 targets MCL-1 for degradation, and the loss of FBXW7 function in leukemia leads to the stabilization of MCL-1, allowing leukemic cells to evade apoptosis and survive under chemotherapeutic pressure.[50]

(v) SREBP1: Recent studies have identified SREBP1, a key regulator of lipid metabolism, as another substrate of FBXW7.[81] SREBP1 plays a role in metabolic reprogramming in cancer cells, and its stabilization in FBXW7-mutant leukemias may contribute to the altered metabolism that supports rapid cell growth and survival under stress conditions.[82]

In addition, FBXW7 also regulates the degradation of other key proteins, such as the cell cycle regulator and negative modulator p27. Stabilization of p27 leads to cell cycle arrest and may promote tumor cell proliferation.[83] Similarly, c-Jun, a transcription factor involved in cellular stress responses and proliferation regulation, is also controlled by FBXW7.[84] When *FBXW7* undergoes mutation or loss of function, the stability of these substrates increases, further driving tumor cell proliferation, survival, and resistance to treatment. Notably, the accumulation of oncogenic proteins such as c-Myc, Notch, cyclin E, and MCL-1, due to impaired FBXW7 activity, becomes a central factor in the pathogenesis of leukemia. This stabilization of key oncogenic proteins not only drives the progression of leukemia but also contributes to resistance to conventional therapies, highlighting FBXW7 as a critical target for therapeutic intervention.

4. Therapeutic targeting of FBXW7 in leukemia

The role of FBXW7 in regulating oncogenic proteins makes it an attractive therapeutic target for treating leukemia, particularly in cases where its loss contributes to resistance to therapy. Therapeutic strategies are being developed to either restore FBXW7 function or target the oncogenic proteins stabilized by *FBXW7* mutations (Figure 5).

4.1. Targeting FBXW7 substrates

Given that the loss of FBXW7 leads to the accumulation of specific oncogenic proteins,[85] therapeutic strategies aimed at these substrates represent promising approaches for overcoming FBXW7-related oncogenesis. Current strategies include:

(i) c-Myc inhibition: The accumulation of c-Myc in FBXW7-deficient leukemias suggests that inhibiting c-Myc could be a promising therapeutic approach. BET-bromodomain inhibitors, such as JQ1,[86] reduce c-Myc transcription by preventing BET proteins from binding to acetylated histones at c-Myc target gene promoters.[87] Preclinical studies have shown that BET inhibitors can reduce c-Myc-driven transcription, leading to decrease leukemia cell proliferation and enhanced apoptosis.[88]

(ii) Notch inhibition: In T-ALL, aberrant Notch signaling is a key driver of disease progression.[89] Gamma-secretase inhibitors (GSIs), which block the cleavage of Notch receptors and prevent the release of NICD, have shown promise in preclinical models of T-ALL.[90] However, the use of GSIs has been limited by gastrointestinal toxicity, highlighting the need for more selective Notch inhibitors or combination therapies that reduce off-target effects.[91]

(iii) MCL-1 inhibition: The stabilization of MCL-1 in FBXW7-deficient leukemia contributes to apoptosis resistance and chemotherapy failure.[92] Small molecule inhibitors of MCL-1, such as S63845, have shown potent activity in preclinical models of leukemia.[93] These inhibitors work by disrupting the interaction between MCL-1 and pro-apoptotic proteins, restoring apoptotic sensitivity and overcoming drug resistance.

4.2. Restoring FBXW7 function

Restoring the function of FBXW7 represents a promising therapeutic strategy, particularly for leukemia cases driven by *FBXW7* mutations. These mutations frequently occur in the WD40 substrate recognition domain, a critical region responsible for the specific binding between FBXW7 and its target proteins.[94] Such mutations impair FBXW7's ability to bind its substrates, thereby hindering the ubiquitination and subsequent degradation of multiple oncogenic proteins, leading to their abnormal accumulation within cells. As a key tumor suppressor, FBXW7 is responsible for the degradation of several pivotal oncogenic proteins, including c-Myc, Notch, and cyclin E. Loss of FBXW7 function disrupts cellular homeostasis, induces uncontrolled cell cycle progression, impairs differentiation, and promotes tumor development.[95] In leukemia, the loss or mutation of *FBXW7* results in the sustained stabilization of these oncogenic substrates, which continuously drive leukemic cell proliferation, accelerate disease progression, and contribute to treatment resistance. Therefore, restoring or substituting FBXW7 function may reinstate proper degradation of these oncogenic proteins, suppress leukemic cell growth, and enhance treatment responsiveness, offering a novel and hopeful direction for targeted leukemia therapy. Several strategies are being explored, including:

(i) Gene therapy: Advances in *CRISPR-Cas9* gene-editing technology have made it possible to correct loss-of-function mutations in *FBXW7*,[96] potentially restoring its tumor-suppressive function.[97] By introducing functional copies of the *FBXW7* gene into leukemia cells, it may be possible to re-establish the degradation of oncogenic proteins, thereby suppressing tumor growth.

(ii) Small molecule stabilizers: Another approach involves the development of small molecules that stabilize FBXW7 or enhance its activity. By promoting the interaction between FBXW7 and its substrates, these molecules could restore the tumor-suppressive function of FBXW7, even in cells with partial loss-of-function mutations.

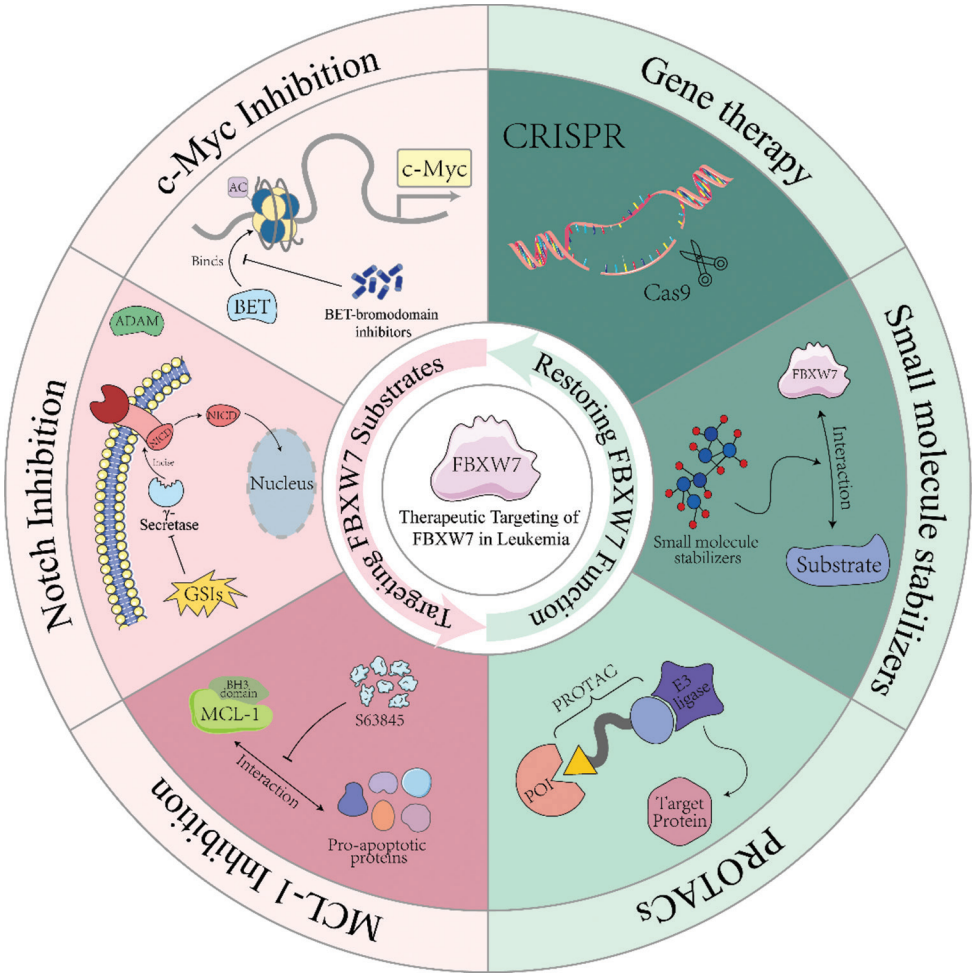


Figure 5. Therapeutic targeting of FBXW7 in leukemia
Abbreviations: AC: Activator complex; ADAM: A disintegrin and metalloproteinase; BET: Bromodomain and extraterminal domain proteins; c-Myc: Cellular Myelocytomatosis oncogene; FBXW7: F-box and WD repeat domain-containing 7; GSIs: Gamma-secretase inhibitors; MCL-1: Myeloid cell leukemia 1; NICD: Notch intracellular domain; POI: Protein of interest.

(iii) Proteolysis-targeting chimeras (PROTACs): PROTACs are an emerging class of therapeutics designed to target specific proteins for ubiquitin-mediated degradation.[98] By harnessing the cell's natural degradation machinery, PROTACs can selectively degrade proteins that are otherwise considered "undruggable."[99] Developing PROTACs that target key FBXW7 substrates, such as c-Myc, could provide a novel therapeutic strategy for FBXW7-deficient leukemias.

5. Challenges and future directions

5.1. Challenges in FBXW7 research

Despite the growing understanding of FBXW7's role in leukemia, several challenges remain:

(i) Mutation heterogeneity: *FBXW7* mutations exhibit significant heterogeneity,[100] typically occurring in various regions of the WD40 domain, which affects substrate recognition.[101] This mutational heterogeneity complicates the development of therapeutic strategies, as different *FBXW7* mutations may lead to dysregulated degradation of distinct substrates, thereby influencing the proliferation, metabolism, and survival pathways of leukemia cells. For example, c-Myc and Notch are primarily involved in cell cycle regulation[102] and differentiation inhibition,[103] while MCL-1 and cyclin E are associated with the regulation of apoptosis and DNA replication stress.[104,105] As a result, different *FBXW7* mutations may lead to the accumulation of specific oncogenic substrates, altering the biological characteristics and therapeutic response of leukemia cells. Some mutations may only affect the degradation of c-Myc, while others may stabilize multiple substrates, thus enhancing the resistance of leukemia cells to treatment.[106] The diversity of these mutations makes

a one-size-fits-all treatment approach ineffective, necessitating the development of personalized therapeutic strategies based on the specific mutation type and substrate stabilization pattern. This approach requires therapeutic strategies targeting the specific degradation dysregulation of substrates to improve the precision and efficacy of treatment.

(ii) Redundancy in degradation pathways: Other E3 ligases, such as β-TrCP, may compensate for the loss of FBXW7 in certain contexts, reducing the efficacy of therapies aimed at restoring FBXW7 function.[107] Understanding the redundancy within the ubiquitin-proteasome system and identifying the contexts in which FBXW7 is indispensable will be key to developing more effective targeted therapies.

(iii) Therapeutic resistance: Leukemia cells with FBXW7 mutations often develop resistance to standard chemotherapies and targeted therapies. This resistance is driven by the stabilization of oncogenic substrates such as MCL-1 and c-Myc, which promote cell survival even in the presence of cytotoxic agents.[108] Overcoming this resistance will require the development of more effective therapies that target these stabilized proteins or their downstream signaling pathways.

(iv) "Undruggable" substrates: Many key FBXW7 substrates, such as c-Myc and MCL-1, have long been considered "undruggable" due to the lack of well-defined small molecule binding pockets.[109] However, recent advancements in drug discovery, particularly the development of PROTAC technology, have opened new possibilities for targeting these proteins. PROTACs overcome the limitation of traditional small molecule inhibitors, which cannot directly bind to their targets, by inducing the degradation of target proteins.[110] This approach provides a novel pathway for treating these challenging targets. Nevertheless, there remain several technical challenges that must be addressed for clinical success. First, the target selectivity of PROTACs needs to be further improved to ensure specific degradation of the target protein without triggering off-target effects.[111] Second, the bioavailability and pharmacokinetic properties of PROTACs require optimization, particularly in terms of stability *in vivo* and the ability to penetrate cell membranes.[112] In addition, the efficacy of PROTACs in different types of tumors or other diseases is not yet fully understood, and enhancing their effectiveness in heterogeneous diseases remains a significant challenge. Only by overcoming these technical obstacles can PROTACs achieve true clinical translation and drive the advancement of targeted therapies for "undruggable" substrates.

5.2. Future directions

To overcome these challenges, several key areas of research should be prioritized:

(i) Advanced preclinical models: Developing genetically engineered mouse models[113] and patient-derived xenografts[114] that accurately recapitulate the spectrum of *FBXW7* mutations found in human leukemia will be essential for studying the biological consequences of FBXW7 loss and testing novel therapeutic strategies. These models will also help to delineate the contexts in which FBXW7 plays a critical role in tumor suppression.

(ii) Identification of novel substrates: Although several key substrates of FBXW7 have been identified, it is likely that additional oncogenic proteins are regulated by FBXW7. High-throughput proteomic approaches, such as mass spectrometry-based interactome studies,[115] could be used to identify new substrates and expand the repertoire of therapeutic targets.

(iii) Combination therapies: Given the complexity of FBXW7's role in regulating multiple oncogenic pathways, combination therapies that target both FBXW7 substrates and compensatory mechanisms are likely to be more effective than monotherapies.[116] Rationally designed combination therapies that include c-Myc or MCL-1 inhibitors, in conjunction with standard chemotherapy or immune checkpoint inhibitors, could enhance treatment efficacy and overcome resistance.

(iv) Restoring FBXW7 function: Gene therapy and small molecule stabilizers offer promising avenues for restoring FBXW7 function in leukemia cells.[117] Continued research into the mechanisms that regulate FBXW7 stability and activity will be crucial for developing these therapies. In addition, small molecules that enhance the interaction between FBXW7 and its substrates may provide an alternative approach to restoring its tumor-suppressive function.

(v) Biomarker development for personalized medicine: As our understanding of the molecular consequences of *FBXW7* mutations deepens, incorporating FBXW7 status as a biomarker of therapeutic response into clinical practice becomes essential for personalized treatment. Biomarkers of therapeutic response are molecular or genetic features that predict how a patient will respond to specific treatments. In cancers such as leukemia, these biomarkers reflect tumor cell sensitivity or resistance to particular therapies. For instance, the status of FBXW7, whether through mutations or functional loss, serves as a key indicator of how tumor cells will respond to targeted therapies or conventional chemotherapy.[118] FBXW7

regulates the degradation of several oncogenic proteins, including c-Myc, Notch, and cyclin E, and mutations in *FBXW7* can lead to the accumulation of these substrates, which, in turn, alters the tumor cell's response to various treatments. For example, the accumulation of c-Myc may increase tumor cell sensitivity to certain chemotherapy drugs,[119] while the stabilization of MCL-1 could enable leukemia cells to evade apoptosis and develop chemotherapy resistance.[120] By monitoring *FBXW7* mutations and the accumulation of its substrates, clinicians can better predict how patients will respond to specific treatment regimens, enabling the development of more targeted therapeutic strategies. Biomarkers based on the *FBXW7* mutation spectrum or substrate accumulation can help identify patients most likely to benefit from particular treatments, including targeted inhibitors or combination therapies. Moreover, the advancement of liquid biopsy techniques, such as circulating tumor DNA analysis,[121] offers the ability to monitor *FBXW7* mutations in real-time, further facilitating personalized treatment approaches. This technology allows for the dynamic tracking of tumor genomic changes during treatment, providing crucial information for optimizing therapeutic plans, adjusting drug dosages, and monitoring recurrence.

6. Conclusion

FBXW7 plays a pivotal role in regulating cell cycle progression, apoptosis, and signal transduction by targeting key oncogenic proteins involved in these processes for ubiquitin-mediated proteasomal degradation. In leukemia, loss or mutation of *FBXW7* leads to the accumulation of substrates such as c-Myc, Notch, and MCL-1, which not only drive leukemogenesis but also contribute to therapeutic resistance. Although directly targeting FBXW7 or restoring its function remains technically challenging, alternative therapeutic strategies aimed at inhibiting its downstream effectors or compensating for its loss have shown promising potential. For instance, synthetic lethality approaches offer novel therapeutic avenues for FBXW7-deficient malignancies. Following FBXW7 inactivation, leukemia cells often become reliant on compensatory survival pathways – such as the mTOR signaling axis – making them selectively vulnerable to mTOR inhibitors without affecting normal cells. Furthermore, advances in gene therapy and gene editing technologies, particularly CRISPR-Cas9, provide a theoretical and technical framework for correcting *FBXW7* mutations. This holds the potential to restore its ubiquitination function, thereby re-establishing the balance of cell proliferation and differentiation. In addition, the growing implementation of precision medicine has enabled the development of individualized therapeutic strategies based on a patient's specific FBXW7 mutational landscape or functional status. By integrating molecular diagnostic data, clinicians can select more targeted drug regimens, thereby enhancing treatment efficacy while minimizing off-target toxicity. Concurrently, the development of therapeutics targeting FBXW7-associated signaling networks is actively progressing, with several candidate compounds already in preclinical or early clinical stages. Looking ahead, the integration of these emerging therapeutic modalities with patient-specific genomic profiling is expected to substantially improve the precision and effectiveness of leukemia treatment, ultimately contributing to enhanced long-term survival and clinical outcomes.

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Conflict of interest

The authors declare no conflicts of interest.

Author contributions

Conceptualization: All authors
Visualization: Xiuming Li
Writing–original draft: All authors
Writing–review & editing: Bin Liu

Ethics approval and consent to participate

Not applicable.

Consent for publication

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References

1. Zhang A, Liu W, Qiu S. Mitochondrial genetic variations in leukemia: A comprehensive overview. *Blood Sci*. 2024;6(4):e00205.

doi: 10.1097/BS9.0000000000000205

2. Choi HS, Kim BS, Yoon S, Oh SO, Lee D. Leukemic stem cells and hematological malignancies. *Int J Mol Sci*. 2024;25(12):6639.

doi: 10.3390/ijms25126639

3. Iyer P, Jasdanwala SS, Wang Y, Bhatia K, Bhatt S. Decoding acute myeloid leukemia: A clinician's guide to functional profiling. *Diagnostics (Basel)*. 2024;14(22):2560.

doi: 10.3390/diagnostics14222560

4. Hosseini A, Dhall A, Ikonen N, *et al.* Perturbing LSD1 and WNT rewires transcription to synergistically induce AML differentiation. *Nature*. 2025.

doi: 10.1038/s41586-025-08915-1

5. Wiese W, Galita G, Siwecka N, Rozpedek-Kaminska W, Slupianek A, Majsterek I. Endoplasmic reticulum stress in acute myeloid leukemia: Pathogenesis, prognostic implications, and therapeutic strategies. *Int J Mol Sci*. 2025;26(7):3092.

doi: 10.3390/ijms26073092

6. Snaith O, Poveda-Rogers C, Laczko D, Yang G, Morrissette JJ. Cytogenetics and genomics of acute myeloid leukemia. *Best Pract Res Clin Haematol*. 2024;37(1):101533.

doi: 10.1016/j.beha.2023.101533

7. Longhitano AP, Slavin MA, Harrison SJ, Teh BW. Bispecific antibody therapy, its use and risks for infection: Bridging the knowledge gap. *Blood Rev*. 2021;49:100810.

doi: 10.1016/j.blre.2021.100810

8. Xiao W, Nardi V, Stein E, Hasserjian RP. A practical approach on the classifications of myeloid neoplasms and acute leukemia: WHO and ICC. *J Hematol Oncol*. 2024;17(1):56.

doi: 10.1186/s13045-024-01571-4

9. Chen L, Zeng P, Tang H, *et al.* Routes and molecular mechanisms of central nervous system involvement in acute myeloid leukemia (Review). *Oncol Rep.* 2024;52(5):146.

doi: 10.3892/or.2024.8805

10. Demir D. Insights into the new molecular updates in acute myeloid leukemia pathogenesis. *Genes (Basel)*. 2023;14(7):1424.

doi: 10.3390/genes14071424

11. Pagliaro L, Chen SJ, Herranz D, *et al.* Acute lymphoblastic leukaemia. *Nat Rev Dis Primers*. 2024;10(1):41.

doi: 10.1038/s41572-024-00525-x

12. Cerqueira P, Pereira S, Costa R, *et al.* Cutaneous manifestation of acute lymphoblastic leukemia. *Cureus* 2024;16(11): e74022

doi: 10.7759/cureus.74022

13. Chen JJ, Tokumori FC, Del Guzzo C, Kim J, Ruan J. Update on T-cell lymphoma epidemiology. *Curr Hematol Malig Rep.* 2024;19(3):93-103.

doi: 10.1007/s11899-024-00727-w

14. Fallati A, Di Marzo N, D'Amico G, Dander E. Mesenchymal stromal cells (MSCs): An ally of B-cell acute lymphoblastic leukemia (B-ALL) cells in disease maintenance and progression within the bone marrow hematopoietic niche. *Cancers* (*Basel*). 2022;14(14):3303.

doi: 10.3390/cancers14143303

15. Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2025 update on diagnosis, therapy, and monitoring. *Am J Hematol*. 2024;99(11):2191-2212.

doi: 10.1002/ajh.27443

16. Kaehler M, von Bubnoff N, Cascorbi I, Gorantla SP. Molecular biomarkers of leukemia: Convergence-based drug resistance mechanisms in chronic myeloid leukemia and myeloproliferative neoplasms. *Front Pharmacol*. 2024;15:1422565.

doi: 10.3389/fphar.2024.1422565

17. Chen D, Wang MY, Tian C. Research progress of targeted therapy for chronic lymphocytic leukemia/small lymphocytic lymphoma --review. *Zhongguo Shi Yan Xue Ye Xue Za Zhi*. 2024;32(2):643-646.

doi: 10.19746/j.cnki.issn.1009-2137.2024.02.049

18. Gueuning C, Lazaro E, Dupuy H, *et al*. Characteristics of large granular lymphocyte leukemia associated with variable common immunodeficiency disorders: A study of 12 cases. *Eur J Haematol*. 2024;113(4):550-557.

doi: 10.1111/ejh.14265

19. Boucher A, Murray J, Rao S. Cohesin mutations in acute myeloid leukemia. *Leukemia*. 2024;38:2318-2328.

doi: 10.1038/s41375-024-02406-4

20. Walter W, Iacobucci I, Meggendorfer M. Diagnosis of acute lymphoblastic leukaemia: An overview of the current genomic classification, diagnostic approaches, and future directions. *Histopathology*. 2024.

doi: 10.1111/his.15338

21. Tosello V, Di Martino L, Piovan E. Targeted metabolomics of tissue and plasma identifies biomarkers in mice with NOTCH1-dependent T-cell acute lymphoblastic leukemia. *Int J Mol Sci*. 2024;25(12):6543.

doi: 10.3390/ijms25126543

22. Yang F, Zhou H, Luo P, *et al.* Celastrol induces DNA damage and cell death in BCR-ABL T315I-mutant CML by targeting YY1 and HMCES. *Phytomedicine*. 2024;134:155937.

doi: 10.1016/j.phymed.2024.155937

23. Cortes-Lopez PN, Guzman-Montijo E, Fuentes-Venado CE, *et al.* Cutaneous fusarium disease and leukaemias: A systematic review. *Mycoses*. 2024;67(7):e13759.

doi: 10.1111/myc.13759

24. Cuglievan B, Kantarjian H, Rubnitz JE, *et al*. Menin inhibitors in pediatric acute leukemia: A comprehensive review and recommendations to accelerate progress in collaboration with adult leukemia and the international community. *Leukemia*. 2024;38(10):2073-2084.

doi: 10.1038/s41375-024-02368-7

25. Cobaleda C, Godley LA, Nichols KE, Wlodarski MW, Sanchez-Garcia I. Insights into the molecular mechanisms of genetic predisposition to hematopoietic malignancies: The importance of gene-environment interactions. *Cancer Discov*. 2024;14(3):396-405.

doi: 10.1158/2159-8290.CD-23-1091

26. He H, Li J, Li W, *et al.* Clinical features and long-term outcomes of pediatric patients with de novo acute myeloid leukemia in China with or without specific gene abnormalities: A cohort study of patients treated with BCH-AML 2005. *Hematology*. 2024;29(1):2406596.

doi: 10.1080/16078454.2024.2406596

27. Bastos Silveira B, Di Carvalho Melo L, Amorim Dos Santos J, *et al*. Oral manifestations in pediatric patients with leukemia: A systematic review and meta-analysis. *J Am Dent Assoc*. 2024;155(10):858-870.e30.

doi: 10.1016/j.adaj.2024.07.014

28. Cobaleda C, Vicente-Duenas C, Nichols KE, Sanchez-Garcia I. Childhood B cell leukemia: Intercepting the paths to progression. *Bioessays*. 2024;46(9):e2400033.

doi: 10.1002/bies.202400033

29. Robak T, Pula A, Braun M, Robak E. Extramedullary and extranodal manifestations in chronic lymphocytic leukemia - an update. *Ann Hematol*. 2024;103(9):3369-3383.

doi: 10.1007/s00277-024-05854-1

30. Sumbly V, Landry I, Sneed C, *et al.* Leukemic stem cells and advances in hematopoietic stem cell transplantation for acute myeloid leukemia: A narrative review of clinical trials. *Stem Cell Investig*. 2022;9:10.

doi: 10.21037/sci-2022-044

31. Schneider K, Zelley K, Nichols KE, Schwartz Levine A, Garber J. Li-Fraumeni syndrome. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, editors. *GeneReviews (R)*. Seattle (WA): University of Washington; 1993.

32. Bhandari J, Thada PK, Killeen RB, Puckett Y. Fanconi anemia. In: *StatPearls*. Treasure Island, FL: StatPearls Publishing; 2024.

33. Barone PD, Tam W, Geyer JT, Leonard JP, Phillips A, Ouseph MM. Nodal T-cell lymphoma transdifferentiated from mantle cell lymphoma with Epstein-Barr virus infection. *Pathobiology*. 2024;92:1-16.

doi: 10.1159/000541974

34. Ionete A, Bardas A, Varady Z, Vasilica M, Szegedi O, Coriu D. modified prophylactic donor lymphocyte infusion (DLI) in an adult T cell lymphoma/leukemia (ATLL) patient-modality of relapse prevention. *Diseases*. 2024;12(9):210.

doi: 10.3390/diseases12090210

35. Shih AJ, Jun T, Skol AD, *et al.* Inherited cancer predisposing mutations in patients with therapy-related myeloid neoplasms. *Br J Haematol*. 2023;200(4):489-493.

doi: 10.1111/bjh.18543

36. Oiwa K, Lee S, Fujita K, Ueda T, Yamauchi T. Clinical features of clonal cytogenetic abnormalities in Philadelphia-negative cells developed during tyrosine kinase inhibitor treatment. *Intern Med*. 2024;63(5):729-732.

doi: 10.2169/internalmedicine.2182-23

37. Park SE, Lee JK, Kang HJ, Hong YJ, Oh AC, Kim H. A rare case of X-linked four-way Philadelphia chromosome translocation with therapeutic challenges and clonal evolution. *Clin Lab*. 2024;70(9).

doi: 10.7754/Clin.Lab.2024.240323

38. Yang K, Fu K, Zhang H, *et al*. PBA2, a novel inhibitor of the beta-catenin/CBP pathway, eradicates chronic myeloid leukemia including BCR-ABL T315I mutation. *Mol Cancer*. 2024;23(1):209.

doi: 10.1186/s12943-024-02129-1

39. Liu Y, Jang H, Zhang M, Tsai CJ, Maloney R, Nussinov R. The structural basis of BCR-ABL recruitment of GRB2 in chronic myelogenous leukemia. *Biophys J*. 2022;121(12):2251-2265.

doi: 10.1016/j.bpj.2022.05.030

40. Al-Rawashde FA, Al-Wajeeh AS, Vishkaei MN, *et al*. Thymoquinone inhibits JAK/STAT and PI3K/Akt/mTOR signaling pathways in MV4-11 and K562 myeloid leukemia cells. *Pharmaceuticals (Basel)*. 2022;15(9):1123.

doi: 10.3390/ph15091123

41. Shires KL, Rust AJ, Harryparsad R, Coburn JA, Gopie RE. JAK2/STAT5 pathway mutation frequencies in South African BCR/ABL negative MPN patients. *Hematol Oncol Stem Cell Ther*. 2023;16(3):291-302.

doi: 10.56875/2589-0646.1064

42. Hegde PS, Andrew G, Gui G, *et al*. Measurable residual FLT3 tyrosine kinase domain mutations before allogeneic transplant for acute myeloid leukemia. *Bone Marrow Transplant*. 2025;60(2):175-177.

doi: 10.1038/s41409-024-02444-7

43. Gener-Ricos G, Bataller A, Rodriguez-Sevilla JJ, *et al*. NPM1-mutated myeloid neoplasms are a unique entity not defined by bone marrow blast percentage. *Cancer*. 2024;130(20):3452-3462.

doi: 10.1002/cncr.35433

44. Zhao Y, Huang Y, Jiang L, *et al*. Impact of different CEBPA mutations on therapeutic outcome in acute myeloid leukemia. *Ann Hematol*. 2024;103(9):3595-3604.

doi: 10.1007/s00277-024-05884-9

45. Lin ZK, Zhang R, Ge Z, *et al*. Characteristics of NOTCH1 mutation in adult T-cell acute lymphoblastic leukemia. *Zhongguo Shi Yan Xue Ye Xue Za Zhi*. 2013;21(6):1403-1408.

doi: 10.7534/j.issn.1009-2137.2013.06.008

46. Takahashi T, Tsukuda H, Itoh H, Kimura H, Yoshimoto M, Tsujisaki M. Primary and isolated adult T-cell leukemia/lymphoma of the bone marrow. *Intern Med*. 2011;50(20):2393-2396.

doi: 10.2169/internalmedicine.50.5857

47. Kraszewska MD, Dawidowska M, Kosmalska M, *et al*. BCL11B, FLT3, NOTCH1 and FBXW7 mutation status in T-cell acute lymphoblastic leukemia patients. *Blood Cells Mol Dis*. 2013;50(1):33-38.

doi: 10.1016/j.bcmd.2012.09.001

48. Wu X, Wang F, Yang X, *et al*. Advances in drug delivery systems for the treatment of acute myeloid leukemia. *Small*. 2024;20(42):e2403409.

doi: 10.1002/smll.202403409

49. Di Fiore R, Suleiman S, Drago-Ferrante R, *et al*. The role of FBXW7 in gynecologic malignancies. *Cells*. 2023;12(10):1415.

doi: 10.3390/cells12101415

50. Zhu Q, Hu L, Guo Y, Xiao Z, Xu Q, Tong X. FBW7 in hematological tumors. *Oncol Lett*. 2020;19(3):1657-1664.

doi: 10.3892/ol.2020.11264

51. Takeishi S, Nakayama KI. Role of Fbxw7 in the maintenance of normal stem cells and cancer-initiating cells. *Br J Cancer*. 2014;111(6):1054-1059.

doi: 10.1038/bjc.2014.259

52. Hu Y, Bruinstroop E, Hollenberg AN, Fliers E, Boelen A. The role of WD40 repeat-containing proteins in endocrine (dys) function. *J Mol Endocrinol*. 2023;71(1):e220217.

doi: 10.1530/JME-22-0217

53. Liang J, Yu M, Li Y, Zhao L, Wei Q. Glycogen synthase kinase-3: A potential immunotherapeutic target in tumor microenvironment. *Biomed Pharmacother*. 2024;173:116377.

doi: 10.1016/j.biopha.2024.116377

54. Cheng Y, Li G. Role of the ubiquitin ligase Fbw7 in cancer progression. *Cancer Metastasis Rev*. 2012;31(1-2):75-87.

doi: 10.1007/s10555-011-9330-z

55. Zeng J, Chen Z, He Y, *et al*. A patent review of SCF E3 ligases inhibitors for cancer: Structural design, pharmacological activities and structure-activity relationship. *Eur J Med Chem*. 2024;278:116821.

doi: 10.1016/j.ejmech.2024.116821

56. Yang Y, Xie Q, Hu C, *et al*. F-box proteins and gastric cancer: an update from functional and regulatory mechanism to therapeutic clinical prospects. *Int J Med Sci*. 2024;21(8):1575-1588.

doi: 10.7150/ijms.91584

57. Bao E, Zhou Y, He S, *et al*. RING box protein-1(RBX1), a key component of SCF E3 ligase, induced multiple myeloma cell drug-resistance though suppressing p27. *Cancer Biol Ther*. 2023;24(1):2231670.

doi: 10.1080/15384047.2023.2231670

58. Fan J, Bellon M, Ju M, *et al*. Clinical significance of FBXW7 loss of function in human cancers. *Mol Cancer*. 2022;21(1):87.

doi: 10.1186/s12943-022-01548-2

59. Bivik Stadler C, Arefin B, Ekman H, Thor S. PIP degron-stabilized Dacapo/p21(Cip1) and mutations in ago act in an anti- versus pro-proliferative manner, yet both trigger an increase in Cyclin E levels. *Development*. 2019;146(13):dev175927.

doi: 10.1242/dev.175927

60. Knudsen ES, Witkiewicz AK, Rubin SM. Cancer takes many paths through G1/S. *Trends Cell Biol*. 2024;34(8):636-645.

doi: 10.1016/j.tcb.2023.10.007

61. Fagundes R, Teixeira LK. Cyclin E/CDK2: DNA replication, replication stress and genomic instability. *Front Cell Dev Biol*. 2021;9:774845.

doi: 10.3389/fcell.2021.774845

62. Ruan F, Ruan Y, Gu H, Sun J, Chen Q. Clitocine enhances the drug sensitivity of colon cancer cells by promoting FBXW7-mediated MCL-1 degradation via inhibiting the A2B/cAMP/ERK axis. *Am J Physiol Cell Physiol*. 2024;327(4):C884-C900.

doi: 10.1152/ajpcell.00310.2024

63. Song X, Shen L, Tong J, *et al*. Mcl-1 inhibition overcomes intrinsic and acquired regorafenib resistance in colorectal cancer. *Theranostics*. 2020;10(18):8098-8110.

doi: 10.7150/thno.45363

64. Fowler-Shorten DJ, Hellmich C, Markham M, Bowles KM, Rushworth SA. BCL-2 inhibition in haematological malignancies: Clinical application and complications. *Blood Rev*. 2024;65:101195.

doi: 10.1016/j.blre.2024.101195

65. Vazquez-Ulloa E, Lin KL, Lizano M, Sahlgren C. Reversible and bidirectional signaling of notch ligands. *Crit Rev Biochem Mol Biol*. 2022;57(4):377-398.

doi: 10.1080/10409238.2022.2113029

66. Chiplunkar SV, Gogoi D. The multifaceted role of Notch signal in regulating T cell fate. *Immunol Lett*. 2019;206:59-64.

doi: 10.1016/j.imlet.2019.01.004

67. Song C, Guo Y, Chen F, Liu W. IRF-1-inhibited lncRNA XIST regulated the osteogenic differentiation via miR-450b/FBXW7 axis. *Apoptosis*. 2023;28(3-4):669-680.

doi: 10.1007/s10495-023-01820-w

68. Liu Z, Liu X, Liu S, Cao Q. Cholesterol promotes the migration and invasion of renal carcinoma cells by regulating the KLF5/miR-27a/FBXW7 pathway. *Biochem Biophys Res Commun*. 2018;502(1):69-75.

doi: 10.1016/j.bbrc.2018.05.122

69. Sun L. F-box and WD repeat domain-containing 7 (FBXW7) mediates the hypoxia inducible factor-1alpha (HIF-1alpha)/vascular endothelial growth factor (VEGF) signaling pathway to affect hypoxic-ischemic brain damage in neonatal rats. *Bioengineered*. 2022;13(1):560-572.

doi: 10.1080/21655979.2021.2011635

70. Yumimoto K, Nakayama KI. Recent insight into the role of FBXW7 as a tumor suppressor. *Semin Cancer Biol*. 2020;67(Pt 2):1-15.

doi: 10.1016/j.semcancer.2020.02.017

71. Elbahoty MH, Papineni B, Samant RS. Multiple myeloma: clinical characteristics, current therapies and emerging innovative treatments targeting ribosome biogenesis dynamics. *Clin Exp Metastasis*. 2024;41:829-842.

doi: 10.1007/s10585-024-10305-2

72. Liang JH, Ren YM, Du KX, *et al.* MYC-induced cytidine metabolism regulates survival and drug resistance via cGas-STING pathway in mantle cell lymphoma. *Br J Haematol*. 2023;202(3):550-565.

doi: 10.1111/bjh.18878

73. McSweeney K, Hoover P, Ramirez-Solano M, Liu Q, Schwartz JR. Overexpression of human SAMD9 inhibits protein translation and alters MYC signaling resulting in cell cycle arrest. *Exp Hematol*. 2024;137:104249.

doi: 10.1016/j.exphem.2024.104249

74. Hu Z, Wu Y, Sun X, Tong Y, Qiu H, Zhuo E. ARMCX1 inhibits lung adenocarcinoma progression by recruiting FBXW7 for c-Myc degradation. *Biol Direct*. 2024;19(1):82.

doi: 10.1186/s13062-024-00532-8

75. Freie B, Carroll PA, Varnum-Finney BJ, *et al.* A germline point mutation in the MYC-FBW7 phosphodegron initiates hematopoietic malignancies. *Genes Dev*. 2024;38(5-6):253-272.

doi: 10.1101/gad.351292.123

76. Pozzo F, Bittolo T, Tissino E, *et al*. Multiple mechanisms of NOTCH1 activation in chronic lymphocytic leukemia: NOTCH1 mutations and beyond. *Cancers (Basel)*. 2022;14(12):2997.

doi: 10.3390/cancers14122997

77. Luo F, Zhang C, Shi Z, Mao T, Jin LH. Notch signaling promotes differentiation, cell death and autophagy in *Drosophila* hematopoietic system. *Insect Biochem Mol Biol*. 2024;173:104176.

doi: 10.1016/j.ibmb.2024.104176

78. Ohtsubo M, Theodoras AM, Schumacher J, Roberts JM, Pagano M. Human cyclin E, a nuclear protein essential for the G1-to-S phase transition. *Mol Cell Biol*. 1995;15(5):2612-2624.

doi: 10.1128/MCB.15.5.2612

79. Guo X, Zhang R, Ge Z, *et al*. Mutations of FBXW7 in adult T-cell acute lymphocytic leukemia. *Zhongguo Shi Yan Xue Ye Xue Za Zhi*. 2015;23(3):612-618.

doi: 10.7534/j.issn.1009-2137.2015.03.002

80. Bincoletto C, Saad ST, da Silva ES, Queiroz ML. Haematopoietic response and bcl-2 expression in patients with acute myeloid leukaemia. *Eur J Haematol*. 1999;62(1):38-42.

doi: 10.1111/j.1600-0609.1999.tb01112.x

81. Yang Z, Hu N, Wang W, *et al*. Loss of FBXW7 correlates with increased IDH1 expression in glioma and enhances IDH1-mutant cancer cell sensitivity to radiation. *Cancer Res*. 2022;82(3):497-509.

doi: 10.1158/0008-5472.CAN-21-0384

82. He Y, Qi S, Chen L, *et al.* The roles and mechanisms of SREBP1 in cancer development and drug response. *Genes Dis*. 2024;11(4):100987.

doi: 10.1016/j.gendis.2023.04.022

83. Zhang W, Ren Z, Jia L, Li X, Jia X, Han Y. Fbxw7 and Skp2 regulate stem cell switch between quiescence and mitotic division in lung adenocarcinoma. *Biomed Res Int*. 2019;2019:9648269.

doi: 10.1155/2019/9648269

84. Lin H, Ma N, Zhao L, Yang G, Cao B. KDM5c promotes colon cancer cell proliferation through the FBXW7-c-Jun regulatory axis. *Front Oncol*. 2020;10:535449.

doi: 10.3389/fonc.2020.535449

85. Meyer AE, Furumo Q, Stelloh C, Minella AC, Rao S. Loss of Fbxw7 triggers mammary tumorigenesis associated with E2F/c-Myc activation and Trp53 mutation. *Neoplasia*. 2020;22(11):644-658.

doi: 10.1016/j.neo.2020.07.001

86. Chen XY, Yan X, Song BY, Sun J, Mu LJ, Li WP. Effects of BET bromodomain inhibitor JQ1 on double-expressor lymphoma cell lines and its mechanism. *Zhongguo Shi Yan Xue Ye Xue Za Zhi*. 2022;30(4):1094-1100.

doi: 10.19746/j.cnki.issn.1009-2137.2022.04.018

87. Veneziani I, Fruci D, Compagnone M, Pistoia V, Rossi P, Cifaldi L. The BET-bromodomain inhibitor JQ1 renders neuroblastoma cells more resistant to NK cell-mediated recognition and killing by downregulating ligands for NKG2D and DNAM-1 receptors. *Oncotarget*. 2019;10(22):2151-2160.

doi: 10.18632/oncotarget.26736

88. Fiskus W, Piel J, Collins M, *et al*. BRG1/BRM inhibitor targets AML stem cells and exerts superior preclinical efficacy combined with BET or menin inhibitor. *Blood*. 2024;143(20):2059-2072.

doi: 10.1182/blood.2023022832

89. Cao L, Ruiz Buendia GA, Fournier N, *et al.* Resistance mechanism to Notch inhibition and combination therapy in human T-cell acute lymphoblastic leukemia. *Blood Adv*. 2023;7(20):6240-6252.

doi: 10.1182/bloodadvances.2023010380

90. Chang YS, Gills JJ, Kawabata S, *et al.* Inhibition of the NOTCH and mTOR pathways by nelfinavir as a novel treatment for T cell acute lymphoblastic leukemia. *Int J Oncol*. 2023;63(5):128.

doi: 10.3892/ijo.2023.5576

91. Sabol HM, Ferrari AJ, Adhikari M, *et al.* Targeting notch inhibitors to the myeloma bone marrow niche decreases tumor growth and bone destruction without gut toxicity. *Cancer Res*. 2021;81(19):5102-5114.

doi: 10.1158/0008-5472.CAN-21-0524

92. Inuzuka H, Fukushima H, Shaik S, Liu P, Lau AW, Wei W. Mcl-1 ubiquitination and destruction. *Oncotarget*. 2011;2(3):239-244.

doi: 10.18632/oncotarget.242

93. Sneyers F, Kerkhofs M, Speelman-Rooms F, *et al.* Intracellular BAPTA directly inhibits PFKFB3, thereby impeding mTORC1-driven Mcl-1 translation and killing MCL-1-addicted cancer cells. *Cell Death Dis*. 2023;14(9):600.

doi: 10.1038/s41419-023-06120-4

94. Pan Y, Liu J, Gao Y, *et al.* FBXW7 loss of function promotes esophageal squamous cell carcinoma progression via elevating MAP4 and ERK phosphorylation. *J Exp Clin Cancer Res*. 2023;42(1):75.

doi: 10.1186/s13046-023-02630-3

95. Xia H, Dufour CR, Medkour Y, *et al.* Hepatocyte FBXW7-dependent activity of nutrient-sensing nuclear receptors controls systemic energy homeostasis and NASH progression in male mice. *Nat Commun*. 2023;14(1):6982.

doi: 10.1038/s41467-023-42785-3

96. Chan DKH, Mandal A, Hester S, *et al.* Biallelic FBXW7 knockout induces AKAP8-mediated DNA damage in neighbouring wildtype cells. *Cell Death Discov*. 2023;9(1):200.

doi: 10.1038/s41420-023-01494-y

97. Zanganeh S, Zahedi AM, Sattarzadeh Bardsiri M, *et al*. Recent advances and applications of the CRISPR-Cas system in the gene therapy of blood disorders. *Gene*. 2024;931:148865.

doi: 10.1016/j.gene.2024.148865

98. Hesham HM, Dokla EME, Elrazaz EZ, Lasheen DS, Abou El Ella DA. FLT3-PROTACs for combating AML resistance: Analytical overview on chimeric agents developed, challenges, and future perspectives. *Eur J Med Chem*. 2024;277:116717.

doi: 10.1016/j.ejmech.2024.116717

99. Wu M, Zhao Y, Zhang C, Pu K. Advancing proteolysis targeting chimera (PROTAC) nanotechnology in protein homeostasis reprograming for disease treatment. *ACS Nano.* 2024;18(42):28502-28530.

doi: 10.1021/acsnano.4c09800

100. Stephenson SEM, Costain G, Blok LER, *et al.* Germline variants in tumor suppressor FBXW7 lead to impaired ubiquitination and a neurodevelopmental syndrome. *Am J Hum Genet*. 2022;109(4):601-617.

doi: 10.1016/j.ajhg.2022.03.002

101. Zhang Q, Mady ASA, Ma Y, *et al.* The WD40 domain of FBXW7 is a poly(ADP-ribose)-binding domain that mediates the early DNA damage response. *Nucleic Acids Res*. 2019;47(8):4039-4053.

doi: 10.1093/nar/gkz058

102. Duan Y, Liu Z, Wang Q, *et al.* Targeting MYC: Multidimensional regulation and therapeutic strategies in oncology. *Genes Dis*. 2025;12(4):101435.

doi: 10.1016/j.gendis.2024.101435

103. Zhang X, Bian H, Wei W, *et al*. DLX5 promotes osteosarcoma progression via activation of the NOTCH signaling pathway. *Am J Cancer Res*. 2021;11(6):3354-3374.

104. Yao W, Bai L, Wang S, Zhai Y, Sun SY. Mcl-1 levels critically impact the sensitivities of human colorectal cancer cells to APG-1252-M1, a novel Bcl-2/Bcl-X(L) dual inhibitor that induces Bax-dependent apoptosis. *Neoplasia*. 2022;29:100798.

doi: 10.1016/j.neo.2022.100798

105. Yu S, Stappenbelt C, Chen M, *et al.* Cyclin E1 overexpression triggers interferon signaling and is associated with antitumor immunity in breast cancer. *J Immunother Cancer*. 2025;13(3):e009239.

doi: 10.1136/jitc-2024-009239

106. Welcker M, Orian A, Jin J, *et al.* The Fbw7 tumor suppressor regulates glycogen synthase kinase 3 phosphorylation-dependent c-Myc protein degradation. *Proc Natl Acad Sci U S A*. 2004;101(24):9085-9090.

doi: 10.1073/pnas.0402770101

107. Dye KN, Welcker M, Clurman BE, Roman A, Galloway DA. Merkel cell polyomavirus Tumor antigens expressed in Merkel cell carcinoma function independently of the ubiquitin ligases Fbw7 and beta-TrCP. *PLoS Pathog*. 2019;15(1):e1007543.

doi: 10.1371/journal.ppat.1007543

108. Jain N, Croner LJ, Allan JN, *et al*. Absence of BTK, BCL2, and PLCG2 mutations in chronic lymphocytic leukemia relapsing after first-line treatment with fixed-duration ibrutinib plus venetoclax. *Clin Cancer Res*. 2024;30(3):498-505.

doi: 10.1158/1078-0432.CCR-22-3934

109. Tong J, Tan S, Nikolovska-Coleska Z, Yu J, Zou F, Zhang L. FBW7-Dependent Mcl-1 degradation mediates the anticancer effect of Hsp90 inhibitors. *Mol Cancer Ther*. 2017;16(9):1979-1988.

doi: 10.1158/1535-7163.MCT-17-0032

110. Zhou C, Yang S, Wang J, *et al.* Recent advances in PROTAC-based antiviral and antibacterial therapeutics. *Bioorg Chem*. 2025;160:108437.

doi: 10.1016/j.bioorg.2025.108437

111. Cornu M, Lemaitre T, Kieffer C, Voisin-Chiret AS. PROTAC 2.0: Expanding the frontiers of targeted protein degradation. *Drug Discov Today*. 2025;30:104376.

doi: 10.1016/j.drudis.2025.104376

112. Wang Y, Deng S, Xu J. Proteasomal and lysosomal degradation for specific and durable suppression of immunotherapeutic targets. *Cancer Biol Med*. 2020;17(3):583-598.

doi: 10.20892/j.issn.2095-3941.2020.0066

113. Li L, Wazir J, Huang Z, Wang Y, Wang H. A comprehensive review of animal models for cancer cachexia: Implications for translational research. *Genes Dis*. 2024;11(6):101080.

doi: 10.1016/j.gendis.2023.101080

114. Janitri V, ArulJothi KN, Ravi Mythili VM, *et al*. The roles of patient-derived xenograft models and artificial intelligence toward precision medicine. *MedComm (2020)*. 2024;5(10):e745.

doi: 10.1002/mco2.745

115. Burton AJ, Hamza GM, Zhang AX, Muir TW. Chemical biology approaches to study histone interactors. *Biochem Soc Trans*. 2021;49(5):2431-2441.

doi: 10.1042/BST20210772

116. Ihara H, Aoki Y, Aoki T, Toyoda M. Binding of bilirubin to serum albumin in Crigler-Najjar syndrome, type I. *Rinsho Byori*. 1986;34(9):1075-1078.

117. King B, Trimarchi T, Reavie L, *et al*. The ubiquitin ligase FBXW7 modulates leukemia-initiating cell activity by regulating MYC stability. *Cell*. 2013;153(7):1552-1566.

doi: 10.1016/j.cell.2013.05.041

118. Niu M, Wang N, Yang D, *et al.* Multi-omics integration reveals immune hallmarks and biomarkers associated with FLT3 inhibitor sensitivity in FLT3-mutated AML. *Blood Sci*. 2025;7(2):e00227.

doi: 10.1097/BS9.0000000000000227

119. Ayyadevara V, Wertheim G, Gaur S, *et al.* DYRK1A inhibition results in MYC and ERK activation rendering KMT2A-R acute lymphoblastic leukemia cells sensitive to BCL2 inhibition. *Leukemia*. 2025;39(5):1078-1089.

doi: 10.1038/s41375-025-02575-w

120. Tantawy SI, Timofeeva N, Sarkar A, Gandhi V. Targeting MCL-1 protein to treat cancer: opportunities and challenges. *Front Oncol*. 2023;13:1226289.

doi: 10.3389/fonc.2023.1226289

121. Li JY, Zuo LP, Xu J, Sun CY. Clinical applications of circulating tumor DNA in hematological malignancies: From past to the future. *Blood Rev*. 2024;68:101237.

doi: 10.1016/j.blre.2024.101237