Dysregulation of FBW7 in malignant lymphoproliferative disorders

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The ubiquitin-proteasome system (UPS) is involved in various aspects of cell processes, including cell proliferation, differentiation, and cell cycle progression. F-box and WD repeat domain-containing protein 7 (FBW7), as a key component of UPS proteins and a critical tumor suppressor in human cancers, controls proteasome-mediated degradation by ubiquitinating oncoproteins such as c-Myc, Mci-1, cyclin E, and Notch. It also plays a role in the development of various cancers, including solid and hematological malignancies, such as T-cell acute lymphoblastic leukemia, diffuse large B-cell lymphoma, and multiple myeloma. This comprehensive review emphasizes the functions, substrates, and expression of FBW7 in malignant lymphoproliferative disorders.

KEYWORDS
FBW7, lymphoproliferative disorders, ubiquitin, Notch, c-Myc

Introduction

Malignant lymphoproliferative disorders are a heterogeneous group of disorders characterized by the abnormal proliferation of lymphocytes, ranging from indolent to highly aggressive neoplasms, including chronic lymphocytic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL), multiple myeloma (MM), and acute lymphoblastic leukemia (ALL). Although targeted drugs have significantly improved the prognosis of patients with malignant lymphoproliferative disorders, a subset of patients have a remarkably poor outcome. Therefore, exploring the underlying mechanisms of malignant lymphoproliferative disorders is critical (1).

F-box and WD repeat domain-containing protein 7 (FBW7), also known as FBXW7, hCDC4, and AGO, is located at chromosome 4q31, which is a genomic region deleted in more than 30% of cancers (2). Oberg and colleagues determined that FBW7’s role in substrate recognition is a key component of the Skp1–Cull1–F–box (SCF)–type E3 ubiquitin ligases (3). FBW7 has three isoforms: FBW7α, FBW7β, and FBW7γ; all of them contain conserved interaction domains of the F-box and WD repeats in the C-terminus. However, their 5′-UTR and N-terminal coding regions are different, forming the
specificity of the expression and function of these three protein isoforms. These three isoforms also have distinct cellular localizations. FBW7α is localized in the nucleoplasm, FBW7β is cytoplasmic, and FBW7γ is nuclear. FBW7α is regulated by protein kinase C and is mainly expressed in mice. FBW7β is beneficial to fight oxidative stress in cells and more expressed in brain tissue. FBW7γ exclusively expressed in skeletal muscle (4, 5).

Substrates of FBW7 in cancer

FBW7 is an important tumor suppressor in cancer development, and FBW7 mutations have been detected in a wide range of human malignancies, including lung cancer, ovarian cancer, colorectal cancer, T acute lymphoblastic leukemia (T-ALL), and MM. The percentage of FBW7 mutations varies across cancers, being up to 20% in T-ALL (2). FBW7 recognizes c-Myc, Mcl-1, and other oncogenic proteins for ubiquitination and subsequent proteasomal degradation, which is closely related to the proliferation, apoptosis, invasion, and metastasis of cancer cells (6–10).

The Myc protein is a transcription factor that has crucial roles in regulating gene expression for cell proliferation, metastasis, and metabolism, and deregulation of the proto-oncogene c-Myc leads to the development of many human cancers, including hematological malignancy such as DLBCL and solid tumors such as gastric carcinoma. The c-Myc protein is ubiquitylated and degraded by the ubiquitin–proteasome system (11–13). FBW7 overexpression results in decreased c-Myc levels, inhibited cell proliferation, and induced apoptosis, while FBW7 mutations can cause c-Myc accumulation, enhanced cell proliferation, and reduced apoptosis. Thus, FBW7 may mediate apoptosis and growth arrest in leukemia-initiating cells through the ubiquitin–proteasome system and degradation of c-Myc (14).

Another oncoprotein, cyclin E, is a crucial component of the cell cycle and regulates the G1 to S-phase transition and promotes DNA replication. However, cyclin E is frequently dysregulated in cancers, and excess cyclin E activity impairs S-phase progression and causes genomic instability. Significantly, cancers with FBW7 mutations have increased levels of cyclin E. Furthermore, protein phosphatases, such as PP2A-B56, dephosphorylate Ser384 during the interphase of the cell cycle, resulting in a decrease in FBW7 levels and increase in cyclin E levels (15).

Moreover, the Notch pathway regulates numerous cellular functions, including differentiation, proliferation, and apoptosis. FBW7 plays a crucial role in regulating the Notch pathway, including Notch upstream regulators and downstream substrates. The oncoprotein Notch, which is also as a target for FBW7-mediated ubiquitylation, participates in the development of many human cancers, such as T-ALL and DLBCL (16, 17). Moreover, FBW7 can inhibit metastasis and invasion of CLL cells by regulating signaling pathways, such as Notch and its downstream target molecules (18).

In addition, Mcl-1, as the pro-survival Bcl-2 family member, inhibits apoptosis by blocking cell death in numerous cancers. For example, loss of FBW7 in T-ALL cells increases Mcl-1 expression and promotes chemoresistance (19). The transcription factors nuclear factor kappa B (NF-κB) and c-Jun are also important in the development of lymphoproliferative disorders. NF-κB2/p100 can interact with FBW7 thereby promoting its degradation in a GSK3β phosphorylation-dependent manner (20). In addition to these proteins, FBW7 can also ubiquitylate several essential proteins, such as BRAF (Table 1).

#### Regulation of FBW7

Mutations or deletions of FBW7 have been implicated poor prognosis, indicating that aberrant regulation of FBW7 is one of the factors for cancer progression. Some of the regulators of FBW7 include p53, Numb, microRNAs (miRNAs), and CCAAT/enhancer binding protein-δ (C/EBP-δ) (35). P53 is a well-known tumor suppressor protein that conserves genome stability after DNA damage. Moreover, dysregulation of p53 is

| Gene | Phosphorylationsites | Kinases | Cancers | Biological functions of substrates | References |
|------|----------------------|---------|---------|-----------------------------------|------------|
| c-Myc | T58, S62 | GSK3 | T-ALL, ATL, DLBCL, CLL, MM | Tumor proliferation, metastasis, glycolysis | (11, 12, 18, 21–23) |
| Notch1 | T2512/E2516 | cdk8 | T-ALL, ATL, DLBCL, CLL, MM | Notch pathway, proliferation, migration and invasion | (17, 18, 24, 25) |
| cyclin E | T380/S384, T62/E66 | CDK2, GSK3 | T-ALL, MM | Cell cycle | (26, 27) |
| c-Jun | T239/S242 | GSK3 | MM | Cell proliferation | (23, 28) |
| Mcl-1 | S159/T163 S121 | GSK3 | T-ALL, DLBCL, PEL, MM | Inhibit apoptosis | (19, 22, 29–31) |
| NF-κB | ND | GSK3 | T-ALL, MM | Cell proliferation, inhibit apoptosis | (28, 32, 33) |
| BRAF | ND | GSK3 | ATL | BET inhibitors resistance | (34) |

ATL, adult T cell leukemia/lymphoma; T-ALL, T cell acute lymphoblastic leukemia; DLBCL, diffuse large B-cell lymphoma; CLL, chronic lymphocytic leukemia; MM, multiple myeloma; PEL, primary effusion lymphoma.
associated with the development of various cancers. Inactivation of FBW7 could lead to premature loss of hematopoietic stem cells and impaired regulation of cell apoptosis by p53 (36). Another transcription factor, C/EBP δ, decreases Notch intracellular domain (NICD) degradation by ubiquitination through inhibition of FBW7 expression and promotes Notch1 mRNA expression in cancer cells (37). Furthermore, miRNAs, such as miR-223, can regulate T-ALL proliferation by reducing FBW7 expression and contributing to drug resistance (32). In addition, miR-27 and miR-214 could also decrease FBW7 expression to regulate cell proliferation in other lymphoproliferative disorders. However, the exact function of FBW7 in malignant lymphoproliferative disorders remains unclear. Understanding the regulation network surrounding FBW7 is crucial for providing insights into the mechanisms of FBW7-mediated malignant lymphoproliferative disorders. In this review, we focus on the role of FBW7 in malignant lymphoproliferative disorders to identify a novel target for future therapies.

Proliferation of T lymphocytes

T lymphoblastic lymphoma/acute lymphoblastic leukemia

T lymphoblastic lymphoma/acute lymphoblastic leukemia (T-LBL/ALL) is a highly aggressive hematologic malignancy caused by the malignant transformation of T-cell progenitors. T-ALL accounts for 15% and 25% of the total number of childhood and adult cases of ALL, respectively. Adults with T-ALL have poor long-term survival. Approximately 50% of them develop recurrence within 1 year, and the remission rate of second-line chemotherapy is only 30%–45%, which ultimately develops refractory leukemia (38, 39). The 5-year survival rate is 10%; however, in patients with recurrent or refractory T-ALL, overall survival (OS) is less than 6 months (40). Therefore, understanding the underlying mechanisms of T-ALL development is critical.

Notch1 is the most common oncogene for T-ALL, and mutations in Notch1 have been reported in more than 60% of T-ALL. Besides, the mutation rate of Notch1 in adults is higher than children. Mutations of Notch1 occur mainly in the heterodimeric domain (HD) region and the proline, glutamine, serine, and threonine domain (PEST). Mutations in the HD domain can result in Notch1 activation by reducing the interaction of the Notch1 subunit. The PEST region regulates protein turnover by targeting proteins to ubiquitin–proteasome complex for subsequent degradation (16, 41). The cross-talk between Notch and NF-κB pathways is vital in T-ALL development, indicating NF-κB signaling is one of the major mediators of Notch-induced oncogenic transformation (42). The activation of the Notch pathway can upregulate NF-κB activity, resulting in abnormal cell proliferation and apoptosis inhibition (42). In addition, the occurrence of T-ALL is also related to the abnormal expression of noncoding regulatory elements and miRNAs, such as miR-19, miR-155, and miR-233 (43).

As early as more than 10 years ago, studies have shown that inactivation of FBW7 could lead to premature loss of hematopoietic stem cells caused by an active cell cycle and impaired regulation of cell apoptosis by p53 (36). FBW7 can regulate the cell cycle in a differentiation-dependent manner and loss leads to the accumulation of c-Myc, which results in the excessive proliferation of immature T cells, ultimately leading to the development of T-ALL or lymphoma (44). The mutation rate of FBW7 in T-ALL is between 8%–20% (45–48). And the deletion or mutation in FBW7 increases the protein level of c-Myc, which in turn increases the number of leukemia initiating cells. Furthermore, inhibition of the expression of c-Myc by small molecule inhibitors can inhibit the proliferation of mouse and human T-ALL cells, suggesting that c-Myc may be the proto-oncogene that drives T-ALL and is regulated by FBW7 (14). Besides, in T-ALL, FBW7 mutation usually cooccurs with Notch1 mutation, which has been widely proven to be an oncogene in T-ALL (49). Mutation of FBW7 can reduce the cellular level of NICD protein degradation, which not only leads to abnormal activation of the Notch pathway but also reduces ubiquitination degradation of proto-oncogenes such as cyclin E and c-Myc (50). Kumar et al. demonstrated that Notch and NF-κB signaling can increase miR-223 gene expression, which in turn downregulates the expression of the onco-suppressor FBW7, known to negatively regulate Notch signaling, thus suggesting that the Notch/miR-223/FBW7 axis may reinforce Notch signaling effect in T-ALL. Furthermore, miR-223 may be involved in the mechanism of g-secretase inhibitor (GSI) treatment of patients with T-ALL; inhibiting miR-223 expression may reduce GSIs resistance (32). Moreover, FBW7 mutations, region of R465C and R479Q, can also resist GSIs treatment by stabilizing NICD and its principle downstream target c-Myc, which may be the mechanism of GSIs resistance in patients with T-ALL (24). Moharram et al. showed the R465C mutation in FBW7 played an important role in T-ALL progression when combined with Notch1 mutation and the R505C mutation in FBW7 impaired Notch1 binding (46). In addition, approximately 60% of patients with T-ALL express the oncogenic transcription factor T-cell acute lymphocytic leukemia 1 (TAL1). Studies have shown that TAL1 can upregulate miR-223 expression by binding to the miR-223 promoter, reducing FBW7 expression, and increasing the expression of downstream substrates c-Myc, Notch1, and cyclin E, which ultimately induce cell proliferation (21, 26). Moreover, other studies also have shown that miR-223 can regulate T-ALL proliferation by reduce FBW7 expression; this indicates that miR-223 could regulate FBW7 activation in T-ALL (51, 52). Mcl-1 is an antiapoptotic protein of the BCL-2 family, which promotes tumor progression by inhibiting apoptosis (53). In T-ALL cell lines, the deletion of FBW7 increases in the expression level of Mcl-1 in a GSK3 phosphorylation-dependent manner and promotes T-ALL progression. Mcl-1 also upregulates resistance in the treatment of
BCL-2 inhibitor (ABT737). However, when the FBW7 function was restored or Mcl-1 lost, the sensitivity to ABT737 was restored (19) (Figure 1).

However, other studies have shown that patients with Notch1/FBW7 mutations have a better prognosis, with 5-year event-free survival of 95.5% and 5-year OS 100% (54). FBW7 deletion can upregulate glucocorticoid receptors in primary T-ALL cells, thereby enhancing their sensitivity to glucocorticoids and improving prognosis (55). In addition, FBW7 mutations do not affect the prognosis of children with T-ALL. Maybe other oncogenes are involved or affected by treatment regimens. Therefore, more studies are still required to confirm the mechanisms related to the role of FBW7 in T-ALL.

Adult T-cell leukemia/lymphoma

Adult T-cell leukemia/lymphoma (ATL) is a rare malignant T-cell monoclonal proliferative disease caused by human T-cell leukemia virus type 1 (HTLV1). Southwestern Japan is one of the most endemic areas for malignancy, along with the Caribbean basin, Central and South America. The Japan Clinical Oncology Group-Lymphoma Study Group proposed four clinical subtypes of ATL: acute, lymphoma, chronic, and smoldering. Nonetheless, the course of ATL is highly variable. Patients with acute, lymphoma, and chronic type with unfavorable prognostic factors, defined by levels of blood urea nitrogen or lactate dehydrogenase at higher than normal or having albumin levels lower than normal, are categorized as having aggressive clinical course; however, chronic type without unfavorable prognostic factors and smoldering type are indolent ATL (56, 57). FBW7 is an important tumor suppressor, but some FBW7 mutations can function as an oncogene. Yeh et al. showed that 25% (8/32) of patients with ATL had mutations in the FBW7 WD40 domain, region of D510E and D527G, which had ability to target and degrade cyclin E, Mcl-1, and c-Myc. Mutation in FBW7 failed to degrade NICD, activating the Notch signaling pathway and ultimately promoting ATL cell proliferation. However, FBW7 expression in wild-type, proliferation of cells was inhibited (25). In addition, c-Myc is a prognostic factor for patients with ATL, and FBW7 downregulation can lead to c-Myc accumulation and ATL cell proliferation (12). Patients with low FBW7 levels and high c-Myc levels experience poor prognosis, with 3-year OS less than 50% (12). Moreover, FBW7 mutations in ATL cells inhibit the degradation of BRAF and provide resistance to BET inhibitors through the RAF-MEK-ERK pathway, which also indicated ERK inhibitor may be the new therapeutic target in ATL (34). Therefore, FBW7 may be a potential target for the treatment of ATL (Figure 1).
Proliferation of mature B lymphocytes

Diffuse large B-cell lymphoma

DLBCL is the most common type of non-Hodgkin lymphoma in adults, accounting for 30%–40% of new diagnoses. DLBCL is classified as germinal center B-cell (GCB) subtype and activated B-cell (ABC) subtype by genetic profiling, and patients with the ABC subtype have significantly poorer outcomes (58). Approximately 60% of patients with DLBCL can cure with regimens such as rituximab, cyclophosphamide, adriamycin, vincristine, and prednisone (R-CHOP). However, 20%–50% of patients will be refractory or will relapse after achieving complete response (59). Therefore, ongoing efforts in the understanding of the mechanism of DLBCL have identified subsets of patients with poor prognosis for immunochemotherapy.

FBW7 expression in patients with GCB-DLBCL was higher than in the ABC-DLBCL subtype, which had an inferior prognosis. The median survival time of patients in DLBCL with low FBW7 expression was 44 months, which was significantly shorter than that of those with high FBW7 expression (81 months) (22). FBW7 overexpression decreased cell viability and increased apoptosis rates in ABC-DLBCL cell lines. In terms of mechanism, stability of Stat3 and phospho-Stat3Tyr705, which are associated with poor survival in ABC-DLBCL, were reduced following FBW7 overexpression in ABC-DLBCL cell lines. The downstream antiapoptotic target genes of activated Stat3, including c-Myc, Mcl-1, Bcl-2, and Bcl-xl, showed decreased mRNA expression following exogenous FBW7 overexpression. Similarly, the negative relationship between FBW7 and Stat3 levels was also confirmed in DLBCL patient samples (22) (Figure 2).

In addition, epigenetic alterations play a vital role in the tumor progression of DLBCL. One study that adopted whole-genome/exome sequencing (WGS/WES) of 619 patients with DLBCL revealed that somatic mutations in KMT2D (19.5%) were most frequently observed, followed by mutations in ARID1A (8.7%), CREBBP (8.4%), KMT2C (8.2%), TET2 (7.8%), EP300 (6.8%), and EZH2 (2.9%) (17). Somatic mutations in the CREBBP and EP300 genes mainly occur in B-cell lymphomas, especially in DLBCL, and often relate to disease relapse and inferior prognosis. The 3-year progression-free survival and OS were 52.6% and 67.8%.

**FIGURE 2**
Schematic diagram of FBW7-mediated oncogene and signaling pathway in B lymphoproliferative malignancies. 1) CREBBP/EP300 mutations inhibit H3K27 acetylation, downregulate FBW7 expression, and activate the Notch pathway to promote cell proliferation. 2) Dysregulation of FBW7 could upregulate Stat3 expression and increase downstream antiapoptotic target genes, including c-Myc, Mcl-1, and Bcl-2, to induce cell proliferation and inhibit apoptosis.
respectively, lower than that of patients without mutation (17, 60). The mechanism suggested that CREBBP/EP300 mutation inhibited H3K27 acetylation, downregulated FBW7 expression, and activated the Notch pathway, ultimately promoting DLBCL proliferation. This indicates that CREBBP/EP300 mutation in DLBCL may regulate cell proliferation via the FBW7-Notch pathway (17) (Figure 2). However, another study reported that FBW7 was a tumor pro-survival factor (61). KMT2D is a tumor suppressor gene of DLBCL. FBW7 degrades KMT2D by ubiquitylation and promotes DLBCL cell growth. Therefore, more clinical studies are required to confirm the mechanisms related to the role of FBW7 in DLBCL.

**Chronic lymphocytic leukemia**

CLL is a clonal proliferative disease of mature B lymphocytes, characterized by the aggregation of small mature lymphocytes in the peripheral blood, bone marrow, spleen, and lymph nodes. In addition, CLL is a heterogeneous disease with variable clinical presentation and evolution. CLL generally has a chronic and indolent course with slow progression. The treatment of watching and waiting is required at early stages, but CLL remains an incurable disease with heterogeneous prognosis. Patients with nonmutated IGHV, Del(17p), and Del(11q) chromosomal aberrations or mutations usually have an aggressive course and poor prognosis and often do not achieve sustained remission (62, 63). Approximately 12% patients with CLL may have Notch1 mutation, which is associated with poor prognosis (64). Patients of CLL with Notch1 or FBW7 mutations have a higher risk of Richter’s syndrome transformation (57%) (65). In addition, approximately 2%–8% of patients with CLL have detected FBW7 mutations, mainly missense mutations, affecting the WD40 domain required for substrate binding, and the mutation sites detected at R465L, R465H and G423V (65–67). FBW7 negatively regulates Notch1. Close et al. used CRISPR/Cas9 technology to edit the WD40 domain in the CLL cell line to cause FBW7 mutations, which could increase the transcription activity and protein level of Notch1 and c-Myc by reducing degradation (18). Moreover, FBW7 mutations in CLL not only increase NICD levels but also increase the expression level of the Notch1 target gene, impeding its degradation through ubiquitination (18). These findings suggest that FBW7 mutations play a role in activating the leukemia-causing Notch1 pathway (Figure 2).

**Primary effusion lymphoma**

Primary effusion lymphoma (PEL) is a highly aggressive B-cell lymphoma with a poor prognosis and median survival of 6.2 months (68). The etiology is associated with Kaposi’s sarcoma associated herpesvirus (KSHV) (69). Latency-associated nuclear antigen (LANA) is a key gene of KSHV, which can interact with FBW7, resulting in inhibiting PEL cell apoptosis by reducing the degradation of Mcl-1 and caspase-3 through ubiquitination (29, 70) (Figure 2).

**Proliferation of bone marrow plasmacytes**

**Multiple myeloma**

MM is a hematologic malignancy characterized by the presence of abnormal clonal plasma cells in the bone marrow, accounting for 15% of adult hematologic malignancies. It is characterized by anemia, hypercalcemia, bone lesions, and kidney dysfunction. It remains an incurable disease, with a 5-year OS of approximately 45% (71–73). Therefore, understanding the underlying mechanisms of MM development is critical.

The NF-κB pathway is important for cell growth, differentiation, and survival. It also plays a vital role in the development of MM (74). The p100 protein, belonging to the NF-family, is the main inhibitor of the noncanonical NF-κB pathway. Clearance of p100 from the nucleus is required for NF-κB pathway activation and MM cell survival. FBW7α can target the nuclear phosphorylation of p100 by GSK3 for degradation through ubiquitination both in vivo and in vitro. Thus, FBW7α and GSK3 function as pro-survival factors by controlling p100 degradation in MM (20, 75). Besides, miRNAs, such as miR-32, miR-27, miR-214, and miR-21, are upregulated in MM (76). Overexpression of miR-27b and miR-214 in MM can mediate the FBW7 and PTEN/AKT/GSK3 pathways blocking degradation by ubiquitinating Mcl-1 and inducing cell proliferation and apoptosis resistance (30). In addition, patients with MM with a lower FBW7 expression and higher miR-32 expression in cancer tissues than in normal tissues, had poorer prognosis, with a median OS <3 years. Overexpression of miR-32 in vitro decreased FBW7 expression and increased the expression of cancer-related proteins, c-Jun and c-Myc (23). These results indicate that miRNAs can regulate FBW7 expression in MM and then affect the expression of its downstream substrates, thus promoting MM proliferation. In all, FBW7 can be both a tumor suppressor gene and a pro-survival gene in MM. Further studies should confirm the mechanisms related to the role of FBW7 in MM (Figure 3).

**Other malignant lymphoproliferative disorders**

Mutations of the FBW7 gene were also detected in B-ALL and mantle cell lymphoma (77–79). MiR-27a is upregulated in
pediatric B-ALL, and its expression is inversely correlated with FBW7 expression and disease progression (80). Further studies are required to clarify this mechanism. In addition, FBW7 overexpression in cutaneous T-cell lymphoma could increase the sensitivity of histone deacetylase inhibitor (HDACi) (81).

Conclusion

FBW7 as a critical tumor suppressor, can recognize various oncogenic proteins and degrade them through ubiquitination to maintain cell growth. However, FBW7 dysregulation is associated with the development of malignant lymphoproliferative disorders. In addition, FBW7 mutations or inactivation is associated with chemoresistance and poor prognosis. Thus, the underlying mechanisms can potentially be targeted for treating malignant lymphoproliferative disorders. Future studies should attempt to elucidate the complex mechanisms underlying the role of FBW7 and its substrates and to identify novel targets for effective treatment of malignant lymphoproliferative disorders. Clinical studies are needed to confirm the significance of FBW7 in tumor development, progression, and resistance to therapies as well as opportunities for targeted therapies.

Author contributions

XW, WG, ZZ and OB designed the study and contributed vital data and analytical tools and wrote the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
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