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Review Article

F-box in breast cancer: mechanism of action and therapeutic potential

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Abstract: Breast cancer remains one of the most prevalent and deadly malignancies among women worldwide. The F-box protein family, a core component of the SCF (SKP1-Cullin1-F-box) E3 ubiquitin ligase complex, plays a pivotal role in determining substrate specificity for ubiquitin-mediated proteasomal degradation. Beyond their classical functions in cell cycle regulation and signaling pathways, F-box proteins are increasingly recognized for their involvement in key oncogenic processes, including breast cancer stem cell (BCSC) maintenance, metastasis, and therapy resistance. Based on differences in their C-terminal domains, F-box proteins are classified into three subfamilies: FBXL, FBXW, and FBXO. Certain members, such as SKP2 and FBXL10, act as oncogenes, whereas others, like FBXW7 and FBXO15, function as tumor suppressors. Notably, some proteins - including FBXO11 and FBXO22 - exhibit dual or context-dependent roles that vary by tissue type or disease stage. With their diverse and critical functions, F-box proteins have emerged as promising therapeutic targets in breast cancer. Current strategies under investigation include small-molecule inhibitors (SMIs) and RNA interference (RNAi). This review highlights recent advances in understanding the molecular mechanisms of F-box proteins in breast cancer and explores their potential in targeted therapy.

Keywords: E3 ligase, F-box, breast cancer, drug resistance, therapeutic strategies

Introduction

Breast cancer is currently the most common malignant tumor in women [1]. According to recent statistics, approximately one in every 20 women worldwide will be diagnosed with breast cancer during her lifetime [2]. Breast cancer can be classified into four subtypes: human epidermal growth factor receptor 2-positive (HER2+) breast cancer, luminal A breast cancer, luminal B breast cancer, and triple-negative breast cancer (TNBC). TNBC accounts for 10-20% of all breast cancers [3, 4]. It carries the poorest prognosis because of limited treatment options, poor therapeutic response, and a high risk of distant metastasis and mortality. Bone is the most common site of metastasis in breast cancer and a major cause of cancer-related mortality [5, 6]. Approximately 20-30% of patients eventually develop metastases. Nearly 90% of breast cancer-related deaths are directly linked to metastatic disease [7]. Apart from surgery, current treatment modalities for breast cancer mainly include radiotherapy, chemotherapy, endocrine therapy, HER2-targeted therapy, and, more recently, immune checkpoint inhibitors for selected patients. These strategies have improved patient outcomes. However, their efficacy is often limited by intrinsic or acquired drug resistance and systemic toxicities. In particular, TNBC lacks effective targeted therapies. This underscores the urgent need for novel treatment approaches [8].

The ubiquitin-proteasome system (UPS) is a fundamental pathway in eukaryotic cells and plays a critical role in tumor development and progression [9-11]. The ubiquitination process mainly involves three types of enzymes: E1 ubiquitin-activating enzymes, E2 ubiquitin-conjugating enzymes, and E3 ubiquitin ligases.

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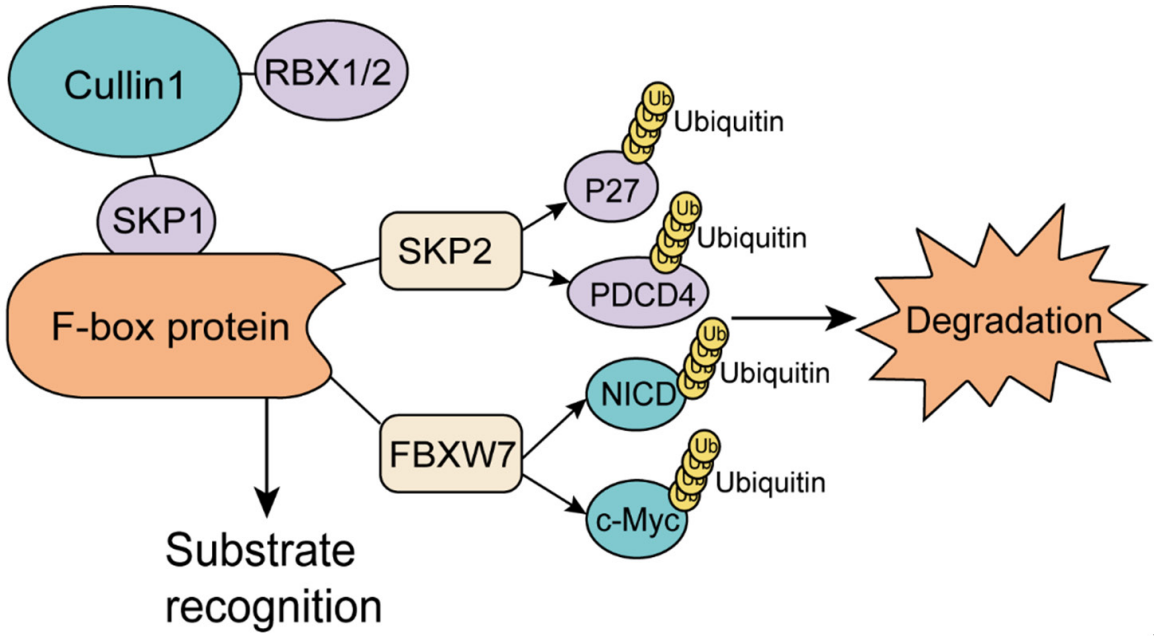

Figure 1. Structure of the SCF E3 ubiquitin ligase complex and role of F-box proteins in substrate recognition. The SCF complex consists of Cullin, SKP1, RBX1/2, and variable F-box proteins (e.g., SKP2, FBXW7) that determines substrate specificity. Representative F-box proteins, such as SKP2 and FBXW7, selectively recognize and mediate the degradation of substrates including P27, PDCD4, NICD, and c-Myc. Abbreviations: SKP1, s-phase kinase-associated protein 1; PDCD4, programmed cell death 4; NICD, NOTCH intracellular domain.

Among them, E3 ligases confer substrate specificity. They play a central role in substrate recognition and regulation. Based on structure and catalytic mechanisms, E3 ligases are divided into three main categories: RING-type, HECT-type, and RBR-type. Cullin-RING ligases (CRLs) are multi-subunit complexes belonging to the RING-type family. The SCF (SKP1-Cullin1-F-box) complex is the largest subgroup of CRLs, and its substrate specificity is determined by F-box proteins [12, 13] (**Figure 1**). F-box proteins play important roles in regulating diverse cellular functions and are closely associated with multiple cancers [14-16]. In breast cancer, F-box proteins exhibit context-dependent roles, functioning as either oncogenes or tumor suppressors depending on the molecular subtype (**Figure 2**). Compared with existing therapies, targeting ubiquitination offers several advantages. One advantage is its ability to directly modulate protein stability and degradation, including oncogenic proteins that are traditionally considered undruggable. Another is its higher selectivity, achieved through the unique recognition between E3 ligases and their substrates. Finally, targeting ubiquitination can also overcome signaling redundancy and therapy resistance by eliminating critical oncogenic or resistance-related factors. Accordingly, as substrate-recognition components of the SCF complex, F-box proteins have emerged as important therapeutic targets and potential biomarkers in cancer biology and drug development. This review summarizes recent advances in the study of F-box proteins in breast cancer. It highlights their roles in tumor initiation and progression and evaluates their potential as therapeutic targets.

Classification of F-box proteins and their functions in breast cancer

The F-box protein family plays a critical role in the initiation, progression, and treatment of breast cancer (**Table 1**). In breast cancer, these proteins regulate the cell cycle, cancer stem cell (CSC) maintenance, tumor metastasis, and drug resistance (**Table 2**) [17]. F-box proteins are broadly classified into three sub-families: the FBXL family with leucine-rich repeats, the FBXW family with WD 40 repeats, and the FBXO family with uncharacterized domains. In the human genome, about 22 FBXL, 10 FBXW, and 37 FBXO proteins have been identified [18].

F-box protein	ER+	HER2+	TNBC
SKP2	↑	↑	↑
FBXL2	N	N	↓
FBXL10	↑	N	↑
FBXL14	N	N	↓
FBXL16	↑	N	↓
FBXL20	↑	N	↑
FBXW2	±	↓	↓
FBXW7	↓	↓	↓
FBXW8	↑	N	N
FBXO3	N	↑	↑
FBXO11	↑	N	↓
FBXO15	↓	↓	↓
FBXO22	±	N	±
FBXO24	↓	↓	↓
FBXO32	↓	N	N
FBXO45	↑	N	±

Figure 2. Subtype-specific expression patterns of F-box proteins in breast cancer. A heatmap showing the differential expression (↑, ↓, ±, N) of representative F-box proteins across ER+, HER2+, and TNBC subtypes. Color-coded symbols reflect the upregulation (red), downregulation (blue), or context-dependent (yellow) expression based on published data. Green squares indicate that the corresponding F-box protein has not been systematically studied in breast cancer, or that its expression level shows no significant change compared to normal breast tissue. Abbreviations: ER+, estrogen receptor positive; HER2+, human epidermal growth factor receptor 2-positive; TNBC, triple-negative breast cancer.

FBXL family (F-box with leucine rich amino acid repeats)

FBXL-type F-box proteins contain an F-box domain and one or more leucine-rich repeats (LRRs). These repeats enable the proteins to bind specific substrates and mediate their ubiquitination. About 22 members of the FBXL family have been identified, and several of them have been found to play important roles in breast cancer [19].

SKP2 (FBXL1): SKP2, also known as p45 or FBXL1, is one of the most extensively studied F-box proteins in breast cancer. It functions as an oncogene and a key regulator of the cell cycle [20]. SKP2 promotes cell cycle progression and inhibits the p53-dependent apoptosis pathway mediated by the p53-inducible gene 3 (PIG3) [21, 22]. It also participates in the DNA damage response. For example, SKP2 ubiquitinates programmed cell death 4 (PDCD4), a tumor suppressor that regulates DNA damage by inhibiting p53 translation [21]. This modification helps explain SKP2's role in DNA repair and tumor development. Clinically, SKP2 overexpression in breast cancer correlates with poor overall survival [23]. Inhibition of SKP2 increases the radiosensitivity of breast cancer cells, and its combination with radiotherapy markedly improves treatment outcomes [21]. Moreover, SKP2 overexpression is linked to activation of the Akt signaling pathway in HER2+ breast cancer [24].

FBXL2: FBXL2 generally acts as a tumor suppressor in cancers. Similar to SKP2, it participates in the ubiquitin-mediated degradation of cyclins [25-28]. However, research on FBXL2 in breast cancer remains limited. Breast cancer stem cells (BCSCs) play a central role in tumor initiation, progression, metastasis, and drug resistance [29]. FBXL2 can target the transcription factor E47 for polyubiquitination and degradation, thereby blocking BCSC differentiation [30]. This process suppresses TNBC progression and reduces paclitaxel resistance induced by BCSCs [31, 32]. Hence, FBXL2 may represent a potential therapeutic target for drug-resistant TNBC.

FBXL10: FBXL10, also known as KDM2B, is a conserved protein widely expressed in human tissues. It regulates diverse physiological processes, including cellular senescence [33], cell proliferation [34], and BCSC self-renewal [35-37]. In breast cancer, FBXL10 acts as an oncogenic factor by stabilizing estrogen-related receptor α (ERRα). It achieves this by inhibiting ERRα polyubiquitination while promoting monoubiquitylation, which enhances ERRα stabili-

Table 1. Classification and functional roles of key F-box proteins in breast cancer

F-box protein	Role	Substrates	Subtype	Biological functions
FBXL family				
SKP2 (FBXL1)	Oncogene	P27, P21, P57, cyclin A, cyclin E, cyclin D1, c-Myc	All subtypes	Cell cycle [22, 106-110]
		PDCD4		DNA damage [21]
		P53		Apoptosis [22]
FBXL2	Tumor-suppressor gene	E47	TNBC	BCSCs and paclitaxel resistance [30]
FBXL10	Oncogene	ERRα	ER+, TNBC	Cell proliferation [39]
		SNAI1		EMT [41]
		microRNA	TNBC	NDY1/EZH2/microRNA/PRC axis and BCSCs [35]
FBXL14	Tumor-suppressor gene	CDCP1	TNBC	Tyrosine phosphorylation-dependent regulation of cellular events [42]
		Twist1		EMT [44]
FBXL16	Tumor-suppressor gene	HIF1α	TNBC	EMT and BCSCs in TNBC [45]
	Oncogene	Unclear	ER+	Mitochondrial respiration and tamoxifen resistance in ER+ breast cancer [47]
FBXL20	Oncogene	PUMA and BAX	ER+, TNBC	Apoptosis and drug resistance [50]
FBXW family				
FBXW2	Oncogene	MSX2	ER+	BCSCs and tamoxifen resistance [62]
	Tumor-suppressor gene	Moesin	ER+, HER2+, TNBC	AKT-Moesin-SKP2 axis [59]
		p65		BCSCs and paclitaxel resistance [57]
FBXW7	Tumor-suppressor gene	NICD	All subtypes	NOTCH/NICD pathway [69]
		mTOR and HIF1α		PI3K/Akt/mTOR pathway [70]
		c-Myc, GAK, cyclin E, cyclin D1, cyclin B1, Aurora-B		Cell cycle [72, 76, 112-114]
		HIF1α, IL-6Rα		Tumor metastasis [117]
		Notch1-IC, MCL-1, HSF-1		Drug resistance [77-79]
FBXW8	Oncogene	NUMB	ER+	BCSCs [82]
FBXO family				
FBXO3	Oncogene	USP4	HER2+, TNBC	FBXO3-USP4-Twist1 axis and PI3K/ERK signaling pathway [95]
FBXO11	Oncogene	p53	ER+	p53/p21 signaling pathway in non-EMT breast cancers [85]
	Tumor-suppressor gene	Snail	TNBC	EMT [84]
FBXO15	Tumor-suppressor gene	SOX2, EGFR, and STAT3	All subtypes	EMT and BCSCs [86]
FBXO22	Oncogene	Unclear	ER+, TNBC	Cell proliferation [90]
	Tumor-suppressor gene	Snail		EMT [90]
		HDM2		Tumor metastasis [91]
		KDM5A		DNA damage and tumor metastasis [10]
		KDM4B		Tamoxifen resistance [92]
FBXO24	Tumor-suppressor gene	LSD1	All subtypes	Tumorigenesis [96]
FBXO32	Tumor-suppressor gene	KLF4	ER+	Cell proliferation [100]
FBXO45	Oncogene	Bim	ER+, TNBC	Apoptosis [93]
	Tumor-suppressor gene	ZEB1	TNBC	EMT [94]

Note: F-box proteins not listed in the table have undefined roles and unknown substrates in breast cancer. Abbreviations: PDCD4, programmed cell death 4; TNBC, triple-negative breast cancer; BCSCs, breast cancer stem cells; ERRα, estrogen-related receptor α; ER+, estrogen receptor positive; HER2+, human epidermal growth factor receptor 2-positive; SNAI1, snail homolog 1; EMT, epithelial-mesenchymal transition; NDY1, not dead yet-1; EZH2, enhancer of zeste homolog 2; PRC, polycomb repressive complex; CDCP1, CUB-domain-containing protein 1; HIF1α, hypoxia-inducible factor 1α; PUMA, p53 upregulated modulator of apoptosis; BAX, Bcl-2-associated X protein; MSX2, muscle segment homeobox 2; NICD, NOTCH intracellular domain; GAK, G-associated kinase; MCL-1, myeloid cell leukemia-1; HSF-1, heat shock factor 1; USP4, ubiquitin specific peptidase 4; SOX2, sex-determining region Y-box 2; STAT3, signal transducer and activator of transcription 3; HDM2, human double minute 2; LSD1, lysine-specific demethylase 1; KLF4, Kruppel-like factor 4; ZEB1, zinc-finger E-box-binding homeobox 1.

Table 2. Functional involvement of F-box proteins in key processes of breast cancer progression

F-box Protein	Cell Cycle	EMT	CSC	Drug Resistance	Apoptosis
SKP2 (FBXL1)	+	N/A	N/A	N/A	N/A
FBXL2	N/A	N/A	-	-	N/A
FBXL10	N/A	+	+	N/A	N/A
FBXL14	N/A	-	N/A	N/A	N/A
FBXL16	N/A	+	+	-	N/A
FBXL20	N/A	N/A	N/A	+	+
FBXW2	N/A	N/A	+/-	+/-	N/A
FBXW7	-	N/A	-	-	N/A
FBXW8	N/A	N/A	+	N/A	N/A
FBXO3	N/A	+	N/A	N/A	N/A
FBXO11	N/A	-	N/A	N/A	N/A
FBXO15	N/A	-	-	N/A	N/A
FBXO22	N/A	-	N/A	-	N/A
FBXO45	N/A	-	N/A	N/A	+

Note: Abbreviations: EMT, epithelial-mesenchymal transition; CSC, cancer stem cell.

ty and transcriptional activity. This activity facilitates ERRα/PGC1β-driven proliferation and tumorigenesis in vitro and in vivo [38, 39]. Functional genomic screening also links FBXL10 dysregulation to resistance against antiestrogen therapy [40]. Moreover, FBXL10 regulates acetylation and transcriptional activity of Snail homolog 1 (SNAI1), which represses E-cadherin and induces epithelial-mesenchymal transition (EMT) [41]. As a result, FBXL10 enhances migration and invasion, while its knockdown reduces lung metastases in mouse models. In summary, FBXL10 promotes proliferation, endocrine resistance, and metastasis in breast cancer.

FBXL14: FBXL14 targets the transmembrane CUB-domain-containing protein 1 (CDCP1), a factor critical for TNBC migration [42]. By promoting CDCP1 degradation, FBXL14 reduces its stability and suppresses downstream prometastatic signaling [18]. FBXL14 also regulates EMT by inducing the degradation of Twist1 [43, 44]. This effect, however, can be counteracted by the deubiquitinating enzyme ubiquitin-specific protease 13 (USP13) [44], highlighting a functional antagonism between USP13 and FBXL14. This interaction warrants further study and may provide novel insights into breast cancer diagnosis and therapy.

FBXL16: The functions of FBXL16 in breast cancer are not yet fully elucidated. In TNBC, FBXL16 acts as a tumor suppressor. It directly binds hypoxia-inducible factor 1α (HIF1α) and promotes its ubiquitin-dependent degradation, thereby blocking HIF1α-driven EMT and angiogenesis [45, 46]. Downregulation of FBXL16 via the p38/miR-135b-3p axis correlates with poor prognosis, underscoring its potential as a therapeutic target for advanced TNBC. In contrast, in estrogen receptor positive (ER+) breast cancer, high FBXL16 expression is associated with worse overall survival. In this context, FBXL16 localizes predominantly to mitochondria, where it supports oxidative phosphorylation and cellular respiration [47]. This metabolic role promotes survival under endocrine therapy and contributes to tamoxifen resistance. Collectively, FBXL16 exerts tumor-suppressive functions in TNBC but oncogenic effects in ER+ disease, highlighting the subtype-specific nature of its activity.

FBXL20: FBXL20 acts as an oncogene in breast cancer [48]. It regulates apoptosis-related proteins, including p53 upregulated modulator of apoptosis (PUMA) and BCL2-associated X protein (BAX) [49-51]. In aggressive breast cancers, FBXL20 is highly expressed and inhibits apoptosis by promoting AKT1-dependent proteasomal degradation of PUMA and BAX. This activity enhances cell proliferation and tumor growth. Furthermore, AKT1 prevents FBXO31 from degrading FBXL20, thereby reinforcing its oncogenic role [50, 52]. Silencing FBXL20 restores PUMA/BAX function and increases

chemosensitivity, partially overcoming drug resistance.

The other FBXLs: Many members of the FBXL family have not yet been studied in breast cancer, and only a few have been preliminarily linked to disease. For example, FBXL12 is significantly upregulated in breast cancer patients with high cyclin E expression and correlates with poor prognosis [53]. Its precise molecular mechanisms in breast cancer remain unclear.

FBXW family (F-box with WD 40 amino acid repeats)

FBXW-type F-box proteins contain WD 40 repeat sequences at the C-terminus. Among them, FBXW2 and FBXW7 have been most extensively studied in breast cancer, while the roles of other FBXW proteins in breast cancer remain poorly defined.

FBXW2: FBXW2 is a F-box protein that acts as a tumor suppressor in several cancers. It promotes proteasomal degradation of oncogenic proteins such as SKP2, β-catenin, and epidermal growth factor receptor (EGFR) [54-58]. In breast cancer, FBXW2 inhibits the AKT-Moesin-SKP2 axis by inducing proteasomal degradation of Moesin, which in turn reduces SKP2 levels and suppresses tumor progression [59]. FBXW2 also regulates cancer stemness and drug response in a context-dependent manner. On one hand, it targets NF-κB p65 for degradation, attenuating sex-determining region Y-box 2 (SOX2) activation, reducing stem-like properties, and reversing paclitaxel resistance; this effect can be blocked by p300-mediated acetylation of p65 [57, 60, 61]. On the other hand, FBXW2 interacts with muscle segment homeobox 2 (MSX2), relieving its repression of SOX2, which enhances stemness and contributes to tamoxifen resistance [62, 63]. Thus, FBXW2 exerts both tumor-suppressive and oncogenic effects depending on substrate context, influencing proliferation, stemness, and therapy resistance.

FBXW7: FBXW7 is a classical tumor suppressor in breast cancer [64]. The human FBXW7 gene is located at chromosome 4q31.3 and is deleted in about 30% of cancers [65]. Three isoforms exist - FBXW7α, FBXW7β, and FBXW7γ - arising from alternative splicing. Research in mouse models have shown that FBXW7 deletion causes degeneration of mammary epithelial cells, promotes malignant transformation, and increases metastatic lung nodules [66, 67]. Functionally, FBXW7 suppresses breast cancer initiation and progression by targeting multiple oncogenic proteins for ubiquitin-mediated degradation, thereby regulating cell cycle, proliferation, EMT, and metastasis. Its well-characterized substrates include NOTCH1-IC, mTOR, HIF1α, cyclin E, c-Myc, and NF-κB components, implicating FBXW7 in the control of several central signaling pathways [68-76]. Rather than acting on a single cascade, FBXW7 serves as a master regulator that simultaneously restrains oncogenic transcription factors, kinases, and survival proteins. In addition, FBXW7 has a key role in drug resistance. By promoting the degradation of resistance-related proteins such as Notch1-IC, myeloid cell leukemia-1 (MCL-1), and heat shock factor 1 (HSF1), FBXW7 enhances chemotherapy sensitivity and can reverse resistant phenotypes [77-79]. Clinically, downregulation of FBXW7 is associated with higher tumor invasiveness, reduced survival, and unfavorable prognosis across breast cancer subtypes [80]. Taken together, FBXW7 is a critical tumor suppressor that integrates multiple signaling pathways, restrains tumor progression, and modulates therapy response, making it both a promising therapeutic target and a potential prognostic biomarker.

The other FBXWs: Research on most FBXW family members in breast cancer is still limited. Several have only been preliminarily reported. For example, NUMB is a tumor suppressor that inhibits NOTCH signaling, stabilizes p53, and maintains stem cell homeostasis [81]. FBXW8 can promote BCSC differentiation by degrading NUMB [82]. Bioinformatics analysis shows that FBXW9 is upregulated in breast cancer and is associated with cancer stemness and poor prognosis [83]. p53 may be one of its important substrates.

FBXO family (F-box only with uncharacterized domains)

FBXO-type F-box proteins contain only the F-box domain and lack other domains such as LRR and WD 40. They are diverse and participate in biological processes including cell cycle regulation, apoptosis, and signal transduction.

FBXO11: FBXO11 may have dual functions in different types of breast cancer. The transcription factor Snail promotes tumor recurrence and metastasis during breast cancer progression by inducing epithelial-mesenchymal transition (EMT) [84]. In metastatic breast cancer, FBXO11 levels are inversely correlated with Snail, suggesting that FBXO11 suppresses metastasis and recurrence by ubiquitinating and degrading Snail. Conversely, in some non-EMT breast cancers, FBXO11 may act as an oncogene by suppressing the p53/p21 pathway, thereby enhancing proliferation and invasiveness [85].

FBXO15: FBXO15 exerts tumor-suppressive effects. High FBXO15 expression promotes ubiquitination and degradation of SOX2, downregulating EMT and CSC pathways and reducing invasiveness [86]. It also negatively regulates ERK and STAT3 signaling [87, 88], thereby reducing EGFR-driven oncogenic activity. Clinically, high FBXO15 expression correlates with improved survival across subtypes, suggesting its potential as an independent prognostic biomarker.

FBXO22: FBXO22 plays dual and context-dependent roles in breast cancer. In primary tumors, it is frequently upregulated, driving proliferation, colony formation, and xenograft growth, thereby supporting tumor initiation [89, 90]. In contrast, FBXO22 suppresses invasion and metastasis by promoting glycogen synthase kinase 3β (GSK3β)-dependent degradation of Snail and ubiquitination of the human homolog of mouse double minute 2 (HDM2) [90, 91]. A W52R mutation within the F-box domain of FBXO22 disrupts its normal activity and consequently enhances the invasive potential of cells. Beyond growth and metastasis, FBXO22 also influences therapy response in a subtype-specific manner. In ER-positive tumors, it remodels estrogen receptor complexes through KDM4B degradation, enhancing tamoxifen antagonism and endocrine sensitivity [92]. In triple-negative breast cancer, FBXO22 degrades KDM5A, relieving p16 repression, promoting DNA damage response, and limiting metastatic spread [10]. Thus, FBXO22 simultaneously promotes primary tumor growth while restricting EMT and therapy resistance in certain contexts.

FBXO45: A recent study revealed that FBXO45 promotes the degradation of the pro-apoptotic protein Bim in breast cancer cells, thereby enhancing cell proliferation and inhibiting apoptosis [51, 93]. Clinically, high expression levels of FBXO45 are significantly associated with poor survival in breast cancer patients. However, other researchers have suggested that FBXO45 may function as a tumor suppressor in more aggressive breast cancer subtypes, such as TNBC. DNAJB9, a member of the heat shock protein 40 family, can promote FBXO45-mediated ubiquitination and degradation of zinc-finger E-box-binding homeobox 1 (ZEB1), inhibiting the metastatic potential of TNBC [94]. Therefore, the DNAJB9-FBXO45-ZEB1 signaling axis may serve as a potential prognostic marker for metastatic breast cancer.

The other FBXOs: FBXO3 can promote PI3K/ERK-mediated breast cancer cell migration and tumor metastasis by regulating the FBXO3-USP4-Twist1 axis [95]. This effect is independent of its E3 ubiquitin ligase activity. FBXO24 mediates the ubiquitination and degradation of lysine-specific demethylase 1 (LSD1), thereby suppressing LSD1-induced tumorigenesis and functioning as a tumor suppressor in breast cancer [96, 97]. FBXO31 is downregulated in breast cancer and may act as a tumor suppressor because it is located in the 16q24.3 loss-of-heterozygosity region of breast cancer [98]. FBXO32 directly targets the zinc finger transcription factor Kruppel-like factor 4 (KLF4) and promotes its degradation [99]. This suppresses in vitro colony formation as well as the occurrence and growth of primary breast tumors in vivo [100]. Some studies suggest that FBXO1, FBXO5, FBXO16, and FBXO28 may be independent poor prognostic factors in breast cancer [101-103].

Summary of the functions of F-box proteins in breast cancer

The F-box protein family exhibits remarkable functional diversity. Some members, such as SKP2 and FBXO3, act as oncogenic factors, whereas others, including FBXW7 and FBXO24, possess tumor-suppressive activity. Additionally, certain proteins, such as FBXO11 and FBXO22, display dual roles (**Figure 3**), highlighting the complexity of their biological functions. Overall, F-box proteins are play critical roles in

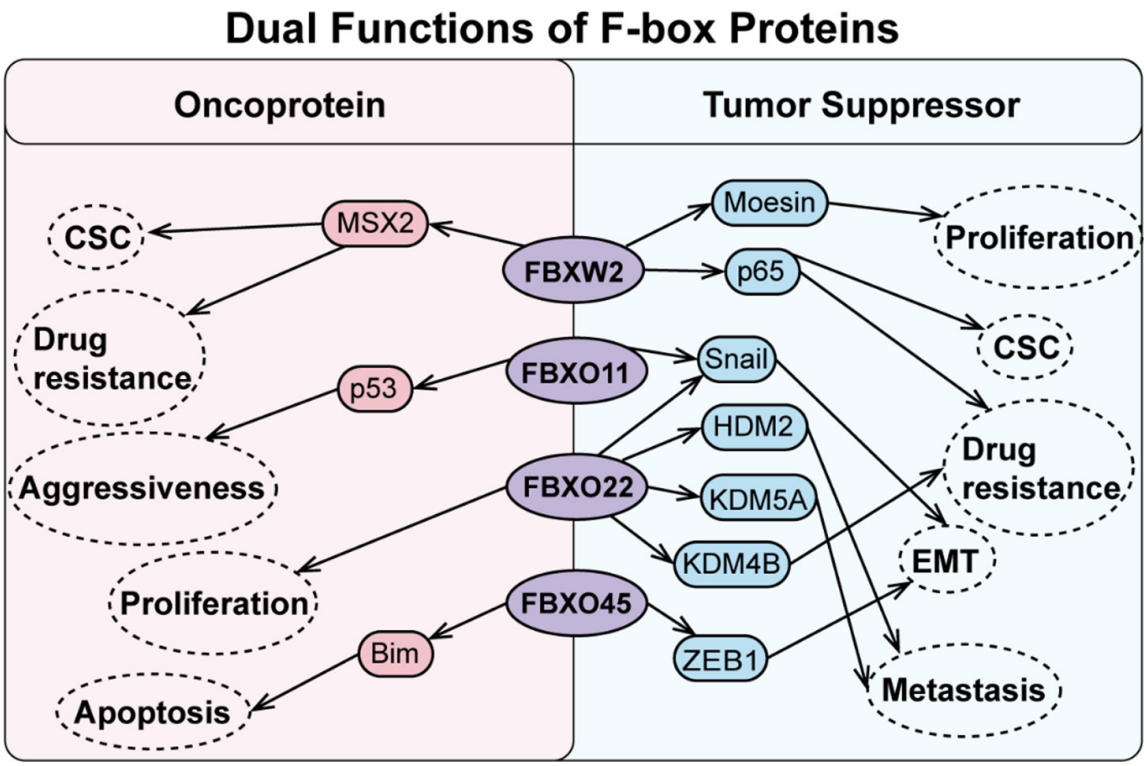

Figure 3. Dual functions of F-box proteins in breast cancer. This diagram illustrates the context-dependent dual functions of selected F-box proteins, including FBXW2, FBXO11, FBXO22, and FBXO45, which can act as either tumor suppressors or oncogenes depending on the cellular environment. Abbreviations: CSC, cancer stem cell; MSX2, Msh homeobox 2; HDM2, human double minute 2; KDM4B, histone lysine demethylase 4B; ZEB1, zinc-finger E-box-binding homeobox 1; EMT, epithelial-mesenchymal transition.

the regulation of breast cancer cell proliferation, metastasis, and drug resistance (**Table 1**).

Molecular mechanisms of F-box proteins in breast cancer

F-box proteins are involved in multiple processes of breast cancer development, including cell cycle regulation, EMT, CSC maintenance, drug resistance, and apoptosis (**Figure 4**). These diverse roles reflect the complexity of ubiquitin-mediated proteolysis in tumor progression.

Regulation of cell cycle and tumor cell proliferation

As substrate-recognition subunits of the SCF ubiquitin ligase complex, F-box proteins play a central role in maintaining cell cycle homeostasis. The orderly progression of the cell cycle depends on the dynamic regulation of cyclins and their kinases [104]. F-box proteins contribute to this process by controlling the expression and activity of these regulators through ubiquitin-mediated degradation [105].

SKP2 (FBXL1) is an oncogenic F-box protein that promotes cell cycle progression. It targets multiple cell cycle-related proteins, including P27 [106], P21 [107], P57 [108], cyclin A [109], cyclin E [109], and cyclin D1 [110]. SKP2-mediated ubiquitination of c-Myc enhances the c-Myc-driven G1/S transition [22]. In addition, FBXL12 and FBXW9 also participate in cell cycle regulation and promote tumor development.

In contrast, FBXW7 is a classical tumor-suppressive F-box protein. It recognizes and degrades multiple oncogenic factors involved in the cell cycle, thereby suppressing excessive cell proliferation [111]. Loss of FBXW7 leads to increased levels of c-Myc, cyclin G-associated kinase (GAK), cyclin E, cyclin D1, cyclin B1, and Aurora-B, all of which promote breast cancer cell cycle progression [72, 76, 112-114].

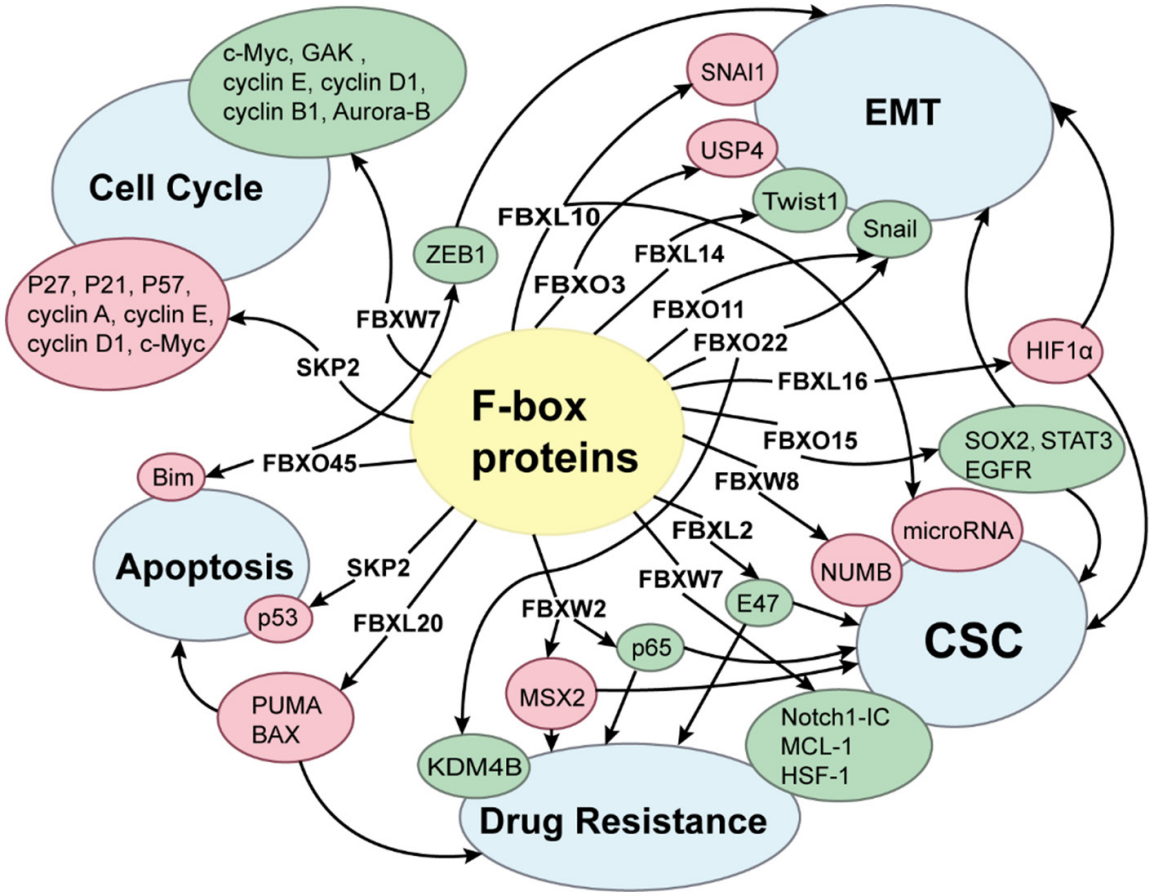

Figure 4. Functional network of F-box proteins in breast cancer. This schematic diagram illustrates the roles of various F-box proteins in key oncogenic and tumor-suppressive pathways in breast cancer. F-box proteins (center, yellow) regulate diverse biological processes, including cell cycle progression, EMT, CSC maintenance, apoptosis, and drug resistance. Arrows represent regulatory relationships. Green nodes indicate tumor-suppressive targets, while red nodes represent oncogenic targets or effects. Abbreviations: CSC, cancer stem cell; SNAI1, snail homolog 1; EMT, epithelial-mesenchymal transition; MSX2, muscle segment homeobox 2; GAK, G-associated kinase; MCL-1, myeloid cell leukemia-1; HSF-1, heat shock factor 1; USP4, ubiquitin specific peptidase 4; SOX2, sex-determining region Y-box 2; STAT3, signal transducer and activator of transcription 3; EGFR, epidermal growth factor receptor; ZEB1, zinc-finger E-box-binding homeobox 1; HIF1α, hypoxia-inducible factor 1 alpha; PUMA, p53 upregulated modulator of apoptosis; BAX, Bcl-2-associated X protein.

Regulation of EMT and breast cancer metastasis

Epithelial-mesenchymal transition (EMT) is an important biological process in breast cancer invasion and distant metastasis [115, 116]. F-box proteins influence EMT both positively and negatively through degradation of transcription factors and signaling mediators.

Some F-box proteins promote EMT. FBXL10 enhances SNAI1 activity and suppresses E-cadherin expression, which facilitates this process [41]. FBXO3 stabilizes USP4, leading to increased Twist1 expression and activation of the PI3K/ERK pathway. Through this axis, FBXO3 promotes breast cancer cell migration and metastasis [95].

In contrast, several F-box proteins act as suppressors of EMT and metastasis. FBXL14 promotes the degradation of Twist1 and reduces metastatic ability [44]. FBXL16 binds to HIF1α and induces its degradation, which blocks hypoxia-driven EMT and angiogenesis in TNBC [45]. FBXO11 and FBXO22 both destabilize Snail, thereby limiting EMT and reducing the invasive capacity of breast cancer cells [84, 90]. FBXO15 targets SOX2 for degradation, which downregulates EMT-related pathways

and decreases invasiveness [86]. FBXW7 also contributes to EMT suppression. Its loss leads to accumulation of HIF1α and IL-6Rα, which promote metastasis in patients, whereas restored expression inhibits EMT, migration, and invasion [117, 118].

Involvement in tumor stemness and drug resistance

Breast cancer stem cells (BCSCs) have self-renewal and multipotent differentiation abilities. They contribute to the initiation, progression, and drug resistance of breast cancer [29, 119]. F-box proteins play critical roles in maintaining BCSC properties and promoting drug resistance.

FBXL10 preserves BCSC self-renewal and enhances resistance to anti-estrogen therapy by regulating epigenetic states and suppressing miRNAs that target polycomb complexes PRC1 and PRC2 [35, 40]. FBXL20 promotes chemoresistance by degrading the pro-apoptotic proteins PUMA and BAX, thereby reducing sensitivity to chemotherapy [50]. FBXW8 induces BCSC differentiation through degradation of NUMB [82], while FBXW9 has been linked to cancer stemness and poor prognosis [83].

In contrast, several F-box proteins suppress stemness and drug resistance. FBXW7 degrades resistance-related proteins such as Notch1-IC, MCL-1, and HSF1, increasing sensitivity to Adriamycin [77, 120, 121], paclitaxel [78, 79], and tamoxifen [122]. FBXL2 targets the transcription factor E47, inhibiting TNBC progression and paclitaxel resistance [30]. FBXL16 regulates HIF1α, restricting CSC maintenance in TNBC and enhancing tamoxifen response in ER+ tumors [45, 47]. FBXO15 degrades SOX2, thereby limiting stemness pathways and reducing invasiveness [86].

FBXW2 plays dual roles in regulating cancer stem cell properties and drug resistance in breast cancer. By degrading MSX2, it relieves the repression of SOX2, leading to SOX2 upregulation and enhanced tamoxifen resistance [62]. In contrast, degradation of p65 by FBXW2 suppresses SOX2 activation, thereby reducing stemness and reversing paclitaxel resistance [57]. These contrasting outcomes highlight the complexity of FBXW2 activity. Further studies are required to clarify its substrate preference and regulatory functions across different breast cancer subtypes and microenvironments.

Regulation of apoptosis

Apoptosis is a fundamental biological process that maintains tissue homeostasis and prevents tumor formation. Breast cancer cells often evade programmed cell death by activating anti-apoptotic mechanisms, thereby promoting tumor growth. F-box proteins regulate the apoptotic pathway. They do so by targeting various apoptosis-related proteins for ubiquitin-dependent degradation. For instance, SKP2 suppresses the p53-PIG3 pathway, reducing apoptosis and promoting tumor development [22]. FBXL20 degrades pro-apoptotic proteins PUMA and BAX, impairing apoptosis and accelerating breast cancer progression [50]. FBXO45 targets Bim for degradation, further inhibiting cell death and enhancing tumor aggressiveness [93].

Progress in targeting F-box proteins for breast cancer therapy

Since the approval of the first proteasome inhibitor, bortezomib, for the treatment of refractory hematological malignancies, research on proteasome inhibitors as anticancer agents has attracted considerable attention [123, 124]. F-box proteins are essential components of the ubiquitin-proteasome system and regulate critical processes in breast cancer, including tumor development, metastasis, and drug resistance [17]. They are also closely associated with patient prognosis (**Table 3**). F-box proteins represent a potential breakthrough for targeted therapy of breast cancer. Therapeutic strategies targeting F-box proteins mainly include small molecule inhibitors (SMIs) and RNA interference (RNAi) (**Figure 5**). These approaches aim to interfere with oncogenic functions, improve treatment efficacy, and overcome drug resistance.

For example, the SKP2 inhibitor SMIP004 [125] was originally developed for prostate cancer. A recent study has shown that combining SMIP004 with radiotherapy significantly enhances the radiosensitivity of human breast cancer cells [21]. MLN4924 (pevonedistat), a small-molecule inhibitor of NAE, is currently in phase I/II clinical trials [126, 127]. It inhibits FBXW2, causing intracellular accumulation of

Table 3. Prognostic significance of F-box proteins in breast cancer

F-box Protein	Expression	Prognosis	Subtype	Reference
SKP2 (FBXL1)	Upregulated	Poor	All subtypes	[21, 22]
FBXL2	Downregulated	Favorable	TNBC	[30]
FBXL10	Upregulated	Poor	ER+, TNBC	[35, 39, 41]
FBXL14	Downregulated	Favorable	TNBC	[42, 44]
FBXL16	Dual (context-dependent)	Poor	ER+	[45, 47]
		Favorable	TNBC	
FBXL20	Upregulated	Poor	ER+, TNBC	[50]
FBXW2	Dual (context-dependent)	Unclear	ER+	[59, 62]
		Favorable	HER2+, TNBC	[57]
FBXW7	Downregulated	Favorable	All subtypes	[64]
FBXW8	Upregulated	Poor	ER+	[82]
FBXO3	Upregulated	Poor	HER2+, TNBC	[95]
FBXO11	Dual (context-dependent)	Poor	ER+	[85]
		Favorable	TNBC	[84]
FBXO15	Downregulated	Favorable	All subtypes	[86]
FBXO22	Dual (context-dependent)	Unclear	ER+, TNBC	[10, 90-92]
FBXO24	Downregulated	Favorable	All subtypes	[96]
FBXO32	Downregulated	Favorable	ER+	[100]
FBXO45	Dual (context-dependent)	Poor	ER+	[93]
		Unclear	TNBC	[93, 94]

Note: Abbreviations: ER+, estrogen receptor positive; HER2+, human epidermal growth factor receptor 2-positive; TNBC, triple-negative breast cancer.

the transcription factor MSX2. This suppresses SOX2 expression, reduces the stemness of breast cancer cells, and increases their sensitivity to tamoxifen treatment [62]. Another study suggested that MLN4924 may selectively inhibit FBXW8 [82]. FBXW7 has multiple oncogenic targets and functionally heterogeneous isoforms. No direct inhibitors targeting FBXW7 have been developed. However, restoring FBXW7 expression via upstream miRNAs, such as miR-27a antagonist Compound 9, can enhance chemotherapy sensitivity [128, 129]. In aggressive breast cancer, the natural product honokiol downregulates miR-188-5p, promoting FBXW7-mediated degradation of c-Myc and reversing adriamycin resistance [130]. Abnormal activation of protein kinase C (PKC) and polo-like kinase 1/2 (PLK1/2) signaling suppresses FBXW7 expression [131, 132]. The PKC inhibitor J-4 and the PLK1/2 inhibitor onvansertib are in preclinical and clinical trials respectively [133, 134]. Both can restore the tumor suppressor function of FBXW7 in breast cancer by inhibiting their respective targets.

In summary, therapeutic strategies targeting F-box proteins in breast cancer are diverse, including drugs and techniques that directly target the protein itself, as well as interventions aimed at upstream and downstream targets in its regulatory network (**Table 4**). In recent years, proteolysis targeting chimera (PROTAC) technology has emerged as a research hotspot [135-138]. It involves constructing a small molecule chimera in which one end contains a ligand recognized by an E3 ligase, and the other end specifically binds the target protein. These ends are connected by a specially designed linker [139]. Because F-box proteins and their recognizable ligands are abundant, PROTACs offer high design flexibility and diverse targeting potential, allowing them to degrade proteins considered undruggable. Compared with SMIs, PROTAC technology has advantages such as strong selectivity, low toxicity, and high bioavailability [135, 140]. It could represent a new class of therapeutics for cancer treatment.

Conclusions

F-box proteins, as substrate-recognition subunits of the SCF E3 ubiquitin ligase, play multifaceted roles in breast cancer [15, 18]. They regulate the cell cycle, EMT, stemness, apopto-

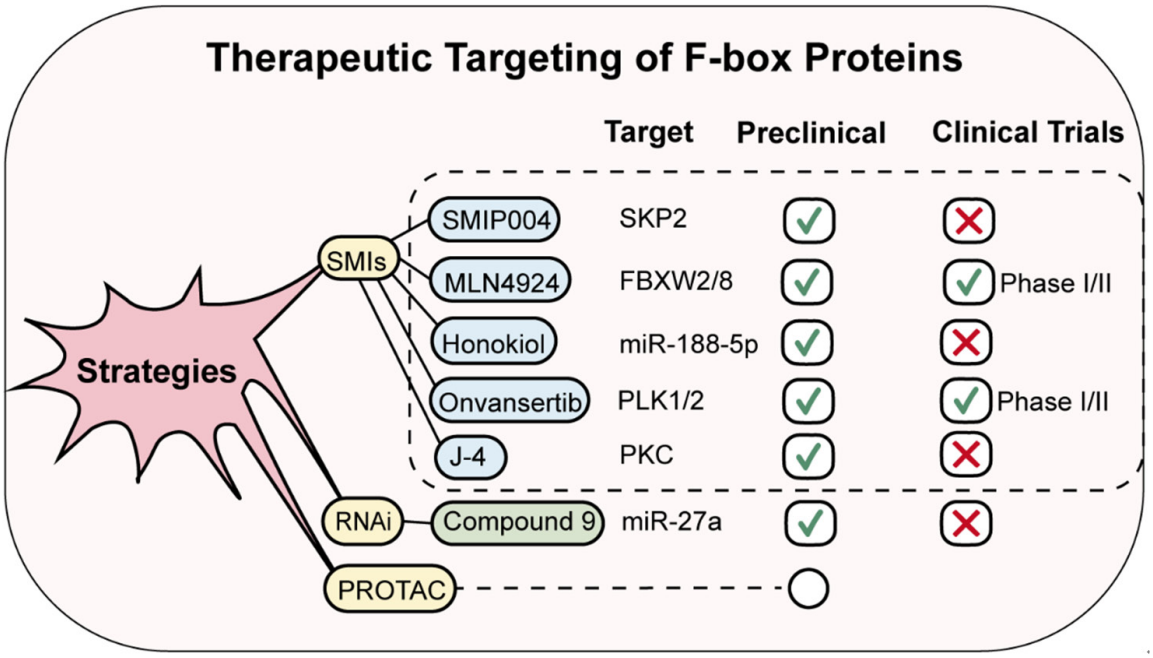

Figure 5. Therapeutic strategies targeting F-box proteins. This figure presents a schematic overview of therapeutic strategies targeting F-box proteins, including SMIs, RNAi, and PROTACs. Recently, there are no direct inhibitors targeting FBXW7 that have been developed. Honokiol and Compound 9 indirectly upregulate FBXW7 by targeting its upstream regulatory microRNAs, miR-188-5p and miR-27a, respectively, thereby suppressing breast cancer progression. Onvansertib and J-4 inhibit PLK1/2 and PKC respectively, restoring FBXW7 expression in breast cancer. In the figure, "√" indicates that relevant studies have been conducted or the approach has entered the corresponding stage. "×" indicates that it has not yet entered that stage. "O" indicates that it is currently being studied. Abbreviations: SMIs, small molecule inhibitors; RNAi, RNA interference; PROTAC, proteolysis targeting chimera; PLK1/2, polo-like kinase 1/2; PKC, protein kinase C.

Table 4. Therapeutic strategies targeting F-box proteins in breast cancer

Target Protein	Strategy	Mechanism	Development Stage	Reference
SKP2 (FBXL1)	SMIP004	Direct SKP2 inhibition	Preclinical	[21, 125]
FBXW2/8	MLN4924 (Pevonedistat)	Direct FBXW2/8 inhibition	Clinical trials (phase I/II)	[62, 82, 126, 127]
PLK1/2	Onvansertib	Targets PLK1/2 to restore FBXW7 expression indirectly	Clinical trials (phase I/II)	[64, 134]
PKC	J-4	Targets PKC to restore FBXW7 expression indirectly	Preclinical	[64, 133]
miR-188-5p	Honokiol (natural product)	Targets upstream regulatory miR-188-5p to upregulate FBXW7 indirectly	Preclinical	[130]
miR-27a	Compound 9 (RNAi)	Targets upstream regulatory miR-27a to upregulate FBXW7 indirectly	Preclinical	[128, 129]

Note: Abbreviations: PLK1/2, polo-like kinase 1/2; PKC, protein kinase C; RNAi, RNA interference.

sis, and drug resistance, thereby influencing tumor progression and treatment outcomes. Importantly, their expression and function differ markedly among molecular subtypes, leading to context-dependent oncogenic, tumor-suppressive, or dual roles (**Figure 2**).

Clinical translation is progressing but remains in its infancy. SMIP004 has shown radiosensitizing effects in breast cancer models, supporting the therapeutic rationale for targeting SKP2. MLN4924 and onvansertib are already under Phase I/II evaluation. Other candidates such as honokiol, J-4, and Compound 9 are still preclinical but provide proof of concept for modulating F-box regulatory networks. These developments underscore that F-box proteins are becoming tangible therapeutic targets,

though dedicated breast cancer-specific trials are still limited.

Biomarker potential is also noteworthy. High SKP2 expression predicts poor survival and therapy resistance, while FBXW7 downregulation correlates with metastasis, recurrence, and reduced chemosensitivity. Other proteins, including FBXL10, FBXL16, and FBXO22, have been implicated in endocrine therapy resistance or subtype-specific progression. These findings suggest that F-box proteins may serve as prognostic and predictive biomarkers. However, prospective validation in large clinical cohorts is needed before clinical application.

Major challenges remain. F-box proteins lack traditional catalytic pockets, making drug design difficult, and many exhibit subtype-dependent dual roles. Moreover, their substrate networks are incompletely understood. Future efforts should focus on: (1) multi-omics integration for precise target identification; (2) rational drug design through high-throughput and structure-based screening; (3) development of new PROTACs with improved selectivity and bioavailability; and (4) combination strategies that integrate F-box targeting with chemotherapy and radiotherapy to overcome resistance and relapse.

In conclusion, F-box proteins are emerging as promising biomarkers and therapeutic targets in breast cancer. Translational advances, such as SMIP004 radiosensitization and MLN4924 clinical trials, highlight their potential impact. With further mechanistic clarification and clinical validation, targeting F-box proteins is expected to become an important part of future breast cancer treatment strategies, ultimately improving prognosis and patient quality of life.

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Disclosure of conflict of interest

None.

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