Functional characterization of FBXL7 as a novel player in human cancers

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F-box and leucine-rich repeat protein 7 (FBXL7), an F-box protein responsible for substrate recognition by the SKP1-Cullin-1-F-box (SCF) ubiquitin ligases, plays an emerging role in the regulation of tumorigenesis and tumor progression. FBXL7 promotes polyubiquitylation and degradation of diverse substrates and is involved in many biological processes, including apoptosis, cell proliferation, cell migration and invasion, tumor metastasis, DNA damage, glucose metabolism, planar cell polarity, and drug resistance. In this review, we summarize the downstream substrates and upstream regulators of FBXL7. We then discuss its role in tumorigenesis and tumor progression as either an oncoprotein or a tumor suppressor, and further describe its aberrant expression and association with patient survival in human cancers. Finally, we provide future perspectives on validating FBXL7 as a cancer biomarker for diagnosis and prognosis and/or as a potential therapeutic target for anticancer treatment.

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FACTS

- FBXL7 is involved in the regulation of many biological processes by targeting diverse substrates for polyubiquitylation and subsequent degradation via proteasome.
- FBXL7 plays an emerging role in the regulation of tumorigenesis and tumor progression.
- FBXL7 expression is controlled by several factors at the transcriptional, post-transcriptional, and post-translational levels.
- Alterations in FBXL7 expression found in human cancers are associated with tumor progression, patient survival, and drug resistance.

OPEN QUESTIONS

- How FBXL7 promotes tumorigenesis and tumor progression in certain cancer types, given that the substrates identified thus far are mainly oncoproteins?
- What are the upstream signalings/kinases responsible for substrate phosphorylation to promote FBXL7-mediated substrate degradation, thereby regulating biological processes, including tumorigenesis?
- What is the role of FBXL7, either as an oncoprotein or as a tumor suppressor, in tumorigenesis under in vivo physiological settings?
- Does FBXL7 serve as a cancer biomarker for diagnosis and prognosis and/or as a potential therapeutic target for anticancer treatment?

INTRODUCTION

Proteolysis via the ubiquitin-proteasome system (UPS) is required to maintain protein homeostasis in eukaryotic cells. By targeting proteins for polyubiquitylation and subsequent degradation by the 26S proteasome, the UPS precisely regulates many physiological and pathological processes, including cell cycle regulation, apoptosis, genomic stability, signal transduction, development, immune response, and tumorigenesis [1–4]. Protein ubiquitylation, a process that covalently attaches a polyubiquitin chain to a substrate, is a three-step enzymatic cascade reaction sequentially catalyzed by E1 ubiquitin-activating enzymes, E2 ubiquitin-conjugating enzymes, and E3 ubiquitin-conjugating enzymes, and E3 ubiquitin ligases. Of the more than 600 ubiquitin ligases, cullin-RING ligases (CRLs) are one of the largest families and mediate approximately 20% of cellular protein degradation via the UPS [5–7]. CRL1, a well-studied member of CRLs and also known as SKP1-Cullin-1-F-box protein (SCF), comprises cullin-1, a scaffold protein, RBX1, a RING protein, S-phase-kinase-associated protein 1 (SKP1), an adaptor protein, and F-box protein, a substrate recognition receptor [8]. F-box proteins, characterized by a conserved F-box motif of 42–48 amino acid, bind to the adaptor protein SKP1 for the assembly of SCF ligase complexes [9, 10]. There are ~70 F-box proteins encoded by the human genome, which are further classified into three subfamilies.
SUBSTRATES OF FBXL7

As a component of the SCF<sub>FBXL7</sub> ligase, FBXL7 plays a key role in the recognition, recruitment, and binding of diverse substrates for targeted ubiquitination and degradation, thus regulating cell cycle progression [16, 21, 22], apoptosis [16, 18, 20], cell migration, invasion, metastasis [23, 24], glucose metabolism [25], DNA damage [26], and drug resistance [33–35] (Fig. 2).

Aurora A

Aurora A, a key player in the formation of mitotic spindle and chromosome segregation, was the first substrate of FBXL7 identified in 2012 [16]. Of 18 F-box proteins, including nine FBXL and nine FBXW subfamily members, FBXL7 was the only one that reduced the protein level of Aurora A upon overexpression in transformed murine lung epithelial cells [16]. Overexpression of FBXL7 promotes the polyubiquitylation and turnover of Aurora A in a time- and dose-dependent manner, but has no effects on its family member Aurora B, which shares 71% sequence identity with Aurora A, indicating the specificity of substrate recognition by FBXL7 [16]. FBXL7 colocalizes with Aurora A and targets it for degradation on the centrosome during mitosis [16]. Biologically, FBXL7 ectopic expression disrupts mitotic spindle formation and induces polyploidy, leading to G2/M arrest and apoptosis [16]. Interestingly, Aurora A inhibits FBXL7 transcription in gastric cancer cells [33]. Thus, the crosstalk between Aurora A and FBXL7 may precisely control cell cycle progression.

Survivin

Survivin, one of the inhibitor of apoptosis (IAP) family members, plays a critical role in apoptosis inhibition and mitosis progression. The expression level of Survivin is elevated in a variety of cancers and is associated with worse prognosis and chemotherapeutic resistance [44, 45]. FBXL7 was identified as a ubiquitin ligase that mediates polyubiquitylation of Survivin to promote its degradation, causing mitochondrial dysfunction and apoptosis [20]. Survivin binds to FBXL7 with the help of its Glu126 residue. Mutation of Glu126 to alanine not only abolished the binding ability of Survivin to FBXL7 but also markedly increased its stability [20]. Overexpression of wild-type Survivin or the FBXL7 binding mutant (E126A) remarkably rescued mitochondrial dysfunction caused by FBXL7 [20]. In addition, Thr34 appears to be critical for FBXL7-mediated Survivin turnover as well [34]. Conversely, mutation of Thr34 to alanine promotes Survivin polyubiquitylation and shortens its protein half-life upon treatment with xanthohumol, a natural compound that substantially inhibits the survival of oral squamous cell carcinoma (OSCC) cells [34]. Moreover, xanthohumol suppresses Thr34 phosphorylation by inhibiting AKT activation to promote FBXL7-mediated Survivin destabilization, leading to apoptosis [34]. It is well-known that phosphorylation of substrates is crucial for them to be recognized by and bind to F-box protein [13], but how Thr34 dephosphorylation induces Survivin degradation mediated by FBXL7 remains unknown.

Consistently, FBXL7 contributes to xanthohumol-mediated inhibition of OSCC xenograft tumor growth by targeting Survivin degradation [34]. Furthermore, FBXL7-mediated ubiquitylation and degradation of Survivin are regulated by Aurora A [33]. VX-880, a small molecular inhibitor of Aurora A, reduces Survivin levels in a proteasome-dependent manner, indicating that FBXL7-mediated Survivin degradation relies on the kinase activity of Aurora A [33]. Mechanistically, as mentioned above, Aurora A activation represses FBXL7 transcriptional expression causing Survivin accumulation, thus contributing to gastric cancer cell growth and resistance to doxorubicin [33].

**c-SRC**
The Src family kinase c-SRC, a non-receptor-type tyrosine kinase, plays a critical role in tumor progression and metastasis [46, 47]. Recently, c-SRC was identified as a substrate for SCF<sub>FBXL7</sub> ubiquitin ligase [24]. FBXL7 recognizes c-SRC upon its phosphorylation at Ser104 within its SH3 domain (a.a.102–116), and then targets the active c-SRC for polyubiquitylation and degradation [24]. Silencing of FBXL7 upregulates c-SRC levels, activates downstream signaling cascades, and subsequently induces the expression of mesenchymal markers to promote EMT, leading to the induction of cell motility, migration, and invasion, which can be reversed by c-SRC inhibition or depletion [24, 48]. More importantly, FBXL7 depletion strikingly increased the metastasis of pancreatic and prostate cancer cells in multiple orthotopically transplanted mouse models in a manner dependent of c-SRC [24]. Consistently, the expression level of FBXL7 is negatively correlated with the expression of c-Src in human prostate and pancreatic carcinoma tissues [24]. Furthermore, some point mutations in FBXL7 that cause the inability to degrade c-Src, were identified in various human cancers [24]. Hence, FBXL7 plays a tumor-suppressive role in preventing tumor progression, particularly metastasis, by promoting c-SRC degradation.

**Snail1**
Snail1, also known as Snail, belongs to the Snail superfamily of zinc-finger transcription factors and is characterized by four consensus zinc-finger motifs responsible for Snail1 binding to the E-box motifs to regulate the transcription of downstream target genes involved in EMT, including E-cadherin, TWIST, ZEB1, collagens, fibronectin, and matrix metalloproteinases [49, 50]. As one of the critical promoting factors of EMT, the turnover of Snail1 is tightly governed by several F-box proteins in some specific cancers, including β-TrCP [51, 52] and FBXO22 [53] in breast cancer cells, FBXO14 [54] and FBXO11 [55, 56] in both breast and colon cancer cells, FBXL5 [57, 58] in breast cancer, colon cancer, gastric cancer, and pancreatic cancer cells, FBXO31 [59] in gastric cancer cells, FBXO45 [60] in prostate cancer cells, and FBXO11 [56] and FBXW7 [61, 62] in lung cancer cells. In human pancreatic cancer BxPC-3 and PAN-1 cells, FBXL7 interacts with Snail1 and promotes its ubiquitylation and degradation via proteasome to suppress EMT, thereby repressing cell migration and invasion. Silencing FBXL7 increases Snail1 levels and tumor metastasis in vivo [23]. Surprisingly, FBXL7 expression in pancreas appears to be lower than that in other specific tissues, where Snail1 is targeted by other E3 ligases, including colon, breast, prostate, and lung tissues (https://www.proteinatlas.org). However, FBXL7 expression both at mRNA and protein levels in pancreatic cancer specimens was further lower than that in matched tumor-adjacent tissues [23]. Interestingly, compared with their corresponding normal tissues, FBXL7 expression is significantly lower in colon adenocarcinoma, lung adenocarcinoma, lung squamous cell carcinoma, and prostate adenocarcinoma (Fig. 3), implying its potential regulation of Snail1 turnover in these specific cancer tissues. However, silencing FBXL7 had no evident effect on the protein levels of Snail1 in either SW620 colon cancer cells or MCF-7 breast cancer cells [57], indicating that FBXL7-mediated Snail1 turnover likely occurs in a manner dependent of specific cell context.

**TACC2**
Transforming acidic coiled-coil-containing protein 2 (TACC2), one of the TACC family members consisting of a conserved TACC domain at the C-terminus, plays a key role in the regulation of centrosome and microtubule dynamics during mitosis [63]. High TACC2 expression found in human cancers, including breast cancer [64], hepatocellular carcinoma [65], and prostate cancer [66], is correlated with poor prognosis, suggesting its tumor-promoting potential. Recently, compared with the smokers without chronic obstructive pulmonary disease (COPD), TACC2 protein levels were found to be reduced in the lung tissues of smokers with COPD [26]. TACC2 plays a key role in protecting lung epithelial cells from DNA damage and cell death induced by cigarette smoke extract. Mechanistically, cigarette smoke exposure increased the phosphorylation of TACC2 at Ser304/399 and...
The expression levels of FBXL7 between human tumor tissues and their corresponding normal tissues. The levels of FBXL7 transcripts are markedly altered in various human cancer tissues, compared to their corresponding normal controls, based on the analysis of Gene Expression Profiling Interactive Analysis (GEPIA) database with tumor and normal tissue samples from The Cancer Genome Atlas (TCGA) and Genotype-Tissue Expression (GTEx) projects. The number of tumor (T) and normal (N) tissues is indicated. BLCA, bladder urothelial carcinoma; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; COAD, colon adenocarcinoma; GBM, glioblastoma multiforme; KICH, kidney chromophobe; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; OV, ovarian serous cystadenocarcinoma; PAAD, pancreatic adenocarcinoma; PCPG, pheochromocytoma and paraganglioma; PARD, prostate adenocarcinoma; READ, rectum adenocarcinoma; SARC, sarcoma; THCA, thyroid carcinoma; THYM, thymoma; UCEC, uterine corpus endometrial carcinoma; UCS, uterine carcinosarcoma. TPM: transcripts per million; *p < 0.05, one-way ANOVA.

REGULATION OF FBXL7

Several studies have shown that FBXL7 expression is controlled by various factors at the transcriptional, post-transcriptional, and post-translational levels (Fig. 2).

Transcriptional regulation
Promoter methylation plays a crucial role in the regulation of FBXL7 expression. Among the 69 genes encoding human F-box proteins, FBXL7 promoter is the most hypermethylated in tumor tissues, based on the analysis of pan-cancer promoter methylation using MethHC and TCGA databases [24]. Hypermethylation of FBXL7 promoter correlates with downregulation of FBXL7 levels and advanced tumor grade in both pancreatic carcinoma and prostate cancer [24, 48]. More importantly, decitabine, an inhibitor of methylase, restores FBXL7 expression levels and inhibits cell migration and invasion, and tumor metastasis in an FBXL7-
dependent manner [24]. Thus, epigenetic suppression of FBXL7 by promoter methylation is an important mechanism for down-regulating the expression of FBXL7, leading to tumor progression and metastasis [24].

In addition, FBXL7 expression level is controlled by transcription factors Forkhead Box protein P1 (FOXP1) [33] and Forkhead Box protein A2 (FOXA2) [25]. Specifically, FOXP1 is recruited to multiple sites within the promoter region of FBXL7 and transactivates the expression of FBXL7 in gastric cancer cells [33]. FOXP1-mediated FBXL7 transcriptional activation is negatively regulated by Aurora A [33]. Aurora A binds to FOXP1 at the FBXL7 promoter and appears to phosphorylate FOXP1 at multiple putative phosphorylation sites, including S440 in its transactivating domain, resulting in the repression of FBXL7 transcription [33]. Given that FBXL7 is a subunit of ubiquitin ligase complex that targets Aurora A for degradation [16], and that Aurora A downregulates FBXL7 via FOXP1, it establishes a feed-forward loop. Thus, downregulation of FBXL7 may contribute to the overexpression of Aurora A, which is associated with worse prognosis in gastric cancer [33]. Moreover, FBXL7 repression by the Aurora A-FOXP1 axis further suppresses FBXL7-mediated Survivin ubiquitylation and subsequent degradation via proteasome, resulting in drug resistance in gastric cancer cells [33]. In addition to FOXP1, another Forkhead Box protein A2 (FOXA2) appears to regulate FBXL7 expression [25]. The protein levels of FBXL7 increased in cells overexpressing FOXA2, but decreased upon silencing of FOXA2. However, whether FOXA2 positively regulates FBXL7 at the transcriptional level requires further investigation, given that FOXA2 can interact with FBXL7 [25]. Taken together, FBXL7 expression is transcriptionally regulated by promoter methylation and transcription factors.

Post-transcriptional regulation

Several microRNAs, including miR-152-5p [17], hsa-miR-520g-3p [42], and mmu-miR-1936 [43], are associated with FBXL7 expression. miR-152-5p represses luciferase reporter activity mediated by FBXL7 mRNA 3′-UTR, thereby negatively regulating FBXL7 expression [17]. Overexpression of FBXL7 almost completely reversed the inhibition of glioma cell proliferation, migration, invasion, and enhanced glioma cell sensitivity to the anti-glioma drug temozolomide by miR-152-5p overexpression [17]. The levels of miR-152-5p were gradually downregulated, whereas FBXL7 expression was gradually upregulated with an increase in tumor grade in glioma tissues [17]. Moreover, the levels of miR-152-5p were inversely correlated with FBXL7 levels in advanced glioma tissues [17]. Therefore, the miR-152-5p-FBXL7 axis appears to play a significant role in glioma progression and in the efficacy of chemotherapeutic drugs. In addition, FBXL7 was identified as a hub gene involved in the pathogenesis of Parkinson’s disease, its expression being higher in the substantia nigra tissues of Parkinson’s disease, compared to that in normal controls [42]. FBXL7 mRNA levels are markedly associated with IncRNA KCNQ1OT1 predicted to target FBXL7 mRNA via hsa-miR-520g-3p based on the construction of a competing endogenous RNAs (ceRNA) network associated with Parkinson’s disease by database analysis [42]. Similarly, FBXL7 was also predicted to be a target of mmu-miR-1936, one of the three substantially upregulated miRNAs identified by bioinformatics analysis in mice with form-deprivation myopia [43], implying a potential role of FBXL7 in myopia development.

Post-translational regulation

Only a few lines of evidence have documented the post-translational modifications of FBXL7, including ubiquitylation [18] and N-myristoylation [73]. FBXL7 does not undergo auto-ubiquitylation, whereas FBXL18 can mediate the ubiquitylation of FBXL7 at Lys109 (Fig. 1), leading to its degradation via the 26S proteasome [18]. Moreover, the N-terminal QFO motif of FBXL7 is essential for its binding to FBXL18 and its degradation, but is dispensable for its ability to form an SCF ligase complex via binding to SKP1 and to destabilize the substrate (Fig. 1) [18]. Biologically, simultaneous silencing of FBXL7 largely reverses apoptosis induction by FBXL18 knockdown [18]. Thus, FBXL7 is a substrate of the SCF<sub>FBXL18</sub> ligase. In addition, by the systematic proteomics analysis of the binding proteins of the FBXL family, FBXL7 was found to interact with three deubiquitylases: USP1, USP12, and USP46 [72], implying that they may stabilize FBXL7 via deubiquitylation. Besides ubiquitylation, FBXL7 was identified to be N-myristoylated [73]. Protein N-myristoylation, a lipid modification, is a process of attaching myristate to the glycine residue of the substrate protein at its N-terminus, which plays a crucial role in the subcellular localization of substrates, signal transduction, immune response, and tumorigenesis [74, 75]. However, further studies are needed to clarify the biological impact of N-myristoylation on FBXL7.

FUNCTIONS OF FBXL7 AND ITS ALTERATION IN HUMAN CANCERS

FBXL7 is abnormally expressed in various cancers, including ovarian [35], pancreatic [23, 24], prostate [24], and brain cancers [17]. The single nucleotide polymorphism (SNP) rs12652447 of FBXL7 is relevant to an increased risk of breast cancer in people carrying breast cancer gene 2 (BRCA2) mutations in breast cancer genome-wide association studies [76]. Moreover, FBXL7 was predicted to be associated with lung tumorigenesis using computational methods [77].

FBXL7 exhibits tumor-suppressive characteristics by mediating degradation of several oncogenic substrates. As mentioned above, overexpression of FBXL7 suppresses cell proliferation and causes apoptosis through destabilizing Aurora A and Survivin in lung cancer cells [16, 20]. FBXL7 knockdown promotes cell migration, invasion, and tumor metastasis via c-Src accumulation in pancreatic and advanced prostate cancers [24]. Moreover, FBXL7 can negatively regulate pancreatic cancer cell migration and invasion via targeting Snail1 for degradation [23]. Consistently, lower FBXL7 expression resulting from promoter hypermethylation predicts worse survival in patients with prostate and pancreatic cancers [24]. Additionally, both mRNA and protein levels of FBXL7 were found to be reduced in pancreatic cancer tissues, compared to those in the corresponding tumor-adjacent normal tissues [23]. To fully understand the alteration of FBXL7 expression level in human cancers, we compared its mRNA levels in human cancer tissues with those in normal tissues using the GEPIA database (http://geopia.cancer-pku.cn/) [78]. As shown in Fig. 3, FBXL7 mRNA levels were substantially decreased in the majority of cancers, including bladder urothelial carcinoma, cervical squamous cell carcinoma and endocervical adenocarcinoma, colon adenocarcinoma, kidney chromophobe, lung adenocarcinoma, lung squamous cell carcinoma, ovarian serous cystadenocarcinoma, pheochromocytoma and paraganglioma, prostate adenocarcinoma, rectum adenocarcinoma, thyroid carcinoma, uterine corpus endometrial carcinoma, and uterine carcinosarcoma. Additionally, the human FBXL7 gene displays rare sporadic mutations in various carcinomas of the lung, breast, liver, stomach, pancreas, large intestine, colon, rectum, and prostate [24]. Some of these mutants disabled FBXL7 to degrade substrates, including 1) P655, P93L, and R310H, which are unable to bind to the substrate, and 2) Q271H, R353Q, T458M, R480H, R480C, and Y145*, which cannot bind to CUL1 and/or SKP1 to form a functional SCF ligase complex [24]. Thus, the downregulation or dysfunction of FBXL7 may cause the accumulation of substrates, promoting tumorigenesis and tumor progression. In contrast, in ovarian cancer patients, higher levels of FBXL7 transcripts correlate with worse overall survival and progression-free survival and also predict a higher risk of recurrence after
adjuvant chemotherapy [35]. Immunohistochemical staining also confirmed that the protein levels of FBXL7 were inversely correlated with the overall survival of ovarian cancer patients [35]. More importantly, FBXL7 levels are markedly correlated with paclitaxel resistance in ovarian cancer cells [35]. Moreover, FBXL7 level negatively correlates with the progression and survival of patients with glioma [17]. FBXL7 mRNA levels gradually increased with increasing glioma grade. FBXL7 silencing inhibits proliferation, migration, and invasion of glioma cells and sensitizes glioma cells and ovarian cancer cells resistant to chemotherapeutic drugs [17, 35]. Thus, FBXL7 may serve as a biomarker for poor prognosis and may be a therapeutic target for patients with glioma and ovarian cancer, particularly those who have undergone chemotherapy. Furthermore, we determined the association between FBXL7 expression and overall survival using the Human Protein Atlas database. As shown in Fig. 4, patients with higher levels of FBXL7 displayed a worse overall survival in various cancers, including colon adenocarcinoma, rectum adenocarcinoma, stomach cancer, head and neck cancer, liver cancer, thyroid cancer, lung cancer, and urothelial cancer, but better survival only in kidney renal clear cell carcinoma, implying the oncogenic characteristics of FBXL7.

CONCLUSION AND FUTURE PERSPECTIVES

In conclusion, FBXL7 plays an important role in the regulation of many biological processes via targeting polyubiquitylation and degradation of diverse substrates (Fig. 2). Alterations in FBXL7 expression in human cancers and its association with tumor metastasis, patient survival, and drug resistance imply that FBXL7 may function as either an oncoprotein or a tumor suppressor. Given that the substrates identified thus far are mainly oncoproteins, the mechanism by which FBXL7 promotes tumorigenesis and tumor progression in certain cancer types is unclear. Thus, it is important to identify additional specific substrates of FBXL7, particularly those critical for the regulation of tumorigenesis, to fully understand the context-dependent roles of FBXL7 in certain cancer types. Additionally, since phosphorylation plays a crucial role in substrate recognition by FBXL7 [24, 26, 34], similar to other F-box proteins [13], exploring the upstream signaling/kinase responsible for substrate phosphorylation would help uncover the mechanisms by which FBXL7 regulates many biological processes, including tumorigenesis. Furthermore, the downregulation of FBXL7 expression in some cancers, including colon adenocarcinoma, lung cancer, ovarian cancer, rectum adenocarcinoma, and thyroid cancer, appears to be paradoxical with the survival analysis showing that higher FBXL7 levels predict a worse prognosis (Figs. 3 and 4). Thus, it is critical to clarify the causal role of FBXL7 in tumorigenesis under in vivo physiological settings. To date, no studies using FBXL7 total knockout or conditional knockout mice have been published, although it has been known that Drosophila harboring Fbxl7 loss-of-function mutations are viable and fertile and show a growth advantage [31]. Studies using genetically modified mouse tumor models that combine FBXL7 knockout mice with oncogene activation (such as KrasG12D) or tumor suppressor inactivation (such as Trp53fl/fl, Ptenfl/fl, or tumor suppressor loss-of-function mutations) are in high demand to elucidate the physiological roles of FBXL7, either as an oncprotein or as a tumor suppressor. Moreover, since the accumulated evidence mainly supports a tumor-suppressive role of FBXL7, a better exploitation of the upstream regulation might provide potential strategies to activate FBXL7 pathway for anticancer treatment. Indeed, increasing FBXL7 levels by decitabine, an FDA-approved histone methylase inhibitor, was able to inhibit metastasis in orthotopically transplanted mouse models of prostate and pancreatic cancer with low FBXL7 levels due to promoter hypermethylation [24]. Another potential approach is to use synthetic lethal strategies to target specific cancers with FBXL7 loss-of-function mutations or decrease in its expression.
levels. For instance, it is worth exploring whether the inhibitors of Aurora A, a negative regulator of FBXL7 expression in gastric cancer cells [33], would lead to synthetic lethality in gastric cancer with decreased FBXL7 expression/function. Taken together, further investigations on FBXL7 and its mechanisms of action are required to determine FBXL7 as a cancer biomarker for diagnosis and prognosis and/or as a potential therapeutic target for anticancer treatment.

DATA AVAILABILITY

Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

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AUTHOR CONTRIBUTIONS

YW and XS performed literature searches and drafted the manuscript. LG revised the manuscript. YZ and XX conceptualized, and finalized the manuscript. All authors have read and approved the final manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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