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Recent advances in SCF ubiquitin ligase complex: clinical implications

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Abstract

F-box proteins, which are subunit recruiting modules of SCF (SKP1-Cullin 1-F-box protein) E3 ligase complexes, play critical roles in the development and progression of human malignancies through governing multiple cellular processes including cell proliferation, apoptosis, invasion and metastasis. Moreover, there are emerging studies that lead to the development of F-box proteins inhibitors with promising therapeutic potential. In this article, we describe how F-box proteins including but not restricted to well-established Fbw7, Skp2 and β-TRCP, are involved in tumorigenesis. However, in-depth investigation is required to further explore the mechanism and the physiological contribution of undetermined F-box proteins in carcinogenesis. Lastly, we suggest that targeting F-box proteins could possibly open new avenues for the treatment and prevention of human cancers.

Keywords

F-box protein; Ubiquitin; Tumor suppressor; Oncoprotein; Human cancer

1. Introduction

The UPS (ubiquitin-proteasome system) governs the degradation of target proteins and plays critical roles in multiple cellular processes including cell proliferation, apoptosis, migration, invasion and cell cycle [1]. It has been known that conjugation of ubiquitin to the targeted

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

substrates and subsequent degradation of the ubiquitinated proteins are two processes in governing protein degradation [2]. There are three enzymes including the ubiquitin-activating enzyme (E1), the ubiquitin-conjugating enzyme (E2), and the ubiquitin ligase (E3) to catalyze these reactions. Specifically, ubiquitin molecules are activated by the E1 enzyme via utilizing ATP and then transferred to the E2 enzyme, and subsequently recruited into the E3 ligases. The E3 complex binds to substrate proteins and further leads to their degradation by the 26S proteasomes [2] (Figure 1). It is acceptable that the substrate specificity for ubiquitination is largely controlled by E3 ligases. Among approximately 600 E3 ligases, they are characterized as multiple families according to their protein sequence homology including the HECT (Homologous to the E6-AP Carboxyl Terminus) family, the RING (Really Interesting New Gene) finger family and the REB (Ring-between-ring) family [3-5].

Among the RING type of E3 ligases, the SCF (Skp1-Cullin1-F-box) complex has been well studied. It has been identified that the SCF complex consists of the scaffold protein Cullin1, the RING finger protein Rbx1, the linker protein Skp1 (S phase kinase associated protein 1), and F-box protein [4] (Figure 2). The function of Rbx1 is to recruit the E2 enzyme, while Skp1 binds to F-box proteins. F-box proteins often recognize substrates when they are properly modified, most of cases involving phosphorylation of the degron motif within the specific substrate, and then recruit the substrates to the SCF complex for ubiquitination [6]. It has been identified that there are 69 F-box proteins in human genome [7, 8]. Based on the substrate binding domains, F-box proteins are characterized as three major subfamilies: the FBXW (F-box with the WD40 motif), FBXL (F-box with the LRR motif), and the FBXO (F-box only) subfamily [8]. These F-box proteins target a wide range of substrates for ubiquitination and destruction and subsequently regulate cellular processes such as cell cycle, cell proliferation, apoptosis, angiogenesis, and metastasis [6]. Thus, dysregulation of F-box proteins contributes to the development and progression of various human diseases including human cancer. Recently, a wealth of literature has shown that aberrant expression of F-box proteins is critically involved in tumorigenesis [6]. Furthermore, F-box proteins have been suggested as biomarkers in clinical implications. Therefore, in this article, we will review the recent advances in our biochemical understanding of how various F-box proteins are dysregulated and lead to tumorigenesis. Moreover, we will summarize possible clinical implications of F-box proteins and further discuss whether some F-box proteins could be biomarkers and therapeutic targets of a variety of human cancers.

2. F-box proteins

Over the past decades, F-box proteins have been intensively investigated using both biochemical approaches and mouse genetic models. It is well documented that F-box proteins could exert their oncogenic or tumor suppressive function, which depends on misregulated degradation of oncoproteins or tumor suppressors by SCF E3 ligases [7]. In this section, we will summarize the recent pathological and biochemical evidence revealing a potential role of F-box proteins in the development and progression of human cancers. Furthermore, given the critical role of F-box proteins in tumorigenesis, the potential clinical implications via targeting F-box proteins will be described.

2.1. Role of the FBXW subfamily in clinical implications

FBXW subfamily contains the WD40 repeat domain and includes 11 proteins, namely FBXW-1 (also known as beta transducin repeat-containing protein, β-TRCP1), FBXW-2, FBXW-4, FBXW-5, FBXW-7, FBXW-8, FBXW-9, FBXW-10, FBXW-11 (also known as β-TRCP2), FBXW-12, and FBXW-15 [6] (Table 1). Many excellent studies have demonstrated that FBXW1 (β-TRCP1) and FBXW11 (β-TRCP2) have context-dependent functions in cancer. It is worthy to mention that β–TRCP recognizes the consensus sequence D-pS-G-X-X-pS (X represents any amino acid) degron and phosphorylation of both serine residues by specific kinases is required for β-TRCP-mediated ubiquitination [9]. β-TRCP1 and β-TRCP2 are two homologues, although they are encoded by two different genes. Structurally, both isoforms contain an F-box domain and seven WD-40 repeats, but they have different sequences in their N-terminal regions [10]. Notably, their biochemical functions are redundant by *in vitro* assays [11].

In support of this concept, depletion of *β-TRCP1* in mice caused minor spermatogenesis defects, which did not affect mouse normal development [11]. This could be possibly due to that β-TRCP2 was still available and may compensate for β-TRCP1 function. It is clear that β-TRCP1/2 exerts its physiological functions via targeting some substrates for ubiquitination and degradation. Since many substrates of β-TRCP have been identified to play a critical role in cell cycle, apoptosis, and migration, dysregulated β-TRCP is involved in tumorigenesis. For example, some cell cycle regulators including Emi1[12], Cdc25A [13, 14], Wee1A [15], cyclin D1 [16], and BTG [17] are the substrates of β-TRCP. REST is degraded by means of β-TRCP during the G2 phase of the cell cycle to allow transcriptional derepression of Mad2, which is an essential component of the spindle assembly checkpoint [18]. Moreover, β-TRCP controls centrosome duplication and separation through targeting PLK4 and CEP68 for degradation, respectively [19, 20]. Studies from various groups have shown that β-TRCP targets Snail [21], the extracellular matrix protein fibronectin [22], and Twist [23], which are involved in cell migration. Additionally, multiple apoptotic proteins such as Mcl-1[24], BimEL [25], PDCD4 [26], and Pro-caspase-3 [27] have been identified as the ubiquitin substrates of β-TRCP.

Emerging evidence has also implicated that β-TRCP plays an oncogenic role in human cancers. In line with this, higher expression of β-TRCP has been validated in various types of human malignances including colorectal cancer [28], hepatoblastoma [29], pancreatic cancer [30], and melanoma [31]. Consistently, studies have defined that β-TRCP promoted cell growth and tumor growth using *in vitro* cell culture and *in vivo* mouse model approaches [32, 33], suggesting that β-TRCP exerts tumorigenic activity. Kuto *et al* found that 38% of MMTV β-TRCP mice developed tumors including mammary, ovarian, and uterine carcinomas [32]. Interestingly, several groups argued that β-TRCP may also have tumor suppressor functions in a tissue-specific manner. For instance, Saitoh *et al.* found that there was a WD-40 substrate binding domain mutation (F462S) in a gastric cancer cells, leading to stabilization of β-catenin and activation of the Wnt signaling pathway, and subsequent tumor development [34]. Later, additional five mutations of *β-TRCP* (A99V, H342Y, H425Y, C206Y, and G260E) were identified in gastric cancer [35]. In keeping with these reports, *β-TRCP* mutations have also been found in prostate cancer [36] and breast

cancer [37]. Due to the fact that β-TRCP substrates include both oncoproteins and tumor suppressors, it is difficult to characterize *β-TRCP* as an oncogene or tumor suppressive gene. Therefore, further in-depth investigation is required to explore the exact role of β-TRCP in tumorigenesis using engineered mouse model in different tissue context. Therefore, β-TRCP could contribute to tumorigenesis in the tissue-specific or cellular context-dependent manner.

FBXW2 has been reported to target hGCM1 (human glial cell missing homolog 1) to the ubiquitin-proteasome degradation system [38]. Moreover, Chiang *et al*. found that ubiquitin-conjugating enzyme UBE2D2 is responsible for FBXW2-mediated hGCM1 ubiquitination and degradation [39]. This group further identified that RACK1 (receptor for activated C-kinase 1) interacted with FBXW2 to up-regulate hGCM1 stability and placental cell migration and invasion [40]. Although FBXW2 gene alteration was not found in human tumors by chromosome mapping and analysis [41], further exploration is necessary to dissect the exact role of FBXW2 in tumorigenesis.

It has been reported that *FBXW4* is mutated, lost or under-expressed in various types of human cancer cell lines and clinical lung cancer patient samples. Notably, FBXW4 expression level is correlated with survival of patients with non-small cell lung cancer, indicating that FBXW4 could be a novel tumor suppressor in lung cancer [42]. On the other hand, FBXW5 has been found to ubiquitinate tumor suppressor DLC1, leading to promotion of non-small cell lung cancer cell growth [43]. Specifically, *FBXW5* knockdown using siRNA restored DLC1 protein expression in non-small cell lung cancer cell lines, resulting in a reduction in the levels of activated RhoA-GTP and in RhoA effector signaling. Importantly, inhibition of FBXW5 led to decrease in cell proliferation in non-small cell lung cancer [43], suggesting that FBXW5 may function as an oncoprotein in non-small cell lung cancer cell growth, but further investigation is warranted to reveal the oncogenic role of FBXW5 *in vivo*.

Extensive studies have identified that FBXW7 (also known as FBW7, hCdc4, hAgo, and SEL10) is involved in several biological processes such as cell growth, proliferation, differentiation, and survival [44]. It has been known that FBXW7 substrates typically contain a conserved CPD (Cdc4 phosphodegron) sequence (L)-X-pT/pS-P-(P)-X-pS/pT/E/D (X represents any amino acid) [44]. Like β-TRCP, FBXW7 recognizes and ubiquitinates its substrates, which requires phosphorylation of the substrate within its degron by a single kinase or multiple kinases [45, 46]. Elegant studies from various groups have revealed that FBXW7 functions largely as a tumor suppressor due to its negative regulation of some oncogenic proteins including Aurora A [47], cyclin E [48], c-Myc [49], c-Jun [50, 51], c-Myb [52-54], G-CSFR (Granulocyte colony stimulating factor receptor) [55], HIF-1α (Hypoxia inducible factor-1α [56, 57], KLF2 (Krüppel-like factor 2), KLF5 (Kruppel-like factor 5) [58, 59], Mcl-1 (Myeloid cell leukemia-1) [9, 60], MED13 (Mediator 13) [61], mTOR (mammalian target of rapamycin) [62, 63], NF1 (Neurofibromatosis type 1) [64], Notch [65, 66], NF-κB2 [67, 68], NRF1 (Nuclear factor E2-related factor 1) [69], JUNB [70, 71] and SREBP (Sterol regulatory element-binding proteins) [72, 73]. Notably, *FBXW7* mutations and deletions have been observed in a variety of human cancers such as T-cell acute lymphoblastic leukemia [74], cholangiocarcinoma, gastrointestinal cancer [75],

bladder cancer [76], colon cancer [77], and prostate cancer [74]. For example, *FBXW7* mutation rate is approximately 30% in T-cell acute lymphoblastic leukemia [78]. Herein, we will not discuss the detailed role of FBXW7 in tumorigenesis because several recent excellent reviews have described the function of FBXW7 in human cancers and clinical implications [78-82].

Notably, FBXW8 (also known as FBW6, FBW8, FBX29, FBXW6, or FBXO29) has been shown to play an essential role in cancer cell proliferation via promoting the proteolysis of cyclin D1 [83]. Interestingly, one study revealed that FBXW8 did not regulate cyclin D1 degradation during normal cell cycle progression [84]. Moreover, disruption of the *FBXW8* gene led to pre- and postnatal growth retardation in mice, suggesting that FBXW8 plays a significant role in growth control [85]. Lin *et al.* reported that FBXW8 regulated the proliferation of human choriocarcinoma cells via G2/M phase transition, which is associated with regulation of several cell cycle regulators such as CDK1, CDK2, cyclin A, cyclin B1 and p27 expression [86]. Recently, Wang *et al.* observed that FBXW8 promoted the degradation of hematopietic progenitor kinase 1 (HPK1), leading to enhancing cell proliferation of pancreatic cancer cells [87]. Moreover, high expression of FBXW8 was observed and targeting FBXW8 by miR-218 inhibited the proliferation of human choriocarcinoma cells [88], indicating that targeting FBXW8 by miR-218 could be a potential approach for the treatment of human choriocarcinoma.

While FBXW9 was reported to promote synaptic transmission in GABAergic motor neurons in *C. elegans*, the physiological role of FBXW9 in tumorigenesis is still uncertain [89]. Additionally, *FBXW10* was identified to have mutations in T-cell prolymphocytic leukemia using whole-genome sequencing and whole-exome sequencing analysis [90]. Feng *et al.* found that FBXW10 is negatively regulated in transcription and expression level by protein O-GlcNAcylation [91]. Notably, the *FBXW12* gene is deleted in its promoter or the mRNA-encoding region in some cases of epithelial ovarian cancer [92]. Moreover, it was found that *FBXW12* was epigenetically silenced by CpGs methylation in epithelial ovarian cancer patients [92]. These findings indicate that FBXW12 could be a tumor suppressor in epithelial ovarian cancer, while further in-depth investigation is required to pinpoint its physiological role in tumorigenesis. One study showed that FBXW15 mediated HBO1 (histone acetyltransferase binding to origin recognition complex) ubiquitin-proteasomal degradation, which is important in DNA replication licensing and cell proliferation [93]. Moreover, this study authenticates that FBXW15 is an ubiquitin E3 ligase subunit to promote HBO1 degradation, leading to controlling cell replicative capacity [93], but its physiological role in tumorigenesis warrants further studies.

2.2.Role of the FBXL subfamily in clinical implications

The FBXL subfamily has 22 members, namely FBXL1 to FBXL22. Each FBXL protein contains an F-box motif and a C-terminal Leu-rich repeat (LRR) domain. FBXL subfamily member proteins could be tumor suppressors or oncoproteins (Table 2). In this section, we will describe their physiological functions in tumorigenesis.

FBXL1, also known as Skp2 (S-phase kinase-associated protein 2), has been well characterized as an oncoprotein. Skp2 protein consists of four distinct domains, namely

destruction domain (D-box), nuclear localization signal (NLS), F-box domain, and C-terminal LRR domain. Skp2 has been identified to exert its oncogenic function through targeting its substrates including p27 [94, 95], p21 [96, 97], p57 [98], TOB1 [99], RASSF1 (Ras association domain family 1) [100], FOXO1 [101, 102], and RBL2 (retinoblastoma-like 2; also known as p130) [103]. Overexpression of a dominant negative type of Skp2 caused cell growth inhibition in breast cancer cells [104]. One study showed that androgen signaling pathway enhanced cell proliferation via upregulation of Skp2 and subsequent targeting p27 [105, 106]. Moreover, deletion of *Skp2* in mice led to resistance to tumor development induced by loss of either *p19 Arf* or the *Pten* protein [107]. Noteworthy, *Skp2* conditional knockout mice further validated its oncogenic function in T-cell lineage [108], B-cell lineage [109], bone marrow [110], liver [111, 112], breast [113], prostate [114], and skin [115]. On the other hands, overexpression of *Skp2* in mice led to tumor development including lymphoma [116], prostate cancer [114], mammary gland tumor [113]. Consistently, overexpression of Skp2 has been frequently observed in a variety of human cancers such as lymphomas [117, 118], pancreatic cancer [119], breast carcinomas [120-124], prostate cancer [125, 126], melanoma [127-129], and nasopharyngeal carcinoma [130, 131]. Importantly, Skp2 expression is associated with histological grade and tumor size in hepatocarcinoma [132]. Similarly, Skp2 amplification is correlated with poor prognosis in human gastric cancer [133]. Taken together, inhibition of Skp2 could be a novel approach for the treatment of human cancers.

FBXL2 has been observed to exert its tumor suppressor-like activity by ubiquitin-mediated degradation of cyclin D3, leading to lung cancer cell growth inhibition and cell cycle arrest [134]. Specifically, overexpression of FBXL2 triggered G2/M arrest and increased apoptosis, whereas depletion of FBXL2 accelerated lung cancer cell growth and enhanced cell viability. Ectopic expression of FBXL2 retarded tumor formation in athymic nude mice, implicating that FBXL2 could serve as a tumor suppressor [134]. Similarly, FBXL2 expression was suppressed in AML (acute myelogenous leukemia) and ALL (acute lymphoblastic leukemia) patient samples [135]. Moreover, FBXL2 induced G0 phase arrest and cellular apoptosis in part via targeting cyclin D2. This study suggests a tumor suppressive effect of FBXL2 in lympho-proliferative malignancies [135]. This group further discovered that FBXL2 ubiquitinated Aurora B to inhibit tumorigenesis [136]. One excellent study from Pagano group showed that FBXL2-mediated degradation of p110-free p85β regulatory subunit governed the PI3K signaling cascade [137]. Altogether, these studies suggest that FBXL2 could have tumor suppressive function.

FBXL3 was initially found as a regulator of the circadian rhythm through targeting Cryptochrome (Cry1/Cry2) proteins [138-140]. Lower expression of Cry1 and Cry2 in glioma tissues was observed, arguing that disturbances in Cry1 and Cry2 stability by FBXL3 could affect normal circadian rhythm, leading to glioma cells survival [141]. Recently, *FBXL3* mutations were found in colon cancer cell lines with microsatellite instability [142]. FBXL5 has been confirmed to modulate Snail1 DNA binding and stability [143]. Therefore, FBXL5 could inhibit Snail1 to suppress cancer cell invasion. Indeed, one study validated that FBXL5 inhibited cell invasiveness due to targeting Snail1 in gastric cancer cells [144]. Moreover, it has been shown that FBXL5 targeted cortactin for ubiquitination-mediated destruction, which is mediated by ERK (extracellular regulated signal kinase), leading to

inhibition of cell migration in gastric cancer cells [145]. Chen *et al.* reported that FBXL5 targeted single-stranded DNA-binding protein hSSB1 to control DNA damage response [146].

FBXL10 (also known as Ndy1, JHDM1B or KDM2B) contains an F-box domain and a JmiC domain with demethylase activity [147, 148]. It has been shown that FBXL10 has H2AK119 ubiquitination activity and histone H3K36 demethylase function [149]. Moreover, FBXL10 was found to be involved in anti-estrogen resistance in breast cancer [150]. Furthermore, FBXL10 was also identified as a transcriptional repressor of c-Fos and a target gene of NF-κB in human cancer [151]. This study demonstrated that FBXL10 functions as an anti-apoptotic protein, binds and represses c-Fos promoter, leading to cancer cells to resist TRAIL (tumor necrosis factor-related apoptosis-inducing ligand)-induced apoptosis [151]. Consistently, depletion of *FBXL10* sensitizes resistant cells to TRAIL, whereas upregulation of FBXL10 inhibits TRAIL-induced apoptosis. TRAIL or proteasome inhibitors repress FBXL10 through inhibition of the NF-κB signaling pathway. These findings suggest that targeting FBXL10 could overcome resistant cancer cells for TRAIL treatment in human cancer [151].

In support of the oncogenic role of FBXL10, transgenic mice that overexpression *FBXL10* in hematopoietic stem cells (HSCs) developed myeloid or B-lymphoid leukemia with complete penetrance [152]. FBXL10 transgenic mice displayed an upregulation of Nsg2 (neuron-specific gene family member 2). HSCs from *FBXL10* transgenic mice exhibited enhanced mitochondrial oxidative phosphorylation genes [152]. This transgenic mouse study dissected FBXL10 as a *bona fide* oncogene via regulation of metabolic proliferation and Nsg2-mediated impaired differentiation [152]. Along these lines, FBXL10 is overexpressed in human PADC (pancreatic ductal adenocarcinoma) and is associated with tumor grade and stage and metastases [153]. In addition, depletion of *FBXL10* abrogated tumorigenicity of cell lines, whereas overexpression of FBXL10 cooperated with KrasG12D to promote PDAC development in mice [153]. Additional in-depth investigation defined that FBXL10 repressed developmental genes and activated a module of metabolic genes, leading to subverting cellular differentiation and driving the pathogenesis of an aggressive subset of PDAC [153]. Yu *et al.* found that FBXL10 is a positive regulator of glycolysis, glutaminolysis, and pyrimidine synthesis in cancer cells [154]. FBXL10 is also overexpressed in various types of cancers, further suggesting that FBXL10 is an oncoprotein [154]. Interestingly, one group found that FBXL10 was downregulated in aggressive brain tumors, indicating that role of FBXL10 in cancer appears to be possibly tissue dependent [155].

It has been recently shown that the hypoxia-controlled FBXL14 governed Snail1 for proteasome degradation [156]. Specifically, FBXL14 interacted with Snail1 and promoted its ubiquitylation and degradation independently of phosphorylation by GSK-3β. Importantly, FBXL14 expression is decreased in tumors [156]. Consistently, Yang *et al.* found that imipramine blue halts head and neck cancer invasion via enhancing FBXL14-mediated Twist degradation [157], suggesting that FBXL14 could function as a tumor suppressor to inhibit invasion in this experimental setting. Although the molecular mechanism of FBXL17 is undermined in tumorigenesis, FBXL17 has been considered as a

potential useful biomarker for breast cancer therapy [158]. Another F-box protein FBXL19 has been discovered to regulate TGFβ1-induced E-cadherin downregulation in part through targeting Rac3 ubiquitination and degradationin esophageal cancer cells [159].

Notably, FBXL20 has been reported to have high expression in human colon tumor samples [160]. Depletion of *FBXL20* by its siRNA inhibited cell proliferation and caused G1 phase arrest as well as induced apoptosis in colon cancer cell lines [160]. In addition, downregulation of FBXL20 increased SET, caspase-3 and E-cadherin, but decreased β-catenin, c-Myc, cyclin D1, p53 and PP2A [160]. This work suggests that FBXL20 promotes carcinogenesis via governing the Wnt signaling pathway and caspase activity [160]. Moreover, overexpression of FBXL20 increased the cell viability and invasion capacity in colon cancer cells, which is correlated with an upregulation of β-catenin and c-Myc, and downregulation of E-cadherin [161]. Taken together, FBXL20 could play an oncogenic role in colon cancer development and progression. Additionally, FBXL20 was validated as a direct miR-3151 target in CN-AML (cytogenetically normal acute myeloid leukemia) [162]. High miR-3151 expression was correlated with shorter disease-free and overall survival. This indicates that FBXL20 is critical involved in CN-AML [162]. However, further investigation is required to determine the physiological role of FBXL20 in various types of human cancers.

2.3. Role of the FBXO subfamily in clinical implications

Within the 69 putative F-box proteins, the 36 F-box proteins were designed as FBXO proteins, consisting the largest subfamily of F-box proteins. FBXO proteins contain the F-box motif and different functional domains other than LRR or WD40 repeats, which have not been fully characterized. In the following paragraphs, we limit our discussion to these FBXO members with functions in tumorigenesis (Table 3).

Notably, FBXO1 (also known as FBX1 or cyclin F) has been considered as a critical regulator of cell cycle progression, although it did not bind or activate any CDKs (cyclin dependent kinases) [163]. Interestingly, FBXO1 oscillates during the cell cycle and its degradation is independent of ubiquitination and proteasome-mediated pathways [163]. Moreover, FBXO1 regulates the nuclear localization of cyclin B1 through a cyclin-cyclin interaction [164]. One elegant study has identified that FBXO1 targets CP110 protein, which is necessary for centrosome duplication, leading to control of the fidelity of mitosis and genome integrity [165]. This group also identified RRM2 (ribonucleotide reductase family member 2) as an ubiquitin substrate of FBXO1 [166]. Specifically, FBXO1 degraded RRM2 to maintain balanced dNTP pools and genome stability, thereby ensuring efficient DNA repair in response to genotoxic stress [166]. Moreover, NUSAP1 was validated as a FBXO1 substrate during the S and the G2 phases of the cell cycle. FBXO1 targeted NUSAP1 in response to DNA damage, leading to sensitizing cells to microtubule-based chemotherapeutics [167]. Altogether, FBXO1 plays a direct role in controlling genome stability through targeting its substrates and implications for cancer development and therapy. In line with this concept, mice with a homozygous *FBXO1* deletion were embryonic lethal and with developmental anormalies [168]. MEFs carrying an FBXO1 deletion displayed cell cycle defects, indicating that FBXO1 is critically involved in cell

cycle progression [168]. In support of this notion, one study showed that FBXO1 was noticeably downregulated in hepatocellular carcinoma (HCC) at both mRNA and protein levels [169]. Importantly, low expression of cyclin F was correlated with tumor size, clinical stage, serum alpha-fetoprotein level and tumor multiplicity, as well as poor overall survival and recurrence-free survival. More importantly, low expression of FBXO1 was an independent poor prognostic marker for overall survival [169]. These studies might speculate that FBXO1 could be a tumor suppressor in part via regulation of cell cycle progression in human cancer.

FBXO4 (also known as FBX4) has been reported to interact with both Pin2 and TRF1 isoforms and promote their ubiquitination, thereby regulating telomere length and cell cycle [170]. Overexpression of FBXO4 led to progressive telomere elongation via reduction of Pin2/TRF1 protein levels, while depletion of *FBXO4* stabilized Pin2/TRF1 and caused telomere shortening as well as impaired cell growth [170]. This study suggests that FBXO4 could control cell growth through targeting Pin2/TRF1 for degradation. Another study revealed that FBXO4 is involved in promoting ubiquitin-dependent degradation of cyclin D1, leading to reduction of cell cycle progression [171]. Depletion of *FBXO4* attenuated cyclin D1 ubiquitination and subsequently increased cyclin D1 levels and accelerated cell cycle progression. Consistently, FBXO4 expression was reduced in tumor-derived cell lines and a subset of primary human cancers, suggesting that FBXO4 could be a tumor suppressor [171]. Furthermore, inhibition of FBXO4 E3 ligase activity led to an accumulation of nuclear cyclin D1 and oncogenic transformation. *FBXO4* mutations, which inhibited the dimerization of the SCF (FBXO4) ligase and contributed to carcinogenesis, have been also observed in human cancer [172]. Moreover, phosphorylation-dependent regulation of SCF (FBXO4) dimerization and activity involved 14-3-3ε [173]. Recently, Lee *et al.* found that *FBXO4* deficiency induced Braf-driven melanoma, which depended on cyclin D1 accumulation in mice, suggesting that FBXO4 dysfunction is a contributor to human malignancy [174]. Interestingly, Chu *et al.* independently discovered that FBXO4 has several isoforms: FBXO4α, FBXO4β, FBXO4γ, and FBXO4δ [175]. FBXO4β, FBXO4δ, and FBXO4δ but not FBXO4α, were found to promote cell proliferation and migration due to inhibition of cyclin D1 degradation [175]. Importantly, *FBXO4* knockout mice facilitated N-nitrosomethylbenzylamine (NMBA), an esophageal carcinogen, induced papillomas, indicating FBXO4 as a possible suppressor of esophageal tumorigenesis [176]. A structure-based computational approach has been performed to rationally design peptide inhibitors of SCF (FBXO4) [177]. Altogether, FBXO4 might function as an anti-tumor protein.

FBXO7 is an F-box protein with a C-terminal specific proline-rich region (PRR) that is important for substrate recognition [178]. Laman *et al.* found that *FBXO7* knockdown reduced Cdk6 association with cyclin D [179]. Moreover, FBXO7 overexpression increased cyclin D/Cdk6 activity and E2F activity and transformed murine fibroblasts, leading to tumorigenic in mice [179]. Strikingly, FBXO7 was highly expressed in human lung and colon cancers compared with normal tissues, suggesting that FBXO7 could play a proto-oncogenic role in these epithelial tumors [179]. Recent studies also showed that a reduction of FBXO7 expression increased cell proliferation, decreased cell size and shortened G1 phase due to decreased p27 and increased levels of S phase cyclins and Cdk2 activity [180]. FBXO7 levels correlated inversely with CD43 expression. Further experiments

demonstrated that FBXO7 has an anti-proliferative function and promotes maturation of precursor cells [180]. In further support the tumor suppressor role of FBXO7, another study reported that FBXO7 negatively regulates the proliferation and differentiation of HSPCs (haematopoietic stem and progenitor cells) in a p53-dependent manner [181].

Notably, FBXO7 expression promoted T cell lymphomagenesis in the absence of *p53* [181]. FBXO7 has also been reported to catalyze the ubiquitination of HURP (hepatoma-upregulated protein), a cell cycle-regulated oncogene that involved in cell growth control in human HCC, demonstrating that FBXO7 could be a possible tumor suppressor in HCC [178]. Consistently, FBXO7 interacted with human inhibitor of apoptosis cIAP1 (the inhibitor of apoptosis protein 1) and promoted its ubiquitination [182]. In line with this, FBXO7 was validated to mediate ubiquitin conjugation to cIAP1 and TRAF2, leading to decreased RIP1 ubiquitination and negatively regulating NF-κB signaling pathway [183]. However, Kang *et al.* found that FBXO7 positively regulated BMP (bone morphogenetic protein)-mediated signaling through targeting NRAGE (neurotrophin receptor-interacting MAGE) protein, and upregulated NF-κB activity [184]. Taken together, FBXO7 might function in a tissue-specific manner.

FBXO11 was reported to target the BCL6 oncoprotein [185]. Specifically, BCL6 is overexpressed in the majority of patients with DLBCL (diffuse large B-cell lymphoma). BCL6 has been found to be targeted for ubiquitination and proteasomal degradation by SCF complex containing FBXO11 [185]. Consistently, *FBXO11* was deleted or mutated in DLBCL cell lines and in primary DLBCLs [185]. Reconstitution of FBXO11 enhanced BCL6 degradation, leading to inhibition of cell proliferation and induction of cell death. Consistently, *FBXO11*-deleted DLBCL cells generated tumors in mice, which were suppressed by FBXO11 reconstitution [185]. One study discovered that FBXO18 promotes DNA double-strand breakage and apoptosis upon DNA replication stress via regulation of activation of ATM and DNA-PK and phosphorylation of RPA2 and p53 [186]. Moreover, it has been reported that FBXO18 is often deleted in melanomas to protect melanoma cells from apoptosis [187].

FBXO32, also known as atrogin-1 or MAFbx (muscle atrophy F-box), is expressed largely in skeletal muscle cells and cardiomyocytes [188, 189]. FBXO32 regulates myocyte cell size and skeletal muscle atrophy as well as muscle homeostasis through targeting multiple substrates including calcineurin, eIF3-f, MyoD, MKP-1 (MAPK phosphatase-1), and IκB (inhibitor of κB) [190-194]. Emerging evidence has indicated that FBXO32 plays a tumor suppressive role in human cancers. Chou *et al.* found that FBXO32 expression is undetectable in ovarian cancer cell lines, but it is observed in the normal ovarian surface epithelium [195]. FBXO32 methylation was found in ovarian cancer cell lines with activation of TGF-β/SMAD4 signaling pathway [195]. Moreover, FBXO32 methylation was associated with shorter progression-free survival. Overexpression of FBXO32 significantly inhibited proliferation of a platinum-resistant ovarian cancer cell line due to induced apoptosis, and also sensitized cells to cisplatin [195]. Consistently, decreased mRNA level and protein expression of FBXO32 were observed in esophageal cancer cell (ESCC) lines and tumor tissues, which correlate with *FBXO32* promoter methylation status [196]. Importantly, FBXO32 methylation status and protein expression were independently

associated with patient survival in ESCC, suggesting that FBXO32 could be a prognostic marker and potential therapeutic target for ESCC patients [196]. It has been found that 3-deazaneplanocin A (DZNep) induced efficient apoptosis in breast cancer cells partly due to increased FBXO32 expression [197]. DZNeP also induced the expression of FBXO32 in human mantle cell lymphoma cells [198]. Moreover, EZH2 (zeste homolog 2) exerted its functions in regulation of the proliferation and survival of PAX3-FOXO1 alveolar rhabdomyosarcoma cells, at least in part, by repressing FBXO32 abundance [199]. Lei *et al.* found that SerpinB5 interacts with KHDRBS3 and FBXO32 in gastric cancer cells [200]. Therefore, further studies are warranted to determine the physiological function of FBXO32 in tumorigenesis.

3. Conclusion and future perspectives

Since some F-box proteins play pivotal roles in tumorigenesis, targeting F-box proteins could be a novel therapeutic strategy for the treatment of human cancers. Indeed, proto-oncoprotein Skp2 has been considered as a promising molecular target for achieving better outcome in cancer patients. Two compounds, namely compound A (SMIP0004) and compound 25 (also known as SZL-P1-41), have been found to inhibit Skp2 [201, 202]. Compound A could block the recruitment of Skp2 to the SCF ligase, leading to cell growth inhibition, apoptosis and cell cycle arrest in multiple myeloma cells [202]. Compound 25 suppressed Skp2 E3 ligase activity, resulting in inhibition of cell survival and Akt-mediated glycolysis and activation of cellular senescence [201]. Strikingly, compound 25 restricts cancer stem cell traits and cancer progression, demonstrating that Skp2 is a novel target for treatment of human cancer [201]. In addition, several compounds that inhibit Skp2 by blocking the binding to its cofactors CKS1 have been discovered [203]. Interestingly, some natural agents including curcumin, quercetin, lycopene, silibinin, epigallocatechin-3-gallate, and Vitamin D3 have also been found to inhibit Skp2 expression in human cancers [204-207]. Due to the non-toxic nature of natural agents, inactivation of Skp2 by natural agents could be a safer approach for the prevention /or treatment of human cancer. It has been reported that loss of Fbw7 led to resistance to Taxol and ABT-737 in cancer cells [60]. Moreover, treatment decisions regarding to anti-tubulin therapeutics depend on the Fbw7 status [9]. Thus, increased Fbw7 through regulation of its upstream regulatory proteins could overcome drug resistance to certain therapeutic drugs. On the basis of the fact that many F-box proteins have various functions in different cancer types, it is reasonable to design personalized medicine targeting the F-box proteins in specific tissues.

In conclusion, F-box proteins have been critically involved in tumorigenesis through targeting their substrates for ubiquitin-mediated degradation. Although some studies have revealed multiple F-box proteins functions in the tumor development and progression, many key remaining questions still need to be addressed. For example, how to develop specific approaches to screen physiological substrates of F-box proteins at endogenous levels? How to discover novel methods to validate these substrates and link these findings to pathological conditions such as cancer? How to identify the conditions which F-box proteins exerts their oncogenic or tumor suppressive functions? How to develop specific inhibitors to inactivate the oncogenic F-box proteins for better treatment of human cancer? To answer these questions, it is important to use tissue specific knockout mice or transgenic mice to

understand contribution of F-box proteins in carcinogenesis. It is also important to detect the pathological gene alternations in cancer patients and discover biochemical substrates of F-box proteins. Furthermore, answering these questions may be useful in further guiding the development of specific inhibitors targeting oncogenic F-box proteins or the discovery of compounds to activate tumor suppressive F-box proteins as novel anticancer treatments.

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Highlights

- F-box proteins play key roles in the development and progression of malignancies.
- F-box proteins exert functions mainly via targeting substrates for ubiquitination.
- F-box proteins function as oncoproteins or tumor suppressors in different cancers.
- F-box proteins inhibitors have been shown to exhibit therapeutic potential.
- Targeting F-box proteins could be a strategy for the treatment of human cancers.

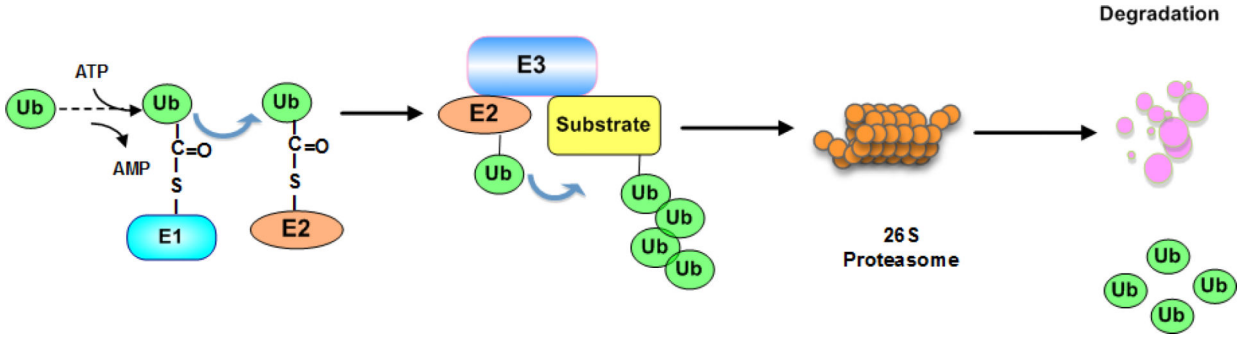

Figure 1.
A schematic illustration of the E1-E2-E3 cascade-mediated ubiquitin transfer process.

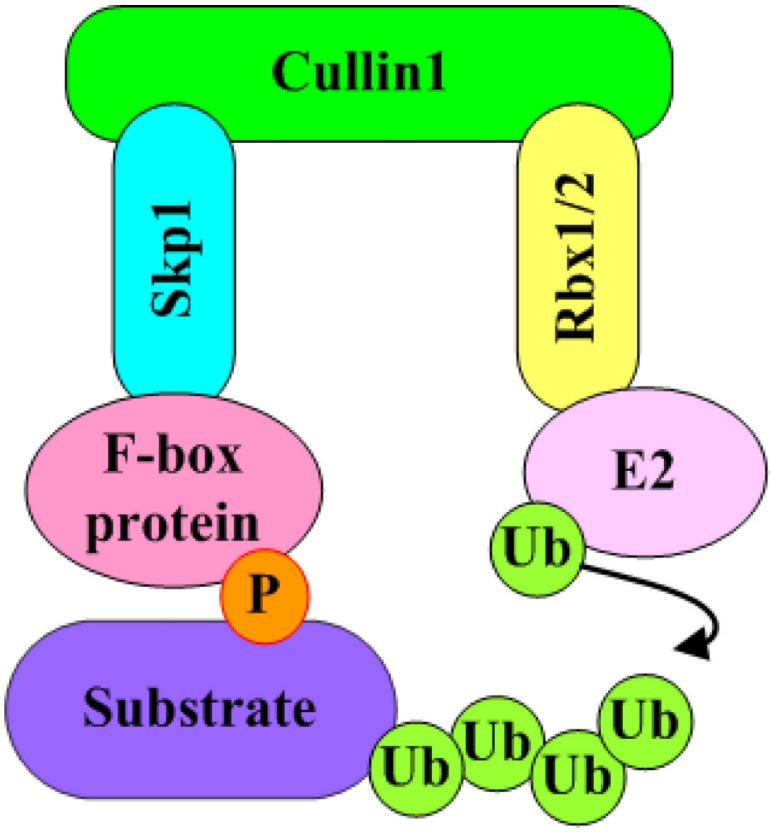

Figure 2.
A schematic illustration of structural organization of the multiple-subunit SCF E3 ubiquitin ligase complexes.

Table 1

Representative substrates of the FBXW subfamily of F-box proteins in clinical implications

Substrates	F-box	Functions	References
Emi1	β-TRCP	Cell cycle	[12]
Cdc25A	β-TRCP	Cell cycle	[13, 14]
Wee1A	β-TRCP	Cell cycle	[15]
cyclin D1	β-TRCP	cyclin, Cell cycle	[16]
BTG	β-TRCP	Cell cycle	[17]
REST	β-TRCP	Cell cycle	[18]
PLK4	β-TRCP	Cell cycle	[19]
CEP68	β-TRCP	Cell cycle	[20]
Snail	β-TRCP	Cell migration	[21]
ECMFn	β-TRCP	Cell migration	[22]
Twist	β-TRCP	Cell migration	[23]
Mcl-1	β-TRCP	Apoptosis	[24]
BimEL	β-TRCP	Apoptosis	[25]
PDCD4	β-TRCP	Apoptosis	[26]
Pro-caspase-3	β-TRCP	Apoptosis	[27]
hGCM1	FBXW2	Transcription factor, Cell cycle	[38]
RACK1	FBXW2	Cell migration and invasion	[40]
DLC1	FBXW5	Tumor suppressor, Cell growth	[43]
Aurora A	FBXW7	Cell cycle	[47]
cyclin E	FBXW7	Protein kinase, Cell cycle	[48]
C-Myc	FBXW7	Transcription factor	[49]
C -Jun	FBXW7	Oncogene	[50, 51],
C-Myb	FBXW7	Transcription factor	[52-54]
G-CSFR	FBXW7	Cell proliferation	[55]
HIF-1α	FBXW7	Transcription factor	[56, 57]
KLF2/5	FBXW7	Cell proliferation	[58, 59]
Mcl-1	FBXW7	Cell death	[9, 60]
MED13	FBXW7	Transcription factor	[61]
mTOR	FBXW7	Cell proliferation	[62, 63]
NF1	FBXW7	Tumor suppressor	[64]
Notch	FBXW7	Transcription factor	[65, 66]
NF-κB2	FBXW7	Transcription factor	[67, 68]
NRF1	FBXW7	Transcription factor	[69]
JUNB	FBXW7	Oncogene, Tumor suppressor	[70, 71]
SREBP	FBXW7	Transcription factor	[72, 73]
cyclin D1	FBXW8	cyclin, Cell cycle	[83]
CDK1/2	FBXW8	Cell cycle	[86]
cyclin A	FBXW8	cyclin, Cell cycle	[86]
cyclin B1	FBXW8	cyclin, Cell cycle	[86]

Substrates	F-box	Functions	References
P27	FBXW8	Cell cycle	[86]
HPK1	FBXW8	Cell growth, Cell cycle	[87]
HBO1	FBXW15	Cell proliferation	[93]

Table 2

Representative Substrates of the FBXL subfamily of F-box proteins in clinical implications

Substrates	F-box	Functions	References
P27	Skp2	Cdk inhibitor, Cell cycle	[94, 95]
P21	Skp2	Cdk inhibitor, Cell cycle	[96, 97]
P57	Skp2	Cdk inhibitor, Cell cycle	[98]
TOB1	Skp2	Cell cycle	[99]
RASSF1	Skp2	Tumor suppressor	[100]
FOXO1	Skp2	Transcription factor	[101, 102]
RBL2	Skp2	Cell cycle	[103]
cyclin D3	FBXL2	cyclin, Cell cycle	[134]
cyclin D2	FBXL2	cyclin, Cell cycle	[135]
Aurora B	FBXL2	Mitosis, Cell cycle	[136]
Cry1/2	FBXL3	Circadian clock, Cell cycle	[138, 139, 141]
Snail 1	FBXL5	Invasion, Cell cycle	[144]
Cortactin	FBXL5	Migration	[145]
hSSB1	FBXL5	DNA damage	[146]
c-Fos	FBXL10	Apoptosis	[151]
KrasG12D	FBXL10	Oncogene	[153]
Snail1	FBXL14	Invasion	[156]
Rac3	FBXL19	Cell adhesion	[159]

Table 3

Representative Substrates of the FBXO subfamily of F-box proteins in clinical implications

Substrates	F-box	Functions	References
CP110	FBXO1	Centrosome duplication, Cell cycle	[165]
RRM2	FBXO1	DNA repair	[166]
NUSAP1	FBXO1	Microtubule, Cell cycle	[167]
Pin2/TRF1	FBXO4	Cell growth	[170]
cyclin D1	FBXO4	cyclin, Cell cycle	[171]
cyclin D/Cdk6/p27	FBXO7	cyclin, Cell cycle	[179]
HURP	FBXO7	Oncogene, Cell cycle	[178]
cIAP1	FBXO7	Apoptosis inhibitor	[182]
NRAGE	FBXO7	Cell cycle	[184]
BCL6	FBXO11	Oncogene	[185]