Chapter 2
The Role of FBXW Subfamily of F-box Proteins in Tumorigenesis

Alan W. Lau, Yueyong Liu, Adriana E. Tron, Hiroyuki Inuzuka, and Wenyi Wei

Abstract In the human genome, 69 putative F-box proteins have been identified which could form a variety of different SCF type E3 ligase complexes to specifically target a wide range of proteins for degradation. F-box proteins can be further subclassified into three families largely based on the presence of three recognizable domains: WD repeats, leucine-rich repeats (LRR), and other types of protein interaction domains. The FBXW subfamily comprises ten proteins that contain both the F-box motif and the WD40 repeat domain, including FBXW-1 (also known as beta-transducin repeat-containing protein and β-TRCP1), FBXW-2, FBXW-4, FBXW-5, FBXW-7, FBXW-8, FBXW-9, FBXW-10, FBXW-11 (also known as β-TRCP2), and FBXW-12 (Fig. 2.1).

Over the past 17 years, intensive research efforts have been devoted, using both mouse genetic models and biochemical approaches, to identify specific ubiquitin substrates for a given F-box protein, which have helped the scientific community to reveal the important contributions of F-box proteins including the three well-studied E3 ligases SCF^{Skp2}, SCF^{FBW7}, and $SCF^{\beta\text{-}TRCP}$ in human cancers (Welcker and Clurman, Nat Rev Cancer 8(2):83–93, 2008; Frescas and Pagano, Nat Rev Cancer 8(6):438–449, 2008). Mechanistically, misregulated degradation of oncoproteins or tumor suppressors by various SCF E3 ligases could lead to tumorigenesis. Thus, F-box proteins could function as either oncoproteins or tumor suppressors, depending on the functional outputs of their ubiquitin substrates.

In this chapter, we summarize the recent genetic, pathological, and biochemical evidence revealing a possible role for FBXW subfamily of F-box proteins in tumorigenesis. To this end, we focus our discussion on our current knowledge accumulated in three major categories: physiological evidence (genetically engineered

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animal models), pathological evidence (human clinical cancer relevance), and biochemical evidence (ubiquitin substrates), all combined will allow for a more thorough understanding for their roles in tumorigenesis (Table 2.4). Given the fact that physiological evidence (primarily through mouse modeling studies) is considered the strongest supportive evidence indicating an involvement of a given F-box protein in tumorigenesis (Tables 2.1 and 2.3), we limit our discussion to those FBXW members that have available mouse genetic models.

Keywords F-box • SCF • FBXW subfamily • FBXW7 • beta-TRCP1 • beta-TRCP2 • FBXW8 • Cullin 1 • Cullin 7 • Tumor suppressor • Oncoprotein • Mouse model • Physiological function

2.1 FBXW1 and FBXW11 (β-TRCP1 and β-TRCP2) have Context-Dependent Functions in Cancer

2.1.1 The SCF$^{\beta\text{-TRCP}}$ E3 Ubiquitin Ligase

FBXW1, also termed β-TRCP (beta-transducin repeat containing protein), is conserved across species and has been well characterized in *Homo sapiens* (β-TRCP1 and β-TRCP2), *Drosophila melanogaster* (Slimb), and *Xenopus* (β-TRCP) [2]. Similar to other F-box proteins, β-TRCP generally recognizes a phosphorylated consensus sequence (DpSGxxpS) in its target substrates [3]. Structurally, β-TRCP contains an F-box motif at its N-terminus, multiple WD-40 repeats at its C-terminus and a dimerization domain near the F-box motif [2, 4]. The F-box motif is a critical 40-amino-acid sequence required for interaction with Skp1, an adaptor component of the SCF complex [5]. WD-40 repeats are protein–protein interaction motifs that form direct contact with target substrates [6]. At this point, the importance of the dimerization domain is currently unknown due to lack of genetic evidence. While it has been previously reported that the homo-dimerization and hetero-dimerization between β-TRCP1 and β-TRCP2 might be important for substrate specificity [4], additional studies are still necessary to further understand the role of dimerization in β-TRCP function (Fig. 2.1).

In humans, β-TRCP exists as two homologues, β-TRCP1 and β-TRCP2, which are encoded by two distinct genes. Structurally, both isoforms contain an F-box domain and all seven WD-40 repeats, with only noticeable sequence differences in their N-terminal regions [7]. To date, the differences between these two proteins remain unknown. Recent studies have suggested that β-TRCP1 and β-TRCP2 are functionally redundant, at least based on various in vitro biochemical assays. If so, this might explain why mice lacking β-TRCP1 develop normally with only minor spermatogenesis defects, as β-TRCP2 is still present and may compensate for loss of β-TRCP1 [8] (Table 2.1). Furthermore, in mouse embryonic fibroblasts, β-TRCP1,

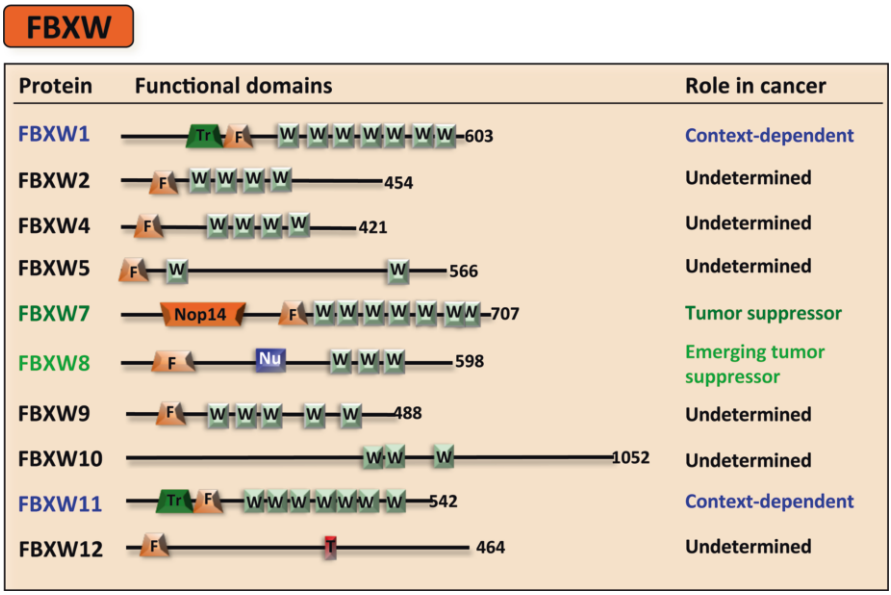

Fig. 2.1 A schematic illustration of functional domains of all known FBXW proteins and their possible roles in cancer. *F* F-box motif, *W* WD40 repeat, *Tr* D domain of beta-TRCP, *Nop14* Nop14-like family domain, *Nu* Nucleoporin Nup120/160-like domain

while contributes, is not completely required for the degradation of certain substrates [8]. Obviously, genetically modified mice deleted of β-TRCP1 and/or β-TRCP2 would be required to fully understand the role of β-TRCP in various cellular processes and whether the two homologues play an individual, synergistic, or redundant role under different experimental conditions.

β-TRCP1/2 targets a range of substrates for ubiquitination and subsequent degradation by the 26S proteasome (Table 2.2). As such, β-TRCP plays a vital regulatory role in multiple biological processes. Interestingly, many known substrates of β-TRCP1/2 are involved in various stages of cancer development and progression. For instance, some known substrates include cell cycle regulators Emi1 [9], Cdc25A [10, 11], Wee1A [12], Cyclin D1 [13], and BTG [14]. Consistent with a role in cell cycle regulation, *Btrc1*$^{-/-}$ mouse fibroblasts displayed increased genetic instability [9, 12] while Drosophila *Slimb* mutants exhibited centrosome and mitotic defects [15]. Furthermore, β-TRCP1/2 has also been shown to ubiquitinate proteins involved in cell migration. These substrates include the transcription factor Snail [16] as well as the extracellular matrix protein fibronectin [17]. Moreover, targets of β-TRCP have also been shown to regulate the cellular expression of various apoptotic proteins including Mcl-1 [18], BimEL [19], PDCD4 [20], and Pro-caspase-3 [21].

Table 2.1 Summary of the knockout mouse models for the FBXW class of F-Box proteins

F-box protein	Whole-body knockout/ phenotype	Tissue-specific knockout	
		Tissue/cells	Phenotype
FBXW1 (β-TRCP1)	*Btrc1*$^{-/-}$: Viable and fertile (male) [8]		
FBXW11 (β-TRCP2)	Reduced fertility (male) [130]		
Context-dependent	Hypoplastic phenotype in mammary glands (female) [26]		
	Abnormal retinal development [139]		
FBXW7	*Fbxw7*$^{-/-}$: embryonic lethal [40, 41]	Gut	Intestinal tumor [115]
Tumor suppressor	*Fbxw7*$^{+/-}$: radiation induced tumorigenesis [54]	Cerebellar anlage	Decreased cerebellar size and defects in axonal arborization [141]
	Fbxw7β$^{-/-}$: normal [140]		
	Compound mice models		
	Fbxw7$^{-/-}$*p53*$^{-/-}$: colorectal cancer (CRC) [59]	Brain	Die after birth [82, 142]
		Liver	Hepatomegaly and steatohepatitis [117]
	Fbxw7$^{+/-}$*Apc*$^{+/-}$: impaired intestinal progenitor and neural stem cell differentiation [143]	Intestine	Impaired differentiation of progenitor cells [48]
		Hematopoietic stem cells (HSCs)	Defective maintenance of quiescence [113]
	Fbxw7$^{+/-}$*p53*$^{+/-}$: tumors in epithelial tissues [54]	Hematopoietic tissue	T-ALL [134]
		T cell	Thymic lymphoma [112]
	Fbxw7$^{+/-}$*Pten*$^{-/-}$: accelerated tumor formation [144]	Leukemia initiating cell	Abrogation of quiescence [122]
			Tumor inhibition [123]
FBXW8	*Fbxw8*$^{-/-}$: smaller littermates [127]		
Emerging tumor suppressor	Abnormal placenta [126]		

2.1.2 The Oncogenic Role of β-TRCP in Cancer Development

As ubiquitin targets of β-TRCP play such indispensable roles in biological pathways related to the various stages of tumorigenesis, it is not surprising that dysregulation of $SCF^{\beta\text{-TRCP}}$ has been implicated in cancer development and progression. To date, multiple studies, both in vitro and in vivo, have suggested that β-TRCP might function as an oncogene and can promote cancer formation when overexpressed (Table 2.3). Currently, elevated levels of β-TRCP have been observed in colorectal cancer [22], hepatoblastoma [23], pancreatic cancer [24], and melanoma [25].

Table 2.2 Summary of identified ubiquitin substrates for β-TRCP1/2

Substrates	Functions/signaling pathways	Phospho-degron (phosphorylation sites)	References
β-catenin	Transcription factor, Wnt signaling pathway	DSGIHS	[6, 35, 147]
Gli2	Transcription factor, Shh signaling pathway	SSAYTVS, DSYDPIS	[148]
Gli3	Transcription factor, Shh signaling pathway	Multiple-degrons	[149, 150]
YAP	Transcription regulator, Hippo signaling pathway	DSGLSMS	[151]
TAZ	Transcription factor, Hippo signaling pathway	SREQSTDSG	[152]
HSF1	Transcription factor, Heat shock response	DSGSAHS	[153]
Nrf1	Transcription factor, Oxidative stress	DSGLS	[154]
Nrf2	Transcription factor, Oxidative stress	DSGIS, DSAPGS, DSGISL	[155]
ATF4	Transcription factor, Amino acid metabolic processes	DSGICMS	[156]
ESE-1	Transcription factor, Epithelial cell differentiation	SSHSSDSG	[157]
FOXO3a	Transcription factor, Apoptosis and metabolic processes	DSLSHS, DSLIST	[28]
c-Myc	Transcription factor, Cell proliferation	ESGSPS	[158]
p63γ	Transcription factor, Apoptosis	–	[159]
p53	Transcription factor, Apoptosis and cell cycle	GSRAHS	[36]
REST	Transcription factor, Neuronal differentiation and cell proliferation	SEGSDDSG, DSGIHS	[160, 161]
Smad4	Transcription factor, TGFβ signaling pathway	–	[162]
Snail	Transcription factor, Cell migration and Mesoderm formation	DSGKGS	[16]
STAT1	Transcription factor, Cytokine signaling pathway	–	[163]
Sp1	Transcription factor, Cell proliferation, apoptosis, differentiation, and lipid metabolism	DSGAGS	[164, 165]
Twist	Transcription factor, Cell migration and myogenesis	DSLSNS	[166]
BTG	Transcription factor, Cell cycle	–	[14]
IkBα	Inhibitor of NFκB signaling pathway	DSGLDS	[7, 34, 35]
IkBβ	Inhibitor of NFκB signaling pathway	DSGLGSS	[33, 167]
IkBε	Inhibitor of NFκB signaling pathway	DGSIGS	[33]
p105	Transcription factor, NFκB signaling pathway	DSGVETS	[168–170]
p100	Transcription factor, NFκB signaling pathway	DSAYGS	[171–173]

(continued)

Table 2.2 (continued)

Substrates	Functions/signaling pathways	Phospho-degron (phosphorylation sites)	References
Bcl10	Adaptor protein, NFκB signaling pathway	DTLVES	[174]
CIKS	Adaptor protein, NFκB signaling pathway	–	[175]
IRAK1	Protein kinase, NFkB signaling pathway	–	[176]
Cdc25A	Protein phosphatase, Cell cycle	SSESTDSG, DDGFLD	[10, 11]
Cdc25B	Protein phosphatase, Cell cycle	DDGFVD, DSGFCLDS, DAGLCMDSPSP	[177, 178]
Plk4	Protein kinase, Cell cycle	DSGHAT	[179, 180]
Wee1A	Protein kinase, Cell cycle	DSAFQE, EEGFGSSS	[12]
Bora	Aurora A kinase activator, Cell cycle	DSGYNT	[181]
Emi1	Inhibitor of APC/C, Cell cycle	DSGYSS	[9]
Cyclin D1	Cyclin, Cell cycle	EEVDLACT	[13]
Securin	Regulatory protein, Cell cycle	DDAYPE	[182]
Per1	Component of circadian core oscillator, Circadian rhythm	TSGCSS	[183]
Per2	Component of circadian core oscillator, Circadian rhythm	SSGYGS	[184]
Claspin	Adaptor protein, DNA damage response	DSGQGS	[185–187]
FANCM	DNA helicases, DNA damage response	DSGYNS	[188]
RASSF1C	DAXX interacting protein, DNA damage response	SSGYCS	[189]
Pro-caspase-3	Cysteine–aspartic acid protease family, Apoptosis	–	[21]
BimEL	Bcl-2 family protein, Apoptosis	SSGYFSD	[19]
Mcl-1	Bcl2-family protein, Cell survival	STDGSLPST	[18]
PDCD4	RNA-binding protein, Apoptosis	DSGRGDS	[20]
AUF	DNA/RNA-binding protein, Transcriptional regulation	SSPRHS	[190]
CPEB	RNA-binding protein, mRNA regulation	TSGFSS	[191]
HuR	RNA-binding protein, mRNA stabilization	EEAMAIAS	[192]
TRF1	DNA-binding protein, Regulation of telomere length	–	[193]
BMI1	Component of a Polycomb group multiprotein PRC1-like complex, Transcriptional repression	DSGSDKANS	[194]
LPCAT1	Acyltransferase, Lipid metabolism	SDQDS	[195]
PFKFB3	Synthesis and degradation of fructose 2,6-bisphosphate, Metabolic processes	DSGLSS	[196]
eEF2K	Protein kinase, Protein synthesis	DSGYPS	[197, 198]
EPO-R	Receptor, Cytokine signaling pathway	DSGISTD	[199]

(continued)

Table 2.2 (continued)

Substrates	Functions/signaling pathways	Phospho-degron (phosphorylation sites)	References
GH-R	Receptor, Growth hormone signaling pathway	DSGRTS, DDSWVEFIE	[200]
IFNA-R1	Receptor, Interferon signaling pathway	DSGNYS	[201, 202]
IL-10R1	Receptor, Cytokine signaling pathway	DSGFGS, DSGICLQE	[203]
PRL-R	Receptor, Growth hormone signaling pathway	DSGRGS	[204]
VEGFR2	Receptor protein kinase, Angiogenesis	DSGLSLPT, DSGMYLAS, DSGTTLS, DDTDTT	[205, 206]
DEPTOR	mTOR inhibitor, PI3K signaling pathway	SSGYFSSS	[207–209]
PHLPP1	Protein phosphatase, PI3K/Akt signaling pathway	QSVLLT, DSLSVE	[210]
H-Ras	GTPase protein, Growth factor signaling pathway	–	[99]
Fibronectin	Extracellular matrix protein, Cell adhesion and migration processes	DSGVVYS, DSGSIVVS	[17]
RCAN1	Calcineurin A binding protein, Calcineurin signaling pathway	–	[211]
SPAR	Rap GTPase activating protein, Postsynaptic regulation	DSGIDT	[212]
Cortactin	Cortical actin binding protein, Actin cytoskeleton organization	–	[213]
DLG	Scaffolding protein, Cell adhesion	DSGLPS	[214]
FGD1	Cdc42 guanine-nucleotide exchange factor, Actin cytoskeleton organization	DSGIDS	[215]
FGD3	Cdc42 guanine-nucleotide exchange factor, Actin cytoskeleton organization	DSGIDS	[216]
Mdm2	E3 ubiquitin ligase, p53 signaling pathway	Multiple-degrons	[217]
Cdh1	Component of APC/C E3 ligase complex, Ubiquitin conjugation pathway	SPDDGNDVS	[218]
UHRF1	E3 ubiquitin ligase, Chromatin regulation	SDTDSG	[219]
USP47	Deubiquitinase, Ubiquitin conjugation pathway	DSGTDS	[220]
BST-2	Type 2 integral membrane protein, Inhibition of virus infection	–	[221, 222]
CD4 (through Vpu)	Membrane protein, T cell activation	DSGNES (Vpu)	[3]
PC2 (through TAZ)	Calcium permeable cation channel, Intracellular calcium homeostasis	–	[223]

Table 2.3 Summary of the transgenic mouse models for the FBXW class of F-Box proteins

	Transgenic mouse model/phenotype				
	Whole-body expression/phenotype		Tissue-specific expression		
F-box protein	Transgene	Phenotype	Tissue	Transgene	Phenotype
FBXW1 (β-TRCP1) FBXW11 (β-TRCP2) Context-dependent	Inducible β -TRCP2 knockdown in *Btrc1*$^{-/-}$ mice	Severe testicular defect [131]	Epidermis	Inducible expression of dominant negative β-TRCP2	Decreased UVB-induced edema, hyperplasia, and inflammatory response [145]
			Intestine, liver, and kidney	Dominant-negative or full-length β-TRCP1	Tumorigenesis [27]
FBXW7 Tumor suppressor	*Fbxw7*^{R482Q}	Died perinatally [146]	Intestine	*Fbxw7*$^{fl(R482Q)/+}$/*Apc*$^{1322T/+}$	Intestinal tumor [116]
	Fbxw7 mutant alleles	T-ALL [114]			

While most of these studies were performed utilizing cell culture based models, multiple in vivo mouse models have also been generated verifying the oncogenic capabilities of β-TRCP (Table 2.3). For example, Kudo et al. observed that tissue-specific expression of human β-TRCP1 in mouse mammary epithelia displayed increased cellular proliferation [26]. Furthermore, of the mice studied, 38 % developed mammary, ovarian, and uterine carcinomas. In addition to these findings, the Besnard-Guerin group also explored the implications of β-TRCP1 overexpression in mouse intestine, liver, and kidney. They observed that 46 % (16/35) of mice with elevated expression of β-TRCP1 developed either intestinal adenomas or hepatic or urothelial tumors [27]. Moreover, in an orthotopic tumor mouse model, Tsai et al. observed that cells overexpressing β-TRCP1 displayed increased tumorigenic activity [28]. It is both these in vivo and in vitro studies that have lent support for β-TRCP1/2 functioning as an oncogene. However, this may not always be the case, as multiple studies have also suggested that β-TRCP may display tumor suppressive capabilities in certain cellular contexts.

2.1.3 β-TRCP, a Possible Tumor Suppressor?

While predominately reported to function as an oncogene, β-TRCP may also function as a tissue-specific tumor suppressor. To this end, while uncommon, mutations in β-TRCP1/2 have been observed in various types of carcinomas. In a gastric cancer cell line, a WD-40 substrate binding domain mutation (F462S) was identified by Saitoh et al. They suggested that this mutation could lead to stabilization of β-catenin and subsequent tumorigenesis through hyper-activation of the Wnt signaling pathway [29]. These findings were later supported by the identification and analysis of five *β-TRCP* missense mutations (A99V, H342Y, H425Y, C206Y, and G260E) found in gastric cancers. In tissues carrying these mutations, moderate to strong β-catenin expression was detected by immunohistochemistry [30]. In further support of a possible tumor suppressive role of β-TRCP, mutations in this F-box protein have also been observed in prostate cancer [31] as well as breast cancer [32].

Interestingly, while substrates of β-TRCP, such as beta-catenin, exhibit oncogenic properties, many β-TRCP substrates are also known tumor suppressors. For example, IκB, a negative regulator of the NFκB oncogene, is a well-documented β-TRCP substrate [7, 33–35]. Furthermore, the FOXO3 tumor suppressor has recently been shown to be a target of β-TRCP1 as well [28]. Moreover, Xia et al. identified p53 to be a novel target of β-TRCP-mediated ubiquitination [36]. Therefore, based on these facts, it is currently difficult to classify β-TRCP as a bona fide tumor suppressor or oncoprotein. It is possible that β-TRCP, while largely oncogenic in nature, may also function as a tumor suppressor in certain cellular contexts or in specific tissues. Hence, as with all E3 ubiquitin ligases, further identification of novel substrates would provide researchers a more genuine understanding of the complex role for β-TRCP in cancer development. The discovery of additional putative substrates would further shed light on whether β-TRCP is an

oncogene, a tumor suppressor in certain cellular contexts, or both. Without a doubt, generation of additional mouse genetic models would also be required to validate the tissue-specific or cellular context-dependent contribution of β-TRCP in tumorigenesis.

2.2 FBW7 Functions Largely as a Tumor Suppressor

The first member of the *FBW7* gene family was originally identified in budding yeast as a regulator of cell cycle-related proteins and designated as Cdc4 [37]. Over the past few decades, FBW7 (also known as FBXW7, hCdc4, hAgo, and SEL10) has been extensively studied and observed to be involved in a number of pivotal biological processes including cell growth, proliferation, differentiation, and survival [1]. Notably, FBW7 is considered a tumor suppressor through its negative regulation of many oncogenic proteins including c-Myc [38], Cyclin E [39], Notch [40, 41], c-Jun [42, 43], Mcl-1 [44, 45], and mTOR [46] (Tables 2.4 and 2.5). Moreover, mutations and deletions in *FBW7* have been identified in a wide spectrum of human cancers including T-cell acute lymphoblastic leukemia [51], cholangiocarcinoma, gastrointestinal cancer [48], bladder cancer [49], colon cancer [50], and prostate cancer [51]. Furthermore, emerging evidence have also demonstrated that dysregulation of FBW7 function can drive tumor development in humans [52]. In addition, microRNAs (miRNAs), as well as alternatively spliced isoforms, have been found to be involved in controlling FBW7 expression in human cancer settings [53]. Therefore, FBW7 is a general tumor suppressor in many human cancers.

Although great strides have been made to identify various downstream ubiquitin targets of FBW7 (Table 2.5), relatively little is known about the upstream signaling pathways that control FBW7 stability and cellular function. Additionally, as a haploinsufficient tumor suppressor [48, 54], understanding FBW7 and its regulatory axis is crucial for providing further insights into the precise molecular mechanism of FBW7 associated tumor suppression, and to further guide the development of therapeutic strategies that target the FBW7 pathway. In this section, we will primarily focus on the regulatory network of FBW7, knockout (KO) and conditional KO mouse models for *FBW7*, and the role of FBW7 in human cancer development.

2.2.1 FBW7 *Gene and Isoforms*

The human *FBW7* gene is located on chromosome 4q32 and encodes three transcripts, α, β and γ, derived from alternative transcriptional start sites that differ in the first exon, resulting in the generation of three different protein isoforms [55]. Each transcript contains its own promoter, although how these transcripts are regulated remains largely unknown with the exception of *FBW7*β, which is regulated by p53 [1]. Recently, Liu et al. reported newly identified alternative splice isoforms for

Table 2.4 Summary of the roles of FBXW class of F-box protein in cancer

Potential role in cancer (tumor suppressor or oncogene)	F-box protein	Gene symbol	Physiological evidence (mouse models)		Pathological evidence in cancer		Biochemical evidence (major substrates)
			Knockout	Transgenic	Overexpression	Mutation/deletion	
Context-dependent	FBXW1 (β-TRCP1) FBXW11 (β-TRCP2)	*BTRC*, *FWD1*, *FBXW1A* *FBXW11*, *HOS*, *FBXW1B*, *BTRC2*, *FBX1B*	Yes [130, 131]	Yes [26, 27]	Yes [132]	Yes [133]	β-catenin, Cdc25A, IκB, DEPTOR
Tumor suppressor	FBXW7	*FBXW7*, *FBXW6*, *CDC4*, *SEL-10*, *FBX30*	Yes [41, 54, 134]	Yes [114]		Yes [135–137]	Cyclin E, c-Myc, c-Jun, Mcl-1
Emerging tumor suppressor	FBXW8	*FBXW8*, *Fbx29*, *FBXO29*, *Fbw6*	Yes [126, 127]			CUL7 mutations in 3-M syndrome [138]	IRS1, TBC1D3, Cyclin D1

Table 2.5 Summary of the identified ubiquitin substrates for the Fbxw7

Substrates	Functions/signaling pathways	Phospho-degron (phosphorylation sites)	References
Cyclin E	Cyclin, Cell cycle	Thr62, Thr380, Ser384	[38, 73, 224]
c-Myc	Transcription factor, Cell proliferation	Thr58	[39, 55]
c-Jun	Transcription factor, Cell proliferation	Thr239	[42, 43]
Notch1	Transcription factor, Notch signaling pathway	Thr2512	[47, 84]
SREBP	Transcription factor, Lipid homeostasis	Thr426, Thr430	[225]
c-Myb	Transcription factor, Cell proliferation	Thr572	[226, 227]
JunB	Transcription factor, Cell proliferation	Thr255, Ser259	[228]
KLF2	Transcription factor, T cell quiescence and migration	Thr173, Ser177, Thr244, Ser248	[229]
KLF5	Transcription factor, Adipoctye differentiation and lipid metabolism	Ser303, Thr324	[139, 230]
KLF13	Transcription factor, Negative regulator of cell proliferation and erythrocyte differentiation	Ser119	[8]
C/EBPα	Transcription factor, Cell differentiation and body weight homeostasis	Thr222	[114]
C/EBPδ	Transcription factor, Immune and inflammatory responses	Thr156, Ser160	[131]
p100	Transcription factor	Ser707	[41, 59, 144]
HIF1α	Transcription factor, Hypoxia signaling pathway	Thr497	[116, 141]
Nrf	Transcription factor, Stress response	Ser271, Ser352	[143]
p63	Transcription factor, DNA damage response and cell differentiation		[140]
GRα	Transcription factor, Nuclear receptor signaling	Ser404	[146]
MED13/13L	Mediator, Transcriptional regulation	Thr326, Ser330	[82]
Mcl-1	Bcl-family protein, Anti-apoptotic signaling	Ser64, Ser121, Ser159	[117, 142]
mTOR	Protein kinase, PI3K signaling	Thr631	[48]
B-Raf	Protein kinase, ERK signaling	Thr401, Ser405	[112]
Aurora A	Protein kinase, Cell cycle	Thr217	[134]
Aurora B	Protein kinase, Cell cycle		[113]
Presenilin	Protease, Notch signaling	Thr116	[122]
SRC-3	Transcriptional co-activator, Circadian rhythm	Ser101, Ser102	[123]
PGC-1α	Transcriptional co-activator	Thr255, Thr295	[127]
DEK	Chromatin regulator, Chromatin modification and mRNA splicing	Thr15, Thr66	[126]
TGIF1	Transcription factor, TGFβ signaling	Thr235	[231]
TopoIIα	Topoisomerase, Mitosis and meiosis	Ser1361	[232]
NF1	Regulator of Ras GTPase activity, Ras signaling pathway	Thr2757	[233]
RCAN1	Calcineurin A binding protein, Calcineurin signaling pathway		[234]
CCDC6	ATM substrate, DNA damage response	Ser359, Ser413, Thr427	[235]
GCSF receptor	Receptor, Cytokine signaling pathway		[236]

*FBW7*α. Three novel exons, located upstream of the previously reported first exon, could constitute seven additional *FBW7*α splicing isoforms [54].

Structurally, the three protein isoforms contain a dimerization domain (DD), an F-box domain, seven WD-40 repeats, and a unique isoform-specific N-terminus, which may provide signals regulating subcellular localization, protein expression pattern as well as function [1]. The DD domain ranges from amino acids 145 to 193, which is required for FBW7 dimerization. The linked FBW7 dimers orientate suprafacially and accommodate multiple geometries for its substrate recognition [57]. It is believed that the heterodimeric FBW7 complex comprises the binding pocket to which phosphorylated substrates might interact [57]. Similar to other F-box proteins, FBW7 is responsible for recruiting specific substrates to the SCF core complex in a phosphorylation-dependent manner. The C-terminal WD domain contains seven WD-40 repeats that form a seven-bladed, barrel-shaped β-propeller structure to form a phospho-degron binding pocket, by which FBW7 recognizes and binds to conserved phospho-motifs present within substrates [57]. Most FBW7 targets contain a single high affinity phospho-motif (I/L-I/L/P-T/S-X-X-S/T/E), which is termed the Cdc4 phospho-degron (CPD) [1].

As mentioned above, the unique N-terminus provides each isoform with a distinct subcellular distribution as well as expression pattern [58]. Specifically, FBW7α is ubiquitously expressed in human tissues and localizes to the nucleoplasm, whereas FBW7β is a primarily cytoplasmic protein and enriched in the brain and thymus. FBW7γ is restricted to heart and skeletal muscle and shows a nucleolar distribution [41, 49, 55, 48]. Owing to the high and ubiquitous expression pattern of FBW7α [49, 55], it is reasoned that FBW7α is the major isoform targeting substrates for degradation. This has recently been confirmed by Grim et al., who established isoform-specific *FBW7*-null mutations in human cells, and found that FBW7α is responsible for the degradation of most FBW7 substrates [59]. Additionally, in spite of the subcellular distribution differences, each isoform showed functional compensation in degrading substrates [60]. These functional redundancies and localization differences offer another layer of complexity for the analysis of FBW7 functions. Although the Reed group reported the collaboration of FBW7α and FBW7γ in promoting Cyclin E ubiquitination, more evidence is still necessary to understand the cooperation of each isoform in FBW7 physiological function [61, 62]. It is likely that additional determinants mediate the interaction between substrate and a specific isoform.

2.2.2 Oncogenic Substrates of FBW7

Most FBW7 substrates are vital regulatory effectors involved in various cellular processes (Table 2.5). For instance, Cyclin E participates in cell cycle regulation [63]; c-Myc and c-Jun are critical for cell cycle progression and cell size determination [64, 65]; Notch functions as a regulator of cell fate determination and

differentiation [66]; and Mcl-1 is an anti-apoptotic Bcl-2 superfamily member [67]. In this section, we will discuss several key substrates that will allow us to understand the critical role of FBW7 in cell cycle control, apoptosis, tumor metastasis, and drug resistance.

2.2.2.1 Cyclin E

Cyclin E is the best-characterized substrate of FBW7. It binds to and activates Cyclin-dependent kinase 2 (Cdk2) and catalyzes the transition from the G1 phase to the S phase of the cell cycle [67]. As a critical regulator of cell cycle procession, the amount of Cyclin E present in the cell is tightly controlled by ubiquitin-mediated proteolysis [68]. FBW7 associates specifically with phosphorylated Cyclin E, and targets Cyclin E for ubiquitination and subsequent degradation by the 26S proteasome [69]. Deregulation of Cyclin E has been frequently found in cancer, and enhanced expression of Cyclin E leads to genomic instability and tumorigenesis [68]. Depletion of FBW7 leads to accumulation and stabilization of Cyclin E in various types of human malignances [38]. Thus, Cyclin E is considered a key mediator of FBW7 tumor suppression. In addition, Cyclin E-induced genomic instability in primary human cells can be prevented by cooperation of the p53 and FBW7 pathways, in which overexpression of Cyclin E activates p53, which in turn inhibits Cdk2/Cyclin E activity by induction of $p21^{Cip1}$ [70]. This finding was further confirmed by Minella et al., who demonstrated that mutant Cyclin E, which cannot be degraded by FBW7, induced genomic instability [69]. More recently, one report has defined Cyclin E as the critical signaling connector by which FBW7 governs APC^{Cdh1} activity [71]. Specifically, depletion of Cyclin E in FBW7-deficient cells reduced the expression of elevated APC^{Cdh1} substrates to levels comparable to those in wild-type cells. Conversely, overexpression of Cyclin E recapitulated aberrant Cdh1 substrate expression, which was originally observed in FBW7-deficient cells [71, 72]. More importantly, a Cdh1 mutant that is resistant to Cdk2/Cyclin E-mediated phosphorylation reversed the elevated expression of various APC^{Cdh1} substrates in FBW7-deficient cells [71]. This finding suggests that Cdk2/Cyclin E inhibitors could serve as effective therapeutic agents for treating FBW7-deficient tumors.

Interestingly, two CPD consensus sequences are found within Cyclin E, which has puzzled researchers for quite some time. One CPD is located in the N-terminus and contains a Thr62 phosphorylation site while another is found in the C-terminus and contains Thr380 and Ser384 phosphorylation sites. T380 is phosphorylated by both the Cdk2 and GSK3 kinases, and the phosphorylated T380 degron directly binds to FBW7 [38]. As such, mutation of T380 disrupts Cyclin E ubiquitylation in vivo and in vitro [73]. Moreover, S384 is uniquely phosphorylated by Cdk2 and this phosphorylation provides a negative charge at the +4 position to further increase the binding affinity to FBW7 [74]. Recent work by the Reed group has begun to shed some light on the importance of these two CPDs by showing that degradation of Cyclin E in vivo requires both FBW7α and FBW7γ [62]. In their model, FBW7α

serves as a cofactor for the prolyl *cis–trans* isomerase Pin1 in the isomerization of Cyclin E. Pin1-mediated isomerization of Cyclin E, and subsequent binding to FBW7α, then drives nucleolar localization of Cyclin E, where it is ubiquitylated by FBW7γ prior to its degradation by the proteasome [62]. However, more evidence is still needed to better understand the substrate specificity of each FBW7 isoform, and to further define the role of each CPD in Cyclin E turnover.

2.2.2.2 Notch

Mammals express four transmembrane Notch receptors (Notch-1, -2, -3 and -4) and five canonical transmembrane ligands (DLL 1, DLL 3, DLL 4, Jagged-1, and Jagged-2) [75]. Deregulated expression of Notch proteins, ligands and targets, including overexpression and activation of Notch, has been reported in multiple solid tumors, including cervical [76], lung [77], pancreatic [78], hepatocellular [79], gastric carcinomas [80] and melanoma [81]. Interestingly, Notch is a well-characterized substrate of FBW7. Work from the Nakayama and Elledge groups have described a molecular mechanism by which Notch degradation is mediated by FBW7 in mice [40, 82]. Furthermore, FBW7 was first identified in *C. elegans* as a negative regulator of Notch by genetic screening [83]. Fryer et al. showed that phosphorylation of Notch in the PEST (rich in amino acids P, E, S and T) domain by Cyclin C/Cdk8 leads to binding of FBW7, resulting in turnover of the complex [84]. O'Neil et al. have also defined a functional CPD within Notch at Thr2512 [85]. In support of Notch being a FBW7 substrate, mice lacking *Fbw7* exhibited elevated Notch expression and subsequently impaired cardiovascular development [40]. Moreover, *FBW7* mutations in leukemic cells were found to result in Notch pathway activation through inhibition of Notch degradation [85]. Recently, it has also been demonstrated that SGK1 (serum- and glucocorticoid-inducible protein kinase 1) significantly reduced Notch stability through FBW7 [86]. Moreover, the intracellular domain of Jagged-1 was also found to interact with the Notch1 intracellular domain and promote its degradation through a FBW7-dependent proteasomal pathway [87].

2.2.3 Aberrant Regulation of FBW7 in Cancer Progression

Although intensive efforts have been made to identify various downstream ubiquitin targets for FBW7, relatively little is known about the upstream signaling pathways that control FBW7 stability and cellular functions as well as the regulation of FBW7 itself. To this end, there is emerging evidence demonstrating that the tumor suppressor functions of FBW7 could be governed by multiple regulators, mutations, alternative splicing as well as upstream cellular signaling pathways.

2.2.3.1 Regulation of FBW7 by Upstream Genes

Recently, *FBW7* has been identified as a *bona-fide* transcriptional target of p53 by Mao and colleagues [54]. p53 is a tumor suppressor and involved in many cellular processes including cell growth, DNA synthesis and repair, differentiation, apoptosis and cellular response to a wide range of biological stresses. Initially, Kimura et al. found that expression of *FBW7* was dramatically upregulated by infecting p53-deficient cells with an adenovirus encoding wild-type p53 [88]. Furthermore, they demonstrated that the first exon of *FBW7* contains a p53-binding site that displays p53-dependent transcriptional activity [88]. In addition, expression of FBW7β was induced in a p53-dependent manner after genotoxic stresses such as UV irradiation, suggesting that *FBW7* is a direct transcriptional target of p53. In line with this finding, Mao et al. subsequently reported that FBW7 mediated the role of p53 in response to DNA damage, indicating that the *FBW7* gene is a p53-dependent tumor suppressor. Taken together, these studies showed that targeting the p53 signaling pathway could potentially influence FBW7 expression, which might provide a feasible approach to restore FBW7 expression during anticancer therapies [54].

Additionally, Pawar et al. reported that the transcription factor C/EBPδ (CCAAT/enhancer binding protein δ) directly inhibited *FBW7* gene expression and induced the accumulation of FBW7 oncogenic targets mTOR and Aurora A. C/EBPδ is one of six isoforms of the C/EBP family that is a highly conserved family of leucine zipper type DNA-binding proteins [89]. By binding to the transcription motif of the *FBW7* promoter, C/EBPδ may block the access of p53, resulting in suppression of *FBW7* transcription [90]. Interestingly, this study also revealed that C/EBPδ promoted breast tumor metastasis, indicating that further investigation is required to determine the molecular mechanisms, especially the contribution of FBW7 in mediating the cellular functions of C/EBPδ in promoting tumor metastasis [91].

Another positive regulator of FBW7, Numb, has also been recently identified. Numb is a membrane-bound protein that associates with Notch-1. In several types of cancers, loss of Numb expression has been observed [92–94]. In approximately half of all human mammary carcinomas, Numb-mediated suppression of Notch signaling is lost in part due to Numb ubiquitination and proteasomal degradation [95]. Recently, it has been shown that one of the predominant Numb isoforms, Numb4, promoted SCF^{FBW7} ubiquitin ligase assembly and activation, leading to enhanced Notch degradation [96]. However, further in-depth investigation is required to understand the physiological contribution of Numb4-mediated regulation of SCF^{FBW7} ubiquitin ligase activity in tumorigenesis in vivo.

2.2.3.2 Regulation of FBW7 by the MicroRNAs (miRNAs)

Another potential group of *FBW7* upstream regulators are micro-RNAs. micro-RNAs are short RNA molecules that average 22 nucleotides long and bind to complementary sequences on target mRNAs, resulting in translational repression or target degradation, leading to gene silencing [97–99]. Recent studies have

shown that multiple miRNAs including miR-27a and miR-223 could regulate FBW7 expression.

Xu et al. first reported that miR-223 could directly regulate the activity of the SCF^{FBW7} ubiquitin ligase [100]. They found that overexpression of miR-223 could increase endogenous Cyclin E protein abundance and activity, leading to increased genomic instability by significantly reducing *FBW7* mRNA levels. Conversely, reduced miR-223 expression resulted in increased FBW7 expression and decreased Cyclin E activity, indicating that *FBW7* could be modulated directly by miR-223 [100, 101]. Consistent with this finding, negative regulation of *FBW7* by miR-223 was also described in gastric tumor tissues, squamous cell carcinoma and esophageal cancers [53, 102]. These data indicate that microRNAs may be involved in the transcriptional regulation of *FBW7* to affect FBW7 substrate degradation and function.

It has also been documented that miR-27a played an oncogenic role in human cancers [103–105]. An inverse correlation between miR-27a expression and FBW7 levels in human tumor samples has been observed, indicating that *FBW7* is a potential target of miR-27a [104, 106]. Recently, Lerner et al. identified that miR-27a suppressed FBW7 expression, leading to a reduction in ubiquitin-mediated degradation and turnover of the FBW7 substrate, Cyclin E [107]. Overexpression of FBW7 caused dysregulation of Cyclin E, resulting in altered cell cycle progression. Conversely, miR-27a knockdown increased FBW7 levels and subsequently decreased the abundance of FBW7 substrates such as c-Myc, c-Jun and Notch-1 in colon cancer derived cell lines. Furthermore, miR-27a overexpression promoted cell growth, whereas miR-27a knockdown inhibited cell proliferation in vitro and tumor formation in vivo in part through regulating FBW7. In addition, miR-27a was found to primarily suppressed FBW7 expression during G1–S phase transition [107].

In addition, miR-25 has also been shown to inhibit FBW7 expression and caused upregulation of c-Myc and KLF5 to promote reprogramming of mouse fibroblast cells to iPSCs [108]. Overexpression of miR-129-5p led to upregulation of FBW7 expression [109]. However, it remains largely unclear how these different miRNAs regulate *FBW7* in a redundant or synergistic manner, and whether different subsets of miRNAs play a primary role in different tissue or cellular context.

2.2.3.3 Regulation of Translational Efficiency by Alternative Splicing

Largely functioning as a tumor suppressor to promote the degradation of multiple oncoproteins, loss of FBW7 expression is frequently observed in various human cancers [50]. However, the exact molecular mechanisms regulating FBW7 expression still remain poorly understood. Using the RACE technique, Liu et al. examined the 5′ region of the *FBW7* gene and identified three novel noncoding exons located in the 5′ untranslated region (UTR). Notably, this region is composed of seven alternatively spliced 5′-UTR forms of *FBW7α* and significant differences in the translational efficiency among these 5′-UTR variants were observed. Furthermore, the mRNA levels of these splice forms were reduced in more than 80 % of all breast cancer cell lines tested and in more than 50 % of all human primary cancers

examined from various tissues. These results suggested that differential expression of *FBW7α* splice forms with different translational properties may serve as a novel mechanism for inactivation of FBW7 in human cancers [49].

2.2.3.4 Dominant Negative Regulation of FBW7 Mutations

FBW7 status has been examined among numerous primary human tumors [110]. In a comprehensive study of over 1,500 human tumors, Akhoondi et al. found that 6 % of tumors examined harbored mutations in the *FBW7* coding regions. Cholangiocarcinoma and T-ALL contained the highest frequency of mutations at 35 % and 31 %, respectively, while only 9–15 % of tumors of the stomach, colon, pancreas, and endometrium contained detectable *FBW7* mutations [54]. Strikingly, nearly half (43 %) of these were missense mutations and resulted in amino acid substitutions at key arginine residues within the WD40 domain (Arg465, Arg479, and Arg505), which are shared by all three FBW7 isoforms. Most of the remaining mutations were nonsense codons that lead to premature termination of FBW7 translation.

Unlike many known tumor suppressors, FBW7 tends to be mutated in only one allele [54]. The mutations including both missense and nonsense mutations result in the inactivation of FBW7 by loss of binding capability to substrates. Impaired substrate binding in full-length FBW7 mutants raises the possibility that these mutations might function as potent dominant negatives. Indeed, several groups have shown that FBW7 hot-spot mutants can dominantly interfere with the ability of the wild-type protein to degrade c-Myc, Sic1, and Cyclin E [50, 57, 85]. Dominant negative FBW7 mutants form heterodimers with wild-type FBW7, and therefore causing loss of binding between dimerized SCF^{FBW7} E3 ligases and target substrates, making FBW7 a haplo-insufficient tumor suppressor [1, 111].

2.2.4 FBW7 Knockout Mouse Models: Implications for Tumor Development

To better understand the underlying mechanisms of tumor formation due to loss of FBW7 function, several FBW7 conditional knockout and knock-in mouse models have been developed (Tables 2.1 and 2.3).

Double allele knockout of *FBW7* is lethal and causes embryos to die in utero at embryonic day 10.5 with growth retardation and impaired vascular development, which might be in part caused by the accumulation of FBW7 substrates Notch-1 and Notch-4 [40, 41]. Due to the limitation of embryonic mortality associated with the *Fbw7*$^{-/-}$ mice, conditional ablation of *Fbw7* in various adult tissues has been developed. So far, conditional inactivation of *Fbw7* in the T-cell lineage, bone marrow, intestine, liver, breast, and brain has been reported (Table 2.1).

Specifically, mice with conditional inactivation of *Fbw7* in the T-cell lineage develop thymic lymphoma partly due to excessive accumulation of c-Myc [112]. Bone marrow (BM)-specific *Fbw7* knockout mice exhibit extremely severe pancytopenia 12 weeks post-deletion of *Fbw7*, and develop T-ALL within 16 weeks due to the accumulation of Notch and c-Myc as well as deregulation of p53-induced exhaustion of hematopoietic stem cells (HSCs) [82, 113]. Interestingly, King et al. demonstrated that, in contrast to these knockout mouse models, HSCs with a *Fbw7* WD40 mutation ($Fbw7^{R465C/+}$) did not compromise HSC functions but increased the proportion of leukemia initiating cells in collaboration with Notch1 in vivo [114]. Mice with *Fbw7* deletion in the gut survived and were fertile without exhibiting any gross phenotypic alteration [115]. However, when crossed with $APC^{min/+}$ mice, intestinal tumors developed due to enhanced APC (Adenomatous polyposis coli-mediated tumorigenesis)-mediated intestinal tumorigenesis via upregulation of the FBW7 substrates Notch-1 and c-Jun [48]. More recent studies have also demonstrated that mice harboring a heterozygous hot-spot mutant (R482Q, which is equivalent of R479Q in human) in the *APC* mutant background ($Fbw7^{R482Q/+}/Apc^{1322T/+}$) developed intestinal tumor more frequently than *Fbw7* heterozygous mice in the same $Apc^{1322T/+}$ background [113, 146]. Furthermore, *Fbw7* deficiency in the liver eventually caused the development of hematomas partly due to accumulation of SREBP and Notch-1 [121]. In addition, $Fbw7^{+/-}$ mice are susceptible to radiation-induced tumorigenesis and irradiated $Fbw7^{+/-}/p53^{+/-}$ mice developed lymphomas in 70 % of total mice examined [54]. These mice also displayed a wide spectrum of different tissue tumors in lung, liver, and ovary [54]. Taken together, FBW7 functions as a haploid insufficient tumor suppressor with single allele deletion capable of promoting tumorigenesis.

2.2.5 *Targeting the FBW7 Signaling Pathway as a Potential Therapeutic Anticancer Strategy*

Although FBW7 behaves as a tumor suppressor, emerging evidence points to FBW7 as a potential therapeutic target. First, FBW7 functions as a pro-survival factor in multiple myeloma by constitutively targeting the NF-κB inhibitor p100 for degradation in a GSK3-dependent manner [118–120]. NF-κB plays a key role in regulating the immune response to infections and is involved in cellular responses to stimuli such as stress, cytokines, and free radicals. In addition, aberrant regulation of NF-κB has been linked to cancer [121]. Second, a number of cancers, including T-ALL, breast cancers and gastric adenocarcinoma often carry mutations in the *FBW7* gene, leading to an accumulation of mitogenic proteins, whereas these mutations do not occur in B-cell malignancies like multiple myeloma [50]. Therefore, FBW7 and GSK3 may serve as promising targets for the treatment of multiple myelomas with constitutive activation of the NF-κB pathway.

More recent reports have revealed that FBW7 plays a pivotal role in the maintenance of quiescence in leukemia-initiating cells (LICs) of chronic myeloid leukemia (CML) [114]. Ablation of *Fbw7* in LICs leads to accumulation of c-Myc and

impaired maintenance of quiescence followed by p53-dependent apoptosis and cellular exhaustion. Furthermore, small-molecule mediated suppression of Myc activity results in the T-ALL remission. *Fbw7* deletion induces LICs into cell cycle progress and thus sensitizes the LICs to Imatinib (Gleevec) treatment [122, 123]. These studies identify FBW7 as an essential regulator of CML's LIC maintenance and open the way for targeting FBW7 activity in CML.

Furthermore, given the frequent loss of FBW7 in various human cancers and the fact that many FBW7 downstream targets are oncoproteins, it will be important to identify the driving oncoproteins in different types of FBW7-deficient human cancers. As these FBW7-deficient tumors are addicted to these driving oncoproteins, targeting specific oncoproteins regulated by FBW7 will be more efficient for cancer treatment.

2.3 The Emerging Tumor Suppressor Role of FBXW8

FBXW8 (also known as FBW6, FBW8, FBX29, FBXW6, or FBXO29) is the only substrate receptor identified for the Cul7-SCF E3 ubiquitin ligase complex. FBXW8 was shown to play a pivotal role in cancer cell proliferation in part by promoting Cyclin D1 degradation during S phase [124], and the turnover of IRS1, a key component of signaling pathways activated by the insulin and insulin-like growth factor 1 (IGF-1) receptors (Table 2.6). In this regard, a recent study showed that mTORC2

Table 2.6 Summary of identified ubiquitin substrates for the FBXW class of F-box proteins other than β-TRCP1/2 and Fbxw7

F-box protein	Substrate	Signaling pathway/functions	References
FBXW2 Undetermined	GCMa	Transcription factor critical for glial and placental cell differentiation	[237]
FBXW5 Undetermined	Eps8	A bifunctional actin cytoskeleton remodeller, a positive regulator of cell proliferation and motility	[238]
	HsSAS-6	Centriolar protein	[239, 240]
FBXW8 Emerging tumor suppressor	IRS-1	An adaptor protein that is one of the major substrates of the insulin receptor kinase	[125]
	TBC1D3	A GTPase activating protein for RAB5	[241]
	Cyclin D1	Cell cycle	[124]
	GRASP65	Stacking factor involved in the postmitotic assembly of Golgi stacks from mitotic Golgi fragments	[129]
	IGFBP2	IGF-binding protein	[127]
FBXW10 Undetermined	HP1alpha and beta	Heterochromatin protein 1alpha and beta	[242]
FBXW15 Undetermined	HBO1	Origin recognition complex, DNA replication licensing	[243]

stabilizes FBXW8 by phosphorylation of Ser86, allowing the insulin-induced translocation of FBXW8 to the cytosol where it mediates IRS-1 degradation [125]. In spite of these studies, it remains unclear whether FBXW8 is necessary for cell cycle progression in normal cells.

FBXW8 is not expressed at a detectable level in adult mouse tissues with the exception of the placenta [126, 127]. Moreover, FBXW8 is dispensable for Cyclin D1 degradation in MEFs [128]. Together, these observations suggest that FBXW8 might be required for Cyclin D1 degradation only in certain cancer cell lines. Two independent groups analyzed the function of FBXW8 in vivo by generating *Fbxw8* knockout mice (Table 2.1). In the first study, exon 2 that encodes the F-box domain was disrupted, leading to approximately 60 % of *Fbxw8*$^{-/-}$ embryos dying in utero, where remaining embryos are born alive and grow to the adulthood [126]. In the second study, a gene-trap approach was used with the targeting vector inserted at the 3′ end of exon 3 of the *Fbxw8* gene. Again, about 30 % of *Fbxw8*$^{-/-}$ mice survived after the birth, but these mice remained smaller in both body weight and organ sizes compared with their wild-type littermates [127]. Phenotypically, both studies showed that *Fbxw8*-deficient mice exhibited prenatal and postnatal growth retardation resulting from a defect in placental development [126, 127]. Given that FBXW8 is dispensable for the degradation of Cyclin D1 in MEFs, the phenotype of Fbxw8-deficient mice may be due to the accumulation of substrates other than Cyclin D1 (Table 2.1). These studies suggest that the accumulation of IRS-1 or other still unknown FBXW8 substrates in the placenta might be responsible for the growth retardation observed in mice deficient in *Fbxw8*.

Additionally, the Cul7^{FBXW8} complex was found to control the morphogenesis of the Golgi apparatus and patterning of dendrites by targeting for ubiquitination the Golgi protein Grasp65 [129]. These findings link the Cul7^{FBXW8} ubiquitin signaling mechanism with the normal development of the brain [129]. Together, these studies revealed FBXW8 as a key factor controlling organismal growth and development. However, more thorough studies are required to further understand the physiological role of FBXW8 in tumorigenesis by generating additional conditional knockout or transgenic mouse models as well as biochemically identifying additional ubiquitin substrates for Cul7^{FBXW8} to reveal the major signaling pathways controlled by Cul7^{FBXW8}.

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