

Table S I . Characteristics and disease associations of F-box protein family members.

A, FBXL						
First author/s, year	Name	Localization	Substrate protein	Biological roles (mechanisms of action) upon binding to substrates	Related diseases	(Refs.)
Shapira <i>et al</i> , 2006; Gao <i>et al</i> , 2009; Lin <i>et al</i> , 2006; Zaytseva <i>et al</i> , 2008; Lu <i>et al</i> , 2004; Asmamaw <i>et al</i> , 2020; Sistrunk <i>et al</i> , 2013	SKP2	Cytoplasm, nucleus	PI3K/Akt, ERK, peroxisome proliferator-activated receptor $\gamma$ , insulin-like growth factor 1, mTOR, mH2A1, CDK8,	Upon binding to PI3K/Akt, ERK, PPAR $\gamma$ , IGF1, mTOR, mH2A1, CDK8, SKP2 regulates cell cycle progression, cell migration, and mediates antiviral activity	Breast cancer, melanoma, pancreatic cancer, gastric cancer, lymphoma, prostate cancer, and nasopharyngeal cancer	(1-7)
Niu <i>et al</i> , 2021; Chen <i>et al</i> , 2011	FBXL2	Membrane	Calmodulin, PIK3R1, PTPN13	Upon binding to Calmodulin, PIK3R1, PTPN13, FBXL2 regulates cell cycle progression, acts as a calmodulin antagonist, and modulates inflammatory pathways	Hepatitis C virus, Cinca syndrome	(8,9)
Ansar <i>et al</i> , 2019; Correia <i>et al</i> , 2019	FBXL3	Nucleus, cytoplasm	CRY1, CRY2, HDAC3, KDM8	Upon binding to CRY1, CRY2, HDAC3, KDM8, FBXL3 regulates biological clock rhythms and protein folding processes	Intellectual developmental disorder with short stature, facial anomalies, speech defects, epilepsy	(10,11)
Nguyen-Dien <i>et al</i> , 2023	FBXL4	Cytoplasm, nucleus, mitochondrion	VCP, PPTC7	Upon binding to VCP, PPTC7, FBXL4 regulates cell cycle progression	Mitochondrial DNA depletion syndrome 13, mitochondrial DNA depletion syndrome	(12)
Ruiz <i>et al</i> , 2014; Wang <i>et al</i> , 2023	FBXL5	Cytoplasm (perinuclear region), nucleus	ACO1/IRP1, IREB2/IRP2, DCTN1/p150	Upon binding to ACO1/IRP1, IREB2/IRP2, DCTN1/p150, FBXL5 regulates iron homeostasis, DNA damage response pathways, and protein folding processes	Spastic paraplegia 38, autosomal dominant Alzheimer disease 3	(13,14)
Moro <i>et al</i> , 2020; Wang <i>et al</i> , 2022	FBXL7	Cytoplasm (microtubule organizing center, centrosome)	AURKA, BIRC5	Upon binding to AURKA, BIRC5, FBXL7 regulates cell cycle, mitosis, and mitochondrial function	Hennekam syndrome, autonomic peripheral neuropathy	(15,16)
Moro <i>et al</i> , 2020; van Jaarsveld <i>et al</i> , 2023	FBXL10	Nucleus (nucleolus, chromosome)	PCGF1-BCORL1, CUL1, UBB	Upon binding to PCGF1-BCORL1, CUL1, UBB, FBXL10 exhibits histone demethylase activity and regulates cell viability and proliferation	Hematologic cancer, large B-cell lymphoma	(15,17)

Brunner <i>et al</i> , 2023; Nita <i>et al</i> , 2016	FBXL12	Cytoplasm	SKP1, CUL1	Upon binding to SKP1, CUL1, FBXL12 regulates cell cycle and T-cell differentiation	-	(18,19)
Morohoshi <i>et al</i> , 2020	FBXL13	Cytoplasm	SKP1, CUL1, TCTE1/DRC5	Upon binding to SKP1, CUL1, TCTE1/DRC5, FBXL13 regulates ciliary/flagellar motility	Rumination disorder, advanced sleep phase syndrome	(20)
Fang <i>et al</i> , 2017; Cui <i>et al</i> , 2018	FBXL14	Cytoplasm	SKP1, CUL1, SNAI1	Upon binding to SKP1, CUL1, SNAI1, FBXL14 regulates cell cycle	-	(21,22)
Cui <i>et al</i> , 2011	FBXL15	Cytoplasm	SMURF1, SMURF2, WWP2	Upon binding to SMURF1, SMURF2, WWP2, FBXL15 regulates cell cycle and mitosis, and acts as a positive regulator of the BMP signaling pathway	Bardet-Biedl syndrome 10, ceroid lipofuscinosis	(23)
Kang <i>et al</i> , 2022	FBXL17	Cytoplasm, nucleus	KLHL12, BCL6, BACH1, SUFU, PRMT1	Upon binding to KLHL12, BCL6, BACH1, SUFU, PRMT1, FBXL17 regulates cellular responses to stimuli and maintains neuronal differentiation and survival	Medulloblastoma	(24)
Zhang <i>et al</i> , 2017; Yu <i>et al</i> , 2023	FBXL18	Cytoplasm	SKP1, CUL1, AKT	Upon binding to SKP1, CUL1, AKT, FBXL18 regulates cell cycle and mitosis	Gliomas, hepatocellular carcinoma	(25,26)
Xun <i>et al</i> , 2023	FBXL19	Cytoplasm, nucleus	RHOA, RAC1, RAC3, IL1RL1, RNF20	Upon binding to RHOA, RAC1, RAC3, IL1RL1, RNF20, FBXL19 regulates cell migration, proliferation, or cytoskeletal reorganization	Psoriasis 10, psoriasis 6	(27)
Wang <i>et al</i> , 2024	FBXL20	Cytoplasm	SKP1, CUL1	Upon binding to SKP1, CUL1, FBXL20 affects synaptic transmission	-	(28)
Hirano <i>et al</i> , 2013	FBXL21	Cytoplasm	CRY1, CRY2	Upon binding to CRY1, CRY2, FBXL21 regulates biological clock	-	(29)

## B, FBXW

First author/s, year	Name	Localization	Substrate protein	Biological roles (mechanisms of action) upon binding to substrates	Related diseases	(Refs.)
Mo <i>et al</i> , 2022; Wang <i>et al</i> , 2023	$\beta$ -TRCP	Cytoplasm, nucleus	SKP1, SMAD3, SMAD4, CTNNB1, NFKBIA, NFKBIB, NFKBIE, NFKB1/nuclear factor NF- $\kappa$ B p105 subunit, ATF4,	Upon binding to SKP1, SMAD3, SMAD4, CTNNB1, NFKBIA, etc., $\beta$ -TRCP regulates cell cycle, mitosis, apoptosis, and the maintenance of cell pluripotency and embryogenesis	Autosomal recessive Robinow syndrome 2, split-hand/foot malformation 1	(30,31)

Yang <i>et al</i> , 2019; Yin <i>et al</i> , 2019	FBXW2	Cytoplasm	CDC25A, DLG1, FBXO5, SNAI1, CDC34, UBE2R2, ZC3H12A, HSF1, IL10RA, UBR2 SKP1, CUL1	Upon binding to SKP1, CUL1, FBXW2 regulates cell migration and protein folding	Acute myeloid leukemia, frontometaphyseal dysplasia 1	(32,33)
Yao <i>et al</i> , 2022	FBXW5	Cytoplasm	CDC20, EPS8, TSC1, TSC2, SASS6, TNFAIP8L1	Upon binding to CDC20, EPS8, TSC1, TSC2, etc., FBXW5 regulates cell cycle, mitosis, and protein folding	Localized chondrosarcoma, Cockayne syndrome A	(34)
Fan <i>et al</i> , 2022; Fujii <i>et al</i> , 2006; Yang <i>et al</i> , 2015; Mao <i>et al</i> , 2004; Mao <i>et al</i> , 2008; Tu <i>et al</i> , 2012 Islam <i>et al</i> , 2021	FBXW7	Cytoplasm, nucleus	SKP1, pseudophosphatase STYX, CCNE1, CCNE2, PSEN1, NOTCH1, SGK1, MYC, USP28, JUN, PRR7, PIN1, FAM83D, MYCN, RECTOR	Upon binding to SKP1, STYX, CCNE1, CCNE2, etc., FBXW7 regulates cell cycle, DNA repair, protein folding, bone homeostasis, and glucose/lipid metabolism	Developmental delay, hypotonia, impaired language, colorectal cancer	(35-40)
	FBXW8	Cytoplasm (perinuclear region, Golgi apparatus in neurons)	CUL7, SKP1, GLMN isoform 1, OBSL1, CUL1, CUL2, CCT6B, PFDN5, CCT2, CCT3, CCT6A, CCT7, VBP1, CCDC8, ARF1, TRIP13, PDCD5, GORASP1, MAP4K1/HPK1, POUF51	Upon binding to CUL7, SKP1, GLMN isoform 1, etc., FBXW8 regulates cell proliferation and differentiation	Three M syndrome 1	(41)
Franz <i>et al</i> , 2015	FBXW1 2	Cytoplasm	SKP1, CUL1, IL22RA1	Upon binding to SKP1, CUL1, IL22RA1, FBXW12 acts as a cell proliferation-inhibiting factor	Mature teratoma of the ovary	(42)

### C, FBXO

First author/s, year	Name	Localization	Substrate protein	Biological roles (mechanisms of action) upon binding to substrates	Related diseases	(Refs.)
Lee <i>et al</i> , 2023	FBXO1	Nucleus, cytoplasm (perinuclear region, cytoskeleton, microtubule organizing center, centrosome, centriole)	SKP1, CUL1, CCNB1, CCP110, MYBL2/BMYB, FZR1/CDH1, RRM2, CDC6	Upon binding to SKP1, CUL1, CCNB1, CCP110, etc., FBXO1 regulates cell cycle transitions, inhibits centrosome duplication and maintains genomic stability	Frontotemporal dementia and/or amyotrophic lateral sclerosis 5, frontotemporal dementia and/or amyotrophic lateral sclerosis 7	(43)

Atkin <i>et al</i> , 2014; Liu <i>et al</i> , 2017; Ji <i>et al</i> , 2022	FBXO2	Cytoplasm (microsome membrane, peripheral membrane protein, cytoplasmic side)	HADHA, GAS, N-cadherin, SUN2, CDK4, CyclinD 1, CyclinD 2, CyclinA 1, ATG4, p53	Upon binding to HADHA, GAS, N-cadherin, etc., FBXO2 recognizes denatured glycoproteins and prevents cytoplasmic aggregate formation	Ngly1-deficiency	(44-46)
Gao <i>et al</i> , 2022.	FBXO3	Nucleus	HIPK2, PML, LPS	Upon binding to HIPK2, PML, LPS, FBXO3 regulates inflammation	Rift valley fever, esophageal neuroendocrine tumor	(47)
Lee <i>et al</i> , 2013; Lian <i>et al</i> , 2015	FBXO4	Cytoplasm	CCND1, TERF1, FXR1	Upon binding to CCND1, TERF1, FXR1, FBXO4 regulates pericentriolar material organization and protein folding	Spermatogenic failure 64, esophageal cancer	(48,49)
Ji <i>et al</i> , 2021; Liu <i>et al</i> , 2021	FBXO6	Cytoplasm	VCP, CHEK1, CUL1	Upon binding to VCP, CHEK1, CUL1, FBXO6 regulates cell cycle, is involved in DNA damage response and regulates protein folding	Ngly1-deficiency, lung cancer	(50,51)
Zhong <i>et al</i> , 2023	FBXO7	Cytoplasm, nucleus	DLGAP5, BIRC2, CDK6, PSMF1, PRKN, PINK1, UXT isoform 2	Upon binding to DLGAP5, BIRC2, CDK6, etc., FBXO7 regulates cell cycle, proliferation, maintains chromosome stability, regulates mitochondrial autophagy, and hematopoiesis	Parkinson disease 15, autosomal recessive early-onset; Parkinson disease 2, autosomal recessive juvenile	(52)
Duan <i>et al</i> , 2012	FBXO11	Nucleus (chromosome)	CIITA, BCL6, DTL/CDT2, SNAI1, BAHD1, PRDM1/BLIMP1	Upon binding to CIITA, BCL6, DTL/CDT2, etc., FBXO11 regulates immune cell differentiation, cell cycle, migration, inflammatory response, and exhibits protein-arginine N-methyltransferase activity	Intellectual developmental disorder with dysmorphic facies and behavioral abnormalities, colorectal cancer	(53)
Liu <i>et al</i> , 2021; Ji <i>et al</i> , 2021	FBXO16	Nucleus	hnRNPL, ULK1, NF-κB p65 subunit	Upon binding to hnRNPL, ULK1, NF-κB p65 subunit, FBXO16 regulates cell cycle	Spastic paraplegia 37, autosomal dominant, spastic paraplegia 26, autosomal recessive	(51,54)
Dobish <i>et al</i> , 2023	FBXO21	Cytoplasm	SKP1, CUL1	Upon binding to SKP1, CUL1, FBXO21 regulates cell cycle	-	(55)
Johmura <i>et al</i> , 2020; Zhang <i>et al</i> , 2019	FBXO22	Cytoplasm (myofibril, sarcomere, Z line)	SKP1, CUL1, KDM4A, TP53, MTOR, BACH1	Upon binding to SKP1, CUL1, KDM4A, etc., FBXO22 regulates cell cycle and acts as a senescence regulator	-	(56,57)

Santra <i>et al</i> , 2009; Zou <i>et al</i> , 2018; Malonia <i>et al</i> , 2015; Liu <i>et al</i> , 2014	FBXO31	Cytoplasm	CCND1, OGT, CD147, SIRT2, GPX4	Upon binding to CCND1, OGT, CD147, etc., FBXO31 regulates cell cycle and acts as a tumor suppressor	Intellectual developmental disorder, autosomal recessive 45, autosomal recessive non-syndromic intellectual disability	(58-61)
Wu <i>et al</i> , 2024; Habel <i>et al</i> , 2021	FBXO32	Cytoplasm, nucleus	TERF1, PTEN, cyclin D, MYC	Upon binding to TERF1, PTEN, cyclin D, MYC, FBXO32 regulates gene transcription and is associated with muscular dystrophy	Left ventricular noncompaction, dilated cardiomyopathy	(62,63)
Zheng <i>et al</i> , 2023; Meng <i>et al</i> , 2018	FBXO38	Cytoplasm (cytosol), nucleus	PDCD1/PD-1, KLF7	Upon binding to PDCD1/PD-1, KLF7, FBXO38 modulates T-cell immunity and acts as a tumor suppressor	Neuronopathy, distal hereditary motor, autosomal dominant 6, neuronopathy, distal hereditary motor, autosomal dominant 2	(64,65)
Richter <i>et al</i> , 2020; Chung <i>et al</i> , 2014	FBXO45	Cytoplasm, nucleus	HEY1, N-cadherin/CDH2, TP73, NMNAT2, FBXW7	Upon binding to HEY1, N- cadherin/CDH2, etc., FBXO45 regulates cell cycle, mitosis, synaptogenesis, and neuronal migration	Spermatogenic failure 64, chromosome 3Q29 microduplication syndrome	(66,67)

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BMP, bone morphogenetic protein; FBXL, F-box proteins with leucine-rich amino acid repeats; FBXO, F-box only protein; FBXW, F-box proteins with WD-40 amino acid repeats; Ngly1, N-glycanase 1.

Table S II . Core molecular mechanisms and biological effects involving FBXO2 in tumor diseases.

First author/s, year	Tumor type	Core mechanism	Key molecules/signaling pathways	E2 ligase	E3 ligase	Biological roles (FBXO2 upon substrate binding)	(Refs.)
Sun <i>et al</i> , 2018	Gastric cancer	FBXO2 regulates EMT to exert its effect	E-cadherin, N-cadherin, vimentin	UBE2D3	SCF-FBXO2 complex (consisting of SKP1, CUL1, RBX1 and FBXO2)	FBXO2 promotes proliferation, migration and invasion; low expression inhibits the proliferation, migration and invasion of GC cells by reducing EMT	(68)
Wei <i>et al</i> , 2018; Zhao <i>et al</i> , 2022	Colorectal cancer	FBXO2 mediates EMT involvement in metastasis through UPS-mediated degradation of tumor suppressor proteins and by influencing the Wnt signaling pathway	N-cadherin, $\beta$ -catenin, Wnt signaling pathway			FBXO2 promotes proliferation, infiltration and distant metastasis; inhibition of FBXO2 can improve prognosis, and the expression levels can be used as a biomarker for metastasis	(69,70)
Ji <i>et al</i> , 2022; Lai <i>et al</i> , 2024	Ovarian cancer	SOX6-FBXO2-SUN2 axis; pathways related to chemotherapy resistance	SOX6, SUN2 (ubiquitination-dependent degradation), PI3K-Akt signaling pathway			FBXO2 inhibits apoptosis and promotes proliferation; related to chemotherapy resistance (knockdown of FBXO2 reduces the IC <sub>50</sub> of cisplatin)	(46,71)
Che <i>et al</i> , 2020	EC	Ubiquitination-mediated degradation of FBN1, regulating the cell cycle and autophagy pathways	FBN1 (degradation), CDK4, CyclinD1/2, CyclinA1, ATG4A/4D	UBE2D2 or UBE2D3		Promotes proliferation; targeting FBXO2 may enable the treatment of EC by regulating the cell cycle and autophagy pathways	(72)
Zhao <i>et al</i> , 2020	Osteosarcoma	Stabilizes IL-6R and activates the STAT3 signaling pathway	IL-6R (stable), STAT3 (phosphorylated and activated)	-	-	Promotes proliferation; inhibition of FBXO2 can shorten the half-life of IL-6R and inhibit the STAT3 pathway	(73)
Buehler <i>et al</i> , 2023; Atkin <i>et al</i> , 2015	GB	Participates in the interaction between glioma and the microenvironment, and regulates synaptic-related molecules	NMDAR subunits (GluN1, GluN2A), synaptic signals	UBE2D3	SCF-FBXO2 complex (consisting of SKP1, CUL1, RBX1 and FBXO2)	Promotes invasive growth; highly expressed in recurrent GB; inhibition can improve survival rate	(74,75)
Guo <i>et al</i> , 2024	Papillary thyroid carcinoma	Ubiquitination-mediated degradation of the tumor suppressor protein p53	p53 (ubiquitination-dependent degradation)			Facilitates cell proliferation and exhibits a positive association with tumor size and metastasis; knockdown can inhibit proliferation and promote apoptosis	(76)

Cheng <i>et al</i> , 2025	Oral squamous cell carcinoma	FBXO2 regulates the transformation of malignant clones, and influences the cell cycle and EMT	Cyclin D1/E1, CDK4/2, E-cadherin, N-cadherin, Vimentin; PI3K-Akt signaling pathway, Cyclin-CDK-pRb-E2F signaling pathway	Promotes the formation of highly malignant clones; enhances proliferation, migration, invasion and anti-apoptotic capabilities	(77)
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FBXO2, F-box protein 2; SCF, S-phase kinase-associated protein 1-Cullin-F-box; UPS, ubiquitin-proteasome system; E1, ubiquitin-activating enzyme; E2, ubiquitin-conjugating enzyme; E3, ubiquitin ligase; EMT, epithelial-mesenchymal transition; CRC, colorectal cancer; OV, ovarian cancer; EC, endometrial cancer; OS, osteosarcoma; GB, glioblastoma; PTC, papillary thyroid carcinoma; OSCC, oral squamous cell carcinoma; FBN1, fibrillin 1; IL-6R, interleukin-6 receptor; STAT3, signal transducer and activator of transcription 3; NMDAR, N-methyl-D-aspartate receptor; p53, tumor protein p53; VEGF, vascular endothelial growth factor; PTEN, phosphatase and tensin homolog; PI3K-Akt-mTOR, phosphatidylinositol 3-kinase-protein kinase B-mammalian target of rapamycin; NRF2, nuclear factor erythroid 2-related factor 2; MAPK, mitogen-activated protein kinase; SUN2, Sad1 and UNC84 domain-containing protein 2; APC/C, anaphase-promoting complex; CDC20, cell division cycle 20; CDH1, cadherin 1; MDM2, murine double minute 2 homolog; FBXL, F-box protein with leucine-rich amino acid repeats; FBXW, F-box protein with WD-40 amino acid repeats; FBP, F-box protein; ROC1, Ring Box Protein 1/RING-box 1/HRT1 (RING-box protein HRT1); CDK, cyclin-dependent kinase; IR, insulin receptor; NAFLD, non-alcoholic fatty liver disease; PD, Parkinson's disease; AD, Alzheimer's disease; NPC, Niemann-Pick C disease; OA, osteoarthritis; IVD, intervertebral disc; GAS, group A streptococcus; gB, Epstein-Barr virus glycoprotein B; SNAIL, Snail homolog 1; TWIST, Twist protein; Mcl-1, myeloid cell leukemia-1 protein; XIAP, X-linked inhibitor of apoptosis protein; GluN1, GluN1 subunit of NMDAR; GluN2A, GluN2A subunit of NMDAR; Ki-67, a nuclear antigen associated with cell proliferation; SIRT2, sirtuin 2; Myc, proto-oncogene Myc; MAPKK6, mitogen-activated protein kinase kinase 6; CDCP1, CUB domain-containing protein 1; USP13, ubiquitin-specific peptidase 13; FBXW7, F-box protein with WD-40 repeats 7; FBXO4, F-box protein with only uncharacterized structural domains 4; FBXO11, F-box protein with only uncharacterized structural domains 11; FBXO31, F-box protein with only uncharacterized structural domains 31; FBXL14, F-box protein with leucine-rich amino acid repeats 14; FBXO22, F-box protein with only uncharacterized structural domains 22; FBXO32, F-box protein with only uncharacterized structural domains 32; FBXO38, F-box protein with only uncharacterized structural domains 38; FBXO45, F-box protein with only uncharacterized structural domains 45; NEDD4-1, neurologically expressed developmentally downregulated 4-1; HECT, homologous to the E6-associated protein C-terminus; CRL, Cullin-RING ligases; CRL1, Cullin-RING ligase 1; FBA, F-box domain; SBD, glycoprotein-binding domain; NFB42, neural F-box 42 kDa; ATG4A, autophagy related 4A cysteine peptidase; ATG4D, autophagy related 4D cysteine peptidase; HGSOC, high-grade serous ovarian cancer; RNASET2, ribonuclease T2; hnRNPL, heterogeneous nuclear ribonucleoprotein L; FZR1, cell-cycle-regulated F-box protein 1; CNTO328, an IL-6R neutralizing antibody; Stattic, a STAT3 inhibitor; UBE2D2, ubiquitin-conjugating enzyme E2 D2; UBE2D3, ubiquitin-conjugating enzyme E2 D3; RBX1, RING-box protein 1; Smyd3, histone methyltransferase Smyd3; BACH1, BTB and CNC homology 1.

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