# SnapShot: F Box Proteins II

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Cell

**Mammals**

| F Box Protein | Substrates | Biological Functions of Substrates | Kinase(s) |
|---|---|---|---|
| Fbxw1/β-TRCP1 (Fbxw11/β-TrCP2) | Atf4 | txn factor, stress pathways | |
| | β-Catenin | txn activator, Wnt signaling | Gsk3 |
| | BimEL | BH3 homology, induces apoptosis | Rsk1, Rsk2 |
| | Bora | Aurora kinase activator, spindle stability | Gsk3, Plk3 |
| | Cdc25A | phosphatase, CDK activator, cell cycle | Chk1 |
| | Cdc25B | phosphatase, CDK activator, cell cycle | |
| | Claspin | replication/DNA damage response | Plk1 |
| | Cyclin D1 | cyclin, cell cycle | |
| | Dlg | cell contact and polarity | |
| | Emi1 | F box protein, APC/C inhibitor, cell cycle | Plk1 |
| | FancM | helicase, DNA damage response | Plk1 |
| | Fgd1 | GEF, Cdc42 regulation | |
| | Fgd3 | GEF, Cdc42 regulation | |
| | Ghr | receptor, growth hormone signaling | |
| | H-Ras | GTPase, signaling, cell growth | |
| | Hsf1 | txn factor, heat shock response | Plk1 |
| | Ifnr | receptor, cytokine signaling | |
| | IκBα | inhibitor of NF-κB | Ikkβ |
| | Mcl1 | BH3 homology, inhibits apoptosis | Gsk3 |
| | p100 | txn factor, NF-κB signaling | Ikkα |
| | p105 | txn factor, NF-κB signaling | Ikkβ |
| | p53 | txn factor, tumor suppressor | Ikk2 |
| | p63 | txn factor, epithelial differentiation | |
| | Pc2 | transmembrane protein, calcium signaling | |
| | Pdcd4 | EIF4A inhibitor, protein synthesis | S6k1 |
| | Per1 | txn activator, circadian rhythms | Ck1ε |
| | Per2 | txn activator, circadian rhythms | Ck1ε |
| | Prl-R | receptor, growth hormone signaling | |
| | Pro-caspase 3 | caspase, apoptosis | |
| | Ptt-g1/Securin | separase inhibitor, spindle checkpoint | |
| | Rcan1 | calcineurin-dependent signaling | |
| | Rest | txn repressor, cell cycle, differentiation | |
| | Sipa1l1/Spar | GAP, signal transduction | Plk2 |
| | Smad3 | txn factor, BMP/TGF signaling | |
| | Snail | txn repression, EMT | Gsk3 |
| | Stat-1 | txn factor, IFN signaling | |
| | Wee1 | kinase, CDK inhibitor, cell cycle | Plk1, Cdk1 |
| Fbxw2 | Gcma | txn factor, placenta development | |
| Fbxw5 | Tsc2 | GAP, mTOR pathways | |
| Fbxw7/Cdc4 | Aurora-A | kinase, cell cycle | |
| | c-Jun | txn factor, cell growth/proliferation | Gsk3 |
| | c-Myb | txn factor, cell growth/proliferation | Nlk |
| | c-Myc | txn factor, cell growth/proliferation | Gsk3 |
| | Cyclin E1/E2 | cyclins, cell cycle | Cdk2, Gsk3 |
| | mTor | kinase, mTOR growth pathways | |
| | Notch1 | transmembrane receptor, Notch signaling | Cdk8 |
| | Pgc-1 | txn coactivator, metabolic pathways | Gsk3, Mapk |
| | Presenilin | Notch signaling | |
| | Src3 | histone acetyltransferase, circadian rhythm | |
| | Srebp | txn factor, sterol lipid synthesis | Gsk3 |

**F Box Proteins**

- FBXW: WD40 repeats
- FBXL: leucine-rich repeats (LRR); possibly other domains
- FBXO: no WD40 or LRR repeats; possibly other domains

**Substrates Unknown**

| F Box Protein | Function |
|---|---|
| Fbxo5/Emi1 | APC/C inhibitor |
| Fbxo18 | DNA damage/recombination |
| Fbxo43/Emi2 | APC/C inhibitor |
| Fbxl10/KDM2B | histone demethylase |
| Fbxl11/KDM2A | histone demethylase |

| | | | |
|---|---|---|---|
| Fbxw8 | Cyclin D1 | cyclin, cell cycle regulation | Mapk |
| | Irs-1 | Cul7 insulin signaling | |
| Fbxl1/SKP2 | Brca2 | DNA repair | |
| | Cdk9 | kinase, txn elongation | |
| | Cdt1 | pre-RC component, DNA replication | Cdk2, Cdk4 |
| | Cyclin A | cyclin, cell cycle | |
| | Cyclin D1 | cyclin, cell cycle | |
| | Cyclin E | cyclin, cell cycle | |
| | E2a | txn factor, T and B cell development | Mapk |
| | E2f1 | txn factor, cell cycle | |
| | Foxo1 | txn factor, cell growth/proliferation | Akt |
| | Mef/Elf4 | txn factor, cell growth/proliferation | Cdk2 |
| | Mkp1 | phosphatase, ERK signaling | Erk |
| | Mll | histone methyltransferase | |
| | B-Myb | txn factor, cell growth/proliferation | |
| | c-Myc | txn factor, cell growth/proliferation | |
| | Orc1 | origin recognition, DNA replication | |
| | p21 | CDK inhibitor, cell cycle | Cdk2 |
| | p27 | CDK inhibitor, cell cycle | Cdk2 |
| | p57 | CDK inhibitor, cell cycle | Cdk2 |
| | Rag2 | recombinase, VDJ recombination | Cdk2 |
| | Rassf1 | tumor suppressor, microtubule dynamics | Cdk4 |
| | p130 | txn repressor, cell cycle | Cdk4, Cdk6 |
| | Smad4 | txn factor, BMP/TGF signaling | |
| | Tal1 | txn factor, erythroid differentiation | |
| | Tob1 | txn factor, cell growth/proliferation | |
| | Ubp43 | de-Ub enzyme, interferon signaling | |
| Fbxl3 | Cry1 | txn repressor, circadian rhythms | |
| | Cry2 | txn repressor, circadian rhythms | |
| Fbxl5 | p150Glued | SMC ATPase, microtubule dynamics | |
| Fbxl6 | Tel (Etv6) | txn factor, cell growth/proliferation | |
| Fbxl12 | p57 | CDK inhibitor, cell cycle | |
| Fbxl20/Scrapper | Rim1 | exocytosis, synaptic plasticity | |
| Fbxl21 | Cry1 | txn repressor, circadian rhythms | |
| | Cry2 | txn repressor, circadian rhythms | |
| Fbxo2/Nfb42 | Integrin β1 | integrin, intergrin signaling | |
| | Nr1 | NMDA receptor, NMDA signaling | |
| | Shps-1 | cytoskeletal, cell communication | |
| Fbxo3 | Hipk2 | kinase, txn corepressor | |
| | p300 | histone acetyltransferase, txn coactivator | |
| Fbxo4 | Cyclin D1 | cyclin, cell cycle | Gsk3 |
| | Trf1 | DNA binding, telomere length regulation | |
| Fbxo6 | Tcrα | T cell receptor, TCR signaling | |
| Fbxo8 | Arf6 | ADP ribosylation, endocytosis | |
| Fbxo7 | Clap1 | Ub ligase, inhibitor of apoptosis | |
| | Hurp | kinetochore-microtubule stability | |
| Fbxo31 | Cyclin D1 | cyclin, cell cycle | Mapk |
| Fbxo32 | Dusp1 | phosphatase, JNK signaling, apoptosis | |
| | Eif3-f | translation, muscle protein synthesis | |
| | MyoD | txn factor, muscle cell differentiation | |
| Fbxo33 | YB-1 | txn, translation, cell growth | |
| Nipa | Cyclin B1 | cyclin, cell cycle | |



See online version for legend and references.

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F box proteins are the variable subunits of Skp1-Cul1-F box protein-Rbx1 (SCF) ubiquitin ligase complexes and dictate the substrate specificity of the ubiquitin ligase. The F box protein is characterized by the F box domain, an approximately 40 amino acid region named for cyclin F (Fbxo1), in which the domain was originally identified. The annotation of known F box proteins is based on the presence of this domain, which has the consensus sequence L P X [E, K] I L X K [I, V] L $X_2$ L D P X D L/R X [L, F] [R, S] K V [S, C] [K, R] [K, R] [W, F] [R, K] X L V D $X_8$ I (L, leucine; P, proline; X, any amino acid; E, glutamic acid; K, lysine; I, isoleucine; V, valine; R, arginine; S, serine; C, cysteine; W, tryptophan; F, phenylalanine; D, aspartic acid). The F box domain mediates binding to Skp1, which links the F box protein to the rest of the SCF complex. However, not all F box proteins form ubiquitin ligase complexes with Cul1 and Rbx1 (for example, Fbxw8, Fbxl10, and Fbxl11), demonstrating that binding of the F box protein to Skp1 is necessary but not sufficient for binding to Cul1.

There are 69 human F box proteins, but the majority of them remain uncharacterized. In this SnapShot, we have listed reported F box protein-substrate pairs in mammals. Additionally, we have included orphan F box proteins with known biological functions but no reported substrates. F box proteins are classified into three families on the basis of their homology domains: FBXWs (WD40 repeats), FBXLs (leucine-rich repeats), or FBXOs (variable or no homology domains). Most F box proteins recognize their substrates through the WD40 repeats, the leucine-rich repeats, or other domains. Substrate recognition generally requires posttranslational modification—most often phosphorylation—of the substrate within a short amino acid degradation sequence (degron). For example, substrates of the F box protein βTrcp usually contain the consensus degron DSGXXS (D, aspartic acid; S, serine; G, glycine; X, any amino acid), where both serines are phosphorylated. The phosphorylated degron is bound in a highly selective manner by the WD40 repeat region of βTrcp. F box proteins may also bind to accessory proteins that play key roles in substrate recognition. For example, the accessory protein Cks1 is required for Skp2-mediated ubiquitination of p27. The targeting of F box proteins to short, phosphorylation-dependent degrons allows a single F box protein to recognize many different substrates in a precisely controlled manner. Even in the presence of its F box protein, a substrate is not recognized by the SCF without activation of the proper kinase. Although multiple substrates are recognized by each F box protein, the overall function of the F box protein can often be generalized. For example, Skp2 is a positive regulator of the cell cycle, Fbxw7 is a negative regulator of cell proliferation, and βTrcp functions as a prosurvival factor. Given their major roles in regulating key cellular functions, alterations of F box proteins have often been found to contribute to oncogenesis.

Although there are established roles for a small number of F box proteins in many diverse pathways, the majority of F box proteins have not yet been matched with any substrates. All reported substrates of the F box proteins listed in this SnapShot are included in the table, even if the evidence is currently limited or if there are conflicting reports. Additionally, when known, the kinases that phosphorylate the substrate degrons are also listed.

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