SnapShot: F Box Proteins I

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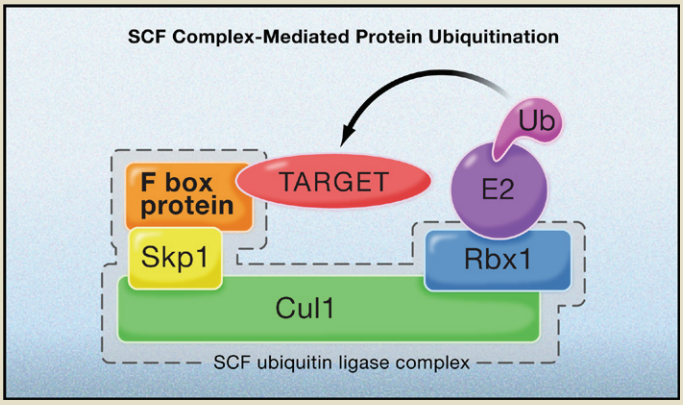
Cell

D. melanogaster

F Box Protein	Substrate	Biological Functions of Substrates or Orphan F Box Proteins	Kinase(s)
Ago	Trh	txn factor, trachea development	
	CycE	cyclin, cell cycle	Cdk2
	dMyc	txn factor, cell growth/proliferation	
	Notch	transmembrane receptor, Notch signaling	
Slimb	ARM	txn activator, Wingless pathway	Sgg
	Ci	txn factor, Hedgehog signaling	CK1
	Cact	txn factor, NF-κB signaling	
	Dl	txn factor, NF-κB signaling	
	E2F	txn factor, cell cycle	
	PER	txn activator, circadian rhythms	Dbt
	PLK4	kinase, cell cycle	
	Rel	txn factor, NF-κB signaling	
CG11033/ dKdm2	histone H2A	core histone component	
CG13213/Fbl6	Yan	txn factor, cell growth/proliferation	
Fbxl4	unknown	calcium signaling	
Jetlag	Tim	txn activator, circadian rhythms	
Ppa	Prd	homeobox txn factor, development	
CG4643/dFsn	Wnd	kinase, synaptic growth	
Morgue	Th/DIAP1	Ub ligase, inhibitor of apoptosis	
Pall	unknown	phagocytosis of apoptotic cells	
Rca1	unknown	APC/C inhibitor	



S. pombe

F Box Protein	Substrate	Biological Functions of Substrates or Orphan F Box Proteins	Kinase(s)
Pof14p	unknown	oxidative stress response	
Fbh1p	unknown	DNA damage/recombination	
Pop1p	Cdc18p	MCM loader, DNA replication	Cdc2p
	Cig2p	cyclin, cell cycle	Cdc2p
	Mid2p	anillin homolog, cytokinesis	
	Rum1p	Cdk inhibitor, cell cycle	Cdc2p
Pop2p	same as Pop1p	see Pop1p	see Pop1p
Pof1p	Zip1p	txn factor, cadmium response	
Pof3p	unknown	genome integrity/telomere function	
Pof6p	unknown	endocytosis/cytokinesis	

S. cerevisiae

F Box Protein	Substrate	Biological Functions of Substrates or Orphan F Box Proteins	Kinase(s)
Cdc4p	Cdc6p	pre-RC component, DNA replication	Cdc28p
	Clb6p	B-type cyclin, cell cycle	Cdc28p, Pho85p
	Ctf13p	CBF3 complex member, chromosome cohesion	
	Far1p	CDK inhibitor, cell cycle, pheromone pathway	Cdc28p
	Gcn4p	txn factor, amino acid synthesis	Pho85p, Srb10
	Gis4p	RAS/cAMP signaling	
	Hac1p	txn factor, unfolded protein response	
	Rcn1p	calcineurin regulation, calcium signaling	Mck1p
	Sic1p	CDK inhibitor, cell cycle	Cdc28p
	Swi5p	txn factor, cell cycle	
	Tec1p	txn factor, filamentation pathway	Fus3p
Met30p	Fzo1p	integral membrane, mitochondrial fusion	
	Met4p	txn activator, sulfur amino acid synthesis	
	Swe1	kinase, Cdk inhibitor, cell cycle	
Amn1p	unknown	mitotic exit network	
Ctf13p	unknown	centromeric/chromosome cohesion	
Dia2p	unknown	DNA replication	
Grr1p	Aro1p	aromatic amino acid synthesis	
	Cln1p	G1 cyclin, cell cycle	Cdc28p
	Cln2p	G1 cyclin, cell cycle	Cdc28p
	Gal2p	galactose permease, galactose pathway	
	Gal4p	txn factor, galactose pathway	
	Gic2p	actin cytoskeleton regulation	Cdc28p
	His4p	multiple enzymatic steps of histidine synthesis	
	Hof1p	cytokinesis	
	Hom3p	aspartate kinase, methionine/threonine synthesis	
	Ime2p	kinase, meiosis activation	
	Mae1p	sugar metabolism and amino acid synthesis	
	Mks1p	txn repressor, regulates metabolic processes	
	Mth1p	negative regulator of glucose signal transduction	Yck1, Yck2
	Pfk27p	kinase, metabolic processes	Snf1
	Tye7p	txn factor, glycolysis	
Mdm30p	Gal4p	txn factor, galactose pathway	
	Mdm34p	mitochondrial morphology	
Ela1p	Rpo21p	RNA Polymerase II subunit	
Hrt3p	unknown	methylmercury resistance	
Mfb1p	unknown	mitochondrial morphogenesis	
Rcy1p	unknown	endocytosis/protein recycling	
Ufo1p	Hop	endonuclease, mating type switching	
	Rad30p	DNA polymerase, lesion bypass	

F Box Proteins

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

See online version for legend and references.

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Cell

F box proteins are the variable substrate adapters for the Skp1-Cul1-F box protein-Rbx1 (SCF) ubiquitin ligase complexes and dictate the substrate specificity of the ubiquitin ligase. Cul1 acts as the scaffold for the SCF complex, recruiting Rbx1 and an E2 ubiquitin-conjugating enzyme to its C terminus and the Skp1-F box protein pair to its N terminus. The number of F box protein genes varies greatly depending on the organism, ranging from ~20 in yeast species (20 in the budding yeast *Saccharomyces cerevisiae*, 17 in the fission yeast *Schizosaccharomyces pombe*) to 27 in the fly *Drosophila melanogaster* to 69 in humans. With little overlap between the *S. cerevisiae* and *S. pombe* F box proteins and only six apparent orthologs conserved between flies, worms, and humans, evolutionary conservation of individual F box proteins appears to be rare. In this SnapShot, we list reported F box protein-substrate pairs in the model organisms *D. melanogaster*, *S. cerevisiae*, and *S. pombe*. Additionally, we include orphan F box proteins with known biological functions but no reported substrates.

The F box protein is characterized by the F box domain, an approximately 40 amino acid region named for cyclin F (or Fbxo1), the protein in which the domain was first identified. The annotation of known F box proteins is based on the presence of this domain, which has the consensus sequence of 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, there is a small interaction interface between the F box protein and Cul1 that likely stabilizes the SCF complex. In fact, the interaction of the F box protein with Skp1 is necessary, but not sufficient, for binding to Cul1 (binding of the Skp1-F box protein pair to Cul1 has not been demonstrated for all F box family members, and certain F box proteins do not appear to form SCF ubiquitin ligase complexes with Cul1).

F box proteins are grouped into three families on the basis of the presence of WD40 repeats (FBXW) or leucine-rich repeats (FBXL), or the absence of either of these domains (F box only; FBXO). FBXO family members often contain additional functional domains with homology to other protein families. Typically, F box proteins recognize their substrates through the WD40 repeats, the leucine-rich repeats, or other domains. Substrate recognition generally requires a posttranslational modification of the substrate in a discreet degradation sequence (degron). This requirement for posttranslational modification suggests that F box proteins have the ability to integrate multiple pathways by "sensing" the activity of other enzymes. Although phosphorylation is the most common posttranslational modification involved in substrate targeting, other posttranslational modifications, such as glycosylation, have been reported. In plants, hormones can also mediate binding between F box proteins and their substrates. A single F box protein can recognize multiple substrates, expanding the functional range of the core SCF scaffold to hundreds of targets and numerous biological processes.

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. The kinases that phosphorylate the substrate degrons are also listed, if known. Although there are established roles for F box proteins in many diverse pathways, the majority of the F box proteins in each organism remain orphans without known substrates.

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