

S2 (table) | Receptors and substrates of cullin–RING ligases that have been implicated in diverse biological processes

Organism	Cullin	Receptor	Implicated substrate	Biological Process	References
<i>S. cerevisiae</i>	Cul1	Cdc4	Cdc6	DNA replication	1–3
			Ctf13	Cell cycle	4
			Far1	Cell cycle	5–7
			Gcn4	Transcription	8–10
			Sic1	Cell cycle	11–14
		Grr1	Cdc4	Autoregulation	15,16
			Cln1/2	Cell cycle	13,17,18
			Gic2	Cell polarity	6,19,20
		Met30	Grr1	Autoregulation	15,16
			Met4	Transcription	21–25
			Met30	Autoregulation	24,26
		Mdm30	Swe1	Cell cycle	27,28
			Fzo1	Mitochondrial shape	29
		Ufo1	Ho	Signal transduction	30,31
		?	Cln3	Cell cycle	11,32
			Ste7	Signal transduction	33
		?	Clb5	Cell cycle	11
<i>S. pombe</i>	Cul1	Pop1/Pop2	Cdc18	DNA replication	34–36
			Rum1	Cell cycle	34–36
			Cig2	Cell cycle	37
		?	Mid2p	Cell cycle	38
	Cul3	Btb3	Btb3	Autoregulation	39
	Cul4	?	Spd1	DNA replication	40
<i>C. elegans</i>	Cul1	SEL-10	LIN-12	Signal transduction	41
	Cul2	VHL	HIF-1	Transcription	42
		ZIF-1	PIE-1, POS-1, MEX-1/-5/-6	Development	43
		?	CKI-1	Cell cycle	44
	Cul3	MEL-26	MEI-1	Cell cycle	45–49
	Cul4	?	CDT-1	DNA replication	50
<i>D. melanogaster</i>	Cul1	Archipelago	Cyclin E	Cell cycle	51
			dMyc	Transcription	52
		Morgue	Diap1	Apoptosis	53
		Partner of Paired	Paired	Transcription	54,55
		Slimb	Armadillo	Development	56–59
			Cactus	Transcription	60,61
			Cubitus interruptus	Transcription	56,57,59,62

		Dorsal E2F Period Relish Timeless	Transcription DNA replication Circadian- clock regulation Transcription Circadian- clock regulation	60 63 64,65 66 65
	Cul4	?	Cdt1	DNA replication
X. laevis	Cul1	β -TrCP Tome-1 ?	β -catenin Xom Wee1 Xic1	Development Development Cell cycle Cell cycle
				68–71 72 73,74 75–77
A. thaliana	Cul1	COI1 EBF1/EBF2 SLF-S2 SLY1 SKP2 TLP9 TIR1 UFO ZTL	RPD3b Rubisco (small subunit) EIN3 S-RNases RGA E2Fc ? AUX/IAA proteins AGAMOUS TOC1	Transcription Photorespiratio n Transcription Signal transduction Signal transduction Transcription Signal transduction Transcription Development Circadian- clock regulation
				78 78 79–81 82 83,84 85 86 87–89 90 91
	Cul3	ETO1	ACS5	Signal transduction
H. sapiens/ M. musculus	Cul1	β -TrCP1 and 2 (FBW1, HOS) + HIV: Vpu	ATF4 β -catenin CDC25a CD4 EMI1 IkB α NF κ B1/p105, NF κ B2/p100 Prolactin receptor SMAD3/4	Transcription Signal transduction Cell cycle Viral modulation Cell cycle Transcription Transcription Signal transduction Signal transduction
				93,94 58,95–98 99,100 101 102,103 60,95,98, 104–111 112–118 119 120,121

		Type-I interferon receptor (IFNAR1) WEE1	Signal transduction	122
	CDC4 (FBW7, SEL10)	Cyclin E Jun Myc Notch1/4 Presenilin-1	Cell cycle Transcription Transcription Signal transduction Regulation	123 124,125 126 127,128 129,130 131
	FBS1 (FBX2, NFB42)	Glycoproteins Herpes simplex virus type 1: UL9	Protein quality control Viral modulation	132 133
	FBS2	<i>N</i> -glycans	Protein quality control	134
	FBX4	α B-crystallin	Heat-shock protein	135
	SKP2 + Cyclin T1	B-MYB CDK9 CDT1 Cyclin D Cyclin E Papilloma virus: E7 E2A E2F1 Myc ORC1 p57 p130 p21 +CKS1 +CKS1 +CKS1	Transcription Transcription Cell cycle Cell cycle Cell cycle Viral modulation Development Transcription Transcription DNA replication Cell cycle Cell cycle Cell cycle Cell cycle	136 137,138 50,67, 139–141 142–144 145,146 147 148 149 150 151 152 153,154 142,144,155, 156 142,145, 157–160
Cul2	SOCS1/3	IRS1/2	Signal transduction	161
	SOCS1	TEL-JAK2 VAV	Cell cycle Signal transduction	162,163 164
	VHL	HIF1 α , HIF2 α RPB7 RPB1 VDU1/2 hnRNP A2 PKC λ	Transcription Transcription Transcription Protein quality control Transcription Signal transduction	165–175 176 177 178,179 180 181

		STRA13	Transcription	182
Cul3	RhoBTB2	RhoBTB2	Cell cycle	183
	?	TOP1	DNA replication	184
	KEAP1	NRF2	Transcription	185, 186
Cul4	DET1/COP1	Jun	Transcription	187
	Paramyxovirus : V proteins	STAT1/2	Viral modulation	188
	?	CDT1	DNA replication	67
Cul5	Adenovirus: E1B-55K, E4ORF6	p53	Viral modulation	189
	HIV: Vif	APOBEC3G	Viral modulation	190

1. Sanchez, M., Calzada, A. & Bueno, A. The Cdc6 protein is ubiquitinated *in vivo* for proteolysis in *Saccharomyces cerevisiae*. *J. Biol. Chem.* **274**, 9092–9097 (1999).
2. Drury, L. S., Perkins, G. & Diffley, J. F. The Cdc4/34/53 pathway targets Cdc6p for proteolysis in budding yeast. *EMBO J.* **16**, 5966–5976 (1997).
3. Elsasser, S., Chi, Y., Yang, P. & Campbell, J. L. Phosphorylation controls timing of Cdc6p destruction: a biochemical analysis. *Mol. Biol. Cell* **10**, 3263–3277 (1999).
4. Kaplan, K. B., Hyman, A. A. & Sorger, P. K. Regulating the yeast kinetochore by ubiquitin-dependent degradation and Skp1p-mediated phosphorylation. *Cell* **91**, 491–500 (1997).
5. Blondel, M. *et al.* Nuclear-specific degradation of Far1 is controlled by the localization of the F-box protein Cdc4. *EMBO J.* **19**, 6085–6097 (2000).
6. Blondel, M., Galan, J. M. & Peter, M. Isolation and characterization of HRT1 using a genetic screen for mutants unable to degrade Gic2p in *Saccharomyces cerevisiae*. *Genetics* **155**, 1033–1044 (2000).
7. Henchoz, S. *et al.* Phosphorylation- and ubiquitin-dependent degradation of the cyclin-dependent kinase inhibitor Far1p in budding yeast. *Genes Dev.* **11**, 3046–3060 (1997).
8. Chi, Y. *et al.* Negative regulation of Gcn4 and Msn2 transcription factors by Srb10 cyclin-dependent kinase. *Genes Dev.* **15**, 1078–1092 (2001).
9. Kornitzer, D., Raboy, B., Kulka, R. G. & Fink, G. R. Regulated degradation of the transcription factor Gcn4. *EMBO J.* **13**, 6021–6030 (1994).
10. Meimoun, A. *et al.* Degradation of the transcription factor Gcn4 requires the kinase Pho85 and the SCF^{CDC4} ubiquitin-ligase complex. *Mol. Biol. Cell* **11**, 915–927 (2000).
11. Bai, C. *et al.* SKP1 connects cell cycle regulators to the ubiquitin proteolysis machinery through a novel motif, the F-box. *Cell* **86**, 263–274 (1996).
12. Feldman, R. M., Correll, C. C., Kaplan, K. B. & Deshaies, R. J. A complex of Cdc4p, Skp1p, and Cdc53p/cullin catalyzes ubiquitination of the phosphorylated CDK inhibitor Sic1p. *Cell* **91**, 221–230 (1997).
13. Skowyra, D., Craig, K. L., Tyers, M., Elledge, S. J. & Harper, J. W. F-box proteins are receptors that recruit phosphorylated substrates to the SCF ubiquitin-ligase complex. *Cell* **91**, 209–219 (1997).
14. Verma, R., Feldman, R. M. & Deshaies, R. J. SIC1 is ubiquitinated *in vitro* by a pathway that requires CDC4, CDC34, and cyclin/CDK activities. *Mol. Biol. Cell* **8**, 1427–1437 (1997).
15. Zhou, P. & Howley, P. M. Ubiquitination and degradation of the substrate recognition subunits of SCF ubiquitin-protein ligases. *Mol. Cell* **2**, 571–580 (1998).
16. Galan, J. M. & Peter, M. Ubiquitin-dependent degradation of multiple F-box proteins by an autocatalytic mechanism. *Proc. Natl Acad. Sci. USA* **96**, 9124–9129 (1999).

17. Barral, Y., Jentsch, S. & Mann, C. G1 cyclin turnover and nutrient uptake are controlled by a common pathway in yeast. *Genes Dev.* **9**, 399–409 (1995).
18. Li, F. N. & Johnston, M. Grr1 of *Saccharomyces cerevisiae* is connected to the ubiquitin proteolysis machinery through Skp1: coupling glucose sensing to gene expression and the cell cycle. *EMBO J.* **16**, 5629–5638 (1997).
19. Hsiung, Y. G. et al. F-box protein Grr1 interacts with phosphorylated targets via the cationic surface of its leucine-rich repeat. *Mol. Cell. Biol.* **21**, 2506–2520 (2001).
20. Jaquenoud, M., Gulli, M. P., Peter, K. & Peter, M. The Cdc42p effector Gic2p is targeted for ubiquitin-dependent degradation by the SCF^{Grr1} complex. *EMBO J.* **17**, 5360–5373 (1998).
21. Kaiser, P., Flick, K., Wittenberg, C. & Reed, S. I. Regulation of transcription by ubiquitination without proteolysis: Cdc34/SCF^{Met30}-mediated inactivation of the transcription factor Met4. *Cell* **102**, 303–314 (2000).
22. Kuras, L. et al. Dual regulation of the met4 transcription factor by ubiquitin-dependent degradation and inhibition of promoter recruitment. *Mol. Cell* **10**, 69–80 (2002).
23. Patton, E. E. et al. SCF^{Met30}-mediated control of the transcriptional activator Met4 is required for the G₁–S transition. *EMBO J.* **19**, 1613–1624 (2000).
24. Rouillon, A., Barbey, R., Patton, E. E., Tyers, M. & Thomas, D. Feedback-regulated degradation of the transcriptional activator Met4 is triggered by the SCF^{Met30} complex. *EMBO J.* **19**, 282–294 (2000).
25. Wheeler, G. L., Quinn, K. A., Perrone, G., Dawes, I. W. & Grant, C. M. Glutathione regulates the expression of γ -glutamylcysteine synthetase via the Met4 transcription factor. *Mol. Microbiol.* **46**, 545–556 (2002).
26. Smothers, D. B., Kozubowski, L., Dixon, C., Goebel, M. G. & Mathias, N. The abundance of Met30p limits SCF^{Met30p} complex activity and is regulated by methionine availability. *Mol. Cell. Biol.* **20**, 7845–7852 (2000).
27. Kaiser, P., Sia, R. A., Bardes, E. G., Lew, D. J. & Reed, S. I. Cdc34 and the F-box protein Met30 are required for degradation of the Cdk-inhibitory kinase Swe1. *Genes Dev.* **12**, 2587–2597 (1998).
28. McMillan, J. N., Theesfeld, C. L., Harrison, J. C., Bardes, E. S. & Lew, D. J. Determinants of Swe1p degradation in *Saccharomyces cerevisiae*. *Mol. Biol. Cell* **13**, 3560–3575 (2002).
29. Fritz, S., Weinbach, N. & Westermann, B. Mdm30 is an F-box protein required for maintenance of fusion-competent mitochondria in yeast. *Mol. Biol. Cell* **14**, 2303–2313 (2003).
30. Kaplun, L., Ivantsiv, Y., Kornitzer, D. & Raveh, D. Functions of the DNA damage response pathway target Ho endonuclease of yeast for degradation via the ubiquitin-26S proteasome system. *Proc. Natl Acad. Sci. USA* **97**, 10077–10082 (2000).
31. Kaplun, L., Ivantsiv, Y., Bakhrat, A. & Raveh, D. DNA damage response-mediated degradation of Ho endonuclease via the ubiquitin system involves its nuclear export. *J. Biol. Chem.* **278**, 48727–48734 (2003).
32. Willemse, A. R. et al. Cdc53 targets phosphorylated G1 cyclins for degradation by the ubiquitin proteolytic pathway. *Cell* **86**, 453–463 (1996).
33. Wang, Y. et al. Regulation of Ste7 ubiquitination by Ste11 phosphorylation and the Skp1–Cullin–F-box complex. *J. Biol. Chem.* **278**, 22284–22289 (2003).
34. Kominami, K. & Toda, T. Fission yeast WD-repeat protein pop1 regulates genome ploidy through ubiquitin-proteasome-mediated degradation of the CDK inhibitor Rum1 and the S-phase initiator Cdc18. *Genes Dev.* **11**, 1548–1560 (1997).
35. Kominami, K., Ochotorena, I. & Toda, T. Two F-box/WD-repeat proteins Pop1 and Pop2 form hetero- and homo-complexes together with cullin-1 in the fission yeast SCF (Skp1–Cullin-1–F-box) ubiquitin ligase. *Genes Cells* **3**, 721–735 (1998).
36. Wolf, D. A., McKeon, F. & Jackson, P. K. F-box/WD-repeat proteins pop1p and Sud1p/Pop2p form complexes that bind and direct the proteolysis of cdc18p. *Curr. Biol.* **9**, 373–376 (1999).
37. Yamano, H. et al. Requirement of the SCF^{Pop1/Pop2} ubiquitin ligase for degradation of the fission yeast S phase cyclin Cig2. *J. Biol. Chem.* **279**, 18974–18980 (2004).

38. Tasto, J. J., Morrell, J. L. & Gould, K. L. An anillin homologue, Mid2p, acts during fission yeast cytokinesis to organize the septin ring and promote cell separation. *J. Cell Biol.* **160**, 1093–1103 (2003).
39. Geyer, R., Wee, S., Anderson, S., Yates, J. & Wolf, D. A. BTB/POZ domain proteins are putative substrate adaptors for cullin 3 ubiquitin ligases. *Mol. Cell* **12**, 783–790 (2003).
40. Liu, C. et al. Cop9/signalosome subunits and Pcu4 regulate ribonucleotide reductase by both checkpoint-dependent and-independent mechanisms. *Genes Dev.* **17**, 1130–1140 (2003).
41. Hubbard, E. J., Wu, G., Kitajewski, J. & Greenwald, I. sel-10, a negative regulator of lin-12 activity in *Caenorhabditis elegans*, encodes a member of the CDC4 family of proteins. *Genes Dev.* **11**, 3182–3193 (1997).
42. Epstein, A. C. et al. *C. elegans* EGL-9 and mammalian homologs define a family of dioxygenases that regulate HIF by prolyl hydroxylation. *Cell* **107**, 43–54 (2001).
43. DeRenzo, C., Reese, K. J. & Seydoux, G. Exclusion of germ plasm proteins from somatic lineages by cullin-dependent degradation. *Nature* **424**, 685–689 (2003).
44. Feng, H. et al. CUL-2 is required for the G1-to-S-phase transition and mitotic chromosome condensation in *Caenorhabditis elegans*. *Nature Cell Biol.* **1**, 486–492 (1999).
45. Furukawa, M., He, Y. J., Borchers, C. & Xiong, Y. Targeting of protein ubiquitination by BTB–Cullin 3–Roc1 ubiquitin ligases. *Nature Cell Biol.* **5**, 1001–1007 (2003).
46. Pintard, L. et al. The BTB protein MEL-26 is a substrate-specific adaptor of the CUL-3 ubiquitin-ligase. *Nature* **425**, 311–316 (2003).
47. Pintard, L. et al. Neddylation and deneddylation of CUL-3 is required to target MEI-1/Katanin for degradation at the meiosis-to-mitosis transition in *C. elegans*. *Curr. Biol.* **13**, 911–921 (2003).
48. Xu, L. et al. BTB proteins are substrate-specific adaptors in an SCF-like modular ubiquitin ligase containing CUL-3. *Nature* **425**, 316–321 (2003).
49. Kurz, T. et al. Cytoskeletal regulation by the Nedd8 ubiquitin-like protein modification pathway. *Science* **295**, 1294–1298 (2002).
50. Zhong, W., Feng, H., Santiago, F. E. & Kipreos, E. T. CUL-4 ubiquitin ligase maintains genome stability by restraining DNA-replication licensing. *Nature* **423**, 885–889 (2003).
51. Moberg, K. H., Bell, D. W., Wahrer, D. C., Haber, D. A. & Hariharan, I. K. Archipelago regulates Cyclin E levels in *Drosophila* and is mutated in human cancer cell lines. *Nature* **413**, 311–316 (2001).
52. Moberg, K. H., Mukherjee, A., Veraksa, A., Artavanis-Tsakonas, S. & Hariharan, I. K. The *Drosophila* F Box protein Archipelago regulates dMyc protein levels *in vivo*. *Curr. Biol.* **14**, 965–974 (2004).
53. Wing, J. P. et al. *Drosophila* Morgue is an F box/ubiquitin conjugase domain protein important for grim-reaper mediated apoptosis. *Nature Cell Biol.* **4**, 451–456 (2002).
54. Das, T., Purkayastha-Mukherjee, C., D'Angelo, J. & Weir, M. A conserved F-box gene with unusual transcript localization. *Dev. Genes Evol.* **212**, 134–140 (2002).
55. Raj, L. et al. Targeted localized degradation of Paired protein in *Drosophila* development. *Curr. Biol.* **10**, 1265–1272 (2000).
56. Ou, C. Y., Lin, Y. F., Chen, Y. J. & Chien, C. T. Distinct protein degradation mechanisms mediated by Cul1 and Cul3 controlling Ci stability in *Drosophila* eye development. *Genes Dev.* **16**, 2403–2414 (2002).
57. Jiang, J. & Struhl, G. Regulation of the Hedgehog and Wingless signalling pathways by the F-box/WD40-repeat protein Slimb. *Nature* **391**, 493–496 (1998).
58. Hart, M. et al. The F-box protein β-TrCP associates with phosphorylated β-catenin and regulates its activity in the cell. *Curr. Biol.* **9**, 207–210 (1999).
59. Noureddine, M. A., Donaldson, T. D., Thacker, S. A. & Duronio, R. J. *Drosophila* Roc1a encodes a RING-H2 protein with a unique function in processing the Hh signal transducer Ci by the SCF E3 ubiquitin ligase. *Dev. Cell* **2**, 757–770 (2002).
60. Spencer, E., Jiang, J. & Chen, Z. J. Signal-induced ubiquitination of IκBα by the F-box protein Slimb/β-TrCP. *Genes Dev.* **13**, 284–294 (1999).

61. Leulier, F. *et al.* Directed expression of the HIV-1 accessory protein Vpu in *Drosophila* fat-body cells inhibits Toll-dependent immune responses. *EMBO Rep.* **4**, 976–981 (2003).
62. Wang, G., Wang, B. & Jiang, J. Protein kinase A antagonizes Hedgehog signaling by regulating both the activator and repressor forms of Cubitus interruptus. *Genes Dev.* **13**, 2828–2837 (1999).
63. Heriche, J. K., Ang, D., Bier, E. & O'Farrell, P. H. Involvement of an SCF^{Slmb} complex in timely elimination of E2F upon initiation of DNA replication in *Drosophila*. *BMC Genet.* **4**, 9 (2003).
64. Ko, H. W., Jiang, J. & Edery, I. Role for Slmb in the degradation of *Drosophila* Period protein phosphorylated by Doubletime. *Nature* **420**, 673–678 (2002).
65. Grima, B. *et al.* The F-box protein slimb controls the levels of clock proteins period and timeless. *Nature* **420**, 178–182 (2002).
66. Khush, R. S., Cornwell, W. D., Uram, J. N. & Lemaitre, B. A ubiquitin-proteasome pathway represses the *Drosophila* immune deficiency signaling cascade. *Curr. Biol.* **12**, 1728–1737 (2002).
67. Higa, L. A., Mihaylov, I. S., Banks, D. P., Zheng, J. & Zhang, H. Radiation-mediated proteolysis of CDT1 by CUL4–ROC1 and CSN complexes constitutes a new checkpoint. *Nature Cell Biol.* **5**, 1008–1015 (2003).
68. Marikawa, Y. & Elinson, R. P. β-TrCP is a negative regulator of Wnt/β-catenin signaling pathway and dorsal axis formation in *Xenopus* embryos. *Mech. Dev.* **77**, 75–80 (1998).
69. Lagna, G., Carnevali, F., Marchionni, M. & Hemmati-Brivanlou, A. Negative regulation of axis formation and Wnt signaling in *Xenopus* embryos by the F-box/WD40 protein β-TrCP. *Mech. Dev.* **80**, 101–106 (1999).
70. Liu, C. *et al.* β-Trcp couples β-catenin phosphorylation-degradation and regulates *Xenopus* axis formation. *Proc. Natl Acad. Sci. USA* **96**, 6273–6278 (1999).
71. Salic, A., Lee, E., Mayer, L. & Kirschner, M. W. Control of β-catenin stability: reconstitution of the cytoplasmic steps of the wnt pathway in *Xenopus* egg extracts. *Mol. Cell* **5**, 523–532 (2000).
72. Zhu, Z. & Kirschner, M. Regulated proteolysis of Xom mediates dorsoventral pattern formation during early *Xenopus* development. *Dev. Cell* **3**, 557–568 (2002).
73. Ayad, N. G. *et al.* Tome-1, a trigger of mitotic entry, is degraded during G1 via the APC. *Cell* **113**, 101–113 (2003).
74. Michael, W. M. & Newport, J. Coupling of mitosis to the completion of S phase through Cdc34-mediated degradation of Wee1. *Science* **282**, 1886–1889 (1998).
75. Chuang, L. C. & Yew, P. R. Regulation of nuclear transport and degradation of the *Xenopus* cyclin-dependent kinase inhibitor, p27^{Xic1}. *J. Biol. Chem.* **276**, 1610–1617 (2001).
76. Furstenthal, L., Swanson, C., Kaiser, B. K., Eldridge, A. G. & Jackson, P. K. Triggering ubiquitination of a CDK inhibitor at origins of DNA replication. *Nature Cell Biol.* **3**, 715–722 (2001).
77. Yew, P. R. & Kirschner, M. W. Proteolysis and DNA replication: the CDC34 requirement in the *Xenopus* egg cell cycle. *Science* **277**, 1672–1676 (1997).
78. Devoto, A. *et al.* COI1 links jasmonate signalling and fertility to the SCF ubiquitin-ligase complex in *Arabidopsis*. *Plant J.* **32**, 457–466 (2002).
79. Potuschak, T. *et al.* EIN3-dependent regulation of plant ethylene hormone signaling by two *Arabidopsis* F box proteins: EBF1 and EBF2. *Cell* **115**, 679–689 (2003).
80. Guo, H. & Ecker, J. R. Plant responses to ethylene gas are mediated by SCF^{EBF1/EBF2}-dependent proteolysis of EIN3 transcription factor. *Cell* **115**, 667–677 (2003).
81. Gagne, J. M. *et al.* *Arabidopsis* EIN3-binding F-box 1 and 2 form ubiquitin-protein ligases that repress ethylene action and promote growth by directing EIN3 degradation. *Proc. Natl Acad. Sci. USA* **101**, 6803–6808 (2004).
82. Qiao, H. *et al.* The F-box protein AhSLF-S2 physically interacts with S-RNases that may be inhibited by the ubiquitin/26S proteasome pathway of protein degradation during compatible pollination in *Antirrhinum*. *Plant Cell* **16**, 582–595 (2004).
83. Itoh, H., Matsuoka, M. & Steber, C. M. A role for the ubiquitin-26S-proteasome pathway in gibberellin signaling. *Trends Plant Sci.* **8**, 492–497 (2003).

84. McGinnis, K. M. *et al.* The *Arabidopsis* SLEEPY1 gene encodes a putative F-box subunit of an SCF E3 ubiquitin ligase. *Plant Cell* **15**, 1120–1130 (2003).
85. del Pozo, J. C., Boniotti, M. B. & Gutierrez, C. *Arabidopsis* E2Fc functions in cell division and is degraded by the ubiquitin-SCF^{AtSKP2} pathway in response to light. *Plant Cell* **14**, 3057–3071 (2002).
86. Lai, C. P. *et al.* Molecular analyses of the *Arabidopsis* TUBBY-like protein gene family. *Plant Physiol.* **134**, 1586–1597 (2004).
87. Gray, W. M. *et al.* Identification of an SCF ubiquitin-ligase complex required for auxin response in *Arabidopsis thaliana*. *Genes Dev.* **13**, 1678–1691 (1999).
88. Gray, W. M., Kepinski, S., Rouse, D., Leyser, O. & Estelle, M. Auxin regulates SCF^{TIR1}-dependent degradation of AUX/IAA proteins. *Nature* **414**, 271–276 (2001).
89. Tian, Q., Nagpal, P. & Reed, J. W. Regulation of *Arabidopsis* SHY2/IAA3 protein turnover. *Plant J.* **36**, 643–651 (2003).
90. Durfee, T. *et al.* The F-box-containing protein UFO and AGAMOUS participate in antagonistic pathways governing early petal development in *Arabidopsis*. *Proc. Natl Acad. Sci. USA* **100**, 8571–8576 (2003).
91. Mas, P., Kim, W. Y., Somers, D. E. & Kay, S. A. Targeted degradation of TOC1 by ZTL modulates circadian function in *Arabidopsis thaliana*. *Nature* **426**, 567–570 (2003).
92. Wang, K. L., Yoshida, H., Lurin, C. & Ecker, J. R. Regulation of ethylene gas biosynthesis by the *Arabidopsis* ETO1 protein. *Nature* **428**, 945–950 (2004).
93. Besnard-Guerin, C. *et al.* HIV-1 Vpu sequesters β-transducin repeat-containing protein (βTrCP) in the cytoplasm and provokes the accumulation of β-catenin and other SCF^{βTrCP} substrates. *J. Biol. Chem.* **279**, 788–795 (2004).
94. Lassot, I. *et al.* ATF4 degradation relies on a phosphorylation-dependent interaction with the SCF^{βTrCP} ubiquitin ligase. *Mol. Cell. Biol.* **21**, 2192–2202 (2001).
95. Fuchs, S. Y., Chen, A., Xiong, Y., Pan, Z. Q. & Ronai, Z. HOS, a human homolog of Slimb, forms an SCF complex with Skp1 and Cullin1 and targets the phosphorylation-dependent degradation of IκB and β-catenin. *Oncogene* **18**, 2039–2046 (1999).
96. Kitagawa, M. *et al.* An F-box protein, FWD1, mediates ubiquitin-dependent proteolysis of β-catenin. *EMBO J.* **18**, 2401–2410 (1999).
97. Latres, E., Chiaur, D. S. & Pagano, M. The human F box protein β-Trcp associates with the Cul1/Skp1 complex and regulates the stability of β-catenin. *Oncogene* **18**, 849–854 (1999).
98. Winston, J. T. *et al.* The SCF^{β-TRCP}-ubiquitin ligase complex associates specifically with phosphorylated destruction motifs in IκBα and β-catenin and stimulates IκBα ubiquitination *in vitro*. *Genes Dev.* **13**, 270–283 (1999).
99. Busino, L. *et al.* Degradation of Cdc25A by β-TrCP during S phase and in response to DNA damage. *Nature* **426**, 87–91 (2003).
100. Jin, J. *et al.* SCF β-TRCP links Chk1 signaling to degradation of the Cdc25A protein phosphatase. *Genes Dev.* **17**, 3062–3074 (2003).
101. Margottin, F. *et al.* A novel human WD protein, h-βTrCp, that interacts with HIV-1 Vpu connects CD4 to the ER degradation pathway through an F-box motif. *Mol. Cell* **1**, 565–574 (1998).
102. Margottin-Goguet, F. *et al.* Prophase destruction of Emi1 by the SCF^{βTrCP/Slimb} ubiquitin ligase activates the anaphase promoting complex to allow progression beyond prometaphase. *Dev. Cell* **4**, 813–826 (2003).
103. Guardavaccaro, D. *et al.* Control of meiotic and mitotic progression by the F box protein β-Trcp1 *in vivo*. *Dev. Cell* **4**, 799–812 (2003).
104. Wu, C. & Ghosh, S. β-TrCP mediates the signal-induced ubiquitination of IκBβ. *J. Biol. Chem.* **274**, 29591–29594 (1999).
105. Yaron, A. *et al.* Identification of the receptor component of the IκBα-ubiquitin ligase. *Nature* **396**, 590–594 (1998).
106. Hatakeyama, S. *et al.* Ubiquitin-dependent degradation of IκBα is mediated by a ubiquitin ligase Skp1/Cul 1/F-box protein FWD1. *Proc. Natl Acad. Sci. USA* **96**, 3859–3863 (1999).

107. Hattori, K., Hatakeyama, S., Shirane, M., Matsumoto, M. & Nakayama, K. Molecular dissection of the interactions among I κ B α , FWD1, and Skp1 required for ubiquitin-mediated proteolysis of I κ B α . *J. Biol. Chem.* **274**, 29641–29647 (1999).
108. Kroll, M. et al. Inducible degradation of I κ B α by the proteasome requires interaction with the F-box protein h- β TrCP. *J. Biol. Chem.* **274**, 7941–7945 (1999).
109. Shirane, M., Hatakeyama, S., Hattori, K. & Nakayama, K. Common pathway for the ubiquitination of I κ B α , I κ B β , and I κ B ϵ mediated by the F-box protein FWD1. *J. Biol. Chem.* **274**, 28169–28174 (1999).
110. Suzuki, H. et al. I κ B α ubiquitination is catalyzed by an SCF-like complex containing Skp1, cullin-1, and two F-box/WD40-repeat proteins, β TrCP1 and β TrCP2. *Biochem. Biophys. Res. Commun.* **256**, 127–132 (1999).
111. Vuillard, L., Nicholson, J. & Hay, R. T. A complex containing β TrCP recruits Cdc34 to catalyse ubiquitination of I κ B α . *FEBS Lett.* **455**, 311–314 (1999).
112. Coux, O. & Goldberg, A. L. Enzymes catalyzing ubiquitination and proteolytic processing of the p105 precursor of nuclear factor κ B1. *J. Biol. Chem.* **273**, 8820–8828 (1998).
113. Orian, A. et al. SCF $^{\beta\text{-TrCP}}$ ubiquitin ligase-mediated processing of NF- κ B p105 requires phosphorylation of its C-terminus by I κ B kinase. *EMBO J.* **19**, 2580–2591 (2000).
114. Ciechanover, A. et al. Mechanisms of ubiquitin-mediated, limited processing of the NF- κ B1 precursor protein p105. *Biochimie* **83**, 341–349 (2001).
115. Cohen, S., Orian, A. & Ciechanover, A. Processing of p105 is inhibited by docking of p50 active subunits to the ankyrin repeat domain, and inhibition is alleviated by signaling via the carboxyl-terminal phosphorylation/ubiquitin-ligase binding domain. *J. Biol. Chem.* **276**, 26769–26776 (2001).
116. Heissmeyer, V., Krappmann, D., Hatada, E. N. & Scheidereit, C. Shared pathways of I κ B kinase-induced SCF $^{\beta\text{-TrCP}}$ -mediated ubiquitination and degradation for the NF- κ B precursor p105 and I κ B α . *Mol. Cell. Biol.* **21**, 1024–1035 (2001).
117. Amir, R. E., Iwai, K. & Ciechanover, A. The NEDD8 pathway is essential for SCF $^{\beta\text{-TrCP}}$ -mediated ubiquitination and processing of the NF- κ B precursor p105. *J. Biol. Chem.* **277**, 23253–23259 (2002).
118. Lang, V. et al. β TrCP-mediated proteolysis of NF- κ B1 p105 requires phosphorylation of p105 serines 927 and 932. *Mol. Cell. Biol.* **23**, 402–413 (2003).
119. Li, Y., Kumar, K. G., Tang, W., Spiegelman, V. S. & Fuchs, S. Y. Negative regulation of prolactin receptor stability and signaling mediated by SCF $^{\beta\text{-TrCP}}$ E3 ubiquitin ligase. *Mol. Cell. Biol.* **24**, 4038–4048 (2004).
120. Fukuchi, M. et al. Ligand-dependent degradation of Smad3 by a ubiquitin ligase complex of ROC1 and associated proteins. *Mol. Biol. Cell* **12**, 1431–1443 (2001).
121. Wan, M. et al. Smad4 protein stability is regulated by ubiquitin ligase SCF $^{\beta\text{-TrCP}1}$. *J. Biol. Chem.* **279**, 14484–14487 (2004).
122. Kumar, K. G. et al. SCF $^{\text{HOS}}$ ubiquitin ligase mediates the ligand-induced down-regulation of the interferon- α receptor. *EMBO J.* **22**, 5480–5490 (2003).
123. Watanabe, N. et al. M-phase kinases induce phospho-dependent ubiquitination of somatic Wee1 by SCF $^{\beta\text{-TrCP}}$. *Proc. Natl Acad. Sci. USA* **101**, 4419–4424 (2004).
124. Koepp, D. M. et al. Phosphorylation-dependent ubiquitination of cyclin E by the SCF $^{\text{Fbw7}}$ ubiquitin ligase. *Science* **294**, 173–177 (2001).
125. Strohmaier, H. et al. Human F-box protein hCdc4 targets cyclin E for proteolysis and is mutated in a breast cancer cell line. *Nature* **413**, 316–322 (2001).
126. Nateri, A. S., Riera-Sans, L., Da Costa, C. & Behrens, A. The ubiquitin ligase SCF $^{\text{Fbw7}}$ antagonizes apoptotic JNK signaling. *Science* **303**, 1374–1378 (2004).
127. Yada, M. et al. Phosphorylation-dependent degradation of c-Myc is mediated by the F-box protein Fbw7. *EMBO J.* **23**, 2116–2125 (2004).
128. Welcker, M. et al. The Fbw7 tumor suppressor regulates glycogen synthase kinase 3 phosphorylation-dependent c-Myc protein degradation. *Proc. Natl Acad. Sci. USA* **101**, 9085–9090 (2004).

129. Tetzlaff, M. T. *et al.* Defective cardiovascular development and elevated cyclin E and Notch proteins in mice lacking the Fbw7 F-box protein. *Proc. Natl Acad. Sci. USA* **101**, 3338–3345 (2004).
130. Tsunematsu, R. *et al.* Mouse Fbw7/Sel-10/Cdc4 is required for notch degradation during vascular development. *J. Biol. Chem.* (2003).
131. Li, J. *et al.* SEL-10 interacts with presenilin 1, facilitates its ubiquitination, and alters A-beta peptide production. *J. Neurochem.* **82**, 1540–1548 (2002).
132. Yoshida, Y. *et al.* E3 ubiquitin ligase that recognizes sugar chains. *Nature* **418**, 438–442 (2002).
133. Eom, C. Y. & Lehman, I. R. Replication-initiator protein (UL9) of the herpes simplex virus 1 binds NFB42 and is degraded via the ubiquitin-proteasome pathway. *Proc. Natl Acad. Sci. USA* **100**, 9803–9807 (2003).
134. Yoshida, Y. *et al.* Fbs2 is a new member of the E3 ubiquitin ligase family that recognizes sugar chains. *J. Biol. Chem.* **278**, 43877–43884 (2003).
135. den Engelsman, J., Keijsers, V., de Jong, W. W. & Boelens, W. C. The small heat-shock protein α B-crystallin promotes FBX4-dependent ubiquitination. *J. Biol. Chem.* **278**, 4699–4704 (2003).
136. Charrasse, S., Carena, I., Brondani, V., Klempnauer, K. H. & Ferrari, S. Degradation of B-Myb by ubiquitin-mediated proteolysis: involvement of the Cdc34–SCF b45Skp2 pathway. *Oncogene* **19**, 2986–2995 (2000).
137. Garriga, J. *et al.* CDK9 is constitutively expressed throughout the cell cycle, and its steady-state expression is independent of SKP2. *Mol. Cell. Biol.* **23**, 5165–5173 (2003).
138. Kiernan, R. E. *et al.* Interaction between cyclin T1 and SCF Skp2 targets CDK9 for ubiquitination and degradation by the proteasome. *Mol. Cell. Biol.* **21**, 7956–7970 (2001).
139. Li, X., Zhao, Q., Liao, R., Sun, P. & Wu, X. The SCF Skp2 ubiquitin ligase complex interacts with the human replication licensing factor Cdt1 and regulates Cdt1 degradation. *J. Biol. Chem.* **278**, 30854–30858 (2003).
140. Kondo, T. *et al.* Rapid degradation of Cdt1 upon UV-induced DNA damage is mediated by SCF Skp2 complex. *J. Biol. Chem.* (2004).
141. Sugimoto, N. *et al.* Cdt1 phosphorylation by cyclin A-dependent kinases negatively regulates its function without affecting geminin binding. *J. Biol. Chem.* **279**, 19691–19697 (2004).
142. Yu, Z. K., Gervais, J. L. & Zhang, H. Human CUL-1 associates with the SKP1/SKP2 complex and regulates p21 $^{CIP1/WAF1}$ and cyclin D proteins. *Proc. Natl Acad. Sci. USA* **95**, 11324–11329 (1998).
143. Russell, A. *et al.* Cyclin D1 and D3 associate with the SCF complex and are coordinately elevated in breast cancer. *Oncogene* **18**, 1983–1991 (1999).
144. Russell, A., Hendley, J. & Germain, D. Inhibitory effect of p21 in MCF-7 cells is overcome by its coordinated stabilization with D-type cyclins. *Oncogene* **18**, 6454–6459 (1999).
145. Nakayama, K. *et al.* Targeted disruption of Skp2 results in accumulation of cyclin E and p27 kip1 , polyploidy and centrosome overduplication. *EMBO J.* **19**, 2069–2081 (2000).
146. Yeh, K. H. *et al.* The F-box protein SKP2 binds to the phosphorylated threonine 380 in cyclin E and regulates ubiquitin-dependent degradation of cyclin E. *Biochem. Biophys. Res. Commun.* **281**, 884–890 (2001).
147. Oh, K. J. *et al.* The papillomavirus E7 oncoprotein is ubiquitinated by UbcH7 and Cullin 1- and Skp2-containing E3 ligase. *J. Virol.* **78**, 5338–5346 (2004).
148. Nie, L., Xu, M., Vladimirova, A. & Sun, X. H. Notch-induced E2A ubiquitination and degradation are controlled by MAP kinase activities. *EMBO J.* **22**, 5780–5792 (2003).
149. Marti, A., Wirbelauer, C., Scheffner, M. & Krek, W. Interaction between ubiquitin-protein ligase SCF SKP2 and E2F-1 underlies the regulation of E2F-1 degradation. *Nature Cell Biol.* **1**, 14–19 (1999).
150. von der Lehr, N. *et al.* The F-box protein Skp2 participates in c-Myc proteosomal degradation and acts as a cofactor for c-Myc-regulated transcription. *Mol. Cell* **11**, 1189–1200 (2003).

151. Mendez, J. et al. Human origin recognition complex large subunit is degraded by ubiquitin-mediated proteolysis after initiation of DNA replication. *Mol. Cell* **9**, 481–491 (2002).
152. Kamura, T. et al. Degradation of p57^{Kip2} mediated by SCF^{Skp2}-dependent ubiquitylation. *Proc. Natl Acad. Sci. USA* **100**, 10231–10236 (2003).
153. Bhattacharya, S. et al. SKP2 associates with p130 and accelerates p130 ubiquitylation and degradation in human cells. *Oncogene* **22**, 2443–2451 (2003).
154. Tedesco, D., Lukas, J. & Reed, S. I. The pRb-related protein p130 is regulated by phosphorylation-dependent proteolysis via the protein-ubiquitin ligase SCF^{Skp2}. *Genes Dev.* **16**, 2946–2957 (2002).
155. Zhang, H., Kobayashi, R., Galaktionov, K. & Beach, D. p19^{Skp1} and p45^{Skp2} are essential elements of the cyclin A-CDK2 S phase kinase. *Cell* **82**, 915–925 (1995).
156. Bornstein, G. et al. Role of the SCF^{Skp2} ubiquitin ligase in the degradation of p21^{Cip1} in S phase. *J. Biol. Chem.* **278**, 25752–25757 (2003).
157. Carrano, A. C., Eytan, E., Hershko, A. & Pagano, M. SKP2 is required for ubiquitin-mediated degradation of the CDK inhibitor p27. *Nature Cell Biol.* **1**, 193–199 (1999).
158. Sutterluty, H. et al. p45^{SKP2} promotes p27^{Kip1} degradation and induces S phase in quiescent cells. *Nature Cell Biol.* **1**, 207–214 (1999).
159. Ganoth, D. et al. The cell-cycle regulatory protein Cks1 is required for SCF^{Skp2}-mediated ubiquitylation of p27. *Nature Cell Biol.* **3**, 321–324 (2001).
160. Spruck, C. et al. A CDK-independent function of mammalian Cks1: targeting of SCF^{Skp2} to the CDK inhibitor p27^{Kip1}. *Mol. Cell* **7**, 639–650 (2001).
161. Rui, L., Yuan, M., Frantz, D., Shoelson, S. & White, M. F. SOCS-1 and SOCS-3 block insulin signaling by ubiquitin-mediated degradation of IRS1 and IRS2. *J. Biol. Chem.* **277**, 42394–42398 (2002).
162. Kamizono, S. et al. The SOCS box of SOCS-1 accelerates ubiquitin-dependent proteolysis of TEL-JAK2. *J. Biol. Chem.* **276**, 12530–12538 (2001).
163. Frantsve, J., Schwaller, J., Sternberg, D. W., Kutok, J. & Gilliland, D. G. Socs-1 inhibits TEL-JAK2-mediated transformation of hematopoietic cells through inhibition of JAK2 kinase activity and induction of proteasome-mediated degradation. *Mol. Cell. Biol.* **21**, 3547–3557 (2001).
164. De Sepulveda, P., Ilangumaran, S. & Rottapel, R. Suppressor of cytokine signaling-1 inhibits VAV function through protein degradation. *J. Biol. Chem.* **275**, 14005–14008 (2000).
165. Lonergan, K. M. et al. Regulation of hypoxia-inducible mRNAs by the von Hippel–Lindau tumor suppressor protein requires binding to complexes containing elongins B/C and Cul2. *Mol. Cell. Biol.* **18**, 732–741 (1998).
166. Aso, T., Yamazaki, K., Aigaki, T. & Kitajima, S. *Drosophila* von Hippel–Lindau tumor suppressor complex possesses E3 ubiquitin ligase activity. *Biochem. Biophys. Res. Commun.* **276**, 355–361 (2000).
167. Cockman, M. E. et al. Hypoxia inducible factor- α binding and ubiquitylation by the von Hippel–Lindau tumor suppressor protein. *J. Biol. Chem.* **275**, 25733–25741 (2000).
168. Kamura, T. et al. Activation of HIF1 α ubiquitination by a reconstituted von Hippel–Lindau (VHL) tumor suppressor complex. *Proc. Natl Acad. Sci. USA* **97**, 10430–10435 (2000).
169. Krieg, M. et al. Up-regulation of hypoxia-inducible factors HIF-1 α and HIF-2 α under normoxic conditions in renal carcinoma cells by von Hippel–Lindau tumor suppressor gene loss of function. *Oncogene* **19**, 5435–5443 (2000).
170. Ohh, M. et al. Ubiquitination of hypoxia-inducible factor requires direct binding to the β -domain of the von Hippel–Lindau protein. *Nature Cell Biol.* **2**, 423–427 (2000).
171. Tanimoto, K., Makino, Y., Pereira, T. & Poellinger, L. Mechanism of regulation of the hypoxia-inducible factor-1 α by the von Hippel–Lindau tumor suppressor protein. *EMBO J.* **19**, 4298–4309 (2000).
172. Ivan, M. et al. HIF α targeted for VHL-mediated destruction by proline hydroxylation: implications for O $_2$ sensing. *Science* **292**, 464–468 (2001).
173. Jaakkola, P. et al. Targeting of HIF- α to the von Hippel–Lindau ubiquitylation complex by O $_2$ -regulated prolyl hydroxylation. *Science* **292**, 468–472 (2001).

174. Masson, N., Willam, C., Maxwell, P. H., Pugh, C. W. & Ratcliffe, P. J. Independent function of two destruction domains in hypoxia-inducible factor- α chains activated by prolyl hydroxylation. *EMBO J.* **20**, 5197–5206 (2001).
175. Yu, F., White, S. B., Zhao, Q. & Lee, F. S. HIF-1 α binding to VHL is regulated by stimulus-sensitive proline hydroxylation. *Proc. Natl Acad. Sci. USA* **98**, 9630–9635 (2001).
176. Na, X. et al. Identification of the RNA polymerase II subunit hsRPB7 as a novel target of the von Hippel–Lindau protein. *EMBO J.* **22**, 4249–4259 (2003).
177. Kuznetsova, A. V. et al. von Hippel–Lindau protein binds hyperphosphorylated large subunit of RNA polymerase II through a proline hydroxylation motif and targets it for ubiquitination. *Proc. Natl Acad. Sci. USA* **100**, 2706–2711 (2003).
178. Li, Z. et al. Ubiquitination of a novel deubiquitinating enzyme requires direct binding to von Hippel–Lindau tumor suppressor protein. *J. Biol. Chem.* **277**, 4656–4662 (2002).
179. Li, Z. et al. Identification of a deubiquitinating enzyme subfamily as substrates of the von Hippel–Lindau tumor suppressor. *Biochem. Biophys. Res. Commun.* **294**, 700–709 (2002).
180. Pioli, P. A. & Rigby, W. F. The von Hippel–Lindau protein interacts with heteronuclear ribonucleoprotein A2 and regulates its expression. *J. Biol. Chem.* **276**, 40346–40352 (2001).
181. Okuda, H. et al. The von Hippel–Lindau tumor suppressor protein mediates ubiquitination of activated atypical protein kinase C. *J. Biol. Chem.* **276**, 43611–43617 (2001).
182. Ivanova, A. V., Ivanov, S. V., Danilkovitch-Miagkova, A. & Lerman, M. I. Regulation of STRA13 by the von Hippel–Lindau tumor suppressor protein, hypoxia, and the UBC9/ubiquitin proteasome degradation pathway. *J. Biol. Chem.* **276**, 15306–15315 (2001).
183. Wilkins, A., Ping, Q. & Carpenter, C. L. RhoBTB2 is a substrate of the mammalian Cul3 ubiquitin ligase complex. *Genes Dev.* **18**, 856–861 (2004).
184. Zhang, H. F. et al. Cullin 3 promotes proteasomal degradation of the topoisomerase I-DNA covalent complex. *Cancer Res.* **64**, 1114–1121 (2004).
185. Kobayashi, A. et al. Oxidative stress sensor Keap1 functions as an adaptor for Cul3-based E3 ligase to regulate proteasomal degradation of Nrf2. *Mol. Cell. Biol.* **24**, 7130–7139 (2004).
186. Cullinan, S. B., Gordan, J. D., Jin, J., Harper, J. W. & Diehl, J. A. The Keap1-BTB protein is an adaptor that bridges Nrf2 to a Cul3-based E3 ligase: oxidative stress sensing by a Cul3–Keap1 ligase. *Mol. Cell. Biol.* **24**, 8477–8486 (2004).
187. Wertz, I. E. et al. Human de-etiolated-1 regulates c-Jun by assembling a CUL4A ubiquitin ligase. *Science* **303**, 1371–1374 (2004).
188. Ulane, C. M. & Horvath, C. M. Paramyxoviruses SV5 and HPIV2 assemble STAT protein ubiquitin ligase complexes from cellular components. *Virology* **304**, 160–166 (2002).
189. Querido, E. et al. Degradation of p53 by adenovirus E4orf6 and E1B55K proteins occurs via a novel mechanism involving a Cullin-containing complex. *Genes Dev.* **15**, 3104–3117 (2001).
190. Yu, X. et al. Induction of APOBEC3G ubiquitination and degradation by an HIV-1 Vif–Cul5–SCF complex. *Science* **302**, 1056–1060 (2003).