PERSPECTIVE

A ubiquitin ligase complex essential for the NF- κ B, Wnt/Wingless, and Hedgehog signaling pathways

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Ubiquitin-dependent proteolysis by the proteasome plays an essential role in a number of key biological processes, including cell cycle progression, transcription, and signal transduction (for review, see Peters et al. 1998). In many cases the target protein is first marked for degradation or processing by phosphorylation. The phosphorylated protein is then recognized and ubiquitinated in a process that requires three proteins (Hershko et al. 1983; for review, see Hershko 1998; Peters et al. 1998). Ubiquitin is first attached to a ubiquitin-activating enzyme (E1) in an ATP-dependent reaction to form a high-energy thiolester bond. The ubiquitin is then transferred from the E1 protein to an E2 ubiquitin-conjugating enzyme, which functions in conjunction with an E3 protein to link ubiquitin to lysine residues in the targeted protein. A specific lysine residue in the conjugated ubiquitin is then attached to a second ubiquitin, and reiteration of this process results in the assembly of a polyubiquitin chain. The polyubiquitinated protein can then be recognized by the 26S proteasome and degraded or processed.

SCF ubiquitin ligase complexes

E1 and E2 proteins have been identified and characterized, and the latter has been shown to comprise a family of related proteins (for review, see Peters et al. 1998). In contrast, much less is known about E3 enzymes. There are examples in which the E3 is involved directly in ubiquitin transfer (for review, see Huibregtse et al. 1998). However, in most cases E3 proteins appear to function as adapters that recruit the target protein to a complex containing an E2 enzyme, thus providing a mechanism for specificity. This mechanism is exemplified by the SCF ubiquitin ligase complex, which was initially identified in studies of the cell cycle in yeast. This complex contains the proteins Skp1, Cdc53/Cul1, and an F-box protein, as illustrated in Figure 1 (for review, see Elledge and Harper 1998; Krek 1998; Patton et al. 1998). The Cdc53/Cul1 protein acts as scaffold for the complex, simultaneously interacting with a specific E2 protein and Skp1.

The Skp1 protein, in turn, interacts with the F-box protein through the F-box motif. A second protein interaction domain in the F-box protein binds specifically to the protein targeted for degradation. In the example shown, this domain is a WD40 repeat sequence although other interaction motifs have been identified in other F-box proteins. Thus, according to the 'F-box hypothesis,' distinct sets of E2s and substrates can be matched with each other through the recruitment of different F-box proteins to the SCF complex. Once the target protein is docked the E2 enzyme transfers ubiquitin from the ubiquitin-E1 complex to the target protein (Fig. 1; for review, see Elledge and Harper 1998; Patton et al. 1998).

Recently, metazoan homologs of each of the yeast SCF components have been identified. In particular, a large number of F-box proteins have been found, including β -TrCP (β -transducin repeat-containing protein), which contains an F-box and a WD40 repeat domain (for review, see Elledge and Harper 1998; Patton et al. 1998). A number of targets of yeast F-box proteins have been identified, including certain Cdk inhibitors, G₁ cyclins, DNA replication proteins, and the transcription factor Gcn4. In contrast, specific targets for the metazoan F-box proteins have not been identified. Recently, in *Genes & Development* (Spencer et al. 1999; Winston et al. 1999) and elsewhere (Jiang and Struhl 1998; Yaron et al. 1998), a specific *Drosophila* F-box protein, Slimb, and its mammalian homolog β -TrCP have been implicated in the regulation of three different signal transduction pathways: NF- κ B, Wnt/Wingless (Wnt/Wg), and Hedgehog. A common link between these pathways is the essential role of the ubiquitin proteasome pathway (Fig. 2).

The NF- κ B pathway

NF- κ B and other members of the Rel family of transcriptional activator proteins are sequestered in the cytoplasm through their association with members of the I κ B family of inhibitor proteins (Fig. 2A; for review, see Baerle and Baltimore 1996). In the case of the inhibitor I κ B α , a variety of extracellular signals, virus infection, or ionizing radiation activate signaling pathways leading to the phosphorylation of two serine residues near the

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Figure 1. Composition and function of SCF ubiquitin ligase complexes (see text for details).

amino terminus of the protein (Ser-32 and Ser-36; for review, see Baldwin 1996). This modification marks the protein for ubiquitination at lysines 21 and 22 and degradation by the proteasome (for review, see Chen and Maniatis 1998). Once freed from I κ B α , NF- κ B translocates to the nucleus, where it binds to specific promoters and activates transcription. Although the upstream events in this signaling cascade have not been fully elucidated, most NF- κ B-inducing signals culminate in activation of a high-molecular-weight I κ B-kinase complex that phosphorylates Ser-32 and Ser-36 in I κ B α (for review, see Maniatis 1997; Scheidereit 1998). The phosphorylation and ubiquitination of I κ B α can be carried out in vitro, and the reaction requires ATP, ubiquitin, E1, an E2 protein (Ubch5 or Ubch7), and a partially purified E3 activity (Alkalay et al. 1995; Chen et al. 1995, 1996). However, prior to the recent studies reviewed here, a specific I κ B α E3 protein has not been identified.

The Wnt/Wg pathway

The ubiquitin/proteasome pathway is also involved in the regulation of the Wnt/Wg signaling pathway. The activity of the transcriptional regulatory protein TCF/LEF-1, a terminal component of this pathway, is regulated by its association with the transcriptional coactivator β -catenin/Armadillo (β -cat/Arm), another component of the Wnt/Wg pathway (Fig. 2B; for review, see Willert and Nusse 1998). In the absence of Wnt/Wg signaling, the β -cat/Arm protein is phosphorylated as a consequence of its association with APC (adenomatous polyposis coli), axin, and the kinase GSK3 β (glycogen synthase kinase 3 β). The phosphorylation sites on β -cat/Arm are strikingly similar to those of I κ B proteins (DSG ψ XS), where ψ is a hydrophobic residue and S corresponds to the two serines that are phosphorylated (Ikeda et al. 1998). This phosphorylation is thought to target β -cat/Arm for ubiquitination and degradation by the proteasome (Aberle et al. 1997; Orford et al. 1997). When the Wnt/Wg pathway is activated, GSK3 β is inhibited and β -cat/Arm accumulates, translocates to the nucleus, and functions as a coactivator with TCF/LEF-1. In the absence of β -cat/Arm, the TCF/LEF-1 protein functions as a repressor of downstream genes.

The Hedgehog signaling pathway

The activity of the transcriptional regulatory protein Cubitus interruptus (Ci), a component of the Hedgehog (Hh) signaling pathway, is also regulated by the ubiquitin-proteasome pathway (for review, see Ruiz i Altaba 1997; Ingham 1998). Normally, the 155-kD Ci protein is part of a microtubule-bound complex containing three other proteins, Costal-2 (Cos-2), Fused (Fu), and Suppressor of fused [Su(fu)]. In the absence of Hedgehog signaling, the 155-kD Ci protein is proteolytically processed to produce a 75-kD amino-terminal protein that is released from the complex and acts as a transcriptional repressor (Fig. 2C; Aza-Blanc et al. 1997). This processing can be blocked by proteasome inhibitors (Ingham 1998), thus implicating the ubiquitin-proteasome pathway. A precedent for such a ubiquitin-proteasome-dependent processing mechanism is provided by the NF- κ B p105 protein, which is the precursor of the p50 subunit of NF- κ B (Fan and Maniatis 1991; Palombella et al. 1994). Proteolytic processing of Ci appears to require phosphorylation by protein kinase A (PKA) (Chen et al. 1998; for review, see Ingham 1998). In the presence of the Hh protein, Ci processing is suppressed. The 155-kD Ci protein accumulates, and, by a mechanism yet to be determined, is released from the microtubule-bound complex (see Ohlmeyer and Kalderon 1998 for recent discussion and references). The intact Ci protein then acts as a transcriptional activator to turn on downstream genes. Thus, the common feature of all three pathways is the signal-dependent phosphorylation and ubiquitination of a regulatory protein and its degradation or processing by the proteasome.

Role of the SCF^{TrCP} complex

The exciting new finding is that one SCF ligase complex (SCF^{TrCP}) may ubiquitinate the protein targets in all three signaling pathways (I κ B α , β -cat/Arm, and Ci). This possibility was first indicated by genetic studies in *Drosophila* that identified a *Drosophila* gene that negatively regulates both the Hh and Wnt/Wg pathways (Jiang and Struhl 1998). This gene, termed Slimb (supernumerary limbs), encodes an F-box/WD40 repeat protein that bears a striking resemblance to yeast F-box proteins found in SCF complexes. In the absence of Slimb, high levels of both Ci and Arm accumulate in a cell-autonomous manner, and both Hh- and Wg-responsive genes are expressed ectopically. The researchers proposed that Slimb is required for the processing of Ci and the degradation of Arm via the ubiquitin-proteasome pathway.

Recently, Slimb was directly implicated in the NF- κ B pathway by the observation that the Slimb protein is required for the activation of the *Drosophila* NF- κ B homolog, Dorsal (Spencer et al. 1999). During dorsoventral patterning of the early *Drosophila* embryo, the Dorsal protein is activated specifically on the ventral side of the embryo by the Toll receptor-signaling pathway (for review, see Morisato and Anderson 1995). This pathway culminates in the degradation of the *Drosophila* I κ B pro-

Figure 2. The role of the ubiquitin–proteasome pathway in the regulated degradation of IκBα and β-cat/Arm, and the processing of Ci. (A) Degradation of IκBα. A variety of signals, including tumor necrosis factor-α (TNF-α) shown here, lead to the activation of an IκB-kinase complex (IKK), which specifically phosphorylates Ser-32 and Ser-36 at the amino terminus of IκBα. This phosphorylation marks the protein for ubiquitination at lysines 21 and 22. Polyubiquitinated IκBα is then recognized by the 26S proteasome and degraded, resulting in the release and nuclear translocation of NF-κB. (B) Degradation of β-catenin. In the absence of Wnt/Wg, a complex of GSK3β, APC, and axin associates with and phosphorylates β-catenin. Although not yet demonstrated directly, this phosphorylation likely targets β-catenin for ubiquitination followed by proteasome degradation. In the presence of Wnt/Wg this process is blocked, leading to the accumulation of β-catenin, which functions as a coactivator for the transcription factor TCF/LEF-1. The β-catenin/TCF/LEF-1 complex then activates downstream genes in the Wnt/Wg pathway. (C) Processing of *Cubitus interruptus* (Ci). In the absence of Hh signaling, the 155-kD Ci protein is bound to microtubules in a complex with three other proteins [cos2, Fu, and Su(fu)]. PKA phosphorylates Ci 155, and this phosphorylation may target the Ci protein for ubiquitination and processing by the 26S proteasome, thus generating a 75-kD amino-terminal protein. The Ci 75-kD protein is thought to function as a transcriptional repressor of downstream genes. In the presence of Hh, phosphorylation of Ci is suppressed, possibly a consequence of inhibiting PKA (for review, see Ingham 1998).

tein, Cactus, allowing the nuclear translocation of Dorsal and the activation of downstream genes such as *twist* and *snail*. In *slimb* mutants, *twist* and *snail* gene expression is no longer induced on the ventral side of the embryo (Spencer et al. 1999). Thus, the F-box/WD40 protein Slimb appears to be a component of an SCF complex required for the ubiquitination of IκB proteins, β-cat/Arm, and Ci. However, until now, there was no direct biochemical evidence to support this model.

β-TrCP is a component of the IκB ubiquitin ligase

Independent studies from three different groups now provide compelling evidence that the β-TrCP protein, a mammalian homolog of the *Drosophila* Slimb protein, is indeed a component of the IκB ubiquitin ligase (Yaron et

al. 1998; Spencer et al. 1999; Winston et al. 1999). First, Ben-Neriah and his collaborators used an affinity purification approach to identify β-TrCP as a protein that binds specifically to phosphorylated IκBα in vitro (Yaron et al. 1998). Second, based on their finding that Slimb is required for the activation of *twist* and *snail* in *Drosophila*, the groups of Chen and Jiang (Spencer et al. 1999) isolated β-TrCP as a mammalian homolog of Slimb, and showed that β-TrCP specifically interacts with phosphorylated IκBα in vitro and in vivo. Third, the groups of Harper and Elledge and their collaborators speculated that a mammalian SCF complex might be involved in the degradation of IκBα and showed that in vitro translated β-TrCP binds to a 21-amino-acid phosphopeptide of IκBα containing Ser-32 and Ser-36 (Winston et al. 1999). In this case, several different mamma-

lian F-box proteins were tested, but only β -TrCP bound to phosphorylated I κ B α . Evidence for an in vivo function of β -TrCP was provided by the observation that a deletion mutant of β -TrCP, lacking the F-box motif, functions as a dominant negative inhibitor of NF- κ B activation (Yaron et al. 1998; Spencer et al. 1999).

Two of the groups showed that the β -TrCP protein functions as a component of an SCF complex (Spencer et al. 1999; Winston et al. 1999). Spencer et al. (1999) found that I κ B α and Skp1, the p65 subunit of NF- κ B, and β -TrCP could be coimmunoprecipitated with epitope-tagged β -TrCP expressed in human 293 cells treated with calyculin A (a phosphatase inhibitor that induces NF- κ B). The association of I κ B α with Skp1 and β -TrCP was not observed in the absence of calyculin A, showing that the phosphorylation of I κ B α is required for its recruitment to the SCF complex. In a complementary approach, Winston et al. (1999) transfected 293 cells with plasmids expressing epitope-tagged β -TrCP, Cull1, and Skp1, and found that all three proteins could be coimmunoprecipitated. In addition, the immunoaffinity-purified complex containing these components could associate with phosphorylated I κ B α immobilized on agarose beads. Taken together, these experiments provide strong evidence that the phosphorylation of I κ B α leads to its association with an SCF complex in vivo, and that the F-box protein in this complex is β -TrCP.

The functional significance of this association was demonstrated elegantly by in vitro ubiquitination experiments using an immunopurified complex isolated from cells transfected with epitope-tagged β -TrCP (Yaron et al. 1998; Spencer et al. 1999; Winston et al. 1999). In two of the studies, specific ubiquitination of I κ B α was observed when the β -TrCP-associated complex was incubated with a phosphorylated I κ B α /NF- κ B complex in the presence of ATP, recombinant E1, and the E2 protein Ubch5 (Yaron et al. 1998; Spencer et al. 1999). Thus, it appears that the SCF complex isolated from transfected 293 cells by immunoaffinity purification does not contain an E2 protein, suggesting that the E2 is bound weakly to the complex and is lost during immunopurification. It is important to note that specific I κ B α ubiquitination was observed only when I κ B α was bound to NF- κ B, suggesting that the structure of I κ B α in the complex is required for the recognition of I κ B α by the SCF complex. Ubiquitination was not observed with Ser32Ala/Ser36Ala mutants, or in the presence of the F-box deletion mutant β -TrCP that acts as a dominant-negative mutant of NF- κ B activation (Spencer et al. 1999). In addition, substitution of lysines 21 and 22 of I κ B α blocked in vitro ubiquitination (Spencer et al. 1999; see also Scherer et al. 1995). In parallel studies Winston et al. (1999) showed that the Skp1, Cull1, and β -TrCP complex immunopurified from 293 cells did not ubiquitinate phosphorylated I κ B α , but could be complemented by the addition of yeast extracts. The yeast extracts likely contributed the E1 and E2 activities necessary for ubiquitination. Additional evidence for a role of the SCF complex in I κ B α ubiquitination was provided by the observation that Skp1, Cull1, and β -TrCP copurify with

I κ B α ubiquitinating activity from cell extracts (Winston et al. 1999), and this activity could be immunodepleted with an anti-Skp1 antibody. Taken together, these observations definitively demonstrate that an SCF complex is required for the signal-dependent degradation of I κ B α , and that the F-box protein β -TrCP functions as the specificity factor in this complex.

A hint that the same mechanism is involved in the recognition and ubiquitination of β -cat/Arm was provided by the observation that a phosphopeptide containing the GSK3 β phosphorylation site on β -catenin can interact specifically with β -TrCP and Skp1 (Winston et al. 1999). This observation is consistent with previous studies showing that a dominant-negative F-box deletion mutant of β -TrCP results in a phenotype consistent with stabilization of β -catenin in *Xenopus* (Marikawa and Elinson 1998). Although additional biochemical studies are required to confirm these findings, it seems likely the β -cat/Arm is indeed ubiquitinated via the SCF complex. The possibility that the same SCF complex is required for processing the *Drosophila* Ci protein has yet to be demonstrated in biochemical studies. However, the observations that Ci processing requires the proteasome, and that Slimb mutants lead to the accumulation of Ci, are highly suggestive of this possibility.

Role of SCF $^{\beta$ -TrCP in the degradation of CD4

An additional target of the SCF $^{\beta$ -TrCP complex is the CD4 protein, through its association with the human immunodeficiency virus (HIV) protein, Vpu (Fujita et al. 1997; Margottin et al. 1998; Schubert et al. 1998). Recent studies have shown that the Vpu protein can simultaneously interact with the CD4 protein and β -TrCP to form a ternary complex, which targets CD4 for proteolysis (Margottin et al. 1998). The Vpu/ β -TrCP interaction, which occurs through the WD40 repeats of β -TrCP, requires the phosphorylation of two serine residues in Vpu. These serines are located within a sequence motif remarkably similar to that containing the phosphorylation sites in I κ B α and β -cat/Arm (Margottin et al. 1998). In addition, the Vpu-dependent degradation of CD4 requires the ubiquitin pathway, and proteasome inhibitors block this degradation (Fujita et al. 1997; Schubert et al. 1998). These observations are consistent with the view that Vpu carries the CD4 protein to the SCF complex where CD4 is ubiquitinated and thus targeted for degradation by the proteasome (Margottin et al. 1998).

Medical implications

The discovery of the ubiquitin ligase complex for I κ B α is an important advance in understanding the mechanisms of regulated proteolysis, and it provides new insights into signaling pathways of considerable medical interest. NF- κ B is a key regulatory protein in the immune and inflammatory responses, and the signaling pathway leading to its activation provides targets for the development of drugs to treat inflammatory diseases. In this regard,

the finding that the SCF ^{β -TrCP} complex can ubiquitinate several different proteins is a disappointment, as the development of selective inhibitors of the complex will be difficult. Of particular concern would be the effects of SCF ^{β -TrCP} inhibitors on β -catenin accumulation. Mutations in APC and β -catenin that lead to the accumulation of the β -catenin protein are associated with a number of different human cancers. It is not surprising that many of the oncogenic mutations in β -catenin localize to the amino acid sequences required for its phosphorylation and ubiquitination (see Winston et al. 1999 and He et al. 1998 for discussion and references). At least one of the oncogenic effects of β -catenin is its ability to function as a coactivator with LEF-1/TCF to promote *c-myc* gene expression (He et al. 1998). Thus, inhibitors of the SCF ^{β -TrCP} complex would be expected to increase the level of *c-myc* expression and possibly lead to oncogenic transformation. At present, the most specific targets for the inhibition of NF- κ B activity are the components of the high molecular weight I κ B kinase complex, a conclusion supported by the recent finding that IKK β , one component of this complex, is inhibited by aspirin (Yin et al. 1998).

References

- Aberle, H., A. Bauer, J. Stappert, A. Kispert, and R. Kemler. 1997. β -Catenin is a target for the ubiquitin-proteasome pathway. *EMBO J.* **16**: 3797–3804.
- Alkalay, I., A. Yaron, A. Hatzubai, A. Orian, A. Ciechanover, and Y. Ben-Neriah. 1995. Stimulation-dependent I κ B α phosphorylation marks the NF- κ B inhibitor for degradation via the Ub-proteasome pathway. *Proc. Natl. Acad. Sci.* **92**: 10599–10603.
- Aza-Blanc, P., F.-A. Ramírez-Weber, M.-P. Laget, C. Schwartz, and T.B. Kornberg. 1997. Proteolysis that is inhibited by Hedgehog targets Cubitus interruptus protein to the nucleus and converts it to a repressor. *Cell* **89**: 1043–1053.
- Baeuerle, P.A. and D. Baltimore. 1996. NF- κ B: Ten years after. *Cell* **87**: 13–20.
- Baldwin, A.S. 1996. The NF- κ B and I κ B proteins: New discoveries and insights. *Annu. Rev. Immunol.* **14**: 649–681.
- Chen, Y., N. Gallaher, R.H. Goodman, and S.M. Smolik. 1998. Protein kinase A directly regulates the activity and proteolysis of Cubitus interruptus. *Proc. Natl. Acad. Sci.* **95**: 2349–2354.
- Chen, Z.J. and T. Maniatis. 1998. Role of the ubiquitin-proteasome pathway in NF- κ B activation. In *Ubiquitin and the biology of the cell* (ed. J.-M. Peters, J.R. Harris, and D. Finley), pp. 303–322. Plenum Press, New York, NY.
- Chen, Z.J., J. Hagler, V.J. Palombella, F. Melandri, D. Scherer, D. Ballard, and T. Maniatis. 1995. Signal-induced site-specific phosphorylation targets I κ B α to the ubiquitin-proteasome pathway. *Genes & Dev.* **9**: 1586–1597.
- Chen, Z.J., L. Parent, and T. Maniatis. 1996. Site-specific phosphorylation of I κ B α by a novel ubiquitin-dependent protein kinase activity. *Cell* **84**: 853–862.
- Elledge, S.J. and J.W. Harper. 1998. Proteolysis in cell cycle control and cancer. *Biochem. Biophys. Acta* **1377**: M61–M70.
- Fan, C.-M. and T. Maniatis. 1991. Generation of p50 subunit of NF- κ B by processing of p105 through an ATP-dependent pathway. *Nature* **354**: 395–398.
- Fujita, K., S. Omura, and J. Silver. 1997. Rapid degradation of CD4 in cells expressing human immunodeficiency virus type 1 Env and Vpu is blocked by proteasome inhibitors. *J. Gen. Virol.* **78**: 619–625.
- He, T.C., A.B. Sparks, C. Rago, H. Hermeking, L. Zawel, L.T. da Costa, P.J. Morin, B. Vogelstein, and K.W. Kinzler. 1998. Identification of c-MYC as a target of the APC pathway. *Science* **281**: 1509–1512.
- Hershko, A. 1998. The ubiquitin system. Past, present, and future perspectives. In *Ubiquitin and the biology of the cell* (ed. J.-M. Peters, J.R. Harris, and D. Finley), pp. 1–17. Plenum Press, New York, NY.
- Hershko, A., H. Heller, S. Elias, and A. Ciechanover. 1983. Components of the ubiquitin-protein ligase system. Resolution, affinity purification, and role in protein breakdown. *J. Biol. Chem.* **258**: 8206–8214.
- Huibregtse, J.M., C.G. Maki, and P.M. Howley. 1998. Ubiquitination of the p53 tumor suppressor. In *Ubiquitin and the biology of the cell* (ed. J.-M. Peters, J.R. Harris, and D. Finley), pp. 323–343. Plenum Press, New York, NY.
- Ikeda, S., S. Kishida, H. Yamamoto, H. Murai, S. Koyama, and A. Kikuchi. 1998. Axin, a negative regulator of the Wnt signaling pathway, forms a complex with GSK-3 β and β -catenin and promotes GSK-3 β -dependent phosphorylation of β -catenin. *EMBO J.* **17**: 1371–1384.
- Ingham, P.W. 1998. Transducing Hedgehog: The story so far. *EMBO J.* **17**: 3505–3511.
- Jiang, J. and G. Struhl. 1998. Regulation of the Hedgehog and Wingless signaling pathways by the F-box/WD40-repeat protein Slimb. *Nature* **391**: 493–496.
- Krek, W. 1998. Proteolysis and the G₁-S transition: The SCF connection. *Curr. Opin. Genet. Dev.* **8**: 36–42.
- Maniatis, T. 1997. Catalysis by a multiprotein I κ B kinase complex. *Science* **278**: 818–819.
- Margottin, F., S.P. Bour, H. Durand, L. Selig, S. Benichou, V. Richard, D. Thomas, K. Strebel, and R. Benarous. 1998. A novel human WD protein, h- β TrCP, that interacts with HIV-1 Vpu connects CD4 to the ER degradation pathway through an F-box motif. *Mol. Cell.* **1**: 565–574.
- Marikawa, Y. and R.P. Elinson. 1998. β -TrCP is a negative regulator of Wnt/ β -catenin signaling pathway and dorsal axis formation in *Xenopus* embryos. *Mech. Dev.* **77**: 75–80.
- Morisato, D. and K.V. Anderson. 1995. Signaling pathways that establish the dorsal-ventral pattern of the *Drosophila* embryo. *Annu. Rev. Genetics* **19**: 371–379.
- Ohlmeier, J.T. and D. Kalderon. 1998. Hedgehog stimulates maturation of Cubitus interruptus into a labile transcriptional activator. *Nature* **396**: 749–753.
- Orford, K., C. Crockett, J.P. Jensen, A.M. Weissman, and S.W. Byers. 1997. Serine phosphorylation-regulated ubiquitination and degradation of β -catenin. *J. Biol. Chem.* **272**: 24735–24738.
- Palombella, V.J., O.J. Rando, A.L. Goldberg, and T. Maniatis. 1994. The ubiquitin-proteasome pathway is required for processing the NF- κ B1 precursor protein and the activation of NF- κ B. *Cell* **78**: 773–785.
- Patton, E.E., A.R. Willems, and M. Tyers. 1998. Combinatorial control in ubiquitin-dependent proteolysis: Don't Skp the F-box hypothesis. *Trends Genet.* **14**: 236–243.
- Peters, J.-M., J.R. Harris, and D. Finley. 1998. *Ubiquitin and the biology of the cell*. Plenum Press, New York, NY.
- Ruiz i Altaba, A. 1997. Catching a Gli-mpse of Hedgehog. *Cell* **90**: 193–196.
- Scheidereit, C. 1998. Signal transduction. Docking I κ B kinases. *Nature* **395**: 225–226.
- Scherer, D.C., J.A. Brockman, Z. Chen, T. Maniatis, and D.W. Ballard. 1995. Signal-induced degradation of I κ B α requires

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- site-specific ubiquitination. *Proc. Natl. Acad. Sci.* **92**: 11259–11263.
- Schubert, U., L.C. Anton, I. Bacik, J.H. Cox, S. Bour, J.R. Benink, M. Orlowski, K. Strebel, and J.W. Yewdell. 1998. CD4 glycoprotein degradation induced by human immunodeficiency virus type-1 Vpu protein requires the function of proteasomes and the ubiquitin conjugating pathway. *J. Virol.* **72**: 2280–2288.
- Spencer, E., J. Jiang, and Z.J. Chen. 1999. Signal-induced ubiquitination of I κ B α by the F-box protein, Slimb/ β -TrCP. *Genes & Dev.* **13**: 284–294.
- Willert, K. and R. Nusse. 1998. β -Catenin: A key mediator of Wnt signaling. *Curr. Opin. Genet. Dev.* **8**: 95–102.
- Winston, J.T., P. Strack, P. Beer-Romero, C. Chu, S.J. Elledge, and J.W. Harper. 1999. The SCF- β^{TRCP} ubiquitin ligase complex associates specifically with phosphorylated destruction motifs in I κ B β and β -catenin and stimulates I κ B α ubiquitination in vitro. *Genes & Dev.* **3**: 270–283.
- Yaron, A., A. Hatzubai, M. Davis, I. Lavon, S. Amit, A.M. Manning, J.S. Andersen, M. Mann, F. Mercurio, and Y. Ben-Neriah. 1998. Identification of the receptor component of the I κ B α -ubiquitin ligase. *Nature* **396**: 590–594.
- Yin, M.J., Y. Yamamoto, and R.B. Gaynor. 1998. The anti-inflammatory agents aspirin and salicylate inhibit the activity of I κ B kinase- β . *Nature* **396**: 77–80.

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References

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