A ubiquitin ligase complex essential for the NF-κB, 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, 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.

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-κB, 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-κB pathway

NF-κB and other members of the Rel family of transcriptional activator proteins are sequestered in the cytoplasm through their association with members of the IκB family of inhibitor proteins (Fig. 2A; for review, see Baeuerle and Baltimore 1996). In the case of the inhibitor IκBα, a variety of extracellular signals, virus infection, or ionizing radiation activate signaling pathways leading to the phosphorylation of two serine residues near the...
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 IkBα, NF-κB 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-κB-inducing signals culminate in activation of a high-molecular-weight IκB-kinase complex that phosphorylates Ser-32 and Ser-36 in IkBα (for review, see Maniatis 1997; Scheidereit 1998). The phosphorylation and ubiquitination of IkBα 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 IkBα E3 protein has not been identified.

The Wnt/Wg pathway

The Wnt/Wg 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 GSK3β (glycogen synthase kinase 3β). The phosphorylation sites on β-cat/Arm reside on the hydrophobic residue S and correspond 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, GSK3β 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-κB p105 protein, which is the precursor of the p50 subunit of NF-κB (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 SCFTrCP complex

The exciting new finding is that one SCF ligase complex (SCFTrCP) may ubiquitinate the protein targets in all three signaling pathways [IkBα, 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 Slmb [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 Slmb, 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 Slmb is required for the processing of Ci and the degradation of Arm via the ubiquitin–proteasome pathway.

Recently, Slmb was directly implicated in the NF-κB pathway by the observation that the Slmb protein is required for the activation of the Drosophila NF-κB 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 Motosato and Anderson 1995). This pathway culminates in the degradation of the Drosophila IkB pro-
tein, Cactus, allowing the nuclear translocation of Dor-
sal and the activation of downstream genes such as twist
and snail. In slimb mutants, twist and snail gene expres-
sion is no longer induced on the ventral side of the em-
byro [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 IkBα, β-catenin, and Ci.
However, until now, there was no direct biochemical evidence to support this model.

**β-TrCP is a component of the IkB ubiquitin ligase**

Independent studies from three different groups now pro-
vide compelling evidence that the β-TrCP protein, a
mammalian homolog of the Drosophila Slimb protein, is
indeed a component of the IkB ubiquitin ligase [Yaron et
al. 1998; Spencer et al. 1999, Winston et al. 1999]. First,
Ben-Neriah and his collaborators used an affinity purifi-
cation approach to identify β-TrCP as a protein that
binds specifically to phosphorylated IkBα in vitro (Yaron
et al. 1998). Second, based on their finding that Slimb is
required for the activation of twist and snail in Dros-
ophila, 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 IkBα 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 IkBα and showed that in
vitro translated β-TrCP binds to a 21-amino-acid phos-
phopeptide of IkBα containing Ser-32 and Ser-36 (Wins-
ton et al. 1999). In this case, several different mamma-

**Figure 2.** The role of the ubiquitin–proteasome pathway in the regulated degradation of IkBα and β-catenin, and the processing of
Ci. (A) Degradation of IkBα. A variety of signals, including tumor necrosis factor-α [TNF-α] shown here, lead to the activation of an
IkB–kinase complex [IKK], which specifically phosphorylates Ser-32 and Ser-36 at the amino terminus of IkBα. This phosphorylation
marks the protein for ubiquitination at lysines 21 and 22. Polyubiquitinated IkBα 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).
lian F-box proteins were tested, but only β-TrCP bound to phosphorylated IκBα. 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-κB 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 IκBα and Skp1, the p65 subunit of NF-κB, 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-κB). The association of IκBα with Skp1 and β-TrCP was not observed in the absence of calyculin A, showing that the phosphorylation of IκBα 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, Cul1, and Skp1, and found that all three proteins could be coimmunoprecipitated. In addition, the immunoaffinity-purified complex containing these components could associate with phosphorylated IκBα immobilized on agarose beads. Taken together, these experiments provide strong evidence that the phosphorylation of IκBα 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 IκBα was observed when the β-TrCP-associated complex was incubated with a phosphorylated IκBα/NF-κB 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 IκBα ubiquitination was observed only when IκBα was bound to NF-κB, suggesting that the structure of IκBα in the complex is required for the recognition of IκBα by the SCF complex. Ubiquitination was not observed with Ser23/Ala/Ser36Ala mutants, or in the presence of the F-box deletion mutant β-TrCP that acts as a dominant-negative mutant of NF-κB activation [Spencer et al. 1999]. In addition, substitution of lysines 21 and 22 of IκBα 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, Cul1, and β-TrCP complex immunopurified from 293 cells did not ubiquitinate phosphorylated IκBα, 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 IκBα ubiquitination was provided by the observation that Skp1, Cul1, and β-TrCP copurify with IκBα 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 IκBα, 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 GSK3β 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 SCFβ-TrCP in the degradation of CD4**

An additional target of the SCFβ-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 IκBα 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 IκBα is an important advance in understanding the mechanisms of regulated proteolysis, and it provides new insights into signaling pathways of considerable medical interest. NF-κB 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 SCFβ-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 SCFβ-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 SCFβ-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-κB activity are the components of the high molecular weight IκB kinase complex, a conclusion supported by the recent finding that IKKβ, one component of this complex, is inhibited by aspirin (Yin et al. 1998).

References

Aberle, H., A. Bauer, J. Stuppert, 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 IκBα phosphorylation marks the NF-κB inhibitor for degradation via the Ub-proteasome pathway. Proc. Natl. Acad. Sci. 92: 10599–10603.

aza-Blanc, P., F.-A. Ramirez-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-κB: Ten years after. Cell 87: 13–20.

Baldwin, A.S. 1996. The NF-κB and IκB 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-κB 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 IκBα to the ubiquitin–proteasome pathway. Genes & Dev. 9: 1586–1597.

Chen, Z.J., L. Parent, and T. Maniatis. 1996. Site-specific phosphorylation of IκBα by a novel ubiquitin-dependent protein kinase activity. Cell 84: 853–862.

Ellenried, S.J. and J.W. Harper. 1998. Proteolysis in cell cycle control and cancer. Biochim. Biophys. Acta 1377: M61–M70.

Fan, C.-M. and T. Maniatis. 1991. Generation of p50 subunit of NF-κB 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 protease 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. Morr, 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.

Ikeeda, 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-3β and β-catenin and promotes GSK-3β-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 IκB kinase complex. Science 278: 818–819.

Margottin, F., S.P. Bour, H. Durand, L. Selig, S. Benichou, V. Richard, D. Thomas, K. Streb, and R. Benarous. 1998. A novel human WD protein, β-TrCP, that interacts with HIV-1 Vpu connects CD4 to the ER degradation pathway through a 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. Genet. 19: 371–379.

OIHmeyer, 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-κB1 precursor protein and the activation of NF-κB. Cell 78: 773–785.

Patton, E.E., A.R. Willems, and M. Tyers. 1998. Combinatorial control in ubiquitin-dependent proteolysis; Don’t Skip 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.

Rui z i Altaba, A. 1997. Catching a Gli-mpse of Hedgehog. Cell 90: 193–196.

Scheideakit, C. 1998. Signal transduction. Docking IκB kinases. Nature 395: 225–226.

Scherer, D.C., J.A. Brockman, Z. Chen, T. Maniatis, and D.W. Ballard. 1995. Signal-induced degradation of IκBα 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. Ben-nink, 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 IκBα 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-βTRCP ubiquitin ligase complex associates specifically with phosphorylated destruction motifs in IκBβ and β-catenin and stimulates IκBα 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 IκBα-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 IκB kinase-β. *Nature* **396**: 77–80.
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*Genes Dev.* 1999, 13:

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