Genetic Evidence for the Essential Role of β-Transducin Repeat-containing Protein in the Inducible Processing of NF-κB2/p100*

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Processing of the nfkb2 gene product p100 to generate p52 is an important step in NF-κB regulation. This step is regulated by a noncanonical NF-κB signaling pathway involving the NF-κB-inducing kinase (NIK). NIK induces p100 processing by triggering phosphorylation of specific C-terminal serines of p100. However, the downstream molecular events leading to p100 processing remain unclear. Here we show that NIK induces the physical recruitment of β-transducin repeat-containing protein (β-TrCP), a component of the SCF ubiquitin ligase complex, to p100. This event required the phosphorylation sites as well as the death domain of p100. Using the RNA interference technique, we demonstrated that β-TrCP is essential for NIK-induced p100 ubiquitination and processing. Interestingly, the constitutive processing of p100 mutants was independent of β-TrCP. These results suggest that β-TrCP is an essential component of NIK-induced p100 processing.

The NF-κB family of transcription factors participates in the regulation of diverse biological processes, including innate and adaptive immune responses, lymphoid organ development and maturation, inflammation, and cell growth and survival (1–4). Deregulated function of NF-κB contributes to the development of various cell malignancies (5, 6). Mammalian cells have five NF-κB proteins, RelA, RelB, c-Rel, p50, and p52, which function as various homo- and heterodimers (7). In most cell types, the NF-κB factors are sequestered in the cytoplasm through physical interaction with specific ankyrin repeat-containing inhibitors, including IκBα and homologues (8). The latent forms of NF-κB can be activated by a large variety of chemical, environmental, and microbial agents, which act by inducing the phosphorylation and subsequent degradation of IκBα (9, 10). This canonical NF-κB signaling pathway depends on a multisubunit IκB kinase (IKK), 1 which is composed of two catalytic subunits, IKKα and IKKβ, and a regulatory subunit, IKKγ (also named NEMO, IKKaset1, or FIP-3) (11). When activated by upstream signals, IKK directly catalyzes the phosphorylation of IκBα at two specific serines, which in turn triggers its ubiquitination. Recent biochemical studies suggest that the β-transducin repeat-containing protein (β-TrCP), also named E3βTRCP, is involved in the ubiquitination of phosphorylated IκBα, although genetic evidence is lacking (11).

Another level of NF-κB regulation is via processing of the NF-κB1 and NF-κB2 precursor proteins p105 and p100, a proteasome-mediated event required for generating p50 and p52, respectively (7, 12). Both p105 and p100 contain ankyrin repeats at their C-terminal portions and function as IκB-like NF-κB inhibitors by forming cytoplasmic complexes with mature NF-κB subunits (13, 14). Thus, the processing of p105 and p100 also serves to liberate the sequestered NF-κB members. It seems clear that the processing of p105 is largely a constitutive event (11), while the processing of p100 is tightly controlled by both negative and positive regulatory mechanisms (15). The C-terminal region of p100 contains a death domain (DD) that functions as a processing-inhibitory domain (PID). Mutant forms of p100 lacking the PID undergo constitutive processing. Interestingly, in some lymphoma cells, the nfkb2 gene is involved in chromosomal translocations that produce C-terminal truncation mutants of p100 lacking the PID, and at least some of these p100 mutants have been shown to undergo constitutive processing (15). These findings raise the possibility that deregulated processing of p100 may contribute to the development of lymphoid malignancies.

The processing of wild type p100 can be induced by a noncanonical NF-κB signaling pathway involving the NF-κB-inducing kinase (NIK) (15). NIK induces p100 phosphorylation at specific C-terminal serines, which serves as a trigger for its inducible processing. Consistently a nik gene mutation in the lymphoplasia mice is associated with the absence of p100 processing, resulting in severe deficiencies in lymphoid organ development (15). More recent studies suggest that NIK induces p100 phosphorylation through a downstream kinase, IKKα (16). Interestingly IKKα is also involved in p100 processing induced by the retroviral oncoprotein Tax (17). In sharp contrast, IKKβ, which is essential for the canonical NF-κB signaling, is completely dispensable for the inducible processing of p100 (16, 17). These findings reveal a novel signaling pathway specifically regulating the processing of p100, which is essential for the development and maturation of lymphoid organs.

While it is clear that phosphorylation triggers the processing of p100, the downstream molecular events involved in this signaling process remain poorly defined. In this study, we have investigated the mechanism of p100 ubiquitination and the role of this posttranslational modification in regulating p100 processing. Using the small interfering RNA (siRNA)-mediated

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1 The abbreviations used are: IKK, IκB kinase; β-TrCP, β-transducin repeat-containing protein; DD, death domain; PID, processing-inhibitory domain; NIK, NF-κB-inducing kinase; RNAi, RNA interference; siRNA, small interfering RNA; GFP, green fluorescent protein; IB, immunoblotting; coIP, coimmunoprecipitation; IP, immunoprecipitation; β-TrCPiR, RNAi-resistant β-TrCP; HA, hemagglutinin; RT, reverse transcription; RIPa, radiolabeled precipitation buffer; SCF, Skp1-Cullin-1/Cdc53-F box protein.
gene suppression technique, we have demonstrated that \( \beta \)-TrCP is an essential component involved in NIK-induced ubiquitination of p100. In NIK-expressing cells, \( \beta \)-TrCP forms a stable complex with p100 but not with a p100 mutant lacking its phosphorylation site. We further demonstrate that \( \beta \)-TrCP-mediated p100 ubiquitination is essential for inducible, but not constitutive, processing of p100.

**MATERIALS AND METHODS**

**Expression Vectors and Antibodies**—Expression vectors encoding NIK and derivatives, p100 and derivatives, and HA-ubiquitin have been described (15, 17). To construct the HA-tagged \( \beta \)-TrCP, the \( \beta \)-TrCP cDNA from Jurkut T cells was amplified by RT-PCR and inserted into the pcDNA-HA vector (18). The \( \beta \)-TrCP\(^{\text{TrCPiR}} \) is a mutant harboring sense mutations in the siRNA targeting site that prevent the binding and degradation by the specific siRNA. The anti-HA monoclonal antibody (horseradish peroxidase-conjugated, 3F10) was purchased from Roche Molecular Biochemicals. The antibody recognizing the N terminus of p100 (anti-p100) was kindly provided by Dr. W. C. Greene (19).

siRNA—siRNA for human \( \beta \)-TrCP and green fluorescent protein (GFP) were synthesized by Dharmacco Research, Inc. (Lafayette, CO). The sequences of \( \beta \)-TrCP siRNA are: GUG GAA UUU GUG GAA CAU CTT (sense) and GAU GUU CCA AAU UUU CCA CTT (antisense). The sequences of GFP siRNA are: GUC ACC UGG ACC GGC ATT (sense) and UGG CCA UGG AAC AGG UAG CTT (antisense).

The sequences of GFP siRNA are: GUG GAA UUU GUG GAA CAU CTT (sense) and GAU GUU CCA AAU UUU CCA CTT (antisense). The sequences of GFP siRNA are: GUC ACC UGG ACC GGC ATT (sense) and UGG CCA UGG AAC AGG UAG CTT (antisense).

\( \beta \)-TrCP and GFP expression vectors encoding p100 and the other indicated proteins were transfected into the 293 cells in 2 ml of culturing medium. 24 h later, the same transfection was performed to achieve high efficiency the transfection. The sequences of GFP siRNA are: GUG GAA UUU GUG GAA CAU CTT (sense) and GAU GUU CCA AAU UUU CCA CTT (antisense). The sequences of GFP siRNA are: GUC ACC UGG ACC GGC ATT (sense) and UGG CCA UGG AAC AGG UAG CTT (antisense).

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**Immunoblotting (IB) and Communoprecipitation (coIP)—** 293 cells were transfected using DEAE-dextran (20) and lysed in RIPA buffer supplemented with protease inhibitors (17). The cell lysates (about 7 g of cell lysates) were performed as described earlier (15). The cell lysates (about 7 g of cell lysates) were performed as described earlier (15).

The sequences of GFP siRNA are: GUG GAA UUU GUG GAA CAU CTT (sense) and GAU GUU CCA AAU UUU CCA CTT (antisense). The sequences of GFP siRNA are: GUC ACC UGG ACC GGC ATT (sense) and UGG CCA UGG AAC AGG UAG CTT (antisense).

**In Vivo Ubiquitin Conjugation Assays—** 293 cells were transfected in six-well plates with HA-ubiquitin and p100 together with the indicated expression vectors. About 30 h posttransfection, the cell lysates in RIPA buffer and immediately subjected to IP using anti-HA. The agarose beads were washed three times with RIPA buffer, and the attached proteins were eluted in SDS loading buffer. The eluted ubiquitin-conjugated p100 was analyzed by IB using horseradish peroxidase-conjugated anti-HA.

**RESULTS**

\( \beta \)-TrCP Is Required for NIK-induced Processing of p100—As described earlier (15), the inducible processing of p100 is associated with its ubiquitination, although it remains unclear whether this is an essential step in p100 processing. Additionally the ubiquitin ligase regulating p100 ubiquitination remains to be identified. We investigated the role of \( \beta \)-TrCP in the processing of p100 using siRNA-mediated gene suppression. As expected from various other studies (22–24), the \( \beta \)-TrCP siRNA efficiently depleted the mRNA of \( \beta \)-TrCP but not that of a control gene, glyceraldehyde-3-phosphate dehydrogenase, as detected by the sensitive RT-PCR analysis (Fig. 1A). More importantly the \( \beta \)-TrCP suppression led to almost complete blockade of NIK-induced p100 processing. This effect was specific since the processing of p100 was not affected in cells transfected with the control GFP siRNA (Fig. 1B, lanes 5–8). Furthermore the \( \beta \)-TrCP RNAi was also able to inhibit NIK-induced processing of endogenous p100 (Fig. 1C). These results provide genetic evidence for an essential role of \( \beta \)-TrCP in the inducible processing of p100.

With the RNAi genetic approach, we were also able to determine whether \( \beta \)-TrCP is essential for proteolysis of IκBα. For these studies, we expressed HA-tagged IκBα with a constitutively activated form of IκKβ (IκKβSS/EE). IκKβSS/EE efficiently induced degradation of IκBα (Fig. 1D, lane 2); however, the inducible degradation of IκBα was completely blocked in cells transfected with the \( \beta \)-TrCP siRNA (lane 4).

FIG. 1. \( \beta \)-TrCP is an essential factor for inducible processing of p100 and proteolysis of IκBα. A and B, 293 cells were either mock-transfected or transfected with \( \beta \)-TrCP siRNA. 283 cells were either mock-transfected with the carrier DNA pcDNA (lane 1) or transfected with \( \beta \)-TrCP siRNA (lane 2) as described under “Materials and Methods.” 24 h after the second transfection, RNA was isolated from the transfectants and subjected to RT-PCR assays using specific primers for \( \beta \)-TrCP or control glyceraldehyde-3-phosphate dehydrogenase (GAPDH). C, suppression of \( \beta \)-TrCP expression results in blockade of NIK-induced p100 processing. 283 cells were either mock-transfected (lanes 1, 2, 5, and 6) or transfected with siRNA for \( \beta \)-TrCP (lanes 3 and 4) or GFP (lanes 7 and 8). 24 h after the second transfection, the cells were then transfected with cDNA expression vectors indicated below the panels (400 ng for p100 and 300 ng for NIK). The processing of p100 was analyzed by immunoblotting assaying for anti-p100 24 h after the DNA transfection. C, \( \beta \)-TrCP RNAi also inhibits the processing of endogenous p100. The transfections were performed as described in B except for the lack of exogenous p100. Additionally, to detect the endogenous p100, more cell extracts (~80 μg) were used in the immunoblotting assay as indicated nonspecific protein bands.

\( \beta \)-TrCP is an essential factor for inducible ubiquitination of p100—We next examined whether \( \beta \)-TrCP is required for the ubiquitination of p100. When expressed in 293 cells, NIK efficiently induced polyubiquitination of p100 as evidenced by the formation of ubiquitin-conjugated heterogeneous p100 adducts (Fig. 2A, lane 2). Remarkably the p100 polyubiquitination was largely abrogated when \( \beta \)-TrCP gene expression was suppressed by RNAi (lane 4). Moreover the RNAi-mediated inhibi-
the expression levels of HA-tagged NIK, NIK mutant, and the cell lysates were directly subjected to immunoblotting to monitor the p100 panel. Finally the molecular interaction between H9252 and p100 was detected by immunoblotting with anti-HA (top panel). In the middle and bottom panels, the cell lysates were directly subjected to immunoblotting to monitor the expression levels of HA-tagged NIK, NIK mutant, and NIK-TrCP (middle panel) as well as of the p100 and processing product p52 (bottom panel). As indicated a nonspecific protein band. B. 293 cells were transfected with HA-tagged NIK-TrCP either alone or together with NIK. Endogenous p100 was isolated by IP using anti-p100 followed by immunoblotting to detect associated NIK-TrCP. C. 293 cells were transfected with the indicated expression vectors and subjected to co-IP (top panel) and immunoblotting (middle and bottom panels) assays as described in A. The expression level of NIK was similar to that shown in the middle panel of A (data not shown). P100SS/AA harbors serine to alanine mutations in its phosphorylation site.

bition of p100 ubiquitination was associated with the marked diminishment of NIK-induced p100 processing (Fig. 2B, lane 4). To further confirm the inhibitory effect of β-TrCP siRNA was specifically caused by the loss of β-TrCP, functional rescue was performed by transfecting the siRNA-treated cells with a β-TrCP mutant harboring sense mutations in the siRNA targeting site (RNAi-resistant β-TrCP or βTrCPmut). As shown in Fig. 2, both the ubiquitination and the processing of p100 were efficiently restored in cells expressing the RNAi-resistant form of β-TrCP (Fig. 2, A and B, lane 6). Thus, β-TrCP is an essential component for regulating the ubiquitination of p100.

NIK Induces the Binding of p100 to β-TrCP—We then examined whether β-TrCP physically interacts with p100 by coIP assays. When expressed in 293 cells, β-TrCP only weakly interacted with p100 in the absence of the processing-inducing kinase NIK (Fig. 3A, top panel, lane 1). However, in the presence of NIK, β-TrCP formed a stable complex with p100 and was readily coprecipitated by the p100 antibody (lane 2). In contrast, a catalytically inactive NIK mutant (NIK(K429A/K430A)) failed to induce the binding of β-TrCP to p100. This functional difference was not due to variation in protein expression since similar amounts of NIK and NIK mutant were detected by immunoblotting in the cell lysates (Fig. 3A, middle panel). The levels of β-TrCP (middle panel) and p100 (bottom panel) were also comparable in the different cell transfectants. Furthermore the NIK-induced β-TrCP binding interaction was tightly associated with the induction of p100 processing (bottom panel). Finally the molecular interaction between β-TrCP and p100 appeared to be strong since β-TrCP also formed a stable complex with endogenous p100 in the presence of NIK (Fig. 3B, lane 3).

Since NIK, but not NIK(K429A/K430A), is unable to induce p100 phosphorylation (15), we reasoned that the phosphorylation site of p100 might be required for β-TrCP recognition. This idea was tested by performing the coIP assays using a p100 mutant (p100SS/AA, see Ref. 15) harboring serine to alanine mutations at its phosphorylation site. As expected, the p100SS/AA did not respond to NIK for processing (Fig. 3C, lane 4). More importantly this p100 mutant also failed to interact with β-TrCP (Fig. 3C, lane 5). This idea was tested by performing the coIP assays using a p100 mutant lacking the DD or the C-terminal region of p100 functions to suppress the constitutive processing (Ref. 15 and Fig. 4C). We have previously shown that a DD located in the NIK Induces the Binding of p100 to β-TrCP independently of NIK. This idea was tested by performing the coIP assays using β-TrCP and p100 C-terminal truncation mutant lacking the DD and additional C-terminal sequences (p100-(1–454)). To our surprise, neither p100DD nor p100-(1–454) was able to bind β-TrCP (Fig. 4A, lanes 4 and 6) even when NIK was expressed in the

 FIG. 3. NIK induces physical interaction of β-TrCP with p100, which requires the phosphorylation site of p100. A, 293 cells were transfected using DEAE-dextran with expression vectors encoding p100 (0.7 μg) and HA-tagged β-TrCP (1 μg) together with either an empty vector (−), HA-tagged NIK (0.5 μg), or a catalytically inactive NIK mutant (NIK Mut). Cell lysates were subjected to immunoprecipitation using anti-p100, and the coprecipitated β-TrCP was detected by immunoblotting using anti-HA (top panel). In the middle and bottom panels, the cell lysates were directly subjected to immunoblotting to monitor the expression levels of HA-tagged NIK, NIK mutant, and β-TrCP (middle panel) as well as of the p100 and processing product p52 (bottom panel), as indicated a nonspecific protein band. B. 293 cells were transfected with HA-tagged β-TrCP either alone or together with NIK. Endogenous p100 was isolated by IP using anti-p100 followed by immunoblotting to detect associated β-TrCP. C. 293 cells were transfected with the indicated expression vectors and subjected to co-IP (top panel) and immunoblotting (middle and bottom panels) assays as described in A. The expression level of NIK was similar to that shown in the middle panel of A (data not shown). P100SS/AA harbors serine to alanine mutations in its phosphorylation site.

 FIG. 4. β-TrCP is dispensable for the constitutive processing of p100 mutants lacking its C-terminal processing-inhibitory domain. A, β-TrCP does not bind to p100 mutants lacking the DD or the entire C-terminal sequences. 293 cells were transfected with HA-tagged β-TrCP together with the indicated p100 or its mutants. CoIP was performed as described in Fig. 3 to detect the binding of β-TrCP to the p100 proteins (upper panel). The level of β-TrCP expression was analyzed by immunoblotting using anti-HA (lower panel). The expression levels of different p100 proteins were comparable (see B). B, immunoblotting analysis of the p100 proteins using the cell lysates from A. C. 293 cells were either mock-transfected (lanes 1–4) or transfected with β-TrCP siRNA (lanes 5 and 6) followed by transfection of cDNA expression vectors encoding wild type p100 (wt) or a p100 mutant lacking its C-terminal portion (1–454) either in the absence (−) or presence (+) of NIK. Processing of the p100 proteins was analyzed by immunoblotting using anti-p100.

 FIG. 5. Binding sequences of β-TrCP in different human proteins. α stands for hydrophobic amino acids. β-cat, β-catenin.
cells (lanes 5 and 7). Consistently NIK did not enhance the constitutive processing of the p100 mutants (Fig. 4B, lanes 4 and 6) but markedly induced the processing of the wild type NIK (lane 2). This result prompted us to determine whether β-TrCP is required for p100 constitutive processing. In sharp contrast to the results obtained with the inducible processing of p100, the constitutive processing of p100 (1–454) was not affected by RNAi-mediated β-TrCP gene suppression (Fig. 4C, lanes 5 and 6). Similar results were obtained with the p100ΔDD (data not shown). Thus, the constitutive processing of p100 appears to be independent of β-TrCP.

Discussion

Processing of the nfkb2 gene product, p100, to generate p52 is an important step of NF-κB regulation, which is specifically involved in the development and maturation of secondary lymphoid organs. Emerging evidence suggests that the mechanism of p100 processing differs from that regulating signal-induced degradation of the labile NF-κB inhibitor IκBα. Our previous studies using the alaphosphasia mice clearly demonstrate an essential role for the NIK kinase in regulating p100 processing in lymphoid organs (15). On the other hand, NIK is not required for cytokine-stimulated degradation of IκBα or the nuclear translocation of the prototypical form of NF-κB (RelA/p50) (25, 26). Further studies reveal that IKKβ, which is critical for the canonical NF-κB signaling pathway, is dispensable for NIK-induced p100 processing, while IKKα is an essential component of the NIK/p100 pathway (16). We have now extended the previous studies by investigating the mechanism of p100 polyubiquitination and its role in p100 processing. Using the powerful siRNA-mediated gene suppression technique, we have provided genetic evidence for the critical involvement of β-TrCP in p100 polyubiquitination (Fig. 2A). Furthermore, inhibition of p100 ubiquitination in β-TrCP-deficient cells results in blockade of the inducible processing of p100 (Figs. 1B and 2B). These findings suggest that polyubiquitination of p100 is mediated through the β-TrCP–specific ubiquitin ligase and serves as an essential step in the inducible p100 processing.

Prior studies using a dominant-negative β-TrCP mutant suggest that β-TrCP also participates in ubiquitination of several other proteins, including IκBα, p105, human immunodeficiency virus Vpu, and β-catenin (11). With the siRNA technique, we can now determine whether β-TrCP is essential for the ubiquitination and proteolysis of each of the putative target proteins. Our RNAi studies have confirmed the essential role of β-TrCP in IKKβ–induced degradation of IκBα (Fig. 1D) and p105 (data not shown). A conserved site for β-TrCP binding, containing phosphorylated serines and flanking residues, has been found in the various putative β-TrCP targets (Ref. 11; see Fig. 5). The β-TrCP binding site in p100 contains most, although not all, of the conserved amino acid residues found in the other proteins (Fig. 5). Mutation of the two conserved serines to alanines within this site in p100 completely abolished its ability to bind β-TrCP (Fig. 3C). Interestingly, in addition to the C-terminal phosphorylation site, the DD of p100 is required for its interaction with β-TrCP (Fig. 4A). Consistent with this finding, the p100 mutant lacking the DD is defective in ubiquitination (15).

We have previously shown that p100 mutants lacking the C-terminal DD undergo constitutive processing (15). Interestingly the processing of these mutants is independent of β-TrCP. Consistently these mutants do not physically interact with β-TrCP. This finding suggests two possibilities regarding how the constitutive processing of p100 is regulated. First, the N-terminal region of p100 may interact with another yet to be identified ubiquitin ligase, which targets p100 mutants for constitutive ubiquitination and proteasome recruitment. Second, the constitutive processing of p100 may not involve ubiquitination. In favor of the second possibility, we have been unable to detect polyubiquitination of the constitutively processed forms of p100 using the in vivo ubiquitination method (Ref. 15 and data not shown). Although these results cannot exclude the possibility for involvement of weak ubiquitination in the constitutive processing of p100 mutants, it nevertheless suggests that strong polyubiquitination is specifically required for the inducible processing of p100.

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