ZNF216 Is an A20-like and IκB Kinase γ-Interacting Inhibitor of NFκB Activation*  

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The transcription factor NFκB plays important roles in immune regulation, inflammatory responses, and anti-apoptosis. Activation of NFκB requires the activity of IκB kinase, a kinase complex that contains two catalytic subunits, IKKa and IKKβ, and a non-enzymatic regulatory subunit, IKKγ. To understand how NFκB activation is regulated at the IKKγ level, we searched for IKKγ-interacting proteins by the yeast two-hybrid system. This search identified ZNF216, a zinc finger protein with novel zinc finger motifs with characteristics of C2H2X2–4C2H2X11C2 at its C-terminal domain (16). It has been shown that A20 is a suppressor of inflammation through attenuating TNF-induced NFκB activation (21). A20 also can inhibit TNF-induced apoptosis, and a recent report suggests that this is mediated through disrupting recruitment of the death domain containing adapter proteins TRADD and RIP to the TNF receptor 1 signaling complex (27). In this report, we identified a novel IKKγ-interacting pro-
tein, ZNF216. ZNF216 contains an A20-like zinc finger (ZnF-A20) domain at its N terminus and an AN1-like zinc finger (ZnF-AN1) domain at its C terminus. In addition to IKKγ, ZNF216 also interacts with RIP, TRAF6, and A20. Overexpression of ZNF216 inhibits NFKB activation triggered by TNF, IL-1, and Toll-like receptor 4 and sensitizes cells to TNF-induced apoptosis. Our findings suggest that ZNF216 and A20 have redundant and distinct functions in regulating NFκB activation and apoptosis.

EXPERIMENTAL PROCEDURES

Reagents—Recombinant TNF, IL-1, and IFN-γ (R&D Systems Inc., Minneapolis, MN), mouse monoclonal antibodies against FLAG (Sigma) and HA (Covance, Berkeley, CA) epitopes, rabbit polyclonal antibodies against IKKγ and RIP (Santa Cruz Biotechnology, Santa Cruz, CA), human embryonic kidney 293 cells (ATCC, Manassas, VA), and the human leukocyte cDNA library (Clontech, Palo Alto, CA) were purchased from the indicated manufacturers.

Constructs—The NFKB (Dr. Gary Johnson, University of Colorado Health Sciences Center) and IRF-1 (Dr. Uli Schindler, Tularik Inc.) luciferase reporter plasmids were provided by the indicated investigators. The mammalian expression plasmids for HA- or FLAG-tagged RIP, IKKγ, IKKα, TRAF6, and p65 were previously described (23, 24). The HA- or FLAG-tagged mammalian expression plasmids for ZNF216 and its mutants were constructed by PCR amplification of the corresponding cDNA fragments and subsequently cloning into a cytomegalovirus promoter-based vector containing an N-terminal HA or FLAG tag.

Yeast Two-hybrid Screening—The cDNA encoding full-length human IKKγ was inserted in-frame into the Gal4 DNA binding domain vector pGBT9 (Clontech). The human leukocyte two-hybrid cDNA library was screened and the isolation of positive clones was performed by following the manufacturer’s protocols.

Northern Blot Analysis—Human multiple tissue mRNA blots were purchased from Clontech. The blots were hybridized with 32P-labeled ZNF216 cDNA in the rapid hybridization buffer (Clontech) under high stringency conditions.

Transfection and Reporter Gene Assays—Transfection of 293 cells was performed with the standard calcium phosphate precipitation method (28). 293 cells (~1 × 10^6) were seeded on 12-well (25 mm) dishes and were transfected the following day. Within the same experiment, each transfection was performed in triplicate, and where necessary, empty control plasmid was added to ensure that each transfection received the same amount of total DNA. To normalize for transfection efficiency, 0.25 μg of PRL-RSV-SV40 plasmid was added to each transfection. Dual specific luciferase reporter assays were performed using a luciferase assay kit (Promega, Madison, WI) by following the manufacturer’s protocol. Firefly luciferase activities were normalized on the basis of Renilla luciferase expression levels.

Co-immunoprecipitation and Western Blot Analysis—Transfected 293 cells from each 100-mm dish were lysed in 1 ml of lysis buffer (20 mM Tris, pH 7.5, 150 mM NaCl, 1% Triton, 1 mM EDTA, 10 μg/ml aprotinin, 10 μg/ml leupeptin, 1 mM phenylmethylsulfonyl fluoride). For each immunoprecipitation, a 0.4-ml aliquot of lysate was incubated with 0.5 μg of the indicated monoclonal antibody or control mouse IgG and 25 μl of a 1:1 slurry of GammaBind G Plus-Sepharose (Amersham Biosciences) for at least 2 h. The Sepharose beads were washed three times with 1 ml of lysis buffer containing 500 mM NaCl. The precipitates were fractionated on SDS-PAGE, and subsequent Western blot analysis was performed as described (23, 24).

RESULTS

Identification of ZNF216 as an IKKγ-interacting Protein—To identify IKKγ-interacting proteins, we used the yeast two-hybrid system to screen a human leukocyte cell cDNA library with full-length IKKγ as bait. We screened a total of ~6 × 10^6 independent clones and obtained 33 β-galactosidase positive clones. Thirteen of these clones encoded ZNF216, a zinc finger protein expressed from human chromosome 9q (31). The biological functions of ZNF216 are unknown.

Sequence analysis suggested that ZNF216 was a 213 amino acid protein and contained two zinc finger domains (Fig. 1A). One zinc finger domain, ZnF-A20, was localized at amino acids 11–35 at the N terminus. ZnF-A20 contains a pattern of CX_{2-4}·CX_1·CX_1·CX_C that is similar to those found in A20, a zinc finger protein inhibiting TNF-induced NFKB activation and apoptosis (16–22). Another zinc finger domain, ZnF-AN1, was localized at amino acids 154–193 at the C terminus. ZnF-AN1 contains a pattern of CX_1·CX_9·CX_1·CX_1·CX_1·CX_HXC_HXC that is similar to that of AN1, a ubiquitin-like protein in Xenopus laevis (32). The intermediate fragment of ZNF216 had no significant homology with known proteins.

Tissue Distribution and Protein Expression of ZNF216—Northern blot analysis suggested that human ZNF216 mRNA
FIG. 2. ZNF216 interacts with IKKγ, RIP, and TRAF6 but not TRAF2. A, ZNF216 and its ZnF-A20 domain interact with IKKγ. 293 cells (~2 × 10^6) were transfected with 3 μg of an expression plasmid for HA-tagged IKKγ, together with 3 μg of an expression plasmid for FLAG-tagged ZNF216 or its mutants, ZNF216-(1–153) or ZNF216-(36–213). Cell lysates were immunoprecipitated with anti-FLAG antibody (αF) or control IgG (C), and Western blot analysis was performed with anti-HA antibody. Expression of IKKγ was confirmed by Western blot analysis of the lysate (L) with anti-HA antibody. Expression of ZNF216 and its mutants was comparable as indicated by Western blot analysis of the lysates with anti-FLAG antibody (data not shown). B, ectopically expressed ZNF216 interacts with endogenous IKKγ. 293 cells (~1 × 10^6) were transfected with 20 μg of an expression plasmid for ZNF216 for 24 h. Cells were lysed, and the lysate was immunoprecipitated with anti-ZNF216 antibody or preimmune serum (C). The immunoprecipitate was analyzed by Western blot with anti-IKKγ antibody. C, ZNF216 and its ZnF-A20 domain interact with RIP. The same experiments were performed as in A, except that HA-tagged IKKγ was replaced with HA-tagged RIP. D, ectopically expressed ZNF216 interacts with endogenous RIP. 293 cells (~1 × 10^6) were transfected with 20 μg of an expression plasmid for ZNF216 for 24 h. Cells were lysed, and the lysate was immunoprecipitated with anti-ZNF216 antibody or preimmune serum (C). The immunoprecipitate was analyzed by Western blot with anti-RIP antibody. E, ZNF216 interacts with TRAF6 but not TRAF2. 293 cells (~2 × 10^6) were transfected with 3 μg of an expression plasmid for FLAG-tagged TRAF6 (left panel) or FLAG-tagged TRAF2 (right panel), together with 3 μg of an expression plasmid for HA-tagged ZNF216. Cell lysates were immunoprecipitated with anti-FLAG antibody (αF) or control IgG (C), and Western blot analysis was performed with anti-HA and anti-FLAG antibodies. Expression of the indicated plasmids was confirmed by Western blot analysis of the lysates (L) with anti-HA and anti-FLAG antibodies. F, TRAF6 interacts with the ZnF-AN1 domain of ZNF216. 293 cells (~2 × 10^6) were transfected with 3 μg of an expression plasmid for FLAG-tagged TRAF6, together with 3 μg of an expression plasmid for HA-tagged ZNF216-(1–153) or ZNF216-(36–213). Cell lysates were immunoprecipitated with anti-FLAG antibody (αF) or control IgG (C), and Western blot analysis was performed with anti-HA and anti-FLAG antibodies. Expression of the indicated plasmids was confirmed by Western blot analysis of the lysates (L) with anti-HA and anti-FLAG antibodies. The above experiments were repeated three times, and similar results were obtained.
was highly expressed in skeletal muscle. It was weakly expressed or undetectable in the brain, heart, colon, thymus, spleen, kidney, liver, small intestine, placenta, lung, and peripheral blood leukocytes (Fig. 1B).

To determine whether ZNF216 was expressed in mammalian cells at the protein level, we raised a rabbit polyclonal antibody against recombinant full-length ZNF216. Western blot analysis suggested that ZNF216 was expressed as a 33-kDa protein in both human rhabdomyosarcoma RD cells and mouse myoblast C2C12 cells (Fig. 1C).

**ZNF216 Interacts with IKKγ, RIP, and TRAF6 in Mammalian Cells**—To determine whether ZNF216 interacts with IKKγ in mammalian cells, we transfected 293 cells with expression plasmids for FLAG-tagged ZNF216 and HA-tagged IKKγ and IKKβ and performed co-immunoprecipitation experiments. These experiments indicated that full-length ZNF216 interacted specifically with IKKγ (Fig. 2A) but not IKKβ (data not shown).

We further examined whether endogenous ZNF216 and IKKγ interact in untransfected cells in the presence or absence of TNF. These experiments failed to detect their interaction (data not shown). One explanation is that our polyclonal anti-ZNF216 antibody is not potent enough for this type of experiment, which requires high quality antibodies. Then we examined whether ectopically expressed FLAG-tagged ZNF216 could interact with endogenous IKKγ. The results indicated that ectopically expressed ZNF216 could interact with endogenous IKKγ in 293 cells (Fig. 2B) and that this interaction was not affected by TNF stimulation (data not shown). In these experiments, IKKγ was shown as two bands around 48 kDa, which is consistent with previous reports (8, 11).

To determine which domain is responsible for the interaction of ZNF216 with IKKγ, we made ZNF216 deletion mutants containing either ZnF-A20 (amino acids 1–153) or ZnF-AN1 (amino acids 36–213) and performed co-immunoprecipitation experiments. The results indicated that ZnF-A20 but not ZnF-
AN1 was required for the interaction of ZNF216 with IKK\(\gamma\) (Fig. 2A).

It has been reported that A20 interacts with RIP in the TNF-R1 complex and TRAF6 in the Toll-interleukin-1 receptor signaling complexes. Because ZNF216 contains an A20-like zinc finger domain, we determined whether ZNF216 can also interact with RIP and TRAF6. To test this possibility, we transfected 293 cells with an expression plasmid for ZNF216 together with an expression plasmid for RIP, TRAF6, or TRAF2. Co-immunoprecipitation experiments indicated that ZNF216 interacted with RIP (Fig. 2C) and TRAF6 (Fig. 2E) but not TRAF2 (Fig. 2F). Furthermore, ectopically expressed ZNF216 interacted with endogenous RIP in 293 cells (Fig. 2D).

Domain mapping experiments further indicated that ZnF-A20 was required for the interaction of ZNF216 with RIP (Fig. 2C), whereas ZnF-AN1 was required for the interaction of ZNF216 with TRAF6 (Fig. 2F).

ZNF216 Inhibited RIP- and TRAF6- but Not p65-induced NF\(\kappa\)B Activation—Because ZNF216 interacts with IKK\(\gamma\), RIP, and TRAF6, we determined whether ZNF216 was involved in the regulation of NF\(\kappa\)B activation mediated by these signaling components. To do this, we performed NF\(\kappa\)B luciferase reporter gene assays in 293 cells. The results indicated that ZNF216 did not activate NF\(\kappa\)B but could inhibit RIP- and TRAF6-mediated NF\(\kappa\)B activation in a dose-dependent manner (Fig. 3, A and B). In these experiments, ZNF216 did not inhibit p65-mediated...
NFκB activation (Fig. 3B). Reporter gene assays further indicated that ZnF-A20 but not ZnF-AN1 was required for inhibiting NFκB activation mediated by RIP and TRAF6 (Fig. 3, C and D).

ZNF216 Inhibited TNFα, IL-1β, and TLR4-induced NFκB Activation—Because ZNF216 inhibits NFκB activation mediated by RIP and TRAF6, proteins involved in TNF- and Toll/interleukin-1 receptor-triggered NFκB activation pathways, we determined whether ZNF216 can inhibit TNFα, IL-1β, and TLR4-triggered NFκB activation in reporter gene assays. As shown in Fig. 4, A–C, ZNF216 and ZNF216-(1–153), but not ZNF216-(36–213), could inhibit TNFα, IL-1β, and TLR4-triggered NFκB activation in a dose-dependent manner. In similar experiments, ZNF216 did not inhibit IFN-γ-induced IRF-1 activation (Fig. 4D).

The Two Zinc Finger Domains of ZNF216 Interacted with Each Other, and ZNF216 Can Form Homo-oligomers—In the course of purifying recombinant ZNF216 protein, we found that ZNF216 existed mostly as homodimers or homotrimers (Fig. 5A). To confirm that ZNF216 can be self-associated in mammalian cells, we transfected 293 cells with FLAG-tagged and HA-tagged ZNF216 and performed co-immunoprecipitation experiments. The result indicated that ZNF216 could interact with itself or form homo-oligomers in 293 cells (Fig. 5B). To test whether an internal interaction existed between ZnF-A20 and ZnF-AN1, we transfected 293 cells with FLAG-tagged ZNF216-(1–153) and HA-tagged ZNF216-(36–213) and performed co-immunoprecipitation experiments. The result indicated that the two zinc finger domains of ZNF216 could interact with each other (Fig. 5C).

ZNF216 Interacted with A20—Because ZNF216 contained an A20-like zinc finger domain and acted similarly with A20 in inhibiting TNFα, IL-1β, and TLR4-triggered NFκB activation, we determined whether ZNF216 can physically interact with A20. We transfected 293 cells with FLAG-tagged A20 and HA-tagged ZNF216 and performed co-immunoprecipitation experiments. The result indicated that ZNF216 interacted with A20 (Fig. 5D). These data suggest that ZNF216 can form a heterocomplex with A20.

ZNF216 Sensitized Cells to TNF-induced Apoptosis—Under most circumstances, NFκB promotes cell survival through induction of anti-apoptotic genes, whereas NFκB inactivation sensitizes cells to apoptosis. In this context, A20 represents an unconventional molecule. Although A20 inhibits TNF-induced NFκB activation, it also inhibits TNF-induced apoptosis. To determine a potential role of ZNF216 in regulating apoptosis, we transfected 293 cells with ZNF216 and examined its effect on TNF-induced apoptosis. The results indicated that ZNF216 could sensitize cells to TNF-induced apoptosis (Fig. 6).

DISCUSSION

Under most conditions, inducible NFκB activation is rapidly attenuated (1–4). Several molecules that inhibit NFκB activation pathways have been identified, such as A20, ZIN, SINK, ABIN1, and ABIN2 (16–25). In this report, we identified ZNF216 as an additional inhibitor of NFκB activation triggered by various stimuli.

ZNF216 shares several similar features with A20. It contains an A20-like zinc finger domain. Like A20, ZNF216 interacts with IKKγ and RIP, and this interaction is medi-
ZNF216 Interacts with IKKγ

Fig. 6. ZNF216 sensitizes cells to TNF-induced apoptosis. 293 cells (~1 × 10^7) were transfected with 0.1 μg of CMV-β-gal vector and 2 μg of the indicated plasmids. Fourteen h after transfection, cells were treated with TNF (20 ng/ml), TNF (20 ng/ml) plus cycloheximide (CHX, 10 μg/ml), or left untreated for 24 h. Cells were then stained with X-gal, and survival blue cells were counted. Data shown are averages and standard deviations of survival blue cell numbers from three independent experiments (transfection was performed in triplicate in each experiment).

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ated through its ZnF-A20 domain. ZNF216 also interacts with TRAF6, and this interaction is mediated through its ZnF-AN1 and/or the intermediate domain. Interestingly, A20 interacts with TRAF6 through its N-terminal domain, but not its seven ZnF-A20 domains at the C terminus (17). ZNF216 inhibits NFκB activation triggered by TNF, IL-1, and TRAF6, suggesting that ZNF216, similar to A20, is an IKKγ-interacting common inhibitor of various NFκB activating pathways.

ZNF216 also has features distinct from A20. ZNF216 contains only one ZnF-A20 domain, whereas A20 contains seven ZnF-A20 domains. ZNF216 contains a ZnF-AN1 domain at its C terminus; the functional significance of this domain is not fully understood. A20 is induced by TNF at the transcription level, but ZNF216 is not induced by TNF at either protein level (Fig. 1C) or mRNA level (data not shown). Most noticeably, ZNF216 sensitizes cells to TNF-induced apoptosis, whereas A20 inhibits TNF-induced apoptosis (17–22). There are two simple explanations for ZNF216-mediated sensitization of cells to TNF-induced apoptosis. First, ZNF216 inhibits NFκB activation and subsequent transcription of anti-apoptotic genes, and this sensitizes cells to TNF-induced apoptosis. Second, ZNF216 may directly neutralize the anti-apoptotic effect of A20 and therefore sensitizes cells to TNF-induced apoptosis. Our demonstration of a physical interaction between ZNF216 and A20 is consistent with the latter hypothesis.

The N-terminal ZnF-A20 and C-terminal ZnF-AN1 domains of ZNF216 can interact with each other. It is possible that under physiological conditions ZNF216 is inactive because of this internal association. Upon stimulation, the two domains may dissociate, exposing the ZnF-A20 domain to interact with other molecules, such as A20, IKKγ, RIP, and TRAF6. The result of these processes may be responsible for ZNF216-mediated inhibition of NFκB activation and sensitization of cells to apoptosis.

The physiological significance of ZNF216 needs to be further investigated. Interestingly, ZNF216 is expressed mostly in skeletal muscles. Previous studies have suggested that NFκB activation is critically involved in TNF-induced skeletal muscle wasting in cachexia (33). Our future experiments will examine whether ZNF216 is a physiological inhibitor of TNF-induced cachexia.
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