A Novel Zinc Finger Protein Interacts with Receptor-interacting Protein (RIP) and Inhibits Tumor Necrosis Factor (TNF)- and IL1-induced NF-κB Activation*

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Receptor-interacting protein (RIP) is a serine/threonine protein kinase that is critically involved in tumor necrosis factor receptor-1 (TNF-R1)-induced NF-κB activation. In a yeast two-hybrid screening for potential RIP-interacting proteins, we identified ZIN (zinc finger protein inhibiting NF-κB), a novel protein that specifically interacts with RIP. ZIN contains four RING-like zinc finger domains at the middle and a proline-rich domain at the C terminus. Overexpression of ZIN inhibits RIP-, IKKβ-, TNF-, and IL1-induced NF-κB activation in a dose-dependent manner in 293 cells. Domain mapping experiments indicate that the RING-like zinc finger domains of ZIN are required for its interaction with RIP and inhibition of RIP-mediated NF-κB activation. Overexpression of ZIN also potentiates RIP- and TNF-induced apoptosis. Moreover, immunofluorescent staining indicates that ZIN is a cytoplasmic protein and that it colocalizes with RIP. Our findings suggest that ZIN is an inhibitor of TNF- and IL1-induced NF-κB activation pathways.

Tumor necrosis factor receptor 1 (TNF-R1) is a prototypical member of the TNF receptor family (1). TNF stimulation of TNF-R1 simultaneously induces three divergent effects: apoptosis, activation of the transcription factor NF-κB, and the serine/threonine protein kinase JNK (1). TNF-R1 contains a death domain, which interacts with the cytoplasmic death dom-

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§§The abbreviations used are: TNF-R1, tumor necrosis factor receptor 1; JNK, Janus N-terminal kinase; TRADD, tumor necrosis factor receptor-associated death domain protein; RIP, receptor-interacting protein; TRAF, tumor necrosis factor receptor-associated factor; FADD, Fas associated death domain protein; IKK, inhibitory κB kinase; NF-κB, nuclear factor kappa B; IRF-1, interferon response factor 1; ZIN, zinc finger protein inhibiting NF-κB; RACE, rapid amplification of cDNA end; RLD, ring-like domain; PRD, proline-rich domain; IL1, interleukin-1; HA, hemagglutinin; IFN-γ, interferon; CMV, cytomegalovirus; X-gal, 5-bromo-4-chloro-3-indolyl-β-D-galactopyranoside; β-gal, β-galactosidase.

main-containing protein TRADD in a TNF-dependent process (2–5). Once TRADD is recruited to TNF-R1, it functions as an adapter protein to recruit several structurally and functionally divergent proteins, including FADD, RIP, TRAF2, and cellular inhibitor of apoptosis protein (cIAP) (2, 4). The interaction of TRADD with FADD leads to apoptosis through activation of a caspase cascade, which is initiated by the interaction of FADD with caspase-8 (2, 6–10). The interaction of TRADD with TRAF2 and RIP activates a downstream IkB kinase complex called IKK, which contains two catalytic subunits, IKKα and IKKβ, and a regulatory subunit, IKKγ/NEMO (11–19). The activated IKK phosphorylates IkBs, leading to their degrada-

RIP is a unique signal transducer in the TNF-R1-mediated NF-κB activation pathway. RIP was first identified as a Fas-interacting protein by the yeast two-hybrid system (20). It was later demonstrated that RIP is a component of the TNF-R1 signaling complex (4, 21). Gene knock-out experiments suggest that RIP is required for TNF-R1-mediated NF-κB activation but is not required for Fas- and TNF-R1-mediated apoptosis (22, 23). RIP is a serine/threonine kinase that contains three domains, including an N-terminal kinase domain, an intermediate domain, and a C-terminal death domain (4, 20). RIP interacts with TRADD through their respective death domains. The intermediate domain of RIP interacts with the RING finger domain of TRAF2, and this interaction is required for RIP-mediated NF-κB activation (21). Recently, it has been suggested that RIP directly interacts with IKKγ and therefore recruits IKK to the TNF-R1 complex (24). However, studies with RIP- and TRAF2-deficient cells indicate that TRAF2, but not RIP, is required for recruitment of the IKK complex to TNF-R1, whereas RIP is required for activating IKK (25, 26). Although RIP is a serine/threonine kinase, its kinase activity is not required for RIP-mediated NF-κB activation (21–23, 25). It has been proposed that RIP may activate IKK through a putative IKK kinase (25), which is probably MEKK3 (27). However, the precise mechanisms responsible for RIP-mediated IKK activation are not known. In addition, it is not known whether or how TNF-R1-mediated NF-κB activation pathway is regulated at the level of RIP.

To better understand how RIP signals, we performed yeast two-hybrid screening for additional RIP-interacting proteins. This search identified a novel RING-like zinc finger domain-containing protein designated as ZIN (zinc finger protein inhibiting NF-κB). Our results suggest that ZIN is an inhibitor of RIP-mediated NF-κB activation pathways.

Experimental Procedures

Reagents—The recombinant human TNF, IL1, and IFN-γ (R&D Systems Inc., Minneapolis, MN), the monoclonal antibodies against the

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ZIN Inhibits NF-κB Activation

Fig. 1. Sequence and tissue distribution of ZIN. A, sequence analysis of ZIN. The four putative RLDs are shaded. The conserved cysteines and histidines in the RLDs are bolded and underlined. The PRD is underlined. The GenBankTM accession number for the nucleotide and amino acid sequences of ZIN is AY062174. B, Northern blot analysis of expression of ZIN mRNA. PBL, peripheral blood leukocyte.

Fig. 2. Expression of ZIN protein in mammalian cells. Expression of ZIN in untransfected RPMI 8226 (lane 2), Jurkat (lane 3), 293 (lane 4) cells, or in 293 cells transfected with an expression plasmid for full-length ZIN (lane 1) was analyzed by Western blot with an anti-ZIN antibody. Approximately 5-fold less lysate was loaded into lane 1 than in lanes 2–4. The experiments were repeated two times, and similar results were obtained.

FLAG (Sigma), Myc (Santa Cruz Biotechnology, Santa Cruz, CA), and the HA epitopes (Covance, Berkeley, CA) were purchased from the indicated resources. The human embryonic kidney 293, the B lymphoma RPMI8226, and the T lymphoma Jurkat cells were purchased from ATCC (Manassas, VA). The rabbit polyclonal antiserum against human ZIN was raised against a 21-mer peptide having the following amino acid sequences of ZIN: KPEKEEQQKRKENGKFRIG. The GenBankTM accession number for the nucleotide and amino acid sequences of ZIN is AY062174. Approximately 5-fold less lysate was loaded into lane 1 than in lanes 2–4. The experiments were repeated two times, and similar results were obtained.

Cell Transfection and Reporter Gene Assays—293 cells (2 × 10^5) were seeded on 6-well (35-mm) dishes and were transfected the following day by the standard calcium phosphate precipitation (29). Luciferase reporter assays were performed using a luciferase assay kit (BD PharMingen) and following the manufacturer’s protocols.

Apoptosis Assays—β-Galactosidase co-transfection assays for determination of cell death were performed as described previously (2, 3, 10, 28, 30). Briefly, 293 cells (2 × 10^5) were seeded on 6-well (35-mm) dishes and were transfected the following day with 0.1 μg of pCMV-β-galactosidase plasmid and the indicated testing plasmids. Within the same experiment, each transfection was performed in triplicate, and where necessary, enough of an amount of empty control plasmid was added to ensure that each transfection continued to receive the same amount of total DNA. To normalize for transfection efficiency, 0.3 μg of the indicated monoclonal antibody or control mouse IgG and 25 μl of a 1:1 slurry of GammaBind G Plus-Sepharose (Amer-sham Biosciences) for at least 1 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 analyses were performed as described (2, 3, 28).

Northern Blot Hybridization—Human multiple tissue mRNA blots were purchased from CLONTECH. The cDNA probe was an ~1.0-kb fragment that encodes for amino acids 9–363. The hybridization was performed with the radiolabeled ZIN cDNA probe in the Rapid Hybridization buffer (CLONTECH) under high stringency condition.

For each immunoprecipitation, 0.4-ml aliquots of lysates were incubated with 0.5 μl of a 1:1 slurry of GammaBind G Plus-Sepharose (Amer-sham Biosciences) for at least 1 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 analyses were performed as described (2, 3, 28).

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of total DNA. Approximately 24 h after transfection, the cells were stained with X-gal as described previously (30). The numbers of survived blue cells from five representative viewing fields was determined microscopically. Data shown are averages and standard deviations of one representative experiment in which each transfection has been performed in triplicate.

**Immunofluorescent Staining**—293 cells cultured on glass coverslips were sequentially plunged into methanol and acetone at −20 °C, each for 10 min. Cells were rehydrated in phosphate-buffered saline and stained with primary antibodies for 1 h at room temperature. Cells were then rinsed with phosphate-buffered saline and stained with either a Cy3 conjugated AffiniPure donkey anti-rabbit IgG (Jackson ImmunoResearch, West Grove, PA) or Alexa FluorTM 488 goat anti-mouse IgG (Molecular Probes, Eugene, OR) for 45 min at room temperature. The cells were rinsed with phosphate-buffered saline and mounted in Gel/Mount™ (Biomeda Corp., Foster City, CA). Cells were observed with a Leica DMRBXA immunofluorescence microscope using ×100 plan objective.

**RESULTS**

**Identification of ZIN**—To identify potential RIP-interacting proteins, we used the yeast two-hybrid system to screen a human B cell cDNA library with full-length RIP as bait. We screened a total of 5 × 10⁶ independent library clones and obtained 26 β-galactosidase-positive clones. The inserts of 9 of the 26 clones are not in-frame with the GAL4 activation domain in the library vector. Among the other 17 clones, two encode for FADD, a death domain-containing protein that has been reported to interact with RIP (21), and one encodes a novel RING-like zinc finger domain-containing protein, which we designated as ZIN. We further studied ZIN because some of the known RIP-interacting proteins, such as TRAF2 and A20, also contain RING or zinc finger domains.

Since the ZIN clone obtained from the yeast two-hybrid screening is not full-length, we obtained its full-length cDNA by a combination of GenBank™ data base searches for ZIN-encoding expressed sequence tag clones and 5’ RACE. These efforts identified a ZIN cDNA of ~2.1 kb that is capable of encoding a 488-amino acid protein (Fig. 1A). The 5′ of the putative start codon (ATG) has an in-frame stop codon, and the 3′ of the cDNA has a poly(A) tail, suggesting that we obtained a cDNA fragment encoding full-length ZIN (data not shown).

Blot searches of the GenBank™ data bases indicate that ZIN has no significant homolog to known proteins except that the C-terminal part of ZIN is almost identical to an uncharacterized, hypothetical protein called TRIAD3 (GenBank™ accession number NP_061884). Structural analysis suggests that ZIN contains four RING-like zinc finger domains (RLDs) at the middle (amino acids 137–352) and a proline-rich domain (PRD) at the C terminus (amino acids 396–482) (Fig. 1A). The N terminus of ZIN has no detectable similarity with any other proteins. The structural properties suggest that ZIN is probably a zinc-binding protein.

Northern blot analysis suggests that RIN is ubiquitously expressed in all examined tissues as two transcripts of ~3.0 and ~6.0 kb, respectively (Fig. 1B). ZIN is expressed at relatively higher levels in peripheral blood leukocytes and testis (Fig. 1B).

**Expression of ZIN Protein in Mammalian Cells**—To determine whether ZIN is expressed in mammalian cells at protein level, we raised a rabbit polyclonal antiserum against a peptide corresponding to amino acids 370–390 of ZIN. Western blot analysis suggests that ZIN is expressed as an ~56-kDa protein in all examined human cell lines, including B lymphoma PRM18226, T lymphoma Jurkat, and embryonic kidney 293 cells (Fig. 2). The size of the endogenous ZIN protein is similar to that of overexpressed ZIN, confirming that the identified ZIN cDNA encodes a full-length protein (Fig. 2). In 293 cells, the ZIN antiseraum also recognized a second higher molecular weight band, which may represent a post-translationally modified or alternatively spliced form of ZIN or a different protein in 293 cells.

**ZIN Interacts with RIP in Mammalian Cells**—To determine whether full-length ZIN interacts with RIP in mammalian cells, we transfected 293 cells with expression plasmids for FLAG-tagged ZIN and HA-tagged RIP and performed co-immunoprecipitation experiments. These experiments suggest that ZIN interacts with RIP in 293 cells (Fig. 3).

To determine which domains of ZIN are required for interaction with RIP, we constructed three deletion mutants of ZIN. These include ZIN-(1–364) that contains the N-terminal domain and the RLDs, ZIN-(127–488) that contains only the RLDs and the C-terminal PRD, and ZIN-(365–488) that contains only the C-terminal PRD (Fig. 3A). Transient transfection and co-immunoprecipitation experiments suggest that the two RLD-containing mutants, ZIN-(1–364) and ZIN-(127–488), but not the RLD-lacking mutant ZIN-(365–488), interact with RIP (Fig. 3B). These data suggest that the RLDs of ZIN are required for interaction with RIP.
ZIN Inhibits RIP- and IKKβ-induced NF-κB Activation—It has been shown that RIP is absolutely required for TNF-R1-induced NF-κB activation (4, 21–26). To determine whether ZIN has a similar function, we performed NF-κB luciferase reporter gene assays. These experiments indicated that overexpression of ZIN could not activate NF-κB in 293 cells (Fig. 4A, A and C). Instead, overexpression of ZIN inhibited RIP-induced NF-κB activation in a dose-dependent manner (Fig. 4A). To exclude the possibility that ZIN affects RIP expression but not RIP signaling, we examined RIP levels in the same lysates by Western blot. As shown in Fig. 4A, RIP levels were not significantly changed with the increased expression of ZIN. These data suggest that ZIN inhibits RIP-mediated NF-κB activation.

The two RLD-containing and RIP-interacting ZIN mutants, ZIN (1-364) and ZIN (127-488) (Fig. 3), also inhibited RIP-mediated NF-κB activation in reporter gene assays (data not shown). In contrast, ZIN (365–488), which does not contain the RLDs and does not interact with RIP (Fig. 3), did not inhibit RIP-mediated NF-κB activation (Fig. 4B). In fact, ZIN (365–488) could weakly activate NF-κB and potentiate RIP-mediated NF-κB activation (Fig. 4B). These data suggest that the RLDs of ZIN are required for inhibition of RIP-mediated NF-κB activation.

Previous studies indicate that RIP activates NF-κB through IKK (11–19). We examined whether ZIN could inhibit IKKβ-mediated NF-κB activation. As shown in Fig. 4C, ZIN also inhibited IKKβ-mediated NF-κB activation, whereas ZIN (365–488) weakly potentiated IKKβ-mediated NF-κB activation (Fig. 4D). In these experiments, neither ZIN nor ZIN (365–488) affected expression levels of IKKα. These data, although unexpected because IKKβ is a downstream protein of RIP, suggest that ZIN can inhibit IKKβ-mediated NF-κB activation.

ZIN Inhibits TNF- and IL1-induced NF-κB Activation—Since ZIN can inhibit RIP- and IKKβ-mediated NF-κB activation, we determined whether ZIN inhibits TNF- and IL1-induced NF-κB activation. As shown in Fig. 5, A and B, ZIN, but not ZIN (365–488), inhibited TNF- and IL1-induced NF-κB activation in a dose-dependent manner. In contrast, ZIN did not inhibit IFN-γ-induced IRF-1 activation (Fig. 5C), suggesting that ZIN specifically inhibits NF-κB activation by TNF and IL1.

ZIN Potentiates RIP- and TNF-induced Apoptosis—Previously, it has been suggested that overexpression of RIP potentially induces apoptosis (20, 21). Since ZIN is a RIP-interacting protein, we examined whether ZIN is involved in RIP-induced apoptosis. As shown in Fig. 6A, overexpression of ZIN did not induce apoptosis, but potentiated RIP-induced apoptosis in a dose-dependent manner.

In 293 cells, TNF alone does not induce apoptosis. However, overexpression of ZIN could consistently sensitize ~30% of transfected 293 cells to TNF-induced apoptosis (Fig. 6B). IKKβ (K/A), an IKKβ kinase-inactive mutant that can inhibit TNF-induced NF-κB activation (17, 28), could also sensitize 293 cells to TNF-induced apoptosis (Fig. 6B).

ZIN Does Not Compete with TRAF2 for Binding to RIP—One of the possible explanations for inhibition of RIP-mediated NF-κB activation by ZIN is that ZIN may dissociate TRAF2 from RIP. TRAF2 contains one RING finger domain and four zinc finger domains at its N terminus (43). It has been shown that the RING finger domain of TRAF2 interacts with the intermediate domain of RIP and that this interaction is important for TRAF2- and RIP-mediated NF-κB activation (21). Since the RLDs of ZIN are also responsible for interacting with RIP, we investigated the possibility that ZIN may compete with TRAF2 for binding to RIP. To do this, we transfected 293 cells with constant amounts of...
expression plasmids for TRAF2 and RIP and increased amounts of expression plasmid for ZIN. Co-immunoprecipitation experiments indicated that ZIN could not compete with TRAF2 for interaction with RIP (data not shown).

Colocalization of RIP and ZIN—ZIN has a putative nuclear localization signal sequence (amino acids 47–52). To determine the cellular localization of ZIN, we performed immunofluorescent microscopy. These experiments suggest that ZIN is mainly localized in the cytoplasm (Fig. 7). To determine whether RIP colocalizes with ZIN, we transfected 293 cells with an expression plasmid for HA-tagged RIP and performed double immunofluorescent staining. These experiments suggest that overexpressed RIP overlaps with endogenous ZIN (Fig. 7). In addition, we noticed that overexpression of RIP caused substantial aggregation of ZIN (Fig. 7), pointing to the possibility that overexpression of RIP leads to the formation of complexes that contain RIP, ZIN, and other molecules.

**DISCUSSION**

During the past several years, tremendous progress has been achieved on the molecular mechanisms of TNF-R1 signaling. TNF stimulation of TNF-R1 leads to recruitment of the adapter protein TRADD to the TNF-R1 signaling complex (2, 4). TRADD recruits FADD and caspase-8 to activate caspase cascades, and this leads to mitochondria-dependent and -independent apoptosis (2, 6–10, 31–35). TRADD also interacts with TRAF2 and RIP, and these interactions lead to NF-kB activation through an IKK-dependent pathway and JNK activation through an MEKK1-MKK4-dependent pathway (2, 4, 11–19). These models have now become paradigms of how all TNF receptor family members signal.

One of the major unsolved questions on TNF-R1 signaling is how TRAF2 and RIP activate downstream IKK. One group proposed a direct interaction between RIP and the IKK subunit of the IKK complex (24). However, studies with RIP- and TRAF2-deficient cells indicate that TRAF2, but not RIP, is
required for recruitment of the IKK complex to TNF-R1, whereas RIP is required for activating IKK, probably through MEKK3 (25–27). Currently, the precise mechanisms responsible for RIP-mediated IKK activation are not known.

We have used the yeast two-hybrid system to identify additional RIP-interacting proteins. This search identified ZIN as a novel RIP-interacting protein. ZIN contains four RLDs at the middle and a proline-rich domain at its C terminus. Overexpression of ZIN inhibits RIP-mediated NF-κB activation, and the RLDs of ZIN are required for this inhibitory activity. Unexpectedly, overexpression of ZIN also inhibited IKKβ-mediated NF-κB activation. In co-immunoprecipitation experiments, however, we failed to detect an interaction between IKKβ and ZIN. The simplest explanation for this observation is that ZIN also targets a downstream signaling component of IKKβ.

ZIN can inhibit TNF-induced NF-κB activation in 293 cells. Since only TNF-R1, but not TNF-R2, is expressed in 293 cells, these data suggest that ZIN inhibits TNF-R1-induced NF-κB activation. This is consistent with the notion that RIP is required for TNF-R1-induced NF-κB activation. Surprisingly, ZIN also inhibits IL-1-induced NF-κB activation. Inhibition of TNF- and IL-1-induced NF-κB activation is not due to a general inhibitory effect of transcription by ZIN because ZIN does not inhibit IFN-γ-induced IRF-1 activation. Our findings suggest that ZIN has multiple targets in TNF- and IL-1-induced NF-κB activation pathways. Currently, we do not know which protein(s) in the IL-1 signaling pathway are targeted by ZIN.

Interestingly, ZIN-(365–488), a mutant that does not interact with RIP, can weakly activate NF-κB and potentiate RIP-, IKKβ-, TNF-, and IL-1-induced NF-κB activation. It is possible that ZIN-(365–488) can at least partially neutralize the inhibitory effect of full-length ZIN.

The structural and functional properties of ZIN are very similar to a previously characterized protein A20 (24, 36–42). Although the sequence of ZIN has no significant homology to A20, both contain putative zinc finger structures. A20 can interact with multiple molecules, including TRAF1, -2, and -6, IKKγ/NEMO, and ABIN (24, 36–42). Overexpression of A20 inhibits TNF- and IL-1-induced NF-κB activation (36–42). Gene knock-out studies have demonstrated a critical role for A20 in inhibition of TNF-induced NF-κB activation and inflammation (41). Interestingly, it has been shown that the zinc finger domains of A20 are also required for its inhibition of TNF- and IL-1-induced NF-κB activation (40).

Since the RLDs of ZIN are responsible for interacting with RIP, it is possible that ZIN may compete with TRAF2 for binding to RIP and therefore inhibit RIP-mediated NF-κB activation. However, co-immunoprecipitation experiments indicate that this is not the case, suggesting that other mechanisms are involved in ZIN-mediated inhibition of RIP-induced NF-κB activation.

Overexpression of ZIN potentiates RIP- and TNF-induced apoptosis in 293 cells. Previously, it has been shown that NF-κB activation can prevent cells from apoptosis induced by TNF and other stimuli (13, 44–46). The simplest explanation for ZIN’s potentiation of RIP- and TNF-induced apoptosis is that ZIN inhibits RIP-induced NF-κB activation and thus sensitizes cells to apoptosis.

Sequence analysis suggests that a bipartite nuclear localization signal sequence exists at amino acids 36–53 of ZIN. This raises the possibility that ZIN is a nuclear protein. However, our immunofluorescent staining experiments suggest that ZIN is mainly localized to the cytoplasm. Moreover, these experiments indicate that overexpressed RIP colocalizes with ZIN and causes the aggregation of ZIN. These data provide additional evidences that ZIN is functionally associated with RIP.

In conclusion, we have identified a novel RING-like zinc finger protein that is capable of inhibiting TNF- and IL1-induced NF-κB activation. The identification of ZIN, like A20, may shed new light on the negative regulation of TNF- and IL-1-induced NF-κB activation pathways. However, the data provided in this study were mostly from protein overexpression; a physiological role for ZIN needs to be defined by experiments dealing with endogenous protein and/or gene knock-out studies.

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