Neurotrophin Receptor-interacting Mage Homologue Is an Inducible Inhibitor of Apoptosis Protein-interacting Protein That Augments Cell Death*

The inhibitor of apoptosis proteins (IAPs) have been shown to interact with a growing number of intracellular proteins and pathways to fulfill their anti-apoptotic role. In the search for novel IAP-interacting proteins we identified the neurotrophin receptor-interacting MAGE homologue (NRAGE) as being able to bind to the avian IAP homologue ITA. This interaction requires the RING domain of ITA. NRAGE additionally communoprecipitates with XIAP. When overexpressed in 32D cells NRAGE augments interleukin-3 withdrawal induced apoptosis, possibly through binding endogenous XIAP. Moreover, NRAGE is able to overcome the anti-apoptotic effect of Bcl-2.

The inhibitor of apoptosis proteins (IAPs) encoded by a recently identified family of highly conserved genes, playing a crucial role in the regulation of apoptosis by interfering with the process of caspase activation (1). The mammalian IAPs consist of the X-linked inhibitor of apoptosis (XIAP, MIHA, ILP), cellular IAP1 (cIAP1, HIAP2, MIHC), cIAP2 (HIAP1, MIHB), NAIP, and survivin (2–6). The inhibitor of T cell apoptosis (ITA) is an avian IAP homologue (7). Members of this family must contain at least one NH2-terminal cysteine-rich baculovirus IAP repeat (BIR) domain, which is required for pro-survival activity, and may also possess a carboxyl-terminal domain solely to indicate this fact.

XIAP on TNFR2-TRAF signaling complex, with the BIR domains being RING zinc finger. XIAP has pro-survival activity, and may also possess a carboxyl-terminal baculovirus IAP repeat (BIR) domain, which is required for pro-survival activity, and may also possess a carboxyl-terminal RING zinc finger.

cIAP1 and cIAP2 were originally identified as part of the TNFR2-TRAF signaling complex, with the BIR domains being responsible for the interaction with TRAFs 1 and 2 (3). XIAP on the other hand was shown to act as a mediator of bone morphogenic protein signaling linking the receptors to the signaling modulators TAB1 (TAK1-binding protein) and TAK1. The RING domain of XIAP binds to the receptor, while the BIR domains are important for recruiting TAB1 (8). XIAP was also shown to interact with nuclear proteins such as XAF1 (9) and can be diverted away from caspase inhibition by Smac/DIABLO (10, 11), as well as being involved in other signaling processes such as JNK1 (c-Jun NH2-terminal kinase) (12) and NF-kB (8) activation.

Another group of proteins important in the regulation of apoptosis is the Bcl-2 family (13). Bcl-2 itself has been shown to play a crucial role in the prevention of apoptosis at the mitochondrial surface impeding the function of the pro-death family members or by obstructing the release of apoptogenic molecules (13).

NRAGE is a very recently cloned neurotrophin receptor-interacting MAGE homologue, uncovered in a two-hybrid search for proteins interacting with the intracellular domain of the p75 neurotrophin receptor (p75NTR). This protein was shown to be involved in the apoptotic response after nerve growth factor (NGF) binding in neuronal cells (14). NGF can mediate a variety of cellular responses, such as survival, differentiation, growth, and apoptosis in neurons, by binding to two types of cell surface receptors, the Trk receptor tyrosine kinases and the p75NTR (15). Interestingly, NRAGE shows a high homology in its carboxyl-terminal with the melanoma associated antigen (MAGE) family, which codes for antigens that present on many human tumors, although their intracellular function is mostly unknown. One exception is needin, a postmitotic neuron-specific growth suppressor that can interact with both intracellular proteins such as E2F1 and p53 and viral transforming proteins such as adenovirus E1A (16).

In this study we identified the pro-apoptotic protein NRAGE as a novel IAP-interacting protein in the yeast two-hybrid system. Furthermore, we show that NRAGE coprecipitates with ITA and XIAP, via the RING zinc finger domain of the IAPs. NRAGE can augment cell death upon growth factor withdrawal in the IL-3-dependent promyeloid leukemic 32D cell line, even in the presence of Bcl-2.

EXPERIMENTAL PROCEDURES

Plasmid Construction—Molecular cloning of ITA was described previously (7). The full-length cDNA was inserted into the ApoI and EcoRI sites of pCDNA3 (Invitrogen). A 5′ PCR product was amplified using the primers 5′-tcgagctctggttcatatatg-3′ and 3′-ggtgctctgacactgac-5′, with pCDNA3-ITA as a template and Pfu polymerase (Stratagene). The PCR product was digested with SalI and Smal, ligated with pCDNA3-ITA Smal/EcoRI, and inserted first into the two-hybrid vector pC86 at SalI/EcoRI then into pC97 at SalI/AatII (17). pCDNA3-HA-ITA construction was described previously (18). The expression vectors for truncated ITA isoforms were generated by PCR using HF DNA polymerase (CLONTECH) on the pCDNA3-HA-ITA tem-

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c-IAP1, c-IAP2 (29) and XIAP (27) were cloned into the blunt-ended SalI site of pPC97 using EcoRI and XhoI-digested and Klenow-treated inserts of pCDNA3 constructs (courtesy J. Reed, Burnham Institute) inserted into the Klenow-treated SalI site in pPC97. pCDNA3myc-XIAP (J. Reed) was first subcloned into the GST fusion vector pGEX-4T-1 using the EcoRI and XhoI sites, before being cloned in frame into the eukaryotic GST fusion vector pEBG. pPC97-NAIAP was constructed by inserting the EcoRV/SaclII-flanked pBluescript NAIAP (19) into Klenow-treated SalI/SaclII sites of pPC97.

Cloning of NRAGE—The largest two-hybrid insert was labeled with [32P]dCTP using the rediprimeTM random labeling system (Amersham Pharmacia Biotech) according to manufacturer’s instructions and used to screen a bacterially expressed S194 murine plasmacytoma cDNA library as described previously (20). The full-length NRAGE cDNA was amplified with Pfu polymerase from a resultant 2.8-kilobase pair putative full-length clone with the forward primer 5'-ggatctcccagcaggtgagtacccctgcagcttcgtgaaaggaggag-3' and the reverse primer 5'-ggcgaattctgccaccatggacgtacccctgcttcgtgaaaggaggag-3'. The largest two-hybrid insert was labeled with [32P]dCTP using the rediprime™ random labeling system (Amersham Pharmacia Biotech) according to manufacturer’s instructions and used to screen a bacterially expressed S194 murine plasmacytoma cDNA library as described previously (20). The full-length NRAGE cDNA was amplified with Pfu polymerase from a resultant 2.8-kilobase pair putative full-length clone with the forward primer 5'-ggatctcccagcaggtgagtacccctgcagcttcgtgaaaggaggag-3' and the reverse primer 5'-ggcgaattctgccaccatggacgtacccctgcttcgtgaaaggaggag-3'. The largest two-hybrid insert was labeled with [32P]dCTP using the rediprime™ random labeling system (Amersham Pharmacia Biotech) according to manufacturer’s instructions and used to screen a bacterially expressed S194 murine plasmacytoma cDNA library as described previously (20). The full-length NRAGE cDNA was amplified with Pfu polymerase from a resultant 2.8-kilobase pair putative full-length clone with the forward primer 5'-ggatctcccagcaggtgagtacccctgcagcttcgtgaaaggaggag-3' and the reverse primer 5'-ggcgaattctgccaccatggacgtacccctgcttcgtgaaaggaggag-3'. The largest two-hybrid insert was labeled with [32P]dCTP using the rediprime™ random labeling system (Amersham Pharmacia Biotech) according to manufacturer’s instructions and used to screen a bacterially expressed S194 murine plasmacytoma cDNA library as described previously (20). The full-length NRAGE cDNA was amplified with Pfu polymerase from a resultant 2.8-kilobase pair putative full-length clone with the forward primer 5'-ggatctcccagcaggtgagtacccctgcagcttcgtgaaaggaggag-3' and the reverse primer 5'-ggcgaattctgccaccatggacgtacccctgcttcgtgaaaggaggag-3'.
were His-positive clones were obtained from this screen, of which 8 the protein expressed in yeast cells did not autonomously activate bait, using a PC12 cDNA library. The ITA-GAL4DB fusion hybrid screen was performed with the full-length ITA cDNA as
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In the search for IAP-interacting proteins, a yeast two-
later identified as NRAGE (14).
Research did show a high degree of identity; THC179960 was as assembled gene THC179960 from The Institute of Genomic homology to any previously described gene, an electronically,
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were scaled up by

trypan blue (Sigma). For protein analysis, the cell number and volume were dispensed into a single well of a flat bottom 24-well tissue culture plate. Cell viability was routinely assessed by staining the cells in

aprotinin, 5 µg/ml leupeptin). Cell debris was removed by centrifugation, and 500 µg of protein supernatants were precleared with 10 µl of protein-A/G-agarose (Amersham Pharmacia Biotech). The lysates were then incubated with the appropriate antiseraum coupled to 30 µl of protein-A/G-agarose overnight at 4 °C. The immune complexes were washed twice in Nonidet P-40 buffer containing 500 mM NaCl. After resuspension in Laemmli buffer and SDS-PAGE, proteins were detected by immunoblot. Anti-FLAG M2 monoclonal antibody (Eastman Kodak Co.) was a generous gift from S. Feller (Institut für Medizinische Strahlenkunde und Zellforschung). Goat polyclonal anti-FLAG raised against the OctA probe and rabbit polyclonal ERK2 antibody were purchased from Santa Cruz, HA-tagged proteins were detected with a monoclonal anti-HA antibody (12CA5). Anti-XIAP rabbit polyclonal antibody (12CA5), and anti-goat IgG horseradish peroxidase (Santa Cruz) was also employed.

Establishment of Stable Cell Lines—The protocol for transfection of Phoenix™ virus packaging cells and establishment of stably transduced 32D cells has been described previously (23). Retroviral ex-

Cell Survival Assays—For the analysis of cell survival, cells were washed three times in tissue culture medium containing 10% FCS but without WEHI cell supernatant. 0.5 × 10^6 cells in a total volume of 1 ml were dispensed into a single well of a flat bottom 24-well tissue culture plate. Cell viability was routinely assessed by staining the cells in trypsin blue (Sigma). For protein analysis, the cell number and volume were scaled up by ×20.

RESULTS

ITA Binds to Overlapping NH2-terminal NRAGE Fragments—In the search for IAP-interacting proteins, a yeast two-

vector, and NRAGE-transduced cells were seeded (0.5 × 10^6) in RPMI 1640 medium supplemented with 10% FCS but lacking IL-3 into the wells of a 24-well plate and cell viability measured at the time points indicated. A is representative of five experiments, each performed in duplicate, with the points of the curves being taken from two of these experiments, measured in duplicate with 150–250 cells counted per measurement, by trypsin blue exclusion. Mean values and S.D. (error bars) are shown. B, the effect of NRAGE on 32D cells protected from IL-3 withdrawal by the expression of Bcl-2 was investigated. 32D parental, Bcl-2, Bcl-2 + empty vector, and Bcl-2 + NRAGE stably expressing cells were seeded as above, and cell viability was measured after 24 h. The results shown in B are representative of four experiments each performed in duplicate, after 24-h IL-3 withdrawal, measured as described previously. The results from two of these experiments are depicted in the figure, mean values and S.D. (error bars) are shown.

XIAP Interacts Directly with NRAGE NH2-terminal Clones in Vivo—To determine whether NRAGE could interact with other IAP family members, direct yeast two-hybrid tests were carried out between the strongest interacting clone (ANRAGEp80) and c-IAP1, c-IAP2, XIAP, and NAIP. XIAP interacted with ANRAGEp80 with an equal intensity of β-galactosidase activity compared with ITA (Fig. 1A, lower panel). XIAP also bound to ANRAGEp70 and ANRAGEp60. However, c-IAP1, c-IAP2, and NAIP did not interact with any of the clones in direct yeast-two-hybrid tests.

ITA Interacts with NRAGE via Its RING Zinc Finger Domain—To independently confirm the ITA-NRAGE two-hybrid interaction we performed coimmunoprecipitation experiments in a higher eukaryotic cell system. The full coding sequence of NRAGE was cloned into a mammalian expression vector as described under “Experimental Procedures,” and HEK293 cells were cotransfected with HA-tagged ITA and FLAG-tagged NRAGE. NRAGE was immunoprecipitated and subsequently immunoblotted using a goat anti-FLAG antibody (Fig. 1B). As shown in Fig. 1B, upper panel, NRAGE was detectable after immunoprecipitation with the 12CA5 antibody using lysates from HA-ITA-expressing lysates (Fig. 1B, lane 2), but not from control cells (Fig. 1B, lane 5). Furthermore, NRAGE coimmunoprecipitated with an ITA deletion construct containing only the RING domain (Fig. 1B, lane 4), but not with the deletion construct containing only the BIR domains of ITA (Fig. 1B, lane 3). These interactions were able to withstand high stringency washes with 500 mM NaCl. In Fig. 1B, lower panel, the presence of the immunoprecipitated ITA proteins used in the co-

precipitation experiments (lanes 2–5) was confirmed by stripping and reprobing the same membrane with the 12CA5 monoclonal antibody. In summary, these experiments demonstrate that ITA interacts with NRAGE with high affinity and that this interaction occurs specifically via its carboxyl-terminal RING zinc finger domain.

XIAP Binds to NRAGE—The same strategy was applied to confirm the XIAP-NRAGE binding. HEK293 cells were tran-
siently transfected with vectors expressing FLAG-NRAGE and GST-XIAP or FLAG-NRAGE and GST only. In Fig. 1C, upper left panel, NRAGE is coimmunoprecipitated with GST-XIAP (lane 2), whereas no coprecipitated protein was detected in the
NRAGE was immunoprecipitated and immunoblotted as a positive control (lane 1). The blot was stripped and reprobed using the rabbit polyclonal XIAP antibody, shown in the lower left panel.

In Fig. 1C, right hand panels, the reverse experiment was performed. GST-XIAP was coimmunoprecipitated with NRAGE (lane 2 upper right panel). Once again, this interaction was stable enough to withstand high salt washing conditions (500 mM NaCl). Immunoprecipitated and immunoblotted GST-XIAP was used as the positive control (lane 1), while GST containing lysate was used as a negative control in this experiment (lane 3). The blots were stripped and reprobed using the FLAG antibody to detect tagged NRAGE, shown in the lower right panel. These experiments confirm NRAGE as a novel XIAP-interacting protein, with a strong binding affinity.

NRAGE Expression in the IL-3-dependent 32D Cell Line Augments Factor Withdrawal-induced Apoptosis—IL-3-dependent 32D cells have been well studied with regard to the process of apoptosis induced by growth factor withdrawal (24, 25). For this reason we established NRAGE and vector stably transduced cell lines, to examine the contribution of NRAGE to this process. NRAGE expression was determined by Western blotting (data not shown). The proliferation rate of these cells was not affected by the stable integration of the retroviral vector or NRAGE protein expression (data not shown). Cell survival after IL-3 withdrawal was measured by trypan blue exclusion. As shown in Fig. 2A, the vector-transduced cells behave identically to the parental cells. In contrast, expression of NRAGE had a dramatic effect on the kinetics of cell death in 32D cells. The survival curves for NRAGE and the vector/parental lines diverge very early on (12 h), and this trend continues throughout the experiment. At the 24-h time point about three times as many dead cells were observed with the NRAGE-expressing cell pool. This indicates that NRAGE greatly accelerates the cell death process upon growth factor withdrawal in this IL-3-dependent promyeloid leukemic cell line.

NRAGE Binds XIAP in Vivo upon IL-3 Withdrawal in 32D Cells—Over a 24-h period we analyzed the interaction of NRAGE with endogenous XIAP in 32D cells. Fig. 3A, upper panel, shows the binding of NRAGE with XIAP is undetectable in proliferating 32D cells; however, 8–12 h after IL-3 withdrawal we observed an induction of binding, trailing off thereafter, and becoming undetectable at 16 h, as seen in Fig. 3A, upper panel.

To investigate the consequence of NRAGE-XIAP interaction in 32D cells after IL-3 withdrawal, we examined endogenous XIAP protein levels. Fig. 3B, upper panel, shows that XIAP cleavage occurs very early in NRAGE-transduced cells and leads to rapid loss of XIAP protein. In contrast, Fig. 3C shows XIAP cleavage is barely detectable in vector-transduced cells at 24-h IL-3 withdrawal, and the loss of XIAP protein occurs at a greatly reduced rate compared with NRAGE expressing cells.

NRAGE Overcomes Bcl-2-mediated Cell Protection—Forced Bcl-2 expression in 32D cells has been shown to be very effective in rescuing the cells from the induction of apoptosis by a variety of stimuli, including withdrawal (21). We therefore wanted to test whether it could also block the death-inducing activity of NRAGE. 32D cells stably expressing Bcl-2 were infected with either the retroviral control vector or the retrovirus containing FLAG-NRAGE and selected as described above. 24 h after IL-3 withdrawal, the 32D cells expressing Bcl-2 gained a 100% increase in survival compared with the wild type cells, and no significant difference was seen in the 32DBcl-2 vector-transduced cells. However the 32DBcl-2 cells expressing NRAGE showed a dramatic reduction in survival, completely abolishing any protection given by Bcl-2 (Fig. 2B).

This would suggest that NRAGE is a pro-apoptotic protein despite Bcl-2 expression, after growth factor withdrawal.

**DISCUSSION**

Besides Bcl-2 proteins, the IAP family members constitute the largest group of pro-survival proteins. Members of this heterogeneous family are mainly defined by the presence of a BIR domain, a novel zinc binding fold, and the ability to suppress apoptosis (26). BIR domains mediate caspase binding and inhibition and are both necessary and sufficient for the anti-apoptotic function of IAP proteins (27). While the anti-apoptotic function of Bcl-2 is well understood (13), very little is known about the mechanisms that control IAP function. In an attempt to define possible regulators we carried out a yeast two-hybrid screen with the avian IAP and ITA and can demonstrate that the newly discovered NRAGE binds to the IAP proteins ITA and XIAP. For ITA, the interaction with NRAGE...
occurs independent of the BIR motif but requires the presence of the RING domain, which is present in c-IAP1, c-IAP2, and XIAP but is lacking in NAIP. Consistent with this we also fail to detect interaction of NAIP with NRAGE. Moreover, our results demonstrate that expression of NRAGE in the IL-3-dependent promyeloid cell line 32D accelerates cell death following growth factor withdrawal even in the presence of Bcl-2. XIAP was previously shown to undergo caspase-mediated cleavage during apoptosis (32). Coexpression of NRAGE led to accelerated XIAP cleavage and further degradation of XIAP during apoptosis in 32D cells, while in the control cells this process occurred at a much reduced rate.

The role of the RING domain of IAPs in the process of apoptosis suppression remains controversial. While the RING domain of c-IAP2 has been shown to be important in TNF-mediated NF-κB survival signaling (28), it was not necessary for caspase inhibition (29). Furthermore, a recent report demonstrated that the RING domains of cIAP1 and XIAP possess ubiquitin ligase activity upon apoptosis induction, resulting in degradation of these proteins (30). It is tempting to speculate that proteins binding to this region might regulate this process.

NRAGE has been shown initially to induce apoptosis signaling by blocking the physical association of p75NTR with TrkA (15). However, in contrast to one of the observations of Salehi et al. (14), we saw no effect on proliferation by stable expression of NRAGE, which could be due to the surviving cell population expressing a level of NRAGE low enough not to induce cell cycle arrest, but still able to interfere with apoptosis. Similarly, IAP proteins cIAP1 and cIAP2 have first been identified as part of the related TNF-receptor signaling complex (3). The ability of NRAGE to interfere with the intrinsic cell death pathway that is triggered by IL-3 withdrawal points to a novel function of NRAGE in apoptosis signaling. It is commonly assumed that Bcl-2 proteins interfere with the process of caspase activation at the mitochondrial level (13), while the IAPs have been shown to act at the receptor level (3) and post-mitochondrially in the assembly of the apoptosome (31). We performed in vitro caspase cleavage assays utilizing recombinant NRAGE and XIAP proteins, but were unable to see an influence of NRAGE on XIAP anticaspase activity (data not shown). We currently have little understanding of exactly which step NRAGE influences XIAP cleavage, and it thus remains to be established whether NRAGE may function on the level of promoting caspase recruitment rather than altering enzyme activity.

Interestingly, we observed a very high level of expression of n rage in mouse brain tissue. It has been previously described that in embryonic chick primary neurons, ITA expression is required for NGF-mediated survival (18). It remains to be seen whether IAP-NRAGE determines the signaling outcome from the NGF receptor. In summary, our data suggest that IAP

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2 B. Jordan, unpublished data.
3 B. Jordan, unpublished data.

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