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Evidence for a role of NF-κB in the survival of hematopoietic cells mediated by interleukin 3 and the oncogenic TEL/platelet-derived growth factor receptor β fusion protein

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ABSTRACT **Interleukin 3 (IL-3) and other hematopoietic cytokines transduce signals that stimulate DNA synthesis and cell survival. In certain chronic myelomonocytic leukemias, a TEL/platelet-derived growth factor receptor β (PDGFRβ) fusion protein is produced as a consequence of the t(5;12) translocation. It contains the amino terminus of the transcription factor TEL fused to the transmembranous and cytoplasmic domains of the PDGFRβ. It is oncogenic as it substitutes for IL-3, thus promoting cell growth and preventing apoptotic cell death. The mechanism by which TEL/PDGFRβ generates survival signals remains undefined. Here, we report that both IL-3 and TEL/PDGFRβ initiate a signaling cascade that leads to the activation of the transcriptional factor NF-κB. In fact, either cytokine deprivation of IL-3-dependent Ba/F3 cells or exposure of TEL/PDGFRβ-expressing cells to the specific inhibitor of the PDGFR tyrosine kinase, CGP53716, caused a strong decrease in NF-κB activity followed by extensive cell death. Further, treatment with the proteasome inhibitor Z-IE(*O-t*-Bu)A-leucinal suppressed IL-3 and TEL/PDGFRβ-dependent survival. The same result was seen upon overexpression of an unphosphorylable form of IκBα. Because both conditions inactivate NF-κB by preventing its translocation into the nucleus, that process seems to be essential for cell survival in response to IL-3 and TEL/PDGFRβ. Moreover, overexpression of a dominant-negative mutant of the protooncogene c-Myc, a downstream target of NF-κB, had a similar effect. We conclude that NF-κB plays an important role in maintaining cell survival in response to IL-3 and TEL/PDGFRβ and that c-Myc may be a downstream effector mediating this effect.**

The strict dependence of hematopoietic cells on cytokines for cell survival and growth is essential for the maintenance of homeostasis, and alterations of this dependence often result in malignant transformation (1, 2). Interleukin-3 (IL-3) is necessary for survival and growth of hematopoietic cells. It acts by binding to specific cell surface receptors composed of two chains, the IL-3-specific α chain and the signal transducing β-chain, which is common to IL-3, IL-5, and granulocyte/macrophage colony-stimulating factor receptors (3). Prevention of apoptotic death by IL-3 implicates Ras activation, which in turn activates both the Raf/mitogen-activated protein kinase and PI3-kinase/Akt pathways (4). Whereas the BAD protein has been identified as a mediator of PI-kinase/Akt-mediated cell survival (5), effectors of the Raf pathway have not as yet been elucidated.

Originally described as regulators of immune and inflammatory responses, the NF-κB family of transcription factors was subsequently shown to play a more general role in cell proliferation and differentiation and has been associated with several viral and nonviral malignancies (6, 7). In non-stimulated cells, NF-κB is sequestered in the cytoplasm through binding to one member of a family of inhibitors known as IκBs. Upon stimulation of the cells with various inducers, two serine residues (Ser-32 and Ser-36) of the IκB protein are phosphorylated (reviewed in ref. 8). This phosphorylation is a signal for ubiquitination and degradation of IκB in the 26 S proteasome and for subsequent translocation of the NF-κB complex to the nucleus (9). Several recent studies have revealed a role of NF-κB in the resistance of different cell types to apoptotic stimuli. For example, in the immature B cell line WEHI 231, NF-κB proteins suppress apoptosis induced by an antibody against surface IgM chains (10). Compared with wild-type cells, cells from mice that lack the NF-κB/Rel A gene are more susceptible to tumor necrosis factor-α-induced apoptosis (11). Similarly, inhibition of NF-κB nuclear translocation enhances apoptotic killing by agents that activate NF-κB (12–14) but not by apoptotic stimuli that do not activate this factor (13). It has also been reported that NF-κB exerts a protective effect against transforming growth factor β1-induced apoptosis (15, 16) and plays a role in the antiapoptotic function of insulin (17). Despite these findings, the target genes that determine cell survival in response to NF-κB activation are largely undefined.

The TEL/PDGFRβ fusion protein (TP) converts IL-3-dependent hematopoietic cells to cytokine independence (18, 19). The protein results from the t(5, 12) translocation, which is a cytogenetic abnormality in chronic myelomonocytic leukemias. This translocation results in fusion of the amino-terminal 154 amino acids of the transcription factor TEL to the transmembrane and cytoplasmic domains of the PDGF receptor β (20). The emerging model from molecular studies is that the helix—loop–helix domain of the TEL part of the fusion protein results in the oligomerization of TP, which leads to constitutive activation of the PDGFRβ tyrosine kinase and stimulation of survival signaling pathways (18, 19). Although the ability of TP to inhibit apoptosis is an important component of its transforming activity, the precise mechanism by which this occurs has yet to be determined.

To explore the mechanism underlying cellular transformation by TP, we have investigated whether NF-κB activity plays a role in mediating the survival of the IL-3-dependent murine

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Abbreviations: IL-3, Interleukin 3; PDGFRβ, platelet-derived growth factor receptor β; TP, TEL/PDGFRβ; EMSA, electrophoretic mobility shift assay; PI3-kinase, phosphatidylinositol-3-kinase; GFP, green fluorescence protein; Z-AL, Z-IE(*O-t*-Bu)A-leucinal.

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bone marrow-derived Ba/F3 cells. Our findings provide strong evidence for an important role of NF-κB in IL-3- and TP-mediated survival of these hematopoietic cells and define c-Myc as one of the possible effectors of the antiapoptotic signal that is delivered by NF-κB.

MATERIALS AND METHODS

Expression Vectors and Reagents. The TEL/PDGFRβ cDNA inserted into the pSRα/MSV/TK/neo vector was from Dr. T. Golub (Harvard University) (20). The reporter plasmid (Igκ)3-conaluc and its control counterpart conaluc, the mutated IκBα (A32/36) encoding plasmid from Dr. A. Israël (Institut Pasteur, Paris), and the dominant-negative c-Myc (MycRX) encoding plasmid from Dr. B. Amati (Institut Suisse de Recherches Experimentales sur le Cancer, Lausanne, Switzerland) have been described (21–23). The pCMV-β-gal was also previously described (24). The pEGFP vector encoding the green fluorescence protein (GFP) was from CLONTECH.

The proteasome inhibitor Z-IE(*O-t*-Bu)A-leucinal (Z-AL) was from Calbiochem, and aspirin, sodium salicylate, and pyrrolidine dithiocarbamate were from Sigma. The specific inhibitor of the PDGFRβ tyrosine kinase, CGP53716, was a generous gift from Dr. E. Buchdunger (CIBA–Geigy).

Cell Culture. Pro-B IL-3-dependent Ba/F3 cells were routinely cultured at 37°C in RPMI 1640 medium supplemented with 10% fetal calf serum and 5% WEHI cell supernatant as a source of IL-3. For experiments, 1 ng/ml of recombinant murine IL-3 (PeproTech, Rocky Hill, NJ) was used instead of WEHI supernatant. Isolation of Ba/F3 cells stably transfected with the expression vector for TEL/PDGFRβ (Ba/F3.TP) has been described (25). These cells were maintained in RPMI medium with 10% fetal calf serum.

Electrophoretic Mobility Shift Assay (EMSA). Nuclear extracts were prepared as described (26). The double-stranded consensus NF-κB probe 5′-AGT TGA GGG GAC TTT CCC AGG C-3′, -3′-TCA ACT CCC CTG AAA GGG TCC G-5′ was end labeled using [γ^{32}-P]ATP and T4 polynucleotide kinase. Binding reactions were carried out in a 20-μl binding reaction mixture [10 mM Tris-HCl, pH 7.5/50 mM NaCl/0.5 mM DTT/10% glycerol/0.2% Nonidet P-40/4 μg of poly(dI-dC)(dI-dC)] containing 5 μg of nuclear proteins and 0.5 ng of the radiolabeled probe. For competition experiments, a 100-fold excess of unlabeled double-stranded NF-κB or AP-1 (5′-CGC TTG ATG AGT CAG CCG GAA-3′; -3′-GCG AAC TAC TCA GTC GGC CTT-5′) oligonucleotide was added prior to the probe. Supershift assays were performed by adding 1 μg of rabbit polyclonal antibodies (Santa Cruz) against the p50 or p65 subunits of NF-κB to the nuclear extracts for 30 min prior to the addition of the labeled probe. Samples were incubated for 45 min on ice and fractionated by electrophoresis on a 6% non-denaturing polyacrylamide gel in TAE buffer (7 mM Tris, pH 7.5/3 mM sodium acetate/1 mM EDTA). Gels were run at 180 V for 2.5 h at 4°C, dried, and autoradiographed.

Reporter Gene Assays. Ba/F3 and Ba/F3.TP cells (1×10^7) were washed twice with serum-free medium and incubated for 10 min at 4°C with 10 μg of (Igκ)3-conaluc-luciferase reporter and 0.5 μg of pCMV-β-gal in OptiMEM medium (GIBCO). Cells were then electroporated at 240 volts/960 μ in a Bio-Rad apparatus. Following a 30-min incubation at room temperature, cells were plated in the appropriate medium for 6 h prior to harvest. Reporter gene activity was determined with the luciferase assay system (Promega). Transfection efficiencies were normalized on the basis of β-galactosidase expression. β-Galactosidase activity was measured using the luminiscent Galacto-Star assay system (Tropix, Bedford, MA).

Apoptosis Assays. Ba/F3 and Ba/F3.TP cells were transiently transfected with expression vectors encoding for the indicated proteins together with the pEGFP expression vector encoding for the green fluorescence protein GFP. Determination of the fraction of transfected cells that had undergone apoptotic changes was as described (24).

Analysis of DNA laddering was done according to the procedure of Smith *et al.* (27).

RESULTS

Induction of NF-κB DNA Binding Activity by IL-3 and TP. To investigate the presence of an NF-κB binding activity in IL-3-treated Ba/F3 and IL-3-independent Ba/F3.TP cells, we analyzed nuclear extracts from both cell lines by EMSA using a ^{32}P-labeled oligonucleotide containing the NF-κB consensus sequence. Both extracts exhibited significant levels of NF-κB DNA binding activity, which appeared in the form of two bands corresponding to distinct DNA–protein complexes (C1 and C2) (Fig. 1*A*). The two complexes were NF-κB specific as they completely disappeared in the presence of a large excess of the unlabeled oligonucleotide containing the NF-κB motif, whereas the same excess of an unrelated oligonucleotide, AP1, was without effect.

To identify the subunits present in the two complexes, antibody supershift experiments were performed. Incubation of nuclear extracts from both Ba/F3 and Ba/F3.TP with anti-p50 antibody completely shifted the C1 and C2 complexes, indicating the presence of the p50 protein in both complexes. In contrast, the anti-p65 antibody shifted only the C1 complex. This allows us to identify the C2 complex as the p50 homodimer and the C1 complex as the p50/p65 heterodimer. These results indicate that a similar NF-κB DNA binding activity was present in IL-3-treated Ba/F3 cells as well as in IL-3-independent Ba/F3.TP cells.

To investigate whether IL-3 might regulate NF-κB activity, we also performed EMSA assays on nuclear extracts from Ba/F3 cells after IL-3 removal. As shown in Fig. 1*B*, NF-κB DNA binding activity was greatly reduced after IL-3 removal, which is consistent with the hypothesis that activation of IL-3 signaling pathways plays a role in mediating this NF-κB activity.

The tyrosine kinase activity of TP is an essential determinant of its transforming potency (18). To establish that NF-κB DNA binding activity in Ba/F3.TP cells requires the kinase activity of the PDGFRβ part of the fusion protein, we used the specific PDGFR kinase inhibitor CGP53716 (28), which completely inhibits the TP-associated tyrosine kinase activity (25). Interestingly, treatment of Ba/F3.TP with CGP53716 also had an inhibitory effect on NF-κB DNA binding activity. This effect is likely to be specific because CGP53716 is unable to inhibit NF-κB DNA binding activity that is mediated by IL-3 in Ba/F3 cells. In addition, IL-3 completely abolished the inhibitory effect of CGP53716 on TP-mediated NF-κB activity, further supporting our conclusion (Fig. 1*B*).

In another approach to assess the activity of NF-κB, we examined the abilities of either IL-3 or TP to activate an NF-κB-dependent reporter gene. Ba/F3 and Ba/F3.TP cells were transiently transfected with the (Igk)3-conaluc plasmid, a luciferase reporter construct containing three κB sites of the Ig κ chain enhancer upstream of the minimal conalbumin promoter (21). As shown in Fig. 1*C*, the luciferase activity measured in cells transfected with the (Igk)3-conaluc plasmid was about 10 fold higher than that measured in cells transfected with the control vector, in both Ba/F3.TP cells and IL-3-treated Ba/F3 cells. Consistent with the EMSA assays, a significant decrease in NF-κB transcriptional activity was observed in Ba/F3 cells after IL-3 removal or in Ba/F3.TP cells treated with CGP53716. As expected, CGP53716 had no effect on NF-κB transcriptional activity mediated by IL-3 in Ba/F3 cells, and its effect was reversed by addition of IL-3 in CGP53716-treated Ba/F3.TP cells. Taken together, these findings demonstrate the ability of IL-3 and TP to activate NF-κB in Ba/F3 cells and raise the interesting possibility that TP and IL-3 might converge to a common signaling pathway to promote NF-κB activation.

Induction of Apoptotic Cell Death Correlates with Inhibition of NF-κB Activity. During apoptosis, internucleosomal fragmen-

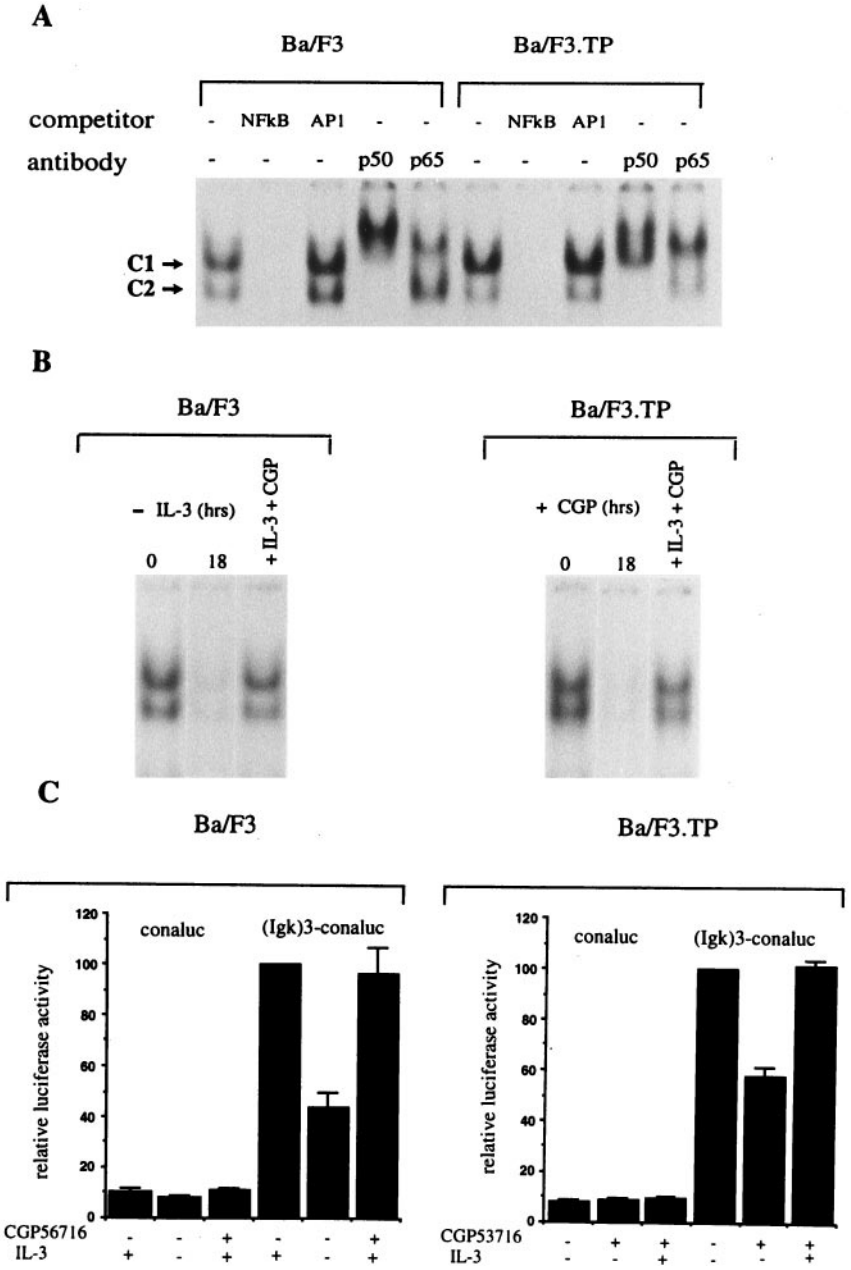

FIG. 1. Reduction of NF-κB activity by IL-3 deprivation of Ba/F3 cells or inhibition of the TP kinase of Ba/F3.TP cells. (*A*) EMSA of nuclear extracts from IL-3-treated Ba/F3 cells or Ba/F3.TP cells. (*B*) EMSA of nuclear extracts prepared 18 h after IL-3-deprivation or CGP53716 treatment of Ba/F3 cells or Ba/F3.TP cells, respectively. (*C*) Cells transfected with pCMV-β-gal together with (Igκ3) conaluc or control conaluc vector were maintained in the presence or absence of IL-3 or 0.3 μM CGP53716. Luciferase activity was measured in cell extracts 4 h after transfection. Results, are the means ± SEM of three independent experiments and are expressed as % of the maximal activity.

tation of nuclear DNA takes place, which results in a laddering pattern when analyzed by gel electrophoresis. To test a possible role of NF-κB in IL-3- and TP-mediated cell survival, we compared the kinetics of apoptotic progression to those of the inactivation of NF-κB. To this end, we used the Ba/F3 cells after removal of IL-3 and the Ba/F3.TP cells after treatment with CGP53716. In both cases, a decrease in NF-κB binding activity occurred (Fig. 2*A*), which preceded DNA laddering (Fig. 2*B*), suggesting that activation of NF-κB is a contributing factor to cell survival. Additional evidence for this conclusion derives from observations that IL-3 blocked the induction of apoptosis (Fig. 2*B*), whereas it restored NF-κB activity in CGP53716-treated Ba/F3.TP cells (Fig. 1).

To provide further evidence for the involvement of NF-κB in IL-3- and TP-mediated cell survival, we used different agents known to inhibit NF-κB activation. The proteasome inhibitor Z-AL has been described as a very potent inhibitor of this activation (29). To determine the importance of NF-κB signaling pathways for the induction of cell survival by IL-3 and TP, we tested the ability of Z-AL to reduce NF-κB activity and to induce apoptosis in Ba/F3 cells. DNA laddering analysis revealed that Z-AL provided a concentration- and time-dependent suppressive effect on IL-3- and TP-mediated cell survival (Fig. 3 *A* and *B*). Apoptosis was also observed upon treatment of cells with other inhibitors of NF-κB activation (i.e., pyrrolidine dithiocarbamate, aspirin, and sodium salicylate) (ref. 30 and results not shown). The proteasome inhibitor Z-AL caused a strong decrease in NF-κB DNA binding activity induced by IL-3 in Ba/F3 and by TP in Ba/F3.TP cells (Fig. 3*C*). Here again, inhibition of NF-κB activity preceded DNA fragmentation. These initial experiments further support the view that activation of NF-κB signaling pathways may indeed contribute to the induction of cell survival by IL-3 and TP.

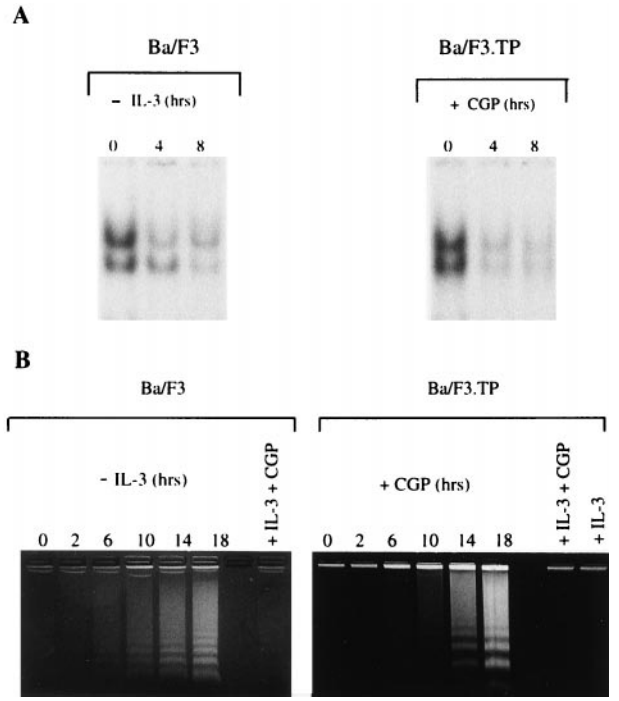

FIG. 2. Kinetics of inhibition of NF-κB activity and induction of apoptosis by IL-3 deprivation of Ba/F3 cells or CGP53716 treatment of Ba/F3.TP cells. (*A*) EMSA of nuclear extracts prepared at different times after IL-3 deprivation of Ba/F3 cells or CGP53716 treatment of Ba/F3.TP cells. (*B*) Cytoplasmic small fragmented DNA assay of control and IL-3-deprived Ba/F3 cells or CGP53716-treated Ba/F3.TP cells. Treatment with IL-3 and/or CGP53716 was performed for 18 h. These are representative experiments independently performed three times.

Overexpression of a Super Repressor Form of IκBα Suppresses the Survival Signal Mediated by IL-3 and TP. To demonstrate that activation of NF-κB is required for IL-3- or TP-induced protection of Ba/F3 cells against apoptosis, we transfected Ba/F3 and Ba/F3.TP cells with an expression vector encoding IκBα (A32/36), a super repressor form of IκBα (22), or with a control pCMV vector. Both were added together with a construct encoding GFP, allowing for the identification of transfected cells and showing that the transfection efficiency was similar (14%) in the control pCMV- and the IκBα (A32/36)-transfected cells. The IκBα (A32/36) contains serine-to-alanine mutations at residues 32 and 36, which confer resistance to signal-induced phosphorylation and subsequent proteasome-mediated degradation. It still binds to NF-κB and therefore behaves like a constitutive repressor of NF-κB activity. Indirect immunofluorescent staining using anti-IκBα antibodies revealed that the overexpression of IκBα correlated with GFP expression (not shown). As shown in Fig. 4*A*, transfection of Ba/F3 or Ba/F3.TP cells with the expression vector encoding IκBα (A32/36) resulted in morphological changes characteristic of apoptosis (i.e., condensation and fragmentation of the nucleus). The nuclei of cells cotransfected with the vector encoding GFP and the control pCMV vector were indistinguishable from the nuclei of the surrounding nontransfected cells.

To quantitate these results, we counted the number of apoptotic cells in the population of transfected cells. Over 50% of Ba/F3 cells transfected with the vector encoding for IκBα (A32/36) showed apoptosis, whereas less than 10% of cells transfected with the pCMV control vector exhibited apoptotic morphology (Fig. 4*B*). A similar result was observed in Ba/F3.TP cells. These findings strongly support the conclusion that NF-κB signaling is required for cell survival mediated by IL-3 and TP in Ba/F3 cells.

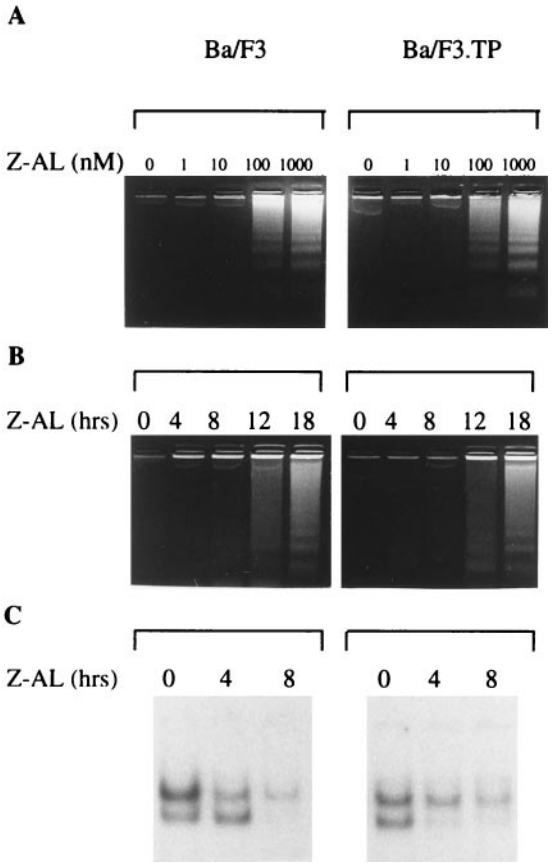

FIG. 3. Induction of apoptosis of Ba/F3 and Ba/F3.TP cells by the proteasome inhibitor Z-AL. (*A*) Cells were treated with different concentrations of Z-AL for 18 h, and apoptosis was determined by DNA fragmentation. (*B*) Kinetics of induction of apoptosis by 1 μM Z-AL. (*C*) EMSA of nuclear extracts prepared from Ba/F3 and BA/F3.TP cells treated for different times with 1 μM Z-AL.

Induction of Apoptosis in Ba/F3 and Ba/F3.TP Cells by a Dominant-Negative Form of c-Myc. Another important function of IL-3 and TP is to increase the expression of the c-Myc protooncogene, a transcription factor that is implicated in the control of normal cell proliferation and induction of neoplasia (25, 31). Similar to the effects on NF-κB activity, IL-3 deprivation of Ba/F3 cells or exposure of Ba/F3.TP cells to CGP53716 strongly decreased c-Myc expression (25). These results and recent observations that c-Myc expression is under NF-κB control and is essential for WEHI 231 cell survival (32, 33) prompted us to test whether inactivation of c-Myc alone is sufficient to mediate apoptosis even when the activity of other NF-κB-responsive genes is unchanged. Thus, Ba/F3 cells were cotransfected with a vector encoding GFP and an expression vector encoding a dominant-negative mutant of c-Myc (MycRX) (23) or with the control pBabe vector. The MycRX mutant contains the helix—loop–helix domain of Max, which blocks the transcriptional activity of c-Myc. Transfection of both Ba/F3 and Ba/F3.TP with the control pBabe vector did not induce apoptotic cell death as revealed by Hoechst staining of nuclei of GFP-positive cells. In contrast, both cell lines transfected with the pEGFP vector, and the construct encoding MycRX exhibited an enhanced proportion of apoptotic nuclei. A quantitative representation of these data is shown in Fig. 5. The strong dominant-negative effect of MycRX on survival of Ba/F3 and Ba/F3.TP suggests that active c-Myc is required in NF-κB-mediated antiapoptotic signaling that is triggered by IL-3 and TP.

DISCUSSION

Apoptosis is governed by families of proteins acting sequentially along a programmed pathway. In the present studies, we

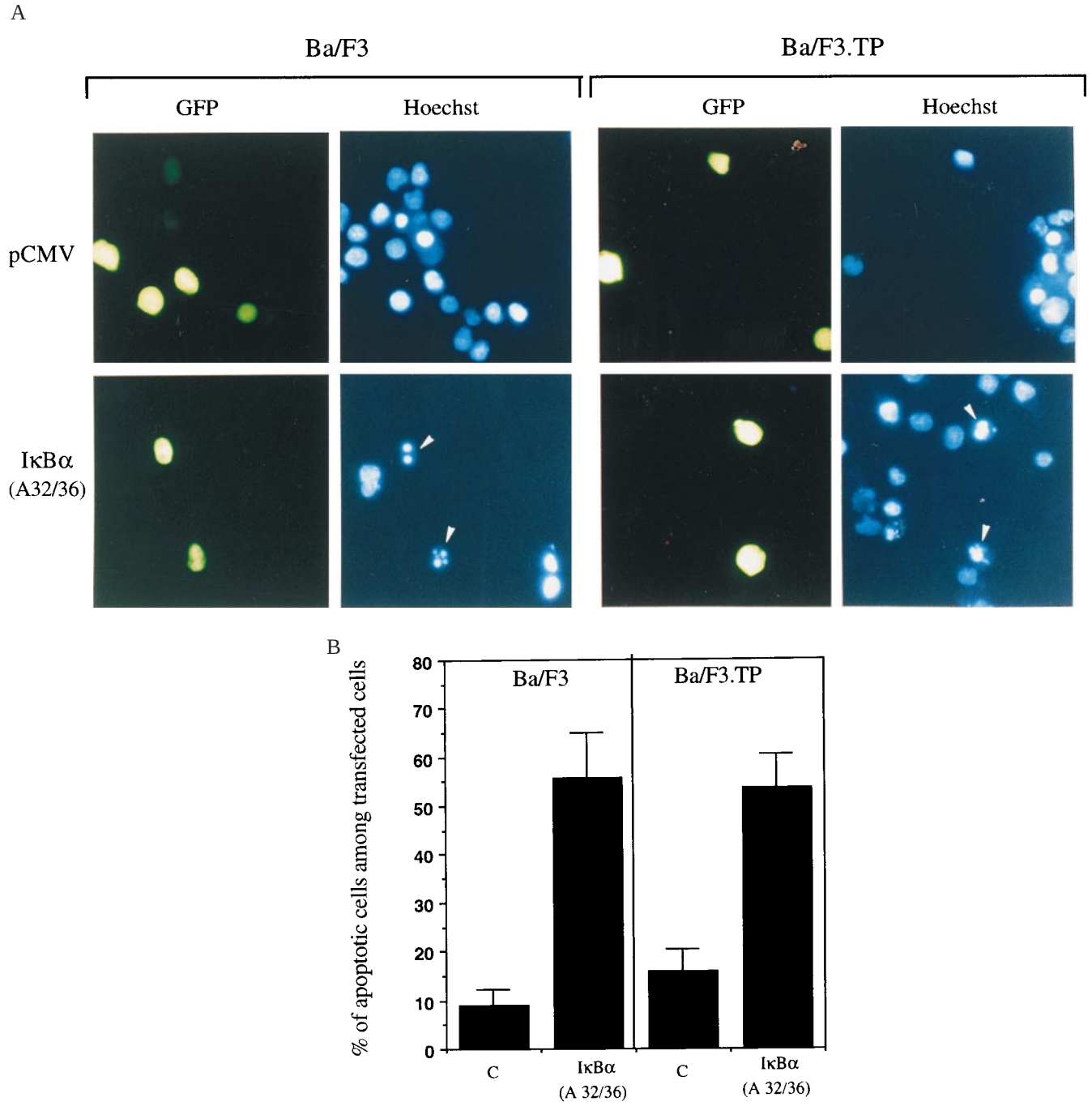

FIG. 4. Induction of apoptosis of Ba/F3 and Ba/F3.TP cells by the IκBα (A32/36) mutant. (*A*) Cells were transfected with 10 μg of the IκBα (A32/36) mutant or the same amount of the corresponding empty vector together with 5 μg of pEGFP plasmid. Ba/F3 and Ba/F3.TP cells were then cultured for 18 h in the presence or in the absence of IL-3, respectively, before evaluation of chromatin alteration by Hoechst staining. Arrows indicate apoptotic nuclei. (*B*) Quantification of apoptosis in control and IκBα (A32/36) transfected cells. Results are expressed as the percentage of apoptotic nuclei in transfected cells and represent the means ± SEM of three independent experiments. An average of 300 transfected cells were examined in each experiment.

demonstrate a central role for NF-κB activity in the survival of IL-3-dependent hematopoietic cells. We show that NF-κB is constitutively expressed in Ba/F3 cells cultured in the presence of IL-3 and that NF-κB activity declines when the cells are deprived of cytokine and commence the process of apoptosis. In addition, we have observed that expression of the oncogenic fusion protein TP, which allows Ba/F3 cells to survive in the absence of IL-3, also results in NF-κB activity. Treatment of Ba/F3.TP cells with a specific inhibitor of the PDGFRβ tyrosine kinase results in a decrease of NF-κB activity accompanied by apoptotic cell death. Inhibition of NF-κB by inhibitors of IκB degradation also induces apoptosis in both Ba/F3 and Ba/F3.TP cells, thus reinforcing the arguments for the antiapoptotic function of NF-κB in these cells. Furthermore, overexpression of a nondegradable form of IκB, which inhibits NF-κB activity, greatly increases apoptosis in both Ba/F3 and Ba/F3.TP cells. All our results are in agreement with the conclusion that NF-κB is an essential mediator of the antiapoptotic signals delivered by IL-3 and by TP. We have observed that NF-κB activity was also present in Ba/F3 cells expressing TEL/ABL or BCR/ABL(p210) fusion proteins and that the proteasome inhibitor Z-AL induced apoptosis in these cells (unpublished results). These results and the fact that BCR/ABL(p210) has recently been shown to activate p65 NF-κB

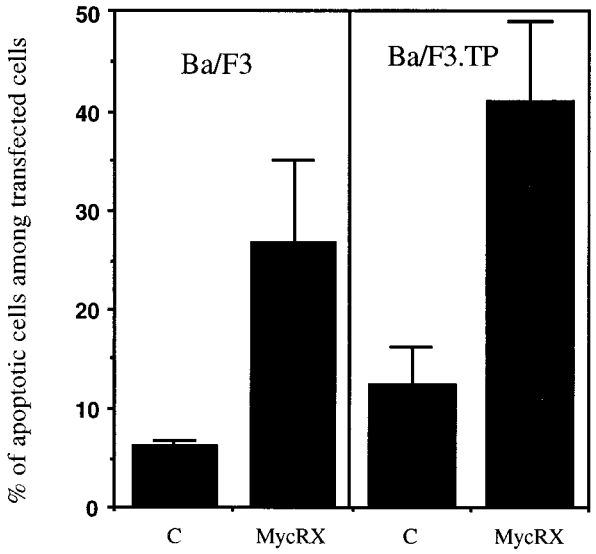

FIG. 5. Induction of apoptosis of Ba/F3 and Ba/F3.TP cells by a dominant-negative mutant of c-Myc. Cells were transfected with 10 μg of the MycRX encoding vector or the same amount of the pBabe empty vector together with 5 μg of pEGFP plasmid. Cell culture and quantification of apoptosis were performed as described in the legend to Fig. 4.

protein (34) raise the possibility that NF-κB activation is a survival signal common to many oncogenic proteins that result from chromosomal translocations.

The signal transduction process implicated in NF-κB activation by IL-3 and TP remains to be established. Many components from signaling pathways that lead to the phosphorylation of IκBα and activation of NF-κB have been described. These include tyrosine phosphorylation events, activation of the Ras–Raf pathway, protein kinase C, and double-stranded RNA-dependent kinase (for review, see ref. 9). As Raf activation by IL-3 has been demonstrated, this pathway could be involved in NF-κB activation. Recently, the PI3-kinase and its downstream target AKT have been implicated in an antiapoptotic effect of IL-3 (4, 5). It would thus be of interest to study whether PI3-kinase is involved in NF-κB activation or whether NF-κB and PI3-kinase constitute independent pathways leading to cell survival.

Like NF-κB, the c-Myc protein has also been implicated in the regulation of cell death, and opposing effects have been reported. Overexpression or inappropriate expression of c-Myc promotes apoptosis in myeloid and fibroblast cells upon removal of factors required for cell proliferation (35, 36). In contrast, several studies on immature B cell models of tolerance have correlated the drop in c-Myc expression with induction of apoptosis (reviewed in ref. 15). In accordance with these observations, we observed that expression of a dominant-negative mutant of c-Myc induced apoptosis in Ba/F3 and Ba/F3.TP cells. Because c-Myc is transcriptionally regulated by NF-κB, our results suggest that the c-Myc protein is a downstream target of NF-κB and is implicated in the promotion of both the survival of normal hematopoietic cells and their transformation.

Uncontrolled cell proliferation has long been thought to be the primary reason for the development of cancer. However, it becomes increasingly evident that the prevention of cell death is an equally important event in oncogenesis. Our findings suggest that NF-κB could be a target for therapeutic intervention in several hematological malignancies.

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