Bcl3, an IκB Protein, Stimulates Activating Protein-1 Transactivation and Cellular Proliferation*

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Bcl3, an IκB protein, was originally isolated as a putative proto-oncogene in a subset of B cell chronic lymphocytic leukemias. Bcl3 was subsequently shown to associate tightly with and transactivate the NFκB p50 or p52 homodimer. Herein, we show that Bcl3 stimulates the activating protein-1 (AP-1) transactivation, either alone or in conjunction with transcription integrators steroid receptor coactivator-1 and CREB-binding protein/p300. The C-terminal 158 residues of Bcl3 exhibited an autonomous transactivation function and interacted with specific subregions of the AP-1 components c-Jun and c-Fos, CREB-binding protein/p300, and steroid receptor coactivator-1, as demonstrated by the yeast and mammalian two-hybrid tests as well as glutathione S-transferase pull-down assays. In addition, anti-HA antibody co-precipitated c-Jun from HeLa cells co-expressing c-Jun and HA-tagged Bcl3, consistent with the idea that Bcl3 directly associates with AP-1 in vivo. Furthermore, microinjection of Bcl3 expression vector into Rat-1 fibroblast cells significantly enhanced DNA synthesis and expression of c-jun, one of the cellular target genes of AP-1. These results suggest that Bcl3 may directly participate in the tumorigenesis processes as a novel transcription coactivator of the mitogenic transcription factor AP-1 in vivo.

The activation protein-1 (AP-1)* transcription factors are immediate early response genes involved in a diverse set of transcriptional regulatory processes, including activation of genes critical for cell proliferation (reviewed in 1). The AP-1 complex consists of a heterodimer of a Fos family member and a Jun family member. This complex binds the consensus DNA sequence (TGAGTCA) (termed AP-1 sites) found in a variety of promoters. The Fos family contains four proteins (c-Fos, Fos-B, Fra-1, and Fra-2), while the Jun family is composed of three (c-Jun, Jun-B, and Jun-D). Fos and Jun are members of the basic leucine zipper (bZIP) family of sequence-specific dimeric DNA-binding proteins (2). The C-terminal half of the bZIP domain is amphipathic, containing a heptad repeat of leucines that is critical for the dimerization of bZIP proteins. The N-terminal half of the long bipartite α-helix is the basic region that is critical for sequence-specific DNA binding.

Transcription coactivators bridge transcription factors and the components of the basal transcriptional apparatus (3). In particular, the functionally conserved proteins CREB-binding protein (CBP) and p300 have been shown to be essential for the activation of transcription by a large number of regulated transcription factors, including AP-1 (4). Similarly, it was recently shown that steroid receptor coactivator-1 (SRC-1) (5), originally isolated as a transcription coactivator of nuclear receptors, also stimulates transactivation by many different transcription factors such as NFκB (6), AP-1 (7), SRF (8), p53 (9), CREB and signal transducers and activators of transcription (10). Based on this rather broad spectrum of action, SRC-1 and CBP/p300 were named transcription integrators. Interestingly, SRC-1 (11) and its homologue ACTR (12), along with CBP and p300 (13, 14), were recently shown to contain histone acetyltransferase activities themselves and associate with yet another histone acetyltransferase protein pCAF (15). In contrast, it was shown that SMRT (16) and N-CoR (17), nuclear receptor corepressors, form complexes with Sin3 and histone deacetylase proteins (18, 19). From these results, chromatin remodeling through histone acetylation-deacetylation was suggested to play an important role in transcription cofactor-mediated transcriptional regulation.

Bcl3 belongs to a family of IκB proteins that also include IκBo, IκBβ, IκBγ, p105, and p100 (reviewed in Ref. 20). These proteins have been shown to modulate transactivation by NFκB, which is important for the inducible expression of a wide variety of cellular and viral genes (reviewed in Ref. 21). Bcl3 was originally isolated as a gene, which was recurrently translocated into the immunoglobulin α locus and highly expressed in a subset of B cell chronic lymphocytic leukemias (22). However, it is currently uncertain whether the translocated and overexpressed Bcl3 directly contributes to the development of this disease. Bcl3 was shown to be a nuclear protein and associate tightly with p50 or p52 homodimers in cells (23, 24). The tethering of Bcl3 to DNA via the p50/p52 homodimers allowed Bcl3 to transactivate directly, while p50/p52 homodimers alone were inert (23, 24). Recently, mice with a targeted disruption in Bcl3 were shown to have immunological defects similar to but distinct from that observed in the p50(−/−) mice, suggesting that Bcl3 could function independently of p50 in vivo (25).

Indeed, we have recently shown that Bcl3 can function as a novel transcription coactivator of retinoid X receptor (RXR) (26). RXR belongs to a family of ligand-dependent transcr-
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Ankyrin repeats of Bcl3 are stippled. Numbers represent amino acids of Bcl3 included in each construct. B, CV1 cells were transfected with 100 ng of lacZ expression vector and vectors expressing various Gal4 and VP16 fusion proteins along with 100 ng of a reporter gene Gal4-Luc (28), as indicated. Normalized luciferase expressions from triplicate samples are presented relative to the lacZ expressions, and the S.D. values are less than 5%. The representative results of three independent experiments are shown here.

RESULTS

Bcl3 Binds to the bLZ Domains of c-Jun and c-Fos—A series of deletion mutants for Bcl3 are schematically shown in Fig. IA. A Gal4 fusion to the full-length Bcl3 or the Bcl3 residues 1–157 (i.e. BclΔ1) showed consistently lower transactivation potential than the basal activity directed by Gal4-DNA binding domain alone (i.e. Gal4/N) in CV1 cells. These results suggested that the full-length Bcl3 or BclΔ1 contained a transcriptionally repressive domain (Fig. 1B). However, this repression of the basal activity was not observed with a mutant form of Bcl3 that lacks the N-terminal 157 residues of Bcl3 (i.e. BclΔ2). Interestingly, BclΔ3 that consists of the Bcl3 residues 289–446 exhibited an autonomous transactivation function. Overall, these results suggest the presence of two independent repressor domains in the N-terminal and central regions of Bcl3 (i.e. the Bcl3 residues 1–157 and 156–289, respectively) as well as a cryptic autonomous transactivation domain at the C terminus (i.e. the Bcl3 residues 289–446). Co-expression of VP16/c-Jun or VP16/c-Fos further enhanced the transactivation mediated by Gal4/Bcl3 but not Gal4/BclΔ1, indicating that the C-terminal region of Bcl3 (i.e. the Bcl3 residues 289–446) constitutes the interaction interface with c-Jun and c-Fos. Interestingly, the transactivation mediated by Gal4 fusions to Bcl3 and BclΔ2, although it contained this C-terminal interaction interface, was not stimulated by co-expression of either of these VP16 fusion proteins. This might have been caused by the N-terminal and central repressive domains of Bcl3, which may actively prohibit the function of transactivation domain VP16 and thus preclude detection of the interactions with Bcl3 and BclΔ2. A series of deletion mutants for c-Jun and c-Fos are schematically shown in Fig. 2A. In yeast, the full-length Bcl3, BclΔ2, and BclΔ3 but not BclΔ1 were found to specifically

EXPERIMENTAL PROCEDURES

Plasmids—LexA, B42, T7, or glutathione-S-transferase (GST) vectors expressing various Bcl3 and SRC-1 proteins were as recently described (6–9, 26). GST fusion constructs to express CBP1, CBP2, CBP3, CBP4, and CBP5 were kind gifts of Dr. Chris Glass (University of California, San Diego). Polymerase chain reaction-amplified fragments of BclΔC1, BclΔC2, BclΔC3, BclΔ1, BclΔ2, and BclΔ3 were subcloned into EcoRI–XhoI restriction sites of the Gal4 fusion vector pCMXGal4/N (28). Polymerase chain reaction-amplified fragments of various c-Jun and c-Fos constructs were subcloned into EcoRI–XhoI restriction sites of the Gal4 fusion vector pCMXGal4/N (28), the B42 fusion vector pJG4–5 (28), the VP16 fusion vector pCMVP16 (28), the B42 fusion vector pJG4–5 (28), and the GST fusion vector pGEX4T (Amersham Pharmacia Biotech), along with the CMV/T7 vector pcDNA3 (Invitrogen, San Diego, CA). Polymerase chain reaction-amplified fragments of p300N (the p300 residues 1–117), p300C (the p300 residues 2041–2157), and CBP-C (the CBP residues 1868–2441) were subcloned into EcoRI–XhoI restriction sites of the B42 fusion vector pJG4–5 (29). The expression vectors for Bcl3, c-Fos, c-Jun, p300, and SRC-1; the transfection indicator construct pRSV-β-gal; the AP-1-responsive reporter construct TRE-Luc; and the Gal4-responsive reporter construct Gal4-Luc were as described previously (7, 8, 26). A polymerase chain reaction-amplified full-length Bcl3 containing EcoRI–XhoI restriction sites was subcloned into EcoRI–XhoI restriction sites of the HA-tagging vector pcDNA3-HA, a kind gift from Dr. Yong-Kuen Jung (KJIST, South Korea), to express HA-tagged Bcl3 (HA-Bcl3).

Yeast Two-hybrid Tests—For the yeast two-hybrid tests, plasmids encoding LexA fusions and B42 fusions were co-transformed into Saccharomyces cerevisiae EGY48 strain (29), containing the lacZ reporter plasmid, SH18–34. Plate and liquid assays of lacZ expression were carried out as described (29).

GST Pull-down Assays—The GST fusions or GST alone were expressed in E. coli (strain DH5α) transformed with expression vectors for c-Jun and HA-tagged Bcl3 as described (29). These extracts were subjected to Western analyses with c-Jun antibody (Santa Cruz Biotechnology, Inc., Santa Cruz, CA) or immunoprecipitation with a monoclonal antibody against HA (Roche Molecular Biochemicals) followed by Western analyses with c-Jun antibody.

Cell Culture and Transfections—CV1 or HeLa cells were grown in 24-well plates with medium supplemented with 10% charcoal-stripped serum for 24 h and transfected with expression vectors and a reporter gene as indicated. After 12 h, cells were washed and refed with Dulbecco’s modified Eagle’s medium containing 10% charcoal-stripped fetal bovine serum either in the presence or absence of the indicated amount of TPA. Cells were harvested 24 h later, and luciferase activity was assayed as described (29), and the results were normalized to the lacZ expression.

Immunofluorescence—Rat-1 fibroblast cells were microinjected with
interact with c-Jun, JunΔ3, c-Fos, and FosΔ2 but not with JunΔ1, JunΔ2, FosΔ1, and FosΔ3 (Table I). These interactions were also confirmed in *in vitro* experiments, in which various GST fusion proteins were expressed, purified, and tested for interaction with an *in vitro* translated Bcl3. Consistent with the yeast results, Bcl3 specifically interacted with GST fusions to c-Jun, JunΔ3, c-Fos, and FosΔ2 but not with GST alone or GST fusions to JunΔ1, JunΔ2, FosΔ1, and FosΔ3 (Fig. 2B). From these results, we concluded that the C-terminal region of Bcl3 binds to the c-Jun residues 238–334 and the c-Fos residues 115–271, each containing the previously described bZIP domain (2). The association of Bcl3 and c-Jun was also confirmed in *in vitro* experiments, as demonstrated by immunoprecipitation experiments in which c-Jun was co-precipitated with HA-monoclonal antibody from cells co-expressing c-Jun and HA-Bcl3 but not from cells expressing c-Jun alone (Fig. 2C). Similarly, HA-Bcl3 bound glutathione-Sepharose-4B beads from cells co-expressing GST-c-Jun but not GST alone.

**Bcl3 Coactivates the AP-1 Transactivation**—To assess the functional consequences of these interactions, Bcl3 was co-transfected into HeLa or CV1 cells along with a reporter construct controlled by TRE. Either TPA treatment or co-expression of c-Fos was previously shown to efficiently activate transactivation of this reporter construct (31). Increasing amounts of cotransfected Bcl3 enhanced the TPA- or c-Fos-induced transactivation in a dose-dependent manner (Fig. 3A, A and C). In contrast, cotransfection of Bcl3 did not affect the basal level of transactivation, the transcriptional activity of Gal4-VP16 (as assessed using the Gal4-Luc reporter construct), or the lacZ expression of the transfection indicator construct pRSV-β-gal in the presence or absence of TPA (results not shown). Interestingly, mutant Bcl3 constructs deleted for the C-terminal regions (i.e., Bcl3ΔC1, Bcl3ΔC2, and Bcl3ΔC3) (Fig. 3B) were as effective as the wild type Bcl3 in coactivating the AP-1 transactivation (Fig. 3C). In contrast, Bcl1A, Bcl12, and Bcl3 were inert, indicating that the Bcl3 residues 1–365 are essential for the AP-1 coactivation (Fig. 3C). Overall, these

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Bcl3, Bcl less than 5%. The representative results of three independent experiments are presented relative to the presence or absence of 50 ng of c-Fos, along with a reporter gene TRE-Luc (31), expression vector encoding Bcl3, SRC-1, or p300, either in the presence of 50 μg of Bcl3. CV1 cells were transfected with 100 μg of lacZ labeled proteins used in the binding reactions were loaded as inputs. cAilically bound material was eluted with reduced glutathione and resolved in vitro. CBP-1, CBP-2, CBP-3, CBP-4, and CBP-5 but not with CBP-2, whereas Bcl3 was recently shown to interact with CBP and SRC-1. Bcl3 Functionally Interacts with Transcriptional Integrators SRC-1 and CBP/p300—Bcl3 was recently shown to interact with RXR and stimulate its transactivation in synergy with SRC-1 (26). Consistent with these results, we found that SRC-1 directly interacts with Bcl3. In yeast, the Bcl3 interaction regions include SRC-A (the SRC-1 residues 1–361), SRC-D (the SRC-1 residues 759–1141), and SRC-E (the SRC-1 residues 1101–1441) (Table I). The C-terminal subregion of CBP (4) was also found to interact with Bcl3 (i.e. CBP-C, the CBP residues 1868–2441). In contrast, Bcl3 was not able to interact with the N-terminal nuclear receptor binding domain and the C-terminal SRC-1 binding domain of p300 (i.e. p300N and p300C, respectively). Similar results were also obtained with Bcl3Δ3, except that the interaction with SRC-A was not detected, suggesting that the interaction with SRC-A should involve the N-terminal region of Bcl3 (i.e. the Bcl3 residues 1–289). Unexpectedly, however, these interactions were not evident with Bcl3 in yeast. These interactions were also examined in in vitro experiments, in which various GST fusion proteins were expressed, purified, and tested for interaction with an in vitro translated Bcl3 or SRC-1 proteins (Fig. 4A). In contrast to the original observation made in the yeast two-hybrid tests (Table I), the CBP-Bcl3 interactions involved more than the C terminus of CBP. The full-length Bcl3 specifically interacted with CBP-1, CBP-3, CBP-4, and CBP-5 but not with CBP-2, whereas Bcl3Δ1 interacted only with CBP-1 and CBP-3. The CBP action profile of Bcl3 was similar to that of the full-length Bcl3 (results not shown). Consistent with the yeast results, however, Bcl3 specifically interacted with the full-length SRC-1, SRC-A, SRC-D, and SRC-E but not with SRC-B and SRC-C (Fig. 4A). Overall, these results, along with the yeast two-hybrid data, indicate that Bcl3 binds to specific subregions of SRC-1 and CBP/p300.

Cotransfection of SRC-1 or p300 alone stimulated the c-Fos-dependent transactivation, as previously shown (7, 32). In addition, co-expression of Bcl3 further stimulated the SRC-1- or p300-enhanced, c-Fos-dependent transactivation (Fig. 4B). These results clearly demonstrate that Bcl3 can coactivate the AP-1 transactivation in cooperation with SRC-1 and p300.

Bcl3 Enhances c-Jun Expression and DNA Synthesis—Next, we have tested whether this Bcl3-mediated coactivation of the AP-1 transactivation affects expression levels of c-Jun in vivo, which contains upstream AP-1 binding sites (33). As shown in Fig. 5A, microinjection of Bcl3-expression vector into Rat-1 fibroblast cells (30) led to increased expressions of c-Jun protein, as assessed by immunostaining with anti-c-Jun antibody. Since AP-1 is a strong mitogenic factor, the putative effects of the Bcl3-mediated AP-1 coactivation were also examined with regard to proliferation potentials. To our surprise, microinjection of Bcl3 expression vector into Rat-1 fibroblast cells enhanced the cellular DNA synthesis activities, as shown by stimulated BrdUrd incorporation (Fig. 5B) and thymidine incorporation (results not shown). In contrast, microinjection of pcDNA3 affected neither c-Jun expression nor DNA synthesis. A relatively high basal level of c-Jun expression as well as DNA synthesis was observed under the experimental conditions we employed, resulting in low-fold increases upon Bcl3 expressions (i.e. only approximately 2.5-fold increase in both cases). However, it was interesting to note that immunostainings for both c-Jun expression and DNA synthesis became dramatically intensified in quality as cells expressed Bcl3 (Fig. 5). From these results, we concluded that Bcl3 stimulates the AP-1 transactivation in vivo and enhances proliferation potential of cells.

**DISCUSSION**

Bcl3 exhibits properties consistent with its potential role as a transcription coactivator, bridging transcription factors to the basal transcription machinery. First, Bcl3 directly interacts with target transcription factors, including p50/p52 homodimers (23, 24), RXR (26), and AP-1 (Table I and Figs. 1 and 2). Second, Bcl3 physically associates with general transcription factors such as TFIIIB, TBP, and TFIIA (26). Third, Bcl3 functionally interacts with transcription integrators SRC-1 and CBP/p300 (Table I and Fig. 4) and contains an autonomous transactivation function (Ref. 26 and Fig. 1).

The AP-1 interaction interface was localized to the region from Bcl3 residue 289 to the C terminus (Table I and Fig. 1). Since Bcl3Δ3 (i.e. the Bcl3 residues 1–365) suffices to coactivate the AP-1 transactivation, the AP-1 interaction interface may localize to the Bcl3 residues 289–365, which include the Bcl3 ankyrin repeats 6 and 7 (Fig. 1A). Interestingly, the autonomous transactivation function of Bcl3 was previously mapped to the Bcl3 residues 156–289 in yeast (26), whereas it was localized to the C-terminal region of Bcl3 (i.e. the Bcl3 residues 289–446) in mammalian cells (Fig. 1B). This discrepancy is likely to have reflected some fundamental differences between yeast and mammalian transcription machinery. The autonomous transactivation functions of Bcl3 (particularly in mammalian cells) as well as the Bcl3-mediated coactivation of AP-1 transactivation may involve recruitment of other essential transcription coactivators such as CBP/p300 and SRC-1. Consistent with this notion, Bcl3 was shown to functionally
cooperate with SRC-1 and CBP/p300 to coactivate the AP-1 transactivation (Fig. 4). Finally, it is interesting to note that Bcl3 contains a number of putative phosphorylation sites, including TPA-responsive MAP kinase sites (for a review, see Ref. 34). There is an exciting possibility that signal-dependent modification of Bcl3 such as phosphorylation may play an important role in stimulating the AP-1 transactivation.

Cross-communications between distinct signaling pathways that lead to combinatorial controls are becoming a common theme in the area of transcriptional regulations and could involve a complex array of different mechanisms. Competition for a limiting amount of common transcription coactivators could serve as an important mechanism, for instance. Bcl3 targets at least three different transcription factors, AP-1, RKK, and the NF-xB p50/p52 homodimers. Therefore, Bcl3 may be involved with the mutually antagonistic interactions between RXX and either NF-xB (35) or AP-1 (for a review, see Ref. 36). Regarding the proliferative function of ectopically expressed Bcl3 (Fig. 5), it is interesting to note that AP-1 and NF-xB may be known to be proproliferative (1, 37). In addition, overexpressed Bcl3 may also oppose the antiproliferative action of retinoids, by relieving the retinoid/RXR-mediated inhibition of AP-1 and NF-xB. These possibilities are currently under investigation.

In conclusion, we have shown that Bcl3 enhances proliferation as a novel transcription coactivator of the mitogenic transcription factor AP-1. Consistent with our results, granulocyte-macrophage colony-stimulating factor and erythropoietin were recently shown to markedly enhance Bcl3 expression in association with stimulation of proliferation (38). Similarly, transgenic mice overexpressing Bcl3 developed normally but showed splenomegaly and accumulation of mature B cells in lymph nodes, bone marrow, and peritoneal cavity (39). These results, along with ours, strongly suggest that Bcl3 should be directly involved with the tumorigenesis processes in a subset of B cell chronic lymphocytic leukemias, in which Bcl3 is recurrently translocated and highly expressed. Thus, further studies of Bcl3 should provide important insights into transcriptional regulatory mechanisms as well as the tumorigenesis processes.

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