We have recently shown that the IkB protein Bcl3 interacts with the retinoid X receptor (RXR) and inhibited the 9-cis-retinoic acid (RA)-dependent transactivations (Na, S.-Y., Kim, H.-J., Lee, S.-K., Choi, H.-S., Na, D. S., Lee, M.-O., Chung, M., Moore, D. D., and Lee, J. W. (1998) J. Biol. Chem. 6, 3212–3215). Herein, we show that a distinct IkB protein Bcl3 also interacts with RXR, as shown in the yeast two-hybrid tests and glutathione S-transferase pull-down assays. The Bcl3 interaction involved two distinct subregions of RXR, i.e. constitutive interactions of the N-terminal ABC domains and 9-cis-RA-dependent interactions of the C-terminal DEF domains. In contrast to IkBa, Bcl3 did not interact with the AF2 domain of RXR. Bcl3 specifically interacted with the general transcription factors TFIIIB, TBP, and TFIIIA but not with TFIIIEe in the GST pull-down assays. TBP and TFIIA, however, were not able to interact with IkBa. Accordingly, Bcl3 coactivated the 9-cis-RA-induced transactivations of RXR, in contrast to the inhibitory actions of IkBa. In addition, coexpression of SRC-1 but not p300 further stimulated the Bcl3-mediated enhancement of the 9-cis-RA-induced transactivations of RXR. These results suggest that distinct IkB proteins differentially modulate the 9-cis-RA-induced transactivations of RXR in vivo.

The nuclear receptor superfamily is a group of transcriptional regulatory proteins linked by a series of conserved structure and function (for a review see Ref. 1). These include six regions of the primary structure, commonly referred to as regions A through F. The N-terminal half of the receptor contains the A/B region, which is highly variable in sequence and length. Region C, the DNA-binding domain, harbors two type II zinc fingers and is highly conserved, whereas region D, also called the hinge domain, is highly variable in length and sequence. The C-terminal half of the receptor contains the E and F regions, which harbor the ligand-binding domain (LBD) and the C-terminal activation function 2 (AF2), respectively. The superfamily includes receptors for a variety of small hydrophobic ligands such as steroids, T3, and retinoids, as well as a large number of related proteins that do not have known ligands, referred to as orphan nuclear receptors (for a review see Ref. 2). The receptor proteins are direct regulators of transcription that function by binding to specific DNA sequences named hormone response elements in promoters of target genes. Transcriptional activation of nuclear receptors involves at least two separate processes: derepression and activation (2). Derepression is mediated in part by interaction of unliganded receptors with corepressors such as N-CoR (3) and SMRT (4). However, ligand binding triggers dissociation of these corepressors and concomitant recruitment of coactivators. These putative coactivators include RIP-140/RIP160 (5, 6), ERAP-140/ERAP-160 (7), TIF1 (8), TRIP1 (9), ARA70 (10), and CBP/p300 (11–13), as well as a group of highly related proteins, SRC-1 (14), AIB1 (15), TIF2 (16), RAC3 (17), ACTR (18), TRAM-1 (19), p/CIP (20), and xSRC-3 (21). Functional analysis of nuclear receptors has shown that there are two major activation domains. The N-terminal domain (AF1) contains a ligand-independent activation function, whereas the extreme C-terminal region (AF2) of the LBD exhibits ligand-dependent transactivation (1). Recent x-ray crystallographic studies of the LBD of nuclear receptors revealed that the ligand binding induces a major conformational change in the AF2 region (22–24), suggesting that this region may play a critical role in mediating transactivation by a ligand-dependent interaction with coactivators. These coactivators are postulated to function to transmit the signal of ligand-induced conformational change to the basal transcription machinery. As expected, many coactivators fail to interact with AF2 mutants of nuclear receptors (5, 8, 16).

The transcription factor NFkB is important for the inducible expression of a wide variety of cellular and viral genes (reviewed in Refs. 25 and 26). NFkB is composed of homo- and heterodimeric complexes of members of the Rel/NFkB family of polypeptides. In vertebrates, this family comprises p50, p65 (RelA), c-Rel, p52, and RelB. These proteins share a 300-amino acid region, known as the Rel homology domain, which binds to DNA and mediates homo- and heterodimerization. This domain also is target of the IkB inhibitors, which include IkBa, IkBx, IkBz, IkBy, Bcl3, p105, and p100 (27). In the majority of cells, NFkB exists in an inactive form in the cytoplasm, bound to the inhibitory IkB proteins. Treatment of cells with various inducers results in the degradation of IkB proteins. The bound NFkB is released and translocates to the nucleus, where it activates appropriate target genes. IkBa is degraded in response to all of the known inducers of NFkB, whereas IkBx is degraded only when cells are stimulated with inducers such as lipopolysaccharide and interleukin-1, which cause persistent activation of NFkB (28). Following degradation of the initial pool of IkB, in response to lipopolysaccharide or interleukin-1, newly synthesized IkBx accumulates in the nucleus as an unphosphorylated protein that forms a stable complex with NFkB and prevents it from binding to newly synthesized IkBa (29, 30). Bcl3 is an

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‡ The abbreviations used are: LBD, ligand-binding domain; RXR, retinoid X receptor; TR, thyroid hormone receptor; RA, retinoic acid; GST, glutathione S-transferase; AF2, activation function 2.
unusual IκB protein in that it can not only inhibit nuclear NFκB complexes but can bind to p50 and p52 dimers on DNA and provide the complexes with transactivating activity (31, 32).

Recently, we have shown that IκBζ specifically interacted with the retinoid X receptor (RXR) and inhibited its 9-cis-RA-dependent transactivation in lipopolysaccharide-treated cells (33). These results led us to examine whether another IκB molecule Bcl3 is also capable of functionally interacting with RXR. Herein, we show that Bcl3 indeed interacts with two subregions of RXR. In contrast to IκBζ, however, Bcl3 did not interact with the AF2 domain of RXR. Furthermore, Bcl3 and IκBζ showed different interaction profiles with general transcription factors. Accordingly, Bcl3 coactivated the 9-cis-RA-induced transactivations of RXR in cotransfections with CV1 cells, alone, or in synergy with SRC-1, in contrast to the inhibitory actions of IκBζ. From these results, we propose that distinct IκB proteins may differentially modulate the 9-cis-RA-dependent transactivations of RXR in vivo.

**EXPERIMENTAL PROCEDURES**

**Plasmids**—Polymerase chain reaction-amplified fragments encoding IκBζΔ4, IκBζΔ5, Bcl3Δ1, Bcl3Δ2, and RXR-LBDΔAF2 were cloned into EcoRI and XhoI restriction sites of the B42 fusion vector pJG4–5 (34). LexA fusions to IκBζ1, IκBζΔ1, IκBζΔ2, and Bcl3, as well as a B42 fusion to RXR-LBD and GST fusions to p50, p65, Bcl3, RXR, RXR-LBD, thyroid hormone receptor (TR), and the AF2 mutant TRα59, were as described previously (33, 34). To express GST/RXR-LBD, GST/RXR-LBDΔAF2, and GST/RXR-LBD, EcoRI restriction sites of pGEX4T (Amersham Pharmacia Biotech), respectively. T7 in vitro translation vectors encoding Bcl3, p50, and IκBζ, as well as mammalian expression vectors encoding RXR, Bcl3, SRC-1, and p300, were as described previously (33). GST fusion vectors encoding TBP and TFIIA, along with T7 vectors encoding TFIIIE and TFIIIB were kind gifts from Dr. David Moore (Baylor College of Medicine, Houston, TX). GST fusion vector encoding CBP1 (amino acids 1–450) was a kind gift of Chris Glass (University of California at San Diego, San Diego, CA). The reporter construct TREp-LUC, the transfection indicator construct pRSV-β-gal, the expression vector for Gal4-VP16, and the reporter construct Gal4-LUC were as described (33, 36). The polymerase chain reaction-based constructs were sequenced against any unwanted sequences that may have been errorously introduced during amplification.

**Yeast Two-hybrid Test**—For the yeast two-hybrid tests, plasmids encoding LexA fusions and B42 fusions were cotransformed into Saccharomyces cerevisiae EGY48 strain containing the LacZ reporter plasmid, SH18-34 (34). Plate and liquid assays of LacZ expression were assayed as described (38), and the results were normalized to the previously described mutant RXR-LBD that lacks the AF2 function (39). The reporter gene was cotransfected with the indicated B42 and LexA plasmids. The indicated B42 and LexA plasmids were transformed into a yeast (424/RXR-LBD) interacted with IκBζΔ1, IκBζΔ2, IκBζΔ3, and IκBζΔ5 but not with IκBζΔ4, localizing the RXR interaction interface to the IκBζ amino acids 253–312. Similary, B42/RXR-LBD interacted with Bcl3Δ2 and Bcl3Δ3 but not with Bcl3Δ1, localizing the RXR interaction interface to the Bcl3 amino acids 289 to the C terminus. The IκBζ-RXR interactions involved the AF2 domain of RXR, as demonstrated by loss of the 9-cis-RA dependence in interactions of IκBζ with its deletional mutants with B42/RXR-LBDΔAF2, a B42 fusion to the previously described mutant RXR-LBD that lacks the AF2 function (39) (Table I). These results are consistent with our previous report (33), in which IκBζ was shown to interact with the AF2 domain of TR. In contrast, however, B42/RXR-LBDΔAF2 still retained the 9-cis-RA-dependent interactions with Bcl3, Bcl3Δ2, and Bcl3Δ3, demonstrating that the Bcl3-RXR interaction did not involve the AF2 domain, distinct from the IκBζ results (33). In addition, LexA fusions to IκBζ, IκBζΔ4, Bcl3, and Bcl3Δ2 were transcriptional activators of the LacZ reporter gene controlled by upstream LexA-binding sites (34). Thus, the autonomous transactivation domains of IκBζ and BcI3 in yeast were mapped to the N-terminal 90 amino acids of IκBζ and the Bcl3 amino acids 156–289, respectively (Table I and Fig. 1).

**RESULTS**

The 9-cis-RA-stimulated Interactions of Bcl3 and RXR Do Not Involve the AF2 Domain—In the yeast two-hybrid tests (34), the full-length IκBζ and Bcl3 interacted with the LBD of RXR in a 9-cis-RA-stimulated manner (Ref. 33 and Table I) but not with the LBD of glucocorticoid receptor (data not shown). A series of deletion mutants were constructed to localize the interaction interfaces (Fig. 1). As shown in Table I, B42 fusion to the LBD of RXR (B42/RXR-LBD) interacted with IκBζΔ1, IκBζΔ2, IκBζΔ3, and IκBζΔ5 but not with IκBζΔ4, localizing the RXR interaction interface to the IκBζ amino acids 253–312. Similarly, B42/RXR-LBD interacted with Bcl3Δ2 and Bcl3Δ3 but not with Bcl3Δ1, localizing the RXR interaction interface to the Bcl3 amino acids 289 to the C terminus. The IκBζ-RXR interactions involved the AF2 domain of RXR, as demonstrated by loss of the 9-cis-RA dependence in interactions of IκBζ with its deletional mutants with B42/RXR-LBDΔAF2, a B42 fusion to the previously described mutant RXR-LBD that lacks the AF2 function (39) (Table I). These results are consistent with our previous report (33), in which IκBζ was shown to interact with the AF2 domain of TR. In contrast, however, B42/RXR-LBDΔAF2 still retained the 9-cis-RA-dependent interactions with Bcl3, Bcl3Δ2, and Bcl3Δ3, demonstrating that the Bcl3-RXR interaction did not involve the AF2 domain, distinct from the IκBζ results (33). In addition, LexA fusions to IκBζ, IκBζΔ4, Bcl3, and Bcl3Δ2 were transcriptional activators of the LacZ reporter gene controlled by upstream LexA-binding sites (34). Thus, the autonomous transactivation domains of IκBζ and Bcl3 in yeast were mapped to the N-terminal 90 amino acids of IκBζ and the Bcl3 amino acids 156–289, respectively (Table I and Fig. 1).

To further characterize these interactions in vitro, various GST fusion proteins were expressed, purifid, and tested for interaction with an in vitro translated Bcl3. These include a full-length RXR, the LBDs of wild type RXR and deletion mutant for the AF2 domain (RXR-LBD and RXR-LBDΔAF2), the N-terminal ABC domains of RXR (RXR-ABC), and full-length TRα, wild type or point-mutated for the AF2 domain (TR and TRα59, respectively) (33, 39). As shown in Fig. 2, Bcl3 constitutively interacted with either the full-length RXR or RXR-ABC. In agreement with the yeast results, however, weak basal interactions of Bcl3 with RXR-LBD or RXR-LBDΔAF2 were

| Ligand       | B42 fusion to |
|--------------|---------------|
|              | RXR-LBD      | RXR-LBDΔAF2 |
| LexA/–       | –             | –           |
| LexA/IκBζ1   | +             | –           |
| LexA/IκBζΔ1  | +             | +           |
| LexA/IκBζΔ2  | +             | +           |
| LexA/IκBζΔ3  | –             | –           |
| LexA/IκBζΔ4  | +             | +           |
| LexA/IκBζΔ5  | –             | +           |
| LexA/Bcl3    | +             | +           |
| LexA/Bcl3Δ1  | +             | +           |
| LexA/Bcl3Δ2  | +             | +           |
| LexA/Bcl3Δ3  | –             | +           |

**Table I Interactions between IκBζs and RXR in yeast**

The indicated B42 and LexA plasmids were transfected into a yeast strain containing an appropriate LacZ reporter gene. At least six separate transformants from each transformation were transferred to indicator plates containing 5-bromo-4-chloro-3-indolyl-β-D-galactopyranoside, and reproducible results were obtained using colonies from a separate transformation. +++, strongly blue colonies after 2 days of incubation and strong interaction; +, light blue colonies after 2 days of incubation and intermediate interaction; +, light blue colonies after more than 2 days of incubation and weak interaction; –, white colonies and no interaction.

The indicated B42 and LexA plasmids were transfected into a yeast strain containing an appropriate LacZ reporter gene. At least six separate transformants from each transformation were transferred to indicator plates containing 5-bromo-4-chloro-3-indolyl-β-D-galactopyranoside, and reproducible results were obtained using colonies from a separate transformation. +++, strongly blue colonies after 2 days of incubation and strong interaction; +, light blue colonies after 2 days of incubation and intermediate interaction; +, light blue colonies after more than 2 days of incubation and weak interaction; –, white colonies and no interaction.

The indicated B42 and LexA plasmids were transfected into a yeast strain containing an appropriate LacZ reporter gene. At least six separate transformants from each transformation were transferred to indicator plates containing 5-bromo-4-chloro-3-indolyl-β-D-galactopyranoside, and reproducible results were obtained using colonies from a separate transformation. +++, strongly blue colonies after 2 days of incubation and strong interaction; +, light blue colonies after 2 days of incubation and intermediate interaction; +, light blue colonies after more than 2 days of incubation and weak interaction; –, white colonies and no interaction.
construct, deduced from the results in Table I are as indicated. Receptor interactions as well as autonomous transactivations of each construct, deduced from the results in Table I as indicated. RID indicates the receptor interaction domain.

Different Interactions of Bcl3 and IκBβ with General Transcription Factors—IκBβ showed autonomous transcripational activities in yeast and mammalian cells (Table I and data not shown). Bcl3 was also shown to have two separate domains that are able to cooperate to confer transactivation functions to otherwise inactive p50 homodimers (31). In our hands, Bcl3 showed autonomous transactivation functions in yeast (Table I), whereas both LexA and Gal4 fusions to Bcl3 efficiently repressed the LexA-LUC and Gal4-LUC reporter gene expressions, respectively (data not shown). Thus, we examined whether IκBβ and Bcl3 are capable of directly interacting with known general transcription factors by using the GST pull-down assays. As expected, the p50-p65 interactions, along with the p50-Bcl3 and p65-IκBβ interactions, were readily detected in this assay system (Fig. 3). In addition, p50 interacted with TFIIB but not with TFIIEα, as described previously (40, 41), whereas p65 interacted with TBP and TFIIA. The latter results further extend previous findings (40–42) in which p65 was shown to interact with TFIIB and TBP. Bcl3 also interacted with TFIIB, TBP, and TFIIA but not with TFIIEα (Fig. 3). In contrast, TBP and TFIIA were not able to interact with IκBβ, attesting to differences between IκBβ and Bcl3 in communicating with the RNA polymerase II preinitiation complex. These results, along with the differences of IκBβ and Bcl3 in recognizing RXR (Table I and Fig. 2), also provide a mechanistic basis for the differential regulations of the RXR transactivations by IκBβ and Bcl3 (see the following cotransfection results).

Bcl3 Stimulates the 9-cis-RA-induced Transactivations of RXR—To assess the functional consequences of these interactions, Bcl3 was cotransfected into CV1 cells along with an RXR expression vector and a reporter construct controlled by TRE-pal, which is transactivated by RXR-RXR homodimers as well as various receptor heterodimers (43). Increasing amounts of cotransfected Bcl3 enhanced the 9-cis-RA-induced transcription of RXR (without significantly affecting the basal level) in a dose-dependent manner, with cotransfection of 50 ng of Bcl3 increasing transcriptional activities approximately 4.5-fold (Fig. 4A). In contrast, cotransfection of Bcl3 affected neither the transcripational activity of Gal4-VP16, as assessed using the Gal4-LUC reporter construct (36) (data not shown), nor the LacZ expression of the transcription indicator construct pRSV-β-gal in the presence or absence of 9-cis-RA (data not shown). In an effort to dissect the mechanistic role of Bcl3, we investi-
C

In an effort to explain the inability of p300 to cooperate with Bcl3, we examined whether Bcl3 and p300 compete to bind to RXR (Fig. 4C). GST-RXR specifically retained radiolabeled Bcl3, which was competed away by increasing amounts of nonlabeled Bcl3, as expected. In contrast, the radiolabeled RXR bound by CBP1, the N-terminal region of CBP harboring the receptor interaction domain, was not competed by nonlabeled Bcl3. These results indicate that Bcl3 and CBP/p300 do not mutually exclude each other in binding to receptors.

**DISCUSSION**

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. The mutual antagonism between nuclear receptors and Jun/Fos (referred to as AP-1), for example, has been suggested to involve direct protein-protein interactions between nuclear receptors and Jun/Fos (for a review, see Ref. 46), as well as a rather indirect competition for a limiting amount of essential coactivators CBP/p300 (11–13). These factors have been shown to be essential for the activation of transcription by a large number of regulated transcription factors (thus, appropriately named as “integrators”), including nuclear receptors (11, 12, 44, 45), AP-1 (47, 48), CREB (49–51), bHLH factors (52), and STATs (53, 54).

In addition, nuclear receptor-mediated blockage of the induction of the Jun N-terminal kinase (i.e., JNK) signaling cascade was recently suggested to be responsible for this antagonism (55).

The mutually antagonistic interactions have been described for the NFκB component p65 and a subset of nuclear receptors including glucocorticoid receptor (56–59), estrogen receptor (60, 61), and progesterone receptor (62). In addition, glucocorticoids, at least in certain cell types, have been shown to increase the synthesis of IκBα, which should then sequester NFκB in an inactive cytoplasmic form (63). Recently, CBP and p300 were shown to coactivate the NFκB component p65 (64, 65), whereas SRC-1, originally identified as a transcription coactivator of nuclear receptors, was found to interact with p50 and coactivate the NFκB transactivations (66). Thus, competition for a limiting amount of CBP and SRC-1 may represent yet another key mechanism to explain the mutual antagonisms of nuclear receptors and NFκB. Adding more twists to the theme, an IκB molecule IκBα was recently shown to directly interact with RXR and function as its transcriptional corepressor (33), whereas another IκB molecule Bcl3 functions as a coactivator of the nuclear receptor RXR, as described in this report. These results attest to a common theme, in which an increasing number of transcription regulators will turn out to participate in regulation of other transcription factors that were previously thought to be unrelated with each other, revealing more divergent regulatory circuits in the eukaryotic transcriptional controls.

The basis for the unexpected IκBα-mediated cross-talks between nuclear receptors and NFκB derives from the fact that we have discovered the cryptic interaction interfaces of IκBα and Bcl3 with nuclear receptors. These interfaces were localized to the IκBα amino acids 253–312 and the Bcl3 amino acids from position 289 to the C terminus (Table I). IκBα contains six ankyrin repeats that constitute the interaction interface with the Rel homology domain of NFκB, whereas Bcl3 contains seven ankyrin repeats (Fig. 1). Among these, ankyrin repeats 1, 5, and 6 of IκBα and ankyrin repeat 3 of Bcl3 contain a single amino acid motif LXXLL, recently shown to mediate the ligand-dependent interaction of the AF2 transactivation domain of the
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receptors with transcription cofactors such as RIP-140, SRC-1, and CBP (20, 67). However, point mutations of these motifs were not able to disrupt the interactions of RXR with IκBβ and Bcl-3.2 Consistent with these results, the Bcl3-RXR interaction did not involve the AF2 domain (Table I and Fig. 2).

IκBβ and Bcl3 showed autonomous transcriptional activities in yeast (Table I). The autonomous transactivation functions of IκBβ and Bcl-3 in yeast were mapped to the N-terminal 90 amino acids of IκBβ and the Bcl-3 amino acids 156–289 (Table I and Fig. 1). These results are in contrast to a previous finding (31), in which both the N-terminal and the C-terminal domains of Bcl-3 were shown to cooperate to coactivate otherwise inactive p50 homodimers in mammalian cells. The reason for this discrepancy is not currently known. However, it is likely to have reflected some fundamental differences between yeast and mammalian transcription machinery. In mammalian cells, IκBβ also showed autonomous transcriptional functions, whereas both LexA and Gal4 fusions to Bcl3 efficiently repressed the LexA-LUC and Gal4-LUC reporter gene expressions (data not shown), attesting to the differences between IκBβ and Bcl3 to communicate with the RNA polymerase II preinitiation complex. Consistent with this, Bcl3 interacted with TFIIB, TBP, and TFIIA, whereas TBP and TFIIA did not interact with IκBβ. Possible interactions of IκBβ with other general transcription factors are currently under investigation. These results, along with the differences of IκBβ and Bcl3 in recognizing RXR (Table I and Fig. 2), may also provide mechanistic basis for the differential regulations of the RXR transactivations by IκBβ and Bcl3 (Ref. 33 and Fig. 4). Finally, it was intriguing that Bcl3 cooperated with SRC-1 but not with p300 to coactivate the RXR transactivations (Fig. 4B). It is notable that SRC-1 was shown to form a complex with CBP/p300 (45). Thus, Bcl3 may have overlapped functions with CBP/p300, or alternatively, its function may involve selective recruitment of SRC-1. Accordingly, it will be interesting to examine whether Bcl3 can exist as a single complex with these factors (i.e. SRC-1 and CBP/p300) or form a different kind of activation complex, particularly with respect to IκBβ. Interestingly, Bcl3 and CBP did not exclude each other from binding to RXR (Fig. 4C), consistent with the former possibility. In particular, the inability of CBP/p300 to synergize with Bcl3 to coactivate the RXR transactivations may reflect enough expressions of CBP in the CV1 and HeLa cells we used. Thus, in certain cell types, we may be able to observe synergistic coactivation of the RXR transactivations by Bcl3 and CBP.

In conclusion, we have shown that distinct IκBβ molecules are capable of differentially modulating the RXR transactivations. The IκBβ results are consistent with the fact that lipoxygenase- and interleukin-1, mediators of the IκBβ actions, are pro-inflammatory (68), whereas retinoids are anti-inflammatory (69). The biological significance for the Bcl3-RXR interactions is not currently known. It is notable, however, that Bcl3 was cloned by virtue of its recurrent translocations in a subset of B cell chronic lymphocytic leukemias (70, 71) and its expressions are cell type-specific, most prominent in spleen, liver, and lung (32). Thus, Bcl3 is likely to significantly affect the RXR functions in these tissues, and RXR may also play critical roles in the potential tumorigenesis mediated by Bcl3.

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