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REVIEW

The IκB proteins: multifunctional regulators of Rel/NF-κB transcription factors

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Eukaryotic organisms have developed elaborate mechanisms to ensure that gene expression is tightly regulated, thereby allowing only certain genes to be expressed in response to a particular developmental or extracellular signal. This selective expression of genes is controlled primarily by the activation of gene-specific transcription factors that can regulate their target genes both positively and negatively. In several cases, preexisting but inactive transcription factor complexes are present that can be subsequently activated in response to a particular signal. One of the most elegant and evolutionarily conserved examples of this class is provided by transcription factors belonging to the Rel family, which includes the mammalian NF-κB and the *Drosophila* Dorsal proteins.

NF-κB was identified initially as a heterodimer of a 50-kD protein (p50) and a 65-kD (p65) protein that was bound in the cytoplasm to a cytoplasmic retention protein called IκB (for review, see Grilli et al. 1993) (p50 and p65 have recently been renamed NFKB1 and RelA, respectively). Activation of NF-κB, which is induced by numerous agents including mitogens and inflammatory cytokines, involves its dissociation from IκB, allowing free NF-κB to be transported into the nucleus where it can regulate genes involved primarily in immune and inflammation responses, as well as certain genes involved in cell proliferation (for review, see Grilli et al. 1993). Similarly, in *Drosophila*, the activation of the Toll receptor leads to the disruption of the complex between the *Drosophila* IκB homolog, Cactus, and the Dorsal protein (Stein et al. 1991; Norris and Manley 1992), allowing translocation of Dorsal into the nucleus where it can regulate genes involved in the formation of the dorsoventral axis.

The idea that IκB proteins function as inhibitory cytoplasmic retention proteins has developed from these studes. However, recent discoveries and the characterization of novel forms of IκB proteins suggest that cytoplasmic retention may be just one mechanism by which these proteins function.

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The IκB proteins: identification and mechanisms of interaction with NF-κB

Studies carried out several years ago by the Baltimore group (Baeuerle and Baltimore 1988a,b) led to the discovery that NF-κB is regulated through its interaction with IκB. It was found that substantial amounts of NF-κB were present in the cytoplasm in a form unable to bind to DNA and that this inhibition of DNA binding was mediated through association with the IκB protein. Moreover, the presence of NF-κB in the nucleus was not associated with IκB, suggesting that IκB retains NF-κB in the cytoplasm (Baeuerle and Baltimore 1988b). Thus, IκB interaction with NF-κB seemed to have at least two consequences: (1) inhibition of DNA binding of NF-κB, and (2) retention of NF-κB in the cytoplasm. Purification of IκB forms associated with NF-κB revealed the presence of two distinct polypeptides of ~37 kD and 43 kD, and these were named IκBα and IκBβ, respectively (Zabel and Baeuerle 1990). Very little is known at present about IκBβ, and therefore it will not be discussed here. The cloning of IκBα and the avian IκBα homolog pp40 demonstrated the presence of structures called ankyrin repeats (Davis et al. 1991; Haskill et al. 1991), previously associated with proteins involved in cell growth and differentiation (Lux et al. 1990). Similar repeats were also identified in the carboxy-terminal region of the p105 and p100 (NFKB2) precursors of the p50 and p52 subunits of NF-κB, respectively, although the functional significance of this relatedness was unclear (also see below).

Subsequent studies have revealed the existence of several other forms of IκB proteins. Homology searches carried out using the IκBα cDNA sequence demonstrated striking similarities with the *bcl-3* oncogene, originally identified by its location adjacent to a chromosomal breakpoint associated with chronic lymphocytic leukemia (Ohno et al. 1990). Further experiments established Bcl-3 as a member of the IκB family (Hatada et al. 1992). A lymphoid cell-specific form of IκB, called IκBγ, has also been identified (Inoue et al. 1992a; Liou et al. 1992). The IκBγ mRNA is generated from an independent transcriptional start site within the p105 gene and encodes a protein that contains the carboxy-terminal ankyrin-con-

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taining region of p105 (Inoue et al. 1992a). The cloning of the Dorsal inhibitor *cactus* has also revealed homologies to the mammalian IκB proteins (Geisler et al. 1992; Kidd 1992). In this review we will focus primarily on the mammalian forms of IκB proteins.

Members of the Rel/NF-κB family exist as dimers, and thus association with IκBα, Bcl-3, and IκBγ can lead to the formation of trimeric or possibly higher order complexes. A different mechanism of interaction has been proposed for the 105-kD (p105) and the 100-kD (p100/lyt-10) precursors of NF-κB subunits, shown recently to function as IκB-like molecules (Rice et al. 1992; Mercurio et al. 1993; Naumann et al. 1993; Scheinman et al. 1993). The difference is attributable to the presence of an amino-terminal dimerization/Rel homology domain in p105 and p100 (a similar domain is absent in IκBα, Bcl-3, and IκBγ; see Fig. 1), which can interact with the complementary regions of NF-κB subunits such as c-Rel and p65. The IκB-like function of p105 and p100 is localized to the carboxy-terminal region that can potentially fold back to interact with the dimerization/Rel homology domain (see Fig. 2). The carboxy-terminal domains of p105 and p100 bear a high degree of homology with other IκB proteins, suggesting that the manner of interaction with the Rel homology domain is likely to be similar in both cases. Moreover, both mechanisms of interaction seem to result in similar biological consequences, that is, cytoplasmic retention and inhibition of NF-κB DNA binding (although Bcl-3 may be an exception; also see below).

All IκB proteins identified to date contain ankyrin repeats. A major proportion of the IκBα, Bcl-3, IκBγ, and Cactus protein sequences contain ankyrin repeats while such repeats are localized to the carboxy-terminal regions of p105 and p100. However, in both cases, ankyrin repeats have been shown to be involved in interaction with the highly conserved Rel homology region of NF-κB family members (Inoue et al. 1992b; Kidd 1992; Nolan and Baltimore 1992; Wulczyn et al. 1992; Hatada et al. 1993), thus establishing these repeats as commonly used interaction motifs among these proteins. Unfortunately, no high resolution structural information is currently available on the nature of interactions between the IκB-ankyrin repeats and the Rel homology region of NF-κB family members.

Specificity of IκB proteins for various Rel/NF-κB family members

Recent studies have shown that the different forms of IκB proteins may preferentially interact with different subunits of NF-κB (see Fig. 1 for summary; for a review of NF-κB family members, see Grilli et al. 1993). Interaction has generally been determined by the ability of IκB proteins to inhibit the DNA binding of NF-κB subunits, although the physiological significance of this inhibition is not clear (see below). These results suggest that the IκBα form is selective for homodimeric and heterodimeric complexes containing p65 or c-Rel (Baeuerle and Baltimore 1989; Beg et al. 1992). On the other hand, the Bcl-3 protein is selective for homodimers of p50 or p52 (Wulczyn et al. 1992; Bours et al. 1993; Nolan et al. 1993), although it has been reported that Bcl-3 can also inhibit the DNA binding of p50–p65 (Kerr et al. 1992). However, titration experiments have demonstrated that the amounts of Bcl-3 that strongly inhibit p50 homodimer DNA binding have no substantial effect on p50–p65 heterodimer DNA binding (Nolan et al. 1993). It is thus possible that Bcl-3 may inhibit p50–p65 DNA binding at relatively higher concentrations than those sufficient to inhibit p50 or p52 homodimer DNA binding. The specificity of IκBγ is unclear because it has been shown to inhibit the DNA binding of p50 homodimers, p50-65, and c-Rel (Inoue et al. 1992a). However, independent expression of the carboxy-terminal domain of p105, approximately corresponding to IκBγ, results in a protein that has been shown to preferentially inhibit p50 homodimer DNA binding (Liou et al. 1992). The p105 and p100 IκB molecules seem to have little or no specificity for particular NF-κB subunits (Rice et al. 1992; Mercurio et al. 1993; Scheinman et al. 1993). Thus, complexes of p105 with p50, p65, and c-Rel have been detected, and complexes of p100 with p50, p52, p65, and c-Rel have also been identified (Rice et al. 1992; Mercurio et al. 1993; Scheinman et al. 1993). However, the relative amounts of different NF-κB subunits bound to p105 or p100 may vary considerably, thereby resulting in the preferential formation of specific homo- or heterodimeric combinations (also see below).

In the following discussion, we will identify potential mechanisms by which IκB proteins may function in the regulation of NF-κB family members (including p50, p65, p52, and c-Rel) and how the divergent mechanisms brought about by the different IκB forms may help to create the complexity necessary for the regulation of NF-κB target genes.

Regulation of NF-κB nuclear transport by IκB proteins

Recent experiments have demonstrated that IκBα displays the properties of the activity that was originally

IκB proteins	Specificity	Apparent Localization	Transcriptional Inhibitor or activator
IκBα	p65,c-Rel	cytoplasm	Inhibitor
Bcl-3	p50, p52	nucleus	activator
IκBγ	p50?	cytoplasm?	Inhibitor
p105	p50,p65,c-Rel	cytoplasm	Inhibitor
p100	p50,p52,p65,c-Rel	cytoplasm	Inhibitor
Rel domain Ankyrin domain			

Figure 1. A summary of the different properties of IκB proteins discussed in this review. The subcellular localization of IκBγ has not been tested directly. Moreover, the specificity of IκBγ is not clear, although it may have some preference for p50 homodimers (for details, see text). In some cases, Bcl-3 may be an inhibitor (see text).

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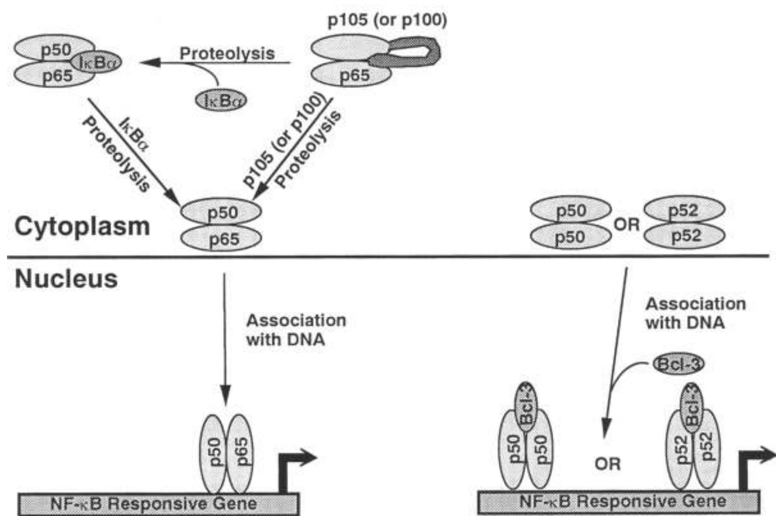

Figure 2. The different mechanisms proposed for the activation of NF-κB family members and the mechanisms by which these proteins can lead to the transcriptional activation of target genes through association of both subunits in the dimeric complex to DNA. The inhibitory functions of IκBα, p105, and p100 and their roles in the activation of NF-κB are shown at *left*; the ability of Bcl-3 to function as a transcriptional coactivator with p50 or p52 homodimers is shown at *right*. The stoichiometry of one IκBα polypeptide associating with a dimeric target may not be necessarily correct. As discussed in the text, IκBα and the carboxy-terminal ankyrin repeats of p105 and p100 likely mask the NLSs of Rel family members leading to cytoplasmic localization as shown. The association of p105 (or p100) with p65 does not suggest the exclusive formation of such complexes (for details, see text). The processing of p100–p65 would lead to a p52–p65 heterodimer.

defined as IκB. IκBα retains NF-κB subunits in the cytoplasm, probably through the masking of their nuclear localization signals (NLSs) (Beg et al. 1992; Ganchi et al. 1992; Zabel et al. 1993). Analysis of the status of IκBα following stimulation of cells with NF-κB inducers revealed that it disappeared rapidly following treatment (see next section), thus unmasking the NLSs and allowing NF-κB to be transported to the nucleus. The IκBγ protein, like IκBα, can also retain Rel/NF-κB family members in the cytoplasm (Inoue et al. 1992a); however, it is presently unclear whether IκBγ is targeted by NF-κB inducers in the same manner as IκBα. It is possible that IκBγ, unlike IκBα, does not regulate NF-κB through a post-translational mechanism but, rather, through its relative abundance in different cell types. For example, it has been found that the IκBγ mRNA is fairly abundant in preB cells but not in mature B cells (Liou et al. 1992). Therefore, down-regulation of the IκBγ message could underlie a mechanism by which constitutive NF-κB forms are generated in the nuclei of mature B cells. Further experiments need to be performed to determine the precise role of IκBγ in the regulation of NF-κB.

The ability of Bcl-3 to retain NF-κB subunits in the cytoplasm has been controversial. It has been shown that Bcl-3 is a nuclear protein, both when transfected alone or when transfected in the presence of p50 or p52 (Bours et al. 1993; Nolan et al. 1993). However, a study by Naumann et al. (1993) reports that transfected Bcl-3 is cytoplasmic and that Bcl-3 retains p50 in the cytoplasm. This apparent discrepancy may be attributable in part to the different methods employed for determining subcellular localizations and/or on the amounts of proteins synthesized in cells following transfections. Studies analyzing endogenous Bcl-3 have shown the existence of two forms present in nuclei, although only one form appears to be cytoplasmic, suggesting that at least some forms of Bcl-3 are nuclear (Kerr et al. 1992). In addition, in vitro experiments performed in this study suggest that an amino-terminal truncation of Bcl-3 may have a different specificity from the full-length protein.

Recent investigations have shown that p105 and p100 can dimerize with other members of the NF-κB family, such as c-Rel and p65, through the amino-terminal Rel homology region (Rice et al. 1992; Mercurio et al. 1993; Scheinman et al. 1993). The carboxy-terminal ankyrin repeat-containing half of p105 can potentially fold back and interact with its own amino-terminal Rel homology region as well as with its NLS (Henkel et al. 1992). Complexes of p105 or p100 with other NF-κB subunits are therefore likely to be localized to the cytoplasm through the masking of their NLSs by the carboxy-terminal ankyrin region of these precursors. Thus, masking of the NLSs of NF-κB subunits by IκB proteins may represent a general mechanism for cytoplasmic retention. Proteolytic removal of the carboxy-terminal half of p105 or p100 would generate an active complex consisting of p50 or p52 homodimers or heterodimers with p65 or c-Rel (see Fig. 2). Indeed it has been shown that nuclear NF-κB present in HIV-1–infected cells may be generated in part through the induced processing of p105 (Rivière et al. 1991). In addition, it has been demonstrated recently that treatment of cells with TPA can lead to the enhanced processing of p105 and p100 (Mercurio et al. 1993); the rates of processing of p105 and p100 were found to be different and also varied in different cell types (Mercurio et al. 1993). These results suggest that the processing of p105 and p100 may lead to different amounts of homodimers and heterodimers at different

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times following stimulation. However, these mechanisms are not likely to be responsible for the rapid nuclear appearance of NF-κB, because the processing is relatively slow. On the other hand, the processed dimeric forms of p105 or p100 with other Rel family members may associate with IκBα in the cytoplasm (see Fig. 2). In this scenario, p105 and p100 complexes may be serving as a "latent storehouse" for NF-κB in the cytoplasm while IκBα-associated complexes may be serving as a more "active storehouse" for NF-κB. The eventual nuclear appearance of NF-κB subunits associated with p105 and p100 would therefore require both the processing of these precursors and the loss of IκBα.

Autoregulation of NF-κB through the transient loss and resynthesis of IκBα

Stimulation of cells with NF-κB inducers can lead to the degradative loss of IκBα (Beg et al. 1993; Brown et al. 1993; Cordle et al. 1993; Henkel et al. 1993; Sun et al. 1993). Five well-established inducers of NF-κB (TNFα, IL-1α, PMA, PMA/PHA, and LPS) all lead to the loss of IκBα and to the concomitant appearance of NF-κB in the nucleus. These results indicate that the loss of IκBα is a general mechanism for the activation of NF-κB. IκBα loss was preceded by phosphorylation (Beg et al. 1993; Cordle et al. 1993), consistent with in vitro models suggesting that phosphorylation of IκB could disrupt its complex with NF-κB (Shirakawa and Mizel 1989; Ghosh and Baltimore 1990; Kerr et al. 1991). It is important to note, however, that the in vivo role of IκBα phosphorylation is presently unclear. In the case of the *Drosophila* Cactus protein, phosphorylation does not seem to disrupt its complex with Dorsal (Kidd 1992), suggesting that phosphorylation of this inhibitor may not be responsible for its dissociation from Dorsal. However, evidence has been presented that phosphorylation of Dorsal by protein kinase A may be involved in its activation (Norris and Manley 1992), which suggests that phosphorylation of other Rel family members may also be involved in their regulation. Furthermore, the identification of the *pelle* gene, which encodes a potential protein kinase as an essential component required for the nuclear transport of Dorsal, has provided conclusive evidence for the involvement of phosphorylation in the activation of a member of the Rel family (Shelton and Wasserman 1993). The direct substrates for the Pelle kinase, however, have not been identified. Interestingly, Pelle is similar to the Raf and Mos serine/threonine kinases.

Interestingly, it has been found that IκBα is stabilized through association with p65 (Scott et al. 1993; Sun et al. 1993). These results indicate that any free IκBα that may be generated, perhaps through phosphorylation, would be immediately targeted for degradation. The degradation of IκBα has been proposed to be mediated by chymotrypsin-like proteases because IκBα loss can be prevented in the presence of inhibitors of such enzymes (Henkel et al. 1993). Inhibition of chymotrypsin-like enzymes can also block the activation of NF-κB, indicating that the loss of IκBα is required for NF-κB activation (Henkel et al. 1993). An intriguing question remains unanswered: How can several apparently unrelated agents lead to the loss of IκBα? Future investigations directed at the identification of potential upstream effector molecules may not only provide answers to this question but also help understand the signal transduction pathways that can lead to NF-κB activation. In this regard, recent studies demonstrate a role for tyrosine kinases, Ras, and Raf-1 (Devary et al. 1993; Finco and Baldwin 1993) and for an isoform of protein kinase C (Diaz-Meco et al. 1993) in the activation of κB site-dependent gene expression and of NF-κB DNA-binding activity.

The IκBα protein reappears rapidly following loss, indicating a potential mechanism for limiting NF-κB activation through the renewed synthesis of its inhibitor (Beg et al. 1993; Brown et al. 1993; Scott et al. 1993; Sun et al. 1993). Furthermore, transient transfection of a plasmid encoding the p65 subunit of NF-κB can lead to an induction of the IκBα mRNA, which indicates that NF-κB may directly regulate transcription of the IκBα gene (Brown et al. 1993; Scott et al. 1993; Sun et al. 1993). Importantly, NF-κB–binding sites have been identified in the promoter region of a porcine IκBα-like gene (de Martin et al. 1993). The transcriptional activation of the IκBα gene by NF-κB, followed by an increase in the levels of IκBα protein, would ensure that NF-κB activation is transient, thus preventing chronic expression of NF-κB–responsive genes. The promoter of the p105 gene also contains NF-κB-binding sites, and the p105 mRNA can be induced by agents that activate NF-κB (Ten et al. 1992; Cogswell et al. 1993). Thus, the renewed synthesis of p105 may be required for its IκB-like function as well as to re-establish the cytoplasmic NF-κB pool.

The IκB proteins as inhibitors of NF-κB DNA binding

Although the ability of IκB forms to inhibit the DNA binding of NF-κB has been well documented, the in vivo significance of these results is still unclear. This is partly because endogenous IκBα, p105, and p100 seem to be localized to the cytoplasm (Rice et al. 1992; Beg et al. 1993; Brown et al. 1993; Mercurio et al. 1993; Scheinman et al. 1993; Sun et al. 1993), raising the possibility that the inhibition of NF-κB DNA binding by these proteins may merely be a consequence of competition for the regions of NF-κB that are involved in DNA binding. However, experiments demonstrating that IκBα can disrupt preformed NF-κB–DNA complexes has led to the suggestion that IκBα may limit the transcriptional activation by NF-κB by actively removing it from κB sites (Zabel and Baeuerle 1990). In addition, recent studies have shown that exogenously introduced IκBα can be found in the nucleus as well as in the cytoplasm (Zabel et al. 1993). Thus, it is possible that newly synthesized IκBα may not only inhibit further NF-κB translocation to the nucleus but may also enter the nucleus on its own and dissociate preformed NF-κB–DNA complexes. Therefore, the eventual depletion of active NF-κB from nuclei may involve both of these potential mechanisms. However, conclusive proof of a nuclear function for IκBα

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would only be obtained by the detection of NF-κB–IκBα complexes in the nucleus. The potential role of Bcl-3 as an inhibitor of p50 and p52 DNA binding will be discussed in the next section.

Bcl-3: a putative transcriptional activator

The IκBα, IκBγ, p105, and p100 proteins may inhibit the ability of NF-κB to activate target genes transcriptionally through retention in the cytoplasm and perhaps by directly displacing NF-κB from DNA. Transient transfection studies have confirmed predictions that these IκB proteins can inhibit the ability of NF-κB subunits to activate transcription (Beg et al. 1992; Fujita et al. 1993). Therefore, it was quite surprising to find that the Bcl-3 form of IκB leads to transcriptional activation through κB sites (Franzoso et al. 1992; Bours et al. 1993; Fujita et al. 1993). Two distinct mechanisms have been proposed to explain the ability of Bcl-3 to activate transcription. One mechanism is through the association of Bcl-3 with p50 homodimers (Franzoso et al. 1992), which may function as repressors of transcription from certain κB sites (Kang et al. 1992; Grilli et al. 1993). Cotransfection of Bcl-3 with p50 could potentially inhibit p50 homodimers from binding to κB sites and thus allow p50–p65 or p65–p65 to interact with these sites. p65 contains a potent transcriptional activation domain leading to a dramatic increase in transcription upon DNA binding. Therefore, in this case, Bcl-3 may act as an activator by functioning as the inhibitor of an inhibitor.

The second mechanism by which Bcl-3 may act as a transcriptional activator is through the formation of a ternary complex with p50 or p52 homodimers (p50B) bound to DNA (Bours et al. 1993; Fujita et al. 1993). Association of Bcl-3 with a p50–DNA or a p52–DNA complex results in the formation of a ternary complex that can function as a strong transcriptional activator (Bours et al. 1993; Fujita et al. 1993). The transcriptional activation ability of this ternary complex is likely mediated by the amino- and carboxy-terminal regions of Bcl-3 (Bours et al. 1993; Fujita et al. 1993). The nuclear localization of Bcl-3 is consistent with its role as transcriptional coactivator.

It is apparent that the proposed mechanisms by which Bcl-3 may activate transcription in the presence of p50 are in seeming contradiction. Franzoso et al. (1992) suggest that Bcl-3 removes p50 from DNA, thus allowing p50–p65 to bind DNA, whereas Fujita et al. (1993) provide evidence for a direct interaction between p50 and Bcl-3, thereby leading to transcriptional activation. A possible explanation for these differences has been provided by Fujita et al. (1993) through the use of two different p50 constructs for transfection studies with Bcl-3. A p50 construct, identical to the one used by Franzoso et al. (1992), encoding a protein of ~60 kD (and thus significantly larger than authentic p50), failed to synergize transcriptionally with Bcl-3 (Fujita et al. 1993). However, a protein that corresponds more closely to authentic p50 was capable of synergism with Bcl-3, indicating that p105 residues carboxy-terminal to authentic p50 may prevent synergism with Bcl-3 (Fujita et al. 1993). These results indicate that the inhibition of p50 homodimer function by Bcl-3 may be attributable to the expression of a protein that does not correspond to authentic p50. It is important to note that the mechanisms proposed by both groups are based on results obtained by overexpression of proteins in cell lines, although Fujita et al. (1993) have also demonstrated that p50 and Bcl-3 can synergize transcriptionally in vitro. However, conclusive proof for the existence of these mechanisms would require the identification of similar mechanisms at work in nontransfected cells. Other studies indicate (as mentioned previously) that Bcl-3 may inhibit p50 or p52 DNA binding (Wulczyn et al. 1992; Nolan et al. 1993). It is likely that Bcl-3 may either remove p50 (or p52) homodimers from DNA or form ternary complexes with them, depending on the source of proteins used, relative concentrations of proteins, post-translational modifications, and perhaps the κB sites being utilized.

It has been shown recently that phosphorylated Bcl-3 can interact with p50 more effectively than unphosphorylated Bcl-3 (Nolan et al. 1993). Thus, phosphorylation of both the Bcl-3 and the IκBα proteins may lead to transcriptional activation by NF-κB. Phosphorylation of Bcl-3 may activate transcription through its association with p50 or p52 homodimers, whereas phosphorylation of IκBα may liberate cytoplasmic NF-κB, resulting in its nuclear translocation and the transcriptional activation of target genes bearing κB sites.

Both p100/p52 and Bcl-3 are potential oncoproteins. The tumorigenic potential of p100/p52 may be the result of the synthesis of a protein that contains the DNA-binding Rel domain but not the inhibitory carboxy-terminal ankyrin domain (Neri et al. 1991). The tumorigenic potential of Bcl-3, on the other hand, is likely mediated through overexpression (Ohno et al. 1990). It is interesting that inappropriate expression of either one of these oncoproteins may have the same net effect of activating κB site-dependent transcription, suggesting that their oncogenic potential may lie in their ability to elevate expression of appropriate target genes.

Conclusions

It is clear from this discussion that association of IκBα, IκBγ, p105, and p100 with certain NF-κB subunits results in loss of their transcriptional activation function while association with Bcl-3 leads to the gain of that function (summarized in Fig. 1). These observations challenge the notion that IκB proteins have an exclusively inhibitory function and suggest that they may be viewed more as modulators of NF-κB function rather than strictly as inhibitors of NF-κB function. It remains to be determined whether p50–Bcl-3 or p52–Bcl-3 complexes are formed in response to particular developmental or extracellular signals and what effect NF-κB inducers have on the formation and dissociation of such complexes. Do agents that cause the loss of IκBα also affect Bcl-3, or is Bcl-3 regulated by a distinct set of signals? At this stage, it is not known whether the regulation of p50 or p52 by Bcl-3

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affects a distinct class of κB site-containing target genes or whether Bcl-3 potentiates the activation of genes that are already known to be NF-κB responsive. In any case, the modulation of NF-κB activity by a multifunctional family of IκB proteins suggests complex mechanisms by which NF-κB participates in the regulation of a wide variety of genes that are involved in key biological processes.

Acknowledgments

We thank members of the Baldwin laboratory for helpful comments on this review. We also thank Dr. P.A. Baeuerle for sharing data prior to publication. Grant support for A.S.B. was provided by the National Institutes of Health, the Arthritis Foundation, the March of Dimes Birth Defects Foundation, and the American Cancer Society.

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Genes Dev. 1993, **7:**
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