Repression of B-Cell Linker (BLNK) and B-Cell Adaptor for Phosphoinositide 3-Kinase (BCAP) Is Important for Lymphocyte Transformation by Rel Proteins

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Abstract
Persistent Rel/nuclear factor-κB (NF-κB) activity is a hallmark of many human cancers, and the Rel proteins are implicated in leukemia/lymphomagenesis but the mechanism is not fully understood. Microarray analysis to identify transcriptional-impactting genes regulated by NF-κB’s oncogenic v-Rel and c-Rel proteins uncovered that Rel protein expression leads to transcriptional repression of key B-cell receptor (BCR) components and signaling molecules like B-cell linker (BLNK), the B-Cell adaptor for phosphoinositide 3-kinase (BCAP) and immunoglobulin λ light chain (Igλ), and is accompanied by a block in BCR-mediated activation of extracellular signal-regulated kinase, Akt, and c-Jun-NH2-kinase in response to anti-IgM. The BLNK and BCAP proteins were also down-regulated in lymphoid cells expressing a transformation-competent chimeric RelA/v-Rel protein, suggesting a correlation with the capacity of Rel proteins to transform lymphocytes. DNA-binding studies identified functional NF-κB-binding sites, and chromatin immunoprecipitation (ChIP) data showed binding of Rel to the endogenous blnk and becap promoters in vivo. Importantly, restoration of either BLNK or BCAP expression strongly inhibited transformation of primary chicken lymphocytes by the potent NF-κB oncoprotein v-Rel. These findings are interesting because blnk and other BCR components and signaling molecules are down-regulated in primary mediastinal large B-cell lymphomas and Hodgkin’s lymphomas, which depend on c-Rel for survival, and are consistent with the tumor suppressor function of BLNK. Overall, our results indicate that down-regulation of BLNK and BCAP is an important contributing factor to the malignant transformation of lymphocytes by Rel and suggest that gene repression may be as important as transcriptional activation for Rel’s transforming activity. [Cancer Res 2008;68(3):808–14]

Introduction
The vertebrate Rel/nuclear factor-κB (NF-κB) transcription factors [c-rel, RelA, RelB, NF-κB1 (p50/p105), and NF-κB2 (p52/p100)] play vital roles in immune, inflammatory, and stress responses and are also implicated in oncogenesis. The viral NF-κB oncoprotein v-Rel and its cellular homologue c-Rel malignantly transform primary chicken lymphocytes in vitro and induce leukemia/lymphomas and mammary adenocarcinomas in animal models (1–5). Consistent with this, Rel/NF-κB is constitutively activated in many human cancers and is key to tumor survival, pathogenesis, and chemoresistance (6). Activation of Rel/NF-κB in human tumors often results from constitutive IKK kinase complex activity or from chromosomal amplification, mutation, rearrangement, and/or overexpression of the c-rel or nf-κb2 genes (7). Nuclear accumulation of the human c-Rel protein is seen in classic Hodgkin’s lymphoma (cHL) and primary mediastinal large B-cell lymphoma (MLBC), and its suppression triggers apoptosis in B cells and sensitized these and other tumor-derived cells to chemotherapy (8–14).

Rel/NF-κB family members show remarkably different oncogenic potentials in primary chicken lymphocytes, which are readily transformed in vitro by v-Rel and c-Rel but not by RelA, RelB, p50/NF-κB1, p52/NF-κB2, or the Rel/NF-κB–activating kinase IKKβ (3, 4, 15). The C-terminal transactivation domains (TAD) of Rel and RelA seem to be important for their different in vitro transforming and tumor-inducing capacities, as chimeras composed of the DNA-binding domain of human RelA fused to the TAD of mouse c-Rel, human c-Rel, or v-Rel (hRelA/v-Rel, hRelA/c-Rel, hRelA/hc-Rel) could transform primary lymphocytes, in contrast to hRelA and chimeras containing the RelA TAD (15). This suggests differential modulation of gene expression important for oncogenesis.

Rel/NF-κB activates the expression of antiapoptotic genes and promotes tumor cell growth by inducing proinflammatory cytokines and D-type cyclins (16). v-Rel transcriptionally activates expression of c-Jun (AP-1), IRF-4, and IAP1 and promotes alternative splicing of telomerase reverse transcriptase, which play important roles in its ability to transform lymphocytes (17–20). Additionally, recent work uncovered that v-Rel transcriptionally represses SH3BGRL and that this is also important for its transforming activity (21). Here, we show that both v-Rel and c-Rel lead to down-regulation of B-cell receptor (BCR)–signaling molecules B-cell adaptor for phosphoinositide 3-kinase (PI3K; BCAP) and B-cell linker (BLNK; BASH, SLP-65) and that this contributes significantly to v-Rel’s transforming activity in lymphocytes. Our results suggest that gene repression may be as important as transcriptional activation for Rel’s transforming activity.

Materials and Methods
Cell lines, microarrays and bioinformatic analyses. Rel and RelA proteins were stably expressed at equivalent levels in the chicken DT40 pre-B-cell line (a gift from J. Manley, Columbia University) by electroportation of bicistronic avian spleen necrosis virus-derived retroviral vectors

Note: Supplementary data for this article are available at Cancer Research Online (http://cancerres.aacrjournals.org/).

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(pJD214-RES-puro), expressing either chicken, mouse, or human c-Rel (cc-
Rel, mc-Rel, hc-Rel), v-Rel, an hRelA/v-Rel chimera, or the human or mouse RelA proteins (hRelA, mRelA), followed by isolation of puromycin-resistant cell lines. Immune cell-specific chicken cDNA microarrays were performed as described (22). Expression profiles were compared with parental DT40 cells by averaging expression data from three independent cell clones expressing each of these proteins using dye-swap experiments, as described in Supplementary Materials. Summary and raw microarray data are available from the GEO database7 (accession number GSE95544). Potential NF-κB-binding sites in the blnk and bcap regulatory regions were bioinformatically predicted using a position-specific scoring matrix developed as described in the Supplementary Materials.

Anti-IgM stimulation. Western blotting, and in vitro kinase assays. DT40 cell lines were stimulated for 10 min with anti-IgM (4 µg/ml; a gift from T. Kurosaki, Kansai Medical University) and analyzed by immunoblotting (23). Other immunoblots were performed as described (15). Antibodies were against Rel, extracellular signal-regulated kinase (ERK), Akt (Santa Cruz), RelA-N (Rockland), actin (Sigma), phosphorylated ERK, phosphorylated Akt (Cell Signaling), Rel-A-HRD (2716; ref. 24), enhanced green fluorescent protein (EGFP; Torrey Pines), ch-BLNK or BCAP (gifts from T. Kurosaki, Kansai Medical University), c-Jun, NF-κB (JNK) activity was determined in in vitro kinase assays with cell lysates immunoprecipitated with anti-JNK1 (Santa Cruz).32P-γ-ATP, and a gluthathione 3-transferase-c-Jun substrate (Cell Signaling), followed by autoradiography and immunoblotting with anti-JNK1, as detailed in the Supplementary Materials.

Reverse transcription–PCR. Reverse transcription–PCR (RT-PCR) was performed within the linear range of the PCR cycle using primers gapdh (ctcctctgcaacctgcag, catctgccatctgatgtg), blnk (ttgcttgaaagctttactctga, acacccaaaacactgtggt), and bcap (gcagcaccagcagctg, gggcaaaatcggca-
taga).

Gel retardation and chromatin immunoprecipitation assays. Gel retardation assays were performed as described (25) using a palindromic νB DNA site (ν-B-PD), ch-bcap (gatgctgaattcgtgggaacttcccacctctcctcctca, ch-bnk (gatgctgaattcgtgggaacttcccacctctcctcctca), hu-bcap (gatgctgaattcgtgggaacttccccc-
tcctcctcctc), or hu-bnk (gatgctgaattcgtgggaacttcccacctctcctcctc) ν-B sites and 293T cells extracts normalized for equivalent Rel protein levels. An anti-v-Rel antibody was used for supershifts. Chromatin immunoprecipi-
tation (ChIP) was adapted from Upstate Biotechnology and ref. 21, and used anti-hc-Rel (NR 1136 or NR 265; gifts from N. Rice, National Cancer Institute), PC-139 (Oncogene Research Products), IgG, or normal rabbit serum (NRS; Calbiochem). DNA was PCR-amplified with primers listed in the Supplementary Materials.

Lymphocyte transformation assays. Primary chicken spleen cells (CSC) were transformed with virus harvested from chicken embryo fibroblasts cotransfected with retroviral vectors coexpressing EGFP, ch-BLNK, or ch-BCAP-Flag with v-Rel. The results of three experiments were calculated as mean ± SD. Animals were used according to the National Cancer Institute Animal Care and Use Committee guidelines under an approved animal study protocol. Additional information is available in the Supplementary Materials.

Results

Microarrays identify a subset of genes down-regulated in DT40 cells expressing Rel proteins. To further clarify the mechanisms that underlie the potent transforming activity of Rel proteins in lymphocytes, we used focused immune system cDNA microarrays (22) to identify genes whose expression is commonly altered in cells expressing NF-κB subunits that transform primary chicken lymphocytes by virtue of a Rel TAD (c-Rel, v-Rel, and hRelA/v-Rel). Expression profiles were analyzed in a context independent of their transforming phenotype by stably expressing the human, mouse, chicken, and viral Rel genes, the hRelA/v-Rel hybrid and human or mouse RelA in the chicken pre-B-cell line DT40 that provided a homogenous lymphocyte background with very low levels of nuclear NF-κB activity (Fig. L4 and data not shown) Three independent cell clones expressing each protein at levels equivalent to those found in v-Rel–transformed CSCs were analyzed (Fig. 1B and data not shown).

As anticipated, several known NF-κB transcriptional targets like cyclin d2, ica, and cytokine mip-1β were commonly up-regulated in DT40 cell lines expressing the various Rel and RelA proteins (GEO database7 accession number GSE95544). Interestingly, a second gene subset was down-regulated in Rel-expressing cells, including important components of the BCR and key players in the BCR-signaling pathway. For example DT40 cells expressing the potently transforming v-Rel showed nearly 25-fold repression of bcap (pik3ap1) and ige, blnk (bash, SLP-63), another important mediator of BCR signaling, was down-regulated by ~9-fold in v-Rel–expressing cells (GEO database7 accession number GSE95544).

Consistent with the down-regulation of BCR components and signaling molecules, stimulation of DT40 cells expressing h-Rel, v-Rel, or hRelA/v-Rel with anti-IgM failed to activate phosphorylated ERK and phosphorylated Akt or induce activation of JNK in contrast to parental DT40 cells and those expressing hRelA (Fig. 1C). Although basal levels of phosphorylated Akt were slightly elevated in v-Rel–expressing cells compared with parental DT40 cells, anti-IgM failed to significantly enhance this response (lanes 5 and 6). These results indicate that Rel protein expression in DT40 cells leads to down-regulation of a specific group of genes important for BCR signaling and is correlated with a crippled BCR response.

Suppression of BLNK and BCAP is characteristic of Rel protein expression. Our finding that Igλ is down-regulated in DT40 cells expressing Rel is consistent with prior studies documenting absence of light chain expression in hematopoietic cells transformed by v-Rel (26). However, little is known of the relationship between down-regulation of BLNK and BCAP and Rel-mediated transformation. Both BLNK and BCAP are key adaptor molecules that activate downstream signaling in response to BCR cross-linking (23, 27, 28). BLNK is a tumor suppressor, and its deficiency is associated with a high incidence of spontaneous pre-B-cell lymphomas (29). On the other hand BCAP participates in the P13K/Akt pathway that promotes B-cell proliferation and survival and also leads to activation of JNK to promote cell death. Given the potential implications of BLNK and BCAP down-regulation for lymphocyte transformation, we further characterized their expression in Rel-expressing cells.

Consistent with the microarray results, BCAP protein levels were significantly reduced in DT40 cells expressing hc-Rel, v-Rel, or hRelA/v-Rel, compared with parental DT40 cells and those expressing RelA (Fig. 2A). Whereas microarrays suggested repression of blnk in cells expressing either Rel or RelA, Western blots of independent cell clones showed that, much like BCAP, BLNK is strongly down-regulated in DT40 cells expressing hRelA/v-Rel, compared with parental DT40 cells and those expressing RelA (Fig. 2A, lanes 2–4 versus lanes 1 and 5). BLNK and BCAP proteins were similarly absent in primary CSC transformed either by v-Rel, hRelA/v-Rel, or hc-Rel (Fig. 2B, lanes 4–6). In contrast, both BLNK and BCAP were abundantly expressed in the avian leukosis virus (ALV)–transformed immature B-cell line TLT-1 and in parental DT40 cells (lanes 1 and 2). Thus,
down-regulation of BLNK and BCAP is not common to transformed avian B-cell lines but is rather correlated with expression of transformation-competent Rel proteins. We thus focused further analyses on Rel proteins.

**The chicken and human blnk and bcap regulatory regions contain genuine NF-κB DNA sites.** Bioinformatic analysis of −3 kb to +3 kb surrounding the transcription start site of chicken blnk and bcap identified a single putative NF-κB site for ch-blnk (C GGGA TCCCC at position 263) and two identical tandemly repeated NF-κB sites upstream of ch-bcap (T GGGA TCCCC at −336 and −326). Putative NF-κB sites were similarly predicted in their human counterparts (hu-blnk GGGAA CT TCC at −265 and hu-bcap C GGGGT TCC at −2,413). Gel retardation assays with hc-Rel, v-Rel, or RelA/v-Rel proteins expressed in 293T cells confirmed their interaction with the predicted ch-blnk and ch-bcap NF-κB sites, although they differed in efficiency (Fig. 3 A and B). A palindromic consensus κB site served as positive control (κB-PD). hc-Rel bound more efficiently to the ch-blnk κB site than v-Rel and hRelA/v-Rel. In contrast, the ch-bcap κB site was favored by hc-Rel and v-Rel versus hRelA/v-Rel, suggesting preference for the Rel DNA-binding domain. Despite the seemingly weaker binding of v-Rel and hRelA/v-Rel versus hc-Rel to the ch-blnk κB site, supershifts confirmed their genuine interaction (Fig. 3C).

Because NF-κB is markedly activated in human MLBCL and cHL due to nuclear accumulation of hc-Rel (8, 9, 11), we also analyzed the κB sites predicted in human blnk and bcap for interaction with hc-Rel in gel retardation assays (Fig. 3D). Like their chicken counterparts, the predicted κB sites in the hu-blnk and hu-bcap promoters bound efficiently to hc-Rel in vitro. These studies
identified genuine NF-κB–binding sites in the chicken and human blnk and bcap regulatory regions.

**hc-Rel is bound to the blnk and bcap promoters in chromatin.** Next, we used ChIP assays to show direct binding of hc-Rel to the endogenous ch-bcap promoter in vivo in DT40-hc-Rel cells, but not in parental DT40 cells (Fig. 4A). Anti–hc-Rel specifically immunoprecipitated the ch-bcap promoter region in DT40-hc-Rel cells, in contrast to the no antibody, IgG, and NRS controls (lane 5 versus lanes 2–4). The extremely GC-rich nature of the ch-blink regulatory region precluded its analysis by ChIP. Consistent with the binding of Rel proteins to the bcap and blnk regulatory regions, semiquantitative RT-PCR confirmed repression of bcap and blnk transcripts in DT40 cells expressing hc-Rel, v-Rel, and hRelA/v-Rel compared with parental DT40 cells (Fig. 4B). This supports the notion that Rel expression is associated with down-regulation of blnk and bcap.

Interestingly, blnk and other BCR signaling components and coreceptors are significantly down-regulated in primary human MLBCL and cHL specimens compared with normal tissue samples (10, 30, 31). Because nuclear accumulation of hc-Rel is characteristic of these tumors, we used ChIP assays to show that endogenous hc-Rel is bound to the hu-blink and hu-bcap promoters in the chromatin of the MLBCL-derived cell line Karpas 1106 (Fig. 4C). Two different anti–hc-Rel antibodies efficiently immunoprecipitated hu-blink and hu-bcap compared with the no antibody, IgG, and NRS controls (Fig. 4C, top and middle, lanes 6 and 7 versus lanes 2–4). In contrast, they failed to immunoprecipitate a region from the control human crp2 gene that lacks an NF-κB–binding site (bottom, lanes 6 and 7). Anti–hc-Rel antibody PC-139 failed to immunoprecipitate hu-blink and hu-bcap, consistent with prior work from our group showing that this antibody does not efficiently pull-down hc-Rel in ChIP. This further substantiates the specificity of hu-blink and hu-bcap ChIP with anti–hc-Rel antibodies NR265 and NR1136. These data show that endogenous hc-Rel in MLBCL-derived tumor cells is bound to the hu-blink and hu-bcap promoter regions in the in vivo context of chromatin.

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8 L.C. Edelstein and C. Gélinas, unpublished data.
Repression of BLNK and BCAP is important for v-Rel-mediated transformation of lymphocytes. Because down-regulation of BLNK and BCAP is seen in DT40 cells expressing Rel proteins, in primary CSC transformed by v-Rel, hRelA/v-rel, or hc-Rel (Fig. 2), and also in human MLBCL and chL tumor cells that depend on c-Rel for survival (10, 30, 31), we postulated that their down-regulation might contribute to Rel’s function in lymphocyte transformation. We assessed the effect of restoring blnk or bcap expression on the transformation of primary chicken lymphocytes by v-rel, which is the most potent transforming member of the Rel/NF-κB family. The blnk or bcap cDNAs were coexpressed along with v-rel using a bicistronic retroviral vector, and their efficient expression was confirmed by Western blot (Fig. 5A). Coexpression of either ch-BLNK or ch-BCAP markedly impaired v-Rel-mediated transformation of primary chicken lymphocytes as it dramatically reduced colony formation in soft agar by 7-fold to 39-fold compared with the EGFP control (Fig. 5B). These results show that suppression of blnk and bcap expression is important for Rel’s transforming activity.

Discussion

Although NF-κB is best known for its transcriptional activation function, recent work with RelA, RelB, and v-Rel showed that it can down-regulate specific genes and that these can significantly affect its role in apoptosis and oncogenesis (21, 32–35). Whereas tumor suppressor alternative reading frame, UV-C, and certain chemotherapeutic drugs can induce RelA to repress transcription of antiapoptotic genes Bcl-xL, XIAP, and/or A20 to sensitize cells to apoptosis, v-Rel down-regulates SH3BGRL that severely impairs its transforming activity although its biological function remains to be determined (21, 33, 34, 36, 37). Here, we show that Rel proteins that can transform primary chicken lymphocytes, including a hRelA/v-Rel chimera, down-regulate expression of BCR component Igκ and BCR signaling adaptors BLNK and BCAP. Their transcriptional down-regulation was most pronounced in cells expressing v-Rel, which is the most potent oncogenic member of the NF-κB family. We also show that Rel binds to the blnk and bcap promoters and that expression of BLNK or BCAP strongly antagonizes lymphocyte transformation by v-Rel. These findings underscore that the ability of Rel to induce gene-specific transcriptional repression of these factors is important for its oncogenic activity in lymphocytes.

NF-κB can use different mechanisms to antagonize gene expression, including direct transcriptional repression as seen for Bcl-xL, X-IAP, TRAF2, c-IAP, FLIP, and SH3BGRL and posttranscriptional repression of IRAK1 and TRAF6 via induction of microRNA (21, 33–35, 38, 39). Although in many cases, the detailed mechanisms remain to be uncovered, down-regulation of Bcl-xL by RelA is promoter-specific and involves association with HDAC1 (33, 34). How recruitment of Rel proteins to the blnk and bcap promoter regions leads to their down-regulation remains to be determined. The histone deacetylase inhibitor trichostatin A (TSA) failed to abrogate down-regulation of blnk and bcap in DT40 cells expressing Rel (data not shown), but we do not rule out involvement of other TSA-insensitive HDACs. Interaction with other transcription factors might also influence the transcriptional outcome, as shown for the Drosophila NF-κB protein Dorsal that is converted from a transcriptional activator into a repressor via interaction with DSP1 (40). Rel might suppress blnk and/or bcap expression by recruiting transcriptional repressors and/or by functionally interfering with activators that regulate their expression. Future studies will help to identify the mechanisms involved.

BCR signaling leads to growth arrest and apoptosis in immature B cells, whereas it promotes survival and proliferation of mature B cells via activation of Rel-dependent antiapoptotic and proproliferative genes (41–47). Both BLNK and BCAP play important roles in BCR signaling (28, 48, 49), and coexpression of either of these molecules potently reduced v-Rel’s ability to transform lymphocytes. In this regard, why would down-regulation of BLNK and BCAP be important for v-Rel–mediated transformation? The answer might reside in the fact that v-Rel–transformed cells are commonly arrested in the early stages of B-cell differentiation, although it can also transform some more mature B cells, T, myeloid, and dendritic cells (1, 50–53), and that BLNK is critically required for B-cell differentiation. Indeed, BLNK is a tumor suppressor and BLNK−/− mice show a high incidence of spontaneous pre-B-cell lymphomas that result from defective B-cell differentiation (29). Reintroduction of BLNK restored BLNK−/− pre-B-cell differentiation and inhibited their capacity

Figure 4. hc-Rel is bound to the endogenous blnk and bcap promoters in vivo. A, ChIP of hc-Rel bound to the ch-bcap promoter in DT40-hc-Rel cells compared with parental cells. ChIP with anti-hc-Rel, IgG, or NRS was PCR-amplified with primers for the ch-bcap promoter. B, RT-PCR showing that Rel protein binding to the ch-blink and bcap promoters coincides with reduced blnk and bcap mRNA levels compared with parental cells. C, ChIP of endogenous hc-Rel bound to the hu-blkn and bcap promoters in MLBCL-derived Karpas 1106 cells. ChIPs with anti-hc-Rel antibodies PC-139, NR265 or NR1136, IgG, or NRS were PCR-amplified with primers for the hu-bcap or blnk promoters or crp2 as control.
upon BCR engagement (27, 49). Given the interplay between the NF-κB and JNK signaling pathways where NF-κB fails to protect cells when JNK activation is sustained (56), it is tempting to speculate that suppression of BLNK, BCAP, and other BCR components like IgM might contribute to v-Rel’s ability to block B-cell differentiation and/or cell death to favor transformation of immature B cells. In this context, Rel’s ability to activate antiapoptotic and proproliferative genes would provide the necessary prosurvival and proproliferative activities to malignant transform lymphocytes in the absence of BCR signaling (14, 16, 43, 44, 57–61).

It is interesting to note that suppression of several BCR components and signaling molecules and activation of Rel/NF-κB are characteristic of human MLBCL and cHL that depend on hc-Rel for survival (10, 62). Indeed both tumor types show significantly decreased expression of BLNK, the cell surface immunoglobulin receptor IgM, tyrosine kinase Blk, the Bruton tyrosine kinase–binding protein SAB and PKCβ (which act downstream of BCAP), and Akt (which lies downstream of BCAP) are also reduced in MLBCL (10, 30, 31). Although the mechanisms by which Rel proteins function in lymphocyte transformation might differ across species (63), our findings with v-Rel in chicken lymphocytes raise the possibility that because resistance to apoptosis and defects in cell differentiation are commonly linked with cancer, persistent Rel protein activation might contribute to the tumor phenotype by helping to downregulate BCR signaling, and at the same time enabling cells to bypass their reliance on BCR signaling for proliferation and survival through Rel’s proproliferative and antiapoptotic activities. Overall, this study highlights a novel link between Rel protein expression, down-regulation of BLNK and BCAP, and Rel-mediated lymphocyte transformation and suggests that gene repression may be as important as transcriptional activation for the transforming activity of Rel proteins.

Figure 5. BCAP and BLNK strongly antagonize v-Rel–mediated transformation of primary chicken lymphocytes. A, immunoblot showing efficient coexpression of BLNK or BCAP and v-Rel. An asterisk marks the position of v-Rel. B, coexpression of BLNK or BCAP with v-Rel markedly reduced primary CSC transformation as detected by colony formation in soft agar. Average of three independent assays.

References

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