Homozygosity for the \textit{aly} point mutation in NF-\kappaB-inducing kinase (NIK) results in alymphoplasia in mice, a phenotype similar to that of homozygosity for deletion of the lymphotixin \textit{\beta} receptor (LT\(\beta\)R). We now find that NF-\kappaB activation by Epstein-Barr virus latent membrane protein 1 (LMP1) or by an LMP1 transmembrane domain chimera with the LT\(\beta\)R signaling domain in human embryonic kidney 293 cells is selectively inhibited by a wild type dominant negative NIK comprised of amino acids 624–947 (DN-NIK) and not by \textit{aly} DN-NIK. In contrast, LMP1/COD40 is inhibited by both wild type (wt) and \textit{aly} DN-NIK, LMP1, an LMP1 transmembrane domain chimera with the LT\(\beta\)R signaling domain, and LMP1/COD40 activate NF-\kappaB in wt or \textit{aly} murine embryo fibroblasts. Although wt and \textit{aly} NIK do not differ in their \textit{in vitro} binding to tumor necrosis factor receptor-associated factor-1, 2, 3, or 6 or in their \textit{in vivo} association with tumor necrosis factor receptor-associated factor 2 and differ marginally in their very poor binding to IxB kinase \textit{\beta} (IKK\textit{\beta}), only wt NIK is able to bind to IKK\(\alpha\). These data are compatible with a model in which activation of NF-\kappaB by LMP1 and LT\(\beta\)R is mediated by an interaction of NIK or a NIK-like kinase with IKK\(\alpha\) that is abrogated by the \textit{aly} mutation. On the other hand, COD40 mediates NF-\kappaB activation through a kinase that interacts with a different component of the IKK complex.

NF-\kappaB-inducing kinase, NIK, is a TRAF2-interacting mitogen-activated protein kinase kinase kinase that potently activates NF-\kappaB (1–3). NIK can activate the IxB kinase (IKK) complex by phosphorylating serine 176 in the activation loop of IKK\(\alpha\) and may directly phosphorylate IKK\(\beta\) (4–6). NIK activation of IKK results in phosphorylation of IxB\(\alpha\) serines 32 and 36, IxB\(\alpha\) ubiquitination and degradation, and NF-\kappaB translocation to the nucleus. Overexpression of a catalytically inactive mutant of NIK (NIK K429A/K430A) has a dominant negative effect on NF-\kappaB activation through most known stimuli including LMP1, TNFR1, TNFR2, RANK, hTollR, CD3/CD28, interleukin-1\(\beta\), human T-cell lymphotropic virus-1 Tax, and LPS (1, 7–11).

NIK has an essential role in lymphoid organ development (12). The \textit{aly} mutation results in a single amino acid change of glycine to arginine at mNIK codon 855 and can be rescued by transgenic expression of wild type NIK (12). Alymphoplasia (\textit{alyaly}) mice not only lack lymph nodes and Peyer’s patches but also have abnormal spleen and thymus development, low serum Ig levels, and impaired B cell proliferation in response to LPS or CD40L (12, 13). LT\(\beta\)R and \textit{alyaly} mice have similar developmental and immunological defects, and NIK has been implicated in LT\(\beta\)R-mediated activation of NF-\kappaB (14, 15). Indeed, LT\(\beta\)R up-regulation of VCAM-1 is abnormal in \textit{alyaly} murine embryo fibroblasts (15). Also, CD40L-induced phosphorylation of IxB\(\alpha\) is abnormal in B lymphocytes from \textit{alyaly} mice, although phosphorylation of IxB\(\alpha\) in dendritic cells is normal (13).

Epstein-Barr virus (EBV) latent infection of human B lymphocytes causes B lymphocyte proliferation through expression of nuclear proteins and an integral membrane protein, LMP1, which mimics constitutively activated TNFRs (16). LMP1 has a short, arginine-rich, N-terminal cytoplasmic domain that is important for anchoring the first transmembrane domain, six hydrophobic transmembrane domains that mediate LMP1 aggregation in lipid rafts, and a 200-amino acid C-terminal cytoplasmic domain that has two sites that mediate EBV-induced B cell proliferation and NF-\kappaB activation (for review see Ref. 17). One site binds TRAF3, 1, 2, and 5, whereas the second site binds TNFR-associated death domain protein (18, 19). NF-\kappaB activation from either site is inhibited by overexpression of K429A/K430A kinase-negative DN-NIK (7). Thus, previous data are consistent with NIK having a significant role in LMP1 activation of NF-\kappaB. The experiments reported here further investigate the role of NIK and of the \textit{aly} mutation in NF-\kappaB activation by LMP1, LT\(\beta\)R, and COD40.

**EXPERIMENTAL PROCEDURES**

Expression Vectors—Wild type hNIK\(_{64–447}\) was amplified by PCR of hNIK cdna with oligonucleotides NF3 (5’ GGATCCCTCTCA-CAGCCCGAGGATCATC 3’) and NR1 (5’ GAATTCCTAGGCGCTTG-TGCCAGCTGGGC 3’) that included BamHI and EcoRI sites and cloned into pGEX-2TK (Amersham Pharmacia Biotec) for bacterial expression. The \textit{aly} hNIK\(_{64–447}\) GST mutant was made by site-directed mutagenesis of the hNIK codon 860 with primers NF5 (5’ AGCTATTCAATCGGGTGAAAGTCCAAATA CAG 3’) and NR6 (5’ CTGTATTGGACTTTACCCGGTATGAGATAGTGG 3’) followed

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by PCR with the BamHI and EcoRI primers and cloned into pGEX-2TK. The BamHI/EcoRI fragments were also used to make wt and aly DN-NIK for mammalian expression by subcloning into pcDNA3 (Invitrogen). Plasmids encoding TRAF1, TRAF2, TRAF3, IKKα, IKKβ, LMP1, CD40, and LMP1/CD40 have been described (7, 16–27). The pCR-F-Traf6 plasmid was obtained from Dr. J. Inoue. The LMP1/LTβR construct was made by cloning the cytoplasmic domain from LTβR into the previously described LMP1 pcDNA3 construct.

**Cell Lines**—293 and 293T cells were cultured as previously described (7). MEFs of aly/aly and wild type mice were obtained from Dr. T. Honjo. Primary MEFs were not amenable to transfection. Therefore, cells were infected with a human papilloma virus 16 E6/E7 retrovirus containing a neomycin resistance cassette (obtained from Dr. P. Howley), and transformed cell lines were selected for G418 resistance and growth advantage. Cells were subsequently grown in Dulbecco’s modified Eagle’s medium with 20% fetal calf serum and antibiotics.

**Transfections and Reporter Gene Assays**—Transfections and reporter assays (7) were done with 350 ng per well of the 3xNF-κB-luc reporter plasmid and 350 ng per well of pGK-β-galactosidase as a transfection control. Measurements of luciferase and β-galactosidase activities were done with an Optocomp I luminometer (MGM Systems).

**Radioimmunoassays** (7) were done with 350 ng per well of the 3xNF-κB-luc reporter plasmid and 350 ng of pGK-β-galactosidase. Also, increasing amounts (0.1, 1, and 2 µg) of either wt or aly DN-NIK were transfected. Raw luciferase values were divided by β-galactosidase values to control for transfection efficiency. The effects of DN-NIK on LMP1-mediated NF-κB activation are expressed as a percentage of the activation with LMP1 transfected alone. Values represent the average from three independent experiments. C, lysates from transfected cells were subjected to SDS-PAGE and IB using either LMP1 or NIK antibody. For LMP1 IB, lanes 1–4 represent cells transfected with LMP1 plus 0, 0.1, 1, or 2 µg of wt DN-NIK. No change in expression of LMP1 was detected in the presence of aly DN-NIK (not shown). For NIK, IB of lysates from cells transfected with LMP1 and 0, 0.1, or 2 µg of wt DN-NIK (lanes 1–3) and 0.1 or 2 µg of aly DN-NIK (lanes 4–5) are shown.

**Effects of wt or aly DN-NIK on LTβR and CD40 Activation of NF-κB**—To evaluate whether the differential effect of the wt and aly DN-NIK is specific for LMP1 and LTβR signaling as opposed to other TNFRs, the effect of wt and aly DN-NIK on NF-κB activation by LMP1, LTβR, and CD40 was assayed in 293T and 293 cells. The LMP1 transmembrane domains were used to provide constitutive, ligand-independent receptor aggregation. Isoegenic expression constructs were made in which the LMP1 C-terminal cytoplasmic domain was replaced with the LTβR or CD40 C-terminal cytoplasmic domains. LMP1 and the LMP1/LTβR chimera activated NF-κB, and the activation was inhibited by wt but not by aly DN-NIK (see Fig. 1 and Fig. 2, A and B). wt and aly DN-NIK did not affect LMP1/LTβR expression, and β-galactosidase levels did not vary more than 2-fold (Fig. 2C and data not shown). These results are consistent with the previous observation that NF-κB activation following LTβR overexpression is inhibited by wt but not by aly DN-NIK (12). In contrast to the effects of wt but not aly DN-NIK on LMP1 or LMP1/LTβR activation of NF-κB, NF-κB activation mediated by an LMP1/CD40 cytoplasmic domain chimera or by CD40 overexpression was inhibited by both wt and aly DN-NIK (Fig. 3). Effects of aly DN-NIK on NF-κB expression by CD40 and LMP1/CD40 expression were not affected by either wt or aly DN-NIK (Fig. 3C and data not shown). These data support a model in which LMP1 and LTβR activation of NF-κB involves a downstream molecular interaction that can be inhibited by wt hNIK aa 624–947 but not by the corresponding fragment with the glycine to arginine mutation at codon 860. LMP1, LMP1/LTβR, and LMP1/CD40 Activation of NF-κB in wt and aly MEFs—To evaluate the direct effect of the aly mutation on LMP1, LTβR, and CD40 activation of NF-κB,
NF-κB activation by isogenic LMP1, LMP1/LTβR, and LMP1/CD40 was assessed in wt and aly/aly MEFs using the co-transfected NF-κB-dependent luciferase reporter and control pGK-β-galactosidase expression plasmids. Before initiating this series of experiments, the MEFs were first transfected with a human papilloma virus 16 E6 and E7-expressing retrovirus so as to enhance their growth and transfection efficiency (24). The surprising result was that LMP1, LMP1/LTβR, and LMP1/CD40 activated NF-κB similarly in wt and aly/aly MEFs indicating that NIK is not essential for NF-κB activation by these receptors in fibroblasts (Fig. 4). Thus, the insensitivity of LMP1 and LMP1/LTβR to aly DN-NIK inhibition of NF-κB activation is not because of a specific and exclusive dependence of these receptors on wt NIK for NF-κB activation.

aly NIK Interacts with TRAFs in Vitro and in Vivo—The aly mutation at codon 860 falls within both the TRAF binding domain (aa 624–947) and the IKK binding domain (aa 947–14604) of LMP1/LTβR and LMP1/CD40 (not shown). Binding of wt and aly DN-NIK was assessed. As reported for full-length NIK (27), FLAG-tagged IKKβ bound very weakly to wt NIK 624–947-GST, at a level of about 1% of input IKKβ (Fig. 6A). Binding of F-IKKβ to aly NIK 624–947-GST was about half the level of binding to wt and about twice as strong as to GST alone (Fig. 6A).

To evaluate the association of Myc-IKKα with wt or aly DN-NIK in vivo, 293T cells were co-transfected with Myc-IKKα and wt or aly DN-NIK expression vectors, lysed in non-ionic detergent, and immune-precipitated with anti-Myc antibody.
recently defined to play a role in regulating NIK activity by preventing the interaction between the C terminus of NIK and IKKα (39). The ATP binding pocket within the conserved MAP kinase domain is ablated by the K429/V430A mutation (1). Thr 559 is the critical residue in the activation loop of the kinase domain that is phosphorylated by Tpl2 and is required for kinase activation (3). The region from aa 624–947 has been defined as the necessary and sufficient TRAF binding domain (1), and is required for kinase activation (3). The region from aa 624–947 has been defined as the necessary and sufficient TRAF binding domain (1),2 whereas an 735–947 within this domain is necessary and sufficient for IKKα binding (3). The alymphoplasia phenotype is caused by a single point mutation (Gly to Arg) occurring at amino acid 855 in mNIK (12) and is in a highly conserved region in hNIK at amino acid 880: BR, basic region; PRR, proline-rich region. B, [35S]methionine-labeled, in vitro-translated TRAFs 1, 2, and 3 or mTraf6 were incubated with wt NIK624–947-GST, aly NIK624–947-GST, or GST alone. The 10% input lane indicates 10% of the total IVT reaction lysate used for each binding assay. Samples were resolved by SDS-PAGE, and binding was analyzed by phosphorimaging. C, 293T cells were co-transfected with F-TRAF2 and either wt or aly DN-NIK. F-TRAF2NIK complexes were immunoprecipitated with anti-FLAG resin (M2, Sigma) followed by IB with anti-NIK antibody. 2% of whole cell lysates were probed with anti-TRAF2 and anti-NIK antibody.

followed by immune blotting for NIK. The efficiency of the Myc-IKKα IP was about 10% (data not shown). wt DN-NIK was readily detected in the immune precipitate, whereas aly DN-NIK was not detectable (Fig. 6B). Thus, the aly mutation results in virtually complete loss of interaction or association of DN-NIK with IKKα.

DISCUSSION

The data presented here indicate that LMP1, LMP1/LTβR, and LMP1/CD40 activate NF-κB similarly in wild type and aly/aly murine embryo fibroblasts. Therefore, NIK either does not have a direct role in NF-κB activation from any of these receptor cytoplasmic domains in MEFs, or another kinase substitutes for NIK in the transfected aly/aly fibroblasts and is unable to substitute under more physiologic conditions in vivo. Although this latter possibility seems a priori unlikely, similar substitution effects have been noted among MAP kinases in yeast, for example (28–33). Further, the similarity between the aly/aly and LTβR−/− phenotypes is most consistent with a physiologically significant role for the aly mutation in LTβR signaling. Moreover, the inability of the aly DN-NIK to specifically block LMP1 and LMP1/LTβR activation of NF-κB in 293 cells supports the notion that these cytoplasmic domains signal through a pathway that is specifically blocked by wt and not by aly DN-NIK. Indeed, the biochemical studies further support the hypothesis that the effect is at the level of NIK per se, in indicating that aly hNIK is most abnormal in loss of interaction with IKKα, is not abnormal in interaction with TRAF1, 2, 3, or 6, and is only minimally evident in diminished very weak interaction with IKKβ.

The simplest explanation of the inability of the aly DN-NIK to block LMP1 or LMP1/LTβR activation of NF-κB is that aly DN-NIK is unable to bind to an essential mediator of that pathway. The aly mutation is within the NIK TRAF binding domain, and the failure of aly NIK to block some TNFRs has been attributed to a putative effect of the aly mutation on TRAF binding. Our data indicate that the aly mutation does not affect NIK binding to or association with TRAF1, 2, 3, or 6, making it less likely that the aly effect is at the level of TRAF interaction with NIK. Instead, we find aly NIK to be highly deficient in binding to IKKα and that both wt and aly mutant NIK bind poorly to IKKβ. Thus, the ability of wt NIK and the inability of aly NIK to block NF-κB activation from LMP1 or LMP1/LTβR are most consistent with a key role for a NIK-like kinase and IKKαs in LMP1 and LTβR activation of NF-κB. Further, the blockade of CD40 and LMP1/CD40 activation of NF-κB by both wt and aly DN-NIK are most compatible with the possibility that CD40 signaling through the IKK complex is mediated by a protein that can be blocked by either the wt or aly NIK C terminus.

During the preparation of this manuscript, two publications appeared that are relevant to these experiments. In one, NIK is found to associate with the p100 precursor to the NF-κB subunit p52 and induce its phosphorylation and proteolytic processing (34). aly NIK, however, is unable to associate with p100 or induce p100 phosphorylation and processing (34). Consistent with these observations, p52 is not detected in aly/aly cells, despite the presence of p100 (34, 35). However, although

\(^2\) M. L. and E. K., unpublished observations.

FIG. 5. wt and aly NIK bind to TRAFs in an equivalent manner. A, a schematic diagram of NIK is shown. N-terminal regions were required for kinase activation (3). The region from aa 624–947 has been defined as the necessary and sufficient TRAF binding domain (1), whereas an 735–947 within this domain is necessary and sufficient for IKKα binding (3). The alyymphoplasia phenotype is caused by a single point mutation (Gly to Arg) occurring at amino acid 855 in mNIK (12) and is in a highly conserved region in hNIK at amino acid 880: BR, basic region; PRR, proline-rich region. B, [35S]methionine-labeled, in vitro-translated TRAFs 1, 2, and 3 or mTraf6 were incubated with wt NIK624–947-GST, aly NIK624–947-GST, or GST alone. The 10% input lane indicates 10% of the total IVT reaction lysate used for each binding assay. Samples were resolved by SDS-PAGE, and binding was analyzed by phosphorimaging. C, 293T cells were co-transfected with F-TRAF2 and either wt or aly DN-NIK. F-TRAF2NIK complexes were immunoprecipitated with anti-FLAG resin (M2, Sigma) followed by IB with anti-NIK antibody. 2% of whole cell lysates were probed with anti-TRAF2 and anti-NIK antibody.

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FIG. 6. wt and aly NIK bind to TRAFs, however aly NIK does not bind to IKKα. A, wt NIK624–947-GST, aly NIK624–947-GST, or GST were used to precipitate either Myc-IKKα or F-IKKβ from transfected 293T cells. GST-bound IKKs were subjected to SDS-PAGE followed by IB for the appropriate tag. IB with IKKα antibody (M110; Santa Cruz Biotechnology) resulted in an identical result (data not shown). B, 293T cells co-transfected with the indicated amounts of wt or aly DN-NIK, along with a constant amount of Myc-IKKα expression vector, and were immunoprecipitated with anti-myc antibody followed by IB with anti-NIK antibody. Lysates contained equivalent amounts of IKKα and DN-NIK proteins (not shown).
p52−/− mice have major defects in germinal center formation and splenic architecture similar to aly/aly and LTβ−/− mice, serum Ig levels and proliferation in response to LPS and CD40L appear relatively normal in p52−/− mice but are abnormal in aly/aly mice (36, 37). Therefore, the deficiency in p100 processing is likely to account for only part of the aly/aly phenotype. In a second very recent paper, B cells from IKKα−/− mice are found to be quite similar to aly/aly B cells in their response to LPS and CD40L (38). This report is consistent with our finding that the inability of aly mice to process p100 into p52 and the inability of aly to interact with IKKα may both contribute to the aly/aly phenotype.

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Effects of the NIK aly Mutation on NF-κB Activation by the Epstein-Barr Virus Latent Infection Membrane Protein, Lymphotoxin β Receptor, and CD40

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