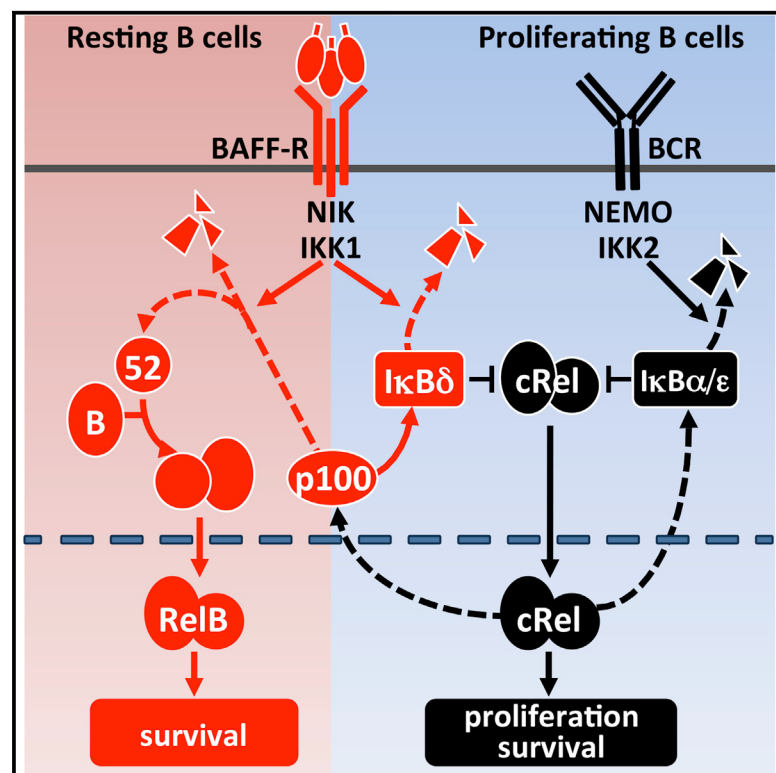


Cell Reports

A Pathway Switch Directs BAFF Signaling to Distinct NF κ B Transcription Factors in Maturing and Proliferating B Cells

Graphical Abstract



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In Brief

Almaden et al. show that BAFF, an activator of the noncanonical NF κ B pathway, provides critical B cell survival signals via RelB or contributes to B cell proliferation via cRel. An iterative systems biology approach revealed *Nfkb2* p100 as a pathway switch that directs noncanonical NF κ B signaling to either RelB:p52 activation or potentiation of cRel:p50.

Highlights

- BAFF enhances in vitro survival of maturing B cells and aids B cell proliferation
- BAFF's activation of RelB is required for enhanced cell survival, but not division
- In proliferating B cells, BAFF neutralizes p100-mediated termination of cRel
- Disrupting IκBδ expression/assembly mimics BAFF's costimulation of B cell expansion

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A Pathway Switch Directs BAFF Signaling to Distinct NF κ B Transcription Factors in Maturing and Proliferating B Cells

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SUMMARY

BAFF, an activator of the noncanonical NF κ B pathway, provides critical survival signals during B cell maturation and contributes to B cell proliferation. We found that the NF κ B family member RelB is required *ex vivo* for B cell maturation, but cRel is required for proliferation. Combined molecular network modeling and experimentation revealed *Nfkb2* p100 as a pathway switch; at moderate p100 synthesis rates in maturing B cells, BAFF fully utilizes p100 to generate the RelB:p52 dimer, whereas at high synthesis rates, p100 assembles into multimeric I κ Bsome complexes, which BAFF neutralizes in order to potentiate cRel activity and B cell expansion. Indeed, moderation of p100 expression or disruption of I κ Bsome assembly circumvented the BAFF requirement for full B cell expansion. Our studies emphasize the importance of p100 in determining distinct NF κ B network states during B cell biology, which causes BAFF to have context-dependent functional consequences.

INTRODUCTION

Mature follicular B cells are largely responsible for thymus (T)-dependent antigenic responses. Two receptors critical for follicular B cell maintenance and expansion are the B cell antigen receptor (BCR) and the B-cell-activating factor receptor (BAFF-R). BCR is critical for antigen-responsive expansion and maintenance of the mature B cell pool (Lam et al., 1997). BAFF-R (and BAFF) is critical for the survival of maturing transitional B cells (Harless et al., 2001; O'Connor et al., 2004; Schiemann et al., 2001), enhances follicular B cells, enhances antigen-responsive B cell expansion *in vitro* (Huang et al., 2004; Rickert et al., 2011;

Schweighoffer et al., 2013), and strengthens T cell-dependent and independent humoral immune responses (Do et al., 2000; Litinskiy et al., 2002). Indeed, whereas initiation of germinal center formation was found to be independent of BAFF, the B cell responsiveness to antigens (via the BCR) is impaired in BAFF-signaling-deficient mice (Rahman et al., 2003; Vora et al., 2003).

BCR and BAFF-R are known to signal to NF κ B via two distinct pathways: the NEMO-dependent “canonical” pathway and the NEMO-independent “noncanonical” pathway, respectively. Activated BCR recruits the Carma1-Bcl10-Malt1-containing complex to the membrane, triggering NEMO ubiquitination and activation of the NEMO-containing IKK complex. This leads to nuclear translocation of preexisting RelA- and cRel-containing NF κ B dimers from the latent I κ B-inhibited cytoplasmic complexes (Hayden and Ghosh, 2008). BAFF-R stimulation sequesters TRAF3, resulting in the stabilization of NIK and activation of a NEMO-independent IKK1 kinase complex. This stimulates p100 processing to p52 and results in nuclear accumulation of RelB:p52 dimers (Claudio et al., 2002).

Recent studies have begun to address the molecular basis for the functional interactions between BCR and BAFF-R. Tonic BCR signaling and associated canonical pathway activity are critical for the constitutive expression of the *Nfkb2* gene generating p100 substrate for NIK/IKK1-dependent processing and production of RelB:p52 dimer in maturing B cells (Cancro, 2009; Stadanlick et al., 2008). Similarly, lymphotoxin-beta receptor-responsive noncanonical pathway activation was found to be dependent on constitutive canonical signaling (Basak et al., 2008). In the context of resting B cells, RelB is a presumed mediator of BAFF's survival functions dependent on tonic BCR. Extending this model to proliferating B cells suggests that heightened BCR-responsive canonical activity might strengthen BAFF-mediated activation of RelB. In other words, a costimulatory role of BAFF in the expansion of activated B cells might be achieved through RelB-mediated enhanced cell survival. However, there are indications that BAFF may in fact not only enhance cell survival but contribute to cell cycle entry of mature

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