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Signalling for B cell survival

Edina Schweighoffer[1] and Victor LJ Tybulewicz[1,2]

The number of mature B cells is carefully controlled by signalling from receptors that support B cell survival. The best studied of these are the B cell antigen receptor (BCR) and BAFFR. Recent work has shown that signalling from these receptors is closely linked, involves the CD19 co-receptor, and leads to activation of canonical and non-canonical NF-κB pathways, ERK1, ERK2 and ERK5 MAP kinases, and PI-3 kinases. Importantly, studies show that investigation of the importance of signalling molecules in cell survival requires the use of inducible gene deletions within mature B cells. This overcomes the limitations of many earlier studies using constitutive gene deletions which were unable to distinguish between requirements for a protein in development versus survival.

Addresses
[1] The Francis Crick Institute, London NW1 1AT, UK
[2] Imperial College, London W12 0NN, UK

Corresponding author: Tybulewicz, Victor LJ (Victor.T@crick.ac.uk)

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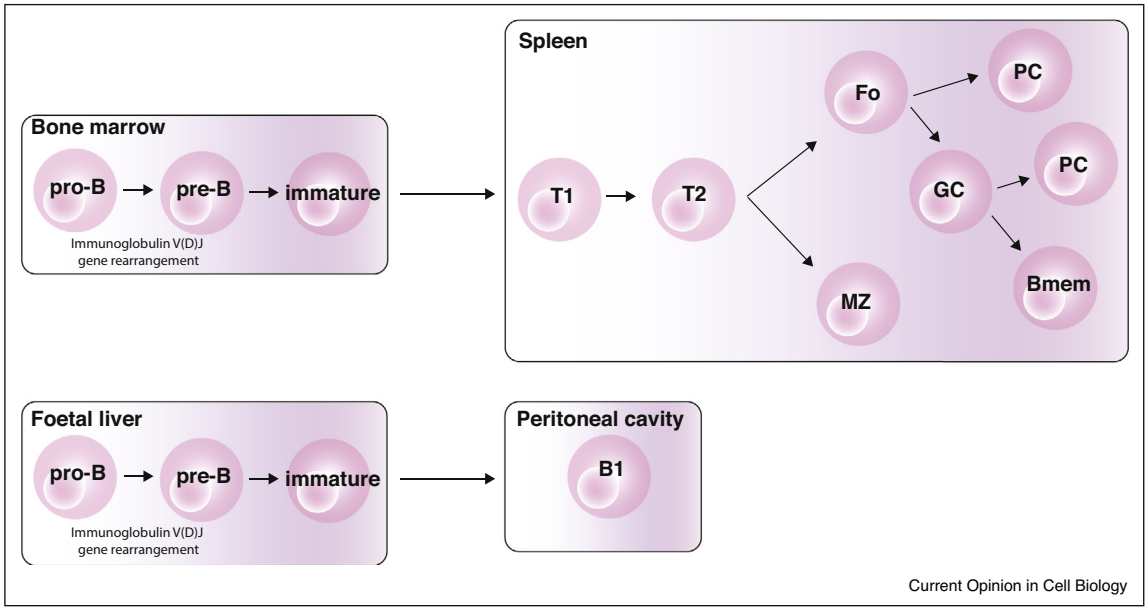
Introduction

B lymphocytes are white blood cells that form a critical part of the adaptive immune system. They develop in the bone marrow through several stages, eventually becoming immature B cells which migrate through the blood stream to the spleen, where, now termed transitional B cells, they complete their maturation into two subtypes of mature B cells: follicular and marginal zone B cells (Figure 1). A third mature B cell subtype, B1 cells, develop from the foetal liver and reside primarily in the pleural and peritoneal cavities. All mature B cells express B cell antigen receptors (BCRs) in the form of surface-bound immunoglobulin (Ig), with each mature B cell expressing a unique BCR. The BCR on naïve B cells is membrane-bound Ig in the form of a heterotetramer comprising 2 Ig heavy (IgH) chains either of the μ or δ isotype (making IgM or IgD respectively) complexed with 2 Ig light (IgL) chains (either κ or λ isotypes). Both IgM and IgD transduce signals through the associated CD79A (Igα) and CD79B (Igβ) chains. These contain an immune receptor tyrosine-based activation motif (ITAM) in their cytoplasmic domains which features two tyrosine residues that are phosphorylated following binding of antigen to the BCR, and are required for signalling through the receptor. Binding of antigen to the BCR, in combination with appropriate cell-cell contacts and cytokines from T cells or other immune cells, causes B cells to proliferate and differentiate into antibody-secreting plasma cells and memory B cells. Plasma cells and memory B cells are long-lived and form the basis of immunological memory.

The numbers of naïve (pre-activation) mature B cells are carefully controlled. This homeostasis is regulated by several receptors, the best studied being the BCR and BAFFR (TNFRSF13C), a receptor for the BAFF cytokine (TNFSF13B). Inducible deletion of the IgH genes or of the ITAM motif in CD79A in mature B cells leads to their rapid death indicating that signalling through the BCR is required for their survival [1,2]. Since the variable regions of the BCR are highly polymorphic, and there is no known antigen or ligand that binds all BCRs, it has been proposed that the BCR transduces a ligand-independent 'tonic' signal which is required for survival, distinct from the signal induced by antigen binding which leads to B cell activation. Further studies showed that key survival signals from the BCR are transduced via phosphoinositide 3-kinase (PI3-kinase) [3].

In mice deficient for either BAFF or BAFFR, B cell development is arrested between the T1 and T2 stages, leading to very few follicular or marginal zone B cells [4]. Direct evidence for a survival function for BAFF/BAFFR came from studies in which blocking antibodies or fusion proteins against either the cytokine or its receptor were injected into mice, leading to the rapid loss of follicular and marginal zone B cells [5–8]. Notably, B1 B cells are largely unaffected by the loss of BAFF or BAFFR, and thus are likely to use other mechanisms. BAFF is synthesised by a broad range of cells [reviewed in 9]. The homeostasis of B cells depends on BAFF secreted by fibroblastic reticular cells [10], whereas BAFF generated by haematopoietic cells such as T follicular helper (Tfh) cells and neutrophils is more important in supporting T-dependent and T-independent antibody responses, respectively [11,12]. Overproduction of BAFF in transgenic mice leads to an increased number of follicular B cells, demonstrating that the level of BAFF sets the overall number of B cells. BAFF transgenic mice are prone to developing autoimmunity similar to human systemic lupus erythematosus (SLE) and Sjögren's syndrome. This observation, combined with elevated levels of BAFF seen in SLE patients, has led to the development of anti-BAFF treatment for human SLE [13].

Figure 1



B cell development. B cells develop in the bone marrow initially as pro-B cells and then pre-B cells, in which IgH and IgL genes are rearranged, eventually generating immature B cells expressing a BCR in the form of IgM. These immature B cells migrate via the circulation to the spleen, becoming transitional type 1 (T1) and then T2 cells and finally completing their maturation into follicular (Fo) and marginal zone (MZ) B cells expressing both IgM and IgD. Activation of mature B cells leads to their differentiation into plasma cells (PC) and germinal centre (GC) B cells and memory B (Bmem) cells. B1 B cells, found primarily in the peritoneal and pleural cavities, are generated predominantly from precursors in the foetal liver.

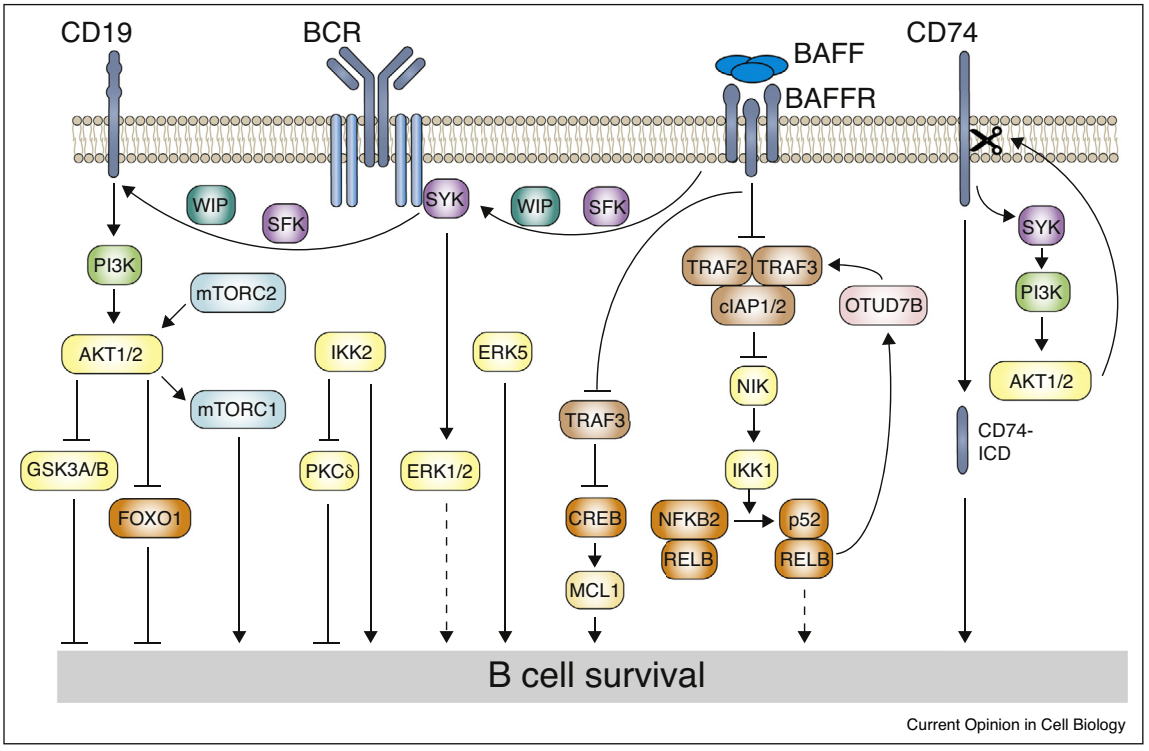
The best characterised signal transduction from BAFFR leads to the activation of the non-canonical NF-κB pathway [14,15]. A critical mediator of this is a complex of the E3 ubiquitin ligases TRAF3, TRAF2 and cIAP1 or cIAP2 (cIAP1/2), which ubiquitinates the NIK kinase, leading to its degradation. Binding of BAFF to BAFFR results in binding of TRAF3 to the cytoplasmic domain of BAFFR and subsequent redirection of the E3 ligase activity of cIAP1/2 to ubiquitinate TRAF3 causing its degradation. This allows NIK to accumulate and phosphorylate and activate IKK1, a kinase that is the critical mediator of the non-canonical NF-κB pathway. IKK1 phosphorylates NFKB2 (p100) leading to its processing into the transcription factor p52, which, with the associated RELB NF-κB transcription factor translocates into the nucleus and regulates transcription (Figure 2). In addition to the non-canonical NF-κB pathway, BAFFR has also been reported to activate AKT and ERK kinases, as well as IKK2, which activates the canonical NF-κB pathway, but the mechanisms by which this occurs are less well understood [16–20].

This review will focus on more recent advances in this area that have considerably changed our views of how these two receptors function.

Cooperation between BAFFR, BCR and CD19

Following antigen binding to the BCR and phosphorylation of the ITAMs of CD79A and CD79B, the SYK tyrosine kinase binds to the phospho-ITAMs, leading to its activation and subsequent signal transduction [21]. Inducible deletion of SYK in mature B cells lead to a loss of about 80% of follicular B cells, suggesting that SYK may transduce tonic BCR signals required for B cell survival [22]. However, unexpectedly, this study showed that SYK was phosphorylated, and presumably activated, following BAFF treatment of B cells. This BAFFR-mediated SYK activation was BCR-dependent, and led to the activation of ERK and PI3-kinase/AKT pathways, which were required for B cell survival. Thus, BAFFR transduces signals via the BCR leading to the activation of SYK, PI3-kinase and ERK (Figure 2). This finding showed that the BCR acts at least in part as an adapter protein in transducing signals from BAFFR. This interpretation has been challenged by a study showing that the small number of remaining SYK-deficient B cells are dependent on BAFFR for survival *in vivo* and are still able to respond to BAFF *in vitro* with increased survival, suggesting that BAFFR can signal independently of SYK [23]. However, both studies agree that BAFF-induced survival *in vitro* is compromised in the absence of SYK. Our own results confirm that *in vivo* survival of SYK-deficient B cells requires BAFFR, but mice with SYK-deficient B cells have elevated levels of BAFF (due to the very reduced number of B cells) which most likely compensates for the less efficient BAFFR signalling, allowing a small number of B cell to survive (ES and

Figure 2



Signalling pathways controlling B cell survival. Signalling from BAFFR to BCR and SYK depends on SRC-family kinases (SFK). Further signalling to CD19 requires either SFK or SYK. Regulation of the actin cytoskeleton by WIP is required for signal transduction from BAFFR to CD19. CD19 transduces signals to the activation of PI-3 kinases (PI3K) leading to activation of AKT1 and AKT2 and subsequent inhibition of GSK3A and GSK3B and FOXO1. Signals from the BCR via SYK lead to activation of ERK1 and ERK2, but it is unclear if this pathway contributes to survival. Both ERK5 and IKK2 (canonical NF-κB pathway) are activated by BAFFR signalling but the mechanism by which this happens is unclear. In the non-canonical NF-κB pathway, BAFFR transduces signals via the TRAF2-TRAF3-cIAP1/2 E3 ligases to NIK and IKK1, leading to processing of NFKB2 (p100) to p52, and translocation of p52/RELB complexes into the nucleus. TRAF3 also directly enters the nucleus and associates with CREB, leading to its degradation. CREB induces expression of MCL1. The non-canonical NF-κB pathway induces expression of OTUD7B deubiquitinase which stabilises TRAF3 and thereby forms a negative feedback loop. CD74 signals via SYK, PI3K and AKT1/2 leading to cleavage of CD74 within the membrane, release of the intracellular domain (CD74-ICD) which translocates to the nucleus and regulates gene expression.

VLJT, unpublished data). Taken together these studies show that BAFFR transduces signals in part via the BCR to SYK/PI3-kinase/ERK, but that the receptor also transduces SYK-independent signals for survival.

The pathway by which the BCR and SYK activate PI3-kinase may involve CD19, a transmembrane molecule that acts as a co-receptor for the BCR and contributes to B cell survival [23,24]. BAFFR signalling induces phosphorylation of CD19, and CD19 is required for BAFFR-induced activation of AKT (Figure 2) [24]. This phosphorylation could be mediated by SYK or by SRC-family kinases.

The mechanism by which BAFFR signals to BCR and CD19 remains unknown. TRAF3 is the only protein known to both directly interact with the cytoplasmic domain of BAFFR, and to transduce signals from the receptor; this interaction is mediated through by residues 154–158 (murine BAFFR). However, the final 8 amino acids of the receptor (168–175) also contribute to BAFFR signalling, but how they do so remains unknown, and may involve interaction with unknown signal transducers [25]. Potentially these residues could be involved in signalling to BCR, SYK and CD19.

Interestingly, B cells deficient in Wiskott–Aldrich Syndrome Interacting Protein (WIP) have defective BAFFR-induced phosphorylation of CD19, activation of AKT and *in vitro* BAFF-induced survival [26••]. In the absence of WIP, the dynamics of the actin cytoskeleton are altered, leading to increased diffusion of both the BCR and CD19, which may contribute to the poorer coupling between BAFFR, BCR and CD19. Thus, signalling from BAFFR to BCR and CD19 requires an intact actin cytoskeleton.

Non-canonical NF-κB pathway

A role for the non-canonical NF-κB pathway in BAFF-induced B cell survival was suggested by analysis of mice in which the NIK or IKK1 kinases had been

deleted early in B cells, resulting in a block at the T2 stage of B cell development, similar to that seen in BAFF-deficient or BAFFR-deficient animals [27–29]. This was further supported by a study showing that constitutive activation of NIK replaces BAFFR-mediated survival signals [30]. However, since in the above studies the *Nik* or *Ikk1* genes had been constitutively ablated, the loss of B cells could be due to a developmental block, rather than a requirement for NIK and IKK1 in B cell survival. More recent studies have deleted these two genes inducibly in mature B cells. Interestingly, inducible loss of NIK from mature B cells showed only a partial loss of follicular B cells, whereas inducible loss of IKK1 had no effect on B cell numbers [24,31•]. These results emphasise the importance of using inducible gene deletion to study the role of proteins in mature B cell survival, in contrast to constitutive deletions which have the complication of potentially affecting development. The partial requirement for NIK and no requirement for IKK1 in B cell survival was surprising in view of the extensive literature showing the activation of NIK, IKK1 and the non-canonical NF-κB pathway by BAFFR signalling. One possibility is that NIK may contribute to BAFF-dependent B cell survival by directly phosphorylating p100, bypassing IKK1 [32]. Alternatively, NIK may contribute by activating IKK2 and the canonical NF-κB pathway [19,33].

Activation of the non-canonical NF-κB pathway allows p52/RELB heterodimers to translocate to the nucleus and activate transcription. Both humans and mice deficient in RELB have no defect in numbers of mature B cells or show only a small reduction in follicular B cells [34,35•,36•]. In contrast, loss of NFKB2 in the B cell lineage resulted in a 50% reduction in the number of mature B cells, which was further reduced to around 20% in mice with a B cell-specific deficiency of both NFKB2 and RELB [35•]. The reduction in the number of B cells was seen from the T2 stage of development onwards, similar to that seen in BAFF or BAFFR deficiency, although the loss of mature B cells is not as severe. These results are consistent with a redundant requirement for NFKB2 and RELB in BAFF-induced B cell survival, but the loss of B cells could also be due to a developmental block.

Mice deficient in both RELB and CREL, an NF-κB transcription factor activated by the canonical NF-κB pathway, show a 50% reduction in mature B cell numbers and the mutant B cells show poor responses to BAFF *in vitro* demonstrating redundancy between factors activated by the two distinct NF-κB pathways [36•]. Once again, these mutations were constitutive, and thus it is not possible to distinguish if the loss of B cells is caused by a developmental block or by defects in B cell survival. Inducible deletions of *Nfkb2*, *Relb* and *Rel* genes in mature B cells would be needed to distinguish these possibilities.

Canonical NF-κB pathway

BAFFR signalling induces activation of the canonical NF-κB pathway [19,20]. Constitutive absence of IKK2, the kinase that activates the canonical NF-κB pathway, or of NEMO a structural protein that associates with IKK2, early in B cell development leads to an arrest at the T2 stage of development [20,37,38]. Furthermore, constitutively active IKK2 allows B cells to survive in the absence of BAFFR implying that the IKK2-driven canonical NF-κB pathway may be important for B cell survival [20]. In support of this, a constitutive deficiency of IKK2 or NEMO in mature B cells leads to a mild reduction in the number of B cells [39]. However stronger support for this conclusion awaits results of inducible deletions of IKK2 or NEMO in mature B cells, which have not yet been reported.

TRAF3 and OTUD7B

Constitutive elimination in B cells of either TRAF2, TRAF3 or cIAP1/2 results in increased numbers of mature B cells that can survive both *in vitro* and *in vivo* in the absence of BAFF, confirming the roles of these E3 ligases as repressors of a BAFFR-induced survival pathway thought to be the NIK-dependent and IKK1-dependent non-canonical NF-κB pathway [40,41].

Recent studies have shown that the relationship between TRAF3 degradation and p100 processing is complex. A TRAF3 mutant that cannot bind to TRAF2 or BAFFR is no longer degraded following BAFFR signalling but cells expressing this mutant still show BAFFR-induced processing of p100 to p52 [42]. Conversely, a mutation of the last 8 amino acids of the cytoplasmic domain of BAFFR in the A/WySnJ strain doesn't affect TRAF3 degradation but blocks p100 to p52 processing. Thus, TRAF3 degradation is neither required nor sufficient for p100 processing.

OTUD7B is a deubiquitinase that is induced by non-canonical NF-κB signalling, which binds to TRAF3, deubiquitinates it and stabilises it, thereby reducing signalling from BAFFR to NIK and IKK1 and forming a negative feedback loop [43].

An interesting recent study shows that some TRAF3 is localised to the nucleus where it binds to the CREB transcription factor and promotes its degradation [44••]. BAFFR-induced signalling leads to degradation of nuclear (and cytoplasmic) TRAF3, resulting in stabilisation of CREB and increased transcription of the *Mcl1* gene which encodes the MCL1 anti-apoptotic protein and hence enhances B cell survival. Thus, TRAF3 regulates more than just the non-canonical NF-κB pathway.

PI3-kinases

BAFFR signalling activates PI3-kinases via BCR, SYK and CD19 [17,18,22,24]. Studies using selective inhibitors have shown that BAFF-induced survival of murine B

cells *in vitro* is strongly impaired by inhibitors of p110δ (PIK3CD) but not p110γ (PIK3CG) PI3-kinases, implying that BAFFR preferentially signals via p110δ [45]. Constitutive elimination of AKT1 and AKT2 kinases, key PI3-kinase effectors, results in a 50% reduction in follicular B cells [46]. Inducible deletions of the PI3-kinases or AKT1/2 have not yet been reported, so it is unclear if these kinases are required for B cell development, survival or both.

ERK MAP kinases

BAFFR signalling activates ERK1 and ERK2 MAP kinases via the BCR and SYK [16,22]. ERK1 and ERK2 may contribute to survival by phosphorylating the pro-apoptotic BIM protein, leading to its degradation [16]. However, a recent study using selective inhibitors of MEK1 and MEK2, kinases that activate ERK1 and ERK2, showed that inhibition of this pathway had no effect on BAFF-induced survival *in vitro* [47••]. In contrast, selective inhibition of MEK5, the activator of the ERK5 MAP kinase, blocked BAFF-induced survival *in vitro* and B cell-specific constitutive deletion of *Erk5* led to loss of around 50% of follicular B cells [47••]. These results suggest that ERK5, but not ERK1 or ERK2 may be required for B cell survival.

PKC

Treatment of B cells with BAFF results in phosphorylation of Protein Kinase C δ (PKCδ) and its translocation from the nucleus to the cytoplasm [48,49]. Nuclear PKCδ promotes apoptosis and, in the absence of PKCδ, numbers of mature B cells increase. Furthermore, PKCδ is a negative regulator of proximal BCR signalling and hence may impact directly on survival signals transduced from the BCR. Further studies will be needed to establish how BAFFR transduces signals to PKCδ, but one possibility is that it occurs via IKK2 [20].

Metabolism

Treatment of B cells with BAFF leads to multiple metabolic changes [50]. BAFF induces activation of PI3-kinases, AKT and mTORC1 pathways which in turn cause B cells to increase in size and protein content and glycolysis [17,18]. BAFFR-induced TRAF3 degradation leads to increased expression of GLUT1 and Hexokinase 2 (HXK2), thereby increasing glucose uptake, anaerobic glycolysis and oxidative phosphorylation [51]. BAFFR signalling also results in upregulation of cell cycle genes such as CYCLIND2, CYCLINE and CDK4, preparing B cells to proliferate in response to mitogenic stimulation through the BCR, CD40 or TLRs [17]. Genetic analysis has shown that elimination of mTORC2 results in loss of around 50% of follicular B cells, potentially because of its role in activating AKT1/2 [52,53]. Surprisingly, loss of mTORC1 does not affect B cell numbers [54,55], potentially because of redundancy with PIM2: both mTORC1 and PIM2 upregulate the anti-apoptotic MCL1 protein [18,56].

A recent study has shown that the GSK3A and GSK3B act as metabolic sensors regulating cell growth and proliferation dependent on nutrient availability [57•]. Inducible loss of both GSK3A and GSK3B in mature B cells led to the loss of both follicular and marginal zone B cells. Interestingly, GSK3A and GSK3B function to restrict cell mass accumulation and to prevent metabolic collapse in nutrient-poor conditions by limiting MYC-dependent growth [57•].

Other emerging pathways

A recent study has highlighted a novel regulatory feature of the BAFF/BAFFR pathway showing that treatment of B cells with BAFF leads to processing and shedding of BAFFR by the ADAM10 and ADAM17 metalloproteases, thereby decreasing BAFF-induced survival [58•]. This process was dependent on expression of TACI (TNFRSF13B) a receptor that also binds BAFF, but does not directly transduce survival signals.

POU2AF1 (BOB.1) is a transcription factor whose expression is induced by BAFF treatment of B cells via both canonical and non-canonical NF-κB pathways [59]. Mice deficient in POU2AF1 have strongly reduced numbers of follicular and marginal zone B cells, suggesting that POU2AF1 is an important effector of survival downstream of BAFFR.

Constitutive loss of the GIMAP1 GTPase results in a block in B cell development at the T2 stage and a complete absence of follicular and marginal zone B cells, similar to the phenotype of mice deficient in BAFF or BAFFR [60•]. A similar loss of mature B cells was also seen after inducible loss of GIMAP1 [60•]. The molecular function of this protein remains unknown, but may involve regulation of NF-κB transcription factors.

Another survival receptor

CD74 is a receptor for MIF and is required for B cell survival [61]. Signalling from CD74 via SYK, PI3-kinase and AKT leads to intramembrane cleavage of CD74 and release of the CD74 intracellular domain (CD74-ICD) [61–63]. The CD74-ICD translocates to the nucleus, associates with RUNX3, RELA and chromatin and acts a transcriptional regulator [64•].

Concluding remarks

The last several years have led to many new insights into how signalling pathways control B cell survival. An important general point that has emerged is the importance of using inducible gene deletions in mature B cells to study the requirements for a protein in survival of B cells. Use of constitutive gene deletions can give misleading results, the best example of which is IKK1, long thought to be critical for the survival of mature B cells, until an inducible deletion of *Ikk1* showed no effect on B cell survival [24]. The same more rigorous approach needs to be applied to all other candidate genes being studied.

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- •• of outstanding interest

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