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B cells and the BAFF/APRIL axis: fast-forward on autoimmunity and signaling

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B-cell activation factor from the tumor necrosis factor family (BAFF) is a key survival factor during B-cell maturation — a delicate immune checkpoint for B cells. Excessive BAFF production at this stage corrupts B-cell tolerance and leads to autoimmunity. Elevated serum BAFF levels have been detected in some patients suffering from various autoimmune conditions. The positive outcomes of currently ongoing clinical trials using BAFF-neutralising agents confirm that this factor plays a major pathological role in rheumatoid arthritis and in systemic lupus erythematosus. Almost a decade after its discovery, BAFF continues to occupy the main stage in Immunology, with more than one hundred BAFF-related articles published per year. In recent years, our understanding of cell signaling and autoimmune mechanisms in this system have seen major advances, refining new possibilities for therapeutic intervention.

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Introduction

The immune system is characterised by a set of sophisticated mechanisms, not only aimed at protecting individuals from infections and cancer development but also designed to maintain immune tolerance by elimination of potentially harmful self-reactive lymphocytes. Immune tolerance is often achieved through a very subtle balance between life and death, only allowing the survival, development and activation of safe and protective immune cells. The B-cell activating factor from the tumor necrosis factor (TNF) superfamily (BAFF, also known as BLyS) has emerged as a crucial factor that modulates B-cell tolerance and homeostasis. Yet, interpretation of specific functions of BAFF remains complex owing to the presence of three receptors, two of which are shared with another ligand — a proliferation-inducing ligand (APRIL). Many reviews and commentaries have been written on BAFF and APRIL [1–10,11••,12], but this field is rapidly evolving and is in constant need of update. This review will particularly focus on some recent findings related to signaling in response to BAFF/APRIL activation and progress made in understanding the harmful autoimmune and malignant events unleashed in response to excessive BAFF production.

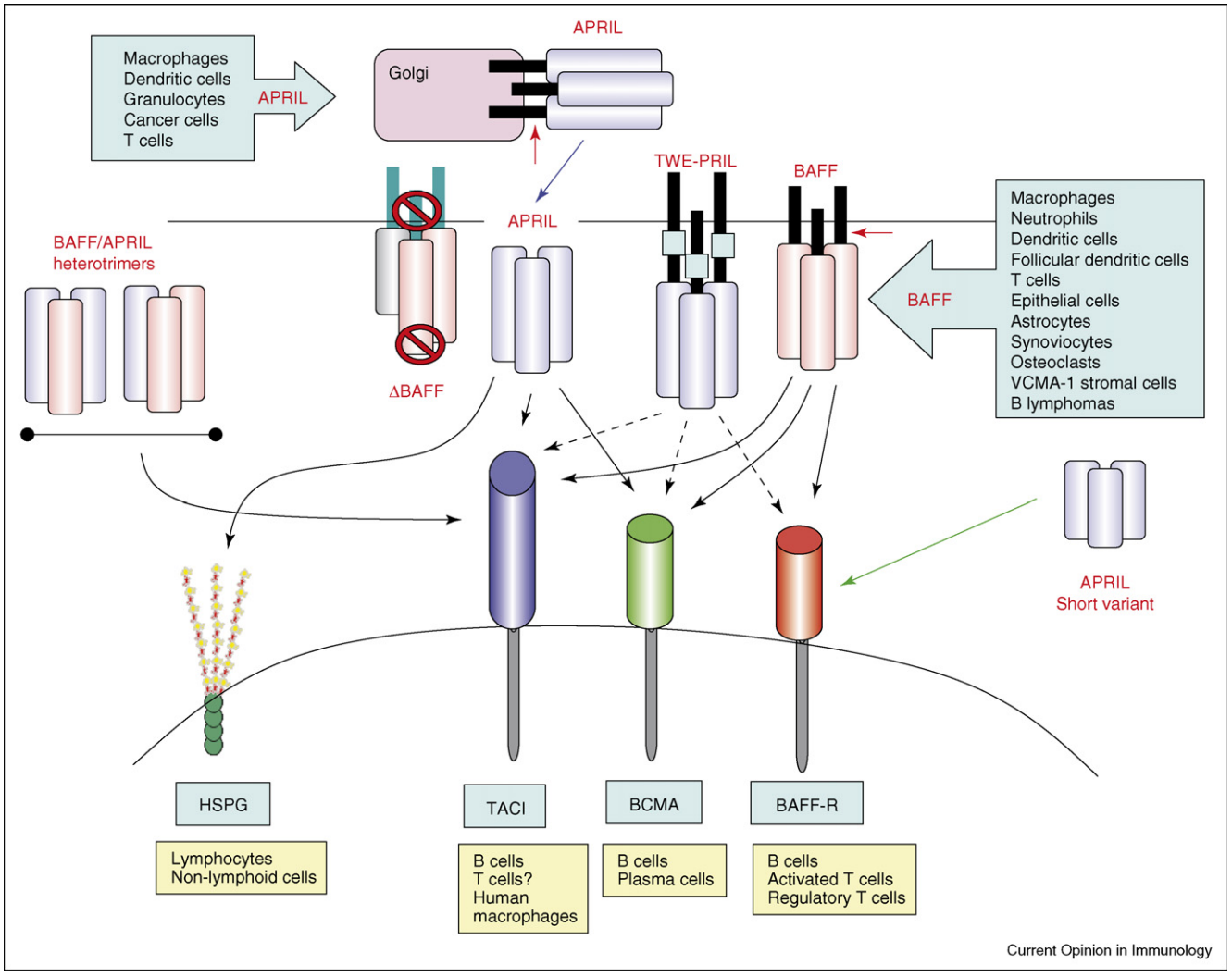
BAFF, APRIL and their receptors

BAFF and APRIL are members of the TNF family (reviewed in [12]). Like many TNF ligands, BAFF is a type II transmembrane protein [13] but it can also be secreted as a soluble homotrimeric or polymeric form after cleavage from the cell membrane (Figure 1). APRIL, by contrast, is cleaved in the Golgi before release and only exists as a secreted soluble form [14]. ΔBAFF is a splice variant of BAFF that is not released from the membrane; it acts as a negative regulator of BAFF function by forming multimers with the full-length version of the protein [15,16] (Figure 1). Heterotrimers of APRIL and BAFF [17] and a biologically active TWEAK–APRIL fusion protein, named TWE–PRIL [18], have also been identified (Figure 1).

Both BAFF and APRIL are expressed by monocytes, macrophages and dendritic cells (DCs) and at lower levels by T cells [12,19,20,21]. Human follicular DCs are also a source of BAFF [22]. Recent work revealed that non-lymphoid cell types also produce BAFF, for example airway [23] and salivary gland epithelial cells [24], fibroblast-like synoviocytes [25], astrocytes [26•], vascular cell adhesion molecule 1-positive stromal bone marrow cells [27] and osteoclasts, of which the latter also express APRIL [28]. Several cytokines such as type interferon (IFN)α, IFNγ, interleukin-10, granulocyte colony-stimulating factor and CD40 ligand (CD40L) as well as lipopolysaccharide (via the production of reactive oxygens [29]) and peptidoglycans can activate BAFF/APRIL production by macrophages, neutrophils and DCs [1].

The three BAFF receptors (Figure 1) — TACI (transmembrane activator and calcium modulator and cyclophilin ligand interactor, also known as TNFRSF13b), BCMA (B-cell maturation antigen, also known as TNFRSF17) and BAFF-R (BAFF receptor, also known as BR3 and TNFRSF13c) — are expressed on B cells [12]. BCMA is preferentially expressed on plasma cells, plasmablasts and tonsillar germinal center B cells [30–33]. BAFF-R is also expressed on activated T cells and regulatory T cells [11]. Intracellular TACI is present in human macrophages and migrates to the cell surface upon activation [34]. BAFF binds specifically to BAFF-R and shares TACI and BCMA

Figure 1



Interaction and expression of ligands and receptors in the BAFF/APRIL system. The top part of the figure shows the different types of ligands. From left to right: forms of BAFF/APRIL heterotrimers [17], a heterotrimer with ΔBAFF with red road signs indicating the impossibility of this ligand to be cleaved and have biological activity [15,16], APRIL cleaved from the Golgi then released as soluble ligand [10], the TWE–PRIL fusion protein [18], and BAFF homotrimers with a red arrow to indicate potential cleavage into a soluble ligand [12]. A short variant form of APRIL is represented (right) [35•]. Cell types that produce BAFF or APRIL are indicated in light blue boxes with an arrow. In the bottom part of the figure, receptors are represented from left to right: heparin sulfate proteoglycans (HSPG), TACI, BCMA and BAFF-R [11••]. Black solid arrows represent strong interactions, green solid arrows represent weak interactions, and broken lines represent interactions that have not been directly demonstrated. Below each receptor is a box that indicates cell types expressing these receptors.

with APRIL [2,12]. However, a recent study demonstrated that a short variant form of APRIL can bind to BAFF-R with low affinity [35•]. In addition, APRIL binds to proteoglycan structures expressed on lymphoid and non-lymphoid cells [11••]. However, whether proteoglycans play a role in concentrating APRIL on the cell surface or triggering signals remains unknown.

Physiological functions of the BAFF/APRIL system

The first indication of the normal function of BAFF came from *in vitro* assays showing the specific survival of maturing transitional type 2 (T2) splenic B cells in cultures supplemented with BAFF, suggesting a role for this protein as a survival factor during maturation of B cells in the spleen [12]. This model was confirmed when B-cell maturation in BAFF-deficient animals was found to be impaired beyond the immature transitional type I (T1) stage that lies immediately before the T2 stage [12]. This was a crucial finding revealing that, in addition to a functional B-cell receptor (BCR), immature B cells need other BAFF-mediated survival signals to fully mature. Current evidence shows that all known BAFF receptors are expressed on B cells at differing

levels depending on their maturation and/or activation state [36–39]. For instance, the level of TACI is low in T1 B cells but is high in T2 and marginal zone (MZ) B cells [33,40]. Furthermore, BCR ligation up-regulates BAFF-R expression on B cells [39,41], which promotes increased sensitivity to BAFF-mediated survival signals as B cells mature.

The role of APRIL is more elusive as conflicting results emerged from two independently generated APRIL$^{-/-}$ mouse models: one showed no obvious phenotype [40] whereas the other showed impaired switching to IgA, bigger germinal centers and increased numbers of effector T cells [42].

BAFF-R is the key receptor that triggers BAFF-mediated survival, as mice deficient in this receptor display a phenotype similar to that of BAFF-null mice [1,8,12]. BCMA-deficient mice are born with no major immune defect apart from impaired survival of some plasma cells in the bone marrow [8]. TACI, by contrast, emerged as a negative regulator of B-cell activation and expansion, as numbers of B cells are increased in TACI-deficient mice, B cells are hyper-responsive, and animals eventually develop systemic lupus erythematosus (SLE)-like disorders and lymphoid cancers [8,43–45]. Moreover, T-independent type II antibody responses are impaired in these mice [44]. Whether TACI plays the same role in humans is now a matter of debate because TACI mutations in humans have been associated with immunodeficiency such as common variable immunodeficiency [46•].

Finally, BAFF expression plays an important role in enforcing B-cell self-tolerance [47]. In particular, the physiological expression of BAFF at limiting levels combined with the impaired ability of certain autoreactive B cells to respond to BAFF survival signals results in the elimination of such specificities from the normal B-cell repertoire before they become mature long-lived cells [48–50]. The corollary of this is that upregulation of BAFF expression *in vivo* can result in the rescue of self-reactive B cells from elimination [49]. This effect explains, at least in part, the greatly increased levels of autoantibody production and associated autoimmune manifestations observed in transgenic mice that overexpress BAFF [51,52]. The link between BAFF and B cell mediated autoimmune disease is explored in more detail below.

Role of BAFF and APRIL in B-cell autoimmunity

Elevated levels of soluble BAFF have been observed in sera and target organs of mouse models that develop SLE [53], collagen-induced arthritis [54] or chemically induced autoimmunity [55]. Similarly, high levels of BAFF were found in sera and target organs of a sub-group of human patients (~20–50%) that have different autoimmune diseases. In many studies, BAFF levels correlated with disease activity and/or titres of pathogenic autoantibodies (Table 1). APRIL and BAFF/APRIL heterotrimers were also reported to be elevated in sera and target organs of autoimmune disease patients (Table 1). This evidence presents a strong case for the pathogenic role of excess BAFF and APRIL in autoimmune diseases. Unique polymorphisms in the *BAFF* gene that can regulate BAFF expression have been identified in mice and humans [56,57]. However, there is little evidence of *BAFF* polymorphisms being associated with any autoimmune diseases [56–58]. Thus, dysregulated expression of BAFF in autoimmune-prone individuals is likely to be determined by other genetic or environmental factors that regulate the responsiveness of BAFF-producing cells. By contrast, polymorphisms in the *APRIL* gene have shown an association to SLE in Japanese patients, implicating it as a susceptibility gene [59].

The pathogenic contribution of BAFF to autoimmune disease is also evident by the therapeutic benefit gained by its neutralization. SLE-prone mice treated with TACI–Ig or BAFF-R–Ig fusion proteins developed less and/or delayed proteinuria, resulting in prolonged survival [53,60,61,62•]. BAFF-R–Ig and TACI–Ig were equally effective at depleting mature follicular and MZ B cells, but did not affect numbers of immature or B-1 B cells. Both treatments also reduced numbers of activated and memory T-cell subsets. The similar disease outcome in TACI–Ig- and BAFF-R–Ig-treated mice meant that the therapeutic component of these constructs could mainly be attributed to neutralizing BAFF. Several studies have suggested that the protective efficacy of TACI–Ig and BAFF-R–Ig occurs through an autoantibody-independent mechanism [53,60,61,62•]. As autoreactive T cells can mediate glomerular damage independent of autoantibodies [63], TACI–Ig and BAFF-R–Ig might therefore achieve protection by eliminating follicular and MZ B cells that are acting as pathogenic antigen-presenting cells [64]. A recent study of BAFF-null SLE-prone mice suggested that the protective mechanism of BAFF neutralization might not necessarily be autoantibody-independent, because autoantibody titres in these animals were not reduced but were skewed towards Ig isotypes inept at causing glomerular pathology [65•].

BAFF antagonists also conferred protection in murine models of rheumatoid arthritis [12,66], multiple sclerosis [67] and Graves' disease [68], broadening their appeal as a therapeutics for human diseases. Blocking BAFF might provide distinct advantages over B-cell depletion therapy that targets CD20 (i.e. rituximab) [69]. First, BAFF receptors and CD20 overlap in many B-cell subsets but they differ in certain populations such as plasma cells, which express BCMA but not CD20. Second, another concern of rituximab is a side-effect leading to elevated serum BAFF levels [70]. Therefore, upon ceasing treatment, newly

Table 1

Pathological role of BAFF and APRIL in various diseases

Disease	Observations in sub-group of patients	Source of excess BAFF/APRIL	References
Autoimmune/allergic diseases			
Systemic lupus erythematosus	Increased levels of BAFF, APRIL and BAFF/APRIL heterotrimers in sera. Correlation with anti-dsDNA autoantibodies and disease activity.	T cells, DCs and probably macrophages	[69]
Sjögren's syndrome	Increased levels of BAFF and APRIL found in sera and in salivary glands. Correlation with anti-Ro/La autoantibodies, rheumatoid factor and total IgG.	T cells, macrophages and epithelial cells	[1]
Rheumatoid arthritis	Increased levels of BAFF, APRIL and BAFF/APRIL heterotrimers found in sera and joint synovial fluid. Correlations with anti-GPI antibodies (APRIL) and rhematoid factor (BAFF).	Macrophages, DCs and neutrophils	[1,103,104]
Multiple sclerosis	Increased levels of BAFF and APRIL found in spinal fluid and in neurological lesions.	Astrocytes and monocytes	[26,105]
Wegner's granulomatosis	Increased serum levels of BAFF.	?	[106]
Bullous pemphigoid	Increased serum levels of BAFF.	?	[107]
Myasthenia gravis	Elevated levels of BAFF in the thymic medulla may support pathogenic B cells present in the thymus.	Macrophages, DCs, lymphocytes and epithelial cells	[108]
Asthma	Excess serum levels of BAFF in IgE- and non-IgE-associated disease. Correlated with severity of asthmatic symptoms.	?	[109]
Infectious disease			
Epstein-Barr virus (EBV)	EBV-encoded LMP1 induces abnormal expression BAFF and APRIL by B cells, which might confer susceptibility to cancer.	B cells	[110]
Human immunodeficiency virus	Elevated BAFF levels in infected patients. Associated with anti-phospholipid autoantibodies.	Myeloid cells	[111]
Hepatitis C infection	Elevated BAFF in sera. Associated with HCV-related SLE, arthralgia and vasculitis.	?	[112]
Cancer			
Hodgkin's lymphoma	Elevated BAFF and APRIL in tumour environment. Binds to TACI and BCMA on malignant B cells, conferring increased survival.	Cancerous B cells and immune infiltrate	[78]
Non-Hodgkin's lymphoma	Elevated BAFF in tumour environment and sera. Binds to TACI and BAFF-R on malignant B cells, conferring increased survival. Higher BAFF levels correlate with aggressiveness of tumour and poor disease outcome.	Cancerous B cells and macrophages	[81,84]
B-cell chronic lymphocytic leukaemia	Elevated BAFF and APRIL in tumour environment and sera. Binds to TACI and BAFF-R on malignant B cells, increasing survival.	Cancerous B cells and nurse-like cells	[5]
Waldenström's macroglobulinaemia	Elevated BAFF in sera and bone marrow environment of tumour. Binds primarily to BAFF-R and TACI on tumour, enhancing survival. BAFF induces IgM production by tumour.	Cancerous B cells	[79]
Multiple myeloma	Excess BAFF and APRIL in sera and bone marrow environment of tumour. Binds primarily to BCMA and TACI on tumour cells, enhancing survival. Low TACI expression by cancer associated with bad prognosis.	Cancerous B cells, monocytes, neutrophils, stromal cells and osteoclasts	[85,86,113]

generated immature cells could be exposed to high levels of BAFF, causing a resurgence of autoimmunity. This could, in theory, be averted by targeting BAFF. BAFF-R–Ig and a monoclonal antibody specific for human BAFF (LymphoStat-B, which is also known as Belimumab) [71] are currently being tested for therapy. In monkeys and humans, both reagents exhibited little adverse toxicity and are effective at neutralizing BAFF, resulting in depletion of mature peripheral B-cell subsets [71–74]. Recently completed phase II clinical trials of LymphoStat-B in rheumatoid arthritis and SLE patients have shown encouraging results [75] (http://www.hgsi.com/products/LSB.html).

BAFF and APRIL in B-cell malignancy

Direct evidence for the role of BAFF and APRIL in B-cell malignancies was demonstrated in mouse models that transgenically overexpressed these molecules. Thus, an increased incidence of B-cell lymphomas was observed in each case [76,77]. In humans, excess BAFF and APRIL have been detected in sera and tumour microenvironments of patients that have various mature B-lineage malignancies (Table 1), most recently in Waldenström macroglobulinemia and Hodgkin's lymphoma [78,79]. Many malignant B-cell types express abnormally high levels of BAFF and APRIL (Table 1) compared with their non-transformed counterparts. Other cells that inhabit or infiltrate tumour microenvironments can also contribute to excessive levels BAFF and APRIL (Table 1). Binding of BAFF or APRIL to their respective receptors significantly increases the survival and proliferation of all malignant B-cell types in culture [78–87]. Conversely, treatment with APRIL and/or BAFF antagonists [83–85] prevented growth and increased apoptosis of tumour

cells, sparking great interest in such reagents for innovative treatment of B-cell malignancies.

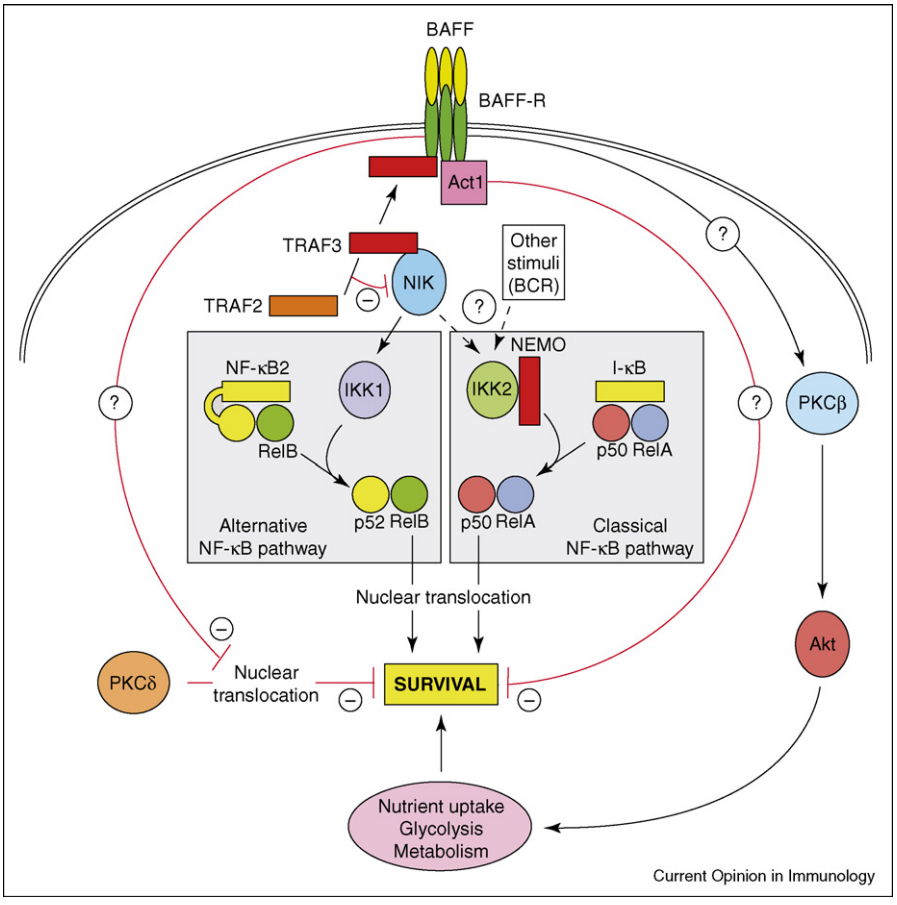
Signaling BAFF-mediated B-cell survival

A major focus of recent investigations has been to elucidate the signaling pathways that mediate the pro-survival signaling of BAFF-R on mature B cells. Activation of the alternative nuclear factor kappa B (NF-κB) pathway (processing of NF-κB2 and the nuclear translocation of p52/RelB heterodimers; Figure 2) is a major outcome of BAFF-R stimulation [60,88]. Recent evidence indicates that BAFF-R triggers this pathway by preventing the constitutive proteosome-mediated degradation of the serine/threonine kinase NIK (NF-κB-inducing kinase) — a process that depends on the binding of NIK to TRAF3 (TNF receptor associated factor 3) [89]. Activated BAFF-R recruits TRAF3 and triggers its degradation, thus allowing NIK protein to accumulate and increase NF-κB2 processing (Figure 2). Consistent with this model, B-cell lines that lack TRAF3 show greatly elevated levels of NIK and NF-κB2 processing [90•]. A similar phenotype is seen in B cells that lack TRAF2 [91], suggesting that TRAF2 and TRAF3 perform co-operative but non-redundant roles in controlling the alternative NF-κB pathway (Figure 2).

BAFF is a weak activator of the classical NF-κB pathway in B cells. Although most of the nuclear translocation of p50/RelA DNA-binding activity triggered by BAFF requires TACI [92], evidence does exist for low level activation of the classical pathway via BAFF-R [92,93•]. The kinetics of this response are much slower than those observed for strong activators of this pathway such as TNF and CD40, raising the possibility that BAFF-R might utilize NIK to activate the classical as well as the alternative NF-κB pathway [94] (Figure 2).

The demonstration that mature NF-κB2-deficient B cells fail to survive in mixed bone marrow chimeras [95] confirms that activation of the alternative NF-κB pathway through BAFF-R is essential for the survival of primary B cells. Although the impaired maturation of

Figure 2



Model of the signaling pathways implicated in BAFF-R-mediated survival signals in primary B cells. Components of several of the key signaling pathways are shown including the alternative and classical NF-κB pathways (boxed in grey). A clear link between BAFF-R and the various signaling pathways has only been established in the case of the alternative NF-κB pathway. Unknown links are indicated by circled question marks and negative regulatory signals by the red inhibitor arrows and circled 'minus' signs. See main body of text for detailed explanations.

NF-κB2-deficient B cells complicates the identification of essential downstream targets, recent evidence suggests that upregulation of the anti-apoptotic kinase Pim2 by alternative pathway activation and subsequent phosphorylation and inhibition of the pro-apoptotic protein Bad are involved [92].

The importance of classical NF-κB activation for mature B-cell survival is indicated by the recent demonstration that B-lineage-specific inactivation of NEMO (NF-κB essential modulator; a component of the I-κB kinase complex essential for activation of the classical NF-κB pathway; Figure 2) results in the specific depletion of mature B cells [93•]. However, because the BCR is essential for mature B-cell survival and is known to be an activator of the classical NF-κB pathway (Figure 2), the extent to which BAFF-R-mediated activation of this pathway is required for mature B-cell survival is difficult to determine. NEMO-deficient B cells express significantly reduced levels of both RelB and NF-κB2 [93•], raising the possibility that impaired activation of the alternative NF-κB pathway might at least partly explain the failure of mature NEMO-deficient B cells to survive. Receptor-independent activation of the classical NF-κB pathway by a constitutively active form of I-κB kinase 2 rescues the maturation and survival of BAFF-R-deficient B cells [93•]. However, because this strategy removes the normal requirement for BAFF-R-mediated activation of the alternative NF-κB pathway, the normal role of BAFF-R-mediated activation of the classical NF-κB pathway in mature B-cell survival still remains uncertain.

Many reports have suggested that signaling of B-cell survival by BAFF is dependent on NF-κB-mediated upregulation of anti-apoptotic bcl-2 family proteins. This remains controversial [35•,96], and several recent studies indicate that the situation might be more complex. For instance, inhibition of the nuclear translocation of the pro-apoptotic protein kinase Cδ appears to be an important component of BAFF-mediated pro-survival signaling [97]. This process could depend on NF-κB activation [93•], but the mechanism by which it is activated by BAFF-R remains unknown (Figure 2).

Another potential mediator of BAFF-mediated survival signals is the serine/threonine kinase Akt. Akt activity counteracts apoptosis at least in part by maintaining a positive bioenergetic balance through the promotion of glucose uptake and glycolysis [98]. BAFF not only triggers Akt phosphorylation in primary B cells [96,99••] but also upregulates the expression of a panel of glycolytic enzymes [99••] and promotes metabolism of glucose and other nutrients [96]. Although protein kinase Cβ and PI3K are required for BAFF-mediated Akt activation [99••], the biochemical link from BAFF-R is once again unknown. Indeed, apart from TRAF3, the only signaling molecule known to be recruited to BAFF-R is the adaptor protein Act1 [100]. Like TRAF3, this protein acts as a negative regulator of BAFF-mediated B-cell survival, but its mechanism of action remains unclear (Figure 2). Elucidation of the connections between BAFF-R and its downstream targets remains a significant challenge in our understanding of how BAFF promotes the survival of mature primary B cells.

Whereas BAFF-mediated survival signals are thought to be important in sustaining the growth of B lymphomas, recent evidence suggests that the signaling pathways involved might differ considerably compared with those in primary B cells. Thus, APRIL as well as BAFF prevent the apoptosis of a pre-B lymphoma cell line [101], myeloma [86], Hodgkin's lymphoma [78] and CLL (chronic lymphocytic leukemia) cells [102]. In the latter case, survival signals depended on TACI- and/or BCMA-mediated activation of the classical NF-κB pathway and did not require BAFF-R-mediated activation of the alternative pathway [102], thus emphasizing the contrast with mature primary B cells.

Conclusions

The BAFF/APRIL system was identified almost a decade ago and its impact upon both basic and clinical research has been profound. The identification of BAFF as the elusive factor that B cells compete for to survive has provided a framework for understanding B-cell homeostasis and self-tolerance. The ability of BAFF/APRIL to promote both autoimmunity and B lymphoma are clear, and the initial results of therapies that target these molecules are promising. Nevertheless, much remains to be learnt. The precise biological roles of TACI and APRIL, in particular, have yet to be fully elucidated. Also, despite the recent insights into the signaling pathways downstream of BAFF-R, many gaps exist including the means by which these pathways link to BAFF-R. Signaling by TACI and BCMA is also largely obscure, but is likely to be important with respect to B lymphoma survival. As we enter the second decade of the BAFF/APRIL era the elucidation of these areas offers much excitement to researchers and holds promise for the development of sophisticated new strategies for therapeutic intervention.

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- • of special interest
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