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Targeting BAFF: Immunomodulation for autoimmune diseases and lymphomas

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Abstract

In an effort to develop more effective treatments for inflammatory diseases, immunologists have targeted numerous molecular pathways, but with limited success. Notable exceptions are anti-TNF agents, which have proved efficacious in a proportion of rheumatoid arthritis (RA) patients. Another TNF family member, termed BAFF ("B cell-activating factor belonging to the TNF family"), plays a central role in autoimmune diseases, as well as in B cell maturation, survival, and T cell activation. Agents that block BAFF have proven to be highly effective in the treatment of certain autoimmune conditions in mice. In addition, phase II data in human clinical trials for RA appear very promising. BAFF is also a survival factor for certain B cell lymphomas. Despite the relatively recent identification of BAFF, this molecule has provided considerable new insight into B cell homeostasis and immune function, and represents an important new molecular target for treatment of autoimmune diseases and lymphomas.

Keywords: Autoimmunity; Immune response; TNF family; BAFF; B cells

Contents

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1. Introduction

A better understanding of the immune system and its regulation heralds new opportunities for intervention in a range of autoimmune and allergic diseases. For instance TNF-neutralizing agents (Remicade, EMBREL) and CTLA4-Ig are revolutionizing anti-inflammatory therapy. Moreover, researchers have started to exploit new strategies, for instance modulating lymphocyte survival, or manipulation of regulatory immune cells, to control the inflammatory response.

Research into the pathogenesis of autoimmune diseases has focused on T cells as the key drivers of disease, particularly in conditions such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and type I diabetes. However, the notion of a role for B cells and antibodies in these diseases has gained support through research with experimental animal models. Also, the recent use of B cell-depleting agents such as Rituximab (anti-CD20) in patients with RA or SLE also emphasizes the important role of B cells in driving several autoimmune disorders. B cells produce pathogenic autoantibodies, but also serve as antigen-presenting cells (APC) that under some circumstances may corrupt the normal processes of T cell co-stimulation or activation.

The discovery of the new TNF-like ligand BAFF ("B cell-activating factor belonging to the TNF family") has shed new light on B cell tolerance and homeostasis. BAFF is an essential survival factor during B cell maturation in the spleen, at a critical stage of B cell development when elimination of self-reactive B cells occurs. In mice, dysregulation of BAFF expression leads to inappropriate survival of self-reactive B cells and the development of severe autoimmune disorders. Moreover, many human autoimmune conditions correlate with higher BAFF levels in the serum. Excessive BAFF production, whether being the cause or consequence of autoimmune reactions, is likely to exacerbate disease pathogenesis through inappropriate stimulation of B cell or T cell activity. For this reason BAFF has emerged as a highly attractive therapeutic target, and currently several biotechnology and pharmaceutical companies have blocking antibodies or decoy receptors in clinical trials. In this review, we will outline the key roles that BAFF plays in the immune system, particularly in autoimmune reactions. In addition, we will introduce new concepts about this ligand and its receptors, and discuss the role of BAFF as a target for treatment of immune related disorders, as well as lymphomas.

2. BAFF

2.1. Expression and regulation of BAFF

BAFF is a member of the TNF ligand superfamily (TNFSF), and was discovered in the late 1990s by various groups, and is also referred to as BLyS, TALL-1, THANK, zTNF-4, TNFSF13B and TNFSF20 (Mackay & Browning, 2002; Mackay et al., 2003). BAFF contains the characteristic TNF homology domain (THD) and adopts the typical trimeric structures that are common to members of this family (Bodmer et al., 2002). It is closely related in structure to another TNFSF molecule called APRIL with which it shares ~50% sequence homology (Bodmer et al., 2002). BAFF and APRIL share 2 receptors and mediate both unique and overlapping functions in the control of immune responses.

The active BAFF molecule exists as a homotrimer, which can be released as a soluble cytokine following proteolysis of the membrane-bound form by members of the subtilisin-like furin family of proteases. This process is regulated at both a stimulus and cell type level (Tribouley et al., 1999; Nardelli et al., 2000; Litinskiy et al., 2002; Scapini et al., 2003). The differential regulation of soluble and membrane bound forms suggests the possibility of distinct functions, however their relative activities and functions are yet to be determined. In addition, the biological activity of BAFF may also be regulated by other mechanisms such as heterotrimer formation, alternative splicing and protein localization. The formation of a heterotrimer incorporating a truncated splice variant called ΔBAFF leads to the formation of an inactive non-cleavable form at the cell surface (Gavin et al., 2003). Suppression of BAFF activity in ΔBAFF transgenic mice indicates that this molecule may play an important role in regulating BAFF activity in vivo (Gavin et al., 2005). Additionally, BAFF forms heterotrimers with APRIL. These have been identified in vitro and in vivo, specifically in the context of some autoimmune diseases (Roschke et al., 2002).

BAFF is expressed in a variety of cells types, predominantly peripheral blood leukocytes and stromal cells of the spleen and lymph nodes (Dejardin et al., 2002; Lesley et al., 2004). Low level expression is also observed in other tissues such as the thymus and lung (Schneider et al., 1999; Tribouley et al., 1999). BAFF production is induced in leukocytes by a variety of proinflammatory stimuli: dendritic cells, macrophages and monocytes stimulated with type I and II interferons, IL-10 and LPS (Moore et al., 1999; Nardelli et al., 2000; Litinskiy et al., 2002; Huard et al., 2004; Ogden et al., 2005) are potent producers of BAFF while neutrophils stimulated with G-CSF and IFNγ (Scapini et al., 2003; Scapini et al., 2004) express BAFF at very high levels. T cells and germinal centre B cells also produce BAFF at low levels following stimulation through the TCR (Schneider et al., 1999; Huard et al., 2004) or CD40L, respectively (He et al., 2004a; Mackay & Tangye, 2004), suggesting autocrine roles in these cell types.

There is growing evidence that non-hematopoietic cell types are also important producers of BAFF. Both astrocytes and fibroblast-like synoviocytes produce BAFF in response to TNF and IFNγ, indicating that stromal cells may be an important source of BAFF during inflammation (Krumbholz et al., 2005b; Ohata et al., 2005). Indeed the inability of wildtype bone marrow to restore normal serum levels of BAFF and reconstitute the peripheral B cell pool in BAFF knockout (KO) host animals (Gorelik et al., 2003) indicates that the non-hematopoietic compartment is the major site of constitutive BAFF production and is critical for regulating the size of the peripheral B cell pool. Thus there are 2 important modes for the regulation of BAFF expression: constitutive expression by

radio-resistant stromal cells, possibly in lymphoid organs, that is critical for regulating B cell homeostasis, and inducible expression in response to inflammatory stimuli, which is presumably important for pathogen clearance (Mackay & Mackay, 2002).

2.2. BAFF receptors

BAFF interacts with 3 receptors from the TNF receptor superfamily (TNFRSF): BAFF receptor (BAFF-R or BR3), transmembrane activator and calcium-modulator and cyclophilin ligand interactor (TACI), and B cell maturation antigen (BCMA, or TNFRSF17), all of which are expressed primarily by B cells. BAFF is the sole ligand for BAFF-R (Thompson et al., 2001), while it shares receptor specificity for TACI and BCMA with APRIL (Mackay & Ambrose, 2003). All 3 receptors lack the death-associated domains common to some TNFRSF molecules, instead interacting with members of the TNF Receptor Associated Factor (TRAF) family of proteins (Hatzoglou et al., 2000; Xia et al., 2000; Xu & Shu, 2002). This suggests involvement in survival and differentiation pathways rather than cell death, although other TNFRSF members lacking a conventional death domain have been shown to trigger cell death via alternative pathways (for instance LTβR).

BAFF-R, TACI and BCMA display unique but overlapping expression patterns, and functional analysis has revealed distinct roles for these 3 receptors in mediating BAFF (and APRIL) signals. Cell surface expression of all 3 BAFF receptors is modulated during the course of B cell development. BAFF binding and receptor expression is minimal on early immature B cells in the bone marrow. Significant amounts of BCMA mRNA and lower levels of BAFF-R and TACI mRNA are detected in the later stages of B cell development (Hsu et al., 2002a) before migration to peripheral lymphoid tissues such as the spleen. At this time BAFF-R and TACI are upregulated by immature B cells, coincident with the acquisition of BAFF responsiveness at the transitional type 1 (T1) stage of development (Cancro, 2004b). BAFF-R is subsequently expressed at high levels on all mature peripheral B cell subsets in spleen, lymph nodes, and peripheral blood (Avery et al., 2003; Moir et al., 2004; Ng et al., 2004). TACI has a distinct expression pattern to BAFF-R being highly expressed in T2, marginal zone and B-1 B cells, while being down-regulated on follicular and germinal centre B cells (Cancro, 2004a, 2004b; Ng et al., 2004). The expression pattern of BCMA is the most restricted of the BAFF receptors, with cell surface expression being confined to germinal centre B cells (Avery et al., 2003; Ng et al., 2004) and bone marrow plasma cells (Cancro, 2004a).

In addition to B cells, there is mounting evidence that T cells also express BAFF receptors. Some reports described TACI expression on activated T cells (Von Bulow & Bram, 1997; Seyler et al., 2005), whilst our own and other studies have pinpointed BAFF-R expression on naïve and memory T cells and T cell lines (Ng et al., 2004; Rodig et al., 2005; Vidal-Laliena et al., 2005). Ye et al. (2004) have also demonstrated particularly high BAFF-R expression on $CD4^+$ $CD25^+$ regulatory T cells. Discrepancies between the various studies may reflect variations in the mode of activation and preparation of the cells analysed.

2.3. Biological roles of BAFF

The discovery of BAFF has provided numerous important insights into the regulation of the B cell repertoire and represents an important link between B cell homeostasis and the development of autoimmune syndromes (Mackay & Browning, 2002; Mackay et al., 2003). Numerous studies have demonstrated that BAFF modulates key events during the lifetime of a B cell, particularly survival and maturation, germinal centre formation, antibody production and class switching (Mackay & Browning, 2002; Mackay et al., 2003). An important distinction in the roles of BAFF is its role in B cell development versus its role as an inflammatory cytokine that modulates immune responses.

Initial experiments using recombinant BAFF demonstrated augmented B cell proliferation, antibody production (Schneider et al., 1999) and class-switching (Litinskiy et al., 2002; He et al., 2004b) after anti-BCR stimulation in vitro. In the absence of BCR stimulation, BAFF significantly increased splenic B cell survival in vitro (Batten et al., 2000) and resulted in the expansion of peripheral B cell numbers when injected into mice (Moore et al., 1999). Thorough dissection of the surviving B cell subsets revealed that BAFF specifically enhanced survival of the immature transitional type 2 (T2) B cells, and when combined with a BCR stimulus, led to the differentiation of the T2 subset to mature B cells (Batten et al., 2000). BAFF up-regulated the expression of both Bcl-X_L and Bfl-1 in vitro (Hsu et al., 2002b), indicating that BAFF promotes B cell survival via the induction of pro-survival Bcl-2 family members. Thus BAFF displays functional pleiotropy in the control of B cell numbers and function.

In accordance with the presence of BAFF receptors on T cells, in vitro experiments revealed a role for BAFF in enhancing T cell activation. BAFF enhances T cell proliferation and cytokine production in response to a range of mitogenic stimuli (Huard et al., 2001; Huard et al., 2004; Ng et al., 2004). In vivo, BAFF levels can modulate the outcome of T cell responses (Sutherland et al., 2005). For instance blockade of BAFF prevents T cell activation and the onset of disease in models of CIA (Wang et al., 2001) and defective BAFF signaling is associated with enhanced survival of allografts (Ye et al., 2004). These data indicate that BAFF is also an important regulator of T cell responses.

BAFF transgenic mice display significant perturbations of the B and T cell compartments, consistent with in vitro observations. These mice have enlarged spleens and lymph nodes due to increased numbers of peripheral B cells, and develop symptoms of systemic autoimmunity with age. The T2, follicular and marginal zone B cell subsets of the spleen are expanded, showing significantly prolonged splenic B cell survival when cultured ex vivo (Batten et al., 2000; Khare et al., 2000), most likely as the result of increased levels of Bcl-2 expression (Mackay et al., 1999). BAFF transgenic mice also display increased spontaneous germinal centre formation

(Mackay et al., 1999) and increased levels of all antibody subclasses (Khare et al., 2000), suggesting an increase in both antibody production and class switching. T cell homoestasis is also disrupted, with increased numbers of effector/memory type T cells detected in BAFF transgenic mice as they age (Mackay et al., 1999). However this phenotype appears to be secondary to an alteration of the B cell compartment, as the T cell compartment remains unaltered in B cell-deficient BAFF transgenic mice (Sutherland et al., 2005).

Conversely, BAFF-deficient mice and those treated with BAFF-blocking reagents display profound defects in peripheral B cell numbers and responses (Yu et al., 2000; Schiemann et al., 2001; Yan et al., 2001a). BAFF KO mice display severely impaired B cell maturation beyond the immature transitional stage, with significant defects in peripheral B cell numbers (Gross et al., 2001; Schiemann et al., 2001). They also fail to upregulate the B cell maturation markers CD21 and CD23 (Gorelik et al., 2004). Antibody responses are severely impaired in response to T-dependant and T-independent antigens and sustained germinal centre reactions were prevented (Rahman et al., 2003).

2.4. The specific functions of the various BAFF/APRIL receptors

Phenotypic analysis of gene-deficient and mutant mice strains has defined roles for the 3 BAFF receptors in mediating the different effects of BAFF. BAFF-R is primarily responsible for mediating BAFF induced survival signals during maturation and maintenance of the mature B cell pool. BAFF-R KO mice and the A/WySnJ strain, which carries a mutation in the *baff-r* gene, have significantly reduced peripheral B cell numbers (Miller & Hayes, 1991; Sasaki et al., 2004; Shulga-Morskaya et al., 2004), mirroring the phenotype of BAFF KO mice (Gross et al., 2001). As BAFF regulates a number of anti-apoptotic Bcl-2 family members, defective induction of these molecules is a likely cause of the defects in B cell survival. Over-expression of Bcl-2 in B cells with defective BAFF-R signaling leads to partial restoration of peripheral B cell numbers (Rahman & Manser, 2004; Sasaki et al., 2004). However Bcl-2 over-expression does not complement for deficiencies in germinal centre formation, reduced IgG responses and the lack of marginal zone B cells in the absence of BAFF, indicating that defects in survival alone cannot account for the impairment in B cell function (Tardivel et al., 2004).

A number of strains of TACI KO mice have been generated, with somewhat differing phenotypes reported (von Bulow et al., 2001; Yan et al., 2001b; Seshasayee et al., 2003). However, some consistent features can be noted. TACI regulates B cell proliferation, antibody class switching and homoestasis. Increased numbers of mature B cells were found in peripheral lymphoid organs of all lines (von Bulow et al., 2001; Yan et al., 2001b; Seshasayee et al., 2003), while 1 line developed SLE-like autoimmunity similar to BAFF transgenic mice (Seshasayee et al., 2003). TACI KO B cells were hyper-proliferative in vitro (Yan et al., 2001b) and in vivo (von Bulow et al., 2001) while activation of TACI using an agonistic antibody reduced normal B cell proliferation (Seshasayee et al., 2003). Collectively, these data suggest that TACI is an important negative regulator of B cell proliferation. While TACI-deficient mice mount normal antibody responses to T-dependant antigens, they display markedly decreased antibody production and impaired class switching in response to T-independent antigens (von Bulow et al., 2001; Yan et al., 2001b). These results correlate with other in vitro studies demonstrating a role for TACI in CD40L-independent class switching (Litinskiy et al., 2002; Castigli et al., 2005b). Interestingly, TACI expression is particularly high on MZ B cells and B1 B cells, two B cell subsets that are key players driving T-independent antibody responses (Ng et al., 2004; Shulga-Morskaya et al., 2004). In addition, MZ B cells and B1 B cell subsets have been shown to contain self-reactive B cells. Thus higher TACI expression on these cells may be a safety feature preventing the potentially harmful expansion of these self-reactive B cells. Analysis of 2 separate human cohorts identified a series of mutations in the *taci* gene that are associated with the development of combined variable immunodeficiency (CVID) (Castigli et al., 2005a; Salzer et al., 2005). These mutations associated with reduced levels of serum IgM, IgG and IgA, and B cells from affected individuals were defective in response to APRIL-induced proliferation and antibody class switching (Castigli et al., 2005a; Salzer et al., 2005). Many patients with mutations in the *taci* gene also develop lymphoproliferative disorders, with the incidence of autoimmune disease in CVID patients with *taci* mutations higher than with the general CVID cohort (Salzer et al., 2005). Thus data from TACI KO mice and human cohorts have defined a number of roles for TACI, both as a positive regulator of antibody responses to T-independent antigens, and a negative regulator of B cell proliferation.

Initial studies using BCMA KO mice did not reveal a fundamental role for this receptor as basic immune functions in these mice appeared normal (Xu & Lam, 2001). However recent work has provided new insight in the function of this receptor and revealed a defect in the long-term survival of plasma cells in the bone marrow, which is consistent with the restricted expression of BCMA to these cells (O'Connor et al., 2004). In vitro stimulation of plasma cells with BAFF induced the expression of the anti-apoptotic proteins Bcl-X_L and Mcl-1, but not Bcl-2, suggesting a qualitative difference of BAFF-mediated signals through BCMA compared to BAFF-R (O'Connor et al., 2004). In addition to mediating these survival signals, activation of BCMA promotes B cells to function as APC to T cells. Crosslinking of BCMA on B cells led to increased expression of MHC class II, CD86, CD80, CD40 and ICAM-1 and resulted in a significantly increased capacity to stimulate T cell proliferation and IL-2 production (Yang et al., 2005). BCMA expression was induced after IL-4 and IL-6 treatment of splenic B cells and further stimulation with APRIL or BAFF promoted the APC function of these cells (Yang et al., 2005). As BCMA is expressed primarily by germinal centre B cells, plasmablasts and plasma cells (Avery et al., 2003; Moreaux et al., 2004; Ng et al., 2004), these results suggest that BCMA may play an important role in regulating collaboration between these B cell subsets and T cells.

2.5. Signaling pathways for BAFF receptors

Analysis of the signaling pathways activated by the 3 BAFF receptors has demonstrated that each interacts with distinct downstream signaling intermediates, primarily via interactions with a differing spectrum of TRAF proteins. BAFF-R recruits TRAF3 alone, TACI recruits TRAF2, -5, -6, and BCMA TRAF1, -2, -3, -5, -6 (Aggarwal, 2003). These differential interactions with TRAF molecules explain the different abilities of these receptors to activate Map kinases and NF-κB. Both TACI and BCMA activate the canonical NF-κB1 pathway, which is quite common for members of the TNFRSF (Aggarwal, 2003). BCMA activates the Jnk and p38 Map kinase pathways, and transcription via Elk-1 (Hatzoglou et al., 2000; Yang et al., 2005), while TACI activates the AP-1 and NF-AT transcription factors (Von Bulow & Bram, 1997). In contrast, BAFF-R does not appear to stimulate Map kinases, NFAT or NF-κB1 pathways, but instead activates the non-canonical NF-κB2 (Claudio et al., 2002; Kayagaki et al., 2002; Ramakrishnan et al., 2004). This alternative activation pathway is dependant upon NF-κB-inducing kinase (NIK)-induced proteolytic cleavage of the p100 precursor to the p52 form, which initiates transcription after dimerisation with Rel-B (Senftleben et al., 2001; Xiao et al., 2001). B cells from NF-κB2 KO mice or the *aly/aly* strain, which carries inactivating mutations in the *nik* gene, are unable to respond to BAFF and fail to survive properly (Claudio et al., 2002), indicating that NF-κB2 activation is a critical step mediating BAFF-induced B cell survival.

Functional studies have elucidated critical interactions between BAFF-R, TRAF3 and NIK that are essential for the BAFF-induced activation of NF-κB2. TRAF3 interacts with BAFF-R, via a unique sequence motif in the intracellular portion of the receptor (Xu & Shu, 2002). Engagement of BAFF at the cell surface results in rapid TRAF3 recruitment to BAFF-R via this unique motif (Ni et al., 2004) and subsequent activation of NIK and p100 processing (Morrison et al., 2005). In the latent state, prior to BAFF-R activation, TRAF3 forms a stable association with NIK, targeting newly translated NIK molecules for ubiquitinylation and constitutive degradation by the proteosome (Liao et al., 2004). After BAFF-R engagement, TRAF3 is recruited to BAFF-R, which results in degradation of TRAF3. Increased levels of NIK protein are subsequently observed, leading to the induction of p100 processing and production of functional p52 subunits (Qing et al., 2005). Thus TRAF3 is likely to be a critical positive regulator of the non-canonical pathway, which is consistent with its recruitment to other TNFRSF members that activate NF-κB2, such as CD40 (Hauer et al., 2005) and LTβR (Force et al., 2000).

Other signaling pathways, such as those mediated by the protein kinase C (PKC) family member PKCδ are also important for signal transduction through BAFF-R. BAFF stimulation of B cells prevents PKCδ translocation to the nucleus, a feature critical for induction of cell death. In addition, PKCδ-deficient mice have increased B cell numbers and develop autoimmune symptoms similar to that of BAFF transgenic mice (Miyamoto et al., 2002; Mecklenbrauker et al., 2004). Thus PKCδ appears to be a negative regulator of BAFF-mediated survival signals in B cells, possibly via repression of a target molecule such as a nuclear transcription factor important in cell death mechanisms. Interestingly, defects in BAFF-induced survival are observed in B cells with specific deletion of c-Myb (Thomas et al., 2005). In these cells, BAFF stimulation results in NF-κB2 activation but does not lead to the down-regulation of nuclear PKCδ levels. Thus c-Myb may represent an important nuclear target of PKCδ action. These data suggest that activation of NF-κB2 alone is insufficient to transmit full BAFF-induced survival signals and that PKCδ plays an additional important role in this process. This is also consistent with the phenotype of NF-κB2-deficient mice, which does not totally resemble that of BAFF-deficient mice (Franzoso et al., 1998). In summary, BAFF-mediated survival is a complex event involving at least 2 separate mechanisms.

The phenotype of TRAF2 conditional KO mice suggests that TRAF2 may also play a role in regulating downstream signaling from BAFF receptors. B cells that are selectively deficient in TRAF2 show increased basal activation of NF-κB2, increased Bcl-X_L expression and enhanced survival ex vivo. The specific expansion of the MZ B cell compartment in secondary lymphoid organs is also observed (Grech et al., 2004). Interestingly, while these mice have many characteristics of increased BAFF stimulation, they do not develop signs of autoimmunity, possibly as the result of a concomitant defect in TRAF2-dependent CD40 signaling (Grech et al., 2004). Of particular note, TRAF2 directly interacts with both TACI and BCMA (Aggarwal, 2003), but is unable to interact with BAFF-R (Xu & Shu, 2002). Thus the enhanced B cell numbers in TRAF2-deficient mice may be the result of impaired negative signals through TACI, or may possibly indicate that TRAF2 plays a role in regulating the interactions of TRAF3 and BAFF-R.

3. BAFF and autoimmunity

3.1. BAFF transgenic mice

Multiple lines of BAFF transgenic mice have been generated, all of which display significant disruptions of the B cell compartment and develop spontaneous autoimmunity. This is characterized by profound B cell hyperplasia, hyperglobulimaemia and production of various circulating autoantibodies and immune complexes (Mackay et al., 1999; Gross et al., 2000; Khare et al., 2000). As they age, BAFF transgenic mice develop proteinuria and severe nephritis leading to kidney failure, reminiscent of human SLE. Mice also develop a secondary condition similar to human Sjögren's syndrome (Groom et al., 2002), characterized by leukocyte infiltration in the salivary glands, destruction of acinar cells and reduced saliva production. Thus, sustained overproduction of BAFF is sufficient to drive systemic autoimmunity. However, there is evidence to suggest that development of BAFF-driven autoimmunity can be affected by additional genetic modifiers. Expression of the BAFF transgene in the presence of either the Sle1 and Nba1 lupus susceptibility regions significantly increased disease

onset (Stohl et al., 2005). One study has also noted that some normal control subjects display elevated BAFF levels in the absence of infection or inflammation (Krumbholz et al., 2005a). These data may suggest that induction of autoimmunity in the context of BAFF over-expression requires permissive genetic predispositions. It may also suggest that BAFF may not be the trigger for autoimmune conditions but may promote and perpetuate self-reactive B cell survival once the autoimmune response is established.

The enhanced production of autoantibodies in BAFF transgenic mice suggests that overproduction of BAFF allows self-reactive B cells to elude normal tolerance checkpoints. Transgenic mouse models that couple defined BCR specificity with expression of cognate self-antigen under the control of endogenous *cis* control elements allow the fate of self reactive B cells to be determined in vivo. When hen egg lysozyme (HEL) specific BCR transgenic B cells encounter HEL as neo-self antigen in vivo they are normally functionally inactivated or deleted from the B cell repertoire (Goodnow et al., 1988, 1989, 1991). Thien et al. (2004) used HEL transgenic mice to test the effects of self-antigen and cellular competition on B cell tolerance in the presence of the BAFF transgene. While no change in B cell tolerance was observed in the bone marrow, abnormal deletion and lack of anergy of self-reactive cells was observed during T1–T2 maturation in the spleen. These self-reactive cells that had eluded clonal deletion were subsequently selected to follicular and marginal zone niches, areas where they are normally excluded. These B cells were not anergised and were fully capable of secreting autoantibody in response to HEL stimulation. However, these results were obtained in conditions limiting the competition of self-reactive B cells with normal B cells and may not represent the physiological situation. Therefore, the role of excessive production of BAFF on B cell tolerance was also tested in situations where self-reactive B cells were out-numbered by competing normal B cells. In this case, normal peripheral negative selection and anergy was observed (Thien et al., 2004).

These conflicting results were intriguing. While survival of self-reactive B cells is highly dependent on the presence of competing normal B cells, it may also be a function of the affinity of the BCR for self-antigen. To test this hypothesis, HEL-specific BCR knocking mice were engineered to produce both high and low affinity HEL-specific self-reactive B cells. The results showed that while B cells of intermediate BCR affinity were able to escape deletion in the presence of competitor cells in a BAFF transgenic host, those with high BCR affinity were normally deleted/anergised. These findings implied that death signals trigged by a high affinity self-reactive BCR upon binding to self-antigen cannot be overturned by BAFF-mediated survival. This conclusion was supported by another study using HEL transgenic mice. Lesley et al. (2004) demonstrated that high affinity self-reactive B cells can only survive where there is increased BAFF supply on a per cell basis, for example, during B cell lymphopenia. These studies suggest that the autoreactive cells that are supported by increased BAFF expression are unlikely to be of a high BCR affinity. Instead it may be the cells of intermediate affinity that are selected into the marginal zone that mediate disease pathology. Our previous studies have shown that affinity maturation and high affinity antibodies are not required for disease (Batten et al., 2004). Therefore, since loss of B cell tolerance in BAFF transgenic mice is relatively minor and subdued, it is tempting to speculate that the abnormal migration/homing of these cells to tissues, rather than their autoimmune nature, is critical for disease pathogenesis in BAFF transgenic mice (Groom et al., 2002).

3.2. Autoimmune animal models and human autoimmune diseases

Transgenic mice that over-produce a single factor-BAFF, develop autoimmunity. Hence over-production and systemic distribution of BAFF in some human patients may also be a cause of autoimmunity. Studies on a number of mouse models of autoimmunity, as well as with autoimmune patients has strengthened this putative association. Spontaneous models of lupus, such as the NZB/W F1 and the MRL.*lpr/lpr* strains, and a model of chemically induced autoimmunity, show increased serum levels of BAFF (Gross et al., 2000; Zheng et al., 2005). Analysis of human patient cohorts reveals that BAFF is systemically elevated in a range of human autoimmune diseases such as SLE (Zhang et al., 2001; Stohl et al., 2003; Pers et al., 2005b), Sjögren's syndrome (Groom et al., 2002; Jonsson et al., 2005; Pers et al., 2005b), RA (Zhang et al., 2001; Pers et al., 2005b) and Wegner's granulomatosis (Krumbholz et al., 2005a). In some autoimmune patients, local elevation of BAFF levels in affected tissues has been observed such as in salivary glands of patients with Sjögren's syndrome (Groom et al., 2002; Lavie et al., 2004; Pers et al., 2005a), rheumatoid synovial fluid (Tan et al., 2003) and lesions in patients with multiple sclerosis (Krumbholz et al., 2005b). Thus local and systemic elevation of BAFF levels are associated with a range of autoimmune conditions, suggesting an important role for this molecule in stimulating B and T cells during autoimmune inflammation.

The mechanisms responsible for BAFF overproduction during the development of autoimmune disease are unclear. There is some evidence to suggest that natural genetic variation can modulate systemic BAFF levels, for instance polymorphisms in the *baff* gene have been associated with increased BAFF production and the development of SLE in humans (Kawasaki et al., 2002). More extensive cohort studies will be needed to further elucidate this in other autoimmune diseases. Alternatively, initial increases in BAFF levels may be driven by innate cells responding to inflammation or infection. The potent induction of BAFF in response to pro-inflammatory stimuli suggests that BAFF is part of the normal response to infectious agents, perhaps serving to increase B cell numbers during clonal expansion or prime T cell activation during an immune response (Mackay & Mackay, 2002). A causative role for BAFF production in response to infection is suggested by the elevated BAFF levels in patients with HIV infection (Stohl et al., 2002). Interestingly, this may be responsible for the high levels of autoantibodies and increased incidences of autoimmune diseases such as SLE that are observed in some HIV patients (Stohl

et al., 2002). Further analysis of BAFF production following experimental infection is needed to elucidate the link between infection and BAFF production. Additionally, immune complexes bound to chromatin can also induce BAFF production from dendritic cells (Boule et al., 2004). As autoantibodies to nuclear components such as chromatin are a consistent feature of SLE, this suggests that BAFF production may be a consequence of the loss of B cell tolerance rather than necessarily causative. Regardless, BAFF production in response to chromatin/immune complexes would initiate a powerful positive feedback loop, further compromising B cell tolerance mechanisms and providing a self-sustaining driver of disease. However, in physiological situations limited BAFF production by APC may also provide a necessary boost to B cell survival and promote clearance of infections. A general model summarizing the likely roles of BAFF in immune responses to infections, or in autoimmune responses, is outlined in Fig. 1.

4. BAFF, APRIL and B cell malignancies

Patients that develop autoimmune syndromes such as SLE, Sjögren's syndrome and RA have an increased risk of developing B cell malignancies (Shaffer et al., 2002). This suggests that common mechanisms may underlie the development of both autoimmunity and lymphoid malignancies. Recent studies have demonstrated that excessive production of BAFF is also associated with the development of a range of mature B cell malignancies, indicating that BAFF may be an important molecular link between autoimmunity and cancer.

BAFF transgenic mice have increased incidence of B cell lymphomas. This is significantly increased in the absence of TNF, resulting in approximately 35% of mice developing tumors (Batten et al., 2004), presumably due to the anti-tumorogenic properties of TNF (Batten et al., 2004).

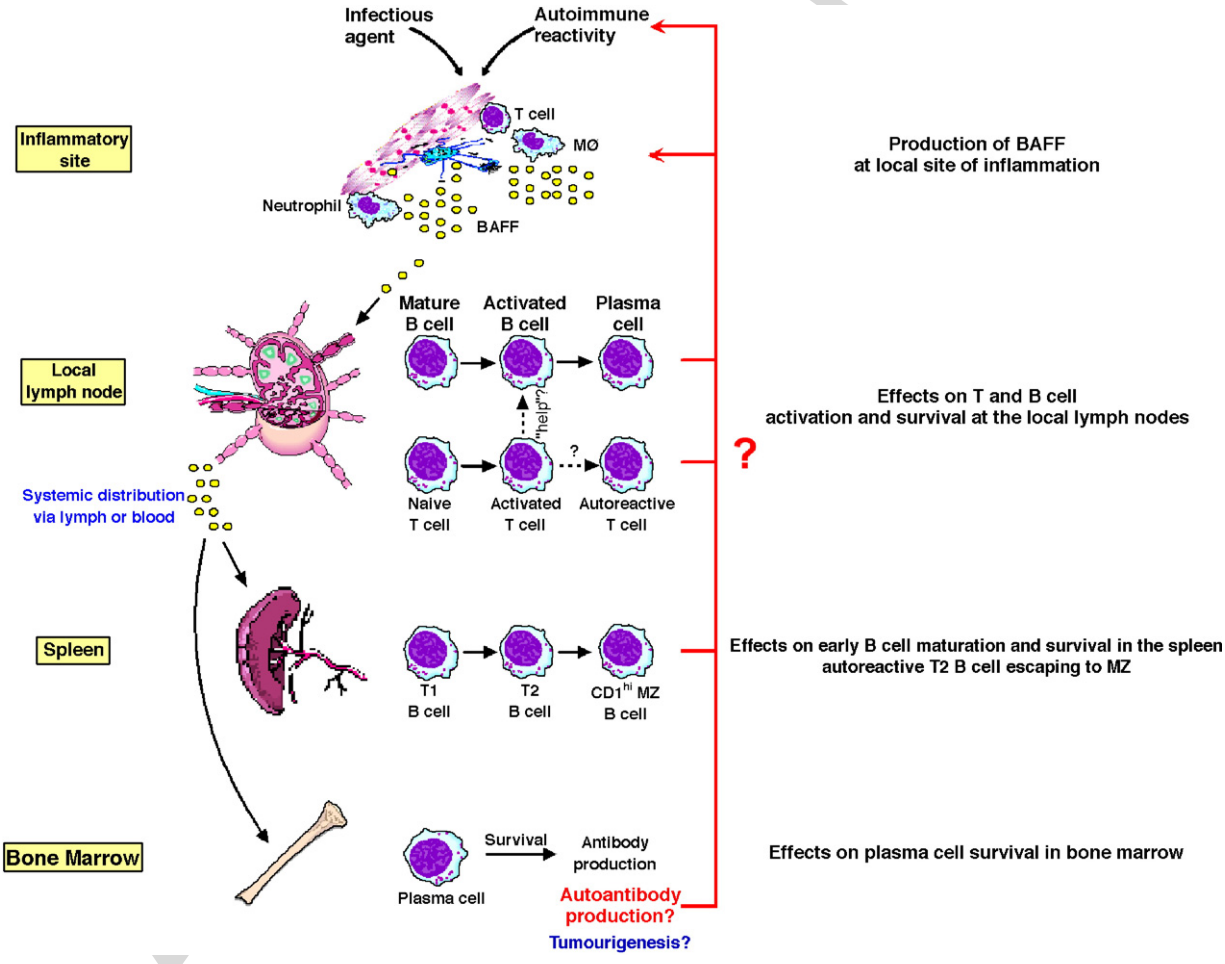

Fig. 1. BAFF and immune responses. BAFF (yellow circles) is produced at inflammatory sites, triggered possibly by infection, autoantibodies, or innate signals that act on neutrophils or macrophages/DC. BAFF not only serves to support local T and B cell function, but it may also exert its effects remotely, either in the local lymph nodes (delivered via the lymphatics) or the spleen (delivered via the lymph and blood). Another site of action might be the bone marrow where plasma cells accumulate. In the lymph node, BAFF provides co-stimulation for T and B cell activation and survival. In the spleen, BAFF promotes B cell maturation, from transitional type 1 (T1) cells to T2 cells, as well as the differentiation of B cells into marginal zone (MZ) B cells. It is also possible that BAFF regulates the nature or size of the Ag receptor repertoire of B cells by regulating negative selection during splenic maturation, particularly at the T1→T2 "immune tolerance checkpoint". In addition, BAFF is also important for the survival of GC B cells and inappropriate signals from BAFF (or APRIL) could also trigger a breakdown in B cell tolerance at this stage leading to the emergence of autoreactive B cells. Finally, BAFF also acts to promote plasma cell survival in bone marrow. The remote actions of BAFF on T and B cell activation, maturation and survival in lymph nodes, spleen and bone marrow might lead to autoimmunity by creating a vicious cycle of breakdown in self-tolerance, production of autoantibodies and continued autoantibody-mediated inflammation and tissue destruction. GC=Germinal centre, MØ=macrophage.

Moreover patients with non-Hodkin's lymphomas (NHL) and multiple myeloma (MM) display elevated serum levels of BAFF and APRIL (Novak et al., 2003; Kern et al., 2004; Novak et al., 2004). Covariant analysis in a cohort of NHL patients inversely correlated serum BAFF levels with the response to treatment and disease-free survival (Novak et al., 2004). The source of BAFF and APRIL probably arises from multiple cell sources, including from the tumor cells themselves (Novak et al., 2002, 2003; He et al., 2004a; Kern et al., 2004; Moreaux et al., 2004; Novak et al., 2004). For instance, BAFF and APRIL production by B cells is normally confined to germinal centre cells (He et al., 2004a), whereas expression of BAFF and APRIL is a common feature of B-cell chronic lymphocytic leukemia (B-CLL), NHL and MM cells (Novak et al., 2002, 2003; He et al., 2004a; Kern et al., 2004; Moreaux et al., 2004; Novak et al., 2004). This may be caused by amplifications in chromosome 13q32–34, which includes the *baff* locus that is commonly amplified in human B cell malignancies (Novak et al., 2002). Interactions between malignant and accessory cells are also likely to be important regulators of BAFF production, as B-CLL and Burkitt's lymphoma cells elicited significant BAFF/APRIL production from the mononuclear cell subsets that are associated with these particular malignancies (Nishio et al., 2005; Ogden et al., 2005).

Molecular characterization of B lymphomas reveals a diverse range of BAFF receptor expression. B-CLL, follicular, mantle cell and marginal zone derived tumors expressed BAFF-R and TACI to various levels (Novak et al., 2002; Kern et al., 2004; Novak et al., 2004). MM cells are striking in their consistent expression of BCMA, with reduced expression of both BAFF-R and TACI (Novak et al., 2003; Moreaux et al., 2004). The unique pattern of BAFF receptor expression on each type of tumor most likely reflects the identity of the pre-neoplastic precursor cell. Transcript profiling of MM revealed that $TACI^{hi}$ cells express a pattern of genes indicative of a mature plasma cell, while $TACI^{lo}$ cells had a transcript profile more characteristic of plasmablasts (Moreaux et al., 2005). The different patterns of BAFF receptor expression across subsets of B cell malignancies implies that each type will be differentially responsive to BAFF and APRIL signals (Moreaux et al., 2005). In vitro stimulation with BAFF or APRIL enhanced tumor cell survival alone (Kern et al., 2004) or in combination with growth factors such as IL-6 and IGF-1 (Novak et al., 2004). Notably, BAFF and APRIL protected tumors from apoptosis in the absence of essential growth factors such as IL-6 and drug-induced apoptosis after treatment with dexamethasone (Moreaux et al., 2004) or flavopiridol. (Kern et al., 2004). These potent anti-apoptotic effects were associated with the induction of numerous Bcl-2 family members such as Bcl-2, Mcl-1 and Bcl-X_L (Novak et al., 2002; He et al., 2004a; Moreaux et al., 2004). Thus autocrine and paracrine production of BAFF and APRIL appears to be important for the survival of a range of malignant B cell types and suggests that these molecules are excellent targets for the generation of novel therapeutic agents against lymphoid cancers.

5. BAFF and APRIL as therapeutic targets

Broad-spectrum immunosuppressants and chemotoxic agents have demonstrated utility in the treatment of autoimmunity and neoplasias, respectively, however their effectiveness is marred by significant unwanted side effects and lack of responsiveness by some patients. New generations of therapies that enable specific cellular or molecular depletion should provide an opportunity to selectively and effectively target pathogenic pathways and reduce nonspecific toxicity. At present only a handful of targeted drugs successfully treat autoimmune diseases, mostly notably the TNF and IL-1β antagonists (Feldmann & Steinman, 2005). As the biology of BAFF and APRIL has unfolded, it became clear that these 2 molecules represented exciting new targets for the development of new anti-inflammatory therapies. Being soluble cytokines, these molecules can easily be neutralized using blocking monoclonal antibodies or decoy receptor fusion proteins. In addition, these factors act on a narrow range of cellular targets, but show strong association with the development of both autoimmune diseases and B cell malignancies. Thus, it is likely that new therapies targeting BAFF and/or APRIL will improve our ability to treat patients with certain autoimmune diseases and/or lymphomas.

5.1. Targeting BAFF and APRIL for autoimmune diseases

Numerous autoimmune diseases are associated with altered B cell function (Kotzin, 1996; Lipsky, 2001; Shlomchik et al., 2001; Firestein, 2003; Martin & Chan, 2004). Many are caused by autoantibodies to defined molecular targets, for example, myasthenia gravis and Grave's disease, while more general autoantibody overproduction and immune complex deposition tend to associate with SLE and RA. Antibody-independent functions such as antigen presentation by B cells and the development of ectopic lymphoid tissue plays an important role in the pathogenesis of SLE, RA, SS and MS (Martin & Chan, 2004). The critical role of BAFF as a regulator of peripheral B cell survival suggests its blockade may be a useful therapy in most diseases that result from the dysregulation of B cell functions, either as autoantibody-producing cells, or as APC. Of note, the therapeutic potential of B cell depleting strategies has been demonstrated by the effectiveness of Rituximab (anti-CD20 B cell depleting agent) in treating SLE and RA (Edwards & Cambridge, 2001; Eisenberg, 2003; Gorman et al., 2003; Oligino & Dalrymple, 2003; Edwards et al., 2004) and results obtained with Lymphostat-B (a BAFF blocking agent) in RA have demonstrated similar efficacy in the treatment of animal models of SLE and RA. Treatment of lupus prone NZB/WF1 and MRL.*lpr/lpr* mice with BAFF/APRIL blockers successfully reduced many of their autoimmune symptoms (Gross et al., 2001; Kayagaki et al., 2002; Liu et al., 2004). Repeated administration of TACI-Ig and BAFF-R-Ig in NZB/WF1 mice substantially decreased total B cell numbers in peripheral blood, reduced proteinuria and increased mean survival (Gross et al., 2001; Kayagaki et al., 2002). TACI-Ig treatment of MRL.*lpr/lpr* mice led to a long-term reduction in splenic B cell and plasma

cell numbers, a reduction in total immunoglobulin levels and anti-dsDNA autoantibodies and rheumatoid factors. This was sufficient to provide a long lasting reduction in proteinuria and improved survival, out to 6 months after treatment (Liu et al., 2004). Importantly, this treatment was effective when given to mice with established autoimmunity, as well as prior to disease onset, implying that this treatment has potential utility for the treatment of established disease in humans. While TACI-Ig treatment was particularly effective in reducing disease parameters and autoantibody production in MRL.*lpr/lpr* mice, it produced only transient reduction of IgG levels in normal B6 animals (Liu et al., 2004). This suggests that TACI-Ig treatment may represent a novel treatment for human SLE, enabling selective depletion of autoreactive B cells and autoantibodies whilst preserving normal humoral responses.

BAFF and APRIL antagonists are also effective in preventing disease progression in models of collagen-induced arthritis (Gross et al., 2001; Wang et al., 2001). Increased systemic BAFF is observed during the course of this model and coincides with the appearance of anti-collagen antibodies (Zhang et al., 2005). Treatment with TACI-Ig resulted in reduced levels of anti-collagen antibodies and T cell responses, and an overall reduction in paw swelling and joint destruction. This suggests that BAFF blockade has potential utility in the treatment of RA, however further experiments testing the efficacy of TACI-Ig following disease onset should establish the potential use of this drug in a therapeutic treatment setting.

Interactions between T and B cells are critical for disease progression in RA particularly in ectopic lymphoid tissue formed in rheumatoid synovium (Takemura et al., 2001a, 2001b; Weyland & Goronzy, 2003; Dunussi-Joannopoulos et al., 2005; O'Neill et al., 2005). Experimental models involving transplantation of synovial tissue from human patients into SCID mice allow the identification of factors that control the maintenance of these lymphoid structures. TACI-Ig treatment of mice containing human synovial grafts led to significant disruption of ectopic lymphoid structures, resulting in reduced numbers of lymphocytes and follicular dendritic cells and decreased production of pro-inflammatory cytokines (Seyler et al., 2005). Thus in addition to regulating survival and autoantibody production, TACI-Ig may prevent the onset of disease in CIA by disrupting the formation of important lymphoid structures. Therefore, BAFF blockers may also be effective in treating other autoimmune diseases that are characterized by the presence of autoantibodies and ectopic germinal centres, for instance Sjögren's syndrome and myasthenia gravis (Vincent et al., 2001). Finally, BAFF and APRIL also affects the activity of T cells, which may also be relevant for the development of autoimmunity.

5.2. B cell malignancies

Specific targeting of B cells has also proven effective in the treatment of B cell malignancies. The anti-CD20 depleting monoclonal antibody Rituximab is a very effective treatment for NHL (Grillo-Lopez et al., 1999; Gong et al., 2005), which suggests that other strategies aimed at depleting B cells may be of similar utility. The role of BAFF and APRIL as important autocrine and paracrine survival factors for a range of B cell malignancies (Novak et al., 2002; He et al., 2004a; Kern et al., 2004; Moreaux et al., 2004) suggests that targeting BAFF and APRIL may allow depletion of neoplastic B cells and this may prove to be an effective treatment for lymphomas. In addition, development of BAFF/APRIL blockers may allow more flexibility for B cell depletion. Rituximab only depletes B cells expressing CD20 on the cell surface, as such this reagent is unable to deplete all B lineage cells especially the antibody producing $CD20^{-/low}$ plasma cells. BAFF and APRIL play an important role in plasma cell survival through BCMA (O'Connor et al., 2004), thus targeting these molecules may allow depletion of this subset. Moreover, BAFF and APRIL blockers might mediate a different type of depletion than Rituximab, which uses Fc receptor dependant mechanisms to deplete cells, rather than withdrawal of survival signals. BAFF-R-Ig was recently shown to complement Rituximab in B cell depletion, and a combination of these 2 reagents proved effective. While Rituximab efficiently depleted recirculating B cells from the blood and lymphoid tissue, it was less effective against non recirculating B cell subsets such as marginal zone B cells (Gong et al., 2005). BAFF-R-Ig efficiently depleted these non-recirculating cells, and in combination with Rituximab led to depletion of over 90% of the peripheral B cell pool (Gong et al., 2005).

5.3. Clinical trials with BAFF and APRIL inhibitors

At present, several companies are developing BAFF and APRIL blocking reagents for human therapy, consisting of specific human monoclonal antibodies and receptor fusion proteins. GlaxoSmithKlein/Human Genome Sciences have developed a humanized anti-BAFF antibody termed LymphoStat-B (Baker et al., 2003) that has recently completed phase II trials for efficacy in SLE and RA. These trials demonstrated that LymphoStat-B was 'safe, well-tolerated, biologically active, and reduces the signs and symptoms of RA at a level of statistical significance'. The results of the SLE cohort are yet to be announced. Genentech/BiogenIdec and Zymogenetics/Serono are both currently in phase I clinical trials with BAFF-R-Ig and TACI-Ig, respectively, for the treatment of SLE, RA and B cell malignancies (see websites below). Thus it is likely that some form of BAFF and APRIL blocking reagent will find utility as a new anti-inflammatory agent in the future.

While it is clear that BAFF and APRIL have important roles in the development of autoimmunity and cancer, our understanding of their biology is still far from complete. It is foreseeable that with increasing comprehension of their specificity and redundancy, a second generation of more specific therapies may provide better therapeutic effects. These may include molecules that target APRIL directly. Receptor agonists and antagonists to BAFF-R, TACI and BCMA could allow targeting each receptor separately, rather than their ligands. Agonistic antibodies to TACI might be of utility in suppressing hyperactive autoimmune B cell responses without blocking

endogenous levels of BAFF and APRIL, which may help preserve normal immune functions. Similarly, blockade of BCMA may allow selective inhibition of antigen presenting functions or plasma cell and MM survival, while leaving the remainder of the B cell repertoire intact.

Websites for further information on clinical trials:

http://sev.prnewswire.com/biotechnology/20050707/DCTH00107072005-1.html#
http://www.biogen.com/site/025.html
http://www.zymogenetics.com/clinical/TACI-Ig.html.

6. Conclusions

The discovery of BAFF and APRIL has advanced our understanding on survival mechanisms for B cell development, tolerance and malignancies. In addition, dysregulation of this system is strongly associated with the development of autoimmune diseases. Recent outcomes from clinical trials using BAFF inhibitors confirmed the importance of this system in human diseases, and have established BAFF inhibitors as a new generation of therapeutic agents for autoimmunity and cancers. In addition, research on BAFF has underscored the importance of certain B cell subsets for autoimmune disease pathogenesis. A better understanding of these cells, extensive transcript profiling, and a clear identification of the human counterpart of these B cell subsets should provide additional therapeutic approaches, for instance depleting pathogenic B cells while preserving healthy B cells. Therefore, further refinement of the B cell-depleting strategy is likely and hopefully will provide a new generation of therapeutics with increased efficacy and safety.

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