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REVIEW

B cell activating factor, its role in autoimmunity, and targeting in autoimmune diseases

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Abstract: B cell activation factor (BAFF), a recently identified member of the tumour necrosis factor (TNF) family, is a key survival factor during B cell maturation and is essential for the development of B cell tolerance. Breakdown of the regulation of BAFF expression results in excessive BAFF production that impairs B cell tolerance and leads to autoimmune phenomena. Consistent with this, BAFF levels are elevated in plasma of patients with various autoimmune diseases.

BAFF is considered to be one of the principal factors that regulate the size and composition of B cell compartment. BAFF acts as an important driving factor for B cell hyperplasia and autoantibody production in autoimmune processes. Thus BAFF has become a very attractive target for the treatment of autoimmune diseases with an altered B cell function. Results of clinical trials have confirmed a crucial role of BAFF in the pathogenesis of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). BAFF inhibitors in the treatment of RA, SLE and other autoimmune diseases are under intensive investigation. However, BAFF biology remains poorly understood. Nonetheless, results of the ongoing studies may enable the development of a new generation of BAFF inhibitors with more selective efficacy and increased safety *(Fig. 2, Ref. 92)*. Full Text (Free, PDF) *www.bmj.sk.*
Key words: BAFF, B cells, autoimmunity.

A breakdown of the immune tolerance can lead to the development of auto-aggressive immune reactions that manifest as autoimmune disorders. Currently, up to 70–80 diseases are known to have an autoimmune pathogenesis and affect about 5 % of the Caucasian population. Our understanding of autoimmunity has improved considerably during the last two decades, mainly due to the development of a number of animal models of these diseases and the identification of genes that may predispose to autoimmunity. Nevertheless, etiology of the majority of autoimmune diseases remains still obscure (1).

For a long time, investigations of the pathogenesis of autoimmune diseases was mainly oriented on T cells, because of their pivotal role in the regulation of immune reactions, especially in rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and type I diabetes mellitus. However, an active contribution of B cells and autoantibodies in these diseases was supported by data from experimental animal models. In addition, recent overwhelming success of B cell depletion therapies using rituximab (anti-CD20 monoclonal antibody) in patients with RA and SLE has demonstrated that B cells may have an important role in their induction.

B cells produce pathogenic autoantibodies, but also serve as the antigen-presenting cells (APC) that under some circumstances may corrupt normal processes of T cell co-stimulation and activations (2). The discovery of BAFF (B cell-activating factor), an essential survival factor during the B cell maturation at a stage when self-reactive B cells are eliminated, has brought more insights into the processes of B cell tolerance and homeostasis.

In BAFF transgenic mice, an increased expression of BAFF results in an inappropriate survival of self-reactive B cells and the development of a severe autoimmune phenotype (2). Moreover, elevated BAFF plasma levels are characteristic for patients suffering from autoimmune diseases like RA, SLE and Sjögren syndrome (SS).

An excessive BAFF production, whether a cause or a consequence of autoimmune reactions, is likely to exacerbate autoimmune disease via an inappropriate stimulation of B cell or T cell activities (2). Data from experimental and clinical studies using blocking antibodies or decoy receptors show that BAFF is an attractive therapeutic target.

The aim of our review is to provide information about BAFF, its structure, receptors and function; additionally, we focus on BAFF as an important potential therapeutic target and present current experimental and clinical experiences in targeting BAFF and its receptors.

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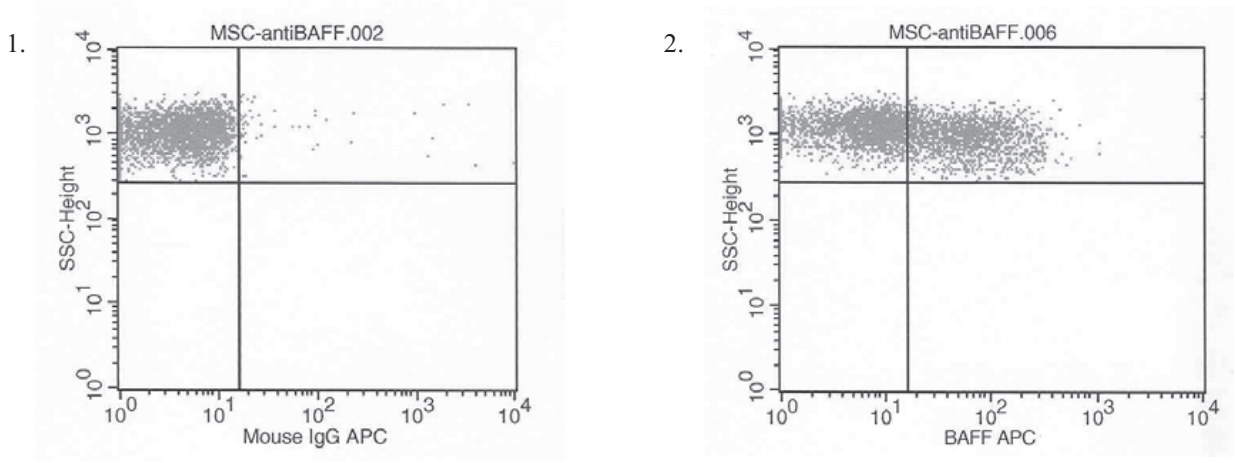

Fig. 1. BAFF expression in mesenchymal stromal cells (MSC) (34). Legend: CD105 and CD166 positive stromal bone marrow cells from patients with rheumatoid arthritis (RA) and osteoarthritis (OA) produce BAFF protein. Flow cytometry, intracellular staining (1. isotype control, 2. MSC from bone marrow of RA patient conjugated with anti-BAFF APC).

B cell activating factor

B cell activating factor (BAFF) (also named BlyS, TALL-1, THANK, zTNF-4 and TNFSF-13B) and apoptosis-inducing ligand (APRIL) are relatively new members of the TNF cytokine family. BAFF was discovered in late 1990s, however the biology of BAFF has been further studied in the recent years only (2–10). Both, BAFF and APRIL are closely related and share approximately 50 % sequence homology (11). The BAFF gene is located on chromosome 13q34 in humans and chromosome 8 in mice. The human BAFF locus is often translocated in Burkitt's lymphoma cells (12).

BAFF carries the characteristic TNF homology domain (THD) and has a typical trimeric structure that is common in all members of the TNF family. TNF ligands are type II membrane proteins, however, many of them are secreted as soluble molecules or are cleaved out of the cell membrane (9). BAFF can exist as a cell surface molecule or it can be proteolytically processed by subtilisin-like furin family-like proteases and secreted in a soluble form. This process is regulated by stimulus or cell type level (13–16). The different regulation of soluble and membrane bound forms suggests a possibility of distinct functions, however their relative activities and functions are yet to be determined.

The biological activity of BAFF may be also regulated by other mechanisms such as heterotrimer formation, alternative splicing and protein localisation. The formation of a heterotrimer incorporating a truncated splice variant called DeltaBAFF leads to the formation of an inactive non-cleavable form at the cell surface and results in a suppression of BAFF activity in DeltaBAFF transgenic mice *in vivo* (17, 18). Additionally, BAFF forms heterotrimers with APRIL, what have been identified both *in vitro* and *in vivo*, specifically in the context of some autoimmune diseases (19).

BAFF is expressed in a variety of cell types, predominantly in peripheral blood leucocytes and stromal cells of the spleen and lymph nodes (20, 21). Low expression is also observed in other tissues such as thymus and lung (22, 13). BAFF production by leucocytes is induced by a variety of pro-inflammatory stimuli. Dendritic cells, macrophages and monocytes stimulated by type I and type II interferons, IL-10 and LPS (lipopolysaccharide) (14, 15, 23–25) are potent producers of BAFF and also neutrophils stimulated with G-CSF or IFN-α express BAFF at very high levels (16, 26). As neutrophils enter the site of inflammation, they release the surface-expressed BAFF in a TNF-dependent manner, and thus may contribute to a local stimulation of autoimmune B cell responses (27). T cells and germinal centre B cells also produce BAFF at low levels following stimulation through the TCR (T cell receptor) or CD40L, respectively, suggesting BAFF autocrine actions (22, 24, 28). There is growing evidence that non-haematopoietic cells are also important producers of BAFF. Both, astrocytes and fibroblast-like synoviocytes, produce BAFF in response to TNF and IFN-α, indicating that stromal cells may be an important source of BAFF during inflammation (29, 30). Indeed, an inability of transplanted wild-type bone marrow to restore normal plasma levels of BAFF and to reconstitute the peripheral B cell pool in BAFF knock-out (KO) host animals indicates that the non-haematopoietic compartment (comprises radio-resistant stromal cells) is the major site of constitutive BAFF production (31). Hence, it seems that these cells are critical for the regulation of the size of the peripheral B cell pool.

The results show that there are two important sources of BAFF expression, constitutive and inducible. The constitutive expression by radio-resistant stromal cells in lymphoid organs is critical for regulating B cell homeostasis and the inducible expression in response to inflammatory stimuli. The latter is presumably important for a pathogen clearance (2, 32). Recent studies revealed other non-lymphoid BAFF producing cell types: air-

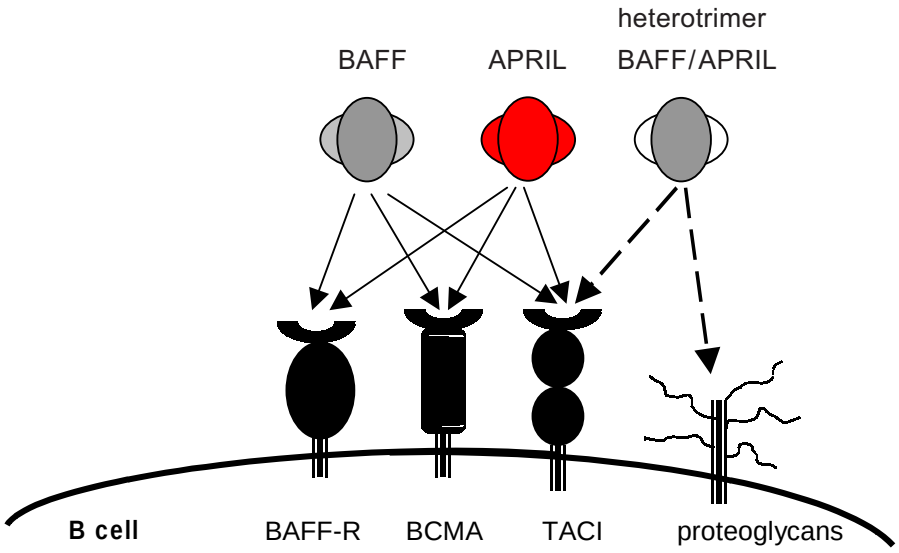

Fig. 2. The interactions between the soluble ligands BAFF and APRIL and their receptors expressed on B cells. Additionally, BAFF forms heterotrimers with APRIL that bind to surface proteoglycans.

way and salivary gland epithelial cells, vascular cell adhesion molecule 1-positive stromal bone marrow cells, CD105 and CD166 positive stromal bone marrow cells from patients with RA and osteoarthritis (OA) (Fig. 1) and osteoclasts (33, 34).

BAFF interacts with three receptors from the TNF receptor superfamily (TNFRSF): the BAFF receptor (BAFF-R or BR3), the transmembrane activator and calcium-modulator and cyclophilin ligand interactor (TACI), and the B cell maturation antigen (BCMA or TNFRSF17), all of them are expressed primarily by B cells (2).

For a long time, BAFF was the only known BAFF-R ligand, however, a recent study demonstrated that also a short variant of APRIL can bind to BAFF-R although with a low affinity (33, 35). Similarly, BAFF shares receptor specificity with APRIL and with other two receptors (TACI and BCMA) (36) (Fig. 2). BAFF-R, TACI and BCMA display unique, but overlapping, expression patterns; functional analysis has revealed distinct roles of these three receptors in mediating BAFF signals.

Cell surface expression of all three BAFF receptors is modulated during the B cell development. Receptor expression and BAFF binding are minimal on early immature B cells in the bone marrow. Significant amounts of BCMA mRNA and lower levels of BAFF-R mRNA and TACI mRNA are detected in the later stages of B cell development before the migration of B cells to peripheral lymphoid tissues occurs (37). At this time, BAFF-R and TACI are up-regulated by immature B cells what coincides with the acquisition of BAFF responsiveness at the transitional type 1 (T1) stage of their development (38). The level of TACI is low in T1 B cells but is high in transitional type 2 (T2) and marginal zone (MZ) B cells. Furthermore, BCR (B cell receptor) ligation up-regulates BAFF-R expression on B cells in an autocrine fashion. This promotes an increased sensitivity to BAFF-mediated survival signals as B cells mature (33). BAFF-R is subsequently expressed at high levels on all mature peripheral B cell subsets in the spleen, lymph nodes, and peripheral blood (39, 40). TACI has a distinct expression pattern to BAFF-R in that it is highly expressed in T2, marginal zone and B-1 B cells, however its expression on follicular and germinal centre B cells is down-regulated (38, 40, 41). Intracellular TACI is present in human macrophages and migrates to the cell surface upon activation (33). Of all BAFF receptors, the expression pattern of BCMA is the most restricted, BCMA being expressed only by germinal centre B cells and the bone marrow plasma cells (39, 40, 41).

There is growing evidence that T cells also express BAFF receptors. TACI and BAFF-R expression has been demonstrated on activated T cells and BAFF-R was detected even on regulatory T cells (9, 33, 42).

The normal function of BAFF was first described in *in vitro* assays demonstrating improved survival of maturing T2 splenic B cells in cultures supplemented with BAFF. This suggested a role of this protein as a survival factor during maturation of B cells in the spleen and was confirmed when B cell maturation in BAFF-deficient animals was found to be impaired beyond the T1 stage that lies immediately before the T2 stage. Hence, apart from signals provided by a functional BCR, immature B cells require also BAFF-mediated survival signals to become fully mature (33).

A number of studies documented that BAFF affects crucial events during the lifetime of B cells, particularly survival and maturation, germinal centre formation, antibody production and class switching (43, 44).

It is important to distinguish two distinct roles of BAFF activities; first, a role of BAFF in B cell development and matura-

tion, and second, a role as an inflammatory cytokine modulating immune responses (2). An augmented B cell proliferation, antibody production and class-switching, after anti-BCR stimulation *in vitro,* were observed when a recombinant BAFF was used in initial experiments (15, 22, 45). Even in absence of the BCR stimulation, BAFF significantly increased splenic B cell survival *in vitro* and resulted in expansion of peripheral B cell numbers (23, 46).

In accordance with the presence of BAFF receptors in membranes of T cells, *in vitro* experiments have proved an important role of BAFF in regulating T cell response. BAFF increases T cell proliferation and cytokine production in response to a range of mitogenic stimuli (24, 40, 47). Also, *in vivo*, T cell responses can be modulated by BAFF levels, e.g. a BAFF blockage prevents the T cell activation and the onset of disease in models of collagen induced arthritis (CIA) and a defective BAFF signalling is associated with an enhanced survival of allografts (48, 49, 50).

Consistent with *in vitro* observations, B and T cell compartments of BAFF transgenic mice show significant defects. In these mice, enlarged spleens and lymph nodes due to increased numbers of peripheral B cells are found, and with age, they develop symptoms of systemic autoimmunity. The T2, follicular and marginal zone B cell subsets of the spleen are expanded, and show significantly prolonged splenic B cell survival when cultured *ex vivo* (46, 51). In the BAFF transgenic mice, an increased spontaneous germinal centre formation and increased levels of all antibody subclasses were found, suggesting a stimulation of both, antibody production and class switching (51, 52). The BAFF transgenic mice display increased numbers of effector/memory type T cells (52). However, this phenotype seems 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 (48).

In contrast, BAFF-deficient mice and those treated with BAFF-blocking reagents have profound defects in peripheral B cell numbers and responses (3, 53). An impaired B cell maturation beyond the immature transitional stage with significant defects in peripheral B cell numbers can be detected in BAFF knockout mice (3, 54). Also, they are not able to up-regulate B cell maturation markers CD21 and CD23 (5). Antibody responses are severely affected in response to T-dependent and T-independent antigens and sustained germinal centre reactions are blocked (4).

Memory B cells (B_{MEM}) and long-lived bone marrow plasma cells (BM-PCs) persist within local environmental survival niches that provide cellular longevity. However, the factors supporting B_{MEM} survival within secondary lymphoid organs and allowing BM-PC persistence in the bone marrow remain poorly understood. A recent study found that long-lived B_{MEM} survival and function are completely independent of BAFF and APRIL. Thus, B_{MEMs} represent the only mature B2 lineage subset whose survival is independent of these ligands. These data define the BAFF/APRIL-dependent and -independent components of long-lived humoral immunity (55).

Finally, expression of BAFF plays an important role in the execution of B cell self-tolerance. The physiological expression of BAFF at limiting levels together with an impaired ability of certain autoreactive B cells to respond to BAFF survival signals result in the elimination of such specificities from the normal B cell repertoire before they become mature long-lived cells. Up-regulation of BAFF expression *in vivo*, however, can result in the rescue of self-reactive B cells from elimination. This effect explains, at least in part, the great increase of autoantibody production and associated autoimmune manifestations observed in transgenic mice that over-express BAFF (33).

Roles of the three BAFF receptors in mediating the different effects of BAFF were described using phenotypic analysis of gene-deficient and mutant mice strains. BAFF-R is primarily responsible for mediating BAFF-induced survival signals during maturation and maintenance of the mature B cell pool. BAFF-R knockout mice and the mutant A/WySnJ strain have significantly reduced peripheral B cell numbers, mirroring the phenotype of BAFF knockout mice (7, 54, 56, 57).

Studies analysing the phenotype of TACI knockout mice yielded conflicting results, although some consistent features could be noted (58, 59, 60). TACI regulates B cell proliferation, antibody class switching and homeostasis. Increased numbers of mature B cells were found in peripheral lymphoid organs of all cell lines, while one line developed a SLE-like autoimmunity similar to BAFF transgenic mice (58, 59, 60). TACI knockout B cells were hyper-proliferative *in vitro* and *in vivo* while activation of TACI using an agonistic antibody reduced normal B cell proliferation (58, 59, 60). To summarize the data, TACI seems to be an important negative regulator of B cell proliferation. While TACI-deficient mice mount normal antibody responses to T-dependent antigens, they display markedly decreased antibody production and impaired class switching in response to T-independent antigens (58, 59). These results correlate with other *in vitro* studies demonstrating a role for TACI in CD40L-independent class switching (15, 61). Moreover expression of TACI is particularly high on mantle zone B cells and B1 cells, the two B cell subsets, which play a key role in driving T-independent antibody responses (40, 57). In addition, MZ B cells and B1 cell subsets have been shown to contain self-reactive B cells. Thus higher TACI expression in these cells may be a safety feature preventing a potentially harmful expansion of self-reactive B cells (2).

Cohort analysis of two separate human groups identified a series of mutations in the TACI gene that are associated with the development of common variable immunodeficiency (CVID) (62, 63). The mutations were associated with reduced levels of plasma IgM, IgG and IgA, and B cells in affected individuals and were also defective in response to APRIL-induced proliferation and antibody class switching (62, 63). Also, lymphoproliferative disorders were documented in many patients with mutations in the TACI gene. The incidence of autoimmune diseases in CVID patients with TACI mutations was higher than in the general CVID group (63). Hence, TACI seems to have several roles; it acts as a positive regulator of antibody responses to T-independent antigens, and, at the same time, it acts as a negative regulator of B cell proliferation, too.

In preliminary studies focused on BCMA, basic immune functions in BCMA-deficient mice appeared normal (64). A re-

cent study, however, found a defect in the long-term survival of plasma cells in the bone marrow of these mice, which is consistent with the restricted expression pattern of BCMA to these cells (65). Activation of BCMA provides signals to B cells and makes them act as APCs for T cells. After the cross-linking of BCMA on B cells, an increased expression of MHC class II, CD86, CD80, CD40 and ICAM-1 was detected and also a significantly increased capacity to stimulate T cell proliferation and IL-2 production was observed (66). Treatment of splenic B cells with IL-4 and IL-6 induced BCMA expression and further stimulation with APRIL or BAFF promoted the APC function of these cells (66). From all these data and the fact that BCMA is expressed primarily by germinal centre B cells, plasmablasts and plasma cells, we can assume that BCMA may play an important role in the regulation of cooperation between these B cell subsets and T cells (2, 39, 40).

BAFF and autoimmunity

Levels of soluble BAFF are elevated in plasma and target organs of mice models that develop SLE, collagen-induced arthritis (CIA), and chemically induced autoimmunity (67, 68, 69). Analogical findings of increased levels of BAFF, but also APRIL and BAFF/APRIL heterotrimers, have been documented in plasma and target organs of a subgroup of human patients (20–50 %) suffering from different autoimmune diseases. Moreover, levels of BAFF seem to correlate with disease activity and/or titres of pathogenic autoantibodies. All these findings document that the overproduction of BAFF may have a pathological role in the development of systemic autoimmunity (33). However, data indicate that BAFF-dependent autoimmune process can be regulated by additional genetic modifiers. For example, earlier disease onset of disease was observed in BAFF-transgenic mice in presence of both the Sle1 and Nba1 lupus susceptibility alleles (70). In both, mice and humans, unique polymorphisms in the BAFF gene that may regulate BAFF expression have been described. Data on their association with autoimmune diseases, however, are limited (71, 72, 73). This may indicate that an impaired regulation of BAFF expression in autoimmune-prone individuals may be affected by other genetic or environmental factors, which regulate the responsiveness of BAFF-producing cells (33). In one study, authors detected elevated BAFF levels in healthy control subjects in the absence of infection or inflammation (74). These data may indicate that induction of autoimmunity in respect to BAFF over-expression requires the permissive effect of genetic predisposing factors. Moreover, BAFF may not be the trigger for autoimmune conditions, but may promote and perpetuate self-reactive B cell survival once the autoimmune response has been established (2).

The increased production of autoantibodies is a typical finding in the BAFF transgenic mice. Increased expression of BAFF may enable self-reactive B cells to escape from normal tolerance checkpoints (2). B cells of intermediate BCR affinity are able to escape from deletion in the presence of competitor cells in a BAFF transgenic host; those with a high BCR affinity are normally deleted/anergised. This indicates that death signals triggered by a high affinity self-reactive BCR upon binding to self-antigen cannot be reversed by survival signals provided by BAFF (2). High affinity self-reactive B cells can only survive in conditions of an increased supply of BAFF per cell, for example, during B cell lymphopenia (21). Autoreactive cells, which are supported by an increased BAFF expression, do not display a high BCR affinity, but are of intermediate affinity and selected into the marginal zone that mediates disease pathology (2). Some previous studies have documented that affinity maturation and high affinity antibodies are not required for the disease development (75). Because the loss of B cell tolerance in the BAFF transgenic mice is relatively minor and mild, one can speculate that the abnormal migration/homing of these cells to tissues is more important for disease pathogenesis than their autoimmune character (76).

An overproduction of BAFF during the development of autoimmune disease is well documented both in mice models and in humans, but mechanisms responsible for this effect are still unclear. Apart from the natural genetic variation, conferred by polymorphisms in the BAFF gene, initial increases in BAFF levels could be explained by the participation of innate cell responses to inflammation or infection.

The finding of a significantly enhanced BAFF production in response to pro-inflammatory stimuli indicates that BAFF may take part in physiological responses to infectious agents. BAFF could possibly increase B cell numbers during clonal expansion or may prime T cell activation during an immune response (32). Further evidence for a role of BAFF in response to infection comes from findings of elevated BAFF levels in patients with HIV infection (77). These data suggest, that overproduction of BAFF may explain high levels of autoantibodies and increased occurrence rates of autoimmune diseases such as SLE in HIV patients (77). Nevertheless, more studies of BAFF expression following experimental infection are required to clarify the role of BAFF production during immune responses to infectious agents.

Immune complexes bound to chromatin are also able to induce BAFF production by dendritic cells (78). Autoantibodies to nuclear components, such as chromatin, are typically found in plasma of SLE patients. Therefore, it can be speculated that production of BAFF may not be the cause, but the consequence of B cell tolerance loss. Production of BAFF as a part of immune responses to chromatin/immune complexes could initiate a powerful positive feedback loop, which may further impair B cell tolerance mechanisms and provide signals for disease persistence (2).

BAFF as therapeutic target

The concept of B cell depleting strategies has already been verified by the overwhelming effectiveness of Rituximab (anti-CD20 B cell depleting agent) in SLE and RA patients (79, 80, 81, 82, 83). Therefore it is not surprising that BAFF and its receptors have become attractive targets for the treatment of B cell mediated autoimmune diseases.

Both, blocking monoclonal antibodies and decoy receptor fusion proteins can be used to neutralize BAFF action. A human antibody (anti-BAFF; LymphoStat-B, Belimumab) that binds soluble BAFF and prevents its interaction with all three receptors with equivalent potency has been developed. Another class of BAFF antagonists is fusion proteins of one of the BAFF receptors with an immunoglobulin. Both TACI-Ig and BAFF-R-Ig are available for studies. They may act differently, as TACI-Ig blocks activities of both, BAFF and APRIL, respectively, whereas BAFF-R-Ig blocks BAFF only. Also, activities of LymphoStat-B may be different from those of BAFF-R-Ig as LymphoStat-B does not block membrane-bound BAFF. Although human BCMA-Ig binds both, BAFF and APRIL, it is seven to eight-times less potent than BAFF-R-Ig, what makes it less effective as a therapeutic agent (84).

A study, in which the effects of the administration of anti-BAFF to primates was studied, showed a decrease in numbers of B cells in secondary lymphoid organs but no effect on plasma immunoglobulin levels. In a phase 1 trial of anti-BAFF administration to patients with SLE, anti-BAFF had a half-life of 13–17 days and reduced a number of circulating B cells as well as plasma anti-DNA antibodies titres in some patients (84).

Application of TACI-Ig or BAFF-R-Ig fusion protein in models of SLE-prone mice resulted in a decreased and/or delayed proteinuria and prolonged survival. The effects of BAFF-R-Ig and TACI-Ig were equivalent in depleting mature follicular and MZ B cells, but numbers of immature B cells were not affected. Administration of both fusion proteins decreased also numbers of activated and memory T cell subsets (33). In lupus prone MRL lpr/lpr mice treated with TACI-Ig, a long-term reduction in splenic B cell and plasma cell numbers was observed and also the total immunoglobulin, anti-dsDNA autoantibodies and rheumatoid factor levels were decreased. Of note, application of TACI-Ig was effective when given to mice prior to disease onset, as well as at the time of an established autoimmunity. Hence, this fusion protein might be used also for the treatment of an established disease. TACI-Ig treatment was primarily effective in reducing disease parameters and autoantibody production in MRL lpr/lpr mice, however in normal animals only a transient reduction of IgG levels was observed (85). This finding indicates that the TACI-Ig treatment may eliminate only autoreactive B cells and autoantibodies without affecting normal humoral responses (2).

Some studies suggested that the action of TACI-Ig and BAFF-R-Ig may be independent of autoantibodies. Considering that autoreactive T cells can mediate glomerular damage independent of autoantibodies, treatment with TACI-Ig and BAFF-R-Ig might protect from renal involvement by elimination of follicular and MZ B cells that can act as pathogenic antigen-presenting cells (86, 87). In contrast, results of a recent study of BAFF-null SLE-prone mice have indicated that the positive effect of the neutralization of BAFF might not be entirely independent of autoantibodies. Although levels of autoantibody titres were not decreased, immunoglobulin isotypes were changed in a way that they were unable to cause glomerular damage (33).

Apart from a significant efficacy of BAFF antagonists in SLE-prone mice models, blocking BAFF also had protective effects in murine models of rheumatoid arthritis, multiple sclerosis and Graves' disease (33). In models of CIA, application of TACI-Ig caused a reduction of anti-collagen antibody levels and T cell responses, and a complete regression in paw swelling and joint destruction. Thus TACI-Ig might be used in the treatment of RA, nonetheless further studies of efficacy and safety of TACI-Ig are needed (2).

In the pathogenesis of RA, the interactions between T and B cells, especially in ectopic lymphoid tissue formed in the rheumatoid synovium, are critical factors to a progression of the disease (88–92). Application of TACI-Ig to mice transplanted with human synovial grafts resulted in a significant destruction of ectopic lymphoid structures. This subsequently reduced numbers of lymphocytes and follicular dendritic cells and decreased production of pro-inflammatory cytokines (9). Thus apart from regulating survival and autoantibody production in CIA, TACI-Ig treatment might also prevent the onset of disease by disrupting the generation of ectopic lymphoid structures. Therefore, the BAFF blockage may be a useful tool in the treatment of autoimmune diseases, which are characterized by increased autoantibody production and formation of ectopic germinal centres (Sjögren's syndrome, myasthenia gravis) (2).

Comparing the B cell depletion therapies that target CD20 (i.e. rituximab) and approaches of blocking BAFF activity (TACI-Ig, anti-BAFF-R, anti-BCMA), the latter may provide further benefits. Target structure expression (BAFF receptors and CD20) overlaps in many B cell subsets. Still, there are differences in certain populations such as plasma cells, which express BCMA but not CD20. Interestingly, elevated serum levels of BAFF are a side effect of the rituximab treatment. That is why, after cessation of depletion therapy, newly generated immature cells can be exposed to high levels of BAFF, leading to reactivation of autoimmune processes. This effect could be theoretically prevented or reversed by concomitant or subsequent neutralization of BAFF activity (33).

At present, BAFF-R-Ig and a monoclonal antibody specific for human BAFF (LymphoStat-B, known as Belimumab) are being tested for treatment of various autoimmune conditions. In monkeys and humans, their efficacy with subsequent depletion of mature peripheral B cell subsets and a low toxicity has been demonstrated. A phase II clinical trial of LymphoStat-B in RA and SLE has been completed recently with promising results (33).

Despite the described important role of BAFF in the development of autoimmunity, the biology of BAFF is still not fully elucidated. With increasing understanding of the BAFF activity and accumulating therapeutic experience with BAFF blocking reagents, a second generation of more specific drugs that may provide better therapeutic effect is expected. Among these, receptor agonists and antagonists for BAFF-R, TACI and BCMA, which could allow individual targeting of each receptor, rather than their ligand, are expected. Other examples may be agonistic antibodies to TACI that could suppress hyperactive autoim-

mune B cell responses without blocking endogenous levels of BAFF or APRIL, which might help to retain normal immune functions (2).

Conclusion

The discovery of BAFF allowed a better understanding of mechanisms of maturation, survival and maintenance of homeostasis of B cells and also a development of B cell tolerance. BAFF is currently considered to be one of the principal factors, which regulate size and composition of B cell compartment and acts as an important driving element of B cell hyperplasia and autoantibody production in autoimmune processes. Deregulation of BAFF production is directly connected to the pathogenesis of autoimmune diseases. As a consequence, BAFF has become an attractive target for the treatment of autoimmune diseases with an altered B cell function. Results of clinical trials of BAFF inhibitors already confirmed their efficacy and importance in human autoimmune diseases. Inhibitors of BAFF belong to a new generation of biologic therapeutic agents for the treatment of autoimmune disorders. Further elucidation of the function of BAFF and its receptors with respect to the regulation of the B cell compartment and B cell tolerance during autoimmune processes will enable the development of a new generation of BAFF inhibitors with more selective efficacy and increased safety.

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