

B Cell-Activating Factor (BAFF)-Targeted B Cell Therapies in Inflammatory Bowel Diseases

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Received: 12 July 2016 / Accepted: 13 September 2016 / Published online: 21 September 2016
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Abstract Inflammatory bowel diseases (IBD) involve dysregulated immune responses to gut antigens in genetically predisposed individuals. While a better elucidation of IBD pathophysiology has considerably increased the number of treatment options, the need for more effective therapeutic strategies remains a pressing priority. Defects of both non-hematopoietic (epithelial and stromal) and hematopoietic (lymphoid and myeloid) cells have been described in patients with IBD. Within the lymphoid system, alterations of the T cell compartment are viewed as essential in the pathogenesis of IBD. However, growing evidence points to the additional perturbations of the B cell compartment. Indeed, the intestinal lamina propria from IBD patients shows an increased presence of antibody-secreting plasma cells, which correlates with enhanced pro-inflammatory immunoglobulin G production and changes in the quality of non-inflammatory IgA responses. These B cell abnormalities are compounded by the emergence of systemic antibody responses to various autologous and microbial antigens, which predates the clinical diagnosis of IBD and identifies patients with complicated disease. It is

presently unclear whether such antibody responses play a pathogenetic role, as B cell depletion with the CD20-targeting monoclonal antibody rituximab did not ameliorate ulcerative colitis in a clinical trial. However, it must be noted that unresponsiveness to rituximab is also observed also in some patients with autoimmune disorders usually responsive to B cell-depleting therapies. In this review, we discussed mechanistic aspects of B cell-based therapies and their potential role in IBD with a special interest on BAFF and BAFF-targeting therapies buoyed by the success of anti-BAFF treatments in rheumatologic disorders.

Keywords B cells · BAFF · Inflammatory bowel diseases

Introduction

Inflammatory bowel diseases (IBD) refer to chronic immune-mediated disorders characterized by gut inflammation, including Crohn's disease (CD) and ulcerative colitis (UC). IBD affects more than one million persons in the USA [1]. While numerous biological pathways have been incriminated, it is generally believed that IBD results from a maladaptive immune response to gut-resident commensal bacteria in a genetically susceptible host. Pro-inflammatory CD4⁺ T cells, such as those involved in Th1 and Th2 responses, are heavily implicated in the pathogenesis of IBD [2, 3]. While Th1 responses are thought to play a fundamental role in CD, Th2 responses dominate the pathobiology of UC. However, additional lymphocytes such as innate lymphoid cells (ILCs) and Th17 cells have recently emerged as key players in the pathogenesis of IBD.

Similar to Th1 and Th2 cells, ILCs and Th17 cells regulate antibody responses by establishing functional

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interactions with B cells in both systemic and intestinal lymphoid organs. Accordingly, several lines of evidence implicate also B cells in the pathogenesis of IBD indicating that the gut humoral immune system of IBD patients suffers from a functional imbalance similar to that notoriously affecting the cellular immune system. In the latter, abnormal pro-inflammatory CD4⁺ T cell responses mediated by effector Th1, Th2, or Th17 cells disrupt homeostasis and causes IBD by outweighing anti-inflammatory CD4⁺ T cell responses orchestrated by Foxp3⁺ T regulatory (Treg) cells. Similar but less obvious and perhaps more complex pro-inflammatory alterations may target the B cell compartment of patients with IBD. Acknowledging our poor understanding of the complexity of B cell responses in IBD may allow a more critical evaluation of recently failed UC-targeting therapeutic attempts involving the CD20-targeting B cell-depleting agent rituximab [4]. We contend that the negative outcome of this approach should not discourage from considering B cells as potential therapeutic targets in IBD, particularly in consideration of the fact that unresponsiveness to rituximab can be also observed in some cases of B cell-related autoimmune disorders.

This review will discuss the putative relevance of B cells in the pathogenesis and treatment of IBD. Our discussion will focus on the biology of B cell-activating factor (BAFF, also known as BLyS or TNFSF13b), a cytokine heavily involved in B cell-related autoimmune diseases, including systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) [5–9]. In these and other inflammatory disorders, inhibition of BAFF has led to encouraging clinical results, which are consistent with a positive role of this cytokine in the activation of pathogenic B and perhaps even T cells [10]. Besides reviewing currently available BAFF-targeting strategies, we will discuss the potential role of BAFF in the pathogenesis and treatment of IBD.

B Cell System and IBD

Humoral Immune System Is Dysfunctional in IBD

Although T cell system is currently dominant in the study of IBD pathogenesis and therapy, multiple lines of evidence suggest a role of B cell lineage in IBD as well.

First of all, humoral homeostasis is disrupted in IBD. In particular, it has been suggested that IBD patients have impaired production of polymeric immunoglobulin A (IgA), a non-inflammatory antibody that enhances intestinal homeostasis by coating commensal bacteria after undergoing transepithelial translocation via the polymeric Ig receptor (pIgR) [11]. IBD is also associated with relative reduction in the production of IgA2, a poorly understood

mucosal subclass usually released along with IgA1 in the large intestine. Besides decreasing the intestinal IgA2/IgA1 ratio, IBD increases local production of the pro-inflammatory antibody IgG [12] and, in some cases, augments B cell expression of the pro-inflammatory cytokine IL-8 [13].

An increase in plasma cells within the intestinal lamina propria of patients with IBD is well documented. The accumulated lympho-plasmacytes can be organized in newly created lymphoid structures in the inflamed intestine, such as isolated lymphoid follicles which comprise of a large number of IgG-producing cells [14–16]. Importantly, these plasma cells are a source of not only IgG but also monomeric IgA [12], the levels of both of which are increased in patients with IBD.

Mucosal IgG in patients with IBD is directed against microbial elements or even autoantigens [17]. The described antimicrobial antibodies include anti-I2, anti-outer membrane protein C (anti-OmpC), anti-CBir1 flagellin (anti-CBir1), and anti-saccharomyces-cerevisiae (ASCA) [18], while IBD-associated autoantibodies include anti-neutrophil cytoplasmic antibodies (ANCA) [2] and anti-epithelial autoantibodies [19]. Additionally, while the role of anti-granulocyte macrophage colony-stimulating factor (GM-CSF) is likely complex, their presence in patients with CD is associated with ileal phenotype as well as a complicated behavior of the disease [20]. Furthermore, NOD2 KO mice treated with anti-GM-CSF antibodies develop transmural ileitis after NSAID exposure, emphasizing the crucial role of this autoantibody in the pathophysiology of ileal CD [20]. It is unclear whether antimicrobial antibodies are the cause or effect of a disrupted epithelial barrier. Nevertheless, their presence in IBD patients could be detected before IBD diagnosis and is associated with a negative disease course [18, 21–24].

B Cell System and Pan-B Cell-Targeting Therapies Have Conflicting Effects in Murine and Human Inflammatory Diseases

Rituximab, a monoclonal antibody targeting CD20, is widely used in inflammatory diseases such as RA or ANCA-associated vasculitis [25, 26]. However, in some patients, paradoxical inflammatory manifestations can occur following rituximab administration [27, 28]. Based on such pro-inflammatory effects of rituximab, the complexity of the B cell compartment is coming to light. While dysfunctional B cell lineage can promote autoimmunity through autoreactive, long-lived plasma cells [29], regulatory B cells may also attenuate inflammation. For example, in experimental murine autoimmune encephalomyelitis model, mice deficient in peripheral B cells (after anti-CD20 treatment) failed to undergo spontaneous recovery and exhibited chronic disease [30, 31]. Additionally, B cells

may also play an anti-inflammatory role. IL-10 produced by B cells has been shown to suppress autoimmunity in several murine models of inflammatory diseases and in humans [32, 33]. Additionally, regulatory B cells may have an anti-inflammatory role independent from IL-10 [34]. Besides their own anti-inflammatory impact, regulatory B cells may promote the anti-inflammatory effect of regulatory T cells. It has been shown in vitro and in vivo that B cells regulate regulatory T cells by inducing FoxP3 via IL-10 and TGF β [35–37]. Moreover, anti-CD20 therapy may induce a decrease in number of regulatory T cells [38, 39].

Adding to this complexity the fact that plasma cells do not express CD20 and tissue resident plasma cells might not be affected by rituximab [40]. Notably, an in vitro study showed that a plasma cells subset expanded in the mucosa of IBD patients and producing granzyme B was resistant to rituximab-induced apoptosis [41]. Conversely, it has been reported that rituximab could improve colonic inflammation [4, 42], while case reports showed that rituximab could conversely trigger colitis [43–45].

In UC, a phase II randomized controlled trial, which included 24 steroid-dependent and/or steroid-resistant patients, did not show a significant improvement in patients treated with rituximab [4].

Due to the reasons mentioned above, this should not exculpate B cells in the pathogenesis of IBD. Rather, we contend that a nuanced strategy targeting specific elements of B cell system should be pursued.

Presenting BAFF

Isoforms, Production, and Regulation

BAFF, a member of the TNF ligand superfamily, is a type II transmembrane protein. Under physiological conditions, membrane-bound BAFF is expressed on cell surface as a homotrimer which can be cleaved by a furin protease. Once cleaved, BAFF is released as a soluble and biologically active 17-kDa molecule [46]. The presence of BAFF 60-mer built from multimers of 20 trimers remains controversial. It would bind and activate transmembrane activator and calcium modulator and cytophilin ligand interactor (TACI), one of the three BAFF receptors [47, 48]. Δ -BAFF is an isoform lacking a short peptide segment in its structure and cannot bind cell surface BAFF receptors. It can regulate BAFF activity by forming inactive trimers with BAFF [49].

Both hematopoietic and non-hematopoietic cells produce BAFF. In steady-state conditions, myeloid cells including monocytes, macrophages, neutrophils, and dendritic cells (DCs) are the main producers of BAFF [9, 50]. G-CSF- or IFN-stimulated neutrophils are a prominent

source of functional BAFF [51]. Macrophages, monocytes, DCs, and follicular DCs are also known to release substantial amount of BAFF [9]. Production of BAFF in these cells is up-regulated by type I interferons (IFNs), IFN γ , TGF β , IL-10, and granulocyte colony-stimulating factor (G-CSF) [52, 53]. BAFF can also be produced in response to bacterial components such as lipopolysaccharide (LPS) [54]. Additionally, TLR activation, in particular TLR4 [52] or TLR9 [55], also induces BAFF production by myeloid cells.

Non-myeloid cells such as T cells [56], activated B cells [57], and mast cells can also produce BAFF [7, 58–61]. In hematopoietic malignancies such as B cell chronic lymphocytic leukemia, BAFF promotes tumor cell survival [62]. A variety of cytokines, including interferon gamma (IFN γ), transforming growth factor beta (TGF β), interferon alpha (IFN α), as well as estrogen and CD40L, are capable of up-regulating the expression of BAFF on myeloid cells [63, 64].

Several studies have demonstrated that non-hematopoietic cells such as stromal cells could also express BAFF. Additionally, BAFF expression has been reported in salivary gland epithelial cells in Sjogren's syndrome [65], by airway epithelial cells [66], placental cytotrophoblasts [67], fibroblast-like synoviocytes in the synovium of patients with RA [63, 68], breast adipocytes [69], osteoclasts in patients with multiple myeloma [70, 71], and astrocytes in patients with multiple sclerosis [72, 73].

Thus, under inflammatory conditions cytokines such as IFNs induce the expression of BAFF by non-hematopoietic cells providing local niches that could promote induction or perpetuation of inflammation.

BAFF Receptors

The biological role of BAFF is mediated by three receptors: TACI, BAFF receptor (BAFF-R/BR-3), and B cell maturation antigen (BCMA) [74]. BR3 binds exclusively to BAFF, while BCMA and TACI can also bind to a proliferation-inducing ligand (APRIL), another TNF family ligand. BCMA has a stronger affinity for APRIL compared to BAFF. BAFF-R and TACI are highly expressed on mature B cell subsets in spleen and peripheral blood; BCMA is restricted to B cells in the germinal center (GC) and bone marrow plasma cells [61]. Both membrane-bound and soluble BAFF can bind BAFF receptors.

BR3 (BAFF-R)

Compared with TACI and BCMA, BR3 plays a much greater role in B cell development. BAFF/BR3 signaling is crucial for the survival and the maturation of transitional B cells. BR3 is a type I membrane protein that is

predominantly found on naive and memory B cells. A/WySnJ mice, which possess a mutant BR3 defective in propagating intracellular signals, have a dramatic impairment of B cell development. These mice have a reduced number of mature peripheral B cells, although bone marrow B cell lymphopoiesis and T1 B cells are preserved [75, 76]. Additionally, BR3-mutant mice have deficiencies in the antibody response, which are similar to those seen in BAFF-deficient mice [75].

BR3 (but not TACI and BCMA) is also expressed on the surface of effector memory T cells [77], implying that BAFF/BR3 pathway may play a role in T cells function as well. Ye et al. [78] reported that the binding of BAFF to BR3 expressed by a subset of CD4⁺ T cells co-stimulates T cell activation and allo-proliferation in vitro and in vivo. Moreover, T cells from BR3 mutant mice are unresponsive to the immunostimulatory effects of BAFF, suggesting that BR3 seems a primary receptor to promote Th1-type responses [61, 77, 78].

Overall, BAFF/BR3 pathway promotes survival and development of transitional and mature B cells and co-stimulates T cells proliferation and cytokines secretion.

TACI

TACI is a type III membrane protein with the ability to bind BAFF and APRIL with high affinity. BAFF trimer can bind TACI but only BAFF 60-mer can activate the signaling pathway [79]. TACI is expressed mainly on B cells and is present at higher levels in memory B cells than in naive B cells in steady state [80]. The role of TACI is poorly understood, and somewhat conflicting functions have been ascribed to it. For example, TACI has been shown to inhibit B cell expansion on the one hand while promoting the differentiation and survival of plasma cells on the other. TACI knockout (KO) mice show lymphoid hyperplasia, marked splenomegaly and accumulation of B cells in lymphoid sites. Additionally, B cells isolated from these mice have the propensity to proliferate and produce increased amounts of immunoglobulins after stimulation in vitro [81]. These data demonstrate that TACI regulates B cell function by limiting the clonal expansion of B cells in a B lymphocyte-induced maturation protein-1 (Blimp-1)-dependent fashion [82] on the one hand and generating long-lived antibody-secreting plasma cells on the other [82]. As further evidence, TACI KO mice develop autoimmunity and fatal lymphoproliferation [83]. TACI may also play a role in T-independent humoral response as TACI KO mice have impaired T-independent responses to type II antigens (such as NP-ficoll), while immune responses to T-dependent antigens such as keyhole limpet hemocyanin (KLH) are maintained [81, 84]. Age affects the expression of TACI on B cells in humans [85] and mice

[86]. This could explain the susceptibility of newborns to infections with encapsulated bacteria and the impaired immunogenicity of polysaccharide vaccines in the newborn [86]. In humans, 7–21 % of individuals with TACI mutations have common variable immunodeficiency (CVID) [87] characterized by an increased susceptibility to infections (especially to encapsulated bacteria), lymphoproliferative, and autoimmune features [87].

BCMA

BCMA is also a type III membrane protein. Its affinity is higher for APRIL than for BAFF. The interpretation of murine studies with regard to BCMA needs to include the fact that BCMA binds APRIL and BAFF with much greater affinity in humans than in mice [88]. BCMA does not appear to impact B cell development and survival as evidenced by the fact that BCMA KO mice have a normal development of B cells and an adequate humoral response against antigens [88–90]. However, BCMA may promote the survival of plasmablasts [91–95] and enhance antigen presentation by mature B cells [96]. Thus, BCMA could participate in maintaining a sustained humoral response. BCMA also regulates T follicular helper cells (T_{FH}) as BCMA deficiency in T cells boosts T_{FH} accumulation, resulting in enhanced GC B cell responses in autoimmune-prone Nba2 mice [97].

To summarize, BCMA promotes the survival of plasma cells and may regulate the expansion of TFH cells but does not have impact on B cell development.

The Impact of BAFF on Immunity

BAFF has an important role in the development and function of immune cells. While B cell function is the primary target of BAFF, other immune populations may be involved as well.

BAFF Promotes B Cell Survival (Fig. 1)

Treating mice with BAFF increases the number of splenic B cells, particularly transitional B cells, and enhances humoral immune responses [98–100]. BAFF augments proliferation and Ig secretion by B cells activated through the B cell receptor (BCR) [88, 98], by decreasing the expression of pro-apoptotic (Bak, Blk, and Bim) molecules while increasing anti-apoptotic (Al, bcl-2, bcl-xL, and Mcl-1) factors [91, 99–103]. The effect of BAFF on B cell survival and longevity seems limited to late transitional and mature B cells [99, 104]. Indeed, in the murine bone marrow, BAFF receptors are not expressed in pro-B and pre-B cells [99, 105]. Normal human B cells first express BAFF receptors at the transitional stage of development

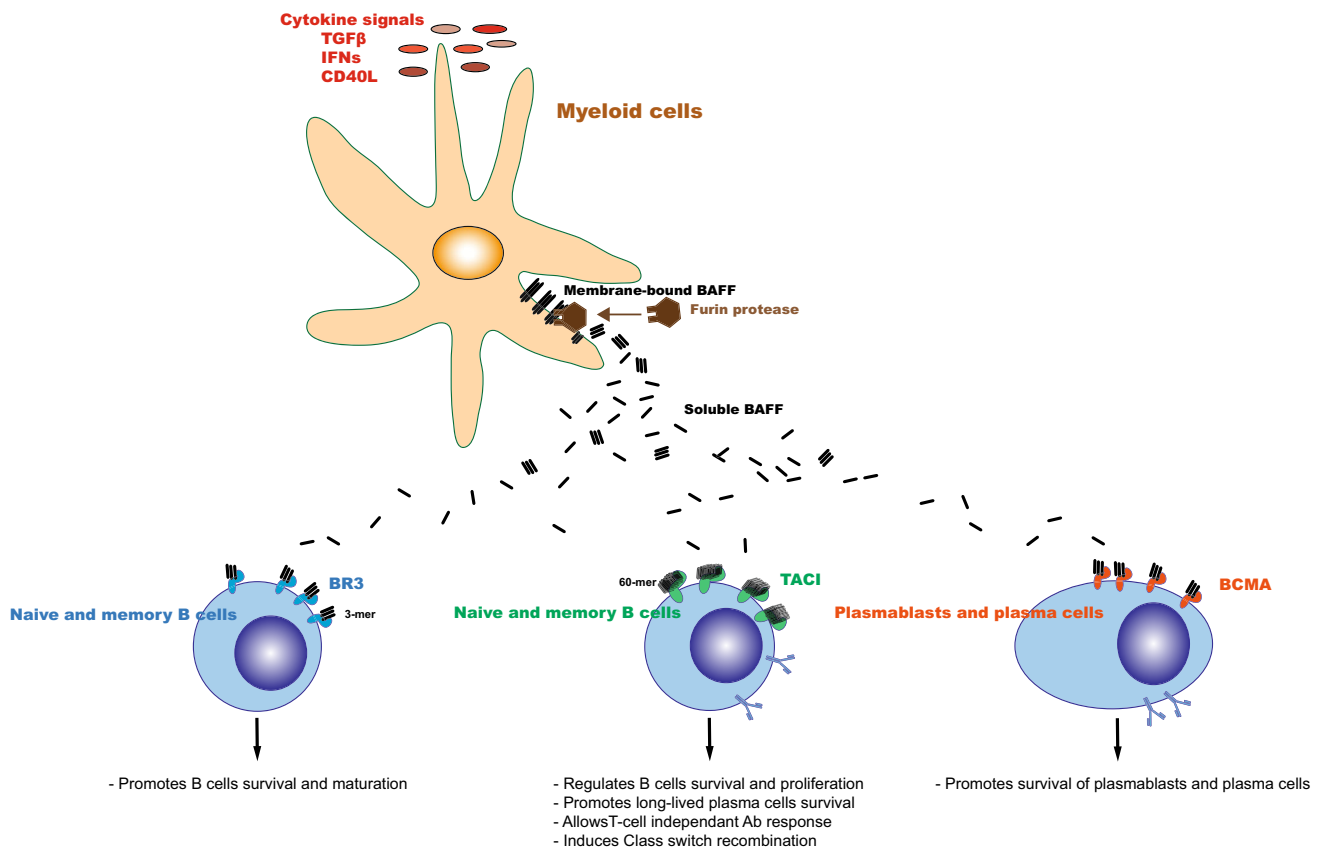


Fig. 1 Role of BAFF in B cells via each receptor

and remain capable of receiving BAFF-dependent signals at least until they terminally differentiate into plasma cell [106]. T_{FH} -derived BAFF signals [107], coupled with engagement of the BCR, promote the positive selection of transitional B cells, their continued maturation [99, 108], and the survival of high-affinity B cell clones.

BAFF Activates Class Switch Recombination (CSR) (Fig. 1)

Naive IgM^+IgD^+ B cells undergo class switch recombination (CSR) of the heavy chain locus to produce IgG, IgA, or IgE. This imparts versatility in function and distribution to the Ig. CSR usually requires a combination of signaling through CD40 receptors combined with the activity of specific cytokines and Toll-like receptors (TLR). BAFF may induce CSR as evidenced by the fact that BAFF transgenic (Tg) mice exhibit highly increased Ig serum levels (especially IgA) [109], while BAFF KO mice show marked decreased serum Ig levels [110]. Furthermore, in vitro assays, DCs stimulated by cytokines that increase the production of BAFF ($IFN\alpha$, $IFN\gamma$, IL-10) augment Ig CSR, while BAFF-inhibition attenuates it [111]. BAFF-mediated Ig CSR may occur through a direct effect on B

cells or indirectly, by inducing B cells to secrete cytokines such as IL-10 [112] (for IgG and IgA CSR) [113] or IL-4 (for IgE CSR) [111, 113].

BAFF Co-stimulates T Cell Activation (Fig. 2)

Although expressed in the majority of B cells, BR3 is also expressed in a wide repertoire of T cells subsets (naïve/activated/memory T cells) [78, 114, 115]. The effects of BAFF on T cell stimulation have been documented both in vitro and in vivo. For example, Huard et al. [116] have demonstrated that BAFF delivers co-stimulatory signal to T cells, resulting in IL-2 secretion and T cell division, in combination with suboptimal TCR stimulation. Additionally, BAFF promotes T cell differentiation into effector cells as defined by $L\text{-selectin}^{lo}/CD44^{hi}$ phenotype [56]. Moreover, BAFF polarizes T cells toward a Th1 phenotype as evidenced by the enhanced production of $IFN\gamma$ and reduced production of IL-4/IL-5 by BAFF-stimulated T cells. BAFF can also be produced by activated T cells, which also up-regulate BR3 perhaps in an autocrine positive feedback loop [56]. The T cell stimulatory effect of BAFF has been confirmed in a number of murine and human studies [54, 61, 78] with the intensity of T cell

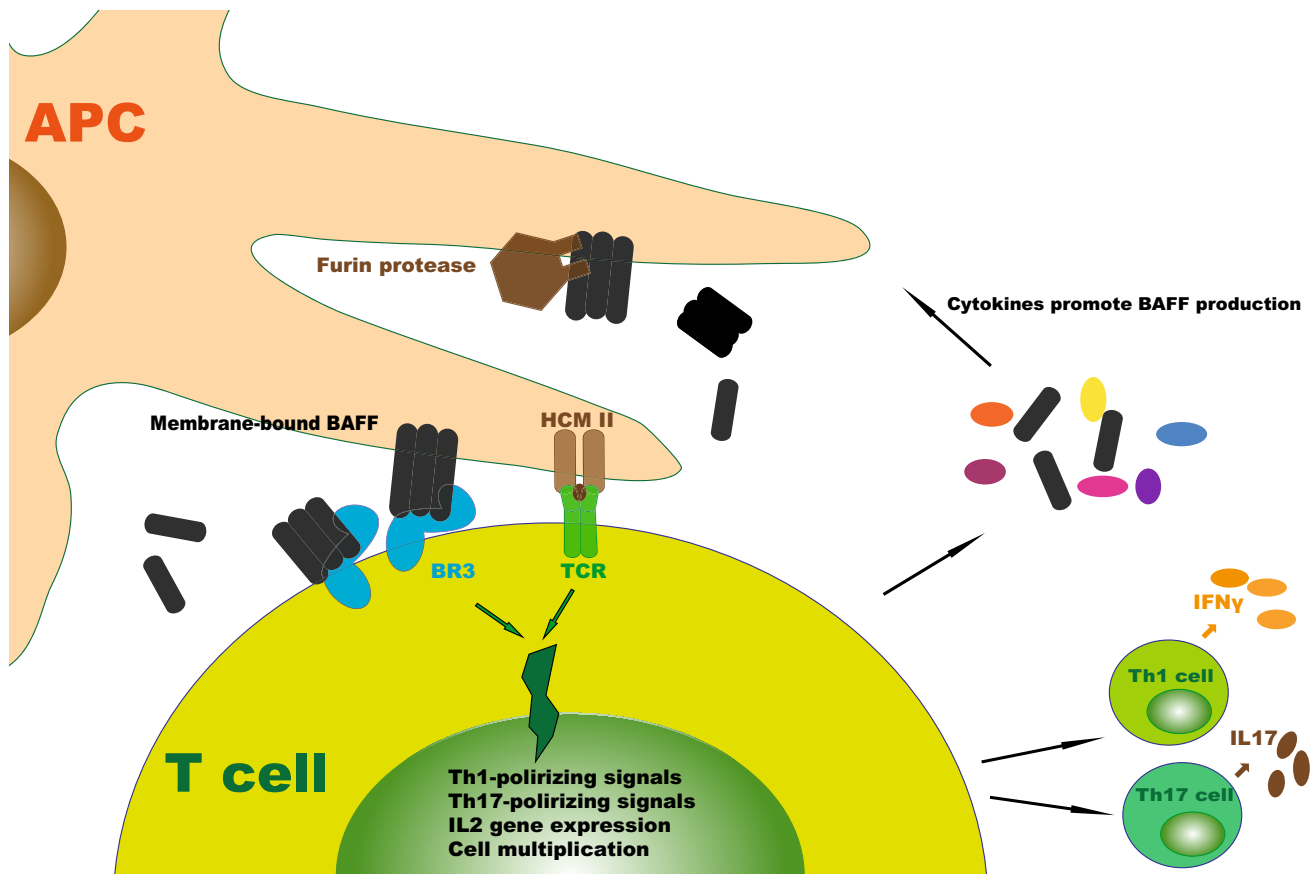


Fig. 2 BAFF impact on T cells

response being compared to anti-CD3/anti-CD28 stimulation [61, 116]. Conversely, inhibiting BAFF has a negative effect on T cell stimulation [54]. Finally, these data are strongly supported by the fact that BAFF Tg mice exhibit accumulation of activated T cells [109]. While some of the T cell effects of BAFF are related to direct effects, mediated via BR3 receptors, other effects may be indirect and related to BAFF-dependent modification of the B cell compartment [56].

In conclusion, BAFF/BR3 pathway co-stimulates T cell activation and proliferation and promotes T cells differentiation into effector cells preferentially producing Th1 cytokines [56].

BAFF Promotes Monocyte and DCs Activation

BAFF promotes the activation and differentiation of monocytes, leading to the production of inflammatory cytokines such as IL-6 [117]. Additionally, BAFF up-regulates surface co-stimulatory molecules on human monocyte-derived DCs and induces the secretion of a large variety of cytokines and chemokines such as IL-6, IL-8, MCP-1, CXCL-1, CCL-5, and TNF α [118]. BAFF-stimulated DCs induced a greater proliferation of allogeneic

CD4 T cell proliferation to a greater extent than control DCs. Finally, BAFF-stimulated DCs secreted enhanced levels of the Th1-polarizing cytokine, IL-12p70, and promoted naive CD4 T cell differentiation into Th1 T cells [118]. Thus, BAFF may regulate the adaptive immune response by directly promoting dendritic cell maturation and function.

BAFF Signaling Pathways Related to Inflammation (Fig. 3)

BAFF Stimulates NF κ B Activity

NF κ B is a family of transcription factors activated by diverse triggers such as pro-inflammatory cytokines, pathogen-associated molecular patterns, cell-bound ligands, and physical stress which plays a critical role in innate and adaptive immunity. NF κ B activation can occur via canonical and non-canonical pathways. In the canonical pathway, activation of the I κ B kinase (IKK) complex leads to the proteasomal degradation of the I κ Bs. This results in the liberation of RelA(p65)/NF κ B1(p50) heterodimers from the inhibitory I κ Bs and their migration into the

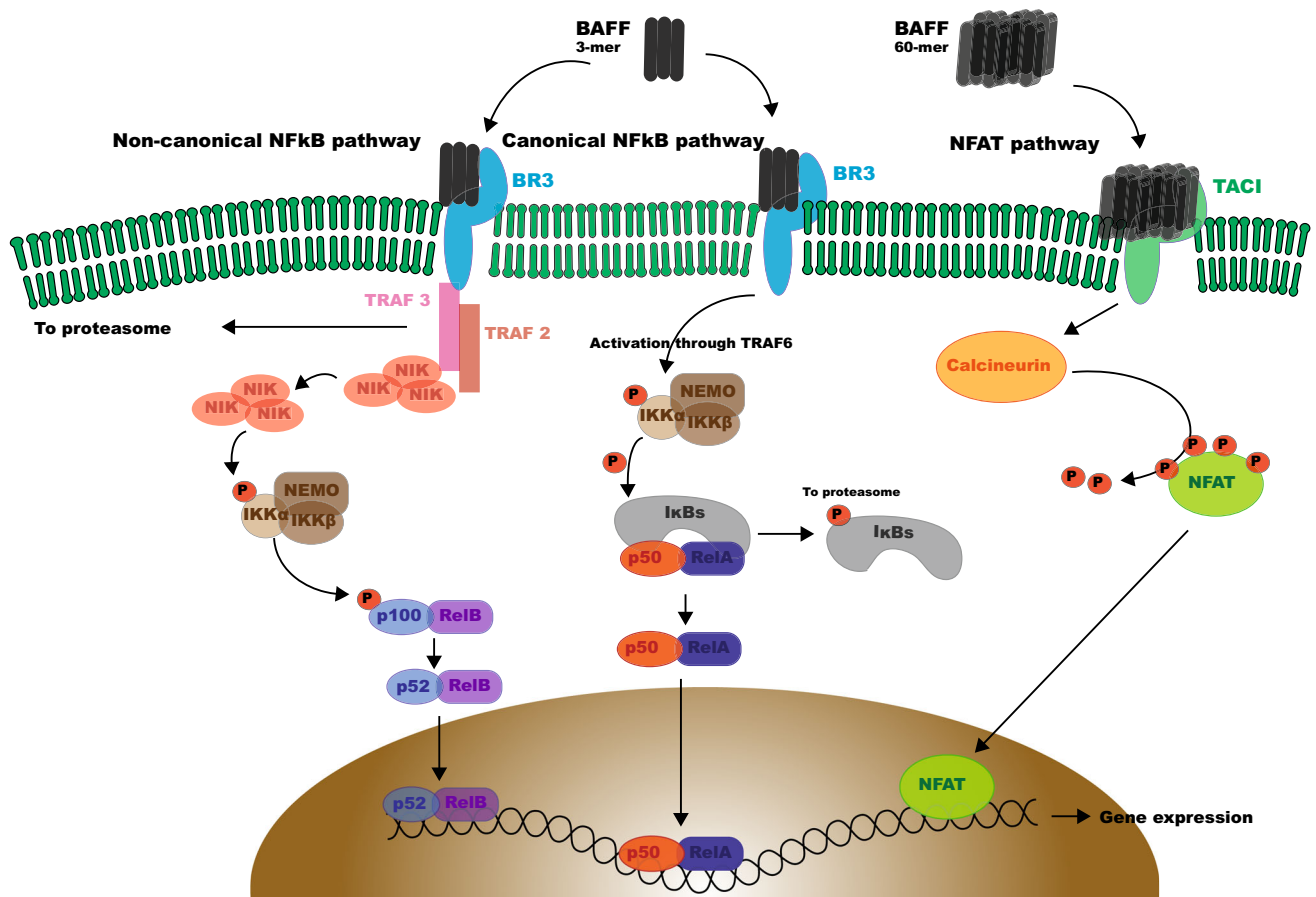


Fig. 3 Inflammatory pathways promoted by BAFF

nucleus to initiate the transcription of a wide variety of target genes. In the kinetically slower non-canonical pathway, activation of the NFκB-inducing kinase (NIK) phosphorylates and activates IκB kinase-α (IKKα). IKKα phosphorylates the NFκB2 protein precursor (p100) leading to p100 processing and release of active mature p52 subunit [119].

Several studies have demonstrated BAFF can activate NFκB via canonical and non-canonical pathways in lymphoid [120–122] and myeloid cells [117]. Activation of the non-canonical pathway is a major component of BAFF signaling in B cells and involves the BCMA, TAC1, and BR3 receptors. This results in the recruitment of TNF receptor-associated factor (TRAF) proteins. Notably, the TRAF proteins are a major group of intracellular adaptors that can bind directly or indirectly to multiple members of the TNF receptor family and activate NIK [121, 122].

BR3 has a single binding site for TRAF3 [123, 124], a negative regulator of non-canonical NFκB activation (via proteosomal degradation of NIK). BAFF signaling via BR3 leads to TRAF3 proteolysis, resulting in a gradual accumulation of NIK and non-canonical NFκB activation. Like

BR3, BAFF signaling via BCMA can also activate non-canonical NFκB signaling [125, 126].

Although activation of non-canonical NFκB is the dominant effect, BAFF can also activate the canonical NFκB pathway in a TRAF6-dependent fashion leading to the liberation of RelA(p65)/NFκB1(p50) heterodimer [127].

Physiological role of NFκB in mediating immune response and inflammation has been well established using genetic approaches or antagonists. Epithelial cells of the infected tissue or resident hematopoietic cells initiate the inflammatory response by triggering pro-inflammatory pathways through NFκB in response to inflammatory stimuli [128]. Activation of NFκB also results in the increased expression of adhesion molecules and chemokines by endothelial cells and in the tissue, leading to the recruitment and activation of effector cells. Additionally, NFκB promotes the production of antimicrobial molecules and the survival of immune cells in the inflammatory area [128].

Beyond BAFF, lots of inflammatory stimuli result in NFκB activation in different cell types, leading to the activation of transcriptional programs with sometimes

conflicting effects but overall promoting inflammation and cell survival [129].

In non-physiological conditions, NF κ B dysfunctional pathway has been involved in inflammatory and tumoral processes [129–131]. For example, inadequate activation of NF κ B leads to its translocation into the nucleus, inducing therefore the expression of cytokines such as IL-6 and TNF α contributing to inflammation and inflammation-associated tumor [129, 130]. Dysfunctional NF κ B pathway leading to increased levels of TNF α is one of the key phenomena in IBD pathogenesis.

Thus, in pathological condition, activation of NF κ B by dysfunctioning BAFF could result in triggering inflammation.

BAFF Can Promote Inflammation Through Th1 and Th17 Pathways

As described above, BAFF-stimulated T cells are polarized toward Th1 cytokine production. B cells, which express TACI, interact with BAFF-expressing DCs through BAFF/TACI, which promotes the development of DCs into antigen-presenting cells capable of efficiently activating T cells [132]. Co-culture studies with T cells and DCs have shown that pretreatment of DCs with BAFF enhances the production of IL-17 [114]. Moreover, BAFF overexpression in BAFF Tg mice promotes Th17 cells generation in vitro and in vivo and aggravates experimental autoimmune encephalomyelitis, a Th17 cell-driven disease [133], while the blockade of BAFF by TACI-IgG reduced Th1 and Th17 cells but not memory T cells [134].

BAFF and Other Inflammatory Pathways

BAFF signaling via TACI activates nuclear factors of activated T cells cytoplasmic calcineurin-dependent 2 and 1 (NFAT2 and NFAT1) [135]. NFAT signaling pathway mediates multiple adaptive T cell functions, but recent studies have shown that calcineurin/NFAT signaling also contributes to innate immunity and regulates the homeostasis of innate cells [136].

Initially, NFATs were discovered in T cells as transcriptional activators of IL-2 [137, 138], a key regulator of T cell immune response. NFAT proteins are regulated by the phosphatase calcineurin that dephosphorylates NFAT proteins to expose their nuclear localization signals, triggering the transport of NFAT proteins from the cytoplasm to the nucleus where it modulates the target genes [139]. NFAT regulates the expression by T cells of several key modulators including IL-3 [140], and TNF α [141]. NFAT1 also regulates the transcription of the polarizing cytokines IFN γ and IL-4, which drive Th1/Th2 cell differentiation [142, 143].

Calcineurin/NFAT signaling in myeloid cells (granulocytes and DCs) has been elucidated more recently. It could be induced by microbial ligation of pattern recognition receptors, such as TLR4, CD14, and dectin 1, thus promoting inflammation, regulating adaptive immunity, and mediating early responses to pathogens [136].

In the transgenic mice carrying a constitutively active NFAT1 mutant (NFATc1^{nuc}), a global inflammatory response with enhanced Th1/Th2 cytokines production and T cell activation is seen although thymocyte development is normal [144].

Additionally, NFATs may participate in TACI-dependent stimulation of COX2 transcription [145, 146]. Finally and similarly to NF κ B, NFAT2 and NFAT1 activate transcription of BAFF that could form a positive feedback loop [147].

As explained further, many evidences raise a role of calcineurin/NFAT signaling in inflammatory diseases pathogenesis and particularly in IBD.

BAFF may also be involved in other inflammatory pathways such as MEKK1/MKK4/JNK cascade triggering by BAFF via BCMA and TACI. This can result in many cellular mechanisms such as inflammation, apoptosis, or immunological response [125, 148].

Clinical Evidence of BAFF-Associated Inflammation

Local and Systemic BAFF Involvement in Inflammatory Diseases

BAFF Tg mice develop features of autoimmune diseases such as SLE [109, 149]. This is likely due to increased survival signals to autoreactive B cells. Moreover, in NZBWF1 and MRL-*lpr/lpr* mice, prone to developing autoimmunity, serum BAFF levels are elevated [150]. Finally, serum levels of BAFF are increased in several immunological diseases such as RA, Sjogren's syndrome, and SLE [151–154].

In addition to finding increased levels of BAFF in the systemic circulation, elevated levels of BAFF in specific tissues are associated with the pathogenesis of inflammatory diseases. For example, in chronic gastritis, BAFF directly promotes the differentiation of pathogenic Th17 cells. Mucosa from *Helicobacter pylori*-positive patients with chronic gastritis is enriched in IL-17 and BAFF, whereas the two cytokines are weakly expressed in *H. pylori*-negative patients with chronic gastritis. In vitro, BAFF is produced by monocyte-derived macrophages after *H. pylori* stimulation. Adding BAFF to monocytes triggers the accumulation of reactive oxygen species, promoting the release of pro-Th17 cytokines, such as IL-23, IL-1 β , and

TGF β . Thus, BAFF drives Th17 responses both indirectly, by creating a pro-Th17 cytokine milieu, and directly, via the differentiation of naïve T cells into Th17 cells [155].

In RA, BAFF levels are increased in synovial fluid due to increased production of local neutrophils and fibroblast-like synoviocyte [68, 156]. BAFF levels are increased in salivary gland of patients with Sjogren's syndrome [157], in cerebrospinal fluid of patients with neuromyelitis optica and multiple sclerosis [158], and in gut lavage fluid of patients with food hypersensitivity [159].

Therapy Targeting BAFF and BAFF-Related Pathways

Given its role in systemic autoimmune disorders, therapies targeting BAFF have become commercially available. Specifically, belimumab, atacicept, blisibimod, and tabalumab target the BAFF pathway and are clinically approved for inflammatory disorders.

Belimumab is a humanized monoclonal antibody inhibiting soluble BAFF. The efficacy and safety of belimumab for SLE was demonstrated in two phase III randomized, controlled studies, BLISS-52 and BLISS-76 [160, 161]. BLISS-76 is a phase III, multicenter, randomized, placebo-controlled trial where 819 antinuclear antibody-positive or anti-double-stranded DNA-positive SLE patients were randomized in a 1:1:1 ratio to receive 1 mg/kg belimumab, 10 mg/kg belimumab, or placebo. Belimumab plus standard therapy significantly improved the SLE responder index (SRI, the primary end point) and reduced SLE disease activity and severe flares. Serious and severe adverse events, including infections, laboratory abnormalities, malignancies, and deaths, were comparable across groups [160]. BLISS-52, another randomized, double-blind placebo-controlled trial of belimumab in patients with active SLE, showed consistent effects on clinical efficacy, serological activity, and glucocorticoid reduction; it showed strong evidence for a dose response to belimumab; and it provided reassurance of safety [161]. Consequent to these two trials, belimumab was approved to treat patients with active, autoantibody-positive SLE who are receiving standard therapy, including corticosteroids, antimalarials, immunosuppressives, and non-steroidal anti-inflammatory drugs, by the FDA in 2011. Additionally, two recent open-label trials of belimumab have shown encouraging results in patients within Sjogren's syndrome [162, 163], and larger, randomized controlled trials are recommended. Finally, in RA, a phase II, randomized, double-blind, placebo-controlled, dose-ranging study involving 520 patients, primary endpoint (American College of Rheumatology criteria ACR20 response at week 24) was met in 1 mg/kg i.v. belimumab (15.9 % placebo vs 34.7 %, $p = 0.01$) but not in 4 (25.4 %, $p = 0.168$) and

10 mg/kg groups (28.2 %, $p = 0.08$). Greater response rates were seen in patients with rheumatoid factors (RF+) and anti-CCP+ [164].

Atacicept, a fully human recombinant fusion protein containing the BAFF-/APRIL-binding extracellular portion of the TACI receptor fused to a modified Fc portion of human IgG1, inhibits both BAFF and APRIL. Blockade of both cytokines affects mature B and plasma cells. Two phase II/III trials have been conducted in SLE. APRIL-LN was a randomized, double-blind, placebo-controlled trial, aimed to evaluate atacicept in combination with corticosteroids and mycophenolate mofetil (MMF) in patients with renal involvement. The trial was stopped prematurely due to the occurrence of IgG deficiency in three on four patients in atacicept group of which two got pneumonia. However, it seemed related to MMF as development of low IgG started before atacicept [165]. In APRIL-SLE trial, 461 patients with moderate-to-severe SLE were randomized to atacicept 75 mg or atacicept 150 mg administered subcutaneously, or placebo twice weekly for 4 weeks and then weekly for 48 weeks. Primary and secondary endpoints were the proportion of patients experiencing at least one flare of British Isles Lupus Assessment Group A or B (BILAG A or B), and time to first flare, respectively. Primary endpoint was not reached with atacicept 75 mg group versus placebo (flare rates 58 vs 54 %). Enrollment in the atacicept 150 mg arm was discontinued prematurely due to two deaths (among 145 enrolled patients). However, a beneficial effect of atacicept 150 mg was strongly suggested (flare rates—OR 0.48, $p = 0.002$ and time to first flare—HR 0.56, $p = 0.009$). Decreased IgG and IgM were frequently reported in all three groups [166]. In RA, phase 2 trials failed to demonstrate efficacy of atacicept. However, atacicept treatment reduced the levels of serum IgG, IgA, and IgM rheumatoid factor and the levels of circulating mature B cells and plasma cells [167, 168].

Tabalumab is a human monoclonal IgG4 antibody neutralizing both soluble and membrane-bound BAFF. Two phase III, 52-week randomized placebo-controlled trials with subcutaneous tabalumab in SLE patients were recently conducted. A total of 2288 SLE patients were randomized (1164 in ILLUMINATE-1 and 1124 in ILLUMINATE-2) to receive SC tabalumab every 2 or 4 weeks or placebo. Patients with severe renal and/or neurologic involvement were not enrolled. Tabalumab showed a good safety profile in both trials. The primary endpoint of SRI-5 was met in trial 2 for a 120 mg every 2-week dose of tabalumab (38.4 vs 27.7 %, $p = 0.002$). Biological activity, as observed, was consistent with the inhibition of the BAFF pathway as demonstrated by changes in anti-dsDNA, B cells, and immunoglobulins. Primary endpoint in ILLUMINATE-1 and key secondary endpoints in ILLUMINATE-2 were not reached. Trials in SLE are

Table 1 Status of the clinical development of BAFF-targeting therapies

Medication	ROA	Condition	Current developmental status
Belimumab			
Human monoclonal antibody inhibiting soluble BAFF	i.v. and s.c.	SLE	2 phase III trials with i.v. belimumab completed (BLISS-76 and BLISS-52) [160, 161] FDA approval of i.v. belimumab in 2011 1 ongoing phase II trial assessing s.c. form (BLISS-SC, NCT01484496)
		SjS	2 phase II trials (i.v. route of administration) completed [162, 163] leading to 1 ongoing phase III trial that assess s.c. belimumab in combination with rituximab (NCT02631538)
		RA	1 phase II trial (i.v.) completed [164]
		Diffuse cutaneous systemic sclerosis	1 phase II trial (data not published to date NCT01670565)
		Idiopathic membranous glomerulonephropathy	1 phase II trial (data not published to date NCT01610492)
		Myositis	1 phase II/III trial (data not published to date NCT02347891) 1 phase III trial (data not published to date NCT01663623)
		Prevention of kidney transplant rejection	1 phase II trial (data not published to date NCT01536379)
		Myasthenia gravis	1 phase II trial (data not published to date NCT01480596)
		Prevention of vasculitis relapse	1 phase III trial (data not published to date NCT01663623)
		Atacicept	
Fully human recombinant fusion protein containing the BAFF-/APRIL-binding extracellular portion of TACI fused to a modified Fc portion of human IgG1 inhibits both BAFF and APRIL	s.c.	SLE	1 phase II/III trial in combination with MMF for lupus nephritis. Withdrawal because of safety concern [165] 1 phase II/III trial completed (data not published. NCT00624338) 1 phase II completed (ADDRESS, NCT01440231). Ongoing phase IIb assessing long-term safety (ADDRESS extension, NCT01972568)
		RA	3 phase II trials completed (1 in combination with rituximab) [167, 168, 189]. Biological effects without reaching clinical endpoints
		Multiple sclerosis and optic neuritis	2 phase II trial (ATAMS study, 255 patients and ATON, 34 patients) in both cases relapse rates were higher in the atacicept groups than in the placebo group [190, 191]. Development was discontinued
Tabalumab			
Human monoclonal IgG4 antibody neutralizing both soluble and membrane-bound BAFF	s.c.	SLE	2 phase III RCT (ILLUMINATE studies, primary endpoint reached in trial 2) [169, 170] Decision not to perform further trials. Discontinuation of tabalumab development
		RA	3 phase III RCT (with or without MTX). No clinical efficacy despite biological changes [172, 176, 192]
		Multiple sclerosis	1 phase II trial (data not published to date NCT00882999)
		End-stage renal disease	1 phase II trial (data not published to date NCT01200290)
		Multiple myeloma	Phase II trial in combination with bortezomib and dexamethasone (data not published to date NCT01602224)

Table 1 continued

Medication	ROA	Condition	Current developmental status
Blisibimod			
Fusion protein of four BAFF-binding domains fused to the N-terminus of the Fc region of a human ab, neutralizing both soluble and membrane-bound BAFF	s.c.	SLE	1 phase IIb trial completed (PEARL-SC) [177] 1 phase III trial ongoing (NCT01395745)
		IgA nephropathy	1 phase II/III ongoing (BRITH-SC, NCT02062684)
		ITP	Withdrawn prior to enrollment (Phase II/III study, NCT0160945)
		Small vessel vasculitis	In combination with MTX, withdrawn prior to enrollment (phase II, BIANCA-SC, NCT01598857)

i.v. intravenous, *ITP* immune thrombocytopenic purpura, *RA* rheumatoid arthritis, *ROA* route of administration, *s.c.* subcutaneous, *SLE* systemic lupus erythematosus, *SjS* Sjogren's syndrome

currently all stopped due to the perception of an insufficient efficacy [169–171]. In RA, despite several encouraging phase II trials [172–175], a large phase III multicenter, double-blind randomized controlled study failed to demonstrate efficacy of SC tabalumab. A total of 1041 patients with moderate-to-severe RA received either tabalumab (120 mg/4 weeks or 90 mg/2 weeks) or placebo. ACR20 response rates, as well as secondary efficacy measures, at week 24 were not different between the 3 groups (120 mg/4 weeks = 34.4 %, 90 mg/2 weeks = 33.5 %, placebo = 31.5 %). Patients in tabalumab groups showed significant decreases in B cells and in serum Ig [176].

Blisibimod is a fusion protein which also has the ability to inhibit soluble and membrane-bound BAFF. The PEARL-SC trial, a dose-ranging randomized, placebo-controlled clinical phase IIb trial, evaluated 547 patients with SLE with anti-double-stranded DNA or antinuclear antibodies and Safety of Estrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index (SELENA-SLEDAI) score ≥ 6 at baseline. Patients were randomized to receive placebo or blisibimod at one of 3 dose levels. The primary end point, measured at week 24, was the SRI-5. Response rates were higher in subjects randomized to the highest dose of blisibimod (200 mg once weekly, $p = 0.02$) compared to placebo. Changes in anti-double-stranded DNA antibodies, complement C3 and C4, and reductions in B cells were noticed with blisibimod. Additionally, tolerance profile was good [177]. A phase III randomized controlled trial is currently ongoing.

Further applications of these BAFF-targeting therapeutics may be developed in other pathological conditions such as vasculitis, multiple sclerosis, and lymphoid malignancies [178, 179] even though no benefit in such diseases has been demonstrated yet.

Current advances in BAFF-targeting therapies are displayed in Table 1.

Why BAFF and IBD?

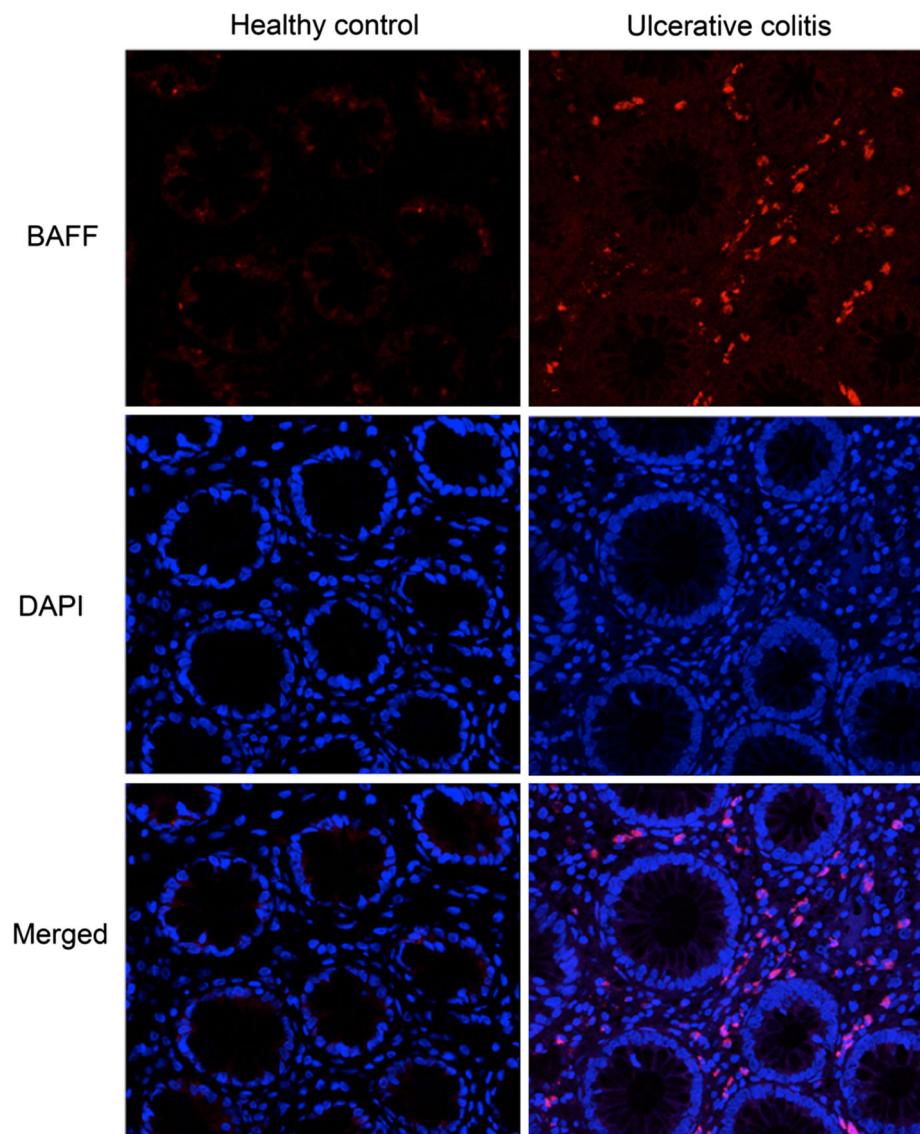
Currently few data are available about the role of BAFF in intestinal inflammation. However, data presented below support a potential role of BAFF in IBD pathogenesis.

Various Intestinal Inflammation Pathways Involved in IBD Could Be Driven by BAFF

In addition to its effects on B cell differentiation and survival, BAFF affects multiple immune pathways as described previously. These include T cell activation, T cell differentiation along the Th1 and Th17 pathways, and the production of pro-inflammatory cytokines such as IL-6 and TNF α by myeloid cells. Additionally, and perhaps even more significantly, BAFF can activate NF κ B via canonical and non-canonical pathways. NF κ B activation is thought to be the major inflammatory pathway in epithelial cells in IBD [2, 3]. Further, activated form of NF κ B is detected in the epithelial cells and macrophages from IBD patients and relates to the intensity of inflammation [180]. Steroids attenuate intestinal inflammation by decreasing NF κ B activation [181], and administration of antisense phosphorothioate oligonucleotides to the p65 subunit of NF κ B suppresses TNBS-induced colitis [131].

Besides NF κ B, NFAT plays an important role in modulating intestinal inflammation. Yet, BAFF activates NFAT1 and NFAT2 through TACI, thus promoting the expression of pro-inflammatory cytokines [135]. As examples, calcineurin/NFAT inhibitors [cyclosporine A (CsA) and FK506 (tacrolimus)] are used in the treatment of IBD [182–184]. Genome-wide association studies have identified leucine-rich repeat kinase 2 (LRRK2), a regulator of NFAT1 as a risk allele in IBD [185]. Moreover, LRRK2-deficient mice have more severe induced colitis [186]. Furthermore, NFAT2 is up-regulated in oxazolone-induced colitis, while its deficiency abrogates colitis due to

Fig. 4 BAFF immunofluorescence staining on colonic biopsies of patients with ulcerative colitis and healthy controls. From Zhang et al. [188]. Springer license agreement 3879570719185



a strikingly reduced production of IL-6, IL-13, and IL-17 by mucosal T lymphocytes [187].

Direct Evidence of BAFF's Involvement in IBD

Recently, Zhang et al. [188] reported on elevated levels of BAFF in the serum, feces, and colonic tissue of IBD patients compared to patients with irritable bowel syndrome (IBS) and healthy volunteers. Interestingly, BAFF levels in all three compartments were higher in IBD patients, and serum BAFF level was correlated with clinical activity, with CRP, and with serum level of various pro-inflammatory cytokines such as TNF α and IL-1 β . Additionally and remarkably, fecal levels of BAFF were higher for patients with inactive IBD compared to IBS patients. This approach allowed correctly discriminating patients according to gastrointestinal disorder type with a

high specificity and sensibility. Furthermore, immunofluorescence staining of colonic biopsies from UC patients showed an increased expression of BAFF by lamina propria immune cells compared to healthy controls (Fig. 4) [188].

Conclusion

The role of B cells in IBD pathogenesis needs to be better defined. BAFF, a key player in B cell biology, may link various B cell-, T cell-, myeloid cell-, and non-hematopoietic cell-related mechanisms involved in IBD. Further, driven by the clinical success of BAFF inhibitors in SLE, there is an increasing interest in the role of BAFF in IBD. We believe that through multiple effects on the mucosal immune system, BAFF could contribute to

intestinal inflammation and that targeting BAFF could be a novel and unexplored strategy in IBD.

Compliance with ethical standards

Conflict of interest None.

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