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REVIEW

The Role of BAFF System Molecules in Host Response to Pathogens

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SUMMARY The two ligands B cell-activating factor of the tumor necrosis factor family (BAFF) and a proliferation-inducing ligand (APRIL) and the three receptors BAFF receptor (BAFF-R), transmembrane activator and calcium-modulating cyclophilin ligand interactor (TACI), and B cell maturation antigen (BCMA) are members of the "BAFF system molecules." BAFF system molecules are primarily involved in B cell homeostasis. The relevance of BAFF system molecules in host responses to microbial assaults has been investigated in clinical studies and in mice deficient for each of these molecules. Many microbial products modulate the expression of these molecules. Data from clinical studies suggest a correlation between increased expression levels of BAFF system molecules and elevated B cell responses. Depending on the pathogen, heightened B cell responses may strengthen the host response or promote susceptibility. Whereas pathogen-mediated increases in the expression levels of the ligands and/or the receptors appear to promote microbial clearance, certain pathogens have evolved to ablate B cell responses by suppressing the expression of TACI and/or BAFF-R on B cells. Other than its well-established role in B cell responses, the TACI-mediated activation of macrophages is also implicated in resistance to intracellular pathogens. An improved understanding of the role that BAFF system molecules play in infection may assist in devising novel strategies for vaccine development.

KEYWORDS APRIL, BAFF, BAFF-R, bacteria, DNA vaccines, parasite, TACI, virus, host response

INTRODUCTION

The so-called "BAFF system molecules," which consist of two ligands and three receptors, are critical for B cell homeostasis (Fig. 1). The ligand B cell-activating factor belonging to the tumor necrosis factor (TNF) family (BAFF) (1), also called B lymphocyte activator (BlyS) (2), TNF- and apoptosis ligand-related leukocyte-expressed ligand 1 (TALL-1) (3), or TNF homologue that activates apoptosis, nuclear factor kappa light-chain enhancer of activated B cells (NF-κB), and c-Jun N-terminal kinase (JNK) (THANK) (4), maintains the survival of mature naive B cells (5, 6) by increasing the levels of the prosurvival molecules B cell lymphoma 2 (Bcl-2) and Bcl-x and by decreasing the levels of the proapoptotic molecule Bcl-2-homologous antagonist/killer (Bak) (7). BAFF is synthesized as a membrane-bound form, which can be further processed to a soluble form by furin convertase cleavage (1), a posttranslational modification process shared by all members of the BAFF system molecules (Fig. 1A). Soluble BAFF can form homotrimers (3-mers) or multimers as large as 60-mers (8). The ablation of BAFF activity by genetic deletion or by using blocking anti-BAFF antibodies results in the depletion of transitional type 2 (T2) B cells, while the T1 B cell population is preserved (Fig. 1B). Also, peritoneal B1 cell numbers are not affected by BAFF deficiency, but the numbers of the splenic subsets follicular (FO) B cells, marginal zone (MZ) B cells, and B1 cells are severely reduced (6, 9, 10). In the absence of BAFF, the decrease in B2 cell numbers is accompanied by a mild reduction in serum IgA levels and a severe decrease in IgG levels. In addition to the dramatic reduction in B cell numbers, BAFF is important for the maintenance of T cells because $CD44^+$ $CD62L^-$ effector/memory T cell numbers are decreased in spleens of BAFF-deficient mice (9). While BAFF is required for B cell homeostasis, the excessive production of BAFF is detrimental to the host. Transgenic mice overexpressing BAFF (BAFF Tg mice) suffer from increased production of autoantibodies, proteinuria, salivary gland destruction, immunoglobulin deposits in the kidney, and splenomegaly, all of which are symptoms of autoimmune diseases reminiscent of systemic lupus erythematosus (SLE) and Sjögren's syndrome (11–13). The development of these autoimmune manifestations in BAFF Tg mice is largely attributed to the dysregulated expansion of B cell compartments, especially MZ and T2 MZ cells (11–14). The proportion of effector T cells is also increased in BAFF Tg mice (11, 12, 14), but the contribution of effector T cells to these disorders is likely to be limited because BAFF Tg mice lacking T cells develop SLE-like symptoms comparable to those of BAFF Tg mice with T cells (15). Like BAFF, a proliferation-inducing ligand (APRIL), the other ligand of the BAFF system molecules, also has membrane-bound and secreted forms (8, 16, 17). It can be intracellularly processed in the Golgi apparatus or on the cell membrane by furin convertase (8, 18) (Fig. 1A). Compared to BAFF, APRIL deficiency or APRIL overexpression (APRIL Tg mice) does not lead to significant abnormalities in the spleen, mesenteric lymph nodes, Peyer's patches, and B cell development (19–21). APRIL deficiency also does not change serum IgG levels but results in lower levels of IgA. In contrast, the only alteration in serum immunoglobulins in APRIL Tg mice is an elevation of IgM levels. The numbers of T cells are not different between APRIL-deficient and wild-type mice except for a slight increase in the percentage of splenic $CD44^{high}$ $CD62L^{low}$ $CD4^+$ T cells. The T cell population in peripheral lymph nodes of APRIL Tg mice is small, whereas T cell viability is high compared to that of littermate controls. Finally, while BAFF and APRIL are equally potent in inducing bone marrow plasma cell survival, the survival of memory B cells is independent of either ligand (22).

The receptor that is responsible for mediating the B cell survival function of BAFF is "BAFF receptor" (BAFF-R) (Fig. 1A and B) (23–25). APRIL engages the two receptors transmembrane activator and calcium-modulating cyclophilin ligand interactor (TACI) and B cell maturation antigen (BCMA), both of which also bind to BAFF (26, 27). In humans, BAFF-R is expressed on most mature B cells beyond pre-B cells, except for plasma cells (28, 29) (Fig. 1B). In contrast, human plasma cells and memory B cells express both TACI and BCMA (29). In mice, BAFF-R expression is more pronounced on FO B cells and germinal center (GC) B cells, while TACI is primarily expressed on MZ B

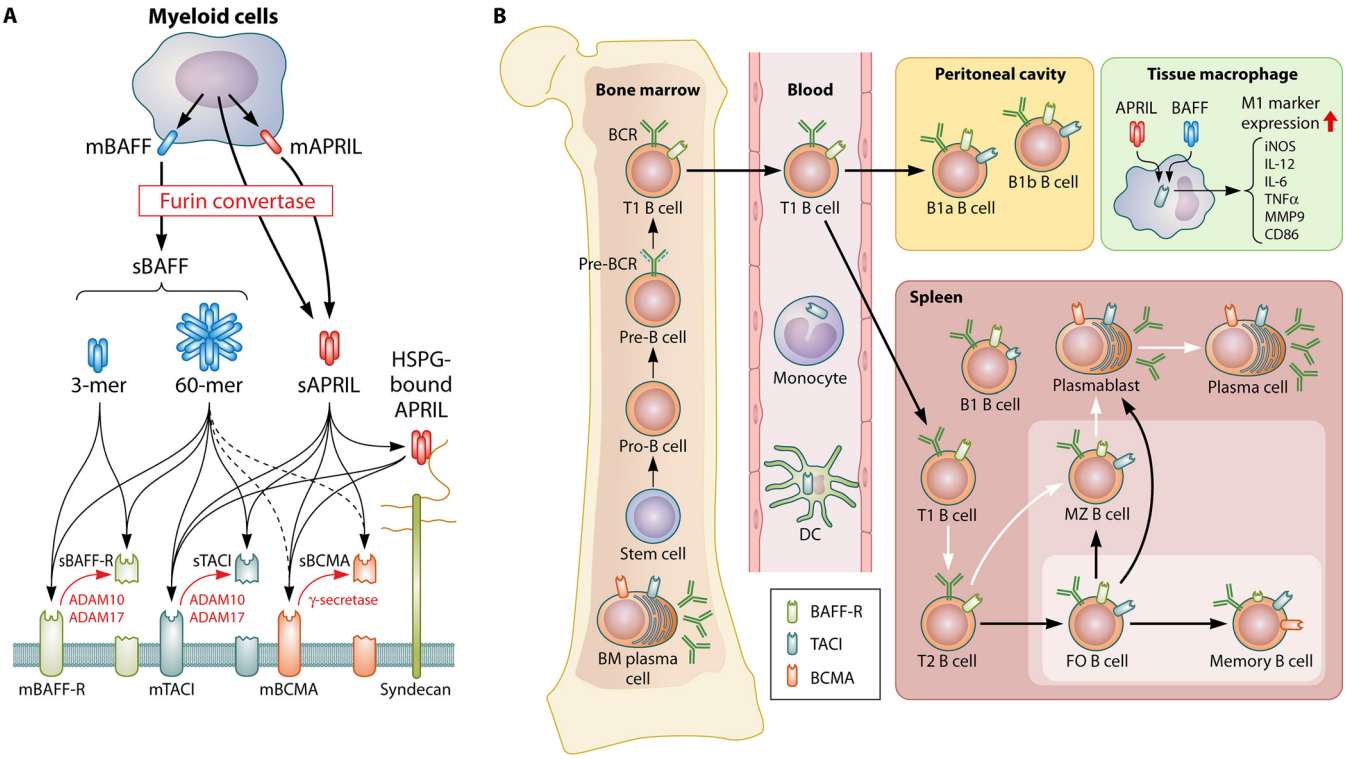

FIG 1 BAFF system molecules. (A) BAFF system molecules are composed of two ligands (BAFF and APRIL) and three receptors (BAFF-R, TACI, and BCMA). BAFF and APRIL are primarily expressed by myeloid cells. BAFF is initially synthesized as a membrane-bound form (mBAFF). BAFF also has a soluble form (sBAFF). The soluble form is produced by the cleavage of mBAFF with furin convertase. sBAFF exists in a homotrimeric (3-mer) or oligomeric (60-mer) form. The cleavage of APRIL by furin convertase occurs in the Golgi apparatus or on the cell membrane. Similar to BAFF, soluble APRIL forms a homotrimer or partners with heparan sulfate proteoglycan (HSPG) to form multimers. Membrane-bound BAFF-R (mBAFF-R) is shed by ADAM10 and ADAM17 following BAFF stimulation. TACI can also be found in a soluble form (sTACI) after the cleavage of mTACI by ADAM10 and ADAM17. The activity of ADAM17 requires the stimulation of B cells by 60-mer BAFF. mBCMA is processed by γ-secretase. The cleaved ectodomains of the three receptors may function as soluble decoy receptors (sBAFF-R, sTACI, and sBCMA) for BAFF and APRIL. (B) BAFF engagement of BAFF-R is essential for the survival and development of B cells beyond the immature T1 B cell stage. TACI is mostly expressed on marginal zone (MZ) B cells, follicular (FO) B cells, and plasma cells. BCMA expression is increased on plasmablasts and plasma cells. BAFF and APRIL also act on macrophages to stimulate the expression of molecules associated with the inflammatory M1 phenotype. BM, bone marrow; BCR, B cell receptor; DC, dendritic cell; iNOS, inducible nitric oxide synthase; TNFα, tumor necrosis factor alpha.

cells, followed by FO B cells, memory B cells, and plasma cells (22, 30). BCMA is found on murine splenic and bone marrow plasma cells (22, 31, 32). Resembling the phenotype of BAFF-deficient mice, BAFF-R ablation strategies demonstrated that BAFF-R is crucial for the survival of mature naive B cells, but it is not needed for the maintenance of memory B cells and long-lived plasma cells in the bone marrow (10). Of the three BAFF receptors, TACI and BCMA are likely to be responsible for the survival of splenic B1a and B1b cells because BAFF-R deficiency does not influence splenic B1 cell numbers (33). TACI mediates the BAFF- and APRIL-induced generation of plasma cells and T cell-independent (TI) immunoglobulin isotype switching and secretion (22, 30, 34–36), whereas the function of BCMA is restricted to the maintenance of plasma cells and antigen presentation by B cells (31, 37–39) (Fig. 1B). Finally, APRIL has been shown to bind heparin sulfate proteoglycans (HSPGs) (8, 40, 41). It is not clear whether APRIL-bound HSPG transduces signals, but the binding of APRIL to HSPG has been suggested to potentiate TACI and BCMA activation through its multimerization, akin to the 60-mer form of BAFF (42).

Membrane-bound receptors of BAFF system molecules are also shed as soluble decoy receptors. TACI and BCMA are constitutively processed by a disintegrin and metalloproteinase 10 (ADAM10) (43) and γ-secretase (44), respectively (Fig. 1A). Soluble TACI antagonizes both BAFF and APRIL, whereas soluble BCMA binds only to APRIL. The processing of BAFF-R is more elaborately regulated than TACI and BCMA processing (Fig. 1A). Smulski et al. recently reported that unlike TACI and BCMA, BAFF-R is not

constitutively shed, and processing requires BAFF stimulation and TACI coexpression (45). Stimulation with a homotrimeric BAFF 3-mer, which triggers BAFF-R but not TACI (46), activates ADAM10 to cleave and release BAFF-R from the membrane in the presence of TACI. In response to the oligomeric BAFF 60-mer that can bind to BAFF-R and TACI, ADAM10 and ADAM17 process BAFF-R and TACI. As APRIL does not induce the cleavage of BAFF-R, the activation of these proteases requires BAFF-R signaling with TACI coexpression. Although not formally shown, cleaved BAFF-R may also function as a decoy receptor, as part of a negative-feedback mechanism, to inhibit B cell responses to BAFF.

The expression of TACI, and, to some degree, BAFF-R, on B cells is regulated by various physiological and microbial signals (30, 47–50). Signals mediated by B cell receptor engagement along with Toll-like receptor (TLR) activation or CD40 ligation induce TACI expression on B cells, render B cells more sensitive to BAFF and APRIL, and promote plasma cell generation and immunoglobulin secretion (30, 36, 47–50). Moreover, the expression of TACI on B cells has been shown to be age dependent. Both human and mouse neonatal B cells express severely reduced levels of TACI (51–53), which appears to be due to weak B cell receptor signaling during the newborn period (50, 52). In human B cells, interleukin-2 (IL-2) and IL-10 can augment B cell receptor- and CD40-mediated TACI expression, although these cytokines do not alter TACI expression by themselves (29). The detection of diminished receptor levels in antibody binding assays such as flow cytometry assays should be cautiously interpreted and requires verification with gene expression analysis and microscopy studies because the occupancy of receptors by bound ligands can also result in a low level of receptor detection (54, 55).

In addition to its well-defined involvement in B cell homeostasis, we recently discovered a role for TACI in promoting the inflammatory (M1) macrophage phenotype. Despite its intracellular location in macrophages, TACI mediates BAFF- and APRIL-induced signals to suppress the expression of molecules (FIZZ1, Arg1, IL-10, IL-1RN, CCL22, CD206, and IL-4Rα) associated with the alternatively activated (M2) macrophage phenotype and induces the expression of M1 markers (MMP9, CD80, and IL-6) (56). A similar observation was made by Chang and colleagues, who reported BAFF-induced inflammatory cytokine secretion from human monocytes and dendritic cells (DCs) through intracellular TACI (57, 58).

The recognition of a central role for BAFF and APRIL in B cell homeostasis catalyzed research in diseases where exaggerated B cell responses are pivotal for pathogenesis. Autoimmune diseases such as SLE, rheumatoid arthritis, and Sjögren's syndrome and hematological malignancies such as multiple myeloma, lymphoma, and lymphocytic leukemia are areas that have benefitted most from research on BAFF system molecules. These studies led to approaches to ablate BAFF/APRIL activity as a treatment strategy, and belimumab, an anti-BAFF antibody, was approved in 2011 by the FDA for the treatment of active SLE. Reviews summarizing the advancements in these areas are available for more information (59–62). In this review, we focus on studies reporting the involvement of BAFF system molecules in response to infections. We divide the review into five sections based on studies covering immunization and infections by viruses, parasites, bacteria, and fungi.

IMMUNIZATION

We begin our review by discussing the immunization studies involving BAFF system molecules because host responses to introduced antigens are directly associated with responses to microbial challenges. Most successful vaccines elicit protection against infectious diseases by activating B cells specific for microbial antigens (63–66). Since the discovery of the BAFF system molecules almost 2 decades ago, primary immunobiological findings related to these molecules have been generated by immunizing mice deficient in each of the five members of the BAFF system molecules. The most dramatic phenotype was observed in BAFF- or BAFF-R-deficient mice immunized with T cell-dependent (TD) and TI antigens (6, 9, 67–70) (Table 1). Both strains of mice exhibited

TABLE 1 Roles for BAFF system molecules in immunization[a]

Molecule	Role(s)	Method(s) of proof	Reference(s)
BAFF	Mediating antibody response to TD and TI antigens	Immunization of BAFF$^{-/-}$ mice with TD and TI antigens	6, 9, 68, 69
	Augmenting antibody responses against vaccines as an adjuvant	Immunization of exptl animals with BAFF-containing vaccines	7, 90–94
APRIL	Inducing IgA isotype switch and production in response to TD and TI-I antigens	Systemic and mucosal immunization of normal, APRIL$^{-/-}$, and APRIL-transgenic mice with TD and TI antigens	19, 71, 72
	Augmenting antibody responses against vaccines as an adjuvant	Immunization of exptl animals with APRIL-containing vaccines	91, 92
		Immunization of APRIL Tg mice with TD and TI-II antigens	20
BAFF-R	Mediating antibody response to TD and TI antigens	Immunization of BAFF-R$^{-/-}$ mice with TD and TI antigens	6, 9, 68, 69
TACI	Mediating antibody response to TI-II antigens	Immunization of TACI$^{-/-}$ mice with TI-II antigens or CVID patients with polysaccharide vaccines	
	TACI expression levels determine antibody responses to TI-II antigens	Responses of newborn mice and XID mice to TI-II antigens	35, 50, 52, 73–75, 79, 80
	Mediating TD antigen-specific plasma cell survival	Immunization of TACI$^{-/-}$ mice with TD antigens	85, 89
	Controlling expansion of Tfh and GC cells	Immunization of HIV-infected patients with influenza vaccine	
BCMA	Contributing to long-term survival of antigen-specific bone marrow plasma cells	Immunization of BCMA$^{-/-}$ mice with a TD antigen	31

[a]TD, T cell dependent; TI, T cell independent; TI-II, TI type II; APRIL Tg, APRIL transgenic; CVID, combined variable immunodeficiency; XID, X-linked immunodeficient; Tfh, T follicular helper; GC, germinal center; HIV, human immunodeficiency virus.

severely impaired antibody responses to TD and TI antigens. The inability of these strains to respond to antigens was attributed to the low number of mature B cells since BAFF-induced BAFF-R activation is essential for the survival and activation of B cell subsets beyond the immature stage (6, 9, 68, 69). A diminished response to TD antigens may also implicate suboptimal T cell responses because BAFF-deficient mice manifest decreased numbers of CD44^{+} CD62L^{-} effector/memory T cells (9).

By analyzing immune responses in immunized APRIL-deficient mice, Varfolomeev et al. suggested that APRIL is redundant with BAFF in T cell activation and humoral responses to TI type II (TI-II) and TD antigens (21). Others, however, reported that APRIL-deficient mice have lower levels of serum IgA than do wild-type mice, and mucosal but not systemic immunization of APRIL-deficient mice with a TD antigen results in diminished antigen-specific IgA antibodies in serum (19) (Table 1). Mucosally immunized APRIL-deficient mice also manifest a selective deficiency in IgA-positive (IgA^{+}) plasma cells in the lamina propria of the small intestine. In contrast to the preserved immune response to TD antigens, defective serum IgA antibody responses are detected in APRIL-deficient mice immunized with TI type I (TI-I) and TI-II antigens (19, 71). Further highlighting the role of APRIL in driving IgA responses to TI antigens, immunization of APRIL-transgenic mice results in significantly elevated IgA antibody production compared to that in wild-type mice (71). Although the level of IgA produced in normal mice intranasally immunized with pneumococcal surface protein A correlates with the levels of BAFF and APRIL expressed by mucosal DCs (72), *in vitro* assessments demonstrated that APRIL induces IgA class switching in naive B cells more efficiently than does BAFF (19, 71). Thus, there seems to be an overall redundancy between BAFF and APRIL in regulating humoral responses, but APRIL is more potent than BAFF in inducing IgA isotype switch signals.

Despite its critical role in the long-term survival of antigen-specific bone marrow plasma cells, immunization of BCMA-deficient mice indicated that BCMA is dispensable for antibody development against TD antigens (31) (Table 1).

The most prominent phenotype associated with TACI deficiency has been observed in TACI-deficient mice immunized with TI-II antigens (73–75) (Table 1). Data from these studies indicated that TACI is needed for the generation of antibody responses against TI-II antigens (35) (Fig. 2A). Also, its expression levels have been shown to be a

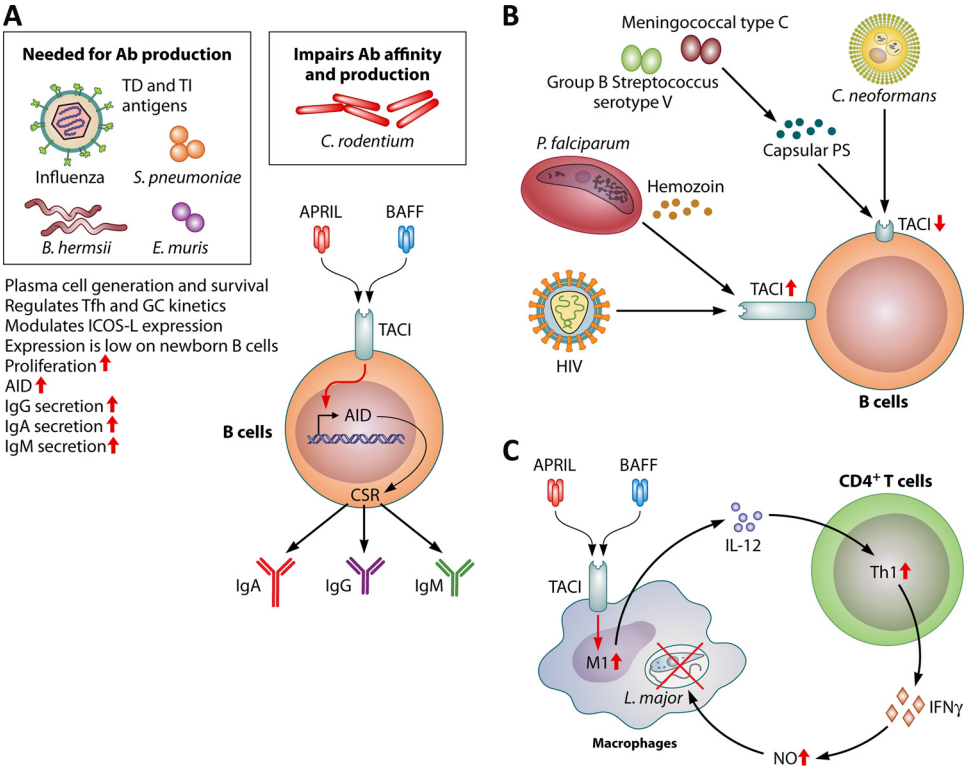

FIG 2 Role of TACI during infection. (A) TACI is mostly expressed on mature B cells and plasma cells. Its elevated expression levels on MZ B cells and B1 cells lead to augmented antibody (Ab) responses against TI-II antigens. Together with the multivalent cross-linking of B cell receptor by polysaccharides, the engagement of TACI by BAFF or APRIL increases activation-induced cytidine deaminase (AID) transcript levels, leading to a polysaccharide-specific antibody isotype switch to IgA and IgG. TACI activation also induces the generation of plasma cells. The requirement for TACI expression to maintain plasma cells also extends to responses against T cell-dependent (TD) antigens. TACI has been shown to regulate the magnitude and kinetics of T follicular helper (Tfh) cell development and germinal center (GC) formation. The consequence of TACI deficiency is mostly detrimental to the survival of plasma cells after immunizations or infections. *Citrobacter rodentium* infection of TACI-deficient mice, however, leads to an enhanced clearance of the bacteria and higher levels of antibacterial antibodies with increased affinity. (B) TACI expression can be modulated by pathogens. Whereas *C. neoformans* and capsular polysaccharides (PS) from a meningococcal type C strain and a group B streptococcus serotype V strain blunt B cell responses to BAFF and APRIL by strongly suppressing TACI expression, B cells from HIV- or *P. falciparum*-infected patients manifest elevated levels of TACI. (C) Expression of TACI in macrophages has been shown to be required for M1 polarization. IL-12 secreted from M1 macrophages induces Th1 responses and IFN-γ production. IFN-γ promotes macrophage inflammatory responses, including nitric oxide (NO) generation, to control intracellular *L. major* infection. TI, T cell independent; ICOS-L, inducible costimulator ligand; CSR, class switch recombination.

determining factor in the magnitude of antibody responses. The upregulation of TACI expression by TLR agonists results in augmented antibody responses against TI-II antigens through enhanced B cell sensitivity to BAFF and APRIL (30, 36, 49), whereas low levels of TACI expression in newborns or downregulated TACI expression by bacterial polysaccharides leads to unresponsiveness to TI-II antigens (52, 76) (Table 1 and Fig. 2B). In addition, our laboratory recently reported that the well-known unresponsiveness of X-linked immunodeficient mice to TI-II antigens (77) is a result of low TACI expression levels on B cells (50) (Table 1). Other evidences for the importance of TACI in the response to TI-II antigens emerge from combined variable immunodeficiency (CVID) patients immunized with polysaccharide vaccines. A subset of CVID patients has been shown to express various levels of TACI on B cells due to a heterozygous mutation in *TNFRSF13B*, the gene encoding TACI (78). By analyzing the responses of CVID patients to pneumococcal polysaccharide vaccines (TI-II antigens), Chinen et al. discovered that patients with the lowest density of B cell TACI expression also have the lowest levels of serum antibodies compared to normal individuals (79) (Table 1). Further supporting the involvement of TACI in host responses to TI-II

antigens, elevated levels of TACI expression on antigen-specific plasma cells in individuals immunized with pneumococcal polysaccharide vaccines have been observed (80). Marginal zone B cells are the B cell subset that is primarily responsible for the development of antibody responses to TI-II antigens (81). In secondary lymph organs, these TACI^{high} MZ B cells recognize soluble antigens and become activated by BAFF and APRIL, which are produced primarily by neutrophils (82, 83) and innate lymphoid cells (84).

Whereas the role for TACI in the response to TI-II antigens is well described, its contribution to the development of antibody responses against TD antigens has only recently been appreciated. Early studies suggested that TACI is dispensable for TD antibody responses (73, 75). However, by immunizing TACI-deficient mice with the TD antigen nitrophenyl-chicken gamma globulin (NP-CGG), Ou et al. recently reported that TACI is required for the survival of plasma cells specific for TD antigens (85). This study also showed that TACI controls the expansion of T follicular helper (Tfh) cells and GC cells by regulating inducible costimulator (ICOS) ligand (ICOSL) (also known as B7H2) expression on B cells, as the interaction of ICOSL with ICOS on Tfh cells stimulates Tfh cell generation (86) (Table 1 and Fig. 2A). Conceivably, TACI may support the fitness of plasma cells by regulating the kinetics of Tfh cell development and GC reactions. Interestingly, while the global deletion of TACI appears to enhance Tfh cell development and GC reactions, with detrimental consequences for plasma cell survival (86, 87), under physiological conditions, the CD40- and IL-21-mediated downregulation of TACI on GC B cells appears to be required for the generation of high-affinity antibody-secreting cells in NP-CGG-immunized mice (88). An increase in TACI expression on plasma cells alone can be relevant for efficient antibody development because B cells of human immunodeficiency virus (HIV)-infected patients who are able to respond to an influenza virus vaccine have been shown to express elevated levels of TACI (89). These patients also present with elevated serum BAFF, APRIL, and IL-2 levels. In contrast, TACI levels remain unaltered compared to prevaccination levels in nonresponder patients (Table 1).

The recognition of a central role for BAFF and APRIL in orchestrating B cell survival and activation led to strategies to incorporate BAFF and APRIL as adjuvants into vaccines. For example, in a mouse study, the coadministration of BAFF with the TI vaccine Pneumovax23 resulted in significantly higher IgM and IgA antibody responses without any enhancement of IgG antibody levels, while BAFF boosted both IgM and IgG responses against TD antigens (7). In parallel, a series of DNA vaccines containing HIV envelope proteins together with BAFF and/or APRIL trimers or in combination with other molecules such as CD40L and IL-12 has been tested in mice and rabbits (90–92). These studies showed that either BAFF- or ARPIL-containing DNA vaccines can augment antibody responses with neutralizing capabilities, but vaccines containing APRIL are consistently superior to those containing BAFF (92). Similarly, the systemic coadministration of BAFF with heat-killed *Pseudomonas aeruginosa* or the veterinary vaccine formalin-inactivated infectious bursal disease virus significantly improves antibody responses (93, 94). How BAFF and APRIL achieve strong antibody responses in these vaccines has not been investigated. One possibility is the targeting of the fused vaccine to B cells since BAFF and APRIL activate B cells by engaging their receptors. Additional targeting of vaccines to other antigen-presenting cells may also contribute to the improved host response since BAFF and APRIL activate macrophages and DCs through TACI (56–58). Further research is needed to elucidate the mechanisms of adjuvant activity afforded by systemically administered BAFF and APRIL with vaccines as well as to assess potentially undesired side effects, since elevated BAFF levels are associated with autoimmune diseases (8).

VIRUSES

HIV

Soon after the discovery of BAFF system molecules, several studies reported the involvement of these molecules in HIV infection and AIDS. These studies suggest an

TABLE 2 Role of BAFF system molecules in viral infection[a]

Molecule	Infection(s)	Phenotype(s)	Reference(s)
BAFF	HIV	Level is increased in serum	95, 97, 98, 101–103
		Viral products trigger BAFF expression	104–106
	HCV	Level is increased in serum; higher BAFF expression level is correlated with poor prognosis	113, 118
	HBV	Level is increased in serum	120, 121
	Influenza virus	Systemic level is increased	128
	RSV	Expression is increased in epithelium and upper airway	133
	Cytomegalovirus and coronavirus	Production by astrocytes and glial cells is increased	134–136
		Production by tonsil B cells is increased	137
	Human metapneumovirus, bocavirus, and rhinovirus	Level is increased in upper airway secretions	133
APRIL	HIV	Level is increased in serum	97
	Influenza virus	Expression is increased in lung	129
	RSV	Expression is increased in epithelia of infected infants	131
	Cytomegalovirus and coronavirus	Production by astrocytes and glial cells is increased	134–136
	RABV	Production by splenic B cells is increased	138
BAFF-R	HIV	Expression is decreased on B cells	110
	VSV and LCMV	Higher susceptibility in BAFF-R$^{-/-}$ mice due to loss of CD169^{+} macrophages	124, 126, 127
	HCMV	Expression is increased on tonsil B cells	137
TACI	HIV	Expression is increased on B cells	110
	Influenza virus	Short-lived plasma cell and diminished antibody responses in TACI$^{-/-}$ mice	87
BCMA	HIV	Expression is increased on B cells	110

[a]HCV, hepatitis C virus; HBV, hepatitis B virus; RSV, respiratory syncytial virus; RABV, rabies virus; VSV, vesicular stomatitis virus; LCMV, lymphocytic choriomeningitis virus; HCMV, human cytomegalovirus.

association between elevated plasma BAFF and APRIL levels and hypergammaglobulinemia in HIV-infected individuals (95–99) (Table 2). Hypergammaglobulinemia appears to be a result of a dysregulated blood B cell compartment characterized by the BAFF-induced expansion of MZ B cells (97, 100–102). Dendritic cells, monocytes, and macrophages are the sources of increased BAFF and APRIL levels during HIV infection (97, 99, 101, 103) (Fig. 3). BAFF production in innate cells is triggered directly by viral products, including double-stranded RNA (104), negative factor (Nef) (105), and the exterior envelope glycoprotein gp120 (106), and indirectly by type I interferon (IFN) secreted from plasmacytoid DCs in response to viral particles (107, 108). Among the HIV molecules, Nef has been reported to induce BAFF expression in human DCs and murine macrophages, but the induction of BAFF expression by Nef is negated if the macrophages are M1 polarized (105, 109). The role for gp120 in HIV infection is especially interesting because this glycoprotein not only stimulates BAFF and APRIL expression in monocytes but also engages human tonsillar IgD^{+} B cells through interactions with mannose C-type lectin receptors (MCLRs). The exposure of tonsillar IgD^{+} B cells to gp120 leads to B cell proliferation, increases in the levels of activation-induced cytidine deaminase (AID) transcripts, and immunoglobulin isotype switching from IgM to IgG and IgA. BAFF further sensitizes B cells by increasing the expression levels of MCLRs on B cells, which augments gp120-induced B cell activation. The increased sensitivity of B cells to gp120 in HIV infection may also be linked to changes in expression levels of BAFF and APRIL receptors because Moir et al. showed that the expression level of BAFF-R is decreased, while the expression levels of TACI and BCMA are increased, on CD21^{low} B cells in HIV-infected viremic patients (110) (Table 2 and Fig. 2B and 4B). Since the TACI expression level determines the sensitivity of B cells to BAFF and APRIL (30, 52), elevated TACI levels on B cells are a likely cause of augmented hypergammaglobulinemia, the most prominent B cell defect associated with HIV infection. Also, the BAFF-induced preferential expansion of CD21^{hi} B cells over CD21^{low} B cells may be the reason for

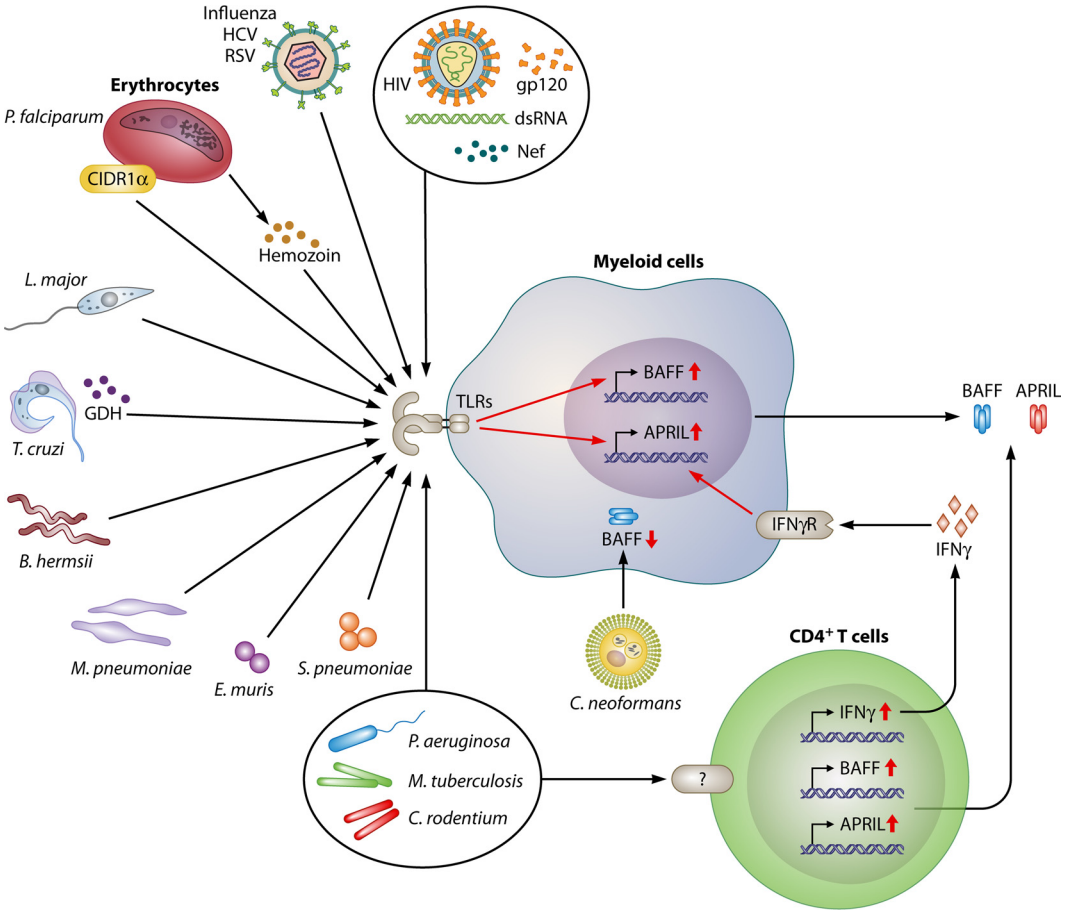

FIG 3 Roles of BAFF and APRIL during infection. Many pathogens induce the expression of BAFF and APRIL in myeloid cells or epithelial cells through the engagement of pattern recognition receptors by pathogen-associated molecular patterns. In addition, pathogen-induced type I and II IFNs can elicit BAFF and APRIL expression. The main consequence of elevated BAFF and APRIL expression levels is the activation of B cells and the induction of pathogen-specific antibody production. Unlike most pathogens, *C. neoformans* has been shown to suppress the expression of BAFF in human PBMCs. Diminished BAFF expression in *C. neoformans* infection is likely a virulence mechanism developed by the fungus because *C. neoformans*-infected patients have low levels of circulating immunoglobulins. TLRs, Toll-like receptors; GDH, glutamate dehydrogenase; CIDR1α, cysteine-rich interdomain region 1α; HCV, hepatitis C virus; RSV, respiratory syncytial virus; Nef, negative factor; IFNγR, interferon gamma receptor; dsRNA, double-stranded RNA.

the persistent activation of MZ B cells in HIV-infected individuals, since CD21 is one of the markers defining MZ B cells as CD21^{hi} (101).

Hepatitis Viruses

Similar to HIV infection, hepatitis C virus (HCV) infection manifests as pathogenic B cell lymphoproliferation and elevated serum autoantibody levels (111, 112). The discovery of increased circulating BAFF levels in HCV-infected patients (113) provided a possible explanation for the Sjögren's syndrome-like autoimmune phenomenon in HCV infection, especially because elevated BAFF-mediated B cell activation is implicated in autoantibody production in autoimmune diseases such as systemic lupus erythematosus (8) (Table 2 and Fig. 3). The expansion of BAFF-sensitive and apoptosis-resistant CD5$^+$ B cells is likely responsible for the appearance of autoantibodies in these patients (113, 114). Further supporting this hypothesis, patients undergoing IFN-α therapy who typically experience an increase in autoimmune manifestations (115, 116) also have increased circulating BAFF levels (117). Paradoxically, BAFF-induced B cell activation appears to be detrimental for the host because Tarantino et al. reported a correlation between higher BAFF levels during the acute phase of HCV infection and the subsequent persistence of HCV infection (118) (Table 2 and Fig. 4B). The underlying reasons

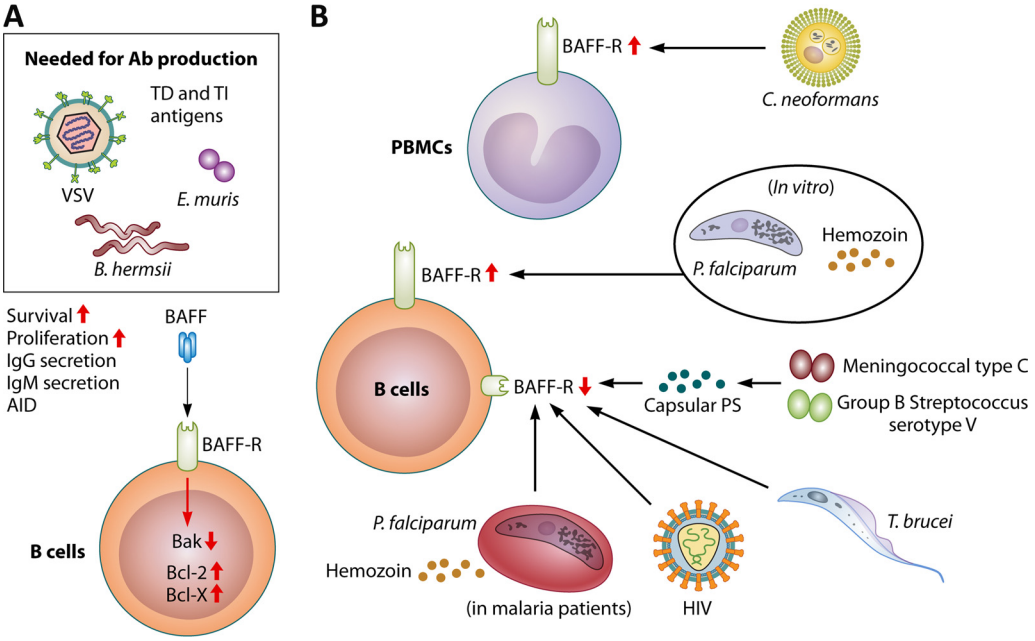

FIG 4 Role of BAFF-R during infection. BAFF-R is detected on B cells as early as the immature B cell stage (Fig. 1), and its expression is diminished with the generation of plasma cells. (A) Engagement of BAFF by BAFF-R simultaneously with B cell receptor stimulation promotes the survival and proliferation of pathogen-specific B cells by decreasing the level of the proapoptotic molecule B cell lymphoma 2 (Bcl-2)-homologous antagonist/killer (Bak) and increasing the levels of the prosurvival molecules Bcl-2 and Bcl-x, leading to the enhanced secretion of isotype-switched and unswitched antibodies. (B) Although the mechanism is not elucidated, bacterial polysaccharides from group C meningococcus and group B streptococcus type V have been shown to downregulate the expression of BAFF-R on B cells. BAFF-R levels on B cells are reduced in HIV-infected patients. A decrease in the BAFF-R level is also observed during the acute phase of *P. falciparum* infection in children as well as experimentally infected adults. The *in vivo* factors responsible for diminished BAFF-R expression in *P. falciparum*-infected patients are unknown. Paradoxically, *in vitro* stimulation of human B cells with the *P. falciparum* schizont fraction or hemozoin results in increased BAFF-R expression. BAFF-R expression is also downregulated on MZ B cells in *T. brucei*-infected mice, leading to a decrease in the number of antiparasite IgM^+ B cells. Unlike malaria and African trypanosomiasis, *C. neoformans* infection upregulates BAFF-R expression in PBMCs.

for this unusual outcome have not been investigated. However, a possibility is the promotion of TI B cell responses to HCV antigens by BAFF, a process known to elicit low-affinity antibody production (119). These antibodies may be poor in viral neutralization, or they may target antigens that are not important for virus neutralization.

Serum BAFF levels are also increased in chronic hepatitis B virus (HBV) infection. Similar to HCV, elevated BAFF levels appear to correlate with disease severity in HBV infection since asymptomatic HBV carriers have the lowest and hepatocellular carcinoma patients have the highest levels of serum BAFF (120). The increased expression of BAFF in HBV patients with more severe disease is likely associated with higher viral loads because HBV e (HBe) antigen induces BAFF production in monocytes, and patients positive for HBe antigen have been shown to have higher serum BAFF levels than HBe-negative HBV patients (121). Although the increase in HBV-induced BAFF levels appears not to aid in host resistance, perhaps paradoxically, higher BAFF expression levels in liver are associated with better IFN-α treatment outcomes in chronic hepatitis B patients (122). Interestingly, a recent study reported an association between polymorphisms in the BAFF gene (*TNFSF13B*) and susceptibility to HBV infection, but these polymorphisms did not lead to increased levels of circulating BAFF (123). Further research is needed to assess the functional consequences of *TNFSF13B* polymorphisms.

Zoonotic Viruses

The two zoonotic viruses vesicular stomatitis virus (VSV) and lymphocytic choriomeningitis virus (LCMV) are frequently used as models to study host responses to viral infections. By using BAFF-R-deficient mice, Xu et al. recently reported that BAFF-R is critical for host resistance to VSV and LCMV infections (124) (Table 2 and Fig. 4A).

Interestingly, the susceptibility of BAFF-R-deficient mice to viral infection appears to be an indirect consequence of mature B cell loss. Lymphotoxin expressed by B cells is known to be required for the maintenance of $CD169^+$ macrophages located in the subcapsular sinus and in the medulla of lymph nodes (125). In the absence of mature B cells, and, thus, lymphotoxin, BAFF-R-deficient mice cannot maintain $CD169^+$ macrophages, which are essential for controlling neurotropic viral infections by secreting type I IFN (125). As $CD169^+$ macrophages also activate B cells located in the underlying follicles, host susceptibility is amplified with the loss of BAFF-R (126, 127). Thus, a consequence of an arrest in mature B cell survival in BAFF-R-deficient mice is the loss of a link between innate and adaptive immune systems during VSV and LCMV infections (124).

Respiratory Viruses

The expression and function of BAFF system molecules in mice infected by viruses with tropism for the respiratory tract have also been reported. For example, BAFF (128) and APRIL (129) expression levels are increased in influenza virus-challenged mouse lungs (Table 2), yet the significance of elevated BAFF and APRIL expression levels in controlling influenza virus infection is not clear, especially because neither APRIL overexpression nor APRIL deficiency impacts host resistance to influenza virus challenge in mice (129). However, BAFF and APRIL may be important in determining the quality of plasma cells generated during a TD response in influenza virus infection. Supporting this hypothesis, Wolf et al. discovered that infection of TACI-deficient mice with influenza virus results in short-lived plasma cells, which appears to be responsible for the increased susceptibility to rechallenge infection with influenza virus (87) (Table 2 and Fig. 2A). The compromised fitness of plasma cells in TACI-deficient mice is possibly due to a suboptimal TD response, as shown by Ou et al., who also detected a reduction in the number of plasma cells in NP-CGG-immunized TACI-deficient mice despite expanded Tfh and GC responses (85).

Respiratory syncytial virus (RSV) is the most common cause of bronchiolitis and pneumonia in infants (130). Both BAFF and APRIL have been implicated in RSV infection because epithelial cells isolated from infants with fatal RSV infection express BAFF and APRIL, which are colocalized with cells expressing type I IFN (131) (Table 2). Furthermore, a positive correlation between BAFF and APRIL levels in nasopharyngeal secretions of RSV-infected infants and levels of antiviral IgA and IgM antibodies in these infants has been established. RSV-induced type I IFN is likely responsible for elevated BAFF and APRIL levels because RSV induces the potent BAFF- and APRIL-stimulating cytokine IFN-β through TLR3 (132). Also, the type I IFN-mediated induction of BAFF from RSV-infected epithelial cells was confirmed by McNamara et al. using cultured airway epithelial cells (133). Those authors also measured elevated BAFF levels in the bronchoalveolar lavage fluid of infants with severe RSV infection as well as in upper airway secretions from children with human metapneumovirus, influenza virus (H1N1), bocavirus, rhinovirus, RSV, and *Mycoplasma pneumoniae* infections (Table 2). Interestingly, despite measuring increased BAFF levels in infected airways, McNamara et al. did not detect elevated APRIL levels following RSV infection (133). This is in contrast to the findings of Reed et al., who emphasized a role for APRIL in better outcomes of RSV infection (131). Further studies are needed to clarify the role of APRIL in the host response to RSV infection.

Viral Infections of the Central Nervous System

Viruses with tropism for the central nervous system induce BAFF and APRIL expression in astrocytes and glial cells (134–136). Interestingly, cytomegalovirus augments BAFF expression by astrocytes through IFN-γ, while APRIL expression is a direct result of virus recognition by astrocytes (136). Cytomegalovirus- and coronavirus-induced BAFF and APRIL are implicated in host resistance because they help maintain virus-specific plasma cells through TACI and BCMA in the central nervous system (136). Furthermore, cytomegalovirus also increases human tonsillar B cell survival by stimu-

TABLE 3 Role of BAFF system molecules in bacterial infection[a]

Molecule	Infection(s)	Phenotype(s)	Reference(s)
BAFF	*M. pneumoniae*	Level is elevated in upper airway secretions	133
	P. aeruginosa	Level is increased in bronchoalveolar lavage fluids and lung homogenates	145
		Coadministration of BAFF with heat-killed *P. aeruginosa* increases Th1 response	93
	M. tuberculosis	Increased serum levels in *M. tuberculosis*-infected patients correlate with disease severity; BAFF is also found in peripheral $CD4^+$ T cells and in pleural effusions of *M. tuberculosis*-infected patients with pleurisy	139
	A. pleuropneumoniae	Adhesin Apa2H1 induces BAFF and APRIL expression on DCs	144
	E. muris	Systemic ablation of BAFF with a neutralizing antibody increases susceptibility of mice	150
APRIL	*M. tuberculosis*	Increased serum levels in *M. tuberculosis*-infected patients correlate with disease severity; APRIL is also found in peripheral $CD4^+$ T cells	139
BAFF-R	*B. hermsii*	BAFF-$R^{-/-}$ mice manifest increased susceptibility	154–156
TACI	*C. rodentium*	Infected $TACI^{-/-}$ mice show enhanced GC reaction and bacterial clearance	149
	S. pneumoniae	$TACI^{-/-}$ mice immunized with heat-killed *S. pneumoniae* do not develop anticapsular antibodies	157
	Meningococcal type C, group B *Streptococcus* serotype V	The capsular polysaccharides downregulate TACI expression on B cells, causing B cell unresponsiveness to BAFF and APRIL	76

[a]Th1, type 1 T helper; DCs, dendritic cells.

lating the expression of BAFF and BAFF-R on these cells (137). In contrast to cytomegalovirus, the involvement of the APRIL-TACI axis in host resistance appears to be questionable because while rabies virus induces APRIL expression in murine B cells, immunization with a recombinant rabies vaccine expressing APRIL does not improve antibody responses, and virus-specific plasma cell generation is not diminished in immunized TACI-deficient mice (138).

BACTERIA

Bacterial Infections of the Respiratory System

Elevated BAFF and APRIL levels have been reported to accompany bacterial infections of the respiratory system. In *Mycobacterium tuberculosis*-infected patients, increased levels of serum BAFF and APRIL appear to correlate with disease severity (Table 3 and Fig. 3). Liu et al. focused on the expression of BAFF and APRIL in $CD4^+$ T cells in *M. tuberculosis*-infected patients and found elevated expression levels of both cytokines in $CD4^+$ cells of patients with active *M. tuberculosis* infection (139). Moreover, there was a correlation between increased BAFF and APRIL mRNA expression levels and elevated IFN-γ levels. Those authors also reported increased BAFF expression levels in pleural effusions of *M. tuberculosis*-infected patients with pleurisy. In another study, APRIL expression was shown to be increased in B cells of *M. tuberculosis*-infected patients after 6 months of anti-*M. tuberculosis* treatment (140). Finally, a recent study confirmed the BAFF- and APRIL-inducing effect of *M. tuberculosis* by measuring serum BAFF and APRIL levels in patients with latent *M. tuberculosis* infection (141). Although the levels of both cytokines were increased in these patients, a significant correlation was present only between BAFF and IgG levels. The importance of elevated BAFF and APRIL levels in *M. tuberculosis* pathogenesis has not been investigated. Increased BAFF and APRIL levels may promote antibody development in *M. tuberculosis*-infected hosts, but the significance of anti-*M. tuberculosis* antibodies remains controversial (142, 143). Another target for BAFF and APRIL is macrophages (56). Further research is needed to unveil whether BAFF- and APRIL-induced M1 polarization of macrophages impacts disease outcomes of *M. tuberculosis* infection.

Actinobacillus pleuropneumoniae is the causative pathogen of porcine pleuropneumonia. An enhancement of pathogen-specific antibody development by elevated BAFF and APRIL levels was demonstrated for *A. pleuropneumoniae* infection (144). The protective antigen Apa2h1 appears to contribute to BAFF and APRIL production in *A. pleuropneumoniae* infection because incubation of mouse DCs with Apa2h1 upregu-

lates the expressions of BAFF and APRIL. Thus, the increase in BAFF and APRIL levels may be instrumental in controlling *A. pleuropneumoniae* infection by boosting the humoral immune response.

Pseudomonas aeruginosa is a respiratory pathogen frequently isolated from the lungs of cystic fibrosis patients. Bronchoalveolar lavage fluids of children with cystic fibrosis contain high levels of BAFF, and increased BAFF expression levels have been measured in lung homogenates of mice infected intranasally with *P. aeruginosa* (145) (Table 3 and Fig. 3). Although this observational study did not provide insight into its function in *P. aeruginosa* infection, an elevated BAFF level appears to drive B cell responses to *P. aeruginosa*, because when heat-killed *P. aeruginosa* is coadministered with an adenovirus expressing full-length BAFF, mice are better protected against lethal respiratory *P. aeruginosa* challenge and mount higher levels of antibody responses in sera and lungs than animals immunized with heat-killed *P. aeruginosa* alone (93). Supporting a role for BAFF in host responses involving T cells, improved protection and higher antibody levels were accompanied by elevated type 1 T helper (Th1) cell responses (88, 146–148). Nevertheless, the contribution of individual receptors to BAFF-mediated T cell responses is less clear and needs to be investigated.

Bacterial Infections of the Gut

Citrobacter rodentium is a rodent pathogen that is frequently used as a model for severe human enteritis. In contrast to all other pathogens tested in TACI-deficient mice, *C. rodentium* challenge of TACI-deficient mice results in improved resistance to infection (149) (Table 3 and Fig. 2B). *Citrobacter rodentium* infection of TACI-deficient mice is accompanied by an enhanced GC reaction, and accelerated bacterial clearance appears to be due to higher-affinity antibodies elicited against bacterial proteins. The development of higher-affinity antibodies is attributed to enhanced BAFF-R-mediated antiapoptotic signals on GC B cells in the absence of TACI-mediated inhibitory signals. How and why enhanced Tfh and GC reactions in TACI-deficient mice result in improved protection against *C. rodentium* infection with increased levels of high-affinity antibodies while promoting poor plasma cell survival in response to NP-CGG immunization (85) and increased susceptibility to influenza virus challenge, mostly because of impaired plasma cell responses (87), remain unknown and warrant further study.

Tick-Borne Bacterial Pathogens

A role for BAFF in the development of TI responses to the tick-borne intracellular pathogen *Ehrlichia muris* has been shown in a murine infection model (Table 3 and Fig. 3). Jones et al. investigated the contribution of an elevated level of BAFF in a fatal *E. muris* infection model (150), which is known to be controlled by IgM-producing $CD138^{high}$ IgM^{high} plasma cells (151, 152). This study showed that the systemic ablation of BAFF with a neutralizing antibody halts the terminal differentiation of bacterium-specific IgM-secreting plasmablasts and renders mice more susceptible to infection, indicating a direct role for BAFF in host resistance. Interestingly, gene expression analysis with anti-BAFF-injected mice suggested that the regulation of CD138 expression and IgM secretion by BAFF involves a posttranslational mechanism. However, the receptor responsible for BAFF action in *E. muris* infection remains unknown.

Lyme neuroborreliosis is a serious complication of tick-borne *Borrelia burgdorferi* infection. Analysis of cerebrospinal fluids of patients with a variety of inflammatory diseases, including Lyme disease, indicated that samples from patients with Lyme neuroborreliosis contain significantly higher BAFF and APRIL levels than do samples from patients with most other diseases (153). Elevated BAFF and APRIL levels are likely responsible for the increased numbers of B cells and plasmablasts as well as elevated IgA and IgM levels in the cerebrospinal fluids of these patients.

Another tick-borne pathogen, *Borrelia hermsii*, the causative agent of relapsing fever, is also controlled by TI IgM responses (154–156). Challenge of BAFF-R-deficient mice, but not TACI-deficient mice, results in an impairment of *B. hermsii* clearance, highlight-

ing the importance of BAFF-R in splenic B1b cell-mediated resistance to *B. hermsii* infection (Table 3 and Fig. 4A).

Infections by Encapsulated Bacteria

Similar to findings with purified polysaccharides (52, 73), TACI expression is required for the development of antibodies against the capsular polysaccharide after injection with heat-killed *Streptococcus pneumoniae* (157) (Table 3 and Fig. 2A). This diminished antibody response in TACI-deficient mice injected with heat-killed *S. pneumoniae* results in greater susceptibility to subsequent pneumococcal challenge than in the *S. pneumoniae*-immunized BAFF-R-deficient or wild-type mice (157). Encapsulated bacteria appear to also modulate the expression of BAFF system molecules. We reported that polysaccharides of meningococcal type C and group B streptococcus type V downregulate the expression of TACI on B cells (76) (Fig. 2B). Downregulation of TACI has biological consequences because after exposure to these polysaccharides, B cells are not able to respond to the TACI ligands BAFF and APRIL. Thus, the suppression of TACI by bacterial polysaccharides appears to be a virulence mechanism adopted by encapsulated bacteria since TACI is essential for the development of antibodies against polysaccharides to efficiently kill encapsulated bacteria. We also showed that meningococcal type C polysaccharide specifically inhibits lipooligosaccharide-induced innate cell activation by competing for CD14 and lipopolysaccharide (LPS) binding protein, two molecules known to enhance TLR4 activation (158). Since LPS is a potent inducer of BAFF and APRIL (159, 160), the inhibitory effect of meningococcal polysaccharides on LPS is likely another example of their virulent properties.

PARASITES

Leishmaniasis and Chagas' Disease

BAFF and B cell responses are important for resisting diseases caused by protozoan parasites (161). However, increased expression levels of BAFF and APRIL can also lead to dysregulated B cell responses and susceptibility to parasites. In visceral leishmaniasis, polyclonal B cell activation and hypergammaglobulinemia are associated with APRIL and BAFF expression in the spleens of infected dogs and in sera of infected mice, which may be responsible for the inefficient humoral immune response and disease progression seen in leishmaniasis (162, 163). Similarly, in the chronic phase of Chagas' disease, hypergammaglobulinemia caused by excessive polyclonal B cell activation is recognized as the source of circulating autoantibodies (164), and BAFF secreted from myeloid cells seems to be responsible for polyclonal B cell activation (165) (Table 4 and Fig. 3). The significance of BAFF in infected humans is not as clear as animal models suggest, because patients with visceral leishmaniasis also manifest elevated serum BAFF levels, but a correlation with serum IgG levels was not found (166). In the same study, a second group of patients with Chagas' disease did not have elevated serum BAFF or increased IgG levels. This observation is interesting, because mice infected with *Trypanosoma cruzi*, the causative agent of Chagas' disease, exhibit elevated levels of serum BAFF, increased numbers of splenic and lymph node $B220^+$ cells, as well as high levels of IgM and IgG production from splenic cells (165). Montes et al. demonstrated that a major component of *T. cruzi*, glutamate dehydrogenase (GDH), induces BAFF secretion from $CD11b^+$ cells (164). Systemic BAFF ablation experiments verified the role of BAFF as the cause of polyclonal B cell activation, because injection of the soluble BAFF receptor BR3:Fc in *T. cruzi*-infected mice decreases total mature B cell numbers in the spleen, serum IgM antibodies against parasite antigens, as well as IgG antibodies against host nuclear antigens (165). Interestingly, BAFF ablation does not change the systemic parasite burden but results in elevated parasite counts in cardiac tissue. The authors of that study suggested that the reduction in B cell numbers is a plausible cause of localized parasite replication in the heart. An alternative explanation may be related to the polarizing effect of BAFF on macrophages, since both BAFF and APRIL drive M1 polarization of macrophages through TACI signaling (56). Given that M2 polarization of macrophages promotes parasite persistence in the myocardium (167), a shift in the

TABLE 4 Role of BAFF system molecules in parasitic infection[a]

Molecule	Infection	Phenotype(s)	Reference(s)
BAFF	*T. cruzi*	Level in serum is increased through activation of myeloid cells by *T. cruzi* GDH	164, 165
	Visceral leishmaniasis	Level is increased in serum and spleen	162, 163
	P. falciparum	Expression by macrophages and monocytes is upregulated by *P. falciparum* metabolites and antigens	170, 175, 177
		Level in serum is increased in children with acute malarial infection	179
		Level is increased in placental samples of patients with placental malaria	178
		Expression is increased in human blood myeloid cells during the acute phase of exptl *P. falciparum* challenge	180
	P. yoelii	Expression is reduced in murine lymphoid DCs	185
APRIL	*P. falciparum*	Level is increased in placental samples of cases of placental malaria	178
BAFF-R	*P. falciparum*	Expression on B cells is upregulated in *in vitro* cocultures with monocytes in the presence of *P. falciparum* metabolites and antigens	177
		Expression is reduced on peripheral B cells of children during acute malarial infection	179
	T. brucei	Expression is reduced, leading to loss of parasite-specific IgM^+ B cells	169
TACI	*L. major*	$TACI^{-/-}$ mice are more susceptible to cutaneous *Leishmania* because of M2-skewed phenotype of macrophages	56
	P. falciparum	Expression is elevated on peripheral B cells of children during acute malarial infection	179
BCMA	*P. falciparum*	Expression is elevated on peripheral B cells of children during acute malarial infection	179

[a]GDH, glutamate dehydrogenase.

phenotype of macrophages as a result of decreased BAFF activity in BR3:Fc-injected mice may be responsible for elevated parasite counts in the heart.

A more direct proof of the consequences of blocking BAFF- and APRIL-mediated macrophage polarization was documented for *Leishmania*-infected TACI-deficient mice (Table 4 and Fig. 2). The so-called "*Leishmania*-resistant" C57BL/6 mouse strain controls cutaneous *Leishmania major* infection by mounting a Th1 response and by the M1 polarization of skin macrophages (168). We observed an increase in the parasite load and more severe skin pathology in *L. major*-challenged TACI-deficient C57BL/6 mice (56). The susceptibility of TACI-deficient mice is primarily due to the M2-skewed macrophage phenotype, because the transfer of macrophages from wild-type C57BL/6 mice is sufficient to render TACI-deficient mice resistant to *Leishmania* infection.

Susceptibility to parasitic infections can also be a result of the parasite-orchestrated suppression of BAFF system molecules. The causative agent of sleeping sickness, *Trypanosoma brucei*, induces a rapid TI antibody response that suppresses the parasite load during the early phase of infection. However, experimentally infected mice succumb to infection by a second wave of infection partially because of the parasite-driven apoptosis of MZ B cells (169). Apoptosis is likely mediated by a reduction in BAFF-R expression and the subsequent downregulation of the antiapoptotic Bcl-2 protein in infected murine MZ B cells (Table 4 and Fig. 4B). These mice not only lose parasite-specific IgM^+ B cells but also are impaired in mounting a humoral immune response to unrelated pathogens and vaccines.

Malaria

Plasmodium falciparum is the causative agent of human malaria, and like *T. cruzi*, *P. falciparum* infection is accompanied by hypergammaglobulinemia, a consequence of parasite-induced polyclonal B cell activation (170–174). During malaria infection, the host's immune system is activated by the *P. falciparum* metabolite hemozoin (malarial pigment) (175) and cysteine-rich interdomain region 1α (CIDR1α), a specific cell surface antigen of *P. falciparum*-infected erythrocytes (176). Macrophages stimulated with hemozoin produce reactive oxygen species that can potentially mediate BAFF expression (170, 175). Indeed, using cocultures of monocytes and naive B cells, Kumsiri et al. demonstrated BAFF secretion from monocytes stimulated with the schizont fraction of *P. falciparum* and hemozoin (177) (Table 4 and Fig. 3). Moreover, both the schizont

fraction and hemozoin stimulate BAFF-R expression on B cells. Thus, it appears that parasite-induced BAFF activity on B cell proliferation and *P. falciparum*-specific IgG production is augmented by the upregulation of BAFF-R expression (Fig. 4B).

Altered expression levels of BAFF system molecules in clinical samples from malaria-infected patients have also been reported. For example, the expression levels of both *TNFSF13B* (BAFF) and *TNFSF13* (APRIL) mRNAs are significantly increased in placental malaria (PM)-positive placenta samples, and increased levels of BAFF, IgG, and IgM are positively correlated with increased placental malarial pigment deposition (a pathological feature of chronic PM) (178) (Table 4). During the acute phase of malaria infection, children have high plasma BAFF levels and elevated B cell TACI and BCMA expression levels, while the BAFF-R expression level is decreased (Fig. 2B and 4B) (179). High plasma BAFF and low BAFF-R expression levels on B cells are also observed in human subjects experimentally challenged with cryopreserved *P. falciparum* (180). A well-established fact about malaria is the slow development of clinical immunity against the parasite due to a defect in the long-term maintenance of malaria-specific memory B cells (170, 181–184). Low BAFF-R expression levels may be an underlying factor for insufficient memory B cell formation in children after natural infection, since BAFF-R provides B cell survival signals. Supporting this hypothesis, BAFF-R expression was shown to correlate with schizont-specific IgM and IgG production (179). Whereas the survival of naive B cells is dependent on BAFF-R signaling, the survival of antibody-secreting cells (ASCs) requires TACI and BCMA signaling (46). However, despite the presence of circulating BAFF in malaria, ASCs may not be receiving sufficient survival signals, because unlike BAFF-R, which responds to both homotrimeric BAFF (3-mer) and oligomeric BAFF (60-mer), TACI signaling is activated only by oligomeric BAFF and membrane-bound BAFF (46). Since the majority of BAFF in circulation is in the trimeric form, the form unable to engage TACI, ASCs may not receive sufficient survival signals (46). Interestingly, experimentally infected individuals exhibit increased BAFF expression levels on inflammatory monocytes as well as on blood DCs during the acute phase of *Plasmodium* challenge (180). The increased BAFF levels on myeloid cells during acute human malaria are in contrast to findings for murine malaria, in which the expression of surface BAFF on DCs is reduced following *Plasmodium yoelii* infection (185). The differences in membrane-bound BAFF expression between human and murine studies can be partly explained by the fact that human BAFF expression was measured on blood myeloid cells, while murine BAFF expression was measured on lymphoid DCs. Nevertheless, it is not clear why membrane-bound BAFF on blood myeloid cells does not provide sufficient survival signals for TACI-expressing ASCs during acute human malaria. It remains to be investigated whether BAFF expression on myeloid cells changes with anatomical location and how the changes in membrane-bound BAFF expression on DCs impact the survival of ASCs.

FUNGI

Cryptococcal meningitis (CM) is caused by the fungi *Cryptococcus neoformans* and *Cryptococcus gattii*. *Cryptococcus neoformans* does not cause any serious disease in healthy individuals, but its infection can lead to life-threatening complications in patients with a compromised immune system, such as those with HIV/AIDS (186). Examination of peripheral blood mononuclear cells (PBMCs) from HIV-negative CM patients showed that the levels of BAFF, TACI, and BCMA were decreased, whereas the APRIL level remained unchanged and the BAFF-R expression level was increased compared to those in healthy individuals (187) (Fig. 4B). A likely outcome of decreased BAFF levels is that these patients have lower serum IgG levels than do healthy immunocompetent individuals (187). The same study also showed that *in vitro* stimulation of PBMCs with BAFF inhibits *C. neoformans* growth (187). This study did not investigate the mechanism of the BAFF-mediated inhibition of *C. neoformans* growth, but the induction of anti-*C. neoformans* antibodies from BAFF-activated B cells may play a role. Another possibility is the killing of *C. neoformans* by macrophages (188) polarized toward the M1 phenotype in response to BAFF stimulation (56). In addition to periph-

eral blood, BAFF and APRIL levels are increased in the cerebrospinal fluid of CM patients (189). Exactly how BAFF expression levels determine host susceptibility to *C. neoformans* infection and the significance of increased BAFF and APRIL levels in the cerebrospinal fluid of CM patients remain to be elucidated.

CONCLUSIONS AND PERSPECTIVES

Most microbes stimulate the expression of BAFF and APRIL in a range of cells through their pathogen-associated molecular patterns by directly engaging molecules such as TLRs or inducing type I and II interferons. Similarly, microbial products can modulate the expression of BAFF and APRIL receptors. The pattern of engagement of BAFF and APRIL receptors on B cells by their ligands determines the type of B cell responses required to control infection by a given pathogen. Both BAFF and APRIL are required when a TI host response is imperative for the control of infection. During these infections, BAFF-R is essential for B cell survival, and TACI expression is critical for the generation of plasma cells. Also, BAFF-R and TACI can mediate signals for immunoglobulin isotype switching and secretion. Since the expression levels of these receptors dictate their function, TLR-mediated increases in the expression of ligands and/or receptors during infection primarily promote B cell activation. Interestingly, pathogens may have evolved to exploit BAFF system molecules and skew the humoral immune response away from its antimicrobial function because the increase in the expression levels of BAFF system molecules does not necessarily benefit the host. The correlation between elevated BAFF levels during the acute phase of HCV infection and poor disease prognosis is a good example of this phenomenon. Furthermore, the breakage of tolerance as a consequence of chronic exposure to BAFF-inducing viruses (HIV and HCV) or parasites (*T. cruzi*) may be related to the preferential activation of polyreactive MZ B cells (14, 141, 142, 168, 169). Pathogens susceptible to antibody-mediated microbicidal host responses appear to prevent the development of antibody responses by downregulating the expression of BAFF and APRIL receptors. In the case of *T. brucei* infection, the suppression of BAFF-R expression benefits the protozoan by driving MZ B cell apoptosis and limiting IgM antibody production. A central role for TACI in mediating the essential second signal for B cell responses to TI-II antigens makes it an attractive target for encapsulated bacteria. To this point, capsular polysaccharides of encapsulated bacteria blunt B cell responses to BAFF and APRIL by downregulating TACI expression. Pathogens may also utilize BAFF-induced and TACI-mediated stimulation of IL-10-producing regulatory B (Breg) cells as a strategy to prevent antibody production (190). The expansion of BAFF-induced non-IL-10-producing B cells in autoimmune diseases (191, 192) and the activation of Breg cells in chronic lymphocytic leukemia appear to be critical for disease pathogenesis (190). The contribution of these IL-10-producing B cells to suppressing humoral and cellular responses during parasitic, bacterial, and viral infections is well recognized (193). Whether pathogen-induced BAFF plays a role in inhibiting host immune responses by activating Breg cells is yet to be explored.

The soluble forms of TACI and BCMA receptors appear to function as decoy receptors for BAFF and APRIL (43, 44). A decoy function has not been shown for BAFF-R, but the shedding of BAFF-R deprives B cells of survival signals (45). The biological significance of these recently described soluble receptors in infections has not been demonstrated. It is conceivable to think that the immune-dampening properties of soluble receptors present an attractive target for the pathogens to exploit them. Possible mechanisms of immune evasion may include the production of molecules with enzymatic properties by the pathogens themselves or the induction of the expression of host proteolytic enzymes to shed membrane receptors.

BAFF and APRIL are also involved in the development of antibodies against pathogen protein (TD) antigens during infection. In TD responses, the activity of ligands varies according to the time and location in which they engage their receptors during infections. For instance, TACI expression on GC B cells determines the magnitude and quality of ASCs exiting the GC. With the exception of *C. rodentium* infection, TACI

deficiency results in an impaired host response and susceptibility to infection. Apart from its well-recognized role in plasma cell maintenance, TACI is also important for macrophage activation, as both BAFF and APRIL can drive the polarization of macrophages toward the M1 phenotype. TACI-mediated M1 polarization of macrophages appears to be critical for controlling the growth of intracellular pathogens such as *Leishmania*. It is conceivable to assume that TACI-mediated macrophage activation may play similar roles in host resistance to other intracellular pathogens. Another unexplored prospect is the influence of TACI-mediated macrophage activation on the development of adoptive immunity to pathogens. Since macrophage responses directly impact the magnitude and quality of T cell responses, modulation of TACI-mediated signals may have implications for macrophage antigen presentation functions. Taken together, an improved understanding of the role of BAFF system molecules in host resistance and susceptibility to infections can catalyze the development of more effective vaccines by devising molecules that can modulate the expression of BAFF system molecules.

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We declare no conflict of interest.

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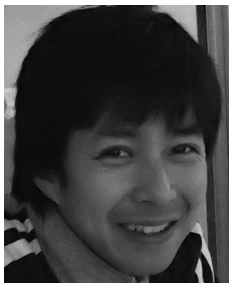

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