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The role of APRIL and BAFF in lymphocyte activation

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The TNF family ligands BAFF (also called BLyS) and APRIL regulate lymphocyte survival and activation. BAFF binds to three receptors, BAFF-R, TACI and BCMA, whereas APRIL interacts with TACI, BCMA and proteoglycans. The contribution of BAFF and APRIL to B-cell and plasma-cell survival, CD154 (CD40L)-independent antibody isotype switching, germinal center maintenance, T-dependent and T-independent antibody responses, and T cell co-stimulation are relatively well understood. Constitutive BAFF produced by stromal cells determines the size of the peripheral B cell pool, whereas inducible BAFF produced by myeloid and other cells supports local survival of B lymphocytes and can be associated with development of autoimmunity when deregulated.

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Introduction

TNF family members are type II transmembrane proteins that spontaneously form homotrimers and are membrane-bound or solubilized ligands for a cognate family of receptors. APRIL (a proliferation-inducing ligand) and BAFF (B-cell activation factor of the TNF family; also called BLyS or TALL-1) were initially identified on the basis of their homology to TNF, although there were few clues as to their physiological functions. These ligands, however, were rapidly implicated in several immunological phenomena that previously lacked a satisfactory molecular explanation, such as peripheral B-cell survival, CD154 (CD40L)-independent antibody isotype switching and the induction of self-reactive B cells. Merging these different fields has proven rather successful and has provided an increasingly coherent overview of the action of BAFF and APRIL in the immune system. This knowledge will certainly translate into therapeutic applications in the near future.

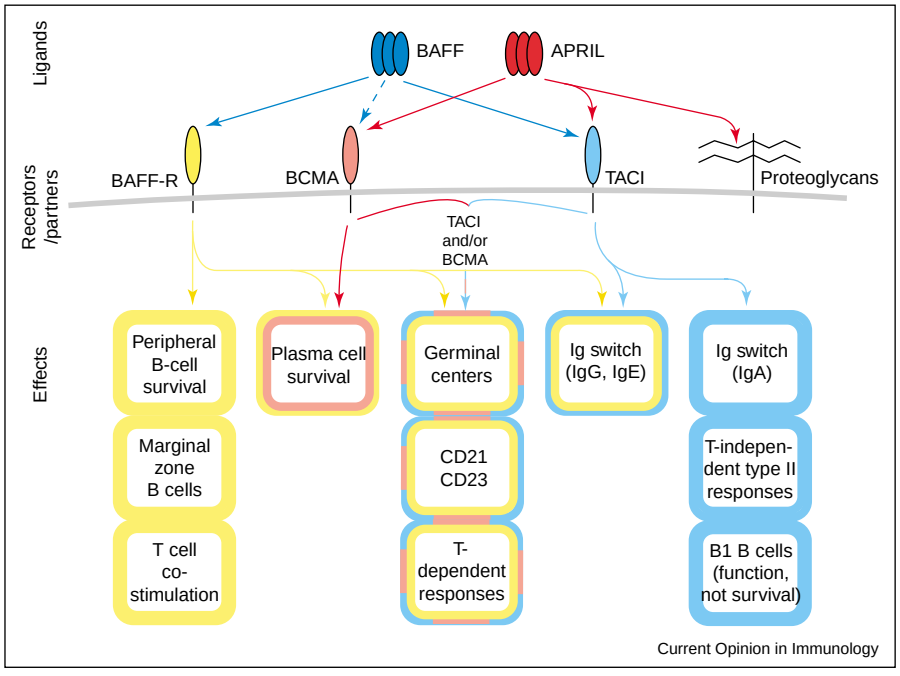
This review focuses on structural and functional aspects of the BAFF–APRIL subfamily, and attempts to describe the roles played by the many receptors of this subfamily in the immune function of healthy individuals.

The interactions of BAFF and APRIL with their receptors and binding partners

Ligand–receptor interactions within the BAFF–APRIL subfamily of TNF ligands are both redundant and specific; for example, BAFF binds to BAFF-R, TACI (transmembrane activator and CAML interactor) and, with lower affinity, to BCMA (B-cell maturation antigen), whereas APRIL binds to TACI and BCMA (Figure 1) [1••,2–5]. In addition, APRIL interacts with proteoglycans, which are structurally unrelated to TNF receptors, and are likely to be the initially unidentified APRIL-specific binding partner that was predicted to exist several years ago (K Ingold *et al.*, unpublished; [6]). This interaction involves acidic sulfated glycosaminoglycan (GAG) sidechains of proteoglycans and basic amino acid residues, which are present in APRIL, but not in BAFF, and is independent from the interaction site for TACI and BCMA (K Ingold *et al.*, unpublished; Figure 2).

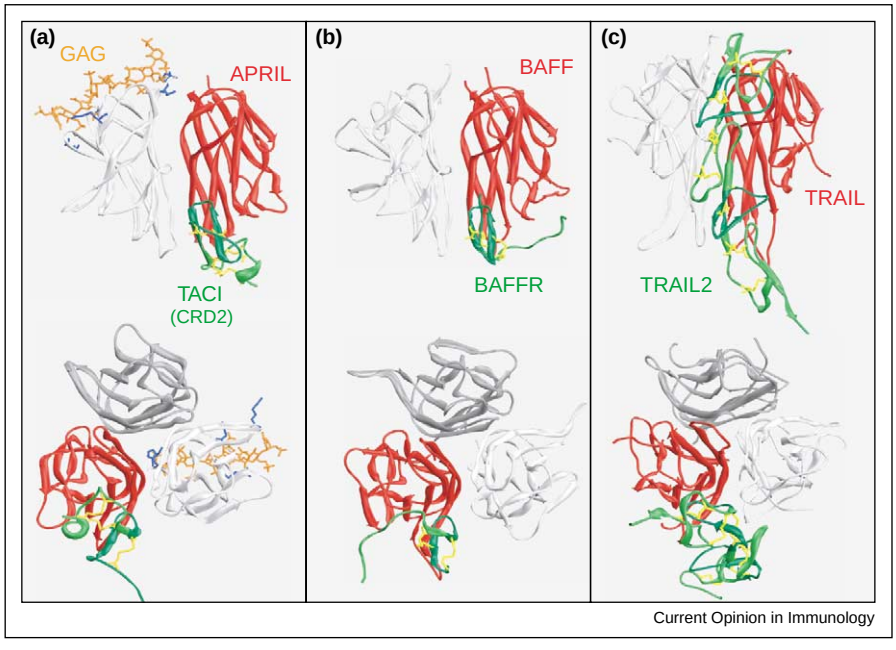
How does BAFF-R distinguish between BAFF and APRIL ligands when TACI and BCMA do not, or rather only incompletely? TNF receptors contain cysteine-rich domains (CRDs) in their extracellular portion, and structural studies indicate that BAFF and APRIL receptors differ from most other TNF receptor family members, as they have a single CRD that contacts one ligand subunit, instead of several CRDs that contact the boundary between two ligand subunits [1••,7–9] (Figure 2). TACI can be classified as a single CRD receptor (although it contains two CRDs) because the amino-terminal CRD does not contribute to ligand binding and is absent in a splice variant encoding a short, functional form of TACI [1••]. BAFF-R, BCMA and TACI all contain a conserved β hairpin structure followed by a more variable motif. The variable motif includes a loop in BAFF-R, or a loop-helix-loop motif in both TACI and BCMA, that adopts different orientations. The hairpin is alone sufficient for BAFF binding [1••,7,9,10], but binding to APRIL requires a specific hydrophobic residue in the hairpin that is found in TACI and BCMA but not in BAFF-R [1••,2]. In addition, the variable motif of BAFF-R is detrimental for APRIL binding, which explains the exquisite specificity of BAFF-R for BAFF but not APRIL [7], whereas the corresponding motifs of TACI and BCMA promote different interactions with ligands and are therefore likely to dictate the differential affinity for BAFF [1••,2].

Figure 1



Ligand specificity and function assignment of BAFF and APRIL receptors in the immune system. The interactions of BAFF and APRIL with their receptors (BAFF-R, BCMA and TACI) are shown in the upper part of the figure. The phenotypic and functional outcomes of BAFF and/or APRIL signaling are listed at the bottom and encircled in color to reflect the involvement of one or more receptors in mediating a particular effect (BAFF-R, yellow; BCMA, pink; TACI, light blue). The assignment of receptor tasks is tentative, as conflicting data exist for some of these functions.

Figure 2



Structural basis for the binding of **(a)** BAFF, **(b)** APRIL and **(c)** TRAIL to receptors and interaction partners. Lateral and bottom views of ligand–receptor complexes are shown (top and bottom panels, respectively). One monomer within each trimeric ligand is shown in red, whereas the receptors are depicted in green with SS-bridges highlighted in yellow. A heparin fragment (GAG, orange) was manually docked onto the basic residues of APRIL (shown in blue) that are believed to mediate interaction with glycosaminoglycans (GAGs). Structures for APRIL, BAFF and TRAIL are based on PDB atomic coordinate files 1XU1, 1OQE and 1DOG, respectively, and heparin is based on file 1FQ9.

BAFF and APRIL have additional structural features of uncertain physiological relevance. TWE-PRIL (TWEAK-APRIL fusion protein) is a fusion protein containing the TNF homology domain of APRIL fused to the amino-terminal portion of another TNF family ligand, TWEAK (TNF-related weak inducer of apoptosis). TWE-PRIL might represent a membrane-bound form of APRIL [11]. In addition, a splice variant of BAFF (ΔBAFF) inhibits regular BAFF by forming inactive heteromers [12]. This strategy could be exploited to poison endogenous BAFF with exogenously added recombinant BAFF mutants [13], and could be used to intervene in autoimmune and other conditions in which BAFF is produced in excess. BAFF can also heterotrimerize with APRIL in undefined stoichiometry [14], although this process appears to be far less efficient than the heterotrimerization of lymphotoxin $\alpha_1\beta_2$, a well-characterized heterotrimer of the TNF family. Finally, recombinant soluble BAFF trimers have a pH-dependent propensity to form spherical structures composed of 20 trimers, whose specific signaling properties largely remain to be explored [7,9,15].

Two pools of BAFF

There are two distinct pools of BAFF in the mouse. A constitutive pool is produced in fixed amounts by radiation-resistant cells (these are possibly stromal cells from lymphoid organs) and controls the size of the peripheral B cell pool [16••,17••]. In addition, an accessory cytokine-inducible pool of BAFF is produced locally by cells of myeloid origin, such as monocytes, macrophages, dendritic cells and neutrophils, other fibroblast-like cells or even astrocytes. This cytokine-inducible pool enables the transient accumulation of additional B-cell populations; for example, at inflammatory sites [16••,18–22]. This concept goes beyond the generally accepted idea that cells of myeloid origin are the main producers of BAFF. Indeed, if bone-marrow-derived cells are the main source of BAFF, lethally irradiated wild-type recipients reconstituted with BAFF-deficient bone marrow should be phenotypically similar to BAFF-deficient mice; however, experimental data reveal that these mice are normal [16••]. Does this mean that BAFF produced by cells of myeloid origin plays no role? This is not the case, because the reverse experiment (wild-type bone marrow transplanted into irradiated BAFF-deficient mice) demonstrates that dendritic cells and macrophages can indeed produce BAFF and locally sustain B cell survival, although they are unable to maintain normal B cell counts and circulating BAFF levels [16••].

BAFF and B cell homeostasis

Cells that produce BAFF constitutively are apparently unaffected by the presence or absence of B cells. If fewer B cells are present than can be sustained by BAFF, the circulating pool of BAFF is augmented and reaches its highest levels in the extreme case of a total B-cell deficiency [17••]. If, on the contrary, more B cells are present than can be supported by BAFF, those cells most dependent on BAFF will die. B-cell survival depends not only on BAFF-R signals but also on basal signals mediated by the B-cell receptor (BCR) that might control, at least in part, BAFF-R expression [23,24•]. Despite its role in B cell survival, if a BCR signal becomes too strong in transitional peripheral B cells it results in anergy or toxicity, most probably as a result of the activation of pro-apoptotic factors such as Bim [17••]. Autoreactive B cells, which have their BCR engaged by self-antigens, might be particularly prone to this type of death induction and require proportionally stronger survival signals than regular cells to escape death. If BAFF is limited, autoreactive B cells die. But if autoreactive B cells are exposed to sufficient BAFF supply, either because they are the only ones present in the experimental system, or because BAFF is produced in excess from a transgene or from hyperactivated dendritic cells (such as those displaying complete deficiency for suppressor of cytokine signaling-1 [SOCS-1]), they will survive and be allowed to reach locations such as the B cell follicle or splenic marginal zone where they are more likely to encounter microorganism-derived polyclonal activators that will precipitate their activation [17••,25,26]. Similar mechanisms might be at work in patients with chronic inflammatory autoimmune diseases.

BAFF-independent B-cell survival

It might be beneficial for essential B cell populations to become independent of BAFF signals in order to prevent their accidental disappearance. The observation that human plasmablasts express both BCMA and BAFF-R and survive in response to both BAFF and APRIL (Table 1; [27]), together with the observation that the survival of long-lived murine bone marrow plasma cells depends on BCMA (Table 2; [28•]), suggests that some cells may indeed partially shortcut the need for BAFF by complementing or replacing the BAFF–BAFF-R system with an APRIL–BCMA survival axis. APRIL recruitment to these cells might be facilitated by the expression of syndecan-1 (also called CD138), a proteoglycan that interacts with APRIL (K Ingold *et al.*, unpublished).

This regulatory system can be circumvented by some lymphoid malignancies that develop an advantage by producing their own BAFF and/or APRIL supply [29–31]. Memory B cells might even survive independently of BAFF and APRIL. Mice immunized with a T-dependent antigen and subsequently administered adenovirus-encoded soluble TACI-Ig (a fusion protein comprising TACI and immunoglobulin acting as BAFF and APRIL inhibitor) displayed pronounced decreases in peripheral B cell and extrafollicular IgM-producing plasma cell numbers, but remained competent for mounting an efficient recall response to the immunizing antigen after termination of the TACI-Ig treatment. This suggests that

Table 1

Cellular distribution of receptor expression (protein level).

Human				Mouse		
Cell type	hBAFF-R	hTACI	hBCMA	Cell type	mBAFF-R	mTACI
Splenic B cells	+++ [27]	No [27]	No [27]	T1 B cells	++ [35]	No [35,39]
Tonsil B cells (non-GC)	+++ [39]	+ [39]	No [39]	T2 B cells	+++ [35]	++ [39] + [35]
GC tonsil B cells	++ [39]	No [39]	+ [39]	Marginal zone B cells	ND	++ [39]
Blood B cells	+++ [30,39,54]	+ (subset) [30,39,54]	No [30,39,54] + (HIV) [54]	Follicular B cells	+++ [35]	+ (++ with anti-μ) [35,39]
Blood memory ($CD27^+$) B cells	+++ [30]	+ [30]	No [30]	Blood B cells	+++ [39]	ND
Peripheral B1 B cells	+++ [30]	+ [30]	No [30]	Peritoneal B1 B cells	+++ [35]	++ [35]
Plasma cell	+ [27]	No [27]	+ [27]			
Blood T cells	+ (subset of $CD4^+$) [39] + (allograft infiltrating $CD3^+$ cells) [53]	No [39]	No [39]	Splenic T cells	+ (subset of $CD4^+$ Most $CD4^+$ $CD25^+$) [39,53]	ND

The left- and right-hand sides of the table show expression at the protein level for human and mouse receptors, respectively. Most data were obtained by FACS analysis using specific antibodies. There is presently no data available regarding the expression of mouse BCMA. No indicates undetectable expression, +, ++ and +++ indicate the presence of increasing amounts of the receptors. Abbreviations: GC, germinal center; ND, not determined.

memory B cells require either no or only minimal amounts of BAFF and APRIL for their survival [32•].

Task assignment within the BAFF–APRIL subfamily

B cell survival

B-cell development and selection in the bone marrow is independent of BAFF [33,34]. Only when B cells exit the bone marrow do they become responsive to BAFF survival signals, more precisely as they progress from transitional T1 to transitional T2 stages in the spleen. Survival requires BAFF and BAFF-R, as deletion of either of these genes results in an identical, significant reduction of peripheral B cells that have developed beyond the T1 B cell stage [35•]. BAFF is, however, not actively implicated in B cell differentiation at this point because B cells

Table 2

Phenotype of null mice in the BAFF–APRIL subfamily.

	BAFF null	APRIL null	BAFF-R null	BAFF-R mutant (A/WySnJ)	TACI null	BCMA null
Peripheral B cell subsets	Impaired +++ [35]	Normal [45,55]	Impaired +++ [35,40][d]	Impaired ++ [56]	Increased [44,57][d]	Normal [58][d]
Serum antibody titers and isotype switching	Reduced antibody titers (except IgA) [33]	Reduced IgA titer [45] (not always seen [55])	Reduced antibody titers (except IgA). [40]	Switching to IgA and IgG occurs [50]	Reduced IgA titer [44] Impaired switching to IgA [45][c]	Normal [50,58]
Plasma cell survival						Impaired [28]
CD21 expression	Impaired +++ [36]		Impaired + [40]	Impaired + [33,56]	Normal [44]	Normal [33,58]
CD23 expression	Impaired +++ [36]		Impaired + [35,40]	Normal [33,56]	Normal [44]	Normal [33,58]
Germinal centers[a]	Impaired ++ no secondary FDC reticulum [42]	Increased number [45]	Impaired + [35] Normal in PP and mLN GCs [40]	Impaired + No Ki67 in B cells [42]		
Marginal zone B cells	Normal proportion [36][b]	Normal [55]	Impaired +++ [40]	Normal proportion [56]	Normal proportion [44,57]	Normal [58]
TI-II responses	Impaired ++ (IgM and IgG) [33,34]	Normal [45,55]	Normal [35] Impaired + [40]	Normal [59]	Impaired ++ [44]	Normal [58]
TD responses	Impaired ++ (IgM and IgG) [33,34]	Normal [55] Impaired IgA to mucosal TD antigen [45]	Normal or slightly impaired IgM [35,40] Impaired IgG [35,40]	Normal IgM Impaired IgG [59]	Enhanced [44,57]	Normal [58]
B1 B cells	Normal [33,34]	Normal [45] (increased in transgenics) [46]	Normal [35,40]	Normal [60]	Normal (no gross loss) [44]	Normal [58]

[a]Germinal centers are induced at a normal density in response to immunization, but exhibit more rapid loss with time. [b]Loss of CD21 and CD23 expression in BAFF null complicates identification of marginal zone B cells in these mice. [c]Naïve B cells from TACI null mice have impaired switching to IgA, IgG1 and IgE in response to APRIL, and to IgA in response to BAFF [50]. [d]Loss of peripheral B cells is identical in BAFFR null and BAFFR x TACI double null mice. Peripheral B cells are not lost in TACI x BCMA double null mice [35]. Abbreviations: GC, germinal center; LN, lymph node; mLN, mesenteric LN; PP, Peyer's patch.

can still progress to the mature stage, and antibodies of various isotypes are made in the absence of BAFF, although only few B cells reach the mature stage under these conditions [36]. Consistent with a 'passive' survival role for BAFF, B cells expressing a phospholipase C (PLC)-γ2 mutant enzyme that affects BCR signaling fail to reach the mature stage despite a functional BAFF survival pathway [37]. In addition, the co-stimulatory effects of BAFF on BCR-stimulated cells are a result of increased survival rather than stimulated cell cycling, whereas CD154 promotes both survival and cycling under identical conditions [24•]. The survival action of BAFF is negatively regulated by TACI [38] and, as TACI is expressed on T2 B cells [35•,39•], it might fine-tune the survival function of BAFF–BAFF-R at this stage. Marginal zone B cell formation also appears to be exquisitely dependent on BAFF-R-mediated signals [40,41].

Surface markers and germinal centers

In addition to their B cell and plasma cell survival activities, BAFF and APRIL support several other functions. Expression of CD21 and CD23, which are markers often used to classify B cell populations, is controlled by BAFF, in part through BAFF-R and in part through BCMA and/or TACI or via indirect mechanisms [36,40•]. Germinal centers can form in BAFF-null, BAFF-R-null and BAFF-R mutant (A/WySnJ) mice, but they are not maintained [35•,42,43]. The defect is more severe in BAFF-null than in A/WySnJ mice, and is apparently mechanistically different. Germinal centers in BAFF-null mice do not build a secondary follicular dendritic cell (FDC) network and do not trap antigen, suggesting that BAFF affects the FDC network either directly or indirectly (e.g. via lymphotoxin β). In BAFF-R-null mice, however, FDC networks are present but B cells fail to proliferate, possibly because TACI and/or BCMA signals, in the absence of BAFF-R, prevent cell cycle progression [42]. In this respect, it is interesting to note that human germinal center B cells express BCMA [39•].

Humoral responses and immunoglobulin switch

BAFF-null and BAFF-R-null mice mount poor but detectable T-dependent antibody responses, which might directly reflect the paucity and reduced survival of peripheral B cells in these mice [33,35•,40•]. The situation is quite different for T-independent type II antibody responses, which require TACI and its ligands, but for which BAFF-R is dispensable [33,35•,44,45]. Gut-associated B cells are derived from B1 B cells and, although they do not require BAFF for survival, they express both BAFF-R and TACI and they give rise to B cell neoplasms in APRIL transgenic mice [35•,46]. In addition, and in contrast to what is observed in the spleen of BAFF-R-null mice, the Peyer's patches and mesenteric lymph nodes develop normal germinal centers in response to gut microflora, which might explain why IgA serum levels remain normal in BAFF-R-null mice [40•]. BAFF and/or APRIL might also increase T-independent antibody responses by prolonging the survival of plasmablasts derived from B1 B cells and marginal zone B cells [47]. Antibody class switching, which occurs in B cells, requires cytokines and, in the case of T-dependent antigens, CD154. CD154-independent class-switch recombination does, however, occur in a BAFF- and APRIL-dependent manner that might be particularly relevant for the production of IgA, as one particular strain of APRIL-null mice displays a selective IgA deficiency and decreased IgA responses to mucosal T-dependent antigens [45,48,49]. BAFF and APRIL induce isotype switching to IgG_1 and IgA and, with the help of IL-4, to IgE [50•]. Interestingly, both BAFF-R and TACI are able to signal isotype switching to IgG_1 and IgE, but the switch to IgA is controlled by TACI only [50•]. Isotype switching controlled by APRIL and BAFF might be achieved, in part, via the induction of IL-10 [50•].

T cell co-stimulation

In addition to regulating multiple B-cell related functions, BAFF is increasingly recognized as an important co-stimulator of T-cell function. Human T cells respond to recombinant or endogenous BAFF by secreting IFN-γ and IL-2, upregulating CD25 (IL-2 receptor α chain) and proliferating in an IL-2-dependent manner [51,52]. BAFF-R is expressed on only a few percent of human and murine T cells, is upregulated upon T cell activation [39•,53•], and is expressed by most murine $CD4^+$ $CD25^+$ regulatory T cells [53•]. BAFF induces BAFF-R-dependent Bcl-2 expression in T cells and might therefore help survival [39•]. Functionally, blockade of BAFF or BAFF-R prevents T-cell mediated allograft heart rejection in the mouse, in synergy with low doses of the immunosuppressive drug cyclosporine A [53•]. Validated antibodies failed to detect TACI expression on T cells, and T-cell responsiveness was impaired only in BAFF- and BAFF-R-deficient, but not in TACI-deficient animals, strongly implicating BAFF-R as the only receptor that mediates BAFF responses in T cells [39•,53•].

Concluding remarks

BAFF is a primordial B-cell survival factor that also has additional roles, including T-cell activation; the contribution of APRIL to plasma cell survival, isotype switching and T-independent antibody responses is now relatively well established. Studies published during the past two years have unveiled the roles played by these different receptors, but much remains to be understood concerning the contribution of BAFF and APRIL signaling pathways in mediating these pleiotropic effects. The expression of selected mutant receptors in receptor-deficient mice is one of several approaches that will broaden our comprehension of the relative importance of these signaling pathways. Considerable efforts have been undertaken to define the function of BAFF and APRIL, and to develop agonists and antagonists of this system that will

hopefully provide new drugs in the future for autoimmune conditions such as systemic lupus erythematosus and rheumatoid arthritis.

Update

The work referred to in the text as (K Ingold *et al*., unpublished) is now in press [61].

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- •• of outstanding interest

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