The role of BAFF and APRIL in regulating human B-cell behaviour: implications for disease pathogenesis

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Abstract

B cells require signals from multiple sources for their development from precursor cells in the bone marrow, and differentiation into effector cells. BAFF and APRIL are members of the TNF superfamily of cytokines and have been identified as critical regulators of B cell development and differentiation. Defects in the production of BAFF and APRIL, and/or expression of their receptors, have been associated with a diverse array of human diseases characterised by perturbed B cell function and behaviour, including autoimmunity, malignancy, and immunodeficiency. This chapter will discuss the role of BAFF and APRIL in normal B-cell physiology, as well as the emerging evidence of their involvement in the pathogenesis of these human immunopathologies.

Introduction

The generation of the mature B cell pool involves the step-wise development of hematopoietic stem cells into pro-B cells, which mature into pre-B cells and then immature B cells (1-3). Immature B cells are then exported to the periphery as transitional B cells which undergo further selection and developmental events to yield mature B cells (4, 5). When mature B cells encounter T-cell dependent (TD) antigen (Ag), they differentiate into high affinity effector cells, namely immunoglobulin (Ig)-secreting cells (ISC) or plasma cells (PC), as well as memory B cells and (3, 6). This process generally occurs within specialized structures in secondary lymphoid tissues called germinal centres (GC) (3, 6) (Figure 1). Thus, mature B cells are responsible for the generation of long-lived humoral immunity. The co-ordinated differentiation of B cells at these different stages of development and maturation is influenced by multiple factors, such as stromal cells and cytokines provided by the bone marrow (BM) microenvironment, strength of interactions with specific Ag, and cross-talk between B cells, Ag-specific T cells, follicular dendritic cells (FDC) and dendritic cells (DC) in peripheral lymphoid tissues (1, 3, 6).

The differentiation of mature B cells into effector cells requires strict regulation so as to facilitate the generation of Ag-specific humoral immune responses whilst simultaneously avoiding the generation of autoantibodies. Receptor/ligand pairs of the tumour necrosis factor receptor (TNF-R)/TNF superfamily play critical roles during B-cell responses. The best characterised of these involve interactions between CD40 (7), CD27 (8), CD134 (OX40) (9) and TNF-R (10) on B cells and their respective ligands (CD40L, CD70, CD134L, TNF-α), usually on $CD4^+$ T cells, which promote B cell proliferation, differentiation and Ig secretion, while ligation of CD30 (11) and CD95 (12) negatively regulate B cell behaviour. During the past 10 years, BAFF and APRIL, ligands of the TNF superfamily, have emerged as potent regulators of multiple functions of human and murine B cells. Here, we will review the role of BAFF, APRIL and their respective receptors in B-cell activation during normal immune responses, as well as in the pathogenesis of a variety of human diseases.

BAFF and APRIL: ligands of the TNF family

B cell activating factor belonging to the TNF family (BAFF) (13-16) and a proliferation-inducing ligand (APRIL) (17) were independently identified based on their homology to the TNF superfamily (reviewed in (18-20)). BAFF and APRIL are produced by hematopoietic cells such as monocytes, macrophages, DCs, astrocytes (21-24) and neutrophils (25, 26), as well as non-hematopoietic cells, namely epithelial cells present in the intestine and respiratory tract (27-29), and FDC in secondary lymphoid tissues (30). Production of BAFF and APRIL by these cell types can be increased following stimulation with a broad range of cytokines [CD40L, IL-10, IFN-α, IFN-β, IFN-γ (21-24, 27), G-CSF (25, 31), the IL-7-related cytokine TSLP (28, 29)] or ligands for specific Toll-like receptors (TLR) (27-29). Expression of both BAFF and APRIL can also be induced in human B cells following infection with Epstein Barr virus (EBV) (32) or dual stimulation through CD40 and the B-cell receptor (BcR) (33).

BAFF binds three receptors belonging to the TNF-R superfamily – BAFF receptor (BAFF-R/BR3) (34, 35), transmembrane activator of and calcium modulator and cyclophilin ligand (CAML) interactor (TACI), and B cell maturation antigen (BCMA). APRIL does not interact with BAFF-R, however it can bind to both TACI and BCMA (36-40). Interestingly, heparin sulfate proteoglycan (HSPG) has been identified as a unique receptor for APRIL (41). In mice, BAFF-R is expressed at low levels on early transitional B cells and upregulated on late transitional, follicular and marginal zone (MZ) B cells (42), however it is absent from pro-B and pre-B cells in the BM. TACI exhibits a similar expression profile to BAFF-R, being low/absent on murine splenic T1 B cells, induced at the follicular stage, and further increased on late transitional and MZ B cells (26, 43). In contrast to both BAFF-R and TACI, BCMA message can be detected in transitional B cells in murine spleen, but then down-regulated at later stages of B cell maturation (43). While neither BAFF-R nor TACI were detected in murine BM PC, these cells did contain mRNA for BCMA (44).

In humans, transitional, naïve, GC and memory B cells are all capable of binding soluble BAFF. Transitional and naïve B cells bind BAFF exclusively through BAFF-R, because TACI and BCMA are

absent from these cells. On the other hand, memory B cells can interact with BAFF through either BAFF-R or TACI, but not BCMA (26, 30, 45-53). Human GC B cells express BAFF-R, albeit at a reduced level compared to naïve and memory B cells, as well as BCMA (26, 30, 51). Expression of TACI by human GC B cells is controversial, as it has been reported to be both absent (26, 30, 51) and present (54) from this B-cell subset. Human plasmablasts acquire expression of BCMA and TACI yet down-regulate BAFF-R (30, 45, 55, 56). Interestingly, PC present in human tonsils retain expression of TACI and BCMA following their maturation from the plasmablast stage (52, 54), but then down-regulate expression of all known BAFF receptors once they undergo terminal differentiation and migrate to the BM (45, 46, 52). Thus, it would appear that normal human B cells first express BAFF receptors at the transitional stage of development and remain capable of receiving BAFF-dependent signals at least until they terminally differentiate into PC (see Figure 1).

Functions of BAFF

(a) B cell survival and proliferation

Murine B cells

A predominant function of BAFF is in promoting and/or sustaining the survival of late transitional and mature murine B cells (reviewed in (18-20)). The mechanism by which BAFF exerts this effect is by altering the ratio between pro-survival and pro-apoptotic molecules. Expression of the anti-apoptotic genes A1, bcl-2, bcl-xL (43, 57) and Mcl-1 (44, 58) was increased following *in vitro* exposure of murine B cells to BAFF, while that of pro-apoptotic molecules Bak (57), Blk (59) and Bim (60, 61) was reduced. As a result of enhanced survival,BAFF could strongly increase proliferation of murine B cells induced by engagement of the BcR (13, 43, 62). The source of BAFF that regulates homeostatic survival during B-cell development is believed to be from non-haematopoietic stromal cells present within BM and/or spleen (63). In addition to its effects at the transitional stage of B-cell development, BAFF – and APRIL – can enhance survival of terminally differentiated murine PC (44).

Studies of mice lacking functional BAFF-R, TACI or BCMA revealed that BAFF exerts its pro-survival effect during B-cell development predominantly through BAFF-R, because spleens from these mice had

a severe reduction in the number of transitional and mature B cells, while B-cell development in mice deficient in TACI (64, 65), BCMA (66-68) or both (69) was intact. These findings established the unique role played by the BAFF/BAFF-R signalling pathway in regulating B cell survival and homeostasis. The impaired survival of developing B cells in mice deficient for BAFF or BAFF-R could be overcome by enforced expression of bcl-2 (70) or bcl-xL (71), supporting the proposal that BAFF maintains B cell survival by modulating expression of anti-apoptotic molecules. This led to the proposal that signals delivered through BAFF-R, in concert with Ag-mediated engagement of the BcR, promotes positive selection of transitional B cells and allows for their continued maturation (43, 72). This was supported by the findings that signalling through the BcR increased binding of BAFF to murine B cells (73), and an intact BcR signal transduction pathway is required for acquisition of BAFF-responsiveness in developing B cells (74).

Human B cells

In contrast to murine B cells, emerging data suggests that B cells from humans and non-human primates are less dependent on BAFF for their development and survival. Unlike murine B cells (72, 75), BAFF has minimal effect on the survival of subsets of human B cells**,** despite the expression of BAFF-R on these cells. BAFF only weakly promoted the survival of human memory B cells, but not transitional, naïve or PC (45, 46, 48, 53, 58, 76, 77) (Figure 1). It is unclear whether the weak effect that BAFF has on the survival of memory B cells is mediated by BAFF-R, TACI or both. However based on the dramatic consequences of BAFF-R deficiency in mice, it is plausible that BAFF-R has this function in human memory B cells. Consistent with these results were the findings that *in vivo* blockade of BAFF in cynomolgus monkeys had no effect on the numbers of putative transitional B cells and tissue PC, while mature peripheral B cells were reduced <2-fold compared to control animals (78-80).

Despite these species differences in the ability of BAFF to support survival of resting human B cells, BAFF (and APRIL) can sustain the viability of (a) naïve B cells stimulated through the BcR, CD21 and IL-4R, which then acquire features of Ag-presenting cells (58, 77), and (b) human memory B cells stimulated with CD40L/IL-2/IL-10, which develop into plasmablasts (30, 45, 51, 55). This latter finding

parallels the ability of BAFF and APRIL to promote survival of plasmablasts arising from activated murine B cells *in vivo* (57, 62, 81, 82). Interestingly, BAFF-R is down-regulated on plasmablasts, while expression of TACI is increased and BCMA induced (30, 45, 52, 55). Furthermore, the effect of BAFF and APRIL on murine plasmablast survival was reduced in the absence of TACI or BCMA and completely abrogated in the absence of both receptors (62). Thus, it is likely that the survival effect exerted by BAFF/APRIL on activated B cells as they differentiate into Ig-secreting cells is mediated by BCMA and/or TACI (Figure 1). Recent findings have proposed that this is achieved by the induction of cyclo-oxygenase 2 and subsequent production of prostaglandin E2, which has known roles in promoting survival of multiple cell lineages (58). It is likely that myeloid cells - monocytes, macrophages, DCs - in spleen and BM provide the BAFF/APRIL that regulates survival of human and murine plasmablasts (20, 23, 45, 63, 82). Recently, a novel function of BAFF was revealed by its ability to preferentially promote chemotaxis of human memory B cells to CXCL13 (83). Thus, BAFF may have a dual function on memory B cells by causing a mild increase in their survival (45), coupled with a greater migratory capacity to lymphoid homing chemokines (83). The production of both CXCL13 and BAFF by cells within lymphoid follicles (i.e. stromal cells, FDC, myeloid cells), and the enhanced response of memory B cells to both ligands, may contribute to the rapid response of memory B cells, relative to naive B cells, that is characteristic of secondary responses to TD Ags.

(b) Class Switch Recombination

Human B cells

Following Ag stimulation, naïve B cells can undergo class switch recombination (CSR) to express and produce the downstream isotypes IgG, IgA or IgE. This allows versatility in both function and distribution of the Ig molecule, while retaining Ag specificity (3). CSR from Cμ to Cγ, Cα and Cε occurs in response to signals delivered through CD40/CD40L, usually in combination with specific cytokines, or TLR ligands (84-86), and is accompanied by characteristic molecular events such as induction of activation-induced cytidine deaminase, a DNA-editing enzyme necessary for CSR, and expression of Ig heavy chain germline transcripts and switch circles (84-86). These events can be detected in human B

cells when stimulated with BAFF or APRIL alone, and are greatly increased in B cells treated with BAFF or APRIL together with IL-4 or IL-10 (22, 29). BAFF may further contribute to CSR by inducing B cells to secrete IL-10 (87), a known switch factor for production of IgG and IgA by human B cells (7). Although CSR from Cμ to Cε was not observed when human B cells were exposed to BAFF or APRIL alone, switching to IgE did occur when combined with IL-4 (22) (Table I). Interestingly, BAFF or APRIL alone were not sufficient to induce secretion of switched Ig isotypes by stimulated human B cells; rather, Ig secretion required additional signals, such as cross-linking of the BcR together with specific cytokines (IL-4, IL-10)(22, 29). Notably, APRIL - more so than BAFF - favoured production of IgA2 by human B cells stimulated with IL-10 and the TLR5 ligand flagellin, while levels of IgA2 secretion were further enhanced by the combination of BAFF together with APRIL (29). BAFF and APRIL also contribute to humoral immune responses by enhancing CSR, acquisition of expression of switched Ig isotypes IgG and IgA, as well as their secretion, by naïve B cells activated by EBV (32) or the TLR3 and TLR9 ligands dsRNA and CpG, respectively (88, 89) (Table I).

The *in vivo* relevance of the *in vitro* findings of a role for BAFF and APRIL in regulating Ig CSR has been examined in the context of interactions between BAFF/APRIL-producing cells, such as DC and epithelial cells, and B cells. It has been proposed that TLR ligands present in microorganisms stimulate innate immune cells (DCs) and non-haematopoietic cells (eg mucosal epithelial cells) to produce BAFF and APRIL. TLR-stimulated epithelial cells can also produce TSLP, which acts in a paracrine loop to augment TLR-induced production of BAFF by DCs. In addition to activating epithelial cells and DCs, microbial stimuli can activate B cells through corresponding TLRs (eg TLR3, TLR9), thereby directly initiating CSR. Thus, BAFF and APRIL, together with TLR ligands, activate CSR and, when combined with DC-derived cytokines including IL-10, co-operate to elicit secretion of switched Ig isotypes by responding B cells, resulting in the generation of an integrated humoral immune response (22, 28, 29, 85, 88, 89) (Table I).

Murine B cells

BAFF and APRIL also induce murine B cells to undergo CSR *in vitro* (90, 91). Specifically, stimulation of murine B cells with BAFF or APRIL resulted in the secretion of IgG1 and IgA. In contrast, IL-4 was required for production of IgE by BAFF- or APRIL-stimulated murine B cells (90, 91). Analyses of gene-targeted mice have revealed important and Ig isotype-specific roles for TACI and BAFF-R in this process. Both APRIL and BAFF failed to induce IgA secretion by naïve B cells from $TACI^{-/-}$ mice, but no such failure occurred in mice whose B cells either expressed a non-functional BAFF-R or lacked BCMA (91). This suggests that TACI is exclusively responsible for eliciting CSR to IgA in response to BAFF or APRIL, and is consistent with impaired switching to IgA in vivo in APRIL-deficient mice (90). TACI-deficient B cells also failed to secrete IgG1 and IgE in response to APRIL plus IL-4, while the response of B cells lacking BCMA or a functional BAFF-R was intact (91). Thus, TACI is also capable of mediating APRIL-induced switching to IgG1 and IgE. Despite the inability to respond to APRIL, $TACI^{-/-}$ B cells synthesised normal levels of IgG1 and IgE in response to stimulation with BAFF/IL-4 (91). This study, therefore, demonstrated that in the absence of TACI, production of these isotypes can be compensated by the BAFF/BAFF-R signalling pathway, revealing redundancy in the abilities of both BAFF-R and TACI to mediate switching to IgG1 and IgE in the presence of corresponding ligands.

The relative roles of BAFF-R and TACI in inducing CSR in human B cells by BAFF and APRIL remain incompletely defined. Curiously, stimulation with the TLR9 agonist CpG strongly induces expression of TACI on human naïve B cells (52). Since BAFF is capable of augmenting CSR induced in human B cells by CpG (88), it is tempting to speculate that this is achieved by BAFF interacting with TACI. This is supported by the finding that siRNA-mediated knock-down of TACI expression on human B cells abrogated the ability of APRIL to induce IgA production by these B cells, however production of IgG was unaffected (92). Taken together, it appears that TACI is required for APRIL-induced production of IgA, but not IgG, whereas BAFF-R contributes to BAFF-mediated CSR to IgG and IgA by human B cells. This is discussed further (see below – *Immunodeficiency*) in the context of humans with loss-of-

function mutations in *TACI* whose B cells failed to secrete IgA in response to activation with either APRIL or BAFF (93).

Aberrant expression of BAFF, APRIL and BAFF receptors in human disease

Dysregulated expression and/or function of BAFF, APRIL and/or their receptors has been implicated in the pathogenesis of a diverse range of human diseases including autoimmunity, haematological malignancies and immunodeficiencies.

Autoimmunity and related diseases

BAFF, APRIL, and BAFF/APRIL multimers are elevated in serum and synovial tissue of patients with autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjogren's syndrome (SjS) (94-102), scleroderma (103), systemic sclerosis (104, 105), atopic dermatitis (106), bullous pemphigoid (107, 108), and Wegener's granulomatosis (109). BAFF has also been detected in neurological lesions of patients with multiple sclerosis (MS) (24). In general, the increased levels of serum BAFF and APRIL were associated with increased levels of autoantibodies (95-97, 99, 101) or disease activity (105, 106). A recent study also reported detection of BAFF in lesions of females with endometriosis, but not in control endometrial tissue, nor patients with other gynaecological conditions such as adenomyosis and uterine fibrosis (110). The presence of BAFF in endometriosis lesions was accompanied by infiltration of substantial numbers of BCMA-expressing plasmablasts, and substantially elevated levels of serum BAFF (110). These findings suggest that an autoimmune/inflammatory component contributes to some of the pathological features of endometriosis.

The cell-type responsible for the increased production of BAFF in some of these conditions has been identified. BAFF is produced by T cells and macrophages infiltrating inflamed salivary glands in SjS (111), and by astrocytes (24) and monocytes (112) in MS. In RA patients, macrophages exclusively produced BAFF, while DC secreted APRIL (101). BAFF-expressing macrophages were also detected in lesions in endometriosis (110). Neutrophils, which can be detected in inflamed synovium, may also contribute to elevated levels of BAFF in RA (101). Several other cytokines, such as soluble CD40L, IL-4, IL-6, IFN-α and IL-10, are elevated in autoimmune conditions (99, 113-116). Furthermore, there is a

large increase in the level of expression of CD40L on T cells and B cells from SLE patients (117). Interestingly, most of these cytokines can augment production of BAFF by myeloid cells *in vitro* (21-24). Thus, it is likely that myeloid cells exposed to CD40L, IFN-α and IL-10 are responsible for the increased serum levels of BAFF in SLE.

In autoimmune diseases, the affected tissues are usually non-lymphoid, and are thus devoid of immune cells. However, inflamed synovial tissue and salivary glands from RA and SjS patients contains large numbers of infiltrating lymphocytes which form GC-like structures comprised of B cells, T cells, DC and FDC (118, 119). The formation of these ectopic GC-like structures likely results from aberrant expression of molecules such as TNFα, lymphotoxin, CXCL13, CCL19 and CCL21, that are required for normal lymphoid neogenesis (80, 119, 120). It was recently revealed that the incidence of ectopic GC in inflamed tissues in RA and SjS correlates with the levels of lymphotoxin, CCL19, BAFF and APRIL (98, 99, 101, 115). Thus, it is likely that BAFF and/or APRIL plays a critical role in the maintenance of ectopic GCs in autoimmune patients, by eliciting (i) pro-survival effects on autoreactive B cells and (ii) inducing them to produce class switched pathogenic autoantibodies, which are characteristic of humoral autoimmune conditions. The ability of BAFF to enhance chemotaxis of memory B cells may also contribute to the infiltration of effector B cells to sites of autoimmune-mediated inflammation (83).

B cell malignancies

Numerous studies have provided convincing evidence that BAFF/APRIL may contribute to malignancies of mature B cells (non-Hodgkin's lymphoma [NHL], chronic lymphocytic leukemia [B-CLL], Hodgkin's lymphoma [HL]), plasmablasts (Waldenstrom's macroglobulinaemia [WM]) and PCs (multiple myeloma [MM]) . Malignant B cells from these patients are all capable of binding soluble BAFF and, in some cases, APRIL (33, 47, 49, 50, 54, 56, 121-124). However, the receptor expression profile of these malignant cells differed as NHL (123), B-CLL (49, 121) and WM (124) B cells co-express BAFF-R and TACI, while HL and MM cells preferentially expressed BCMA and TACI (47, 54, 56, 125). In contrast to NHL, B-lymphomas in the central nervous system exhibited a heterogeneous phenotype, with variable expression of BAFF-R, TACI and BCMA (24). Malignant B cells isolated from patients with B-CLL

(49, 121, 126), NHL (50, 122, 123), HL (54), MM (47, 56) and WM (124) were all capable of responding to the stimulatory effects of BAFF and/or APRIL *in vitro*, demonstrating expression of functional receptors.

A possible role of BAFF and APRIL in human B cell malignancies may lie in their aberrant expression and production. First, expression of BAFF and APRIL is greater in B-CLL (49, 121, 127), NHL (33, 50) and MM (47, 56, 126) than in normal B cells. Second, levels of serum BAFF and APRIL are elevated in patients with NHL (122, 123), B-CLL (121, 127) and WM (124). Notably, those NHL patients with the highest levels of serum BAFF/APRIL had reduced survival and poorer prognosis than those with lower levels (123, 128). A complementary mechanism whereby BAFF may contribute to the development of some lymphomas came from the observation that EBV infection of primary human B cells induces expression of both BAFF and APRIL (32). The significance of this is that several B cell malignancies develop following immortalisation of normal human B cells by EBV (129). Interestingly, patients with SjS are predisposed to B cell malignancies, particularly NHL (99). Because patients with NHL have increased levels of serum BAFF (122, 123), it is tempting to speculate that increased levels of serum BAFF in SjS contributes not only to the development of autoimmune manifestations of this syndrome, but also to B cell malignancies frequently observed in these patients (99). Third, the microenvironment of the malignancy may improve survival and persistence of malignant B cells. For instance, BAFF was detected in the BM of myeloma patients at higher levels than that observed for samples of normal BM (47); cells infiltrating tissue-restricted NHL and HL express and secrete high levels of BAFF/APRIL which promotes the viability of the malignant B cells (54, 130); nurse-like cells, which can be isolated from B-CLL patients, contain abundant amounts of BAFF and APRIL and improve the survival of B-CLL cells (126); and tumour-infiltrating neutrophils are the main source of APRIL in cases of NHL (128).

BAFF protects normal B cells from apoptosis by modulating expression of members of the bcl-2 family of molecules (reviewed in (18, 19)). This is also likely to be the mechanism by which BAFF and APRIL

preserve the viability of malignant B cells. *In vitro* exposure of B cells from patients with NHL, HL, B-CLL or MM to BAFF or APRIL increased expression of the pro-survival proteins bcl-2, mcl-1 and bcl-xL and decreased the pro-apoptotic regulator bax (50, 54, 56). Similarly, survival, and expression of pro-survival proteins, were reduced when malignant B cells were cultured in the presence of BAFF antagonists (33, 49, 54, 56). Taken together, it is possible that aberrant and/or excessive production of BAFF or APRIL by malignant B cells themselves (ie autocrine) or by supporting cells present within the microenvironmental niche occupied by the malignant B cells (ie paracrine) may facilitate their growth and survival. Consequently, blocking interactions between BAFF and APRIL and their receptors may be a feasible therapeutic approach for treating some B cell malignancies.

TACI mutations in Immunodeficiency

The central role of the BAFF family of molecules in regulating B cell survival and function has led naturally to an examination of their place in human humoral immunodeficiencies. This endeavour has concentrated on two poorly understood adult immunodeficiency disorders: common variable immunodeficiency (CVID) and IgA deficiency (IgAD). CVID is the most common adult immunodeficiency requiring treatment. It is a heterogeneous disorder manifest by hypogammaglobulinaemia resulting in recurrent upper and lower respiratory tract and gastrointestinal infections (131, 132). Most cases occur sporadically, but 10-20% have a family history; kindreds with both autosomal dominant and recessive genetics have been described. About one-third of patients will have lymphoproliferation (lymphadenopathy, splenomegaly) as part of their presentation, and there is a heightened prevalence of autoimmunity. IgAD is a common immunodeficiency, accounting for about 1:600 patients in the Western world, and is characterised by low to absent serum and mucosal concentrations of IgA. The condition is frequently asymptomatic, but those who develop infections typically display a similar spectrum to CVID (131, 132).

The last decade has seen the discovery of a number of well-defined genetic defects that account for CVID in very small numbers of patients. These include deficiency of ICOS in nine reported cases, most likely involving common ancestry (133, 134), and deficiency of CD19 in five other patients (135, 136) .

There are also patients with 'leaky' mutations in *Btk* (137, 138) and *SH2D1A* (139-141), who present similarly to CVID but are in fact atypical cases of X-linked agammaglobulinaemia and X-linked lymphoproliferative disease, respectively. On the other hand, the vast majority of CVID patients remain unexplained genetically and pathophysiologically, including those with a positive family history.

Genetics of TACI mutation in humoral immunodeficiencies

In 2005, two groups independently examined cohorts of patients with CVID or IgAD for mutations in *TNFRSF13b*, which encodes TACI (142, 143). Mutations were found in 5-10% of patients with familial and sporadic CVID (Fig 1), and included homozygous and heterozygous cases. Of 162 CVID patients analysed by Salzer et al. (142), 3/27 familial and 10/135 sporadic cases had *TNFRSF13b* mutations; all patients had low IgG levels at diagnosis, whilst most also had low IgA and about half had low IgM levels. Pneumococcal antibody responses were generally poor. B-cell numbers were preserved, but there was a reduction in memory B cells. Lymphoproliferation and autoimmunity were frequent in these patients, although these features are also common in unselected cohorts of patients with CVID (131, 132). These findings were largely supported by Castigli et al. (143), who documented *TNFRSF13b* mutations in 4/19 CVID patients (3 homozygous and one compound heterozygote), all of whom had reduced IgG and IgA levels, normal IgM, and poor pneumococcal antibody responses. A positive family history was noted in three of these cases, the pedigree also showing family members harbouring identical TACI mutations that manifest phenotypically as either CVID or IgAD. Furthermore, one of the 16 patients with IgAD also harboured a TACI mutation, with perfect segregation with IgAD in that family. No TACI mutations were found in 50 control subjects.

The six mutations uncovered in these two studies either had, or were predicted to have, critical effects on TACI function. The most frequent mutation, C104R, altered a cysteine residue essential for protein folding and thus abolished BAFF binding. A181E changed a neutral amino acid to a charged residue in the transmembrane region, S144X and 204InsA abolished protein expression, R202H was predicted to alter TACI interaction with CAML, and S194X resulted in a truncated intracellular domain due to the introduction of a premature stop codon.

These genetic studies were expanded by both groups in follow-up studies published in 2007 (144, 145). The first report included up to 852 CVID patients in cohorts spanning Sweden, Germany and the USA (144). *TNFRSF13b* was found to be a highly polymorphic gene, with nucleotide differences frequently detected in normal subjects, including the same mutations previously associated with CVID (Figure 2). Only C104R and A181E were significantly associated with CVID, although in certain populations (eg Swedish patients for C104R and German patients for A181E), the association did not reach significance. 204InsA was rare, being found only in two CVID patients and no controls. The report also studied 474 Swedish IgAD patients, with only R202H being found more frequently than in the control population; however family studies showed no segregation between this mutation and IgAD. A similar study of 212 CVID patients and 124 controls by Castigli et al. (145) largely confirmed these findings, with only C104R and A181E being significantly associated with CVID, although they reported a number of rare TACI alleles that were found only in CVID patients. All 34 patients with IgAD had wild type *TNFRSF13b*, and taken together with the Swedish study, essentially excluded a role for TACI in this condition.

Most recently, another expanded CVID cohort (which included some patients previously reported in (144)) was studied (146). *TNFRSF13b* mutations were found in 50/602 (6%) CVID patients compared with 12/589 (2%) of controls. Biallelic mutations were present in 11 subjects, all of whom had CVID, whereas none of the controls had biallelic mutations. C104R was significantly associated with CVID, but this was not found for A181E. Again, a number of rare *TNFRSF13b* mutations were only found in CVID patients. Six families of CVID patients with heterozygous *TNFRSF13b* mutations were studied, and three showed segregation with CVID whilst the remainder did not, suggesting that in the heterozygous state, the C104R mutation might be acting as a disease modifier rather than being directly causative.

Taken together, the conclusions from these studies are threefold. First, homozygous *TNFRSF13b* mutations have only been found in patients with CVID. Second, some rare heterozygous *TNFRSF13b* mutations have also so far only been found in CVID, leaving open the possibility that these may truly be causative in the heterozygous state. Third, there is a significant association between C104R and possibly

A181E with CVID, albeit with incomplete penetrance, such that the mutation is more frequent in CVID but may also be found in healthy subjects.

Functional implications of TNFRSF13b mutations in B-cell responses

These genetic studies immediately posed questions as to the functional changes that accompany alterations in TACI structure that account for adult-onset loss of Ig production, the hallmark of CVID. Models to answer this question must not only explain the physiology of complete loss of TACI function, as is the case in patients with biallelic mutations, but also the weaker dominant negative effect in heterozygotes.

Complete loss of TACI function has been studied in at least two independently-generated strains of gene-targeted mice (65, 147, 148). TACI-deficient mice have normal B cell development, yet B-cell numbers were elevated and proliferative responses were increased, with one strain showing a propensity for the development of B-cell lymphoma. These findings implied a negative regulatory role for TACI (65, 147, 148). Such a role was supported by studies in which an agonistic anti-TACI mAb was used to stimulate human naïve B cells concomitantly activated with CD40L, BAFF or anti-BAFF-R (149). TACI activation consistently resulted in decreased proliferation and IgG production by the activated B cells. Furthermore, TACI expression on B cells increased during activation, leading the authors to speculate that TACI might function as a delayed brake on B-cell function analogous to the role of CTLA4 on T cells (149).

On the other hand, a positive role for TACI in type II T-cell independent Ab responses has also been demonstrated in $TACI^{-/-}$ mice, which have poor pneumococcal vaccine responses and low IgA and IgM, but normal IgG, levels. There is also an established role for BAFF and APRIL in isotype switching by human and murine B cells (22, 28, 29, 89, 91), although redundancy in the BAFF/APRIL receptor system makes specific roles for each receptor in human B-cell differentiation difficult to isolate. Some progress has been made by Sakurai et al. (92), who explored the differential roles of the two main APRIL receptors on mature B cells, TACI and HSPG. They first demonstrated that APRIL bound equally to each of these receptors, then examined responses of naïve B cells to stimulation with CD40L, BAFF and

APRIL in the presence of (i) siRNA to diminish TACI expression and/or (ii) heparitinase to eliminate HSPG binding. Engagement of TACI in isolation was insufficient to increase proliferation and Ig production by B cells. However, abrogation of TACI expression increased B-cell responses to BAFF, consistent with a negative regulatory role for TACI, as demonstrated in earlier experiments. It was shown further that either engagement of HSPG by APRIL, or BAFF-R by BAFF, was sufficient for IgG production and proliferation, but simultaneous stimulation of both TACI and HSPG was necessary for IgA production, such that loss of either abrogated this response (Figure 3). Based on these studies, one would expect that in vivo loss of TACI function could result in impaired IgA production (although BAFF-R stimulation could potentially compensate for this loss), whilst there should be minimal effect on IgG production and B-cell proliferation, if not potential enhancement (in the case of BAFF) resulting from loss of negative regulation. This would be consistent with findings from studies of murine B cells which revealed that TACI is predominantly responsible for eliciting CSR to IgA in response to BAFF and APRIL (91).

In vitro studies of B-cell function in human homozygous TACI mutants have been limited. Original studies demonstrated that the C104R, but not A181E, mutation abolished BAFF binding when expressed in the human embryonic kidney cell line 293, although APRIL binding could not be studied due to the high expression of HSPG by these cells (143). EBV-transformed B-cell lines from TACI mutant homozygotes (C104R, S144X) failed to bind APRIL in a staining system that neutralised HSPG binding. Not surprisingly, B cells isolated from TACI mutant homozygotes failed to respond to APRIL stimulation in terms of B-cell proliferation and CSR (142), again in the setting of neutralisation of HSPG. Thus, the lack of functional TACI expression seems to abrogate the positive effects of APRIL in the absence of HSPG, but the effect of homozygous mutations on the negative regulatory effects mediated by TACI remains to be determined, as do the functional changes in the setting of intact HSPG binding.

In heterozygotes, expression of a mutant surface protein need not necessarily alter cellular response to ligand, which could simply bind to wild-type receptors, notwithstanding the possibility of

haploinsufficiency. However Garibyan et al. (150) demonstrated that murine TACI assembled into trimers within the endoplasmic reticulum, independent of ligand binding, and that C104R mutant TACI was co-expressed in a trimeric receptor complex with wild type TACI. Thus, in the heterozygous state, theoretically only one in eight trimers would be fully functional. Ligand binding studies demonstrated normal APRIL binding to EBV-transformed B-cell lines from TACI heterozygotes (142, 146), although others found binding was variable even between patients with the same mutation (151). Garibyan et al. demonstrated normal BAFF binding to the hybrid mutant C104R/wt TACI heterotrimer (150), but there was a reduction in NFκB signalling in response to BAFF, consistent with a dominant negative effect. These findings are reminiscent of the effects of mutations in the gene encoding human CD95, which demonstrated a requirement for pre-association of CD95 monomers into trimeric structure and that such assembly was compromised by heterozygous mutations in CD95 (152).

Given that a degree of receptor dysfunction accompanies the heterozygous state, one might therefore expect that functional studies in heterozygotes might be similar to homozygous deficiency. Such studies have generated conflicting results, which in general do not seem to reflect in vitro studies in normal B cells. Early reports demonstrated that B cells from TACI heterozygotes failed to produce IgG or IgA in response to APRIL, but also enigmatically failed to produce IgA in response to BAFF (143). On the other hand, B cells from CVID patients themselves often display impaired function in vitro, as demonstrated by Zhang et al. who showed that whilst B cell proliferation and isotype switching is variably impaired in C104R heterozygotes, this was not substantially different from CVID patients with wild-type TACI (151). Furthermore, family members harbouring heterozygous C104R mutations but without CVID showed normal B cell responses! This study (151) has important implications in terms of choosing appropriate controls for functional analysis, although it did not use purified B cell cultures and relied on relatively insensitive proliferation assays.

Despite progress in the field of TACI mutation and CVID, the area continues to generate controversy. There seems little doubt that homozygous TACI mutations result in CVID (146), but there is also strong association in the heterozygous state particularly with the C104R and A181E mutations. Biochemical

and functional data showing that the heterozygous state also impairs TACI signalling is consistent with this association (150, 151). Although functional studies support a possible role for *TNFRSF13b* mutations in dysregulated CSR, they fall far short of explaining the CVID phenotype, given the redundancies in the BAFF/APRIL receptor system, since studies in normal B cells suggest that BAFF-R signalling generally should be able to compensate for loss of TACI function, at least in terms of signals provided by BAFF. Furthermore the functional effects of *TNFRSF13b* mutation in the setting of an intact HSPG receptor have not been studied. However the role of TACI in CSR in normal human B cells *in vivo* seems minor in comparison to BAFF-R and HSPG, studies of which show a non-redundant role only in IgA production, whilst the genetic association with IgAD has been largely refuted. If defects can be demonstrated, the link between TACI and CVID may lie in differential expression of BAFF versus APRIL in specific microenvironments, which may affect CSR or B-cell or PC longevity. Murine and human studies imply that TACI has predominantly a negative regulatory role in B-cell function, hence loss of function could result in B-cell over-activity, possibly explaining the propensity of affected CVID patients to develop lymphoproliferation, although it is unclear whether this is any more prevalent in CVID patients who have TACI mutations compared with those with wild-type TACI. Finally, the observation that B cells from CD40L deficient patients with hyper-IgM syndrome fail to undergo CSR *in vivo* despite an intact BAFF/APRIL system (reviewed in (153)) would suggest either that the latter pathway is of relatively minor importance, or that it is only relevant to B cells at a stage distal to CD40L activation. Further studies on specific B cell subsets from heterozygous and homozygous C104R TACI mutant patients, along with carefully chosen controls, are needed to resolve these conflicting data.

Conclusions

It is well established that molecules expressed and produced by stromal cells, $CD4^+$ T cells, myeloid cells (eg DC), and FDC are essential initially for the development of pluripotent stem cells into mature naïve B cells, and subsequently for their differentiation into effector cells, such as memory and Ig secreting cells. The last decade has seen an explosion in our understanding of the fundamental roles of

BAFF, APRIL and the receptors BAFF-R, TACI, BCMA and HSPG in these processes. It is now clear that specific interactions between these receptor/ligand pairs have important roles in B-cell development, CSR, and the maintenance of Ig-secreting cells. We have also gained an enormous appreciation that dysregulated signalling through these receptor/ligand complexes may underlie the development of a diverse array of human diseases, including autoimmunity, haematological malignancies and immunodeficiency. However, these studies have also highlighted the complexities of the interactions between these molecules, and many questions and issues remain unresolved. These include: the specific role of BCMA and HSPG; the apparent paradoxical ability of TACI to deliver both positive and negative signals to activated B cells; the signals that modify and regulate expression of receptors for BAFF and APRIL, as well as the production of these cytokines themselves; the exact mechanisms whereby aberrant interactions between these molecules contribute to the development of human diseases; and whether or not BAFF has the same role in the development of human B cells as it does in models of murine B-cell ontogeny. These unresolved issues, together with the targeting of the BAFF/APRIL/receptor axis as a means of treating autoimmunity and B-cell malignancy (78, 80, 154-156), will ensure a continued focus on the biology and regulation of function of members of the BAFF family on immune responses for at least the next decade.

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Table I: Induction and amplification of class switch recombination and Ig secretion by BAFF and APRIL

Ig isotype	Induced by	Enhanced by	Secreted in response to:	Source of BAFF/APRIL	Reference
IgG1, IgG2	• BAFF, APRIL	• IL-4, IL-10	*Total IgG*: • BAFF/anti-Ig ± IL-15 • APRIL/anti-Ig ± IL-15	DC stimulated with • CD40L • IFN-α • IFN-γ Monocytes stimulated with • LPS • IFN-α • IFN-γ	(22, 29)
IgG3	• BAFF/IL-4 • APRIL/IL-4 • BAFF/IL-10 • APRIL/IL-10	ND			
IgG4	BAFF + IL-4 APRIL + IL-4	ND			
IgA1, IgA2	• BAFF • APRIL	• TGF-β	*Total IgA*: • BAFF/anti-Ig ± IL-15 • APRIL/anti-Ig ± IL-15		
IgE	• BAFF/IL-4 • APRIL/IL-4	ND	ND		
IgA2	• APRIL/IL-10	• TLR5 ligand (Flagellin)	APRIL, IL-10, • Flagellin	• intestinal epithelial cells stimulated with TLR5 ligand ± TSLP	(29)
IgG1, G2, G3	• CpG (TLR9 ligand)	• IL-10	*Total IgG* • BAFF	• IFN-α stimulated DC	(88)
IgG1, IgG2, IgG3, IgA1, IgA2, IgE	• EBV	• BAFF • APRIL	ND	• EBV-infected B cells	(32)
IgG1	• TLR3 ligand (poly I:C; ds RNA mimic)	• IL-10	*Total IgG and IgA* • poly I:C/ IL10/BAFF	• TLR3-stimulated plasmacytoid and mucosal DC	(89)

ND – not done

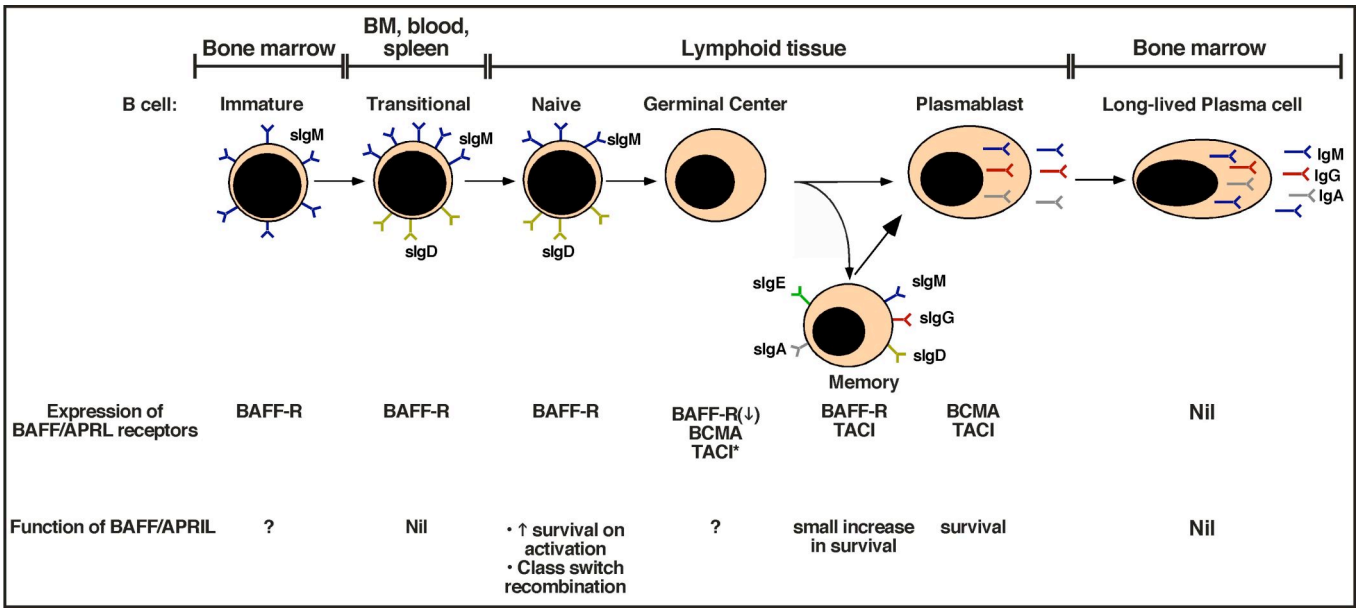

Figure 1: Expression of receptors for BAFF and APRIL, and their functions, during human B cell development and differentiation

The expression of BAFF-R, TACI and BCMA at the different stages of B cell development (immature → transitional B cell) and differentiation (mature B cell → GC → memory B cell/PC), as well as the function of BAFF/APRIL at distinct stages of human B-cell maturation, are indicated.

* indicates uncertainty, since GC B cells have been reported to lack or express TACI

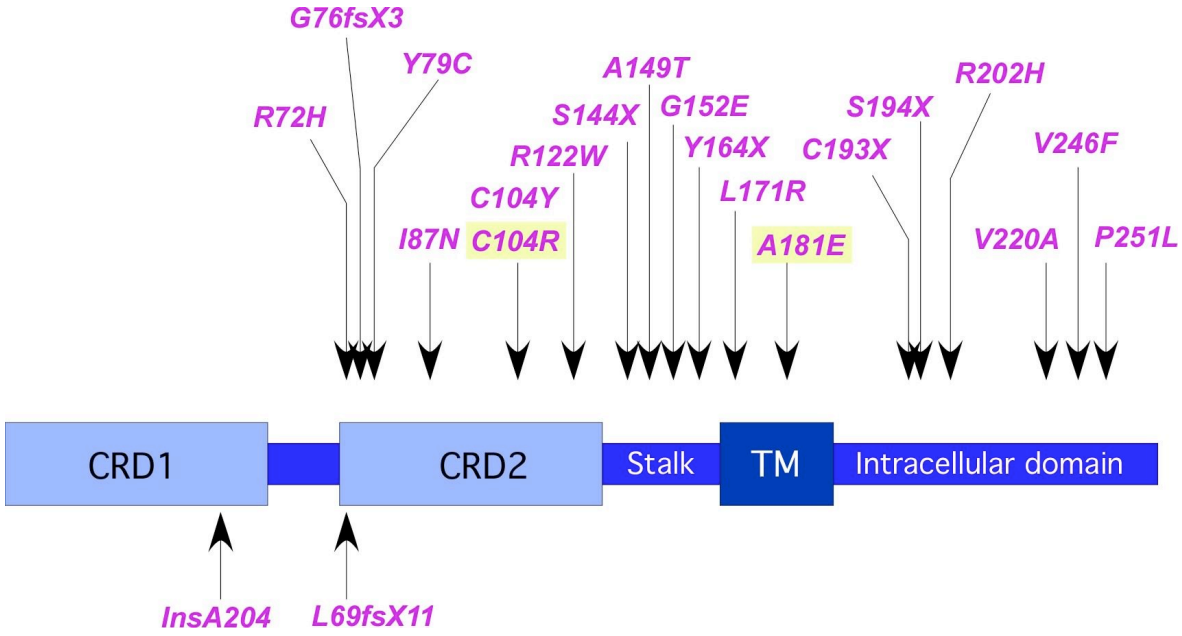

Figure 2. Mutations within the TNFRSF13B gene that encodes TACI

Missense mutations affecting the affecting the open reading frame of TACI are shown. The two most closely associated with disease highlighted.

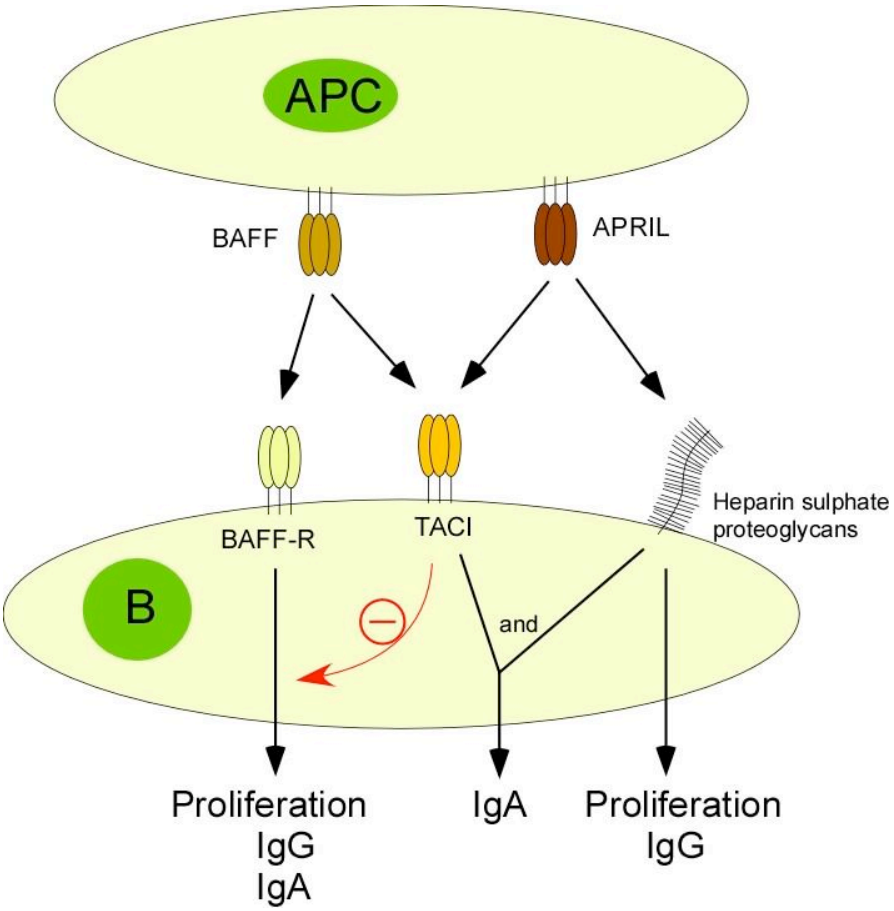

Figure 3. Relative roles of BAFF-R, TACI and HSPG in B-cell isotype switching

This model is based on experiments reported by Sakurai et al (92).