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Cytokine & Growth Factor Reviews 19 (2008) 263–276
Cytokine Growth Factor Reviews
www.elsevier.com/locate/cytogfr

TACI, an enigmatic BAFF/APRIL receptor, with new unappreciated biochemical and biological properties

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Abstract

BAFF is a B cell survival factor that binds to three receptors BAFF-R, TACI and BCMA. BAFF-R is the receptor triggering naïve B cell survival and maturation while BCMA supports the survival of plasma cells in the bone marrow. Excessive BAFF production leads to autoimmunity, presumably as the consequence of inappropriate survival of self-reactive B cells. The function of TACI has been more elusive with TACI$^{-/-}$ mice revealing two sides of this receptor, a positive one driving T cell-independent immune responses and a negative one down-regulating B cell activation and expansion. Recent work has revealed that the regulation of TACI expression is intimately linked to the activation of innate receptors on B cells and that TACI signalling in response to multimeric BAFF and APRIL provides positive signals to plasmablasts. How TACI negatively regulates B cells remains elusive but may involve an indirect control of BAFF levels. The discovery of TACI mutations associated with common variable immunodeficiency (CVID) in humans not only reinforces its important role for humoral responses but also suggests a more complex role than first anticipated from knockout animals. TACI is emerging as an unusual TNF receptor-like molecule with a sophisticated mode of action.

Keywords: BAFF; APRIL; TACI; BAFF-R; BCMA; CVID; TLR; Autoimmunity; Signalling; B cell activation; Plasmablast

1. Introduction

B cell Activating Factor from the TNF family (BAFF, also termed BLyS, and TNFSF13b) has been identified almost a decade ago and extensive work on this cytokine has led to important new discoveries defining the mechanisms governing B cell survival, maturation and tolerance [1–4]. The development of several mutant mouse models in this system has established that interaction of BAFF with its BAFF receptor (BAFF-R, BR3, TNFRSF13C) is the driver of B cell survival and maturation [1–4]. In addition, major progresses have been made identifying the signalling events associated with BAFF-R-mediated B cell survival [1–4]. BAFF binds to two other receptors, transmembrane activator and calcium-modulator and cyclophilin ligand (CAML) interactor (TACI, TNFRSF13B) and B cell maturation antigen (BCMA, TNFRSF17) also recognizing another TNF-like ligand: A proliferation-inducing ligand (APRIL, TNFSF13) [1–4] (Fig. 1). These two receptors have more restricted functions compared to BAFF-R, with TACI controlling T cell-independent B cell antibody responses, isotype switching and B cell homeostasis, whereas the function of BCMA is mostly limited to the survival of plasma cells residing in the bone marrow [1–4].

Excessive BAFF production in BAFF transgenic (Tg) mice leads to the development of severe autoimmune disorders similar to systemic lupus erythematosus (SLE) and Sjögren's syndrome (SS) [5,6]. Moreover, elevated serum

Abbreviations: APRIL, A proliferation-inducing ligand; BAFF, B cell activating factor of the TNF family; BCMA, B cell maturation antigen; CSR, class switch recombination; CVID, common variable immunodeficiency; HSPG, heparan sulfate proteoglycans; SS, Sjogren's syndrome; TACI, transmembrane activator and calcium-modulator and cyclophilin ligand (CAML) interactor; TI-2, T cell type 2.

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doi:10.1016/j.cytogfr.2008.04.006

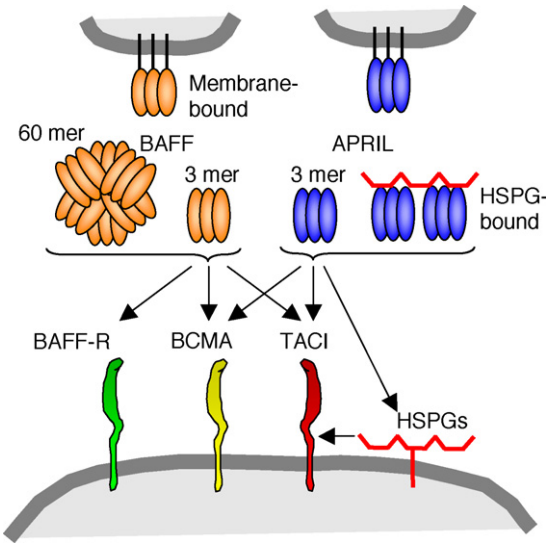

Fig. 1. Ligand–receptor interactions in the BAFF/APRIL system. The figure shows the various forms of BAFF and APRIL that differ in their multimerization status.

BAFF levels in humans also correlate with the development of several autoimmune conditions [7]. Since ablation of BAFF-R prevents B cell maturation [1–4], it has always been difficult to properly address the role of this receptor in mature B cell tolerance, but it was postulated that excessive BAFF favoured survival and escape of auto-reactive B cells during B cell maturation. How TACI provides positive signals driving T-independent B cell response [8,9] and survival of activated B cells and plasmablast [10], but also delivers negative signals suppressing B cell activation [8,9,11] has been a long-standing mystery. In this review, we will detail the latest exciting and intriguing aspects of the biology of TACI, such as the specific ligand requirements necessary to trigger signals through this receptor, its role in B cell function, macrophages, autoimmunity and cancer, its relationship with the innate activation mechanisms as well as its emerging implication in human immunodeficiency.

2. The BAFF/APRIL system

2.1. General ligand–receptor interactions

BAFF and APRIL are membrane-bound ligands that can be processed to soluble forms by proteolytic cleavage [12,13]. Soluble forms of these ligands contain the C-terminal, homotrimeric TNF-homology domain that mediates binding to receptors. BAFF contains a 10 amino acid-long loop that protrudes out of this domain and that serves to assemble twenty soluble BAFF 3-mers into a virus-like particle [14]. In contrast to BAFF, APRIL forms trimers but not higher order structures. It however contains a basic surface that is absent in BAFF and that can mediate interaction with proteoglycans [15,16].

As mentioned above, BAFF binds to three receptors of the TNF-R family, TACI, BCMA and BAFF-R (reviewed in [17]) (Fig. 1). TACI binds to APRIL and BAFF with high affinity, and also interacts with heparan sulfate proteoglycans (HSPGs) [18]. BCMA binds to APRIL with high affinity, and to BAFF with a lower affinity. The low affinity of monomeric BCMA for BAFF is overcome by an avidity effect when BCMA is dimerized [19], raising the question of whether APRIL only or both APRIL and BAFF can act as agonists for membrane-bound BCMA *in vivo*. Finally, BAFF-R binds to BAFF only, but with high affinity [19,20]. There is an exception with regard to the strict specificity of BAFF-R binding to BAFF: mouse BAFF-R weakly binds to mouse (but not human) APRIL, and although this may be of no physiological relevance, high experimental doses of recombinant soluble mouse BAFF-R may inhibit mouse APRIL in addition to BAFF [21].

HSPGs are glycoproteins that can be either cell-associated or part of the extracellular matrix. Their glycan portion is rich in negatively charged sugars, such as iduronic acid or sulfated sugars, enabling them to bind a variety of positively charged basic proteins, such as growth factors or chemokines. This binding can display some specificity, possibly related to the spacing and density of charged residues in the interacting pairs. TACI and APRIL do interact with HSPGs, such as syndecan-1 on plasma cells [15,16,18].

2.2. Signalling through BAFF-R and TACI

BAFF signalling is strongly associated with the survival of peripheral B cells at various stages of differentiation. The signalling pathway downstream of BAFF was elucidated using B cell-specific mutant mice and revealed a central implication of both canonical and non-canonical NF-κB pathways and their regulation by TRAF proteins (Table 1, Fig. 2). A hallmark of BAFF signalling in B cells is the NIK- and IKKα-dependent processing of NF-κB2 from the p100 to the p52 subunit [22–24]. This is of likely relevance *in vivo* as the B cell compartments of B cell-specific NIK-deficient (aly/aly), IKKα-null and NF-κB2-null mice are reduced, and as B splenocytes from these mice are unresponsive to BAFF and present impaired survival *ex vivo* [22,25,26]. Mice with basal IKKα activity but impaired responses to further activation of this kinase (IKKα-AA) display an intermediate phenotype, with B cells partially unresponsive to BAFF [22,26,27]. Conversely, mice with constitutive expression of p52 have more B cells [28]. Taken together, these data indicate that the non-canonical NF-κB pathway is a key downstream element of BAFF signals. However, the canonical NF-κB pathway can also mimic BAFF signalling, as inactivation of NEMO in B cells, and to a lesser extent NF-κB1, also leads to B cell deficiency, whereas expression of constitutively active IKKβ enlarges the peripheral B cell compartment and promotes survival of B cells *ex vivo*, which do not display further survival increase in response to BAFF

[26,29] (Table 1). These results suggest that constitutive activation of the canonical NF-κB pathway can mimic BAFF signalling, in part through up-regulation of key players of the non-canonical pathway (Fig. 2).

BAFF-mediated survival involves NF-κB-dependent up-regulation of anti-apoptotic Bcl-2 family members, inhibition of the pro-apoptotic Bcl-2 family member Bad by the NF-κB-dependent kinase Pim-2, and prevention of PKCδ translocation in the nucleus (Table 1, Fig. 2). Importantly, NF-κB up-regulates integrins required for the localisation of B cells in the marginal zone and further contributes indirect survival signals through integrin-mediated Akt activation [26]. This is in line with the observation that BAFF signals or constitutive NF-κB activation lead not only to B cell survival, but also to the expansion of marginal zone B cells, while the mere blockade of apoptosis in the absence of BAFF signals rescues follicular but not marginal zone B cells [5,29–32].

BAFF-R interacts exclusively with TRAF3 through an atypical TRAF-binding sequence, whereas TACI interacts with several TRAFs, including TRAF3. TRAF3 acts as a negative regulator of non-canonical NF-κB by maintaining low levels of cellular NIK [33]. TRAF2 and Act1 may promote the inhibitory activity of TRAF3, whereas BAFF-R and possibly TACI relieve it [31,34]. Act1 is a TRAF3-interacting protein induced in response to LPS, CD40L and possibly BAFF signalling, and that is believed to act as a negative feedback regulator of non-canonical NF-κB [34]. How BAFF-R inactivates TRAF3, and how TRAF-3 inactivates NIK at the molecular level is currently poorly understood.

BAFF-R mainly signals non-canonical NF-κB [35], but also activates canonical NF-κB with slow kinetics and weak amplitude, as convincingly demonstrated by comparing Bcl-2 transgenic B cells expressing BAFF-R or not [36]. TACI is a strong activator of canonical NF-κB, but also triggers p100 processing [37]. Most studies looking at BAFF-mediated survival have used B splenocytes, and although BAFF-R probably accounts for most of the survival outcome, TACI also contributes some of it. Indeed, TACI and BAFF-R-mediated signalling in murine B splenocytes lead to similar responses, including survival and MHC-class II up-regulation [38], in line with the idea that signalling through these two receptors converge at some level. In the future, monocytes may represent a good model for the study of TACI signalling events, as they do not express BAFF-R and apparently survive in response to BAFF in a TACI-dependent manner [37].

Besides its ability to promote cell survival, TACI was also reported to promote negative signals in B cells or B cell lines, especially in response to anti-TACI monoclonal antibodies, including inhibition of proliferation and weak induction of apoptosis [11,39]. The signalling events leading to B cell inhibition were not investigated. In summary, current evidence indicate that BAFF supports the B cell compartment *in vivo* through BAFF-R-mediated de-repression of the NF-κB pathway. TACI may activate B cell survival in a similar manner or trigger B cell inhibition through unknown mechanisms, possibly in a cell- or ligand-dependent context.

2.3. The case of TACI: ligand binding versus signalling

APRIL was reported to co-stimulate B cells in conjunction with BCR stimulation [40], a result that we could only reproduce with cross-linked APRIL [16], yielding the first hint that TACI may respond to multimeric ligands. Similarly, while studying BAFF-induced monocyte survival, Chang et al. reported that TACI responded to some commercial BAFF preparations (presumably aggregated), but not to others that were however able to support B cell survival [37]. Further studies established that BAFF-R and TACI differ in their requirements for ligand oligomerization in order to transmit productive signals. BAFF-R is activated by all forms of BAFF, whereas TACI specifically requires membrane-bound BAFF, cross-linked BAFF or cross-linked APRIL, or BAFF 60-mer in order to signal, but is unresponsive to soluble BAFF 3-mer [38]. This situation is reminiscent of TNF and its receptors: TNF-R1 responds to all forms of TNF, whereas TNF-R2 only responds to membrane-bound (or cross-linked) TNF [41]. Similar to TNF-R2, Fas and CD40 are also preferentially activated by membrane-bound, but not soluble trimeric ligands [42,43]. Interestingly, plasmablasts down-regulate BAFF-R and become unresponsive to BAFF 3-mer [38,44], but survive in response to oligomerized forms of BAFF or APRIL in a TACI- and possibly BCMA-dependent manner [38]. Cells expressing membrane-bound BAFF or APRIL may trigger TACI or BCMA in target B cells, as could be the case in the bone marrow [45–47]. Soluble APRIL bound to proteoglycans may also be able to perform this function [48], and BAFF 60-mer might represent a TACI activator with a long range of action. BAFF 60-mer was detected in the plasma of BAFF Tg mice and TACI$^{-/-}$ mice, but not in healthy wild type mice [38]. The relative contribution of these various ligands to TACI activation *in vivo* is currently unexplored. In summary, although TACI binds to BAFF and APRIL, it is only activated when these ligands are multimerized. TACI provides positive signals in response to multimeric ligands in activated B cells and in plasmablasts that have become unresponsive to BAFF-R.

3. The biological role of TACI

3.1. TACI expression

TACI is mainly expressed on B cells, especially on activated B cells, but early data suggested that TACI was also expressed on a subset of T cells [49] and two separate studies have confirmed a strong TACI signal not only in the spleen but also in the thymus by Northern blot analysis

Table 1
Implication of the NF-kB pathway in BAFF-mediated survival effects

Genetic modification	Type of experiment	B cell phenotype (T1, T2, FO, MZB, B1)	Effect on NF-κB activation	*Ex vivo* survival and response to BAFF	Remarks	Refs
NEMO$^{-/-}$ in all B cells (Mb-1Cre)	*In vivo* phenotyping	Block at T1 transitional stage, no MZB, no B1	Canonical NF-κB blocked	Not determined	Slightly milder phenotype than BAFF-R$^{-/-}$	[29]
BAFF-R$^{-/-}$	*In vivo* phenotyping	Block at T1 transitional stage, no MZB. B1 present	Not determined	Not determined	Less B cells, but still able to mount humoral responses to TD antigens. Reduced CD21 and CD23 expression (not as much as in BAFF$^{-/-}$)	[110]
Bcl2 Tg (in B cells)	BAFF stimulation *ex vivo*	B cell hyperplasia	Normal	Not determined	BAFF induces phosphorylation of IkBα with slow kinetics (12–24 h) and increases p100 processing	[29]
Bcl2 Tg × BAFF-R$^{-/-}$	BAFF stimulation *ex vivo*	Presence of mature B cells. No MZB.	No activation of canonical and non-canonical NF-κB in response to BAFF	Not determined	No phosphorylation of IkBα, no increased p100 processing in response to BAFF	[29,110]
Knock-in IKKβ-EE (constitutively active) in B cells (CD19-Cre)	*In vivo* phenotyping; BAFF stimulation *ex vivo*	Hyperplasia of mature B cells subsets (2-fold), including MZB (5-fold). (B1 not shown)	Canonical NF-κB constitutively active	Enhanced survival *ex vivo*. BAFF only slightly increases survival	Higher but still regulated expression of CD21 and CD23. Higher expression of p100, RelB, BclXL	[29]
Knock-in IKKβ-EE in B cells (CD19-Cre) × BAFFR$^{-/-}$	*In vivo* phenotyping	Normal mature B cells subsets, including MZB (with correct expression of CD21, CD23)	Canonical NF-κB constitutively active	Enhanced survival *ex vivo*. Unresponsive to BAFF	PKCδ translocation in the nucleus and cell death is inhibited (via Bcl2 family members)	[29]
IKKα$^{-/-}$. Bone marrow radiation chimera	*In vivo* phenotyping	Less mature B cells (IgD+, IgMlow) in spleen and LN (4–6-fold)	Non-canonical NF-κB impaired (little p100 processing)	Not determined	Reduced number of mature B cells. Correlates with increased cell death	[22]
Knock-in IKKα-AA (non-activable). Radiation chimera	*In vivo* phenotyping	Slightly less mature B cells (IgD+, IgMlow) in spleen	Non-canonical NF-κB partially impaired (p100 accumulates)	Not determined	Milder phenotype than IKKα$^{-/-}$ (because of basal IKKα activity (?))	[22]
Knock-in IKKα-AA. Bone marrow chimera in B cell-deficient mice (μMT)	*In vivo* phenotyping; immunization	Normal B cell number. Little CD138+ plasma cells in the spleen. No GL7+ GC B cells	Non-canonical NF-κB impaired	Not determined	Diminished recall responses and affinity maturation. Impaired T-B collaboration. Normal anti-CD40-induced proliferation	[27]
NIK mutation (aly/aly). Bone marrow radiation chimera	*In vivo* phenotyping; immunization	Small B cell follicles in the spleen. No MZB. Impaired GC formation	Non-canonical NF-κB impaired (no p100 processing)	Not determined	No switch to IgG	[24,25]
Wild type	*Ex vivo* B splenocytes	Normal	Normal	Normal survival. Responsive to BAFF	p100 processing. BclXL and A1 and Pim-2 induced in response to BAFF	[26]
IKKα$^{-/-}$. Bone marrow radiation chimera	*Ex vivo* B splenocytes		Non-canonical NF-κB impaired	Impaired survival *ex vivo*. Unresponsive to BAFF	No p100 processing. BclXL and A1 induced. Pim-2 not induced	[26]

Table 1 (*Continued*)

Genetic modification	Type of experiment	B cell phenotype (T1, T2, FO, MZB, B1)	Effect on NF-κB activation	*Ex vivo* survival and response to BAFF	Remarks	Refs
NF-κB2$^{-/-}$	*Ex vivo* B splenocytes		Non-canonical NF-κB impaired	Impaired survival *ex vivo*. Unresponsive to BAFF	No p100 (−/−). BclXL and A1 induced. Pim-2 not induced	[26]
Knock-in IKKα-AA (non-activable).	*Ex vivo* B splenocytes		Non-canonical NF-κB partially impaired	Mildly impaired survival. Partially responsive to BAFF	Partial p100 processing. BclXL and A1 and Pim-2 induced	[26]
NF-κB1$^{-/-}$	*Ex vivo* B splenocytes		Canonical NF-κB impaired	Mildly impaired survival *ex vivo*. Responsive to BAFF after 12 h	p100 not shown. BclXL and A1 and Pim-2 induced	[26]
BAFF-R$^{-/-}$	*Ex vivo* B splenocytes	In principle enriched in transitional cells	Mainly non-canonical NF-κB impaired	Impaired survival. Unresponsive to BAFF	No p100 processing	[26]
TACI$^{-/-}$	*Ex vivo* B splenocytes		Mainly canonical NF-κB impaired	Normal survival *ex vivo*. Responsive to BAFF after 12 h	p100 processing	[26]
Pim-2$^{-/-}$	*Ex vivo* B splenocytes		Normal	Impaired survival ex vivo. Unresponsive to BAFF	Compensatory mechanisms in vivo must exist, as no B cell depletion is seen in Pim2$^{-/-}$ mice	[26]
TRAF3$^{-/-}$ in B cells (CD19-Cre)	*In vivo* phenotyping. *Ex vivo* B splenocytes	Hyperplasia of mature B cells subsets (3-fold), including MZB (6-fold). (B1 not shown)	Non-canonical NF-κB activated. Canonical NF-κB still responsive to anti-CD40	Increased survival *ex vivo*. Unresponsive to BAFF	Increased p100 processing. Decreased PCKδ translocation in nucleus. Spontaneous GC formation, B cells *in vivo* unaffected by TACI-Ig	[32]
TRAF2$^{-/-}$ in B cells (Mx1-Cre, typeI IFN-inducible. TRAF2 deleted in B cells without IFN treatment)	*In vivo* phenotyping. *Ex vivo* B splenocytes and LN cells	Selective expansion of MZB (5-fold). Presence of numerous MZB-like cells in LN. No expansion of B1 B cells (shown to be B cell intrinsic)	Non-canonical NF-κB activated. Canonical NF-κB unresponsive to anti-CD40	Increased survival *ex vivo* (splenic FO cells, LN B cells). Response to BAFF not tested	Increased p100 processing (only slightly further increased by BAFF). TRAF3 up-regulated	[31]
Act1$^{-/-}$ in B cells (CD19-Cre)	*In vivo* phenotyping. *Ex vivo* B splenocytes	About 2-fold increase of follicular, MZB, T1 and T2 B cells subsets. Increased plasma cells in Act1$^{-/-}$	Canonical and non-canonical NF-κB hyper-responsive to BAFF (and anti-CD40)	Normal survival. Hyper responsive to BAFF (more survival than in wt)	Act1 induced by LPS and CD40-signals (and possibly BAFF). Hypergamaglobulinemia. Autoimmunity and inflammation in Act1$^{-/-}$	[34]
Act1$^{-/-}$ × BAFF$^{-/-}$	Serum Ig levels	Hypogamaglobulinemia (similar to that of BAFF$^{-/-}$)		Not determined		[34]
TRAF3$^{-/-}$. Fetal liver radiation chimera	*In vivo* phenotyping. *Ex vivo* B splenocytes	Not described	Non-canonical NF-κB activated. Canonical NF-κB still responsive to anti-CD40	Increased survival *ex vivo*. Unresponsive to BAFF	Increased p100 processing. In transformed B cells (v-ABL), up-regulation of NIK protein	[33]
TRAF3$^{-/-}$ × NF-κB2$^{-/-}$	Survival	Not described		Not determined	TRAF3$^{-/-}$ lethal perinatally. TRAF3$^{-/-}$ × NF-kB2$^{-/-}$ viable. B cell phenotype unfortunately not reported	[33]

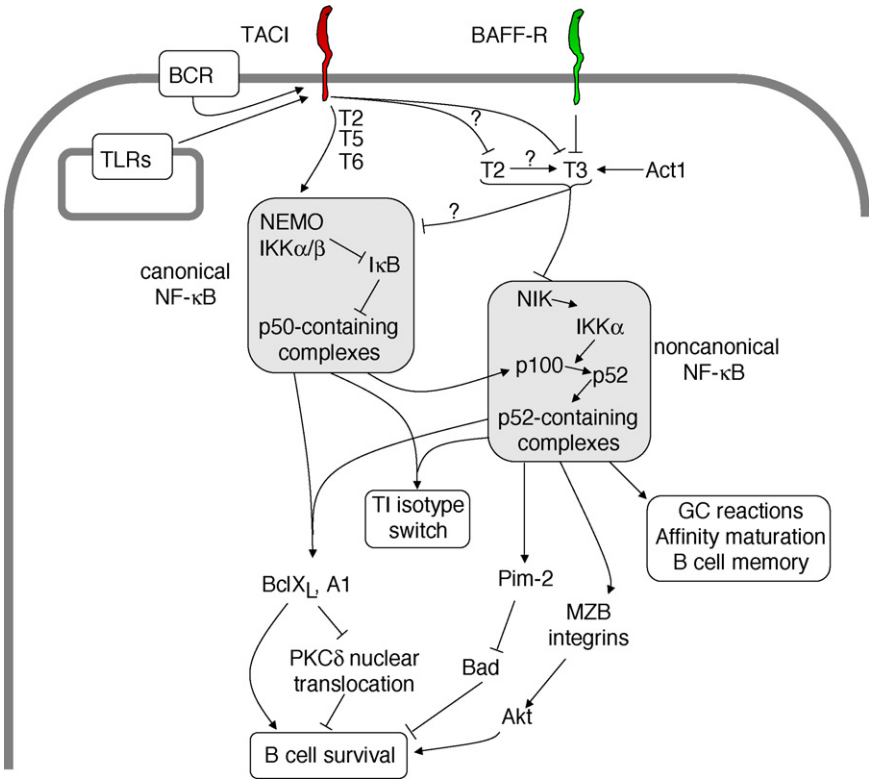

Fig. 2. Implication of TRAFs and NF-κB in BAFF-R and TACI signalling. The model shown is based on data obtained *in vivo* and *ex vivo* with mice listed in Table 1. The core signalling units of canonical and non-canonical NF-κB are shaded.

[49,50]. However, development of mouse and human TACI-specific monoclonal antibodies failed to confirm TACI expression on the surface of both mouse and human T cells [51,52]. This does not exclude a possible expression of TACI on a small subset of T cells and/or under specific circumstances. Interestingly, the number of $CD4^+$ T cells is elevated in the Peyer's patches of $TACI^{-/-}$ mice [9] and the small intestine was another tissue where TACI expression was reproducibly high by Northern blot [49,50]. TACI also appears to be expressed by human macrophages and to mediate their survival [37], providing a potential alternative explanation for TACI expression in tissues where numbers of B cells are usually low. The role of T cells in driving autoimmune disorders in $TACI^{-/-}$ mice remains to be addressed.

3.2. Opposite actions of TACI on B cell number and TI-2 responses

Analysis of $TACI^{-/-}$ mice revealed major alteration of the B cell compartment with, on the one hand, high number of hyper-reactive B cells [8,9,11], a condition leading to autoimmunity and lymphomas (see Section 4). This major defect in B cell homeostasis suggested that TACI is an inhibitory receptor for the general B cell population [8,9,11]. On the other hand, $TACI^{-/-}$ animals are unable to mount normal T cell-independent type 2 (TI-2) immune responses [8,9]. This point is particularly important as accumulating evidence suggest a tight connection between Toll-like receptor (TLR) activation and TACI expression in driving T cell-independent B cell activation [53–56]. In addition, TACI expression is particularly high on MZ and B1 B cells [7,53], known as innate B cells that are good responders to TLR activation [57,58]. Therefore, TACI probably controls activation and survival of plasmablasts derived from innate B cells, and thus TI-2 humoral responses [38,54,59]. Deletion of TACI would therefore specifically affect the function of these cells, while leaving naïve and follicular B cells untouched, or even de-repressed (Fig. 3). How TACI exerts its negative effect on the general B cell population remains unclear. TACI expression is induced in activated B cells, and may provide a direct negative feedback in these cells to prevent their inappropriate expansion [11,39]. This effect could also be indirect, by rendering cells sensitive to extrinsic apoptotic stimuli. Interestingly, B cells stimulated with LPS up-regulate TACI and BAFF-R and, in the additional presence of BAFF, further induce Fas expression and become sensitive to FasL-mediated apoptosis [56]. Although BAFF-R was proposed to be important for the observed Fas up-regulation [56], an important contribution of TACI cannot be excluded. Like $TACI^{-/-}$ mice, T cell-deficient *lpr* mice, which are deficient in Fas signalling, develop B lymphomas [60]. One could postulate a model whereby TLR4/TACI may regulate B cell activation via induction of susceptibility to Fas killing. TACI may also exert its negative regulation on the B cell pool indirectly, by

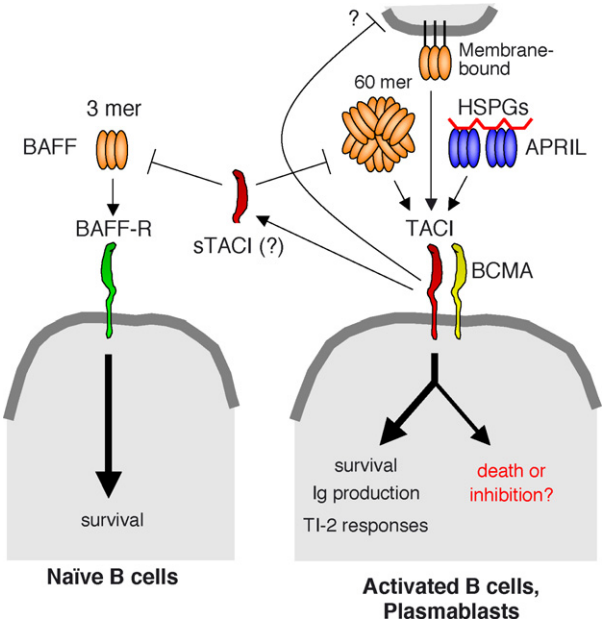

Fig. 3. Model for the opposing functions of TACI on B cell number and T-independent humoral responses. Naïve B cells do not express TACI and rely on BAFF/BAFF-R signals for their survival. Activated B cells and plasmablasts, especially those originating from "innate" B cells, express TACI and receive TACI-dependent differentiation or survival signals in response to multimeric BAFF or APRIL. TACI also provides direct or indirect negative signals in most B cells, either by providing inhibitory signals, or by decreasing circulating BAFF levels by uncharacterised mechanisms (possibly inhibitory signals in BAFF producing cells or neutralization of circulating BAFF). In TACI$^{-/-}$ mice, the vast majority of BAFF-R expressing cells expand in response to increased BAFF levels, whereas B cells involved in TI-2 responses are impaired due to lack of TACI-dependent survival/differentiation signals.

regulating circulating BAFF levels, which are indeed elevated in TACI$^{-/-}$ mice [38]. TACI may induce reverse signalling in BAFF producing cells to down-regulate BAFF production. Such a reverse BAFF signalling has been suggested previously in the context of T cell priming by dendritic cells [61]. Alternatively, TACI may be processed and released as a soluble decoy receptor that may counteract the action of BAFF. In this respect, recombinant TACI is efficiently processed *in vitro* and *in vivo* at sites that would release an active TACI decoy [62]. Finally, one may postulate that TACI leads to internalisation and degradation of bound BAFF. Thus, the dual role of TACI may be explained on the one hand by a crucial role for the differentiation or survival of plasmablasts derived in particular from innate B cells, and, on the other hand, by direct or indirect inhibitory signals delivered in TACI expressing cells and/or by the control of circulating BAFF levels (Fig. 3).

3.3. TACI in plasma cell differentiation and isotype switching to IgA

TACI promotes plasma cell differentiation in response to TI-2 antigens [59]. In line with these results, TACI enhanced plasma cell differentiation in cooperation with CD40 [63]. Also, TACI is highly expressed in short-lived antibody forming cells in a model of anti-chromatin B cells [44] as well as in normal B cells [64]. TACI expression in these cells persisted after BAFF-R down-regulation [44], consistent with their ability to receive TACI-dependent survival signals [38,44]. Here again, TACI may exert a regulatory role and was shown to inhibit antibody production co-stimulated by BAFF and CD40 [39], and to reduce proliferation of plasmablast precursors in TI-2 responses [59]. Therefore, TACI appears important for plasma cell differentiation and antibody production by short-lived plasma cells, while regulating other aspects of B cell activation.

IgA levels are reduced in TACI$^{-/-}$ mice. APRIL is thought to be the main ligand driving this effect as APRIL$^{-/-}$ mice have a deficiency in IgA production, although this aspect was not confirmed in a separate line of APRIL$^{-/-}$ mice [65,66]. Conversely, over-expression of APRIL leads to increased IgA levels [67]. APRIL enhances B cell proliferation and plasmablast survival, although plasmablast survival is possibly triggered via BCMA [68]. Both BAFF and APRIL can induce class switch recombination (CSR) to IgG and IgA through up-regulation of activation-induced deaminase (AID) [69], and this appears to be triggered via both TACI and BAFF-R [70]. Yet, in contrast to APRIL$^{-/-}$ mice, levels of IgA in BAFF$^{-/-}$ mice are not significantly different from that of WT mice, while all other antibody isotypes are severely diminished [65,71]. B1 B cells are thought to produce IgA contributing to basal IgA levels in the serum, and these cells develop normally in BAFF$^{-/-}$ mice [71,72]. Collectively, these data suggest that the APRIL-TACI axis is critical for CSR to IgA. This notion was supported by TACI siRNA experiments showing that TACI, in collaboration with HSPG, triggers CSR and IgA production in response to APRIL [73]. Consistent with the reported interaction of TACI with HSPGs [18], these data suggest that HSPGs are likely part of the TACI signalling complex, because APRIL responses were compromised by heparitinase treatments (that degrade HSPGs) and because APRIL effects could be mimicked by a combination of anti-TACI and anti-HSPG antibodies [73]. Finally, IgA class switching is greater in MZ and B1 B cells relative to B2 B cells [7,74], presumably reflecting the higher TACI expression on these cells [7,53].

3.4. Reverse TACI signalling in dendritic cells for T cell priming?

B cells and dendritic cells cooperation is critical to generate APC competent to prime naïve CD8 T cells to further differentiate into cytotoxic T lymphocytes (CTL) [61]. CTL do not expand in B cell-deficient mice reconstituted or not with TACI-deficient B cells, establishing a need for a contact between TACI presumably expressed on B cells and BAFF expressed on APC to generate APCs competent to prime [61]. This report suggested that reverse signalling through BAFF inside APCs may be the

mechanism of APC activation as the effect could be reproduced using soluble TACI instead of B cells, although in this study the effect of an irrelevant Fc-containing fusion protein was not shown and TACI-independent effects could not be ruled out [61]. As TACI interacts with HSPGs, and as HSPGs can activate TLR4 [75,76], the question of whether DCs were activated in this study by reverse BAFF signalling or by TLR4 signalling remains open.

4. The role of TACI in autoimmunity

4.1. Autoimmunity in TACI$^{-/-}$ mice versus BAFF Tg mice

Excessive production of BAFF triggers SLE-like autoimmunity in mice [5]. Similar autoimmune disorders develop in TACI$^{-/-}$ mice, but with some noticeable differences [11]. BAFF is critical at the immature transitional stage during splenic B cell maturation and allows type 1 to type 2 (T1/T2) transition by providing survival signals [72,77,78]. As a result, BAFF overexpression in BAFF Tg mice does not affect the number of T1 B cells but increases that of B cells beyond the T1 B cell stage, primarily T2, mature and MZ B cells [5]. In contrast, in TACI$^{-/-}$ mice, the effect on B cell expansion affects all mature B cells and also early immature T1 B cells in the spleen [11]. Basal levels of antibodies in TACI$^{-/-}$ mice are relatively normal [8,9], except for significantly reduced IgA levels [8], in sharp contrast with BAFF Tg mice in which the levels of all antibody isotypes, and in particular IgA, were elevated [5,78]. The elevated BAFF levels of TACI$^{-/-}$ mice may contribute to B cell hyperplasia [38], but do not allow for the development of hypergammaglobulinemia, suggesting that either TACI is required for this process or that a large excess of BAFF is needed. Another striking difference between TACI$^{-/-}$ and BAFF Tg mice is the development of lymphoma in 15% of 7-month-old animals, a feature never seen in age-matched BAFF Tg mice, unless these lack TNF [78], or in a separate colony of TACI$^{-/-}$ mice (Susan Kalled, BiogenIdec Inc., personal communication). Interestingly, mice over-expressing APRIL develop B1 cells-associated neoplasm [67], and this questions the role of APRIL as a trigger of TACI-mediated B cell negative regulation.

4.2. Autoimmunity in BAFF Tg mice: is TACI involved?

As BAFF is critical for B cell survival [4,79], autoimmunity seen in BAFF Tg mice has always been attributed to inappropriate survival of self-reactive B cells that would be rescued from immune check points during maturation when self-reactive B cells binding to self-antigen are normally eliminated or neutralized (anergy) [4,79]. This attractive idea was however not fully confirmed using mice engineered to produce HEL-specific B cells and expressing HEL in the presence of a BAFF transgene, as these mice did not display massive corruption of B cell tolerance [80]. This was especially true when self-reactive HEL-specific B cells competed with normal B cells, an experimental set up reflecting physiological situations [80]. In these experiments, strongly self-reactive B cells were deleted normally despite the presence of high BAFF levels, and the only populations that expanded were self-reactive B cells of low/intermediate affinity, principally composed of MZ B cells [80]. In conclusion, self-reactive B cells that compete with normal B cells for anatomical niches in the spleen are deleted at an early maturation stage, when they do not express sufficient levels of BAFF-R to be rescued by high BAFF levels in BAFF Tg mice [3,81]. This result did however raise a number of questions on the exact mechanism leading to severe autoimmunity in BAFF Tg mice. Could weakly self-reactive B cells alone be responsible?

Both B cells and T cells play central roles in the pathogenesis of SLE in humans and in mouse models of the disease [82–84]. B cells produce autoantibodies, some of which may be pathogenic and trigger pro-inflammatory reactions via activation of complement molecules [82]. B cells, in particular MZ B cells that are known as powerful activator of naïve T cells [85], can also present antigens to T cells. In return, T cells can provide help to autoantibody-producing B cells and themselves participate in complement-dependent inflammatory processes [86,87]. The innate immune system, in particular plasmacytoid dendritic cells (pDC) activated through TLR 7/9, produces type I IFNs which in turn fuel further the activation of self-reactive B and T cells [88]. In BAFF Tg mice the proportion of effector T cells is increased, in line with the observation that BAFF can up-regulate Bcl-2 and speed both the division rate and the differentiation of T cells into effector cells in a BAFF-R-dependent manner [51]. However, the effect of BAFF on T cells of BAFF Tg mice is a likely consequence of increased B cell numbers, as B cell-deficient BAFF Tg mice have normal numbers of effector T cells [89]. This effect was not solely dependent on MZ B cells, because lymphotoxin-deficient BAFF Tg mice lacking MZ B cells still had an expanded effector T cell compartment, albeit not as large as that of control BAFF Tg mice [77].

Therefore, an overall observation of the system at this stage suggested that excess BAFF was increasing B cell survival, leading to the expansion of low/intermediate affinity autoreactive MZ B cells, resulting in excessive APC-dependent activation of T cells, which responded further to excess BAFF production and became potentially pathogenic effector T cells. This picture fitted the accepted concept in the field that self-reactive B and T cells cooperate to trigger autoimmune manifestations. However, to our surprise, this model did not apply to BAFF Tg mice.

Intriguingly, functional Foxp3^{+} regulatory T cells (T_{reg}) were expanded in BAFF Tg mice [53] bringing doubts on the exact contribution of effector T cells in the development of

autoimmunity in BAFF Tg mice. We therefore generated T cell-deficient BAFF Tg mice that developed autoimmune disorders undistinguishable from that of T cell-sufficient BAFF Tg mice, pointing to T cell-independent pathogenic activation of B cells in BAFF Tg mice [53]. T cell independent activation of B cells occurs via the activation of innate receptors such as TLR [90]. Interestingly, reconstitution of BAFF Tg mice with bone marrow lacking MyD88, a signalling adaptor shared by several TLR [88], protected the reconstituted mice against nephritis [53], showing that expression of MyD88 in B cells is critical for disease progression [53]. In conclusion, disease in BAFF Tg mice is a T cell-independent process initiated by the emergence of low/intermediate affinity self-reactive B cells that have the particularity to be MZ and B1 B cells, known as ''innate'' B cells [57], particularly responsive to TLR activation and central to T-independent B cell responses [55,91,92]. These cells produce large amount of autoantibodies following TLR activation, a process further augmented by high levels of BAFF [10,53]. Immunoglobulin deposition in the kidneys, in particular IgG isotypes, leads to C3 complement fixation and activation of the inflammatory reaction [10] (Fig. 4).

MZ and peritoneal B1 B cells, which respond well to TLR activation and T cell-independent antigens [91,93] also express the highest levels of TACI on the cell surface [51,55]. Interestingly, TLR4, 7 or 9 activation specifically and strongly up-regulate TACI expression on B cells [53–56]. Conversely, BAFF stimulation of B cells up-regulate TLR7/9 expression on follicular and MZ (but not B1) B cells in a TACI-dependent manner ([53] and Joanna Groom, unpublished observation). It is noteworthy that BAFF Tg mice produce BAFF 60-mer, an efficient TACI agonist [38]. B1 B cells, which are thought to contribute to kidney inflammation in BAFF Tg mice [77], unlike MZ-like B cells that target salivary glands [77,78], are especially responsive to TLR7 activation for TACI expression [53]. Accordingly, reconstitution of BAFF Tg mice with TLR9$^{-/-}$ bone marrow did not prevent nephritis is the recipients, suggesting that TLR7 or both TLR7 and 9 may be important in driving disease in BAFF Tg mice [53]. In conclusion, the current data suggest a strong cooperation between TLR activation and TACI expression, a mechanism, which may be critical for T cell-independent B cell immune responses and which can be corrupted when BAFF is over-expressed, leading to autoimmunity.

These data implicating TACI as a likely mediator of BAFF-mediated auto-immunity create a novel TACI-related paradox: How can both the presence and absence of TACI lead to autoimmunity in BAFF Tg and TACI$^{-/-}$ mice, respectively? Is TACI a friend or a foe in autoimmunity? Autoimmunity in BAFF Tg and TACI$^{-/-}$ mice may rely on different cell populations: T cell-independent, TACI-dependent innate B cells supported by BAFF in the case of BAFF Tg mice, and yet to be characterized TACI-

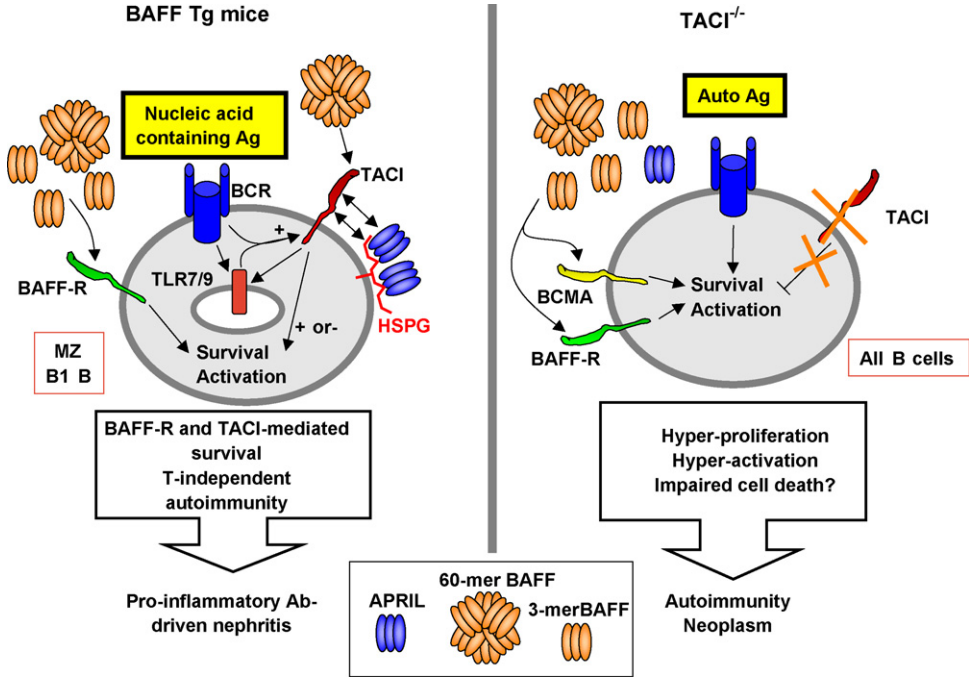

Fig. 4. Comparing autoimmunity in BAFF Tg mice and TACI$^{-/-}$ mice. In BAFF Tg mice (left panel) excess levels of BAFF expand self-reactive MZ and B1 B cells. TLRs are activated after internalisation of autoreactive B cell receptors bound to either dsDNA or to immune complexes containing nucleic acids, leading to TACI expression that in turn increases TLR7/9 expression in response to the elevated BAFF level, creating a positive feedback loop. In this case, oligomeric BAFF or HSPG-crosslinked APRIL may contribute to TACI activation. B cells are activated to produce IgG2c and IgG2b autoantibodies that deposit in the kidney and promote inflammation through complement fixation [53]. In TACI$^{-/-}$ mice (right panel), lack of TACI leads to B cell hyper-proliferation and activation and possibly impaired cell death, which may account for the development of lymphomas in these animals. Auto-antibodies may be produced by de-repressed B cells that are probably distinct from those active in BAFF Tg mice.

independent or TACI-repressed B cells that may benefit from elevated BAFF levels and whose dependence on T cells is unknown in the case of TACI-/- mice. The analysis of autoimmunity and circulating antibody levels in T cell-deficient TACI$^{-/-}$ mice and in BAFF Tg × TACI$^{-/-}$ mice should help clarifying these issues.

5. TACI in humans

5.1. Expression on human cells and tumours

BAFF-R is widely expressed on human B cell subsets such as naïve, memory B cells and plasma cells (PCs) [51], but not on PCs from the bone marrow (BM) and spleen [94,95]. BCMA is expressed on PCs from tonsils, spleen and BM [94,95], but also on tonsillar memory B cells and in germinal center (GC) B cells, the latter being TACI-negative and BAFF-R^{low} [51,94]. TACI is expressed in CD27^{+} memory B cells, tonsillar and BM PCs, in a subpopulation of activated CD27^{-}, non-GC cells [51,53,95] and in a small subset of naïve B cells in the blood and tonsils [95], consistent with the idea that, similar to the mouse system, TACI is an inducible receptor.

Indeed, like in mice, CpG/TLR9 but also activation of human B cells with anti-μ plus CD40L, IL2 and IL10 up-regulate TACI expression on the cell surface [53,96]. TACI up-regulation on activated B cells is an early event that depends on ERK1/2 signalling pathway but which is independent on cell division [95].

TACI is also expressed on many different lymphoma types such as multiple myeloma (MM) [97–99], Hodgkin lymphomas (HL) [100] and non-Hodgkin lymphomas (NHL) [101,102]. TACI^{lo} and TACI^{hi} MM patient subgroups have been observed with a poorer prognosis associated with TACI^{lo} MM patients [98,103]. HL do not express BAFF-R and show enhanced proliferation in response to BAFF and APRIL [100], suggesting that TACI and BCMA promote the growth of these cells. In contrast, NHL cells not only express BAFF-R, TACI and/or BCMA, but also BAFF and APRIL, which collectively support an autocrine mechanism for survival [101,102]. APRIL seems to play an equally important role as BAFF in promoting tumor cell growth and whether this is achieved via BCMA or TACI is unclear. Neutralization of BAFF and/or APRIL decreases survival of lymphoma cells and this promising new strategy to treat lymphomas is currently tested in the clinic.

5.2. Common variable immunodeficiency (CVID)

CVID is a rather common (1:25,000) heterogeneous spectrum of primary immunodeficiencies that is diagnosed after elimination of other known causes of immunodeficiency (reviewed in [104]). TACI mutations, which are detected in about 8% of CVID patients but also in about 1% of the control population, are significantly associated with CVID in only three cases [105–108]: (a) when both alleles are mutated. This was never observed in the control population and always lead to antibody abnormalities and very often to CVID; (b) when one TACI allele carries the C104R mutation that disrupt the ligand binding site; (c) when one TACI allele carries the A181E mutation which is located in the transmembrane domain but whose functional effects are unknown. Association of the latter mutation with CVID was not always statistically significant. These mutations exist in the control population and do not always perfectly segregate with the disease in familial cases of CVID, indicating that they may predispose to rather than cause CVID [104]. Other TACI mutations are most probably polymorphisms. The initial report that TACI mutations in human were associated with selective IgA deficiency in addition to CVID, a phenotype reminiscent of TACI$^{-/-}$ mice, was not confirmed in larger scale studies [105–107].

CVID affects mostly adults and is characterised by immune abnormalities such as recurrent bacterial infections and hypogammaglobulinemia. CVID patients also have a higher risk of developing autoimmune diseases and several types of cancers. The nature of the TACI mutations in human renders phenotypic comparison with TACI$^{-/-}$ or TACI$^{+/-}$ mice difficult. For example, TACI C104R constitutively associates with wild type TACI [109], potentially "poisoning" the TACI signalling complex engaged by multimeric ligands, a situation clearly different from that of a null allele. However, two brothers with a homozygous S144X mutation can be considered human TACI$^{-/-}$, because they express no TACI at the RNA and protein level, and because their TACI molecule has a premature truncation [108]. Although their parents could not be analysed, they were not reported with CVID, consistent with the normal phenotype of heterozygote TACI$^{+/-}$ mice. In contrast to TACI$^{-/-}$ mice, but like most CVID patients, both brothers had low IgG, IgA and IgM levels. One developed CVID and had splenomegaly, whereas the other was clinically unaffected but showed elevated number of B cells and CD8^{+} T cells. This suggests that TACI may also regulate the size of the B cell pool in human, and further shows that other genetic or environmental factors influence progression to CVID. Several patients with TACI mutations temporarily not on Ig-replacement therapy were negative for pneumococcal polysaccharide serotypes, suggesting that T-independent responses are affected. The hypothesis that TACI plays a direct role in such TI responses is however challenged by the healthy TACI$^{-/-}$ (S144X) individual who presented normal levels of these antibodies [108]. In summary, the study of CVID patients indicates that TACI is probably more important for antibody production in human than it is in mice, and that its role is not limited to the control of immunoglobulin switch but probably regulates survival or differentiation of immunoglobulin secreting cells. The precise phenotype of the immunodeficiency, of the autoimmune manifestations and of the susceptibility to lymphomas probably depends not only on the type of TACI mutation but also on other environmental and genetic cues.

6. Conclusions and remaining questions

The past 3 years have brought some important new information about the role of TACI in the BAFF/APRIL system. Regulation of TACI expression is intimately linked to activation of innate receptors on B cells such as TLR [10,53–55], and this may explain the critical role of TACI as a driver of T cell-independent immune responses [8,9]. We now know that autoimmunity in BAFF Tg mice is a T cell-independent process [53], and current data suggest that TACI may play a greater role in this disease than first anticipated in view of the phenotype of TACI$^{-/-}$ mice. The reason for autoimmunity and lymphoma in TACI$^{-/-}$ mice remains a mystery, in part because of our poor understanding of TACI signalling properties. Yet, important progresses are currently made in that direction with the discovery of novel TACI functions triggered by HSPGs or oligomeric BAFF and APRIL, but not trimeric ligands [18,38]. It will be important to better understand the physiological and pathological relevance of the contradiction between negative regulatory roles of TACI in B cells versus its function as an inducer of activated B cell and plasma cell survival. The role of TACI in promoting the maturation of DC into APC competent to activate CTLs is also an interesting area to explore which may lead to application in vaccination and cancer treatment [61]. Dissecting the causal relationship leading to excess BAFF production in TACI$^{-/-}$ mice is another important area of investigation, and the discovery of HSPGs as additional TACI ligands may help explaining some of its functions [18]. Yet, we also need to understand more about the respective roles of BAFF and APRIL on TACI and how HSPGs fits into that picture. Appreciating the potential benefits or side effects of partial or total inhibition of TACI signalling, especially in cells not dependent on BAFF for their development such as B1 B cells and monocytes, is particularly important in view of the development of BAFF-specific versus BAFF/APRIL neutralizing agents in the clinic. Expression of TACI on macrophages [37] and its strong regulation by TLR activation on B cells indicate that TACI is a key molecule connected to innate immune functions. In conclusion, TACI has emerged as a truly unusual TNF receptor-like molecule with a sophisticated mode of action. Future work deciphering further the role of TACI is likely to uncover exciting new mechanisms that can potentially be exploited to develop novel therapeutic strategies in autoimmunity, cancer and possibly immunodeficiency.

Acknowledgements

FM is supported by the National Health and Medical Research Council, the NSW Lupus association and the Rebecca Cooper foundation. PS is supported by grants of the Swiss National Research Foundation.

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