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Seminars in Immunology 18 (2006) 284–289

seminars in
IMMUNOLOGY

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Review

The role of the BAFF/APRIL system on T cell function

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Abstract

BAFF is a key factor controlling B cell survival and maturation and its over-expression promotes B cell-mediated autoimmune disorders and participates in the progression of B cell lymphomas. Yet, BAFF and a related ligand APRIL are expressed by T lymphocytes and modulate their functions. BAFF and APRIL promote T cell activation and survival. BAFF over-expression in transgenic (Tg) mice enhances T helper 1 (Thl)-driven delayed-type hypersensitivity (DTH), but inhibits T helper 2 (Th2) cell-mediated allergic airway inflammation in mice. Some of these effects are also dependent on BAFF-induced modification of the B cell compartment. Therefore, direct BAFF/APRIL signalling in T cells and/or T cell modulation in response to a BAFF-modified B cell compartment may play an important role in inflammation and immunomodulation.

Keywords: BAFF; BLyS; APRIL; T lymphocytes; Autoimmunity; Inflammation

1. Introduction

BAFF (B cell activating factor belonging to the tumor necrosis factor (TNF) family also termed BLyS, TALL-1, zTNF-4, THANK, and TNFSF13) is a homotrimer, member of the TNF superfamily expressed on the cell surface or cleaved and secreted [1,2]. Another related TNF ligand, A proliferation-inducing ligand (APRIL, also known as TALL-2, TRDL1 or TNFSF13)[3] shares two receptors with BAFF, transmembrane activator and calcium-modulator and cyclophilin ligand (CAML) interactor (TACI) and B-cell maturation antigen (BCMA, TNFSFR17) [1,2]. In contrast to BAFF, APRIL is cleaved from the Golgi and only exists as a secreted soluble ligand [4]. BAFF also specifically binds to a third receptor, BAFF receptor (BAFF-R, also known as BR3) [1,2]. Interestingly, APRIL binds to proteoglycan structures on the cell surface, however, it is unclear whether this interaction leads to physiological signalling or helps concentrating APRIL on the cell surface for better cross-linking of the receptors, a feature essential for efficient signalling [5,6]. APRIL/BAFF heterotrimers have been detected in the serum of patients with rheumatic disease and appear to bind only to TACI [7]. In addition, a spliced variant form of BAFF was identified which can form non-cleavable and functionally inactive homotrimers with normal BAFF subunits [8,9]. Finally, an alternative splicing event in the TWEAK/APRIL locus leads to the formation of a TWEAK/APRIL hybrid ligand named TWE-PRIL, composed of the APRIL extracellular domain and TWEAK transmembrane portion. This ligand is biologically active possibly via TACI, BCMA and, possibly proteoglycan structures [10].

The discovery of BAFF has shed new light on the importance of finely tuned B cell survival for B cell tolerance during B cell maturation and activation [1,2,11–13]. BAFF particularly supports survival of splenic immature transitional and mature B cells. Thus, maturation beyond the immature transitional type 1 (T1) stage is impaired in BAFF-deficient mice ($BAFF^{-/-}$) [13–15]. Mice over-expressing BAFF develop autoimmune disorders similar to systemic lupus erythematosus (SLE) and Sjögren's syndrome (SS) in humans, possibly as the result of improper B cell survival, predominantly affecting the maturing splenic transitional type 2 (T2) and the marginal zone (MZ B) cell populations (reviewed in refs. [13,14,16–19]). Indeed, when the hen egg lysozyme (HEL) transgenic system was used to assess the effect of excess BAFF production on B cell tolerance, results revealed a BAFF-induced escape of low/intermediate affinity self-reactive B cells, in particular MZ B cells [20]. BAFF-induced autoimmunity in BAFF transgenic (Tg) mice appears to be highly dependent on B cells and possibly the

Abbreviations: APRIL, a proliferation-inducing ligand; BAFF, B cell activating factor belonging to the TNF family; BAFF-R, BAFF receptor; BCMA, B cell maturation antigen; DTH, delayed type hypersensitivity; OVA, ovalbumin; TACI, transmembrane activator and calcium-modulator and cyclophilin ligand (CAML) interactor

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doi:10.1016/j.smim.2006.04.005

production of autoantibodies [21]. Previous studies in BAFF Tg mice lacking TNF and, therefore, unable to mount proper T-dependent immune response and form germinal centres to improve antibody affinity, developed autoimmune symptoms as severe as those seen in the original BAFF Tg mice [21]. This work revealed that the role of T cells in BAFF-induced autoimmunity was either minimal or un-conventional. However, the status of the T cell compartment in BAFF Tg mice is clearly altered with the expansion of the effector T cell compartment [16]. This unusual aspect prompted the study of the exact role the BAFF/APRIL system on T cell functions. In this review, we have collated all recent findings and attempted to establish the place of T cells in BAFF/APRIL-mediated biological activities.

2. Expression of BAFF, APRIL and receptors on T cells

Expression of BAFF by T cells has been a controversial issue for some time with groups clearly detecting expression, particularly in activated T cells [22–25], while several other studies were unable to show significant BAFF production [26–29]. In many reports, BAFF mRNA expression by T cells is rather weak compared to that of dendritic cells [24], which was also reflected at the protein level [25]. As activated T cells also express APRIL [23,30], the possibility of BAFF/APRIL heterotrimers formation by T cells and their inadequate detection with currently available anti-BAFF monoclonal antibodies may have contributed to the relative difficulty in establishing BAFF protein production by T cells. The fusion protein TWE-PRIL is expressed on resting and activated primary T cells [10].

Similar difficulties arose when investigators analysed BAFF and APRIL receptor expression on T cells. TACI was first described to be expressed on activated human circulating T cells using a polyclonal anti-TACI antibody for staining [31,32]. However, another group reported decreased TACI mRNA expression upon T cell activation [33]. Several independent clones of monoclonal anti-mouse and human TACI antibodies were later generated but failed to detect TACI on mouse blood, lymph node and spleen-derived activated T cells and human blood and tonsil-derived activated T cells, respectively [24]. In addition, gene array experiments using RNA from many subsets of activated human T cells failed to show TACI expression [24]. Moreover, TACI-deficient mice display minimal T cell alterations such as increased numbers of $CD4^+$ T cells in the Peyer's patches [34], which could be the indirect consequence of autoimmune disorders developing in these animals [35]. Recently, a study detected a small subset of $TACI^+$ T cells in synovial tissue samples from patients with synovitis, in particular in samples presenting diffuse lymphoid infiltrates [36]. TNF receptor shedding is quite common in many inflammatory conditions [37] and whether this surface staining reflects soluble TACI binding to surface BAFF/APRIL ligands on activated T cells or true surface TACI expression must be verified with a parallel analysis of TACI mRNA expression in this small subset of $TACI^+$ T cells. Alternatively, it is possible that T cells homing to tissues may differentially regulate TACI expression compared to circulating or lymphoid organ-residing T cells. Expression of TACI on T cells has been further supported by the fact that APRIL acts as a survival factor for T cells [23]. However, the newly identified heparan sulfate proteoglycan (HSPG) structures present on activated T cells as additional binding molecules for APRIL [5,6] may change this notion, and this aspect requires further functional characterization to support a role for TACI and/or HSPG on T cells. In addition, a short variant form of mouse APRIL has been shown to bind to BAFF-R (see the article by Bossen and Schneider in this issue) and may contribute to APRIL-mediated effects in T cells.

Analysis of BAFF-R expression on T cells proved to be as difficult as that of TACI. An early report showed that BAFF-R mRNA expression in $CD4^+$ T cells decreased upon activation [38]. Later use of anti-BAFF-R mAbs showed that BAFF-R expression increased on the surface of a subset of activated human tonsillar and splenic mouse $CD4^+$ T cells [24,39]. Our experience has shown that the degree of CD3 stimulation is critical, as high concentrations of cross-linking antibodies tend to prevent up-regulation of BAFF-R expression (our unpublished observation). Interestingly, BAFF-R is also expressed on most $CD4^+CD25^+$ regulatory T cells [39].

In contrast, BCMA is not expressed on T cells and appears to be a B cell-specific BAFF/APRIL receptor, in particular on plasmablasts [15,17,40].

3. Direct modulation of T cell responses by BAFF and APRIL in vitro

BAFF acts directly on T cells to enhance human T cell response to anti-CD3 activation [24,41]. This effect was shown to be a true co-stimulatory effect rather than increased basal T cell survival. Same results were obtained with mouse splenic T cells stimulated with anti-CD3 mAb plus BAFF [24]. Interestingly, this effect was only obtained when BAFF was immobilized but not when used in soluble form [24,41,42], suggesting that interaction between BAFF and its receptor on T cells required some level of stability to induce signalling, perhaps an interaction consistent with that of membrane BAFF rather than soluble BAFF. Similar results were obtained using ovalbumin (OVA)-specific T cell receptor (TCR) Tg T cells activated with an OVA peptide together with BAFF [24]. However, in this case it seems that addition of BAFF increased Bcl-2 expression in activated mouse T cells, suggesting a possible survival role for BAFF in splenic T cells [24]. Therefore, higher basal T cell survival may have provided the assays with more live cells able to respond to activation, hence the increased number of dividing T cells observed. Importantly, endogenous BAFF produced by activated T cells is very important for T cells to respond to anti-CD3 mAb-mediated activation. Anti-CD3-mediated activation of T cells in the presence of decoy Ig fusion-protein receptors such as BCMA-Ig, TACI-Ig (both blocking endogenous BAFF and APRIL) or BAFF-R-Ig (blocking only endogenous BAFF) prevented proliferation of T cells in response to activation [24]. This inhibitory effect can be over-ridden by addition of anti-CD28 antibodies, used as an alternative co-stimulatory signal (Andrew Sutherland, unpublished results). The BAFF co-stimulatory effect is dependent on BAFF-R as A/WySnJ-derived T cells, which expressed a defective BAFF-R, were unable to

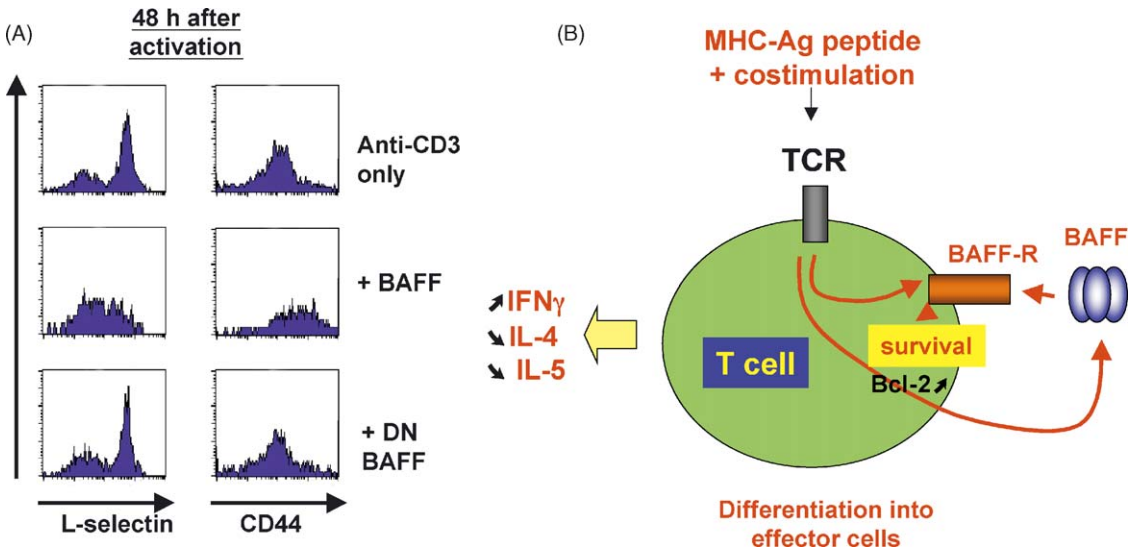

Fig. 1. The role of BAFF and BAFF-R during T cell activation. (A) Purified splenic CD4+ T cells were stimulated 48 h with anti-CD3 with or without BAFF or heat-inactivated BAFF (DN BAFF). Cells were stained with antibodies to CD4, L-selectin (CD62L) and CD44 as indicated and analysed by FACS. Representative histograms are shown. (B) Upon activation T cells produce BAFF and up-regulate BAFF-R on the surface. BAFF signalling acts as a co-stimulator of T cell activation may be in part via increased basal survival. T cells then differentiate into effector cells preferentially producing Thl cytokines.

respond to BAFF-induced co-stimulation while being perfectly responsive to anti-CD28 antibody-mediated co-stimulation [24]. BAFF-R-specific blocking by mAbs also inhibited BAFF co-stimulatory effects on T cells activation [24]. As BAFF-R has a limited and unusual extracellular binding domain [43], its role in T cell co-stimulation assays in vitro may explain why immobilized rather than soluble BAFF is effective in these assays [24,41,42]. In contrast, TACI-deficient T cells responded normally to BAFF co-stimulatory signals in vitro [24]. One report showed increased response of TACI$^{-/-}$ T cells to anti-CD3 plus BAFF [35], further validating the idea that BAFF-R triggers this effect and also implicating TACI as a potential negative regulator of T cell activation. Alternatively, this result may depend on the age of the mice used for TACI$^{-/-}$ T cell collection, as these mice develop autoimmune disorders linked to the expansion of the B cell compartment [35] and the increased proportion of effector T cells which are more likely to respond better ex vivo than WT T cells (our unpublished observation).

Interestingly, addition of BAFF in mouse T cell activation assays accelerates the differentiation of T cells into effector L-selectin^{low}/CD44^{high} T cells (Fig. 1A). In addition, T cells stimulated in the presence of BAFF secrete more IFNγ and less IL-4 or IL-5, suggesting that BAFF may be a T helper1 (Th1) response-promoting cytokine. Collectively, these results led to a new model for T cell activation and differentiation (Fig. 1B). Upon activation T cells produce BAFF and up-regulate BAFF-R on the surface. BAFF signalling via BAFF-R acts as a co-stimulator of T cell activation, an effect that may result, in part, from increased basal survival. T cells then differentiate into effector cells preferentially producing Th1 cytokines (Fig. 1B). As BAFF is also highly expressed by antigen-presenting cells such as dendritic cells and macrophages, its production may be an important feature shaping the quality of T cell activation and differentiation during immune responses.

APRIL also co-stimulates anti-CD3-induced T cell activation [44]. However, scientists at Zymogenetics Inc. have engineered a trimeric APRIL protein with high specific activity (ZZ APRIL), which lacks co-stimulatory activity on both human and mouse T cells [45]. These results are more in line with the predominant expression of BAFF-R but not TACI on activated T cells. Addition of APRIL to T cell cultures does not promote cell survival [46]. While a function for APRIL on T cells via TACI is unclear, recent work uncovered potential new receptors for APRIL on T cells. The idea was not novel as earlier studies had noted that APRIL could bind to cells which did not express the known BAFF receptors [30,47]. Two groups recently identified HSPG as additional APRIL binding structures [5,6]. Binding of APRIL to HSPG can be abrogated with heparin treatment. Although, APRIL binding to T cells is clearly mediated via HSPG [5,6], the role of this interaction on primary T cells is unclear. The interaction can promote the proliferation of Jurkat cells, a T cell line [6], but not that of primary T cells [5,6]. Interestingly, heparin alone has a stimulatory role on T cell activation [6], and whether this effect is related to the inhibition of endogenously produced APRIL binding to HSPG remains to be established.

4. Modulation of T cell function in BAFF, APRIL and receptor mutant or transgenic mice (Table 1)

In vitro studies described above have confirmed the role of BAFF as a co-stimulating/survival factor of activated T cells. However, the physiological importance of BAFF function in T cells in vivo remains to be established. We have shown that Thl-mediated DTH was mostly normal in BAFF$^{-/-}$ mice, suggesting that BAFF is not required for T cell activation and Thl differentiation in vivo. As mentioned above, we have shown that anti-CD28 antibody co-stimulation can compensate for the lack of BAFF-mediated co-stimulatory sig-

Table 1
T cell status in BAFF, APRIL and receptor mutant or transgenic mice

Mice	T cell phenotype	References
Knockout mice		
BAFF$^{-/-}$	Normal Th1-mediated DTH	[42]
	Normal response in Th1-mediated Experimental Autoimmune Encephalomyelitis (EAE)	(Ian Sutton, unpublished observation)
	Modest increased of allograft survival, significantly increased when combined with a non-effective low dose of cyclosporin A.	[39]
	Normal numbers and proportion of naïve and effector/memory T cells	[15]
APRIL$^{-/-}$	Normal T cell development and numbers	[52]
	Normal T cell responses	[52]
	Increased percentages of CD44^{high}/CD62L^{low} effector/memory T cells	[53]
BAFF-R *mutant* (*A/WySnJ line*)	Anti-CD3-activated T cells do not respond to BAFF-induced co-stimulatory signals	[24]
	Normal T cell response to anti-CD28-mediated co-stimulation of anti-CD3 activation.	[24]
	Normal T cell proliferation in response to antigens in vivo.	[56]
	CD4$^+$ T cells provide normal T cell help to B cells	[56]
TACI$^{-/-}$	Normal T cell proliferation to anti-CD3 in vitro and co-stimulation following addition of BAFF	[24]
	Normal allograft rejection	[39]
	Normal T cell numbers and responses	[57]
	T cells hyper-proliferative in response to anti-CD3 + BAFF	[35]
	Increased numbers of CD4$^+$ T cells in Peyer's Patches	[34]
	Impaired CD8 T cell priming	[54]
BCMA$^{-/-}$	Normal T cell numbers and function	[58]
BCMA$^{-/-}$ *x* TACI$^{-/-}$	Same as TACI$^{-/-}$	[59]
Transgenic mice		
BAFF Tg mice	Increased proportion of effector/memory T cells	[16]
	Two fold increase in T cell numbers in the spleen and mesenteric lymph nodes	[16]
	Enhanced Th1-mediated DTH responses	[42]
	Suppressed Th2-mediated allergic airway inflammation	[42]
APRIL Tg mice	Increased survival of CD4$^+$ and CD8$^+$ T cells	[23]
	Enhanced survival of superantigen-reactive T cells linked to increased of Bcl-2 expression	[23]
	Increased T cell proliferation	
	Increased production of IL-2 by activated CD8$^+$ T cells	
	Reduced percentages of T cells in peripheral lymph nodes	
TACI Tg mice	No T cell phenotype described	[48,60]
mBCMA Tg mice (binds murine APRIL well but not mouse BAFF)	No T cell phenotype	[60]

nals (Andrew Sutherland, unpublished data), therefore, normal DTH responses in BAFF$^{-/-}$ mice, supported by alternative co-stimulatory molecules, was expected. However, another study showed delayed T cell-mediated allograft rejection of a transplanted heart in BAFF$^{-/-}$ mice, in particular when combined with cyclosporine A at a dose which given alone did not significantly prolong survival of the graft [39]. This work suggests a potential stimulatory effect of BAFF on T cell-mediated graft rejection. Alternatively, mature and MZ B cells, missing in BAFF$^{-/-}$ mice [15,48], may play an important role in activating T cells participating in cardiac graft rejection, possibly as antigen-presenting cells [49].

Interestingly, the proportion of effector T cells (CD4$^+$ and CD8$^+$) is increased in BAFF Tg mice [16,42]. We later showed that this phenomenon was dependent on the presence of B cells, as the effector T cell compartment was unchanged in BAFF Tg mice lacking B cells [42]. DTH responses were enhanced and prolonged in BAFF Tg mice and this aspect was also dependent on the presence of B cells, as DTH responses were normal in BAFF Tg mice lacking B cells [42]. Conversely, BAFF Tg mice were protected against OVA-induced allergic airway inflammation and this protection was independent of the presence of B cells, and BAFF Tg lacking B cells were equally protected in this model [42]. This result was surprising and suggested a possible regulatory role for BAFF in T cell activation in some settings. Previously, other studies have shown that BAFF increased CD25 expression on activated T cells [41]. While this aspect may reflect increased activation, it may also indicate expan-

sion/increased survival of $CD25^+$ regulatory T cells. Moreover, BAFF-R, which mediates increased Bcl-2 expression in activated T cells [24], is expressed on most $CD25^+$ regulatory T cells [39]. In support of this possibility, we made an intriguing observation using BAFF Tg-derived B and T cells adoptively transferred into lymphopenic $RAG1^{-/-}$ mice, looking at the production of autoantibodies (rheumatoid factors, RF). In BAFF Tg mice, the numbers of B cells greatly exceed that of T cells with B/T ratios 4 to 1 or higher [16]. In this situation, it is likely that potential regulatory T cells are out-numbered and overwhelmed in BAFF Tg mice. As lymphocytes of BAFF Tg mice do not express the transgene (which is under the control of a liver-specific promoter) [16], it is possible to adoptively transfer these cells in recipient lymphopenic mice at a more normal B/T ratio and look at their function away from BAFF over-expression. When we transferred equal numbers of BAFF Tg-derived B cells with WT T cells, significant production of RF in the recipient mice was detected (Fig. 2). In contrast, when equal numbers of BAFF Tg-derived B and T cells were injected in the lymphopenic host, production of RF was greatly reduced (Fig. 2), suggesting the possible presence of regulatory T cells in the BAFF Tg-derived T cell population, as opposed to WT-derived T cells. Further work is needed to understand the possible role of BAFF in regulatory T cell modulation. Moreover, indirect effects such as BAFF-mediated production of IL-10 by B cells [50], in particular from the expanded marginal zone B cell compartment [51] may play a role in negatively regulating aspects of T cell function.

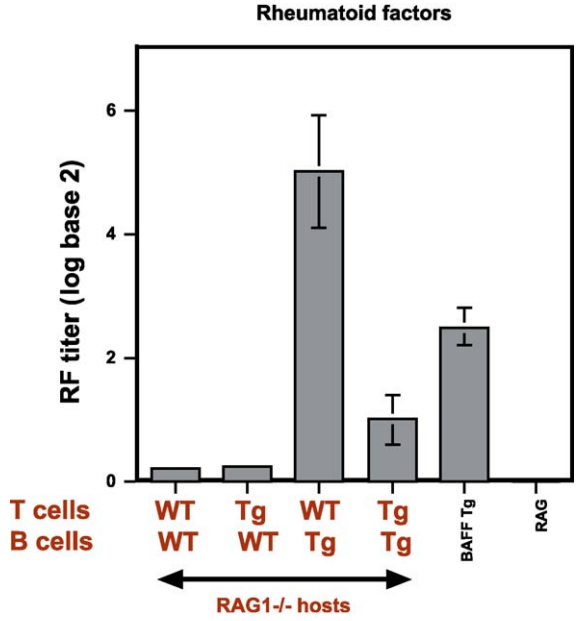

Fig. 2. BAFF Tg mice-derived T cells can suppress production of rheumatoid factors by BAFF Tg-derived B cells after transfer into $RAG1^{-/-}$ mice. T and B cells were purified from WT and BAFF Tg which express the BAFF Tg under a liver specific promoter and not from lymphocytes [16]. Equal numbers of T and B cells collected from either WT or BAFF Tg mice were injected in $RAG1^{-/-}$ mice iv. Two weeks later mice were bled and their serum analysed for the presence of rheumatoid factor by ELISA. The sera of the donor BAFF Tg mice (pooled) and that of a $RAG1^{-/-}$ mouse un-injected with cells are shown as controls on the right of the bar graph. Data are shown as the mean and standard deviation for three mice analysed per group.

The importance of APRIL on T cell function in vivo remains unclear as studies performed on separate lines of APRIL-deficient mice gave slightly different results. One study reports no abnormality in T cell numbers and function in $APRIL^{-/-}$ mice [52]. Results in the second line of $APRIL^{-/-}$ mice showed significantly increased percentages of $CD44^{high}/CD62L^{low}$ effector/memory T cells but no gross abnormality of T cell responses [53]. Work on T cell-specific human APRIL Tg mice showed that APRIL expression can increase T cell survival in vitro and in vivo via up-regulation of the pro-survival oncogene Bcl-2 [23]. Interestingly, increased survival of APRIL Tg T cells in vitro was not suppressed by addition of TACI-Ig or BCMA-Ig, which both neutralise APRIL [23]. This may be indicative of an intrinsic survival advantage of these transgenic T cells [23] similar to BAFF Tg-derived B cells which survived better ex vivo but do not express the transgene [14]. Alternatively, as APRIL binds HSPG using a different domain than the BCMA and TACI binding domain [5,6], and can bind to BCMA and HSPG at the same time [6], it is conceivable that the survival advantage of APRIL Tg T cells is somewhat dependent on binding to HSPG. More work is needed to assess the role of APRIL via HSPG in vivo.

Little is known about the role of the APRIL/BAFF system on CD8 T cell activation. A recent study suggested that direct contact between B cells and dendritic cells (DC) was essential for the activation of CD8 T cells [54]. The key mechanism for this B cell-DC interaction involves the binding of TACI expressed on B cells to surface BAFF expressed on DC [54]. Indeed, $CD8^+$ T cell priming is impaired in B cell-deficient mice and can be rescued by injection of wild type B cells or injection of TACI-Ig fusion protein but not $TACI^{-/-}$ B cells [54]. Authors proposed a new model by which TACI could induce reverse signalling through surface BAFF in DC, a feature essential for priming of naïve CD8 T cell. This study, however, never directly confirmed this model, using BAFF-deficient DC for instance. In addition, a recent study has shown TACI binding to Syndecan-2 [55], which may lead to additional biology involving TACI. TACI-Ig treatment of DC in vitro prior to transfer to B cell-deficient mice did not significantly promote CD8 T cell priming in vivo, suggesting that this system may be slightly more complicated [54].

5. Conclusions and perspective

While the role of BAFF in B cell biology is dominant, it is now clear that, either directly or indirectly, this cytokine can modulate T cell function in vitro and in vivo. Recent data showing a protective effect of BAFF production against T cell-mediated inflammation, combined with the observation of BAFF-R expression on most regulatory T cells, is particularly interesting as further experiments may uncover useful new mechanisms for the regulation of T cells and possibly new options for therapeutic intervention in inflammation. The discovery of HSPG as additional APRIL binding receptors remains to be further investigated to answer some of the remaining key questions about the signalling capacity of these structures and/or their role in concentrating ligands at the surface of some cells. Finally, the work on

BAFF Tg mice has revealed that modification of the B cell compartment can indirectly influence the quality of T cell responses and a better understanding of this indirect B cell-mediated modulation of T cell responses may provide new ideas for the control of adverse T cell responses in autoimmunity/inflammation or, conversely, stimulate the regulatory component of the T cell population.

Acknowledgments

We would like to thank Shane Grey, Marcel Batten, Lai Guan Ng, Andrew Sutherland, Ian Sutton, Frederic Sierro, Stuart Tangye and Pablo Silveira for critical reading of the manuscript and unpublished observations. Fabienne Mackay is a Wellcome Trust senior research fellow and is also supported by the National Health Medical and Research Council in Australia and the New South Wales Lupus association.

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