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REVIEW

# B cells flying solo

Joanna Groom and Fabienne Mackay

**Systemic autoimmunity such as systemic lupus erythematosus (SLE) is associated with the loss of B-cell tolerance, B-cell dysregulation and autoantibody production. While some autoantibodies may contribute to the pathology seen with SLE, numerous studies have shown that dysregulation of T-cell function is another critical aspect driving disease. The positive results obtained in clinical trials using T-cell- or B-cell-specific treatments have suggested that cooperation between T and B cells probably underlies disease progression in many patients. A similar cooperative mechanism seemed to explain SLE developing in mice overexpressing the B-cell-activating factor from the tumor necrosis factor family (BAFF). However, surprisingly, T-cell-deficient BAFF transgenic (Tg) mice develop SLE similar to T-cell-sufficient BAFF Tg mice, and the disease was linked to innate activation of B cells and production of proinflammatory autoantibody isotypes. In conclusion, dysregulated innate activation of B cells alone can drive disease independently of T cells, and as such this aspect represents a new pathogenic mechanism in autoimmunity.**
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Immunology has come a long way since the days of virtual theories of antibodies entering cells as templates to be reproduced into identical molecules. Thanks to Sir Frank MacFarlane Burnet's concept of clonal selection,[1] and the work of many that followed, we are no longer obliged to compute 'magic' as one plausible parameter driving immune processes. In fact, immunologists now have access to the entire human genome, as well as the transcriptome of most immune cell subsets. Most cytokines and other immune molecules have been knocked out, or studied with monoclonal antibodies, resulting in detailed information on the processes that give rise to innate immunity, adaptive immunity and inflammation. In short, immunologists live and work in a world of detailed knowledge, such as molecular sequences, and compete to uncover the remaining mysteries of immunology using, as a base, the dogmas established by pioneers such as Burnet.

Jerne, Talmage and Burnet worked in an era when speculation was tolerated and advancing barely substantiated wild ideas was acceptable. This contributed to animating the scientific debate and stimulated scientific initiatives that uncovered new knowledge. Unlike Jerne, Talmage and Burnet, today's immunologists enjoy the benefit of very advanced technologies and immunological systems to substantiate any new claims of novel immune mechanisms.

In the year 50 BC (50 years since Burnet's Concept) focus has shifted to understanding the functional roles of enigmatic subsets such T regulatory cells, T-helper 17 cells, marginal zone (MZ) B cells and plasmacytoid dendritic cells. In addition, society is seeking translation of research findings into new therapies for immunological diseases, as well as new vaccines for AIDS, malaria and flu and so on. It is worth questioning whether immunology has provided a good return on investment. How many effective anti-inflammatory therapies have emerged in the past 50 years? We still don't really understand the basis of autoimmune diseases. Undoubtedly, vaccines have been immunology's greatest contribution to world health.

Immune mechanisms have now become so complex that the attention of immunologists is sometimes totally absorbed by the tiny details, and less by the big picture. It is becoming clearer that the immune system is intimately associated with other systems such as the nervous system and the metabolic system. The concept of immune connectivity to other systems is not novel, although immunologists have been slow to uncover the significance of these connections. Semaphorins, for instance, originally described as factors promoting neuronal growth, are now recognized as key molecules controlling dendritic cell and T-cell functions.[2] Work in my laboratory revealed that neuropeptide Y, a factor produced in response to psychological stress, and one of it's receptors, Y1, promote strong immunoregulatory functions.[3] Molecules involved in lipid metabolism are also essential for proper dendritic cell responses, and airway inflammation.[4]

This review will focus on addressing one important area of uncertainty remaining in the immune system, the exact role of B cells in driving systemic autoimmune diseases.

## A FEW CERTAINTIES AND MANY MORE DOUBTS ABOUT B CELLS

### B-cell development and maturation

B-lymphocytes develop in the bone marrow from hematopoietic stem cell precursors. The developing B cells must progress through various

The Autoimmunity Research Unit, The Garvan Institute of Medical research, Darlinghurst, New South Wales, Australia
Correspondence: Professor F Mackay, Autoimmunity Research Unit, The Garvan Institute of Medical research, 384 Victoria Street, Darlinghurst, New South Wales 2010, Australia.
E-mail: f.mackay@garvan.org.au
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intermediate stages of differentiation such as proB and preB stages before becoming immature B cells ready to leave the bone marrow.[5] This developmental process is dependent on the expression of key transcription factors[6] and appearance of heavy and surrogate light-chain pairs on the cell surface, which culminate in expression of the heavy and light chain, pairing to form the B-cell receptor (BCR).[5,7] However, the observation of IgA secretion in μMT mice, which do not express IgM or IgD and have a developmental block at the proB cell stage, had raised the possibility of an alternative/primitive pathway for B-cell development that forms B cells capable of responding to natural infection but not to conventional immunization.[8]

Once formed, immature B cells enter the blood and migrate to the spleen where they will mature.[5] In mice, maturation also involves a series of intermediate stages.[9] Immature B cells enter the spleen as transitional type 1 (T1), which can differentiate into transitional type 2 (T2) B cells.[10] Within the latter group, two subsets have been identified, T2 follicular cells that give rise to follicular B cells and T2 MZ cells that are precursors of MZ B cells.[11,12] A third intermediate subset has been designated as T3, but these cells do not give rise to mature B cells and correspond to a small pool of anergic B cells sequestered from the normal maturation pathway.[13,14] For the most part, mechanisms responsible for whether a B cell should differentiate into a follicular versus a MZ B cell are not known. As the MZ B-cell compartment contains more self-reactive B cells, the nature of the signal triggered through the BCR of these cells as opposed to follicular B cells may have decided their particular differentiation and localization in the splenic MZ.[15,16] In addition, both the BCR and expression of the B-cell-activating factor from the tumor necrosis factor (TNF) family (BAFF, also termed TNFSF13b, BLyS) are required for this process.[17,18] Yet, how these two signals interact to promote B-cell maturation and differentiation is unknown.

In the peritoneal cavity and the mesenteric lymph nodes reside B1 B cells composed of two subsets, B1a and B1b.[19] These B cells undergo renewal and may have originated from the fetal liver.[19] However, this possibility remains controversial as the bone marrow may also be a source of B1 B cells and the absence of the spleen prevents the maintenance of B1a B cells.[20] Regardless of their origin, B1 B cells do not appear to require BAFF to develop and survive,[21,22] although it is possible that BAFF may play a stimulatory role during their activation as the number of B1 B cells increases in mice overexpressing BAFF as they age.[23]

Markers used to identify mouse and human B-cell subsets often differ. As a result we have a more limited knowledge of human B-cell maturation, although recent studies have identified the human equivalent of transitional immature B cells.[24,25] The nature and phenotype of B1 B cells in humans remains unclear and more work is needed to understand human B-cell biology and phenotype, a key goal now that B-cell therapies are more widely used.

**B-cell tolerance**

Thanks to the development of many BCR/self-antigen transgenic models, considerable progress has been made in the understanding of the normal mechanisms responsible for the elimination of self-reactive B cells.[26–28] Self-reactive B cells are purged at various checkpoints during their differentiation.[5,26] This process starts in the bone marrow where self-reactive B cells can die or undergo receptor editing, which will change their specificity away from self-reactivity.[5,26] In the periphery, strongly self-reactive B cells are also eliminated either rapidly, or after several days becoming anergic and unresponsive to stimulation by self-antigen.[5,26] The small residuum of self-reactive B cells that escaped negative selection compete with normal B cells for anatomical niches and survival factors.[26] Consequently, it was predicted that excessive production of a survival factor such as BAFF shall break B-cell self-tolerance and allow strongly self-reactive B cells to survive. This is true when self-reactive B cells do not compete with normal B cells,[29,30] but when they do, the picture is not what one would have expected.[30] In this situation, strongly self-reactive B cells are normally eliminated and only low-affinity self-reactive B cells expand, many having an MZ phenotype.[30] The reason for this difference may relate to the timing of deletion, which differs depending on whether self-reactive B cells do or do not compete with other B cells. In the absence of competition, self-reactive B cells gain access to sites where they can undergo maturation to a later transitional stage at which time they express sufficient levels of BAFF receptor (BAFF-R), respond to BAFF production and survive. By contrast, when self-reactive B cells compete with other B cells they fail to mature and are deleted at an earlier transitional stage before they can express sufficient BAFF-R levels to be rescued by excess BAFF, thereby, explaining why negative selection in the presence of high BAFF level was minimally affected in this situation.[30]

This work has also revealed that low/intermediate-affinity self-reactive B cells are more resistant to negative selection, and/or more responsive to BAFF, resulting in the preferential recruitment into the MZ compartment.[30] Whether this mechanism is some kind of quality-control process designed to sequestrate weakly reactive B cells in the MZ compartment away from T-cell help, or whether it reflects the normal ability of the immune system to allow some degree of self-reactivity as a trade off for achieving sufficient diversity to efficiently combat infection, remains unclear. This work also revealed that high BAFF levels alone do not lead to a major breakdown of B-cell tolerance in normal individuals, perhaps explaining why variations in BAFF serum levels one would expect following occasional infections do not usually lead to autoimmunity.

**B-cell activation**

B cells can be activated in a T-cell-dependent or -independent manner. B cells carry somatically rearranged BCRs that they use to recognize, bind and internalize antigens in their native form.[31] This leads to their activation, although to be efficient the process usually requires CD4 T cell help, which provides key costimulatory signals such as CD40L.[32] The quality of the T-cell help will also determine the nature of isotype switching.[33] Upon initial interaction with T cells at the interface between the T-cell and B-cell zones in secondary lymphoid organs, an activated B cell can differentiate immediately into a short-lived plasma cell within extrafollicular proliferative foci or migrate toward the B-cell follicle where they participate in the germinal center (GC) reaction and undergo somatic hypermutation and affinity maturation.[34–36] Recent work using the hen egg lysozyme BCR and antigen system has revealed that affinity for the antigen plays a major role in deciding whether a B cell will differentiate into a plasma cells in proliferative foci or enter the GC.[37,38] Following affinity maturation in GC, B cells may differentiate into long-lived plasma cells or become memory B cells.[38] While some cytokines and key transcription factors have been shown to favor one differentiation pathway versus another,[39] the mechanisms regulating this process are largely unknown. Maintenance and activation of B-cell-mediated immunological memory is also an area requiring a lot more exploration, in particular the localization of memory B cells, many of which accumulate in the MZ but also in the follicle as suggested by a recent report.[40] Progress in the identification of additional markers may improve our understanding of the formation and biology of memory B cells.[40] On the other hand, some long-lived plasma cells migrate to

the bone marrow, a niche allowing their survival. The chemokine receptor CXCR4 appears to play a key role here,[41] which is not limited to cell migration but extends to the promotion of plasma cell survival within the bone marrow.[42] Persistence of humoral protection is another area that has not been fully explored.

T-cell-independent activation of B cells is perhaps a neglected area that is recently receiving greater attention.[43] B-cell activation to antigens in their environment is not limited to activation of the BCR. B cells are able to act as antigen-presenting cells (APCs) and as such also respond to a broad class of pathogens via innate, pattern recognition receptors such as Toll-like receptors (TLRs).[44] However, B cells are not equal in their APC functions. Activated B cells are better APC than naïve B cells.[45] In addition MZ and B1 B cells are stronger responders to TLR activation, which has resulted in them being described as 'innate' B cells,[46–48] perhaps reflecting the fact that MZ and B1 B cells constitute the first line of antimicrobial defense positioned at key entry points near the MZ sinus in the spleen[49] and the peritoneal cavity,[50] respectively.[51,52] Interestingly, MZ B cells are better APC than other B cells.[53] MZ and B1 B cells appear to be cellular components acting at the interface of the innate and adaptive immune system.[50] While their function during infections is evident, their role, including antigen presentation capacities in autoimmune processes, is another area requiring more work.

## B CELLS IN AUTOIMMUNITY: MORE EVIL THAN FIRST THOUGHT

### The old picture

The pathogenic role of autoantibodies in organ-specific autoimmune diseases has been clearly established. For instance, this is the case for idiopathic thrombocytopenic purpura, an autoimmune condition involving autoantibodies, which promote the destruction of platelets.[54]

The role of autoantibodies in systemic autoimmune disease has been a lot more obscure in the past. Two decades ago, any suggestion that B cells may play a pathogenic role in systemic autoimmune diseases would have been received with polite scepticism and an immediate objection arising from observations made in the clinic. For instance, most rheumatologists would have argued that a role for B cells while possible seems inconsistent. Thus, there is often a wide variation between the type and titers of autoantibodies and the severity of disease such as SLE, Sjögren's syndrome (SS) or rheumatoid arthritis (RA). As the presence of ectopic GC in lesions, which is a hallmark of a T-cell-dependent mechanism, was a stronger indicator of severity/poorer outcome, attention was focused on defects in T-cell activation/tolerance as a primary contributor to autoimmune disorders.[55] By contrast, the role of self-reactive B-cell activation tended to be viewed as a manifestation of tissue damage, with elevated autoantibodies levels leading to immune complexes depositing and fuelling inflammation.

### A gradual change of wind

In 1999, Mathis and co-workers published spectacular unexpected findings in a genetically manipulated model of non-obese diabetic mouse strain, which became relevant for the study of RA.[56] These mice developed spontaneous RA, driven by a specific anti-glucose phosphate isomerase autoantibody.[57] Serum transfer from these mice triggered rapid and severe arthritis in the recipient animals.[57] This study suggested that in some conditions B cells produce powerful pathogenic autoantibodies with strong proinflammatory functions. The mystery in this case is the nature of the autoantigen, which is widely expressed in the body, yet the pathogenic antibodies only trigger damage in the joints and nowhere else. Since, more reports have described autoantibodies with strong pathogenic activities.[58]

At that time, observations in the clinic had also placed the B cell back onto the autoimmunity map. B-cell-depleting agents such as rituximab (anti-CD20) originally developed to target B lymphomas were shown to suppress symptoms of autoimmunity in individuals suffering from anti-TNF-resistant RA.[59,60] Despite positive results in clinical trials, the nature of autoantibodies produced was often variable and inconsistent with disease severity, and, therefore investigators struggled understanding the exact role of B cells in these autoimmune conditions. One possibility argued is that unidentified autoantibodies other than rheumatoid factors, anti-DNA or antinuclear autoantibodies are produced and these trigger pathogenic mechanisms. This hypothesis, however, did not always verified in animal models. For instance, MRL-lpr mice engineered to produce B cells unable to secrete autoantibodies develop SLE,[61] suggesting in this model that production of autoantibodies was dispensable. In what particular circumstances B cells present self-antigen to T cells and how this may lead to severe corruption of T-cell tolerance in autoimmunity remains a vast area of investigation.

### The T-cell connection

Steroids and immunosuppressants are currently widely used to treat many patients suffering from autoimmune conditions such as SLE or RA.[62] Their efficacy lies in their ability to suppress inflammation but more specifically their ability to reduce T-cell activation.[62] There is no doubt that a defect in T-cell tolerance and activation is the strong underlying cause of disease in many animal models of autoimmunity and many patients with autoimmune diseases.[63,64] Inhibition of T-cell activation or T-B-cell interaction is an effective way to prevent autoimmunity in a number of animal models of SLE.[65,66] More recently, mutation of the *Roquin* gene, which specifically perturbs the function of follicular helper T cells, induces development of SLE in mice.[64] In humans, various human leukocyte antigen haplotypes have been associated with susceptibility to SLE.[63,67] T-cell signalling in SLE patients can be abnormal and analysis of anti-DNA autoantibodies has revealed somatic mutations, suggestive of T-dependent affinity maturation.[63,67] As mentioned above, autoantibody producing B cells also appear central to the pathogenesis of SLE. For instance, autoantibodies to TRIM21/Ro52 in SLE and SS, which can cause heart block in children from autoantibody-positive mothers.[68] Therefore, the current picture involves a tight cooperation between self-reactive T and B cells as the central cellular connivance driving disease.

Dysregulation of the innate immune system, activation of monocytes, dendritic cells or neutrophils and overproduction of inflammatory cytokines have also been thought to be play an important role side by side with impaired B-cell and T-cell tolerance/regulation.[67,69,70] These mechanisms may be linked. For instance, accumulation of apoptotic cell-derived nucleic acids can lead to TLR-dependent activation of plasmacytoid dendritic cells (pDCs), production of type I interferons, which stimulate DC maturation, and self-reactive T- and B-cell activation.[71–73] TLR9 is involved in the pathology of several mouse models of SLE.[74,75] In contrast, in the MRL-lpr model TLR9 has a protective role and deficiency in TLR9 exacerbates SLE.[76] This protection may occur, in part, via enhanced interleukim-10 production from TLR9-activated MZ B cells,[46,47] a population also expanded in MRL-lpr mice.[77] In contrast, TLR7 deficiency has a protective effect in the MRL-lpr model.[19,76] The MRL-lpr model is T-cell-dependent,[65] and MRL-lpr mice crossed onto BAFF-R-mutant mice show impaired B-cell maturation, but develop SLE.[78] Collectively, this work has unravelled a potential diversity in the respective

contribution of T and B cells in these autoimmune conditions, with models being more T-cell-dominant and others perhaps more B-cell-dominant.

## THE ROLE OF BAFF IN AUTOIMMUNITY, WHEN EVIDENCE CAN BE DECEPTIVE

### Evidence fitting the T/B cell cooperative model in sick BAFF Tg mice

BAFF is a TNF-like cytokine essential for the maturation and survival of peripheral B cells.[79–81] It binds to three receptors BAFF-R, transmembrane activator, calcium modulator and cyclophilin ligand interactor (TACI), and B-cell maturation antigen.[17] All three are expressed on B cells as they mature[17,82] BAFF-R expression is also upregulated on activated T cells and constitutively expressed on regulatory T cells (Tregs).[82,83]

BAFF transgenic (Tg) mice produce autoantibodies, leading to immune complex nephritis and salivary gland destruction, features reminiscent of SLE and SS, respectively.[84,85] Elevated BAFF levels are detected in some human autoimmune conditions, including SLE.[80,85] Like most SLE mouse models, disease in BAFF Tg mice correlates with clear abnormalities of the B-cell compartment, leading to inappropriate BAFF-induced survival of self-reactive B cells.[86] Moreover, we have shown that MZ B cells and B1 B cells may play tissue-specific roles in the pathogenesis of SLE in BAFF Tg mice.[23,85,87] MZ B cells appear to target the salivary gland,[85] whereas the B1 B cells are associated with inflammation in the kidney.[87] However, as mentioned above, excessive production of BAFF has a minimal effect on B-cell tolerance especially in physiological situations where self-reactive B cells compete with a large excess of normal B cells.[30] Excessive BAFF production leads to accumulation of weakly self-reactive B cells and a role for these B cells in driving severe autoimmunity could only be explained by the subsequent affinity maturation of these B cells and the production of high-affinity autoantibody. Yet, BAFF Tg mice lacking GC structures where B-cell affinity maturation takes place, develop severe autoimmune disease similar to GC-sufficient BAFF Tg mice.[23,87] These unexpected findings forced the consideration of an alternative system, which alone or in association with the production of weakly self-reactive B cells would promote severe autoimmune disorders in BAFF Tg mice.

T cells are the obvious suspects and indeed BAFF has direct and indirect effects on T cells.[88] Upon activation, T cells upregulate BAFF-Rs on the surface and produce BAFF.[88] BAFF binding to T cells speeds T-cell differentiation into effector T cells, augments the expression of the prosurvival oncogene Bcl-2 and favors the production of T-helper 1 cytokines by activated T cells such as interferon-$\gamma$.[82,89] A larger proportion of effector T cells are present in BAFF Tg mice;[84] however, this phenotype is linked to the expansion of the B-cell compartment as BAFF Tg mice lacking B cells have normal numbers of effector T cells. As the MZ B cell compartment is also expanded in BAFF Tg mice[86] and these cells have a powerful APC function on naïve T cells,[53] it is conceivable that MZ-driven activation of T cells has led to abnormal T-cell activation. However, MZ B cells are not the only B cells responsible for the expansion of the effector T-cell compartment, as BAFF Tg mice lacking lymphotoxin and MZ B cells also have a larger effector T-cell compartment, albeit not as expanded as that of the original BAFF Tg mice.[87] Therefore, a model emerges whereby excessive BAFF production leads to expansion of the B-cell compartment, including weakly self-reactive B cells. Having greater APC attributes, MZ B cells may have contributed to inappropriate activation of T cells. Upon activation, T cells upregulate BAFF-Rs and secrete BAFF. BAFF binding to BAFF-Rs on T cells contributes to exacerbate the inappropriate activation of T cells and together with B-cell activation, this may have led to the severe autoimmune symptoms seen in BAFF Tg mice.

### Mixed messages from Tregs and pDC

As mentioned above, a model involving both T and B cells driving disease in BAFF Tg mice seemed likely, until we made an unusual observation looking at Tregs in BAFF Tg mice.[90] The Treg numbers were augmented in the thymus, blood, spleen and lymph nodes,[90] a finding that was inconsistent with a major role for T cells in driving disease in BAFF Tg mice, as Tregs purified from BAFF Tg mice were shown to actively suppress T-cell activation *ex vivo*.[90] Therefore, it is likely that increased numbers of Tregs in BAFF Tg mice play a censoring role on activated T cells. A look at pDC activation also did not reveal any particular change in BAFF Tg mice compared with control animals,[90] in contrast to other mouse models of SLE.[71] The involvement of Tregs and the apparent lack of pDC role in BAFF Tg mice add confusion to a picture where the role of T cells has become more and more obscure.

### The unlikely truth revealed

To understand the exact role of T cells in driving disease in BAFF Tg mice, we crossed BAFF Tg mice onto mice lacking all T cells.[90] To our surprise, T-cell-deficient BAFF Tg mice developed SLE of severity similar to that of T-cell-sufficient BAFF Tg mice.[90] This result demonstrated that in the presence of high levels of BAFF, B cells were contributing to the disease independently of T cells. In search of the pathogenic role of B cells, we discovered that expression in B cells of MyD88, a signalling component used by many TLRs and cytokines such as interleukin-1,[91–93] was essential for disease in BAFF Tg mice. In addition, signalling through TLR7 and TLR9, receptors playing an important role in T-cell-independent B-cell activation,[71] upregulated TACI expression on B cells and to a lesser extent BAFF-R.[90,94–96] Conversely, BAFF signalling via TACI but not BAFF-R or B-cell maturation antigen upregulated TLR7 and TLR9 expression on B cells (our unpublished observation). Therefore, a stimulatory loop is appearing whereby TLR7/9 activation upregulated TACI expression, which in turn upregulated TLR7/9 expression. Whether this cross-talk between TACI and TLR7/9 plays a role in driving the pathogenic mechanisms seen in BAFF Tg mice requires further attention, in particular defining which MyD88-depedent mechanism is at play. We know that lack of TLR9 expression in B cells does not protect BAFF Tg mice.[90] The role of TACI in autoimmunity is also unclear. Autoimmunity and lymphomas develop in TACI-deficient mice, suggesting that TACI has a negative regulatory role in B Cells.[97,98] However, recent work suggests that levels of BAFF are elevated in TACI$^{-/-}$ mice and this may have contributed to driving disease in these mice.[99] Complicating this picture, oligomeric but not trimeric BAFF can activate TACI, a form detected in BAFF Tg and TACI$^{-/-}$ mice.[99] Moreover, rather than acting as a negative regulator, TACI signalling appears to promote B-cell activation and plasmablast survival.[99] Nevertheless, assuming that elevated BAFF is the real trigger of autoimmunity seen in TACI$^{-/-}$ mice, clearly, BAFF-R and/or B-cell maturation antigen but not TACI drive the disease. It still remains to be determined whether disease in TACI$^{-/-}$ mice is driven by a similar mechanism to that seen in BAFF Tg mice.

### A new form of SLE

Our work has revealed a new form of SLE revolving around the dysregulation of B-cell tolerance and innate B-cell activation.[90] Excessive BAFF production leads to the expansion and survival of

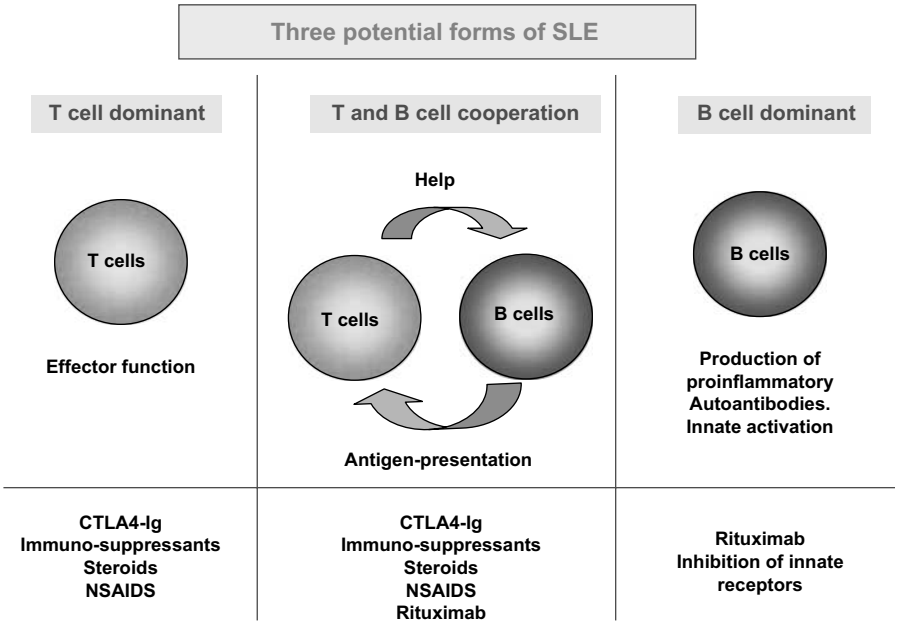


**Figure 1** Three potential forms of SLE. Left panel: SLE driven by a specific T-cell defect. Middle panel: SLE driven by the cooperation between self-reactive T and B cells. Right panel: SLE driven by the innate activation of B cells and production of proinflammatory autoantibodies. SLE, systemic lupus erythematosus.

low-affinity self-reactive B cells, many of which are MZ B cells.[30] This population is known to contain self-reactive B cells such as rheumatoid factors (RF) and anti-DNA B cells.[100,101] In addition, these cells are very good responders to T-cell-independent antigens that activate TLRs.[46,47] MZ B cells are also the first line of defense against pathogens such as bacteria and viruses,[100] which may explain the transient appearance of RF and anti-DNA autoantibodies in patients suffering from an incidental infection;[102,103] MZ B cells and possibly B 1 B cells respond very well to TLR activation compared with follicular B cells.[104] We, and others, have shown that this response is further enhanced in the presence of BAFF.[90] This leads to increased production of autoantibodies by self-reactive B cells from BAFF Tg mice.[90] We have shown that IgG2b/c isotypes are particularly proinflammatory and their production is associated with C3 deposition in the kidney and the development of nephritis.[90]

In short, excess levels of BAFF expand self-reactive MZ and B1 B cells.[30] BAFF signals promote TLR activation following internalization of autoreactive BCRs bound to either double-stranded DNA or to immune complexes containing nucleic acids. BAFF enhances TLR signals, which lead to production of IgG2c and IgG2b antibodies. Autoantibodies deposit in the kidney and promote inflammation through complement fixation. In conclusion, dysregulated innate activation of B cells alone can drive disease independently of T cells, and as such this aspect represents a new pathogenic mechanism in autoimmunity.

## CONCLUSIONS

About 22–25% of SLE patients and 35–40% of patients suffering from SS have elevated BAFF levels in the serum.[81] How many of these patients may be suffering from a B-cell-dominant disease? There is no doubt that T cells with or without B cells play an important role in driving autoimmunity in patients. The efficacy of some immunosuppressants and CTLA4-Ig in clinical trials[105] is a clear indication that suppressing T-cell activation and help to B cells has beneficial effects in many patients with SLE or SS, but not all. A closer look at the non-responders or individuals benefiting from B-cell-depleting treatments, their levels of BAFF and possibly expression of TACI and TLR7/9 may give clues to whether a subgroup of patients exists with a B-cell-dominant mechanism. Identification of such a new group of patients may improve the management of their disease (Figure 1), a better stratification of patients for the purpose of clinical trials and the design of novel therapeutic agents capable of disarming the innate activation of B cells.

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