Commentary

B cells, BAFF/zTNF4, TACI, and systemic lupus erythematosus

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Abstract

B cells and B-cell/T-cell collaborations are instrumental in the pathophysiology of systemic lupus erythematosus (SLE). This commentary highlights in particular the newly discovered role of B-cell-activating factor (BAFF; also known as TALL-1, THANK, BlyS, and zTNF4) as a positive regulator of B-cell functions, such as B-cell activation and differentiation. Two members of the tumor necrosis factor(TNF)-receptor superfamily were recently identified as receptors for BAFF on B cells. The interaction between BAFF and its receptors may be important in the pathogenesis of lupus. Advances in our understanding of abnormalities in immune regulation in lupus might provide the opportunity to improve our current therapeutic approaches to this disorder.

Keywords: BAFF, SLE, TACI, TNF, TNF receptor superfamily

Introduction

B cells are believed to be central to the pathogenesis of SLE. Specific patterns of autoantibodies are characteristically detected in lupus; in addition, a direct pathogenic role of these autoantibodies has been convincingly demonstrated for at least some, such as anti-dsDNA, anti-Ro, and anti-cardiolipin antibodies. Besides secreting pathogenic antibodies, recent studies have shed important new light on the role of B cells in shaping the immune repertoire, thereby pointing to new ways in which B cells may contribute to the pathogenesis of lupus. In contrast to mice deficient in T-cell receptors, mice lacking B cells do not develop M cells in the gut, suggesting that B cells are involved in the organogenesis of gut-associated lymphoid tissue [1]. Since M cells can function as professional antigen-presenting cells, it was unexpected that B cells play a 'directing' role during the development of these cells. An important murine model for lupus is the MRL-lpr/lpr mouse, characterized by Fas deficiency, double negative T cells, autoantibodies, vasculitis, and glomerulonephritis. Chan *et al* [2] showed that MRL-lpr/lpr mice deficient in antibody secretion still develop nephritis and vasculitis. This finding challenged the standard view that the major contribution of B cells in promotion of autoimmunity in murine lupus is by antibody production, and led to the speculation that B cells may play a promoting role as antigen-presenting cells in the course of the disease. Chan *et al* suggested that their findings are consistent with the presence of an amplification loop between cognate B and T cells, resulting in an increase of memory and effector T cells [2]. This latter interpretation is consistent with a recent study by David Gray and colleagues [3] demonstrating that T_H cell memory depends on the presence of B cells but is clearly independent of the presentation of peptides by these B cells. Further studies [4,5] have found that IgM-deficient mice develop autoimmune features suggestive of lupus, including the production of anti-dsDNA antibodies. Since a similar autoimmune tendency

BAFF = B-cell-activating factor; SLE = systemic lupus erythematosus; TACI = transmembrane activator and CAML-interactor; TNF = tumor necrosis factor; TRAF = TNF-receptor-associated factors.

has been reported in human patients deficient for IgA [6], it is conceivable that immunoglobulins are also instrumental in self-regulation. Therefore, it appears that we are just beginning to understand an integrated network of different immune-cell compartments where B cells seem to be of more central importance than was previously appreciated.

A consistent finding in lupus is intrinsic B-cell hyperreactivity. Upon stimulation of the B-cell receptor, lupus B cells show abnormally high Ca influxes followed by higher concentrations of inositol triphosphate and tyrosine phosphorylated proteins, as compares to B cells from normal controls [7], indicating a unique, intrinsic abnormality of B cells in SLE. However, an overwhelming B-cell overactivity induced by signaling through membrane receptors cannot be excluded. In this context, stimulation via complement receptor 2 has been suggested to contribute to signaling abnormalities in lupus [8], since the ligand of this receptor, C3d, was identified to be part of immune complexes in lupus [9].

Anti-dsDNA antibodies present in SLE are generally IgG with high affinity for antigen, and display somatic mutations in the immunoglobulin variable regions. These are molecular characteristics of antibodies arising in an antigen-driven, T-cell-dependent response. Furthermore, blocking B-cell/T cell costimulation with CTLA4Ig or anti-CD40 ligand in murine lupus results in dramatic effects on anti-DNA antibody titers, renal disease, and survival [10–14]. Clearly, B-cell/T-cell cognate interactions are critical in lupus; inhibition of costimulation is a novel and potentially very useful approach to the treatment of human autoimmune disease.

BAFF/zTNF and TACI, a novel ligand/receptor pair

Interactions between tumor necrosis factor (TNF)-like ligands and their receptors are crucial to the regulation of the immune response, via induction of apoptosis or by promoting cell survival and proliferation [15]. The recent discovery of interacting molecules belonging to these ever-growing families has afforded important insights into normal and pathological immunity, while facilitating the development of a new approach to therapeutic modulation of autoimmune disease by blocking a novel pathway of B- and T-cell interaction.

BAFF (B-cell-activating factor) was identified as a member of the TNF family in 1999 by several independent research groups and consequently is alternatively referred to in the literature as TALL-1, THANK, BlyS, and zTNF4 [16–19]. BAFF is expressed on dendritic cells, monocytes/macrophages, and T cells. It quickly became clear that BAFF is a positive regulator of B-cell function, with effects on cell survival, activation, and differentiation. Soluble BAFF costimulates B cells activated by anti-IgM [16] or by IL-4 [20], and may also have weaker direct stimulatory effects [20].

By means of receptor-cloning methodology, two previously orphan members of the TNF-receptor superfamily, known as TACI (transmembrane activator and CAML-interactor) and BCMA (B-cell-maturation antigen), were found to be the receptors for BAFF on B cells [21–24]. Soluble receptor (TACI-Ig: a fusion protein of the extracellular domain of the receptor with the Fc portion of an immunoglobulin molecule) prevented binding of BAFF to B cells and inhibited its stimulatory effect on human and murine B cells *in vitro* [25]. Blocking the interaction of BAFF receptor with TACI-Ig in immunized mice results in significantly decreased numbers of antigen-specific IgM and IgG antibodies. Moreover, treated mice were found to be devoid of germinal centers [21]. These data and others suggest that the interaction between BAFF and TACI, in an analogous fashion to the related costimulatory pair CD40 ligand/CD40, is crucial for the normal development of antigen-specific humoral responses. In contrast to mice treated with TACI-Ig, however, mice deficient in CD40 ligand and CD40 have normal IgM responses, suggesting that the interaction between BAFF and TACI may occur earlier in B-cell activation. It is important to note that soluble TACI also inhibits T-cell-independent responses [23]. More recent studies have addressed the molecular mechanisms involved in BAFF binding to its receptor [21,23,26]. Similar to other members of the TNF-receptor family that lack a death domain [15], the intracellular domain of TACI associates with TNF-receptor-associated factors (TRAF) and activates NFκB and c-Jun NH_2 terminal kinase, thus presumably transducing signals for B-cell proliferation and survival.

BAFF and autoimmunity

The discovery that BAFF mediates a strong signal for B-cell proliferation and survival led researchers to consider a role for this molecule in diseases characterized by B-cell hyperactivity. Important confirmation of a possible role of BAFF in the pathogenesis of autoimmunity came from transgenic studies. In BAFF-transgenic mice (under control of a liver specific promotor), Mackay *et al* [10] found a significant expansion of the peripheral B-cell compartment (spleen and lymph nodes), with mature cells exhibiting an activated phenotype. Numerous germinal centers were present without immunization, and the number of plasma cells was increased. Some but not all BAFF-transgenic mice displayed marked hyperglobulinema, with circulating immune complexes and a positive rheumatoid factor, high titers of antibodies against single-stranded and double-stranded DNA, and immunoglobulin deposition in the kidneys. Similar results were reported by Khare *et al* [20], who generated TALL-1 transgenic mice under the control of a beta actin promoter. The transgenic mice had marked B-cell hyperplasia and hypergammaglobulinemia. Furthermore, there was a progressive increase in serum IgM and IgG anti-dsDNA antibody titers over time, followed by immune-complex nephritis and renal

dysfunction. The serological manifestations and renal involvement in both BAFF transgenic models are strongly reminiscent of SLE. Moreover, high serum concentrations of BAFF were found in two murine models of lupus (NZB × NZW F_1 and MRL-lpr/lpr), with an increase in serum BAFF concentrations over time paralleling worsening disease activity [25].

The positive regulatory effects of BAFF on B cells and on T-cell-dependent humoral responses, the autoimmune phenotype of BAFF transgenic mice, and the high levels of BAFF in lupus-prone mice suggest that blocking the interaction between BAFF and its receptor with TACI-Ig may be a useful therapeutic approach in murine lupus [25]. Female 21-week-old B/W mice were treated with TACI-Ig three times weekly for 5 weeks. Mice treated with a high dose of TACI-Ig had a markedly delayed onset of proteinuria. Importantly, treatment also resulted in a meaningful difference in survival, with 100% of the animals receiving TACI-Ig surviving to 38 weeks versus only 47% of controls. Although anti-dsDNA antibody titers did not decline, treated mice exhibited a decrease in peripheral-blood B cells.

Conclusion

Clearly, we do not yet fully appreciate the myriad immune defects found in SLE. In this commentary, we discussed some of the recent experimental approaches to defining novel roles for B cells and B-cell/T-cell collaboration in the pathophysiology of SLE. These discoveries have provided new insights into our understanding of abnormalities in immune regulation in lupus, and might eventually provide the opportunity to improve the specificity and effectiveness of therapeutic approaches to this complex disease.

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