HHS Public Access

Author manuscript

Autoimmunity. Author manuscript; available in PMC 2018 February 01.

Published in final edited form as:

Autoimmunity. 2017 February ; 50(1): 37–41. doi:10.1080/08916934.2017.1280028.

B cell contribution of the CD4+ T cell inflammatory phenotypes in systemic lupus erythematosus

Seung-Chul Choi and **Laurence Morel***

Department of Pathology, Immunology, and Laboratory Medicine, University of Florida, Gainesville, FL 32610, USA

Abstract

Systemic lupus erythematosus is an autoimmune disease in which the effector molecules responsible for tissue damage are antibodies directed against a large number of self-antigens, among which nucleic acids complexed with proteins play a prominent role. These pathogenic autoantibodies are produced by plasma cells differentiated from activated autoreactive B cells, a process that requires complex interactions between multiple components of the immune systems. A key step in the activation of autoreactive B cells is provided by $CD4^+$ T cells through cytokines and cell-to-cell contact. Lupus $CD4^+$ T cells are autoreactive and they present an activated inflammatory phenotype that has been shown to contribute to disease. In addition to their role in antibody production, B cells have other effector functions, the most important ones being antigen presentation to and co-stimulation of $CD4^+$ T cells, as well as the secretion of cytokines. Here we review what is known, largely based on mouse models, how these B cell effector functions contribute to the $CD4^+$ T cell inflammatory phenotypes in lupus. When possible, we compare $CD4^+$ T cell activation by B cells and by dendritic cells, and speculate how these interactions may contribute to the disease process.

Keywords

Follicular helper T cells; Th17; Treg; B1-a cells; marginal zone B cells

Introduction

It is well documented that systemic lupus erythematosus (SLE) is an autoimmune disease driven by pathogenic autoantibodies (autoAbs), and consequently SLE has been referred to as a disease of B cell hyperactivity [1]. The multiple factors leading to B cell hyperactivity in SLE have been recently reviewed [2]. The requirement of autoantibodies for tissue injury was formally demonstrated in MRL/lpr mice, a classic model of spontaneous lupus, which were protected by a mutation that eliminated the ability of B cells to secrete antibodies [3]. Numerous clinical trials targeting B cells have been conducted, either directly for B cell

*Corresponding author: Department of Pathology, Immunology and Laboratory Medicine, University of Florida, Gainesville, FL 32610-0275, USA., Tel: (352) 392-3790, Fax: (352) 392-3053. morel@ufl.edu.

Declaration of Interest section

The authors have no conflict of interest to disclose. This work was partially supported by a grant R01 AI058150 from the NIH to LM. Both SSC and LM are employed by the University of Florida.

depletion mediated through an anti-CD20 antibody (rituximab), or indirectly through an antibody targeting BAFF (belimumab), a major B cell survival factor that is over expressed in SLE patients [4]. Belimumab has shown a modest efficacy in reducing disease activity in some SLE patients and became the first (and only so far) biologic treatment to be approved by the US Food and Drug Administration for the treatment of SLE. B cell depletion therapy with rituximab has failed to show end-point efficacy in clinical trials [5], but it is still used off-label with success in cases of refractory SLE [6]. One paradoxical effect of B cell depletion is to increase BAFF levels, which may exacerbate flares by stimulating and amplifying non-deleted autoreactive B cells [7]. Interestingly, rituximab has shown efficacy in two other autoimmune diseases, rheumatoid arthritis and multiple sclerosis, but the mechanisms by which B cell depletion has therapeutic effects in these diseases appears to be either by preventing B cells to produce inflammatory cytokines or to present antigens to autoreactive $CD4^+$ T cells, rather than through the production of autoAbs [8].

B cells are indeed more than the precursors of antibody-secreting cells, and they actively participate to immune responses with a variety of effector functions, the most important ones being antigen (Ag) presentation to and co-stimulation of $CD4^+$ T cells, as well as the production of cytokines, which can be either pro-inflammatory (IL-6, TFNα) or anti-inflammatory (IL-10). It has been suggested that B cells could modulate the autoimmune process through these functions [9]. B cells are also distributed in different subsets along their differentiation that have overlapping but distinct effector functions [10]. There is evidence that for a distorted distribution of these B cell subsets in lupus mice [11] and patients [12], and hence a different contribution of these B cells to immune responses. Here, we will summarize the evidence showing how B cells contribute to SLE pathogenesis through effector functions other than antibody production. Although many immune cell subsets have been shown to participate into the disease process in lupus through an amplification loop [13], this review will focus on how B cells regulate the effector functions of $CD4^+$ T cells, which is the most documented B-cell-to-immune-cell interaction.

B cell vs. DC activation of $CD4^+$ T cells in lupus

The role of conventional B cells as antigen-presenting cells (APC) has been established in the 1980s' (see [14] for an excellent discussion), and their contribution to the immune response is non-redundant with that of professional APCs. First, B cells present only specific Ag that they internalize through their B cell receptor (BCR), ensuring a linked recognition with cognate $CD4^+$ T cells that is crucial for a coordinated immune response. This Ag-specificity also allows the activation of rare T cells by minute amounts of Ag [15–17], which is an obvious key feature of an efficient T-dependent immune response. Second, Ag-presentation by B cells tends to occur later than Ag-presentation by dendritic cells (DCs), and it has been proposed that B cells play a greater role of the reactivation of memory T cells [18].

B cells can also activate $CD4^+$ T cells through the production of cytokines in response to TLR activation. B cells and DCs express various TLRs at different levels, and accordingly, these two cell types respond with a different pattern of cytokine secretion to TLR stimulation [19]. During cognate B:T cell interactions, paracrine stimulation of T cells by B

cell-secreted cytokines could be critical in T cell polarization. TLR-stimulated B cells secrete IFNγ, which may prime Th1 cell induction, and IL-6, which may promote or maintain the polarization of Th17 and follicular helper T (Tfh) cells. B cells were shown to be less efficient than DCs in inducing Treg cells, but the maximal Treg polarization was obtained with a mixture of B cells and DCs [20]. These observations have been made with cells from normal mice, and it would be very interesting to investigate to which extent this occurs in lupus, a disease in which each of these three T cells subsets (Th1, Th17, Tfh) are expanded [21–23]. Indeed, TLR7 stimulation of DCs, which is commonly associated with lupus, inhibits Treg polarization through the production of IL-6 [24]. This study did not examine the effect of TRL7-stimulated B cells on Treg polarization, but it is likely that it would be similar. Various TLRs are also expressed differently among B cells subsets [19], which leads to their different cytokine response to the corresponding TRL ligands, adding another potential layer of complexity. Innate-like B-1 cells and marginal zone (MZ) B cells are the main producers of IL-10, a complex cytokine with both pro- and anti-inflammatory functions [25]. IL-10 produced by B cells (Breg) is generally thought as having immunosuppressive activity on T cells [26]. The number or function of Breg is defective in lupus [27], which may lead to an unrestrained production of type I IFN by pDCs [28] in addition to a direct effect on T cells [29].

Depletion of $CD11c^+$ DCs in the MRL/lpr lupus-prone mice resulted in a significant reduction of autoimmune pathology in both kidneys and skin, as well as T cell expansion [30]. Interestingly, DC-deficient MRL/lpr mice produced reduced levels of autoAbs, but similar levels of total IgG than their DC-sufficient controls. This has been interpreted as the autoAbs being mostly produced by extra-follicular plasmablasts, while total IgG is produced by post-germinal center (GC) plasmablasts that are less affected by DCs depletion. Surprisingly, however, the absence of DCs had very little impact on spontaneous T cell activation, suggesting that the chronic activation of T cells by autoAg is performed by B cells rather than DCs. This suggests a complex and only partially overlapping distribution of labor between lupus B cells and DCs in activating pathogenic T cells. Another level of complexity was revealed by the analysis of the consequences of B-cell vs. DC-specific deletion of MyD88, and therefore their ability to signal in response to TLR activation, in the same MRL/lpr model of lupus [31]. The same group had previously shown that TLR7 was required for the production of anti-RNA autoAbs as well as clinical disease, and that TLR9 was required for the production of anti-DNA autoAbs [32]. Deletion of MyD88 in B cells greatly decreased the production of total IgG and eliminated autoAbs, while the mice with MyD88-deficient DCs had normal levels of IgG and modestly reduced levels of some autoAbs. Since these autoAbs are T-dependent, these results demonstrate the critical role played by TLR-activated B cells in stimulating autoreactive T cells in the production of autoAbs. The differential role of TLR-activated B cells and DCs is not likely to be through follicular helper T cells (Tfh), which were both reduced in DC-and B-cell-specific MyD88 deficiency. However, only $CD4^+$ T cells from B-cell deficient MRL/lpr mice or MRL/lpr mice with MyD88-deficient B cells showed a significantly reduced spontaneous $CD4^+$ T cell activation and effector memory phenotype. This suggests that B cells activate T cells in a qualitatively different manner than DCs, which may be more favorable to autoreactive T cells. Surprisingly, given the critical role of DCs in nephritis mentioned above [30], MyD88-

deficiency in B cells but not in DCs was protective for renal pathology, while the reverse was true for dermatitis. In support of their role of in lupus nephritis, B cells have been found in close proximity of Tfh-like cells in the kidneys of nephritic patients [33], although inflammatory myeloid cells have also be shown to play a prominent role in autoimmune renal pathology [34]. These results suggested the existence of tissue-specific differences in the relative importance of B cell vs. DC activation of T cells that are more salient in lupus than in non-autoimmune mice due to the chronic TLR activation by nucleic acids. Indeed, a recent study suggests that autoreactive spontaneous Tfh cells may be activated by B cells through a different mechanism than Tfh cells induced by immunization with a foreign Ag [35]. Specifically, IFN-γR expression and STAT1 signaling in B cells is required for a full induction of spontaneous Tfh cells in autoimmune B6.*Sle1b* mice through T-bet expression and IFN-γ production by B cells. This IFN-γ-dependent activation of Tfh by B cells leads to the production of autoAbs.

B-1a cell activation of effector T cells

B-1a cells are generally excluded from classical T-dependent immune responses [36]. This innate-like subset of B cells has an enhanced APC capacity as compared to conventional B cells (B2) that was recognized over 20 years ago [37]. Syngeneic peritoneal B-1a cells expanded IL-10, IFNγ and IL-4 producing $CD4^+$ T cells in an Ag-dependent manner, while splenic B-1a cells expanded Th17 cells as compared to conventional B cells *in vitro. In vivo*, the same Ag-pulsed peritoneal B-1a cells induced a greater $CD4^+$ T cell proliferation [38]. Allogeneic B-1a cells induced a strong expansion of inflammatory $CD4^+$ T cells secreting IFNγ, IL-17 and TNFα in an Ag-dependent manner, while in the same conditions, B2 cells expanded Treg cells [39]. In addition to Ag presentation, it was shown that CD44 and CD86 expression was required for the B-1a cells to expand inflammatory T cells [40]. Conversely, IL-17A promoted pulmonary B-1a cells during influenza virus infection by induction of Blimp-1 and NF-kB, which are key transcription factors for B-1a cell differentiation [41]. This suggests that there a mutual amplification between B1-a cells and Th17 cells that may play a protective role against specific pathogens.

B-1a cells are expanded in lupus-prone mice [42] and SLE patients [43]. In lupus-prone mice, B-1a cells are found not only in their expected location in the peritoneal and pleural cavities, but also in inflamed tissues, such as the kidneys and the thymus [44], in a CXCL13/CXCR5-dependent manner [45]. Moreover, there is evidence that $CD4^+$ T cells migrate to the peritoneal cavity where they encounter B-1a cells [38]. In addition, B-1a cells from the lupus-prone NZM2410 mouse express high levels of co-stimulatory molecules and have high APC functions [46]. Finally, B-1a cells from lupus mice have a different receptor repertoire [47], and they are enriched for a sub-population expressing PDL-2 that is more autoreactive [48], but whose function is currently unknown [49]. The effect of B1-a cells on T cells in lupus has not yet been directly evaluated. However, given their numbers, location in inflamed tissues where $CD4^+$ T cells are also found, their skewed repertoire toward autoreactivity and high co-stimulatory activity, it likely that lupus B-1a cells contribute to the activation of autoreactive T cells, therefore participating in the multicellular feedforward activation loop that has been described to sustain lupus pathogenesis [13]. In support of this hypothesis, we have found that the expression of the *Sle2c1* locus, which is responsible for

the B-1a cell expansion in the NZM2410 model, increases Th17 cell polarization and promotes nephritis in Fas-deficient mice [50].

MZB cell activation of effector T cells

MZB cells are innate-like B cells that share many characteristics with B-1a cells, including their predominance in T-independent immune responses [51]. The splenic marginal zone is relatively devoid of T cells. However, MZB cells rapidly respond to TLR activation by moving into the follicles, where they encounter $CD4^+$ T cells. In this context, MZB cells have superior APC and priming functions as compared to follicular B cells, resulting into Th1-polarization and expansion [52]. MZB cells can also suppress protective $CD4^+$ T cell responses, as it was shown with *Leishmania*, which is presented to T cells by MZB cells, but also induce the production of IL-10 by the same MZB cells [53]. We have shown that MZB cells spontaneously migrate to the follicles in NZM2410 lupus-prone model [54, 55], resulting in increased interactions with $CD4^+$ T cells. Furthermore, MZB cells from lupus-prone mice showed enhanced responses to TLR activation as compared to MZB cells from non-autoimmune mice [56]. Interactions between MZB cells and $CD4^+$ T cells from lupus-prone mice resulted in a mutually enhanced activation, suggesting an amplification loop that contributes to the pathogenic process.

A more specialized function has been described for MZB cell precursors (MZP) that accumulate in the spleen of BXD2 mice, another spontaneous model of lupus [57]. In these mice, MZPs shuttle Ag to germinal centers (GC) in a type 1 IFN-dependent manner. Deficiency for the type 1 IFN receptor (*Ifnar*) resulted in MZPs being retained in the MZ area and in a reduced number of spontaneous GCs. Moreover, *Ifnar*-deficiency suppressed T-dependent Ab responses in response to immunization in these mice [58]. This was associated with a down-regulation of CD86 expression, which is expressed at the highest levels on MZPs. Accordingly, MZPs showed the highest $CD4^+$ T cell co-stimulation activity as compared to MZB and follicular B cells that was inhibited by an anti-CD86 blocking Ab. Interestingly, the importance of CD86 in T cell activation by B cells was demonstrated independently for both B-1a cells (see above) and MZB cells. CD86-deficiency (and not CD80-deficiency) restored the retention of MZB cells in the MZ area in lupus-prone B6.*Sle1.Sle2.Sle3* mice, which was associated with an absence of anti-DNA IgG production and a significant reduction in renal pathology [55]. Taken together, these results have identified MZB and MZP cells as unique activators of T cells in a manner that is amplified by type 1 IFN, a class of cytokines that is center to lupus pathogenesis.

A complex multicellular mechanism supports the involvement of MZB and MZP cells in autoimmune pathogenesis. MZB/MZP cells and MZ macrophages (MZM) depend on each other for retention in the MZ area, and MZMs are progressively lost in lupus-prone mice [55, 59]. In the absence of MZMs, apoptotic debris accumulate and load the MZB/MZPs that are translocated to the follicles in response to type 1 IFN produced by DCs in the MZ sinus. Apoptotic debris are highly immunogenic through TLR7/9 activation and are central to the pathogenic process in lupus. Although not directly demonstrated, it is likely that these apoptotic debris contribute directly, or indirectly through TLR activation, to the activation of autoreactive $CD4^+$ T cells. The loss of MZMs is due to the disruption of activation signals

coming from the MZB/MZPs through the expression of membrane lymphotoxin-α1β2 (mLT) [60]. More precisely, mLT signaling induces the expression of megakaryoblastic leukemia 1 (MKL1), a transcriptional coactivator that regulates the mechanosensing pathway, which is required to activate the phagocytosis of apoptotic cells. This complex mechanism involving MZB/MZP, type 1 IFN-producing DCs, and MZMs and leading to the activation of autoreactive Tfh cells and the production of autoAbs has been validated in two genetically different mouse models of lupus, BXD2 and B6.*Sle1.Sle2.Sle3*, and is therefore likely to be an important contributor to autoimmune pathogenesis.

Regulation of T:B cell interaction by SLAM family genes

The SLAM gene family encodes for receptors which, along with their adaptors SAP and EAT-2, regulate immune cell to cell interactions, including interactions between $CD4^+$ T cells and B cells [61]. Mutations in SAP are responsible for X-linked lymphoproliferative disease (XLP), which is characterized by multiple immunological abnormalities, including a paucity of GCs and impaired T-dependent humoral responses. T:B interactions regulated by SAP and Ly108 (*Slamf6*) as well as CD84 (*Slamf5*) are necessary for GC formation [62]. Mutations in SLAM family genes [63] as well as in EAT-2 [64] have been associated with lupus susceptibility in mice. The SLAM family genes are arranged in a cluster in tight linkage disequilibrium, and it has been difficult to delineate the contribution of each gene to the autoimmune process [65]. *Ly108* has been the best characterized, with evidence that a differential distribution of splice isoforms impairs B cell [66, 67] as well as $CD4^+$ T cell [68, 69] tolerance in a cell-intrinsic manner. It has also been shown that B cells and $CD4^+$ T cells specific for a low affinity peptide that express the *Sle1*-lupus susceptibility alleles of the SLAM gene cluster engage in shorter interactions than B and T cells expression the non-autoimmune alleles [70]. There is evidence that these brief interactions allow for a greater sampling of partners for optimal binding, leading to a greater chance for activation of autoreactive cells. This is so far the only evidence that polymorphisms in SLAM genes may contribute to systemic autoimmunity not only through intrinsic impairments of B cells and T cells, but also through their interactions. A deeper investigation in that direction may characterize this process in more details.

Concluding remarks

SLE is essentially a B cell disease because autoantibodies are the ultimate effector molecules. The participation of $CD4^+$ T cells in the production of these autoantibodies has been well documented. T cell targeting therapies have been proposed as an alternative to the existing B cell targeting approaches to prevent T cell help to autoreactive B cells [71]. This unidirectional B-cell centric driving force in lupus pathogenesis is however over-simplified. There are well-documented examples, either in lupus models or extrapolated from other systems, that B cells regulate $CD4^+$ T cell functions in a non-redundant manner with dendritic cells. This is especially true considering the different B cells subsets that may respond differentially to inflammatory signals. Therefore, a better understanding of the consequences of either B or T cell depletion or targeting in lupus should include the characterization of B:T cell amplification loops that may be critical for pathogenesis.

References

1. Lipsky PE. Systemic lupus erythematosus: an autoimmune disease of B cell hyperactivity. Nat Immunol. 2001; 2:764–6. [PubMed: 11526379]
2. Bird AK, Meednu N, Anolik JH. New insights into B cell biology in systemic lupus erythematosus and Sjogren's syndrome. Curr Opin Rheumatol. 2015; 27:461–7. [PubMed: 26164595]
3. Shlomchik MJ, Madaio MP, Ni D, et al. The role of B cells in lpr/lpr-induced autoimmunity. J Exp Med. 1994; 180:1295–306. [PubMed: 7931063]
4. Vincent FB, Morand EF, Schneider P, et al. The BAFF/APRIL system in SLE pathogenesis. Nat Rev Rheumatol. 2014; 10:365–73. [PubMed: 24614588]
5. Duxbury B, Combescure C, Chizzolini C. Rituximab in systemic lupus erythematosus: an updated systematic review and meta-analysis. Lupus. 2013; 22:1489–503. [PubMed: 24135078]
6. Beckwith H, Lightstone L. Rituximab in systemic lupus erythematosus and lupus nephritis. Nephron Clin Pract. 2014; 128:250–4. [PubMed: 25471633]
7. Ehrenstein MR, Wing C. The BAFFling effects of rituximab in lupus: danger ahead? Nat Rev Rheumatol. 2016; 12:367–72. [PubMed: 26888554]
8. Lino AC, Dorner T, Bar-Or A, et al. Cytokine-producing B cells: a translational view on their roles in human and mouse autoimmune diseases. Immunol Rev. 2016; 269:130–44. [PubMed: 26683150]
9. Mariño E, Grey ST. B cells as effectors and regulators of autoimmunity. Autoimmunity. 2012; 45:377–87. [PubMed: 22432804]
10. Allman D, Pillai S. Peripheral B cell subsets. Curr Opin Immunol. 2008; 20:149–57. [PubMed: 18434123]
11. Sang A, Zheng YY, Morel L. Contributions of B cells to lupus pathogenesis. Mol Immunol. 2013; 62:329. [PubMed: 24332482]
12. Anolik JH. B cell biology: implications for treatment of systemic lupus erythematosus. Lupus. 2013; 22:342–9. [PubMed: 23553777]
13. Liu Z, Davidson A. Taming lupus-a new understanding of pathogenesis is leading to clinical advances. Nat Med. 2012; 18:871–82. [PubMed: 22674006]
14. Popi AF I, Longo-Maugeri M, Mariano M. An Overview of B-1 Cells as Antigen-Presenting Cells. Front Immunol. 2016; 7:138. [PubMed: 27148259]
15. Malynn BA, Romeo DT, Wortis HH. Antigen-specific B cells efficiently present low doses of antigen for induction of T cell proliferation. J Immunol. 1985; 135:980–8. [PubMed: 2409164]
16. Townsend SE, Goodnow CC. Abortive proliferation of rare T cells induced by direct or indirect antigen presentation by rare B cells in vivo. J Exp Med. 1998; 187:1611–21. [PubMed: 9584139]
17. Rivera A, Chen CC, Ron N, et al. Role of B cells as antigen-presenting cells in vivo revisited: antigen-specific B cells are essential for T cell expansion in lymph nodes and for systemic T cell responses to low antigen concentrations. Intern Immunol. 2001; 13:1583–93.
18. Fuchs EJ, Matzinger P. B cells turn off virgin but not memory T cells. Science. 1992; 258:1156–9. [PubMed: 1439825]
19. Barr TA, Brown S, Ryan G, et al. TLR-mediated stimulation of APC: Distinct cytokine responses of B cells and dendritic cells. Eur J Immunol. 2007; 37:3040–53. [PubMed: 17918201]
20. Moore C, Sauma D, Reyes PA, et al. Dendritic cells and B cells cooperate in the generation of CD4(+)CD25(+)FOXP3(+) allogeneic T cells. Transplant Proc. 2010; 42:371–5. [PubMed: 20172352]
21. Pollard KM, Cauvi DM, Toomey CB, et al. Interferon-gamma and systemic autoimmunity. Discov Med. 2013; 16:123–31. [PubMed: 23998448]
22. Koga T, Ichinose K, Tsokos GC. T cells and IL-17 in lupus nephritis. Clin Immunol. 2016 Apr 21. pii: S1521-6616(16)30069-9. doi: 10.1016/j.clim.2016.04.010
23. Blanco P, Ueno H, Schmitt N. T follicular helper (Tfh) cells in lupus: Activation and involvement in SLE pathogenesis. Eur J Immunol. 2016; 46:281–90. [PubMed: 26614103]
24. Hackl D, Loschko J, Sparwasser T, et al. Activation of dendritic cells via TLR7 reduces Foxp3 expression and suppressive function in induced Tregs. Eur J Immunol. 2011; 41:1334–43. [PubMed: 21469103]

25. Geginat J, Larghi P, Paroni M, et al. The light and the dark sides of Interleukin-10 in immune-mediated diseases and cancer. Cytokine Growth Factor Rev. 2016 Mar 8. pii: S1359-6101(16)30019-3. doi: 10.1016/j.cytogfr.2016.02.003
26. Candando KM, Lykken JM, Tedder TF. B10 cell regulation of health and disease. Immunol Rev. 2014; 259:259–72. [PubMed: 24712471]
27. Blair PA, Norena LY, Flores-Borja F, et al. CD19(+)CD24(hi)CD38(hi) B cells exhibit regulatory capacity in healthy individuals but are functionally impaired in systemic Lupus Erythematosus patients. Immunity. 2010; 32:129–40. [PubMed: 20079667]
28. Menon M, Blair PA, Isenberg DA, et al. A regulatory feedback between plasmacytoid dendritic cells and regulatory B cells is aberrant in systemic lupus erythematosus. Immunity. 2016; 44:683–97. [PubMed: 26968426]
29. Flores-Borja F, Bosma A, Ng D, et al. CD19+CD24hiCD38hi B cells maintain regulatory T cells while limiting TH1 and TH17 differentiation. Sci Transl Med. 2013; 5:173ra23–ra23.
30. Teichmann LL, Ols ML, Kashgarian M, et al. Dendritic cells in lupus are not required for activation of T and B cells but promote their expansion, resulting in tissue damage. Immunity. 2010; 33:967–78. [PubMed: 21167752]
31. Teichmann LL, Schenten D, Medzhitov R, et al. Signals via the adaptor MyD88 in B cells and DCs make distinct and synergistic contributions to immune activation and tissue damage in lupus. Immunity. 2013; 38:528–40. [PubMed: 23499488]
32. Christensen SR, Shupe J, Nickerson K, et al. Toll-like receptor 7 and TLR9 dictate autoantibody specificity and have opposing inflammatory and regulatory roles in a murine model of lupus. Immunity. 2006; 25:417–28. [PubMed: 16973389]
33. Liarski VM, Kaverina N, Chang A, et al. Cell distance mapping identifies functional T follicular helper cells in inflamed human renal tissue. Sci Transl Med. 2014; 6:230ra46.
34. Davidson A. What is damaging the kidney in lupus nephritis? Nat Rev Rheumatol. 2016; 12:143–53. [PubMed: 26581344]
35. Domeier PP, Chodisetti SB, Soni C, et al. IFN-γ receptor and STAT1 signaling in B cells are central to spontaneous germinal center formation and autoimmunity. J Exp Med. 2016; 213:715–32. [PubMed: 27069112]
36. Berland R, Wortis HH. Origins and functions of B-1 cells with notes on the role of CD5. Ann Rev Immunol. 2002; 20:253–300. [PubMed: 11861604]
37. Zimecki M, Kapp JA. Presentation of antigen by B cell subsets. II. The role of CD5 B cells in the presentation of antigen to antigen-specific T cells. Arch Immunol Ther Exp (Warsz). 1994; 42:349–53. [PubMed: 8572891]
38. Margry B, Wieland WH, van Kooten PJ, et al. Peritoneal cavity B-1a cells promote peripheral CD4+ T-cell activation. Eur J Immunol. 2013; 43:2317–26. [PubMed: 23719868]
39. Zhong X, Gao W, Degauque N, et al. Reciprocal generation of Th1/Th17 and T(reg) cells by B1 and B2 B cells. Eur J Immunol. 2007; 37:2400–4. [PubMed: 17683116]
40. Wang Y, Rothstein TL. Induction of Th17 cell differentiation by B-1 cells. Front Immunol. 2012; 3:281. [PubMed: 22973276]
41. Wang X, Ma K, Chen M, et al. IL-17A promotes pulmonary B-1a cell differentiation via induction of blimp-1 expression during influenza virus infection. PLoS Pathog. 2016; 12:e1005367. [PubMed: 26735852]
42. Duan B, Morel L. Role of B-1a cells in autoimmunity. Autoimmun Rev. 2006; 5:403–8. [PubMed: 16890894]
43. Griffin DO, Rothstein TL. A small CD11b(+) human B1 cell subpopulation stimulates T cells and is expanded in lupus. J Exp Med. 2011; 208:2591–8. [PubMed: 22110167]
44. Morshed SRM, Mannoor K, Halder RC, et al. Tissue-specific expansion of NKT and CD5+B cells at the onset of autoimmune disease in (NZB×NZW)F1 mice. Eur J Immunol. 2002; 32:2551–61. [PubMed: 12207339]
45. Ishikawa S, Matsushima K. Aberrant B1 cell trafficking in a murine model for lupus. Front Biosci. 2007; 12:1790–803. [PubMed: 17127421]

46. Mohan C, Morel L, Yang P, et al. Accumulation of splenic B1a cells with potent antigen-presenting capability in NZM2410 lupus-prone mice. Arthritis Rheum. 1998; 41:1652–62. [PubMed: 9751099]
47. Holodick NE, Zeumer L, Rothstein TL, et al. Expansion of B-1a cells with germline heavy chain sequence in lupus mice. Front Immunol. 2016; 7:108. [PubMed: 27047495]
48. Zhong X, Lau S, Bai C, et al. A novel subpopulation of B-1 cells is enriched with autoreactivity in normal and lupus-prone mice. Arthritis Rheum. 2009; 60:3734–43. [PubMed: 19950285]
49. Lee RA, Mao C, Vo H, et al. Fluorescence tagging and inducible depletion of PD-L2-expressing B-1 B cells in vivo. Ann N Y Acad Sci. 2015; 1362:77–85. [PubMed: 26291441]
50. Xu Z, Cuda CM, Croker BP, et al. The NZM2410-derived lupus susceptibility locus Sle2c1 increases TH17 polarization and induces nephritis in Fas-deficient mice. Arthritis Rheum. 2011; 63:764–74. [PubMed: 21360506]
51. Martin F, Oliver AM, Kearney JF. Marginal zone and B1 B cells unite in the early response against T-independent blood-borne particulate antigens. Immunity. 2001; 14:617–29. [PubMed: 11371363]
52. Attanavanich K, Kearney JF. Marginal zone, but not follicular B cells, are potent activators of naive CD4 T cells. J Immunol. 2004; 172:803–11. [PubMed: 14707050]
53. Bankoti R, Gupta K, Levchenko A, et al. Marginal zone B cells regulate antigen-specific T cell responses during infection. J Immunol. 2012; 188:3961–71. [PubMed: 22412197]
54. Duan B, Croker BP, Morel L. Lupus resistance is associated with marginal zone abnormalities in an NZM murine model. Lab Invest. 2007; 87:14–28. [PubMed: 17170739]
55. Duan B, Niu H, Xu Z, et al. Intrafollicular location of marginal zone / CD1d hi B cells is associated with autoimmune pathology in a mouse model of lupus. Lab Invest. 2008; 88:1008–19. [PubMed: 18607347]
56. Zhou Z, Niu H, Zheng YY, et al. Autoreactive marginal zone B cells enter the follicles and interact with CD4+ T cells in lupus-prone mice. BMC Immunol. 2011; 12:7. [PubMed: 21251257]
57. Wang JH, Li J, Wu Q, et al. Marginal zone precursor B cells as cellular agents for type I IFN-promoted antigen transport in autoimmunity. J Immunol. 2010; 184:442–51. [PubMed: 19949066]
58. Wang JH, Wu Q, Yang P, et al. Type I interferon-dependent CD86(high) marginal zone precursor B cells are potent T cell costimulators in mice. Arthritis Rheum. 2011; 63:1054–64. [PubMed: 21225691]
59. Li H, Wu Q, Li J, et al. Cutting edge: Defective follicular exclusion of apoptotic antigens due to marginal zone macrophage defects in autoimmune BXD2 mice. J Immunol. 2013; 190:4465–9. [PubMed: 23543760]
60. Li H, Fu YX, Wu Q, et al. Interferon-induced mechanosensing defects impede apoptotic cell clearance in lupus. J Clin Invest. 2015; 125:2877–90. [PubMed: 26098211]
61. Cannons JL, Tangye SG, Schwartzberg PL. SLAM family receptors and SAP adaptors in immunity. Ann Rev Immunol. 2011; 29:665–705. [PubMed: 21219180]
62. Cannons JL, Qi H, Lu KT, et al. Optimal germinal center responses require a multistage T cell:B cell adhesion process involving integrins, SLAM-associated protein, and CD84. Immunity. 2010; 32:253–65. [PubMed: 20153220]
63. Wandstrat AE, Nguyen C, Limaye N, et al. Association of extensive polymorphisms in the SLAM/CD2 gene cluster with murine lupus. Immunity. 2004; 21:769–80. [PubMed: 15589166]
64. Talaei N, Yu T, Manion K, et al. Identification of the SLAM adapter molecule EAT-2 as a lupus-susceptibility gene that acts through impaired negative regulation of dendritic cell signaling. J Immunol. 2015; 195:4623–31. [PubMed: 26432891]
65. Wang A, Batteux F, Wakeland EK. The role of SLAM/CD2 polymorphisms in systemic autoimmunity. Curr Opin Immunol. 2010; 22:706–14. [PubMed: 21094032]
66. Kumar KR, Li LN, Yan M, et al. Regulation of B cell tolerance by the lupus susceptibility gene Ly108. Science. 2006; 312:1665–9. [PubMed: 16778059]
67. Wong EB, Soni C, Chan AY, et al. B cell-intrinsic CD84 and Ly108 maintain germinal center B cell tolerance. J Immunol. 2015; 194:4130–43. [PubMed: 25801429]

68. Wang N, Keszei M, Halibozek P, et al. Slamf6 negatively regulates autoimmunity. Clin Immunol. 2016 Jun 28. pii: S1521-6616(16)30117-6. doi: 10.1016/j.clim.2016.06.009

69. Keszei M, Detre C, Rietdijk ST, et al. A novel isoform of the Ly108 gene ameliorates murine lupus. J Exp Med. 2011; 208:811–22. [PubMed: 21422172]

70. Sinai P I, Dozmorov M, Song R, et al. T/B-cell interactions are more transient in response to weak stimuli in SLE-prone mice. Eur J Immunol. 2014; 44:3522–31. [PubMed: 25209945]

71. Comte D, Karampetsou MP, Tsokos GC. T cells as a therapeutic target in SLE. Lupus. 2015; 24:351–63. [PubMed: 25801878]