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The regulation of autoreactive B cells during innate immune responses

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Abstract

Systemic lupus erythematosus (SLE) highlights the dangers of dysregulated B cells and the importance of initiating and maintaining tolerance. In addition to central deletion, receptor editing, peripheral deletion, receptor revision, anergy, and indifference, we have described a new mechanism of B cell tolerance wherein dendritic cells (DCs) and macrophages (MΦs) regulate autoreactive B cells during innate immune responses. In part, DCs and MΦs repress autoreactive B cells by releasing IL-6 and soluble CD40L (sCD40L). This mechanism is selective in that IL-6 and sCD40L do not affect Ig secretion by naïve cells during innate immune responses, allowing immunity in the absence of autoimmunity. In lupus-prone mice, DCs and MΦs are defective in secretion of IL-6 and sCD40L and cannot effectively repress autoantibody secretion suggesting that defects in DC/MΦ-mediated tolerance may contribute to the autoimmune phenotype. Further, these studies suggest that reconstituting DCs and MΦs in SLE patients might restore regulation of autoreactive B cells and provide an alternative to immunosuppressive therapies.

Keywords

Systemic lupus erythematosus; B cell tolerance; Autoimmunity; Dendritic cell; Macrophage; Smith antigen

Learning tolerance: a B cell's story

A diverse B cell repertoire is critical in combating pathogens, but inherent in generating diversity is the threat of autoimmunity. In the bone marrow, central tolerance mechanisms such as deletion or receptor editing remove high-affinity autoreactive B cells before they exit to the periphery [1–10]. Those that escape are subject to receptor revision [8, 11–14], peripheral deletion [15, 16], or a shortened lifespan because they fail to enter B cell follicles [17–22]. In rare cases, autoreactive B cells are fully functional but indifferent to their specific antigen [23–25]. Finally, many low-affinity autoreactive B cells are maintained in an unresponsive state known as anergy. Anergic B cells do not receive sufficient activation signals to differentiate into plasma cells or secrete immunoglobulin (Ig) in response to antigenic or mitogenic stimulation [26–29]. Their proliferative responses to B cell receptor (BCR) or toll-like receptor (TLR) signaling as well as their lifespans vary in different models [18, 30–35]. Some anergic B cells transduce BCR-derived signals [30, 32, 36–40], while others exhibit desensitized BCRs [30, 33, 41]. Quiescence is dependent on chronic exposure to self-antigen and occupancy of the BCR [42, 43]. Furthermore, ERK activation is

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critical in sustaining anergy during polyclonal stimulation by TLR ligands [27, 28]. Recently, it was demonstrated that anergy can be mediated by DCs and MΦs. In the presence of TLR ligands, DCs and MΦs release IL-6 and sCD40L that selectively represses Ig secretion from autoreactive B cells [44, 45]. In the absence of DCs/MΦs and their soluble factors, autoreactive B cells regain the ability to secrete Ig, indicating that this mechanism of tolerance is reversible. These data suggest that autoreactive B cells must be maintained in close proximity to DCs/MΦs during innate immune responses to prevent autoimmunity.

The affinity and avidity of the antigen-BCR interaction determines whether developing B cells will be deleted, edited, anergized, or ignored [46]. Self-reactive B cells that survive these developmental checkpoints tend to bind self-antigens with low affinity and they remain anergic in the absence of costimulation by cognate T cells. Many of the early transgenic (Tg) models expressed BCRs with high affinities. However, concerns were raised that these models may not adequately reflect how bona fide low-affinity self-antigens are regulated [1, 26]. To study the tolerance mechanisms regulating low-affinity B cells, new Ig Tg models were generated that expressed BCRs specific for double-stranded (ds) DNA, single-stranded (ss) DNA, rheumatoid factor (RF), insulin, and Smith antigen (Sm).

A short history of Sm

Sm antigens are conserved proteins that are indispensable in RNA splicing. In 1966, Sm was identified as a unique autoantigen, the first non-histone target of autoantibodies in systemic lupus erythematosus (SLE) patients [47]. Named for 15-year-old Stephanie Smith, antibodies to Sm became one of the diagnostic criteria for SLE [48], detectable in 5–30% of SLE patients [48, 49]. Later studies correlated anti-Sm titers with kidney disease [50–53].

The autoantibodies isolated from patient sera proved invaluable in the initial studies of the Sm proteins [54]. The small nuclear RNA (snRNA U1, U2, U4, or U5) in each small nuclear ribonucleic particle (snRNP) is predicted to thread through the center of a heptameric ring of Sm proteins (E, F, G, D1, D2, D3, and B/B') [55]. Three of the Sm proteins (D1, B, and D3) have long, positively charged tails that contact the pre-mRNA in the 5′ splice site region [56]. This interaction stabilizes the commitment complex formed when U1 snRNP binds the pre-mRNA substrate [57]. The remaining snRNPs, U2 and U4/U5/U6 (the triple snRNP) bind to pre-mRNA, rearrange to form the splicesome, and remove introns from the transcript [58].

Self-antigens composed of protein and DNA or RNA can co-ligate the BCR with TLRs, potentially overcoming tolerance mechanisms and activating autoreactive B cells. For example, concomitant ligation of the BCR and TLR9 by chromatin:IgG immune complexes (ICs) activates RF-specific B cells in the absence of T cell help or overt TLR stimulation [38, 59, 60]. Signaling through both the BCR and TLR9 is necessary to activate NF-κB in these B cells [37]. Recently, RNA-IgG ICs were shown to activate RF-specific B cells via TLR7 [39]. TLR7 binds ssRNA, a viral antigen that acts as a sensor of infection as well as a component of the U1 snRNP splicing complex, a known autoantigen in SLE [61, 62]. Aberrantly high expression of TLR7, or an increased burden of ICs and/or apoptotic cells, aggravates disease in lupus-prone mice. For instance, the gene duplication of TLR7 in *Yaa* mice results in hyperactive B cells, exacerbation of disease in lupus-prone models, and shifts autoantibody specificities to RNA [63, 64]. Reducing TLR7 gene expression ameliorates disease and increases survival [63]. Hence, the combination of self-proteins and TLR ligands within ICs and on the surface of apoptotic cells can mistakenly activate autoreactive B cells and result in autoimmunity.

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Arresting and silencing Sm-specific B cells

Sm-specific autoantibodies are a hallmark of both human and murine lupus. To identify the mechanisms that regulate Sm-specific B cells, the 2–12H Tg mice were generated [35, 65]. In this model, an Ig heavy chain, 2–12H, was identified from an Sm-specific hybridoma derived from an MRL/*lpr* mouse. The 2–12H chain pairs with a variety of light chains, giving rise to B cells specific for Sm and/or ss-DNA. B cells from the 2–12H model express BCRs of multiple affinities that develop and are regulated on a non-autoimmune background.

Tolerance to Sm is dependent on several cell types. B cells are the most obvious suspects in SLE since disease pathology is mediated by autoantibodies. In vivo, Sm-specific B cells are regulated since 2–12H Tg mice have low titers of anti-Sm antibodies [35, 66]. However, ex vivo non-subsetted 2–12H B cells (uncontaminated by DCs and MΦs) are activated by TLR stimulation (LPS, CpG, dsRNA) in vitro but their Ig secretion is lower than that of C57BL/6 controls [35, 67]. The follicular (FO) B cell subset is repressed by DCs and MΦs secreting IL-6 and sCD40L, while secretion by the MZ B cell subset is partially repressed, but only by MΦs and sCD40L [45]. Some MZ B cells and peritoneal B-1 cells ignore endogenous levels of Sm, but an increase in the number of apoptotic cells can activate peritoneal and MZ B cells [66, 68, 69]. Sm-specific B cells arrested at the pre-plasma cell stage, interrupting plasma cell differentiation and preventing Ig secretion [32].

Restricting the light chain that pairs with 2–12H allowed for the analysis of Sm-specific B cells of moderate and low affinity [32, 70]. The 2–12H/Vκ4 Tg mouse was generated to examine regulation of higher affinity anti-Sm responses [70]. B cells from this mouse are distributed among splenic transitional, FO, and MZ subsets, as well as the peritoneal B-1 subset [70]. 2–12H/Vκ4 B cells are anergic and all subsets are hyporesponsive to LPS in vitro. Additionally, MZ B cells exhibit a block in BCR signaling [70]. LPS-stimulated 2–12H/Vκ4 B cells are repressed by IL-6 and sCD40L (unpublished data). To study low-affinity anti-Sm responses, the 2–12H/Vκ8 Tg mouse was created [32]. In this model, only transitional and FO B cells are present and these cells are regulated by anergy [32]. As in the previous anti-Sm models, 2–12H/Vκ8 B cells are susceptible to IL-6- and sCD40L-mediated repression [44, 45].

T cells are implicated in SLE and Sm-specific T cells are present in the repertoires of both normal and autoimmune mice [71]. Sm-specific T cells in 2–12H Tg mice are anergic and do not proliferate in response to B cells presenting Sm [71]. Anergic T cells are also unable to upregulate CD40L and provide costimulation to their cognate B cells [72]. Anti-Sm B cells do not secrete Ig in vivo [35, 65], perhaps because they are deprived of T cell costimulation. However, in autoimmune situations, autoreactive T cells induce class-switching and somatic hypermutation of anti-Sm B cells, resulting in high levels of pathogenic high-affinity IgG autoantibodies [73, 74]. Paradoxically, anti-Sm B cells are required to tolerize Sm-specific T cells from C57BL/6 mice, but they activate Sm-specific T cells from MRL/*lpr* mice [71, 75, 76]. This indicates that although T cells are necessary for the development of autoantibodies and disease, they are also regulated by autoreactive B cells in normal individuals.

DCs and MΦs regulate innate and adaptive immune responses by tolerizing or activating T and B cells. The continued ingestion and presentation of self-antigens or the acute presentation of foreign antigen by DCs/MΦs either tolerizes or activates T cells to drive adaptive immune response. The activation of DCs during innate immune responses induces the secretion of IL-6 that promotes immunity by releasing $CD4^+$ T-helper cells from their

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inhibitory functions [77]. This promotes polyclonal activation of naive B cells, the production of neutralizing antibody and the clearance of the invading pathogen.

In addition to regulating T cells, DCs and MΦs affect the fate of B cells. They activate naïve B cells by secreting type I interferon, IL-6, and B lymphocyte stimulator (BLyS) [78–80]. They also repress Ig secretion by B cells that have been chronically exposed to antigen. Our laboratory showed that DCs and MΦs regulate autoantibody production, in part through their secretion of IL-6 and sCD40L [44, 45]. Repression is selective in that naïve B cells (not chronically exposed to antigen) are unaffected by the presence of IL-6 and sCD40L while Ig secretion by autoreactive B cells is repressed (Fig. 1a). Coupled with the data showing that IL-6 de-represses regulatory T cells, a mechanism emerges explaining how the pleiotropic affects of IL-6 produced by DCs and MΦs simultaneously promotes immunity and represses autoimmunity during innate immune responses. Signal transduction through many cell surface receptors influences neighboring receptors.

For example, crosstalk between the IFN-αβ and IL-6 receptor (IL-6R) signaling pathways augment transcription factor binding and gene expression in mouse embryonic fibroblasts (MEFs) [81]. Similarly, stimulation of B cells with sCD40L, IL-4, and LPS reprograms the BCR signaling pathway, enhancing ERK activation and bypassing the requirement for phosphatidylinositol 3-kinase (PI3-K) [82–86]. The findings that only B cells chronically exposed to self-antigen are susceptible to repression by IL-6 and sCD40L suggests that chronic BCR-derived signals “reprogram” the outcome of IL-6R and CD40 signal transduction. On a molecular level, the ability of IL-6 and sCD40L to repress Ig secretion reflects diminished BLIMP-1 and XBP-1 mRNA and protein levels. These data indicate that regulation occurs upstream of transcriptional activation. In support of this, pharmacologically inhibiting MEK restores LPS-induced Ig secretion. This suggests that the ability of IL-6/sCD40L to repress TLR4-induced Ig secretion is MEK/ERK-dependent (unpublished data).

Susceptibility of B cells to IL-6/sCD40L requires that B cells be chronically exposed to antigen, consistent with a central role for the BCR in tolerance. High-affinity neo-self-antigens direct a unique tolerance scheme compared to low-affinity self-antigens. Anergic B cells from high-affinity models are characterized by elevated phospho-ERK [42, 87]. In addition, the binding of high-affinity antigen to the BCR and constitutive MEK/ERK activation is sufficient to repress TLR4 and TLR9-induced Ig secretion [27, 28]. In the low-affinity Sm model (2–12H/Vκ8) basal phospho-ERK levels are comparable to those in the HEL model. However, unlike the HEL model, the binding of soluble SmD or snRNPs coupled with elevated phospho-ERK levels does not repress TLR-induced Ig secretion (unpublished data). This indicates that ERK is only part of the “BCR-derived” signals that regulate innate immune responses in vivo. Although B cells expressing high-affinity receptors can be repressed by IL-6 and sCD40L, antigen stimulation is sufficient. In contrast, B cells expressing low-affinity receptors for bona fide self-antigens (Sm and ssDNA) do not achieve sufficient BCR-derived signals to influence TLR4-induced Ig secretion and depend on additional signals from IL-6/sCD40L (unpublished data).

The finding that DCs secrete IL-6 while MΦs secrete IL-6 and sCD40L suggests that the anatomic location within the secondary lymphoid organs might dictate how autoreactive B cells are regulated. Marginal zone B cells are solely repressed by sCD40L while FO B cells are repressed by IL-6 and sCD40L [45]. This specificity may result from the anatomic location, since different subsets of DCs and MΦs localize to specific regions of the spleen. For example, B cells are retained in the marginal zone by MΦs [88] and they are regulated by MΦ-derived sCD40L. However, upon activation and differentiation into pre-plasma cells, they may become susceptible to repression by IL-6 secreted by DCs within the

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periarteriolar lymphoid sheath (PALS). Thus, depending on the anatomic location of the autoreactive B cell, DCs and/or MΦs can repress autoantibody production during innate immune responses.

Failed tolerance: Sm-specific autoantibodies in a murine model of SLE

MRL/*lpr* mice are a well-characterized murine model of SLE, with adult-onset disease mediated by autoantibody deposition and tissue destruction. The prevalence of anti-Sm autoantibodies in human SLE patients and MRL/*lpr* mice is approximately 25% [89, 90]. BCR Tg models have been bred onto the MRL background, allowing B cells of known specificities to be followed throughout development. Developmental arrest, FO exclusion, and receptor editing are defective in MRL/*lpr* mice [91, 92]. Expression of the 2–12H transgene in MRL/*lpr* mice increases the prevalence of the anti-Sm response, accelerates disease, and leads to higher serum anti-Sm levels [65]. Sm-specific B cells from 2–12H mice are arrested at the pre-plasma cell stage, while B cells from the 2–12H/MRL/*lpr* mice bypass this checkpoint and become activated [93].

The presence of class-switched autoantibodies in MRL/*lpr* mice suggests a breakdown in tolerance within the adaptive immune response. In MRL/*lpr* mice where somatic hypermutation and isotype switch recombination are blocked ($AID^{-/-}$), lupus-like symptoms such as glomerulonephritis, proteinuria, and immune complex deposition are ameliorated [94]. Early studies showed a critical role for T cells in disease because thymectomized MRL/*lpr* mice failed to develop lupus-like disease [95]. Subsequently, it was shown that defects in central deletion and the number and function of T-regulatory cells allow $CD4^+$ T-helper cells to activate autoreactive B cells, induce terminal differentiation and autoantibody production [96–101].

Dysregulation of the innate immune system is apparent in MRL/*lpr* mice [39]. ICs containing RNA or chromatin stimulate RF-specific B cells through TLR7 and TLR9 to secrete anti-Sm and anti-chromatin [38, 39]. Consistent with a role for TLRs, autoantibody responses were reduced in $MyD88^{-/-}$/MRL/*lpr* mice [39] and disease was ameliorated [102]. $TLR7^{-/-}$/MRL/*lpr* mice exhibit reduced autoantibody titer and gene duplication of TLR7 shifts autoantibody specificities toward RNA, exacerbating disease [63, 64]. This reveals TLR7 as a key receptor in promoting autoimmunity when tolerance is overcome [63, 103]. Like $TLR7^{-/-}$/MRL/*lpr* mice, $TLR9^{-/-}$/MRL/*lpr* mice exhibited lower titers of anti-DNA autoantibodies. However unlike $TLR7^{-/-}$/MRL/*lpr* mice, they remain plagued by accelerated kidney disease and increased mortality [103]. These data suggest that TLR9 induces anti-DNA responses but also has an anti-inflammatory effect, possibly through its induction of regulatory T cells [104, 105]. The function of regulatory T cells in $TLR9^{-/-}$/MRL/*lpr* mice is impaired, potentially allowing autoreactive cells to exacerbate disease [106]. These data indicate that innate immune responses have tremendous and opposing effects on autoantibody production and disease in MRL/*lpr* mice.

Defects in DC/MΦ-mediated tolerance are evident in lupus-prone mice. Our studies indicate that secretion of IL-6 and sCD40L by DCs/MΦs, as well as reprograming of IL-6R and CD40 in autoreactive B cells, promote tolerance during innate immune responses. This implies that defects in either the secretion of IL-6/sCD40L or the selective response of autoreactive B cells to these factors regulate autoantibody production. Our studies indicate that DCs and MΦs from MRL/*lpr* mice are unable to repress autoreactive B cells (Fig. 1b). Defects in DC/MΦ-mediated repression are coincident with diminished secretion of IL-6 and sCD40L and failure to sustain IL-6 mRNA production and activation of the IκB/NFκB pathways [107]. Similarly, we found that IL-6 and sCD40L fail to repress B cells from

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lupus-prone mice (unpublished data). The finding that lupus-prone mice harbor defects in DCs/MΦs and B cells suggests the influence of an environmental stimulus.

Apoptotic cells: dangerous in death

Apoptotic cells pose a unique challenge to the immune system since they are a rich source of nuclear antigens, including DNA, ICs, nucleosomes, histones, snRNPs and snRNAs, Ro, La, and Sm. These self-antigens can be modified by phosphorylation and/or alternate protein cleavage, revealing novel epitopes that were not available during the induction of B and T cell tolerance [108–111]. During cell death, self-antigens are distributed in large and small blebs on the cell surface and act as targets for autoreactive B cells in a membrane-bound, multimeric form [112–114]. The display of self-antigens on apoptotic cells is necessary to develop autoantibodies. For instance, autoantibodies to cytoplasmic but not nuclear antigens develop when nuclear fragmentation is blocked in apoptotic cells [115]. Therefore, it is imperative that scavenger cells such as MΦs and DCs quickly clear apoptotic cells and their associated self-antigens to minimize inflammatory and autoimmune responses.

Apoptotic cells are bound and cleared by a variety of receptors on DCs and MΦs. Ingestion of apoptotic cells reduces the secretion of proinflammatory cytokines by DCs and MΦs, inhibiting their maturation and controlling the activation of T cells and autoimmune responses to apoptotic cells [116–121]. Decreased clearance of apoptotic cells and defects in phagocytosis by MΦs in SLE patients and lupus-prone mice may lead to autoimmunity [69, 108, 122–124]. The increase in apoptotic cells and antigens could dysregulate DCs and MΦs, triggering a chronic anti-inflammatory response that downregulates the production of cytokines important for B cell tolerance [45, 107].

If apoptotic cells fail to be cleared efficiently, they may become necrotic and expel self-antigens and TLR ligands that are opsonized by autoantibodies, forming ICs [125, 126]. Like apoptotic cells, ICs present self-antigens in a multimeric form and enhance phagocytosis by DCs and MΦs [127, 128]. While apoptotic cells stimulate anti-inflammatory responses, ICs bind to Fc receptors (FcRs) and elicit inflammatory responses from MΦs and DCs [128]. Individual FcRs have distinct activating and inhibitory functions to ensure balance in a normal immune system. Activating FcRs include FcγRI and FcγRIII, which phagocytose ICs and provoke inflammatory responses from DCs and MΦs [129–131]. These receptors are necessary and sufficient for glomerulonephritis in (NZB/NZW) F1 mice [132–134]. Co-ligation of TLR9 and FcγRIII by chromatin:IC induces more DC activation than ligation of FcγRIII alone, indicating that TLRs synergize with FcR signaling [135]. In contrast to the activating FcRs, FcγRIIB is an inhibitory FcR with various functions depending on cell type. It modulates MΦ phagocytosis, DC maturation, BCR signaling, IgG secretion, and the expansion of autoreactive IgG-producing B cells [134, 136–145]. Autoantibodies and glomerulonephritis develop in certain strains of mice deficient in FcγRIIB, affirming its role in preventing autoreactive B cell activation [146, 147]. Additionally, antigen internalized by DCs through FcγRIIB, but not FcγRI or FcγRIII, is presented in its native form and activates antigen-specific B cells [148]. ICs and FcRs have important roles in the immune system, but their dysregulation can result in autoantibody secretion and nephritis.

Clearance of apoptotic cells and their associated autoantigens is crucial in preventing activation of B cells, DCs, MΦs, and T cells. When mice are immunized with apoptotic cells or exhibit a defect in apoptotic cell clearance, Sm-specific antibodies are detectable in the serum and MZ and B-1 B cells are inappropriately activated [66, 68, 69]. This suggests that recognition of autoantigens on apoptotic cells can drive B cell terminal differentiation [66, 68]. Impaired clearance of apoptotic cells in *Fas*^{lpr} [69] and *mer*^{kd} [149, 150] mice prevents

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BCR-mediated reprograming of IL-6R and CD40 (unpublished data). These data suggest that exposure of autoreactive B cells to apoptotic cells or ICs can impact DC/MΦ-mediated tolerance. In summary, apoptotic cells and the self-antigens they display can play both autoimmune and anti-inflammatory roles. Imbalances in apoptotic cell clearance or cellular responses result in inflammatory responses and autoimmune disease.

Selective repression: new treatments for SLE?

Systemic lupus erythematosus is primarily a B cell-mediated autoimmune disease, with symptoms arising from autoantibody deposition and inflammation in target organs, such as the kidneys, skin, and brain. Until recently, treatments for SLE were dependent on immunosuppression, which depresses immune function and causes dangerous side effects such as opportunistic infections [151]. Therapies that target specific cell types or biologic processes are now being developed, with the hopes that they will be more powerful and have less harmful side effects. For instance, chimeric anti-CD20 (rituximab), depletes peripheral B cells and reduces the severity of SLE symptoms in many patients [152]. However, a subset of patients is resistant to rituximab treatment [151]. Additionally, rituximab recently failed a late-stage study when its efficacy in achieving a clinical response was no greater than a placebo [153]. In murine studies of human CD20, B cells in autoimmune-prone strains were refractory to depletion by rituximab [154], compared to non-autoimmune-prone strains. Other biologic agents being studied or developed target complement activation, B cell-T cell interactions, cytokines, TLRs, interferon, or direct removal of antibodies from circulation. However, developing therapies to target each lupus-related autoantigen would be cumber-some and slow. A more efficient approach would be a therapy that selectively targeted autoreactive B cells through a common trait to restore tolerance. In previous studies, we determined that DC- and MΦ-mediated repression via IL-6 and sCD40L is effective on B cells of multiple specificities. These data suggest that any B cell chronically exposed to antigen would be susceptible to DC/MΦ-mediated tolerance. We are currently determining whether the lack of these soluble factors promotes autoimmunity in normal mice during innate immune responses. Preliminary data indicate that Sm-specific B cells adoptively transferred into chimeric mice lacking IL-6 and sCD40L become activated and secrete autoantibodies (unpublished data). This is consistent with our model indicating that DCs/MΦs and their secreted products regulate autoreactive B cells during innate immune responses. Future experiments will examine if tolerance can be restored in lupus-prone mice reconstituted with a mix of autoimmune and non-autoimmune hematopoietic stem cells. If DC/MΦ-mediated tolerance is found to be defective in SLE patients, future therapies could target their in vivo activation or introduce normal DCs/MΦs to reinstate B cell tolerance of newly emerging B cells following B cell depletion therapy. One approach would be non-myeloablative bone marrow transplant (BMT) or nonmyeloablative hematopoietic stem cell transplant (HSCT) to promote mixed chimerism. This may reinstate tolerance by providing a pool of DCs/MΦs that repress autoreactive B cells. Such an approach has shown promise in controlling B cell-mediated autoimmune disease in humans and mouse models [155–160], resulting in remission of rheumatoid arthritis in a human patient [158] and reduction in lupus-like disease in mice [155, 157].

Summary

The autoreactive B cells that incite multi-organ damage in SLE patients become dysregulated long before clinical symptoms appear. Autoantigens and TLR ligands released from apoptotic cells can overcome the tolerance of autoreactive B cells. Autoreactive T cells provide costimulation and promote the secretion of high-affinity, class-switched autoantibodies. These autoantibodies can bind nuclear self-antigens, form ICs, and provoke inflammatory responses from DCs and MΦs. Fortunately, DCs and MΦs specifically repress

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autoreactive B cells during TLR stimulation by secreting IL-6 and sCD40L. Restoring normal DC and MΦ function in SLE patients might repress autoreactive B cells and re-establish balance among the complex components of the immune system.

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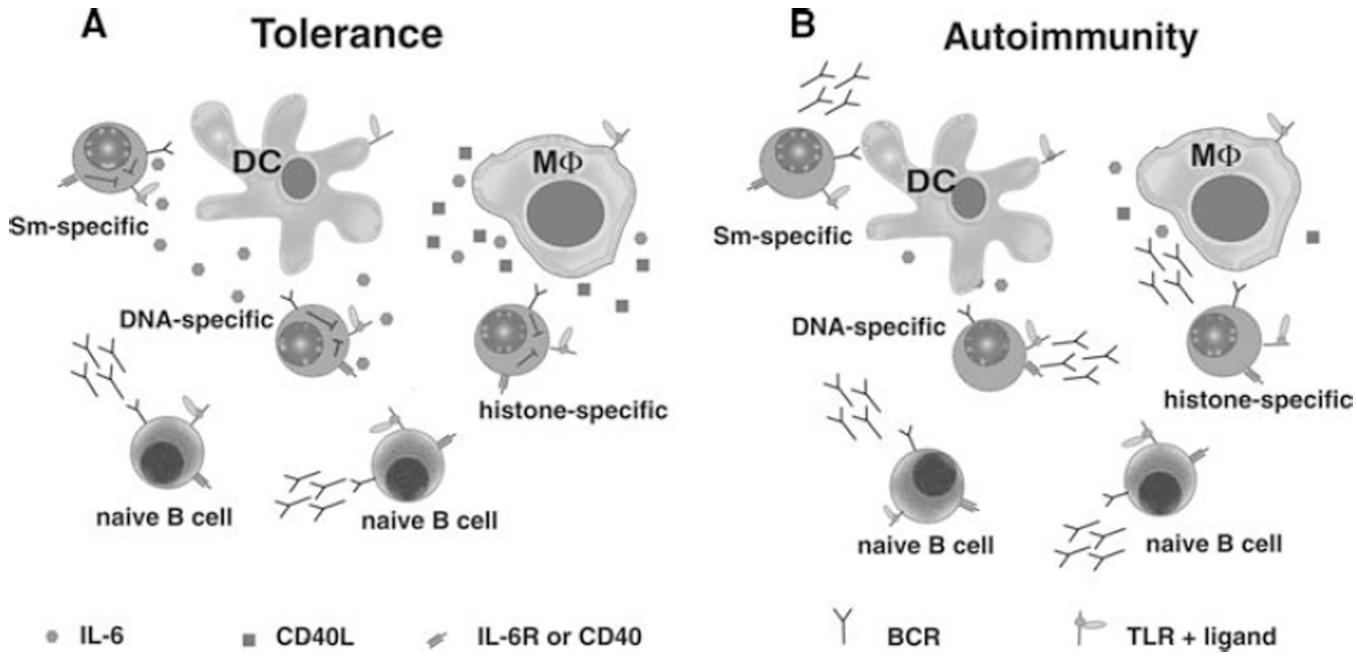

Fig. 1.

DCs and MΦs repress antibody secretion from autoreactive B cells via IL-6 and sCD40L. (**a**) In non-autoimmune mice, B cell tolerance is maintained during innate immune responses by DCs and MΦs. Although TLR stimulation promotes Ig secretion by B cells, it simultaneously induces DCs and MΦs to secrete IL-6 and sCD40L. These soluble factors repress Ig secretion from autoreactive B cells while allowing innate stimuli to produce a polyclonal response by naïve B cells. (**b**) In lupus-prone mice, DCs and MΦs are defective in the production of IL-6 and sCD40L, allowing both autoreactive and naïve B cells to produce Ig in response to TLR stimulation