Cellular Mechanism of Immunology in Systemic Lupus Erythematosus

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Abstract

To date, the mechanism of systemic lupus erythematosus (SLE) has not been thoroughly deciphered. Recent research demonstrated that CD138+ T cells accumulate in an SLE murine model, indicating that they are autoreactive T cells that significantly promote autoantibody production. Double negative (DN) T cells have been demonstrated to participate in the progression of SLE, but their detailed mechanism and the role in SLE remain unclear. Importantly, the expression of CD138 in CD3+ T cells plays a key role in the progression of lupus; it causes the accumulation of autoreactive T cells, including DN T cells, by significantly preventing their apoptosis. T helper 1 cells and interferon gamma both prevail in SLE; they may play essential roles in building the inflammatory condition of SLE. Defects occur in regulatory B (Breg) cells during their expansion in SLE, resulting in more differentiation of activated B cells into plasma cells; this subsequently increases antibody production. Myeloid-derived suppressor cells (MDSCs) enhance the expansion of Breg cells. However, the sustained increase of cytokine levels in SLE promotes the differentiation of more MDSCs into macrophage and dendritic cells, resulting in the defective expansion of MDSCs. The defective expansion of Breg cells and MDSCs breaks the immune-tolerance milieu in SLE, resulting in increased autoantibody secretion from those abnormal plasma cells. This review discusses recent advances regarding the detailed roles and mechanisms of these immunocytes in SLE.

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Abstract

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that is characterized by the production of multiple autoantibodies, including anti-nuclear antibody (ANA) and anti-double-stranded deoxyribonucleic acid (dsDNA) antibody [1, 2]. The production of these autoantibodies detrimentally affects multiple tissues and organs[3-5]. It is believed that B cells play central roles in adaptive immune responses as they specialize in the production of antibodies. However, SLE has so much variability and complexity that both T and B cells participate in the progress of SLE[6-8].

Despite the mechanism of SLE being so complex and unclear, recent research has achieved some advances. It has been demonstrated that double negative (DN) T cells accumulate significantly in both lupus mice and SLE patients [9-11], but the mechanism of this accumulation has not yet been thoroughly deciphered. Recent research reveals that the majority of accumulated DN T cells express CD138 in lupus mice, and that the expression of CD138 decrease the level of apoptosis in CD3+ T cells, compared with that in CD3+CD138- T cells[12-14]. In addition, other immunocytes, such as myeloid-derived suppressor cells (MDSCs), T helper 1 (Th1) cells, and regulatory B (Breg) cells have also been found to participate in SLE. Here, we discuss recent developments and research advances regarding the mechanisms underlying the immune system function in SLE.

CD138+ T cells

Accumulation of CD138+ T cells in an SLE murine model

Syndecan-1 (sdc-1, CD138) is a heparan sulfate proteoglycan that modulates multiple biological and immune activities, such as cellular multiplication and differentiation [15]. CD138, which is also expressed in epithelial cells and other adherent cells, has been thought to be a marker for plasmablasts and plasma cells in lymphocytes, which have been suggested to have originated from activated B cells[16, 17]. CD138 has also been found on the surfaces of CD3 expressed T cells. CD138+ T cells have also been reported to be plasmablastic B-cell neoplasms in clinical cases [18]. However, these abnormal CD138+ cells, i.e., CD138+ T cells, have also been identified in lupus mice; they were found to accumulate in spleens, lymph nodes, gut, and peripheral tissues in lupus mice as their ages increased [12-14].

CD138+ T cells mainly derive from DN T cells; a proportion of them derives from CD4+ T cells [13, 14]. The frequency at which CD138+ T cells are derived from CD8+ T cells is negligible[14]. CD138+ T cells have been shown to constitute a small fraction of cells in the spleen of non-lupus prone mice, but not to significantly accumulate in MRL/lpr mice [14]. This indicates that Fas-deficiency results in the accumulation of CD138+ T cells. Compared with CD138- T cells, CD138+ T cells have a lower level of proliferation [14]. Importantly, the apoptotic number of CD138+ T cells has been shown to decrease dramatically, compared with CD138- T cells (unpublished data by Tianhong Xie et al.). Significantly increased levels of live cells and decreased apoptosis levels in CD138+ T cells induce the accumulation of CD138+ T cells in lupus mice, but hyper proliferation does not [14].

Mechanism of CD138 expression in CD3+ T cells of MRL/lpr mice

Current research on CD138+ T cells remains limited, and little is known about the mechanism underlying the CD138 expression in CD3+ T cells. A recent study revealed that CD138+ T cells accumulated in MRL/lpr mice, but not in non-lupus prone mice [14]. Furthermore, CD3+ T cells in MRL/lpr mice have been shown to exhibit significantly defective activation and proliferation, compared with the cells in MRL/MPJ mice (unpublished data by Tianhong Xie et al.). Importantly, previous research has demonstrated CD138+ T cells exhibit significantly lower proliferation and activation in MRL/lpr mice, compared with CD3+CD138- T cells [14]. The activation levels of CD3+ T and CD138+ T cells have also been shown to be inversely correlated with the frequency of CD138+ T cells in splenocytes (unpublished data by Tianhong Xie et al.). It has also been suggested that the mechanistic target of rapamycin controls the expression of CD138 in T cells. Furthermore, rapamycin has been reported to significantly reduce the expression of CD138 and the frequency of CD138+ T cells[14]. However, an *in vitro* effort to decrease the frequency of CD138+ cells in CD3+ T cells with rapamycin treatment was unsuccessful. On the contrary, phorbol 12-myristate 13-acetate and Ionomycin treatments were found to significantly decrease the frequency of CD138+ cells in CD3+ T cells and induce the specific apoptosis of CD138+ T cells (unpublished data by Tianhong Xie et al.). This suggests that the defective activation of CD3+ T cells in MRL/lpr mice probably leads to the expression of CD138 in CD3+ T cells.

CD138+ T cells may be autoreactive T cells that promote autoantibody production in a CD4 receptor-dependent manner

Previous research has demonstrated that DN T cells play an important role in the progression of disease and that they contribute to the tissue injury of SLE [6, 19, 20]. The accumulation of plasma cells is also a cardinal feature of SLE [12, 21-23]. Interestingly, meanwhile, the majority of CD138+ plasma cells in an SLE murine model have been revealed to be subsets of CD3+ and CD138+ T cells [12-14]. Moreover, most CD138+ T cells are also DN T cells that are CD4 and CD8 double negative [12-14]. Immature T cells experience positive selection and negative selection, thus becoming mature single positive T cells that cannot recognize self-antigens [24, 25]. Auto-reactive T cells are deleted by Fas-mediated apoptosis during negative selection in the thymus [26]. Fas-deficiency may allow auto-reactive T cells to pass through negative selection [27, 28]. The production of autoantibodies has detrimental effects on multiple organs and plays a key role in the progression of diseases, such as SLE[29]. It was previously thought that SLE was mainly associated with autoreactive B cells [3-5] and was induced by the secretion of autoantibodies from plasma cells originating from autoreactive B cells [16]. However, recent studies suggested that T cells may play a more important role in the development of SLE [6-8, 14]. Importantly, recent research has demonstrated that CD138+ T cells significantly promote autoantibody production both *in vivo* and *in vitro* [7, 14, 30]. It has also been suggested that CD138+ T cells may be key to uncovering the underlying mechanism of SLE.

It has been demonstrated that autoantibody production in lupus mice is dependent on CD4 expression, but not on the accumulation of DN T cells[7, 14, 30]. Simultaneously, CD138+ T cells have been shown to significantly increase autoantibody production in an SLE murine model, in a CD4 receptor dependent way. They have also been revealed to promote tissue injuries when self-antigens are exposed to the immune system [7, 14, 30]. However, CD138+ T cells have been revealed to accumulate only in Fas-deficient lupus mice (i.e., not in non-lupus prone mice) [12-14]. This finding indicates that Fas deficiency also results in the accumulation of CD138+ T cells in MRL/lpr mice, in addition to DN T cells. These results indicate that the accumulated CD138+ T cells are auto-reactive T cells that avoid apoptosis during negative selection (induced by Fas-dependent apoptosis)[12-14]. We speculate that the expression of CD138 in CD3+ T cells is therefore probably caused by the failure of activation in auto-reactive T cells before exposure to self-antigens. This likely induces the defective apoptosis of CD138+ T cells and the subsequent accumulation of CD138+ T cells in MRL/lpr mice. When auto-reactive B cells are activated by self-antigens, the auto-reactive CD4+ T cells may then be activated by the expression of major histocompatibility complex (MHC)-II in auto-reactive B cells. CD4+CD138+ T cells may therefore be the accumulated auto-reactive CD4+ T cells that activate auto-reactive B cells; they may promote the formation of the abnormal plasma cells that secrete autoantibodies (Figure 1).

DN T cells

Expression of CD138 prevents T cell apoptosis and contributes to accumulation of DN T cells

DN T cells are a subset of T cells that are CD3 and B220 positive and are negative for both CD4 and CD8. DN T cells have been found to accumulate in the peripheral blood of SLE patients and in an SLE murine model [9-11]. They were found to account for <7% in the T cells of healthy mice[6], and resulted in profound lymphadenopathy in an SLE murine model[10, 31]. DN T cells have been shown to express activation-associated antigens, such as CD44, Ly-6C, CD138, and CD69 [13, 26, 32-34]. Interestingly, it has recently been shown that a majority of DN T cells express high levels of CD138 [12-14]. Moreover, the expression of CD138 in T cells has been demonstrated to significantly prevent the apoptosis of T cells [14]. Thus, it appears that the expression of CD138 contributes to the accumulation of DN T cells in lupus mice by decreasing the number of apoptotic DN T cells (Figure 2). However, the underlying mechanism for the expression of CD138 in CD3+ T cells remains undeciphered.

DN T cells participate in tissue injury in SLE

The role that DN T cells play in SLE is still a subject of debate. Some studies have indicated that the accumulation of DN T cells is not associated with anti-dsDNA antibody production and tissue injury[7, 35, 36], but recent studies have indicated that DN T cells play an important role in the development of SLE[6, 19, 37]. Researchers have demonstrated that DN T cells can accumulate in the spleen and simultaneously significantly infiltrate the kidney in lupus mice [6, 37]. The adoptive transfer of DN T cells into preclinical young lupus mice was also demonstrated to obviously cause or exacerbate tissue injuries and promote the progression of lupus in an SLE murine model[6, 19]. DN T cells in lupus mice are strongly cytotoxic. The over-expression of FasL in hyperactivated cytolytic DN T cells may result in autoimmune disease and may attack tissues that express small amounts of Fas receptors [6, 19, 20, 37].

The origin of DN T cells is still unclear

The origin of DN T cells is still undeciphered, with different studies obtaining contrasting results. To date, no study has provided direct evidence that DN T cells derive from CD4+ T or CD8+ T cells. Some researchers believe that DN T cells derive from CD4+ T or CD8+ T cells that pass through positive selection and have down-regulated expressions of CD4 or CD8 [26, 35, 36, 38, 39]. Other researchers believe that DN T cells derive from CD4+ T cells [38, 39]; evidence suggests that DN T cell frequency significantly increased in purified CD4+ T cells *in vitro* and that rIL-2 and rIL-15 enhance the conversion of CD4 T cells to DN T cells via allogeneic mature BM DC stimulation [39]. In addition, recent research has shown that CD4+CD138+ T cells in an SLE murine model exhibited downregulated CD4 expressions and simultaneously expressed B220 (unpublished data in preview by Tianhong Xie et al.), which is commonly expressed on the surfaces of DN T cells and nonselected CD8+ T cells [26]. It was previously believed that these nonselected B220+CD8+ T cells were the precursor from which DN T cells were derived [26]. We speculate that B220+CD4+CD138+ T cells may be the precursors that are converted into DN T cells, which in turn are derived from CD4+ T cells. This remains unclear, however, and more evidence is needed regarding whether B220+CD4+CD138+ T cells are able to further convert to CD138+ DN T cells.

Some researchers have suggested that DN T cells instead derive from CD8+ T cells. The idea that DN T cells originate from CD8+ T cells is mainly based on the evidence that the hypomethylation of the gene loci encoding the CD8 coreceptor in DN T cells indicates the previous expression of CD8 in DN T cells [9]. Treatment with an anti-CD8 mAb has been shown to significantly prevent the accumulation of DN T cells in lupus mice [35]. Previous studies have also found that the expansion of DN T cells is regulated by MHC-I[36]. The downregulation of the surface expression of CD8 has also been observed in the activated CD8+ T cells of lupus mice, after T-cell receptor stimulation [40, 41]. Additionally, one study has provided a new insight into the origin of DN T cells, proposing that DN T cells may originate from non-selected autoreactive CD8+ T cells [26, 42], which co-express CD44 and B220 [26]. Defects in Fas signaling lead to the IL-15/IL-2-dependent survival of non-selected CD44+B220+CD8+ T cells and DN T cells [26]. Some researchers have even proposed the idea that DN T cells do not derive from either CD4+ T or CD8+ T cells[10]. Instead, they have suggested

that DN T cells derive from immature double positive thymocytes that downregulate the expressions of CD4 and CD8 to convert into *bona fide* DN T cells[10]. It has been speculated that DN T cells may accumulate owing to the dysfunction of apoptosis induced by Fas deficiency [10].

Th1 may play an important role in SLE progression

In vivo inflammation is induced by the immune complex, and if further activated, it can result in multiple organ injuries and promote the development of disease in SLE [43]. A previous study reported that the levels of multiple cytokines in the serum were increased in MRL/lpr mice [44], and researchers also believe that the polarization of T cells in SLE involves changes from Th1 to Th2 cells and that IFN-α promotes the differentiation of activated B cells into plasma cells, thus playing an essential role in the progression of disease [45, 46]. Recently, detailed research has begun to reveal the important role that IFN-γ plays in the development of lupus in MRL/lpr mice [44, 47-49].

Firstly, serum IFN-γ levels have been found to be significantly higher in both SLE patients and SLE murine models [44, 47]. IFN-γ has been demonstrated to dramatically promote the proliferation and accumulation of DN T cells and to significantly increase the expression of FasL on the surfaces of DN T cells in lupus mice[48, 49]. Simultaneously, the accumulation of plasma cells is regarded to be a cardinal character in SLE [12, 21-23]. Meanwhile, researchers have recently identified that the majority of accumulated plasma cells are expressed in the T cell marker CD3 and that the majority of these CD138+ T cells are also DN T cells[12, 14]. These findings suggest that these abnormal T cells may play a more important role in SLE, but not only in B cells.

Previous studies have also shown that the frequency of Th1 cells in Fas-deficient lupus mice are significantly higher *in vivo* , but this is not true for Th2 [12, 50]. Evidence suggests that IFN-γ-/- lpr mice exhibit significantly relieved symptoms of lupus, compared with IFN-γ+/+ lpr mice [48]. IFN-RII deficiency has been suggested to significantly protect MRL/lpr mice from the development of significant autoimmune associated lymphadenopathy, autoantibodies, and renal disease, compared with IFN-RI deficiency in MRL/lpr mice [51, 52]. These results indicate that IFN-γ and Th1 cells may be involved in the mechanisms of lupus development and tissue injuries in MRL/lpr mice. Recent research has even proposed that IFN-γ is required for the TLR7-promoted development of autoreactive B cells [51].

B cells

Autoreactive B cells play an important role in SLE

B cells are regarded to play a central role in the adaptive immune response. It was believed that autoreactive B cells in SLE were able to further differentiate into abnormal plasma cells secreting autoantibodies after their activation by self-antigen and autoreactive T cells [30, 53-55]. Immature B cells originate from stem cells in bone marrow; their diversity among BCR specificities is generated by the random rearrangement of gene segments during early B-cell development [56, 57]. After experiencing positive selection, pro-B and pre-B cells have been shown to both express mIgM and become immature B cells [56, 58]. Autoreactive immature B cells suffer from apoptosis and are deleted during negative selection [56, 57]. Although the mechanism through which autoreactive B cells pass through negative selection remains unclear, some researchers believe that Fas signaling is involved in the apoptosis of autoreactive B cells [59] and that peripheral B cells may be activated by foreign antigens. Fas-deficiency has been shown to possibly result in the failure of autoreactive B cells to undergo apoptosis in an SLE murine model [59, 60]. Then, MHC-II, when present with self-antigens in activated autoreactive B cells, may interact with autoreactive CD4+ T cells and activate autoreactive T cells [7, 30]. Autoreactive B cells differentiate into plasma cells secreting autoantibodies with the help of autoreactive CD4+ T cells. Furthermore, the production of autoantibody has been reported to be independent of CD4+ T cells [7, 14, 30].

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In addition to abnormal B cells, IFN-α is the cytokine that induces the differentiation of activated B cells into plasma cells, contributes to the migration of leukocyte, and promotes the production of antibodies[22, 61-63].

However, the role of IFN-α is still disputed. Most researchers believe that IFN-α is essential to inducing SLE and promoting its progression [61, 64, 65]. IFN-α may enhance the antigen-presenting abilities of monocytes and dendritic cells, which may result in self-antigens being presented and the subsequent breakage of immunological self-tolerance[66]. However, some researchers have demonstrated that IFN-γ, but not IFN-α, promotes the development of SLE; IFN-α has even been shown to play a protective role in SLE [48, 51, 67]. Although the frequency of plasma cells has been demonstrated to be significantly increased in lupus mice, the majority of CD138+ plasma cells have been revealed to be abnormal T cells and those expressing the marker CD3 [12-14]. However, B cells in lupus mice have been found not to accumulate significantly; contrarily, the frequency of B cells has been shown to decrease dramatically, compared with that of healthy mice [12, 68]. Moreover, IFN-α has been reported to suppress Th1 polarization by inhibiting IL-12 secretion and preventing IFN-γ production via signal transducer and activator of transcription 1 (STAT1) [69, 70]. However, some researches have also shown that the frequency of Th1 cells, but not that of Th2 cells, in Fas-deficient lupus mice is significantly increased*in vivo* [12, 50, 71, 72].

Immune-tolerance impairment function of Breg cells participates in the mechanism of SLE

Breg cells participate in regulating immune responses and building the immune-tolerance milieu in autoimmune diseases and infections[73-75]. Breg cells suppress immune responses by decreasing the total immunoglobulin G (IgG) level, thus inhibiting the generation of plasma cells and reducing the production of antibodies in plasma cells [76-78]. Some studies have proposed that IL-10+ Breg cells in SLE patients and SLE murine models have expansion defects; therefore, the frequency of Breg cells in B cells significantly decreases after *in vitro* stimulation, thus impairing immunosuppressive function [22, 79, 80]. Moreover, it has recently been reported that plasmacytoid dendritic cells (pDCs) and Breg cells build an auto-regulatory feedback mechanism. However, the regulatory feedback mechanism is compromised in SLE. PDCs induce fewer IL-10+ Breg cells and conversely promote more differentiation of plasma cells from activated B cells, via IFN-α secretion [22]. This indicates that when compromised, the regulatory functions of Breg cells break the balance between immune response and immune-tolerance (Figure 3). Previous research [22] has also indicated that the defective expansion of regulatory B cells is induced by the altered STAT3 activation of B cells in SLE. Thus, they play an important role in the mechanism of SLE.

Myeloid-derived suppressor cells

Role of MDSCs in SLE is still controversial

MDSCs are the myeloid precursors of dendritic cells, macrophages, and granulocytes [81, 82]. They play a regulatory role[81, 83, 84] in the immune system by suppressing T cell proliferation [82], secreting regulatory cytokines[85], and inducing T cell apoptosis[86]. Recent research has indicated that MDSCs can enhance the expansion of the regulatory B cells, both *in vivo* and*in vitro* [87]. However, the role that MDSCs play in SLE has not yet been thoroughly deciphered.

Some researchers believe that MDSCs can promote the progression of lupus, based on the evidence that MDSCs accumulate in many organs in SLE and chronic inflammation conditions [88]. MDSCs have been shown to significantly decrease the differentiation of CD4+ T cells to Th1 and to suppress the secretion of TNF-α, IL-6, and IFN-γ[83]. Simultaneously, when accumulated, MDSCs have the potential to differentiate into macrophage and dendritic cells, in response to inflammatory cytokines, such as TNF-α, IL-6, and IFN-γ[89, 90]; these have been found to be significantly increased in SLE [91]. Macrophage and dendritic cells have also been regarded to positively contribute to the pathogenesis of SLE [92, 93]. Previous research has also demonstrated that the transfer of MDSCs into lupus mice significantly ameliorates the symptoms of SLE, including preventing autoantibody secretion and relieving renal tissue injuries[87]. Simultaneously, the infusion of MDSCs has been shown to decrease follicular helper T cells, Th1 cells, and Th17 cells in the spleens of lupus mice. MDSCs have also been found to enhance the expansion of the regulatory B cells and their frequency via inducible nitric oxide synthase [87].

Sustained increase in cytokine levels in SLE may induce defective expansion of MDSCs

Research has shown that the early depletion of MDSCs in lupus mice can significantly accelerate SLE during the progression of renal injury and the formation of auto-reactive plasma cells [94]. Contrarily, the depletion of MDSCs with more advanced disease has been shown not to affect the progression of lupus [94]. It has been established that the MDSC population would expand in response to inflammatory stimulation to suppress inflammation[83, 95]. Compared with that of non-lupus prone mice, the MDSC populations of lupus mice have been shown to abate when in an inflammation condition [95]. Recent *in vivo* mouse studies have demonstrated that defects occur during the expansion of MDSCs in lupus mice when responding to inflammation compared with the expansion of MDSCs in non-lupus prone mice [95]. Increased level of cytokines, such as TNF-α, IL-6, and IFN-γ, can build the inflammatory milieu in SLE [44, 68, 89, 90]. MDSCs have the potential to differentiate into macrophage and dendritic cells in inflammatory conditions, such as under increased levels of TNF-α, IL-6, and IFN-γ [89, 90]. According these results, we speculate that MDSCs may play a regulatory role in the immune system in SLE and that increased level of cytokines (including TNF-α, IL-6, and IFN-γ) induce the expansion of MDSCs in SLE. Simultaneously sustained increases in the levels of cytokines, such as TNF-α, IL-6, and IFN-γ, may also promote more MDSCs to differentiate into macrophage and dendritic cells. This can break the balance between self-tolerance (induced by MDSCs) and inflammation (induced by the sustained increase in cytokines; Figure 4). This imbalance may decrease the expansion of MDSCs, or result in so-called "proliferation defects" in MDSCs.

Conclusion and perspective

This article reviews the roles and mechanisms of immunocytes that participate in the progression of lupus. The expression of CD138 in autoreactive T cells in lupus plays a key role in its progression, resulting in the accumulation of autoreactive T cells in the spleens of lupus mice by preventing the apoptosis of CD3+ T cells. Th1 cells and IFN-γ may participate in building inflammatory conditions in SLE. The defective expansions of IL-10+ Breg cells and MDSCs contribute to increasing the formation of abnormal plasma cells and to the production of autoantibody. We propose that inhibiting the expression of CD138 in autoreactive T cells may be key to preventing the accumulation of autoreactive T cells in SLE. Thus, additional studies are warranted that target the underlying molecular mechanism of the CD138 signaling pathway in CD138+ T cells in SLE. Studies should also aim to prevent the expression of CD138 in CD3+ T cells, which may be the most promising and effective therapy for SLE.

Authors' contributions

Both authors contributed equally.

Disclosures

The authors declare no conflict of interests.

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Figure legends

Figure 1. Autoreactive T cells pass through negative selection due to Fas-deficiency [27, 28]. Fas-deficiency may result in the generation of autoreactive B cells [59, 60]. The expression of CD138 in T cells induces apoptosis defects and leads to the accumulation of autoreactive T cells [14]. Autoreactive CD4+ T cells further activate the expression of MHC-II in autoreactive B cells with self-antigens [7, 14, 30] and also promote the formation of autoreactive plasma cells that secrete autoantibodies.

Figure 2. DN T cells derived from CD4 [38, 39] and CD8[26, 35, 40, 41] positive cells. Single-positive T cells for which CD4+ T cells or CD8+ T cells downregulate their coreceptor (CD4 or CD8, respectively); they may convert into DN T cells[10]. Expression of CD138 induces apoptosis defects in DN T cells and results in their accumulation.

Figure 3. In healthy people, pDCs and Breg cells build an auto-regulatory feedback mechanism in the immune system[22]. However, the regulatory feedback mechanism is compromised in SLE [22], which breaks the balance between immune response and immune tolerance.

Figure 4. Population of MDSCs will expand in response to inflammatory environments, such as increased cytokines (including IFN-γ, IL-6, and TNF-α [83, 95]), thus suppressing inflammation[83]. In SLE, sustained increases in the levels of cytokines (such as TNF-α, IL-6, and IFN-γ) promote the differentiation of MDSCs into macrophage and dendritic cells [89, 90]; this breaks the balance between self-tolerance induced by MDSCs and inflammation induced by cytokines.

Figure 1

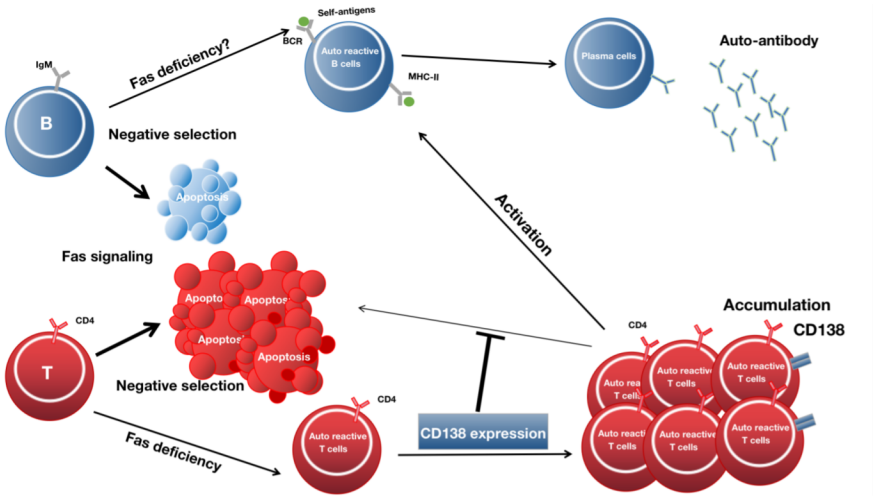

Figure 2

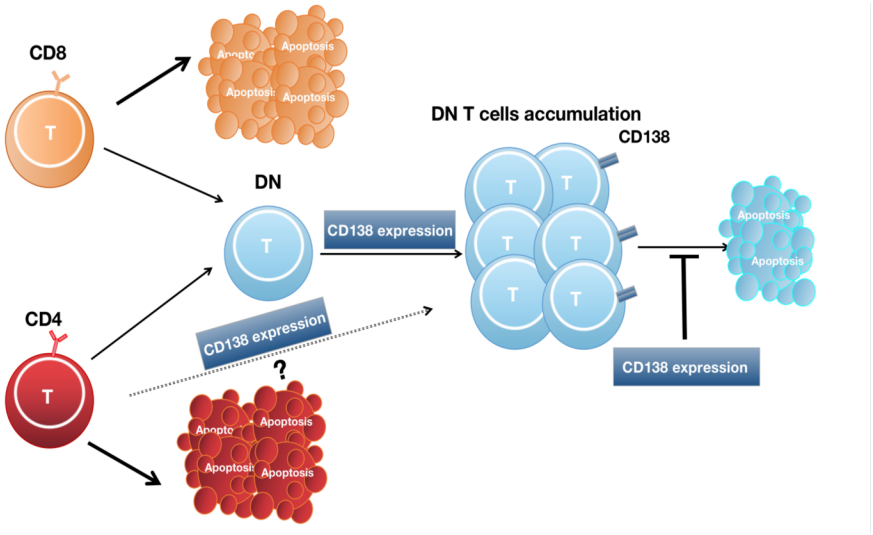

Figure 3

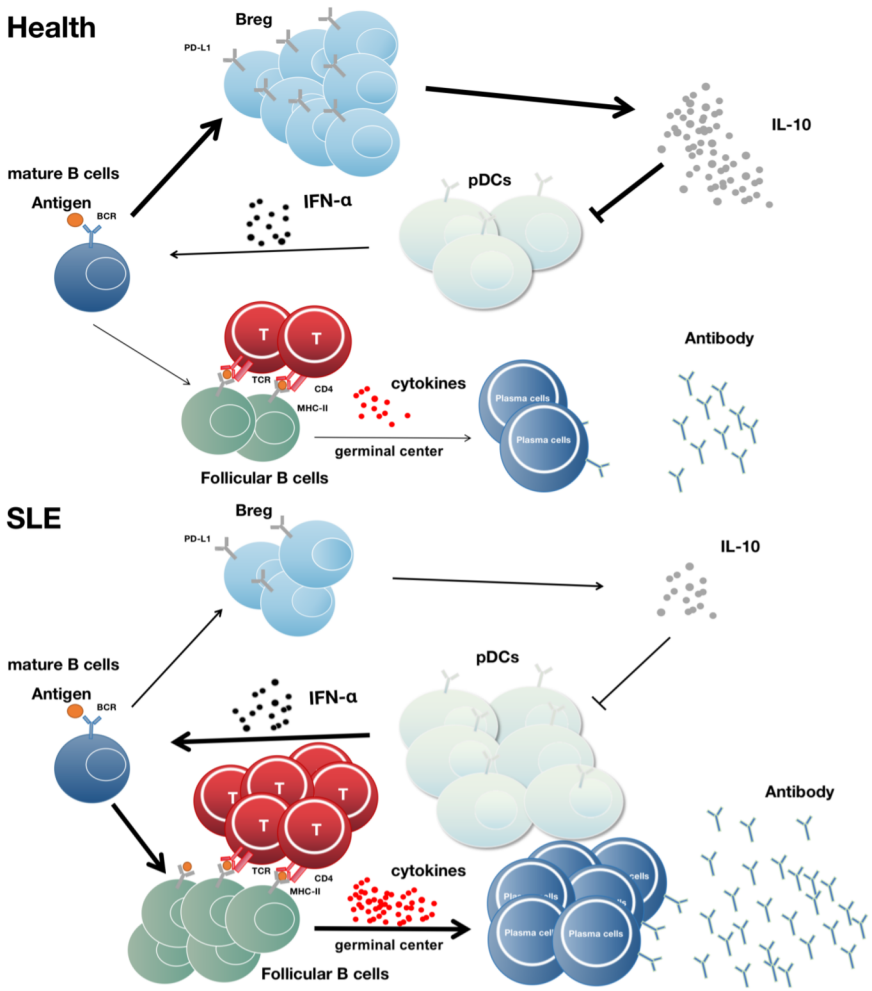

Figure 4