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The role of CD8+ T-cell systemic lupus erythematosus pathogenesis: an update

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Abstract

Purpose of review—Systemic lupus erythematosus (SLE) is a serious autoimmune disease with a wide range of organ involvement. In addition to aberrant B-cell responses leading to autoantibody production, T-cell abnormalities are important in the induction of autoimmunity and the ensuing downstream organ damage. In this article, we present an update on how subsets of $CD8^+$ T cells contribute to SLE pathogenesis.

Recent findings—Reduced cytolytic function of $CD8^+$ T cells not only promotes systemic autoimmunity but also accounts for the increased risk of infections. Additional information suggests that effector functions of tissue $CD8^+$ T cells contribute to organ damage. The phenotypic changes in tissue $CD8^+$ T cells likely arise from exposure to tissue microenvironment and crosstalk with tissue resident cells. Research on pathogenic IL-17-producing double negative T cells also suggests their origin from autoreactive $CD8^+$ T cells, which also contribute to the induction and maintenance of systemic autoimmunity.

Summary—Reduced $CD8^+$ T-cell effector function illustrates their role in peripheral tolerance in the control of autoimmunity and to the increased risk of infections. Inflammatory cytokine producing double negative T cells and functional defects of regulatory $CD8^+$ T cell both contribute to SLE pathogenesis. Further in depth research on these phenotypic changes are warranted for the development of new therapeutics for people with SLE.

Keywords

CD8T cells; lupus; systemic lupus erythematosus

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by autoantibody production with the presentation of inflammation and damage in multiple organs with serious life-threatening complications [1]. The cause of autoimmunity is multifactorial and various immune cell type abnormalities are involved in the pathogenesis

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of the disease (reviewed in [2]). Besides the aberrant expansion of autoreactive B cells, abnormalities in numerous T-cell subsets also contribute to the development of autoimmunity and systemic inflammation through direct action or cytokine production (reviewed in [3]). In this article, we focus on the role of $CD8^+$ T cells in SLE pathogenesis and review how each of the various subsets contributes to the progression of autoimmunity (Fig. 1).

CYTOTOXIC $CD8^+$ T CELL

Cytotoxic T lymphocytes (CTL), the most abundant type of $CD8^+$ T cells, are characterized by their cytolytic activity through the expression of perforin and granzymes, as well as cytokine production, including IFN-γ and TNF-α. With specific T-cell receptors recognizing foreign antigens presented by antigen presenting cells, such as dendritic cells or macrophages, naïve $CD8^+$ T cells differentiate into effector cells and expand exponentially. These expanded activated effector CTLs are cytotoxic against cells expressing nonself antigens – either virus-infected cells or cancer cells. After controlling the infection, the majority of these effector T cells undergo apoptosis, while a small portion of activated CD8+ T cells differentiate into memory T cells, a resting state that can be promptly reactivated upon demand.

$CD8^+$ T cells from the peripheral blood of SLE patients frequently display a reduction in effector function, including attenuated granzyme B and perforin production [4]. The impaired cytolytic defect in $CD8^+$ T cells likely contributes to the pathogenesis of autoimmunity [5]. Genetic elimination of perforin production in lupus-prone mice results in accelerated disease progression and confirms the role of CTLs in halting autoimmunity [6]. These data likely suggest the role of $CD8^+$ T cells in the establishment and maintenance of peripheral tolerance, and defects in their cytolytic function results in failure to remove autoreactive B cells. In graft-vs.-host murine lupus models, both perforin-mediated and Fas-ligand-mediated cytotoxicity are required for optimal control of autoreactive B cells [7,8]. Enhancing cytolytic function of CTL suppresses B-cell autoreactivity and limits disease progression [9,10], but whether such treatment could apply to help reduce autoreactive B cells in patients remains to be investigated.

Reduced cytolytic function of CTLs in lupus patients also poses another unfavorable outcome in lupus patients, because this reduction of T-cell effector function correlates with higher risk of infection [11] including a defect in controlling latent Epstein–Barr virus (EBV) [12,13]. Prescription of immunosuppressive medications could explain part of these defects, but T-cell function is still greatly diminished even in those taking low doses of immunosuppressive drugs [14]. Further, lupus-prone mice are highly susceptible to infections [15]. Poor latent EBV control also poses another unfavorable effect on lupus pathogenesis, since molecular mimicry of latent viral protein EBV nuclear antigen-1 (EBNA-1) progressively contributes to the production of autoantibodies [16]. Consistent with the above findings, reduced EBNA-1 specific T-cell response correlates with higher disease activity measured by SLEDAI score in SLE patients [17]. The functional defects in lupus $CD8^+$ T cells are also linked to changes in the expression of several surface proteins. Signaling lymphocytic activation molecule family member 4 (CD244), also known

as natural killer (NK) cell receptor 2B4 and thought to modulate cytolytic activity, is downregulated in $CD8^+$ T cells from SLE patients [18]. CD38, cell surface expressing cyclic ADP ribose hydrolase, is a major regulator of cellular NAD^+ levels through its catalytic function of NAD^+ to synthesize ADP ribose and cyclic ADP-ribose. Studies of tumor infiltrating lymphocytes reveal that the expression of CD38 represents an irreversibly dysfunctional group of $CD8^+$ T cells, which fail to recover cytokine production after ex vivo stimulation, and such fixed dysfunctional state of the $CD38^+$ $CD8^+$ T cell is strongly associated with a discrete chromatin landscape [19]. Similarly, dysfunctional $CD38^+$ $CD8^+$ T cells are also found expanded in the peripheral blood of SLE patients, with features of reduced granzyme and perforin production, and this functional defective state represents the result of CD38-dependent activation of histone methyl-transferase EZH2 in limiting chromatin accessibility of several key gene loci responsible for the regulation of T-cell effector function including RUNX3, EOMES and TBX21 [20■■]. Increased frequencies of these dysfunctional $CD38^+$ $CD8^+$ T cells correlate with a high risk of infection in SLE patients. Inhibition of CD38 could potentially reverse these adverse effects on CTL function. Administration of daratumumab, an anti-CD38 antibody, not only suppresses autoreactive plasma cells and reduces autoantibody titers, but also restored cytotoxicity of peripheral $CD8^+$ T cells in two SLE patients [21].

$CD8^+$ T CELL IN DAMAGED ORGAN

In SLE patients with class III or IV nephritis, $CD8^+$ T cells are one of the predominant infiltrating immune cells, and their accumulation in periglomerular areas correlates with the degree of disease activity [22]. These $CD8^+$ T cells presenting with effector memory phenotype are also found in the urine sediment, and are thought to contribute to tissue damage [23]. T cell receptor sequencing of infiltrating T cells shows clonal expansion and, interestingly, the same clonotype persists in the kidney years later in the repeat kidney biopsy tissue [24]. Taken together, these data suggest that the infiltrating $CD8^+$ T cells in nephritic kidney are tissue-resident and likely expand locally as disease exacerbates. However, whether this whole process involves antigen-specific T-cell response and the nature of the local autoantigen remains to be investigated. Several therapeutic approaches have been designed to target these tissue resident memory cells. The Janus kinase inhibitor tofacitinib not only blocks cytokine receptors necessary for aberrant T-cell activation, but also effectively prevents the expansion of tissue-resident memory T cells in murine lupus nephritis [25]. These memory $CD8^+$ T cells in nephritic kidneys also express high voltage-dependent Kv1.3 potassium channels, and targeted knockdown of Kv1.3 suppress CD40L expression and IFNγ production in a humanized mouse model of lupus nephritis [26■]. These tissue resident memory suppressing therapeutics also improve the outcome of kidney damage in lupus-prone mice, suggesting the role of tissue-resident memory $CD8^+$ T cells in organ damage pathogenesis.

The nature of kidney infiltrating T cells is long thought to be functionally active and through their cytolytic function contribute to tissue damage. However, contrasting evidence by Tilstra *et al.* [27] surprisingly demonstrated near complete abolishment of the effector function in kidney-infiltrating of both $CD4^+$ and $CD8^+$ T cells. These data raises the questions about the functionality of kidney infiltrating T cells, and whether chronic antigen

exposure can lead to exhaustion locally at the site of inflammation. However, single-cell RNA-sequencing of lupus nephritis biopsy samples did not reveal features of exhausted cell subsets, and the clusters of NK and $CD8^+$ T cells were noted to express high numbers of *GZMB* and *GZMK* transcripts [28■]. These seemingly discrepant data likely suggest the complex nature of lupus, with the result of heterogeneous features of kidney infiltrating T cells. Another intriguing cause of T-cell functional changes may stem from tissue microenvironment as the result of tissue inflammation and damage. These alterations of in situ cues instruct phenotypic changes of infiltrating T cells, and could be used to selectively suppress the local inflammatory response. Local tissue hypoxia was found to result from organ damage in lupus nephritis followed by the subsequent activation of the transcription factor hypoxia-inducible factor-1 (HIF-1) which controls cell survival and adequate glycolytic metabolism required for effector function in kidney-infiltrating T cells [29■]. These data indicate the therapeutic potential of HIF-1 inhibition to block microenvironmental cues to restore tissue infiltrating T-cell functionality and reverse organ damage. Changes in local metabolite concentrations could also serve as an important route to control the crosstalk between resident tissue cells and infiltrating T cells. Renal tubular epithelial cells downregulate arginine degrading enzyme arginase 1 through the response of IL-23 receptor and calcium/calmodulin kinase IV (CaMK4). The resulting increase in free L-arginine promotes proliferation of infiltrating T cells, and targeted CaMK4 inhibition in renal tubular epithelial cells prevents the expansion of T cells locally [30■]. These data suggest phenotypic difference between systemic and local $CD8^+$ T cells could arise from metabolic changes in the damaged tissue, and these phenotypic alterations could serve as potential therapeutic targets.

DOUBLE NEGATIVE T CELLS

Double negative T cells, a particular group of αβ T cells without surface expression of either CD4 or CD8, are thought to contribute to SLE pathogenesis as one of the major sources of IL-17 production [31]. Despite our limited knowledge about this population, current information suggests its derivation from self-reactive $CD8^+$ T cells in tissues expressing autoantigens [32]. Transcriptome analysis has confirmed gene expression profile similarities between double negative T cells and $CD8^+$ T cells [33], and double negative T cells share a skewed oligoclonal T-cell receptor repertoire with $CD8^+$ T cells in patients with autoimmune lymphoproliferative syndrome [34]. These data strongly suggest the possibility of lineage transition from $CD8^+$ T cells to double negative T cells, and this process involves downregulation of CD8 surface expression through cAMP-responsive element modulator α (CREMα)-dependent transcriptional silencing of *CD8A* and *CD8B* [35]. CREMα suppression of CD8 is mediated through histone methylation of the *Cd8* locus mediated by the recruitment of DNA methyltransferase 3a and histone methyltransferase G9a [36]. Double negative T cells are expanded in lupus mice carrying *lpr* or *gld* variants as disease progresses [37,38]. These murine lupus models have defects in T-cell apoptosis due to loss of function of the Fas mutation, and prevent activation induced cell death despite repeated T-cell receptor stimulation. These murine models are especially useful to depict the pathogenic role of double negative T cells, as T-cell receptor stimulation of $CD8^+$ T cells also promotes loss of surface CD8 expression to form double negative T cells

[39]. Taken together, these double negative T cells in lupus arise likely from autoreactive $CD8^+$ T cells as a result of chronic stimulation by autoantigen presented from apoptotic cells [40■■]. Furthermore, changes of cytokines in the inflammatory milieu, including reduction of TGF-β and elevation of IL-23 also contribute to the loss of tolerance and expansion of IL-17 producing double negative T cells [40■■]. Double negative T cells can also provide aberrant B cell help to augment anti-DNA autoantibody production [41]. In addition to the murine models, these double negative T cells are highly expanded in the peripheral blood and inflamed kidneys of lupus patients, further indicating their pathogenic role in the development of systemic autoimmunity and organ damage [42]. In summary, unlike the regulatory double negative T cell that can inhibit activation and proliferation of antigen-specific $CD8^+$ T cells [43], double negative T cells in autoimmune diseases predominantly present with pathogenic and proinflammatory phenotypes. These phenotypic differences likely stem from the presence of autoantigens from apoptotic cells and cytokines that promote the inflammatory phenotype.

$CD8^+$ REGULATORY T CELLS

Numerous subsets of $CD8^+$ T cells, either natural or inducible, possess a cell suppressive activity similar to that of regulatory $CD4^+$ T cells. The natural $CD8^+$ $CD25^+$ T regulatory cells express high levels of Foxp3 and exert their inhibitory function mainly through the secretion of transforming growth factor β1 (TGF-β1) and contact-dependent suppression through the cytotoxic T-lymphocyte-associated antigen 4 [44]. $CD8^+$ T regulatory T cells can also be induced by continuous antigen stimulation with $CD14^+$ monocytes [45], or coculture with CD40 ligand-activated plasmacytoid dendritic cells [46], or CD40-activated B cells [47]. The suppressive activity of these inducible $CD8^+$ T regulatory T cells depends on IL-10 production [46,48] and TGF-β secretion [49].

The immune suppressive function of regulatory $CD8^+$ T cells can also alleviate autoimmunity in lupus. In lupus prone NZB × NZW F1 mice, the immune tolerance induced by administering artificial peptide pConsensus depends on the activity of TGF-β secreting $CD8^+$ T cells [49], and the inhibitory activity of these $CD8^+$ suppressor cells depends on the expression of the transcription factor Foxp3 [50]. $CD8^+$ regulatory T cells can have been reported during the induction of tolerance by nucleosomal histone peptides in lupus prone SWR × NZB F1 mice, and their suppressive function depended upon TGF-β secretion [51]. In another tolerogenic model induced by complementarity-determining region-1 peptide for NZB × NZW F1 lupus mice, Foxp3-expressing $CD8^+$ cells promoted the expansion and suppressive function of $CD4^+$ $CD25^+$ regulatory T cells [52]. In addition to these tolerogenic models, ex-vivo-generated autologous $CD4^+$ and $CD8^+$ regulatory T cells help ameliorate autoimmunity in a graft-vs.-host model presenting with lupus-like syndrome [53]. Studies of peripheral blood mononuclear cells from SLE patients have reported that $CD8^+$ suppressive cells are functionally impaired with reduced IL-10 and TGF-β production [54,55]. In patients with refractory disease who receive autologous hemopoietic stem cell transplantation, immunological remission depends on the suppressive activity of TGF-β producing $CD8^+$ regulatory T cells [56]. These data imply the potential therapeutic exploitation of $CD8^+$ regulatory T cells in SLE patients, but the key to bolster their suppressive activity to induce immune tolerance remains to be investigated.

CONCLUSION

Reduced effector function of peripheral blood $CD8^+$ T cells promotes autoimmunity by failing to induce peripheral tolerance by removing autoreactive B cells, and by controlling the risk of infection. In contrast, at least part of the effector function of tissue $CD8^+$ T cells remain intact, and correlates with the extent of organ damage. The difference in effector phenotype likely stems from metabolic changes in the tissue microenvironment and from the crosstalk with tissue resident cells. IL-17-producing double negative T cells and dysfunctional regulatory $CD8^+$ T cell also contribute to disease pathogenesis. Recent studies have helped us understand better the immunopathology of $CD8^+$ T cell and their subsets but more information is needed for the development of new therapeutic strategies.

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KEY POINTS

- Reduction in systemic $CD8^+$ T-cell effector function contributes to the induction of autoimmunity as a result of failure to remove autoreactive B cells, and the control of infections.
- IL-17-producing double negative T cells originate likely from autoreactive $CD8^+$ T-cell and promote systemic autoimmunity.
- Functional impairment in regulatory $CD8^+$ T cells contributes to disease pathogenesis.

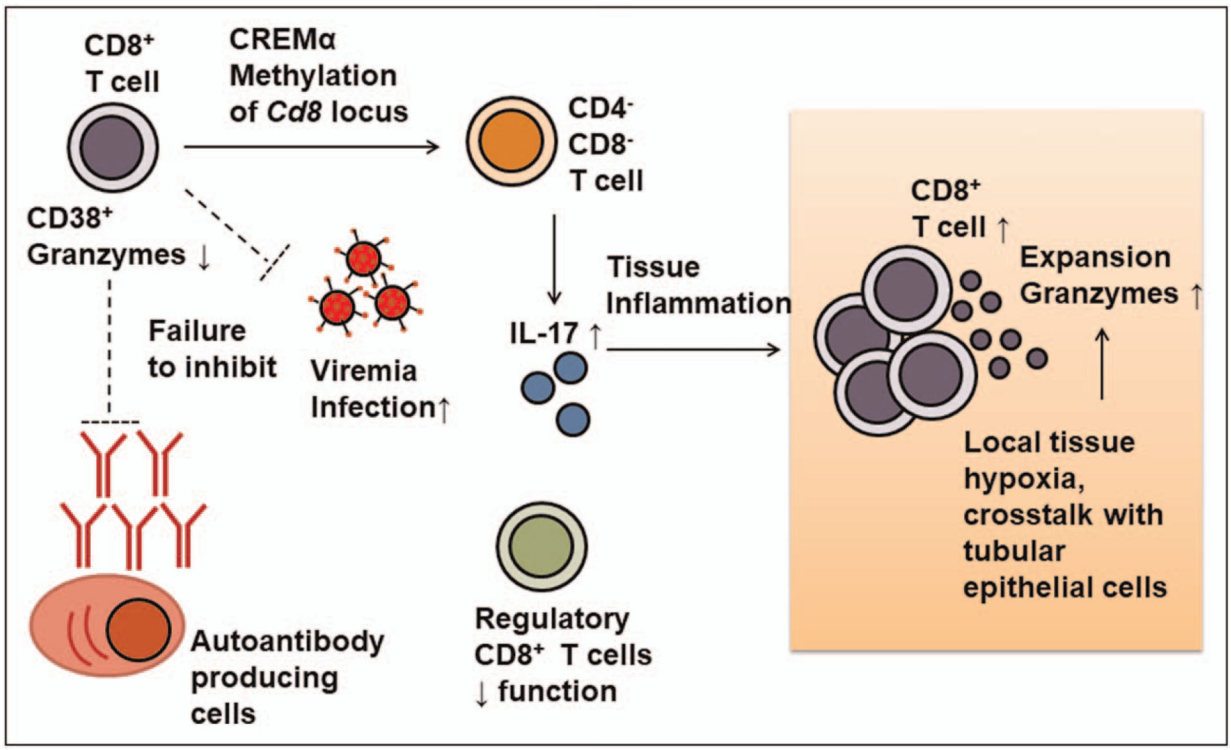

FIGURE 1.

Immunopathology of various $CD8^+$ T-cell subtypes and contribution to pathogenesis. Reduced cytolytic function of systemic $CD8^+$ is related to the expanded $CD38^+$ subpopulation and correlates with the increased risk of infection. Functional defects of cytotoxic T cells also result in failure to remove autoreactive B cells and thus increase autoantibody producing cells. Functional defects in regulatory $CD8^+$ T cells also contribute to the loss of peripheral tolerance. Meanwhile, methylation of *Cd8* locus through cAMP-responsive element modulator α and the inflammatory milieu lead to generation and expansion of IL-17-producing $CD4^-CD8^-$double negative T cells. Tissue infiltrating $CD8^+$ T-cell cause tissue damage as a result of exposure to changes in tissue metabolic factors, such as hypoxia and arginine levels.