CD8+ T regulatory cells in lupus

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Abstract

T regulatory cells (Tregs) have a key role in the maintenance of immune homeostasis and the regulation of immune tolerance by preventing the inflammation and suppressing the autoimmune responses. Numerical and functional deficits of these cells have been reported in systemic lupus erythematosus (SLE) patients and mouse models of SLE, where their imbalance and dysregulated activities have been reported to significantly influence the disease pathogenesis, progression and outcomes. Most studies in SLE have focused on CD4+ Tregs and it has become clear that a critical role in the control of immune tolerance after the breakdown of self-tolerance is provided by CD8+ Tregs. Here we review the role, cellular and molecular phenotypes, and mechanisms of action of CD8+ Tregs in SLE, including ways to induce these cells for immunotherapeutic modulation in SLE.

Keywords

immune tolerance • CD8+ Tregs • lupus • immune homeostasis • anti-DNA Ab

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by widespread inflammation, autoantibody production, and immune complex deposition. SLE affects major organ systems in the body, with lupus nephritis as a leading cause of death.[1–3]

In SLE, immune homeostasis is impaired. Many investigations have attempted to modulate the abnormal immune regulation in SLE, having as a therapeutic goal the restoration of immune self-tolerance and the suppression of the activity and number of pathogenic cells and the production of autoantibodies by inducing T regulatory cells (Tregs).[4–10] Many biotechnology and pharmaceutical companies are also currently working to translate the knowledge on the biology of Tregs and/or to bioengineer Tregs into transformational medicines that could benefit patients with various inflammatory and autoimmune diseases including SLE.

While a decrease in the number and/or function of CD4+ Tregs has been extensively studied in SLE,[11–19] the role and characterization of CD8+ Tregs in the disease is less clear. Our group identified and characterized a CD8+ T cell subset that prevented the generation of pathogenic autoantibody production and maintained immune self-tolerance in murine lupus.[6, 8]

The investigation of the regulatory networks, genes, and signaling pathways involved in the regulation of the functional activity and survival of CD8+ Tregs can be important for the development of therapies of restoration of immune homeostasis in SLE and other autoimmune diseases. The critical questions toward a clinical translational use of the findings are: (1) What is/are the precise surface phenotype(s) of the CD8+ Tregs which suppress autoantibody production? (2) What are the critical molecular elements in the CD8+ Tregs that are required for their survival, expansion, and suppression of helper T cell activity and suppression of autoantibody production by B cells? (3) What are the roles of transforming growth factor (TGF)-β, Bcl2, regulator of G-protein signaling (RGS) proteins, and interferons (IFNs) expression in the suppressive mechanisms of the CD8+ Tregs? (4) Can peptides that target Major Histocompatibility Complex (MHC) I/II T-cell domains augment the CD8+ Treg activity in SLE patients?

This review will discuss the aspects of Treg-mediated immune regulation, current knowledge in the field and approaches of Treg-based immunotherapy for improved management of SLE.

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Table 1: CD8$^+$ T$_{reg}$ markers and mechanisms of action.

| Subset | Natural/induced | Markers | Mechanism of action | Ref. |
|--------|----------------|---------|---------------------|------|
| CD8$^+$FoxP3$^+$ (mice) | Induced | PD-1$^{hi}$, CD62L$^{hi}$, CCR7$^{low}$ | Secretion of TGF-β | [6, 8, 21] |
| CD8, CD8α, CD25$^{hi}$, CD28$^{hi}$, FoxP3, CTLA-4, CD103, CD122, CXCR3, LAG-3, CD127$^{low}$ (mice, humans) | Natural/induced | CD25$^{hi}$, CD28$^{hi}$, FoxP3, CTLA-4, CD103, CD122, CXCR3, LAG-3, CD127$^{low}$ | Secretion of IL-10, Reduction of IFN-γ, Cell-to-cell contact dependent | [20, 22–25] |
| CD8, Qa-1, NKG2A (CD94) (mice) | Natural | Qa-1 (mice), HLA-E (humans), Ly49 | Suppress T effector cells, use perforin | [23, 26–29] |
| CD8, CD25, FoxP3 (humans) | Natural | CD8, CD25, FoxP3, CD127$^{low}$ (mice and humans) | Suppress T effector cells | [22] |
| CD8 (mice) | Natural | CD28$^{CD28^+}$, CD103, CD122, ICOS$^+$ in mice | Suppress T effector cells | [22, 30–36] |
| CD8, ILT3/ILT4 (mice) | Natural | ILT3, ILT4 | Make APCs tolerogenic | [37, 38] |
| CD8, CD103 (mice) | Induced | CD103 | | |
| CD8, CD25, CXCR3 (CD183) CD178 (ICOS) (humans) | Natural | CD8$^{CD25^+}$, CD183$^+$, CD178$^+$FoxP3$^+$ | Suppress B cells proliferation and IgG production | [40] |
| CD8, CD28 (humans) | Natural | CD8$^{CD28^+}$ | Inhibit T cell proliferation and cytotoxic functions | [21, 33] |

APC, antigen presenting cells; ILT, Ig-like transcript; IgG, immunoglobulin; LAG-3, lymphocyte activation gene 3; PD-1, programmed death-1; ICOS, Inducible co-stimulator.

**Cellular and molecular phenotypes of CD8$^+$ T regulatory Cells (T$_{reg}$)**

Although several cellular and molecular markers have been described for the identification of CD8$^+$ T$_{reg}$ (see Table 1, Figure 1, 2 and [20]), there is no single surface marker that is specific for CD8$^+$ T$_{reg}$.

Isolated CD8$^+$ T$_{reg}$ frequently express several genes that include CD8$^+$, FoxP3, CD25$^{hi}$, CD28$^{hi}$, CTLA-4, CD122, CD103, CD38, CD45RA, CD45RO, CD56, CXCR3, lymphocyte activation gene 3 (LAG-3), and CD127$^{low}$.[20, 22–25]

Analogous to the CD8$^+$CD122$^+$ T cells found in mice, Shi et al. showed that in humans CD8$^+$CXCR3 (CD183$^+$) T cells were regulatory in nature and mediated suppressive functions through IL-10.[41] In mice, CD8$^+$CD122$^+$ T cells contained populations which were both positive and negative for the expression of programmed death-1 (PD-1); however, the suppressive activity was only present in the PD-1$^+$ subset and depended on production of IL-10.[42] Also in mice, Deng et al. reported that CD8$^+$CD103$^+$ T$_{reg}$ inhibited the progression of lupus nephritis by attenuating glomerular endothelial cell injury.[43] and the adoptive transfer of CD8$^+$CD103$^+$ inducible T$_{reg}$ (iT$_{reg}$) to Murphy Roths Large (MRL)/lpr mice associated with decreased levels of autoantibodies, reduced renal pathological lesions, lowered renal deposition of IgG/C3, and less proteinuria.[43]

CD8$^+$CD28$^+$ and CD8$^+$CD28$^{low}$ T$_{reg}$ were reported in mice and in human,[44] while CD8$^+$CD183$^+$CD25$^{hi}$CD278$^+$ T$_{reg}$ that inhibited B-cell proliferation and immunoglobulin (IgG), IgM, IgA production were identified by Gupta and colleagues in humans.[45] Our group showed that the treatment of (New Zealand Black X New Zealand White)F1 (BWF1) lupus-prone mice with the anti-DNA-based peptide pCons induced distinct populations of CD8$^+$ T$_{reg}$.[6, 8, 30–31] Those CD8$^+$ T$_{reg}$ included both CD8$^+$CD28$^+$ and CD8$^+$CD28$^{low}$ but the expression of FoxP3 and TGF-β mRNAs was higher and longer-lasting in the T$_{reg}$ of the CD8$^+$ subset.[46] Other pCons-induced molecular markers[6, 8, 30–31] included are RGS2$^{low}$, RGS16, RGS17, Bcl-2 Associated X-protein (BAX$^{low}$), glutamic pyruvate transaminase (GPT-2$^{low}$), and growth arrest and DNA damage inducible 45β protein (GADD45β). The phenotype of the pCons-induced CD8$^+$ T$_{reg}$ that protected lupus mice and reduced anti-DNA autoantibodies and proteinuria[6, 8, 21, 33] also included programmed cell death-1 (PD1$^{low}$), CD62L$^{hi}$, and CCR7$^{low}$ (Singh et al., in press, Front Immunol (2021) doi: 10.3389/fimmu.2021.718359).

**Cellular and molecular markers of CD4$^+$ T$_{reg}$**

There are similarities and differences between CD8$^+$ T$_{reg}$ and CD4$^+$ T$_{reg}$. Compared to CD8$^+$ T$_{reg}$, CD4$^+$ T$_{reg}$ have been better characterized (Table 2). Markers for human and murine CD4$^+$ T$_{reg}$ include CD25, FOXP3, CD127$^{low}$, GITR, CTLA-4, CD28, GARP, HLA-DR, CD45RA, CD45RO, ICOS, Bcl-6, CCR6, CD39, CD73, CD49d, and Helios.[40, 46, 47] Nencini et al. showed that CD4$^+$CD25$^{low}$ and GITR$^+$ T cells had a regulatory phenotype and suppressed the proliferation of T effector cells, were expanded in inactive lupus patients.[48] Others found that human T$_{reg}$ preferentially expressed tumor necrosis factor receptor 2 (TNFR2), in addition to CD25, FoxP3, and CD45RO markers.[49, 50] and Okubo et al. demonstrated that tumor necrosis factor-alpha (TNF-α) or a TNFR2 agonist promoted the expansion in vitro of TNFR2$^+$ T$_{reg}$ with a strong suppressive function.[51]
Also CD4\(^+\)FoxP3\(^+\) type-1 regulatory (Tr1) cells that express IL-10 are involved in the maintenance of tolerance and display strong immunosuppressive functions.\[52–54\] Duhen et al. identified CD4\(^+\) T\(_{reg}\) subsets based on the expression of chemokine receptors, with differentially expressed lineage-specific transcription factors that responded differently to Th1, Th2, and Th17.\[55, 56\] Pesenacker et al. and Afzali et al. defined a new subset of T\(_{reg}\) in human cord blood with a CD4\(^+\)CD161\(^+\) phenotype that, although proinflammatory in nature, had a similar suppressive potential as conventional T\(_{reg}\).\[57, 58\] while Chung et al., and Linterman et al. identified a subset of CD4\(^+\) T\(_{reg}\) expressing CXCR5 and Bcl6 that localized in the germinal centers of both mice and humans.\[59, 60\] Other tissue-resident T\(_{reg}\) can be mostly activated cells with memory suppression.\[61, 62\]

**Induction of CD8\(^+\) and CD4\(^+\) T\(_{reg}\) in SLE**

Homeostatic balance in the controlled regulation of the immune response is impaired in lupus patients.\[60\] and decreased numbers of CD4\(^+\) and CD8\(^+\) T\(_{reg}\) associate with accelerated and deteriorating pathology in animal models and in humans with SLE.\[4, 12–16, 21\] indicating that T\(_{reg}\) play an important role in the protection from SLE.\[6, 8, 21, 23, 26, 32–35, 81, 82\]

We reported that both CD4\(^+\) and CD8\(^+\) T\(_{reg}\) are functionally deficient in both BWF1 mice and patients with SLE (they are as well reduced in other autoimmune conditions).\[4–10, 76–78\] While CD4\(^+\) T\(_{reg}\) have been intensively studied,\[60–67\] less is known about the CD8\(^+\) T\(_{reg}\) in the suppression of autoimmunity.

**Functional properties of peptide-induced CD8\(^+\) and CD4\(^+\) T\(_{reg}\) in SLE**

The functional properties of CD8\(^+\) T\(_{reg}\) can be modulated by the administration of anti-DNA-based peptides to alter disease progression.\[6, 8, 21, 83–89\] We showed that BWF1 lupus mice were protected from autoimmune disease after i.v. injection of high doses of pCons, an artificial peptide based on the VH sequence of murine anti-dsDNA antibodies that is presented by both MHC class I and II molecules.\[83\] Immune tolerance induced by the pCons peptide associated with an expansion of both CD8\(^+\) and CD4\(^+\) T\(_{reg}\) that independently suppressed the proliferation of naïve CD4\(^+\) T cells and B cells.\[6, 8, 21, 30\] PCons induced CD4\(^+\) T\(_{reg}\) with high FoxP3 expression and suppressed anti-DNA autobody production both in vitro and in vivo but also induced an expansion of CD8\(^+\)\[6, 21, 30\] that suppressed autoimmune responses in a FoxP3-dependent manner.\[6, 8, 21\] After pCons administration, CD8\(^+\) T\(_{reg}\) developed a unique genetic/molecular profile consisting of the upregulation of genes including FoxP3, Trp53, Bcl2, CCR7, IFNAR1, and Ifi202b (Table 3). Downregulated genes included RGS2, GPT2, BAX, PD1, CTLA4, CD122, GADD45, and phosphodiesterase 3b (PDE3b).\[82\] In all, their

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**Table 2: CD4\(^+\) T\(_{reg}\) markers and mechanisms of action.**

| Subset | Natural/induced | Markers | Mechanisms of Action | Ref. |
|--------|----------------|---------|----------------------|------|
| CD4\(^+\) T\(_{reg}\) (mice, humans) | Induced/natural | CD4, CD25, FoxP3, IL-10, IL-35,GITR, CD127\(^{low}\) | Suppress T effector cells, cell-to-cell contact, downregulation of CD80/CD86, metabolic disruption | [18, 40, 63–75] |
| CD4\(^+\) T\(_{reg}\) (humans) | Natural | CD4, CD25, GARP, CD45RA/R0, CCR6 Helios, CD127\(^{low}\) | Suppress T effector cells | [35, 40, 46, 47, 63, 76–78] |
| Th1, Th2, Th3 | Natural | CD4, CD25, CXCR CXCR3\(^{+}\) T cells that can produce IFN-\(\gamma\), IL-4 | Suppress T effector cells through IL-10, TGF-\(\beta\), IFN-\(\gamma\), IL-4 | [63–67] |
| IL-17\(^\ast\) FoxP3\(^+\) T\(_{reg}\) (mice, humans) | Natural | CD4, FOXP3, CCR6, RORy\(t\) | Suppress CD4\(^+\) T cell proliferation | [40, 46, 47] |
| CD45RA\(^+\) FoxP3\(^{low/-}\) T\(_{reg}\) (mice, humans) | Natural | CD4, CD45RA, FOXP3 | Resting T\(_{reg}\) | [40, 46, 47] |
| Follicular T\(_{reg}\) (mice) | Natural | CD4, Foxp3, CXCR5, Bcl6 | Germinal centers | [40, 46, 47] |
| CD4\(^+\)CD25\(^{low}\)GITR\(^+\) (humans) | Natural | CD4\(^+\)CD25\(^{low}\)GITR\(^+\) | Suppress T effector cells | [48] |
| CD4\(^+\)CD25\(^{CD45RA/R0}\) CXCR2\(^+\)FoxP3\(^+\) CD45RO\(^+\) (humans) | Natural/induced | CD4\(^+\)CD25\(^{CD45RA/R0}\) CXCR2\(^+\)FoxP3\(^+\) CD45RO\(^+\) | Suppress T effector cells | [51] |
| CD4\(^+\)CD161\(^+\) FoxP3\(^+\) (humans) | Natural | CD127\(^{low}\), IL-2, IFN-\(\gamma\), IL-17 | Suppress T effector cells | [57, 58] |
| CD4\(^+\)CXCR5\(^+\) FoxP3\(^+\) (mice, humans) | Natural | CD4\(^+\)CXCR5\(^+\) | Suppress B-cell antibody production | [59] |
| Follicular CD4\(^+\)Bcl6 FoxP3\(^+\) T\(_{reg}\) (mice, humans) | Natural | CD4\(^+\)Bcl6 FoxP3\(^+\) | Suppress germinal center reactions | [60] |

APC, antigen presenting cells; T\(_{reg}\), T regulatory cells; Tr1, type-1 regulatory.
suppressive capacity depended on the expression of FoxP3, PD1, and IFI202b.\textsuperscript{[8, 39]}

While extensive studies have evaluated the role of CD4\textsuperscript{+} T\_reg as suppressor of autoimmune responses, the mode of action of CD8\textsuperscript{+} T\_reg have been explored less\textsuperscript{[6, 8, 16, 18, 21, 92–96]} but shown to prevent lupus-like disease in murine graft versus host disease (GVHD).\textsuperscript{[97–99]}

The induction of CD8\textsuperscript{+} Cytotoxic T lymphocytes (CTLs) is responsible for the killing of autoantibody-producing B cells and the inhibition of murine lupus.\textsuperscript{[100]}

A nucleosomal histone peptide in (SWR × NZB)F1 (SNF1) mice delays lupus nephritis and B-cell activation by inducing (CD4\textsuperscript{+} and CD8\textsuperscript{+}) TGF-β\textsuperscript{+} T\_reg in mice\textsuperscript{[85, 101, 102]} and also blocks pathogenic autoimmune responses in human SLE.\textsuperscript{[103]}

Interestingly, SLE patients treated with methylprednisolone have CD8\textsuperscript{+} T\_reg associated with decreased disease activity.\textsuperscript{[104]} and CD8\textsuperscript{+} T\_reg are induced by all-trans retinoic acid.\textsuperscript{[105]}

The MHC class 1b molecule Qa-1 restricted CD8\textsuperscript{+} α/α\ T cells has been shown to regulate immunity in mice,\textsuperscript{[27, 106, 107]} and a population of Qa-1-restricted CD8\textsuperscript{+} T cells can inhibit murine lupus-like disease by targeting autoreactive CD4\textsuperscript{+} T follicular helper cells (T\_F\_H).\textsuperscript{[23, 28]} Peptide-specific CD8\textsuperscript{+} T\_reg that suppress partly through perforin have also been described\textsuperscript{[23, 26, 28, 29]}; other tolerogenic peptides based on the light chain complementarity-determining region

Table 3: Gene changes in CD8\textsuperscript{+} T\_reg induced by anti-DNA antibody-based peptide in lupus mice.

| Upregulated genes          | Downregulated genes                  |
|---------------------------|--------------------------------------|
| Foxp3, IL-2, TGFB, CD25, CD28, Trp53, CD122, Bcl2, CCR7, IFNAR1, IFI202b | RGS2, GPT2, BAX, PD1, CTLA-4, GADD45β, PDE3b |

PDE3b, phosphodiesterase 3b; RGS, regulator of G-protein signaling; T\_reg, T regulatory cells.

Figure 1: CD8\textsuperscript{+} T\_reg SLE. In SLE, subsets of CD8\textsuperscript{+}CD25\textsuperscript{+}FoxP3\textsuperscript{+} T\_reg—whose additional phenotypic markers are schematically depicted here—can suppress the activity of T effector (T\_eff) cells and APCs, also suppressing autoantibody production through the secretion of TGF-β and other cytokines/chemokines. APC, antigen presenting cells; LAG-3, lymphocyte activation gene 3; SLE, systemic lupus erythematosus; T\_reg, T regulatory cells; and T\_eff, T effector. Modified from Martha R. Vieyra-Lobato, Jorge Vela-Ojeda, Laura Montiel-Cervantes, Rubén López-Santiago, Martha C. Moreno-Lafont, “Description of CD8+ Regulatory T Lymphocytes and Their Specific Intervention in Graft-versus-Host and Infectious Diseases, Autoimmunity, and Cancer”, Journal of Immunology Research, vol. 2018, Article ID 3758713, 16 pages, 2018. https://doi.org/10.1155/2018/3758713
1 (hCDR1) of human anti-dsDNA antibodies that induce CD4⁺CD25⁺ and CD8⁺CD28⁻ Tregs, which suppressed lymphocyte proliferation and autoantibody production in BWF1 lupus mice have also been described.⁹¹,¹⁰⁻¹⁸

**Transcription factors and mechanisms of action of Tregs**

FoxP3 is a critical transcription factor in the regulatory activity of both CD4⁺ and CD8⁺ Tregs.¹⁰⁹ A decreased expression of FoxP3 results in loss of tolerance to self-antigens in SLE patients,¹¹⁰ and SLE patients have a decreased expression of FoxP3 as compared to healthy matched controls.¹⁷⁷

Recent studies have shown that both CD4⁺ and CD8⁺ Tregs express another transcription factor, Helios, which appears as essential for the maintenance of a stable phenotype and suppressive activity during inflammation and autoimmunity.¹¹¹ Helios is a member of the Ikaros gene transcription factor family expressed by FoxP3⁺ Tregs (both in mice and humans). It is thought that Helios⁺ cell subsets arise from thymus while

**Figure 2:** Schematic representation of the mechanisms of immune suppression of CD8⁺ Tregs in SLE. A. CD8⁺ Tregs secrete cytokines/chemokines such as TGFβ, IL-10, and CCL4 that suppress immune responses. B. CD8⁺ Tregs can also suppress in a cell contact-dependent fashion that may depend on the surface expression of membrane-bound TGFβ (and/or CTLA-4). C. MHC class I-restricted CD8⁺ Tregs are capable to kill activated CD4⁺ T effector (Teff) cells that express Qa-1/HLA-E. D. CD8⁺ Tregs can render APCs tolerogenic by downregulating co-stimulatory molecules such as CD80 and CD86, and upregulating inhibitory receptors such as ILT3 and ILT4.

APC, antigen presenting cells; ILT, Ig-like transcript; SLE, systemic lupus erythematosus; and Tregs, T regulatory cells. Modified with permission from Ref # 20, Dinesh RK et al, Autoimmun Rev. 2010 Jun;9(6):560-8. Copyright, 2010, Elsevier.
Helios− subsets are induced from FoxP3+ T cells. Helios− T cells are highly suppressive and express more highly demethylated Treg-specific demethylated region (TSDR) that facilitates FoxP3 transcription and therefore expression. Helios− human memory Tregs appear to co-express (T cell immunoreceptor with Ig and ITIM domains (TIGIT) and Fc receptor-like protein 3 (FCRL3)) and suppressive Helios− FoxP3+ Tregs, with migratory potential are expanded in inflamed tissues of SLE patients with active disease.

It seems that transcription factor, BTB Domain And CNC Homolog 2 (Bach2), is also important for Treg+ function. A recent study has shown that Bach2- and Fas-dependent manner.

Another transcription factor, nuclear factor erythroid 2-related factor 2 (NRF2), is a transcriptional activator which regulates oxidative stress. Although specific functions of NRF2 in Tregs are not fully understood, a recent study has shown that NRF2 is a negative regulator of Treg function and that FoxP3-specific activation of NRF2 results in the loss of immune tolerance and the accumulation of IFN-γ-producing T effector cells and inflammation. In SLE, several lines of evidence suggest that NRF2 plays a central role in the pathogenesis of the disease by exerting anti-inflammatory effects—although others show pro-inflammatory effects. One study showed that aged female NRF2-deficient mice were prone to develop a condition closely resembling human SLE and another study in B6/lpr mice associated NRF2 deficiency with lupus nephritis and Th17 cells. Mechanistically, NRF2 binds together with small Maf proteins to the antioxidant response element (ARE) in the regulatory regions of target genes and with KEAP1 (Kelch ECH associating protein 1), a repressor protein that binds to NRF2 and promotes its degradation by the ubiquitin-proteasome pathway. Genetic deletion of Keap1 resulted in higher percentages of Treg+ and reduced systemic inflammation in murine GVHD.

Notwithstanding the above consideration, the general mechanisms of actions of the Treg+ include: (1) suppression of T and B cells through inhibitory cytokines; (2) induction of cytolysis in target cells; (3) targeting antigen presenting cells (APC) such as dendritic cells, and (4) metabolic disruption in target cells.

Treg+ secrete inhibitory cytokines such as IL-10, TGF-β, and IL-35 that can suppress target cells including APCs and CD4+CD25+ T effector cells. For example, pCons-induced Treg+ secreted TGF-β and IL-10, observed in other studies.

The cytolysis of target cells by Treg+ involved perforin and granzyme B.

Treg+ can also target directly APCs to suppress their function or render them tolerogenic through an upregulation of inhibitory receptors such as Ig-like transcript (ILT)-3 and ILT-4 [57, 38]. Bezie et al. showed that CD8+FoxP3+ Treg+ depend on the expression of CTLA-4 to suppress T effector cells in vitro, and other studies found that Treg+ can downregulate costimulatory molecules such as CD80 and CD86 on the APCs. Finally, the “metabolic disruption” in target cells by Treg+ causes suppression of T effector cells by utilizing/sequestering IL-2 and/or IL-15, thereby depriving the target cells of critical growth factors.

Concluding remarks

Studies and findings on Treg+ are ready to be translated into approaches for the restoration of immune tolerance in SLE and advancement toward clinical settings. In particular, the bioengineering of Treg+ and the use of polyclonal and antigen-specific Treg+ cell therapies based on CD4+ and CD8+ chimeric-antigen-receptor (CAR) Treg+ in ongoing investigations by many biotechnology and pharmaceutical companies are providing encouraging results that appear to rapidly translate into the clinical practices. More research will allow to fine-tuning and avoid off-target effects in different Treg+-based immunotherapies, optimizing the immunotherapeutic benefits for SLE patients.
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