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Regulatory T Cells (Tregs) in systemic lupus erythematosus

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ABSTRACT

***Background*:** Systemic lupus erythematosus (SLE) is a complex autoimmune disease characterized by the loss of immune tolerance and the production of autoantibodies targeting various nuclear antigens. Regulatory T cells (Tregs), crucial for maintaining immune homeostasis, exhibit significant dysregulation in SLE, contributing to its pathogenesis, clinical presentation, prognosis, and response to treatment. These abstract reviews the multifaceted correlation between Tregs and SLE. In SLE pathogenesis, a deficiency in both the number and suppressive function of Tregs is implicated. Reduced Treg frequency in peripheral blood and tissues, particularly in disease flares, correlates with increased disease activity and severity. Functional defects, including impaired cytokine production (e.g., IL-10, TGF-β), reduced expression of suppressive molecules (e.g., CTLA-4, Foxp3), and diminished ability to suppress effector T cell proliferation, further contribute to the loss of immune tolerance. These defects allow the escape of autoreactive lymphocytes, leading to the production of autoantibodies and the subsequent organ damage characteristic of SLE. Aberrant Treg development and differentiation processes, potentially influenced by genetic factors and environmental triggers, are also believed to play a role. The clinical presentation of SLE is significantly influenced by the degree of Treg dysfunction. Patients with severely impaired Treg function tend to present with more severe disease manifestations, including nephritis, lupus cerebritis, and vasculitis. Conversely, individuals with relatively preserved Treg function may experience milder disease courses and fewer organ-specific complications. The heterogeneity of SLE clinical presentation likely reflects the variable degrees of Treg deficiency and dysfunction observed among patients. Furthermore, the fluctuation in Treg numbers and function during disease flares and remissions suggests their potential as biomarkers for disease activity and prognosis. The prognostic significance of Tregs in SLE is increasingly recognized. Lower baseline Treg counts and impaired Treg function are associated with increased disease activity, a higher risk of severe organ damage, and reduced overall survival. Conversely, higher Treg numbers and enhanced suppressive capacity are linked to better disease control and improved prognosis. Therefore, Treg status can potentially serve as a valuable prognostic marker, aiding in risk stratification and personalized treatment strategies. Treatment strategies in SLE are now being explored to target and modulate Treg function. Immunosuppressive agents, while effective in controlling inflammation, often have broad immunosuppressive effects, potentially further depleting Tregs. However, strategies aimed at selectively enhancing Treg function, such as Treg-based cell therapies or the modulation of Treg-related signaling pathways, hold promise for more targeted and effective interventions. Further research is essential to develop novel therapeutic approaches that selectively restore or enhance Treg function, leading to improved disease control, reduced organ damage, and improved long-term outcomes for patients with SLE. The potential of Tregs as both biomarkers and therapeutic targets highlights their central role in the management and treatment of this complex autoimmune disease.

Keywords: Regulatory T Cells, systemic lupus erythematosus

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease that associates with a progressive deterioration of the mechanisms of immune tolerance. An impaired ability to discriminate between foreign and self-antigens results in autoimmune attacks in which both the innate and adaptive arms of the immune system take part. The prevalent pathologic manifestations of the disease result from aberrant production of autoantibodies and the release of proinflammatory mediators that promote and/or exacerbate tissue damage. Ultimately, these events can occur in multiple organs and can cause a prolonged local inflammatory response that can lead to compromised organ function [1]

Given that the severity and symptoms of SLE are often heterogeneous among patients, the investigations on the molecular mechanisms of the disease pathogenesis have often resulted in complex pictures that have included multiple components. Among them, dysregulated numbers and/or function of T regulatory cells (Tregs) have been reported by many groups (reviewed in [1]), as well as impaired mechanisms of Tregs activities on their target cells (Fig. 1).

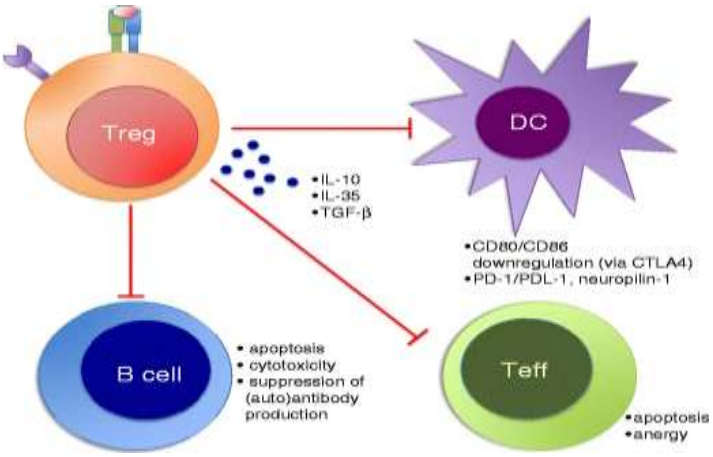

Fig 1: Schematic mechanisms of Treg-mediated suppression on Teffs, B cells, and APCs (DCs). The figure shows the Treg-mediated paracrine effects through cytokines, cytotoxicity, apoptosis, suppression of antibody production, contact-dependent induction of anergy, inhibition of costimulatory signals (needed for cell activation)

T regulatory (Treg) cells are a specialized subset of CD4+ T cells that play a critical role in maintaining immune homeostasis and preventing autoimmunity by actively suppressing immune responses. They are essential for controlling the immune system's tolerance to self-antigens and preventing excessive inflammatory responses to foreign antigens. [2]

Regulatory T (Treg) Cells: Development and Function

1. Developmental Heterogeneity

Treg cells are characterized by the transcription factor FOXP3, which is critical for their function and stability. They constitute about 5–10% of peripheral CD4+ T cells in humans and mice. FOXP3 expression is stable and reliable for mouse Treg cells but less so in humans, where other markers like high CD25 and low CD127 expression are also used to identify Treg cells. [3]

There are two main subtypes of Treg cells based on developmental origin: Thymus-derived Treg (tTreg) cells: These develop directly in the thymus and form a stable population. Peripheral Treg (pTreg) or induced Treg (iTreg) cells: These develop from conventional CD4+ T cells in response to antigen stimulation in the periphery, often influenced by cytokines like TGF-β and IL-2. While tTreg cells maintain stable suppressive functions, pTreg cells exhibit plasticity, which allows them to convert into effector T cells, such as T helper 1 (TH1) or TH17 cells, in response to environmental conditions like infection. [4]

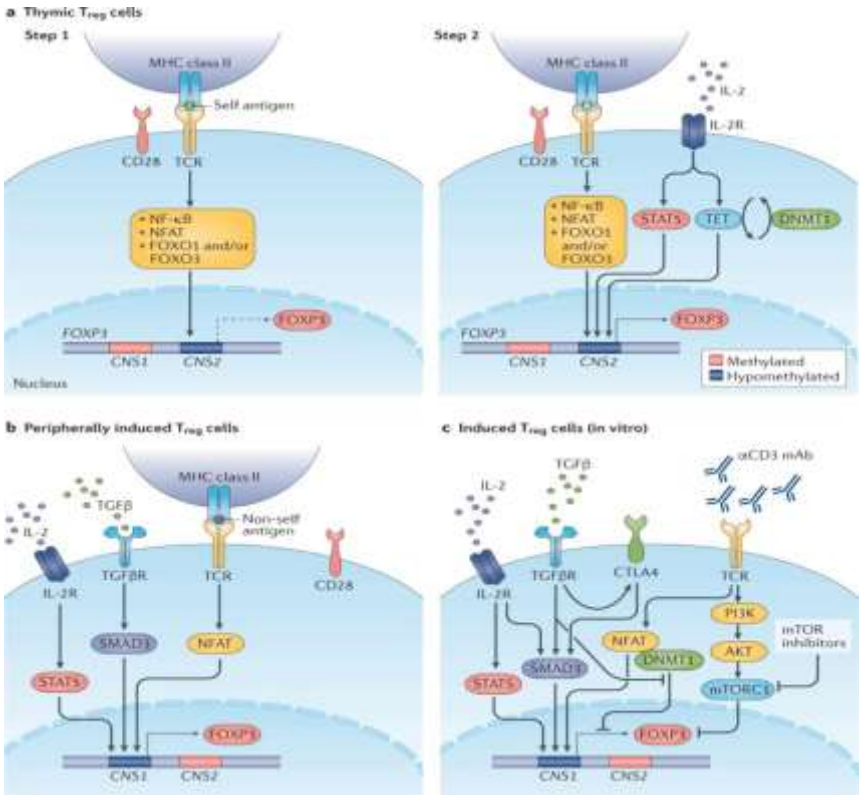

Fig. (2): Overview of Treg Cell Development in vivo and in vitro. a | In the thymus, regulatory T (Treg) cell development begins with T cell receptor (TCR) expression and interleukin-2 receptor (IL-2R) activation. Moderate TCR interaction with self-antigens induces CD25 (IL-2Rα) expression, which supports FOXP3 upregulation via IL-2 signaling. IL-2R also maintains FOXP3 expression by activating STAT5 and preserving CNS2 hypomethylation. **b |** In peripheral tissues, naive CD4+ T cells develop into Treg cells in response to IL-2 and transforming growth factor-β (TGFβ), driven by TCR interaction with non-self-antigen-MHC and CNS1. **c |** In vitro, FOXP3 expression in induced Treg (iTreg) cells is short-lived, supported by TGFβ and IL-2, which activate STAT5 and SMAD3. However, CNS2 remains partially methylated, leading to unstable FOXP3 expression. [5]

Key Developmental Signals

A two-step model governs tTreg development: TCR and CD28 signaling initiates FOXP3 expression in response to self-antigens, leading to Treg cell progenitors. IL-2 signaling then promotes full maturation into functional FOXP3+ Treg cells through the activation of STAT5 and epigenetic changes. TGF-β plays a less clear role in tTreg cell development, though it is critical for pTreg cells. Other co-stimulatory molecules, like GITR and OX40, help sensitize Treg cells to IL-2. [6]

Functions and Mechanisms of Suppression

Treg cells employ multiple mechanisms to suppress immune responses: Cytokine secretion: IL-10, IL-35, and TGF-β are potent anti-inflammatory mediators. Modulation of dendritic cells (DCs): Treg cells convert DCs to a tolerogenic state via CTLA4, CD39, CD73, and other surface molecules. IL-2 sequestration: High expression of CD25 allows Treg cells to "trap" IL-2, limiting its availability to effector T cells and NK cells. Treg cells also exhibit direct cytotoxicity towards effector cells, particularly in the tumor microenvironment. [7]

Subsets of Treg Cells: Naive or resting Treg (nTreg) cells: These have not encountered antigen and express low levels of activation markers. Effector Treg (eTreg) cells: These are activated and exhibit enhanced immunosuppressive activity, especially in tissues. Tissue-resident Treg cells adapt to the local environment, influencing tolerance in specific tissues like the gut and adipose tissue. [8]

Role of mTOR and PI3K Signaling: mTOR signaling: Treg cells have low mTOR activity compared to effector T cells, which is necessary to prevent excessive inflammation. However, some mTORC1 activity is essential for Treg cell function, particularly

in lipid metabolism and survival. PI3K signaling: This pathway is downregulated in Treg cells by PTEN, a phosphatase that prevents overactivation of inflammatory signals. PTEN also maintains Treg stability by inhibiting excessive mTOR activity. [9]

Key Molecules in Treg Cell Function: STAT5: Promoted by IL-2 signaling, STAT5 is critical for Treg cell survival and function. FOXP3: Central to Treg cell identity, controlling many of their immunosuppressive functions. CTLA4: Inhibits co-stimulatory molecules on antigen-presenting cells, thereby limiting effector T cell activation. [10]

Role of Regulatory T (Treg) Cells in SLE

Systemic lupus erythematosus (SLE) is a chronic inflammatory disorder characterized by overactivation of the immune system, leading to autoantibody production and immune complex deposition. Self-antigens from apoptotic cells activate plasmacytoid dendritic cells via TLR7 and TLR9, triggering type 1 interferon production and interaction with pathogenic T cells and B cells. This overactivation of Th1 and Th17 responses, coupled with reduced regulatory T cells (Tregs), contributes to immune dysfunction and tissue damage. Genetic factors, including variations in the FoxP3 gene, affect Treg stability and contribute to SLE susceptibility. Epigenetic changes, along with environmental triggers, also play a role in disease onset. Natural Tregs suppress immune responses through inhibitory cytokines (IL-10, IL-35, TGF-β) and mechanisms like cell-contact inhibition and competition for IL-2. Tregs also regulate dendritic cells to maintain immune tolerance [11]

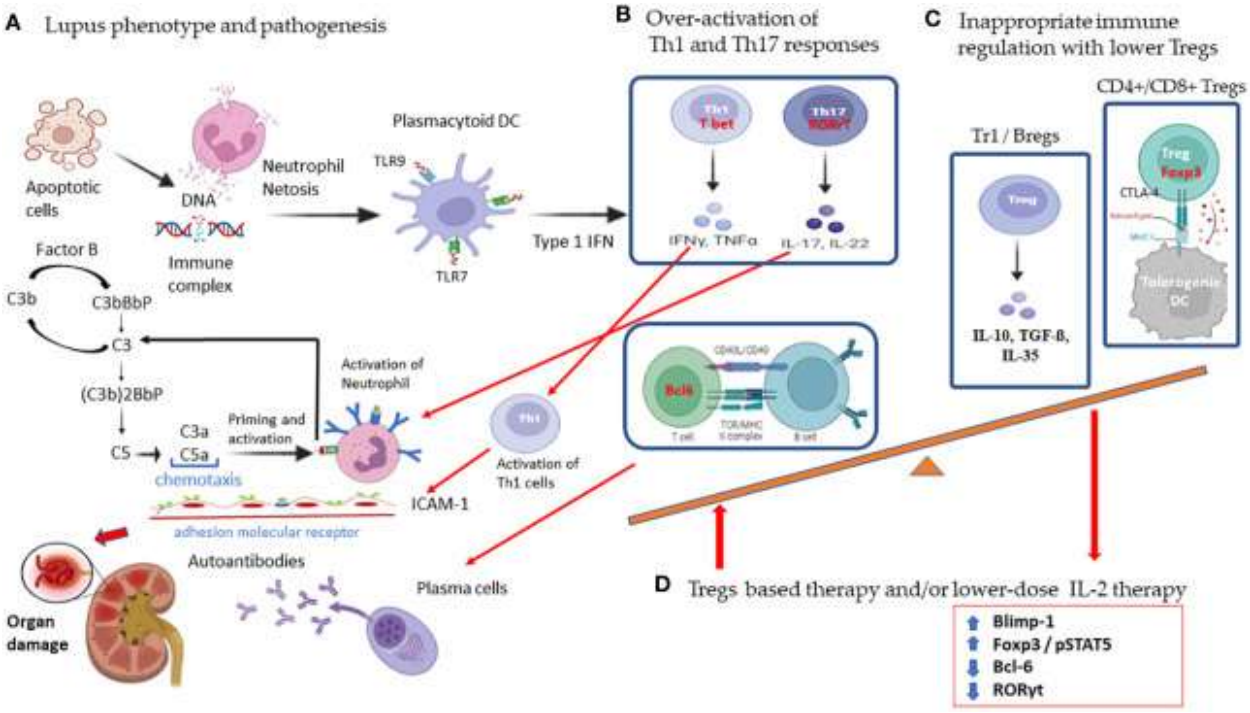

Fig. (3): Schematic of SLE Pathogenesis and Low-Dose IL-2 Therapy. (A) In systemic lupus erythematosus (SLE), increased apoptosis and defective clearance lead to immune complex formation against self-antigens. These immune complexes trigger neutrophil netosis and activate plasmacytoid dendritic cells to engage pathogenic T cells. (B) Overactivation of Th1 and Th17 responses leads to high type 1 interferon, cytokine, and adhesion molecule expression, causing tissue damage and anti-DNA autoantibodies. (C) Reduced Treg cells disrupt immune homeostasis, worsening lupus. (D) Low-dose IL-2 therapy promotes Treg differentiation via STAT5 and FoxP3 activation, inhibiting Th17 development and restoring Treg function through cytokine secretion (IL-10, TGF-β, IL-35) and suppression of dendritic cells and effector T cells. [12]

Imbalance of immune regulatory cells in SLE

Numerical and functional deficits of abnormalities in Treg subtypes have been reported to have a significant impact on the pathogenesis and outcome from patients with autoimmune disorders Elucidation of the roles of various subsets of Treg dedicated

to immune balance will provide a novel therapeutic approach that governs immune tolerance for SLE remission. However, no definitive phenotypic markers or functions have been recognized to distinguish between these Treg subtype populations in SLE. [13]

Natural Regulatory T Cells (Tregs) in SLE

In systemic lupus erythematosus (SLE), studies report conflicting results regarding Treg levels, with both increased and decreased frequencies observed. These discrepancies may stem from differences in study methods and patient treatment regimens. For instance, high-dose glucocorticoid therapy has been shown to increase circulating Tregs. However, a meta-analysis indicates that active lupus patients typically have a lower Treg/CD4+ T cell ratio compared to those with inactive disease or healthy individuals. Tregs in lupus are prone to apoptosis, further reducing their numbers and contributing to disease activity [14,15]

Restoring the balance between Treg and Th17 cells is crucial for reducing SLE symptoms. Th17 cells are key in SLE pathogenesis, and dysregulation between Treg and Th17 cells correlates with altered gene expression, such as FoxP3 and RORγt. Studies suggest that treatments like recombinant IL-2 can rebalance Tregs and effector T cells, improving disease outcomes. Additionally, T follicular helper (Tfh) cells, which promote high-affinity autoantibody production, are elevated in lupus patients, while follicular regulatory T cells (Tfr) that suppress Tfh cells are reduced. Increasing Tfr cells through therapies could potentially alleviate SLE. [16,17]

CD8+ Regulatory T Cells in SLE

CD8+ Tregs, known for their ability to control T cell activation and maintain immune homeostasis, are diminished in lupus patients. These cells suppress effector T cells through mechanisms like cytokine secretion, cell-contact inhibition, and competition for IL-2. Studies show that therapies, including autologous stem cell transplants and high-dose methylprednisolone, can increase CD8+ Treg levels and reduce disease activity. Additionally, experimental approaches, such as using peptides or plasmid DNA, have demonstrated success in enhancing CD8+ Tregs, providing a potential therapeutic avenue for lupus. [18]

Correlation between Tregs with Clinical Presentation and Prognosis of SLE

The clinical manifestations of SLE are highly heterogeneous, ranging from mild skin rashes to severe organ damage, including lupus nephritis, central nervous system involvement, and cardiovascular complications. The severity and specific clinical features of SLE are significantly influenced by the extent and nature of Treg dysfunction. Several studies have demonstrated a correlation between reduced numbers of circulating Tregs and the severity of disease activity. Furthermore, the functional capacity of Tregs in SLE patients is often impaired, meaning they are less effective at suppressing autoreactive immune responses even when present in seemingly normal numbers. This functional defect manifests in reduced expression of crucial suppressive molecules like CTLA-4 and GITR, and impaired production of immunosuppressive cytokines. [19]

The link between Treg dysfunction and specific clinical manifestations is increasingly apparent. For example, reduced Treg numbers and/or impaired Treg function have been associated with the development and severity of lupus nephritis, a major cause of morbidity and mortality in SLE. Similarly, there's evidence linking Treg deficiency to the severity of skin manifestations, such as malar rash and discoid lupus. The involvement of Tregs in other clinical features, such as arthritis, serositis, and hematological abnormalities, is also being actively investigated, suggesting a more pervasive role of Treg deficiency in the broader SLE phenotype. [20,21]

The mechanisms underlying Treg dysfunction in SLE are complex and not fully elucidated. Genetic factors contributing to impaired Treg development or function are likely involved. Epigenetic modifications affecting Foxp3 expression are also implicated. Moreover, the inflammatory milieu present in SLE, characterized by high levels of pro-inflammatory cytokines like IFN-α and TNF-α, can further impair Treg suppressive function. These cytokines can directly inhibit Treg activity or skew the differentiation of T cells away from a Treg lineage, exacerbating the immune dysregulation observed in SLE. [21:23]

The understanding of the role of Tregs in SLE pathogenesis has fueled the exploration of novel therapeutic strategies. Boosting Treg numbers or enhancing their function represents a promising approach to restore immune tolerance and alleviate disease symptoms. Strategies currently under investigation include adoptive transfer of ex vivo expanded Tregs, modulation of the inflammatory milieu using targeted therapies, and the development of small molecules that enhance Treg functions. [24:26]

The functional capacity of Tregs, rather than just their absolute numbers, is a critical determinant of prognosis. Even in patients with seemingly normal Treg counts, impaired suppressive function can lead to poor outcomes. This functional impairment can manifest as reduced expression of key molecules involved in Treg-mediated suppression, such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) and glucocorticoid-induced TNF receptor (GITR), or a diminished ability to produce immunosuppressive cytokines, such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β). Assessing both Treg numbers and their functional capacity offers a more comprehensive approach to predicting prognosis. [27]

Specific clinical manifestations of SLE are strongly linked to Treg status. For instance, patients with severe lupus nephritis, a major cause of morbidity and mortality in SLE, often exhibit significantly lower Treg numbers and impaired Treg function compared to patients with milder disease. Similarly, the severity of skin manifestations, joint involvement, and other organ-specific complications correlates with the degree of Treg dysfunction. This underscores the importance of Treg assessment in predicting the potential for future organ damage and overall disease severity. [28,29]

Therapeutic interventions aimed at manipulating Tregs are actively being explored to improve SLE prognosis. Strategies such as adoptive transfer of ex vivo expanded Tregs are showing promise in preclinical models and early clinical trials. Other approaches focus on modulating the immune environment to enhance Treg function, such as the use of immunomodulatory drugs that target pro-inflammatory cytokines or pathways that negatively affect Treg activity. However, further research is needed to optimize these strategies and to identify reliable biomarkers to predict which patients will respond most favorably to Treg-focused therapies. [30]

In summary, the relationship between Treg status and SLE prognosis is complex but increasingly well-defined. Both the number and functional capacity of Tregs are strong predictors of disease activity, organ damage, and overall patient outcome. Further research into the precise mechanisms underlying Treg dysfunction in SLE, and the development of novel therapeutic strategies targeting Tregs, holds great promise for improving the prognosis and quality of life for individuals affected by this challenging autoimmune disease. Integrating Treg assessments into clinical practice may enhance risk stratification and guide personalized treatment approaches. [31]

Targeted-Treg Therapies in SLE

Regulatory cell-based therapies aim to restore immune balance in SLE by enhancing Treg function. Conventional treatments rely on corticosteroids and immunosuppressants, but newer approaches focus on boosting Treg populations to improve immune tolerance. High-dose corticosteroids, for example, have been shown to promote Treg differentiation by inducing monocytes to produce TGF-β and activate Tregs via the miR-342-3p-mTOR axis. [32,33]

Antigen-specific Tregs can be expanded using autologous tolerogenic dendritic cells (DCs) combined with autoantigenic peptides. Another promising area is targeting the mammalian target-of-rapamycin (mTOR) pathway. Rapamycin, alone or with all-trans retinoic acid, has reduced disease activity and balanced Th17/Treg cells in SLE patients. Similarly, histone peptide therapies have shown potential in treating lupus nephritis by restoring Th17/Treg balance and suppressing interferon and anti-dsDNA antibody production. [33,34]

Further advancements in Treg therapies include antigen-specific nanoparticles and engineered Tregs with autoantigen-specific TCRs or chimeric antigen receptors (CARs), offering a more precise and effective approach to treating SLE. [35]

Regulatory T Cells in Lupus Nephritis

Regulatory T cells (Tregs) are a subset of T cells that play a crucial role in maintaining immune homeostasis and preventing autoimmunity by suppressing excessive immune responses. In the context of lupus nephritis (LN), a severe manifestation of systemic lupus erythematosus (SLE) affecting the kidneys, Tregs are of particular interest due to their role in modulating the immune system's hyperactivity, which is characteristic of this autoimmune condition. [36]

Tregs and Their Role in Lupus Nephritis

Treg Function: Tregs express the transcription factor **FoxP3**, which is essential for their suppressive function. They limit the activity of effector T cells (Teffs), B cells, and dendritic cells, which are implicated in the pathogenesis of lupus nephritis. In LN, a dysregulation of Treg function or a reduction in Treg numbers has been observed, which contributes to the unchecked

immune activation that damages the kidneys. [37]

Treg Deficiency in Lupus: Patients with lupus nephritis often exhibit a reduced number of functional Tregs. These defective Tregs are less effective at controlling the immune system's attack on the body's own tissues, particularly the kidneys. The diminished Treg function may be due to genetic, epigenetic, and environmental factors that affect Treg differentiation, stability, and suppressive capabilities. [38]

Treg Imbalance: An imbalance between Tregs and effector T cells (Teffs) is a key feature of lupus nephritis. In healthy individuals, Tregs keep Teff-mediated immune responses in check, but in LN, Teffs become overactive, contributing to kidney inflammation and tissue damage. Restoring the balance between Tregs and Teffs is considered a potential therapeutic strategy in LN. [39]

Cytokine Environment: The local cytokine milieu in lupus nephritis can influence Treg function. Pro-inflammatory cytokines such as **IL-6** and **IL-17** can destabilize Tregs or convert them into pro-inflammatory **Th17 cells**, further exacerbating the disease. Conversely, anti-inflammatory cytokines like **IL-10** and **TGF-β** support Treg stability and suppressive function. In lupus nephritis, the cytokine environment often favors inflammation, leading to impaired Treg activity. [40]

Therapeutic Potential: Restoring Treg function or increasing their numbers is a promising therapeutic strategy in lupus nephritis. Approaches include: **Treg-based therapies**: Expanding Tregs in vitro and reintroducing them into patients. **Pharmacological agents**: Drugs such as **low-dose IL-2** or **Rapamycin** that selectively promote Treg expansion without activating Teffs. [41]

CD4+ T Cells in Lupus Nephritis

CD4+ T cells are central to the pathogenesis of SLE and lupus nephritis. They comprise several subtypes, including T helper 1 (Th1), T helper 2 (Th2), T helper 17 (Th17), and regulatory T cells (Tregs). In lupus nephritis, studies have demonstrated a dysregulated immune response driven by an imbalance between pro-inflammatory and anti-inflammatory T cell subsets. [42]

Pro-inflammatory CD4+ T cells, especially Th17 cells, are key contributors to the inflammation and autoimmunity observed in lupus nephritis. Th17 cells secrete **IL-17**, a potent cytokine that promotes tissue inflammation and recruits neutrophils to sites of damage, such as the kidneys. Elevated levels of IL-17 have been detected in the kidneys and serum of lupus nephritis patients, linking this T cell subtype directly to disease severity [43]

By contrast, **Tregs** act as a counterbalance to these effector T cells, suppressing excessive immune activation. CD4+CD25+ regulatory T cells, in particular, are essential in controlling the overactive immune response and maintaining tolerance to self-antigens. [44]

CD25: A Marker of Regulatory T Cells and its Role in Immune Tolerance

CD25, the alpha chain of the **interleukin-2 receptor (IL-2R)**, is highly expressed on Tregs, allowing them to respond to **IL-2** signaling for their development, survival, and function. **IL-2** is a key cytokine in Treg biology, as it sustains their immunosuppressive activity and prevents the overexpansion of effector T cells. CD25 expression distinguishes Tregs from conventional activated T cells, which only transiently express CD25 during immune activation [45]

CD4+CD25+ Tregs in Lupus Nephritis

Several studies have demonstrated that **CD4+CD25+ Tregs** are functionally impaired in both SLE and lupus nephritis. These defects may include a reduction in Treg numbers, decreased suppressive function, or aberrant signaling pathways that impair Treg activity. [46]

Quantitative Deficiency of Tregs: Research has shown that lupus patients often have **reduced numbers of circulating Tregs** compared to healthy controls. Miyara et al. (2005) first reported that SLE patients had lower frequencies of CD4+CD25+ Tregs, correlating with disease activity. Similar findings were later confirmed in patients with active lupus nephritis (Zhao et al., 2011), suggesting that a lack of functional Tregs contributes to the immune dysregulation seen in lupus nephritis. [47]

Functional Impairment of Tregs: Even when present in sufficient numbers, Tregs in lupus nephritis may exhibit defective function. **Impaired suppressive activity** has been documented in CD4+CD25+ Tregs from lupus patients, with these cells being less effective at controlling the proliferation and activation of effector T cells. One study found that Tregs from SLE patients had

a diminished ability to suppress cytokine production, particularly **IFN-γ** and **IL-17**, which are implicated in renal inflammation in lupus nephritis. [47]

Defective IL-2 Signaling in Lupus: IL-2 is crucial for Treg survival and function. In SLE and lupus nephritis, there is often a **deficiency in IL-2** production or defective IL-2 signaling pathways, which contributes to Treg dysfunction Lower IL-2 levels impair the maintenance of the CD25-expressing Treg population, reducing their ability to control autoreactive T cells and prevent tissue damage in the kidneys. Therapeutic strategies that aim to restore IL-2 signaling, such as low-dose IL-2 administration, have shown promise in promoting Treg expansion and improving immune tolerance in animal models of lupus nephritis [48]

Therapeutic Strategies Targeting Tregs in Lupus Nephritis

Tregs not only regulate immune responses but also aid in cellular repair. Strategies to enhance Tregs, such as **adoptive Treg transfer**, **cytokine-based therapies** (e.g., IL-2, IL-2/mCD25), and **non-cytokine approaches** (e.g., small molecules, mesenchymal stem cells), are under investigation for their potential to achieve remission in LN (Figure 4). [49]

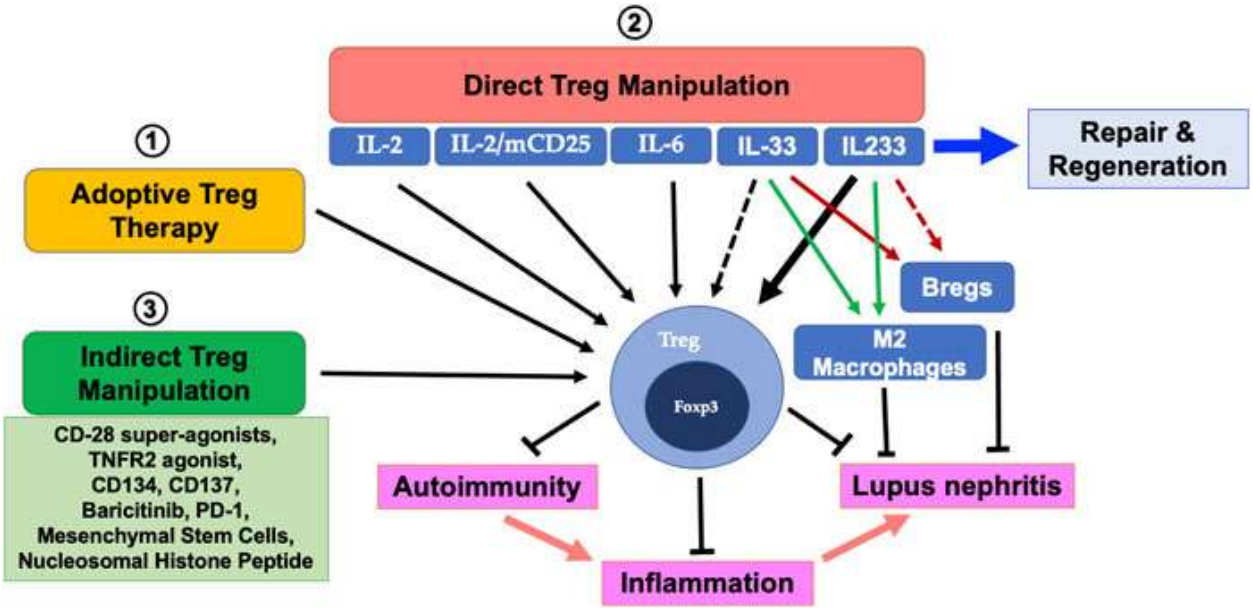

Fig. (4): illustrates various Treg supplementation therapies for autoimmunity and LN: **1-Adoptive Treg Transfer Therapy**: Successful in reducing inflammation and protecting against tissue damage. **2-Cytokine-Based Therapies**: IL-2 and related cytokines can robustly expand Tregs and potentially prevent autoimmunity and LN. **3-Non-Cytokine-Based Approaches**: Utilizing agonists, small molecules, and other agents to support Treg expansion and target LN. [50]

Low-Dose IL-2 Therapy One of the most promising therapeutic approaches in lupus nephritis involves the use of **low-dose interleukin-2 (IL-2)** to selectively expand Tregs. IL-2 is essential for Treg survival and function, particularly through its interaction with the **CD25** (IL-2 receptor alpha) on Tregs. In lupus nephritis, IL-2 levels are often insufficient, leading to impaired Treg function and reduced numbers [51]

Mechanism: Low-dose IL-2 therapy aims to promote the selective expansion of Tregs without affecting effector T cells. By increasing Treg numbers and enhancing their suppressive function, IL-2 therapy may restore immune balance and prevent autoimmune-driven kidney damage. [52]

Preclinical and Clinical Evidence: Animal studies have shown that low-dose IL-2 can reduce kidney inflammation and improve renal function in lupus-prone mice Early-phase clinical trials in patients with SLE have demonstrated that low-dose IL-2 is well tolerated and increases Treg numbers, leading to reduced disease activity These findings suggest that low-dose IL-2 therapy may be a viable treatment option for lupus nephritis. [53]

Adoptive Transfer of Ex Vivo Expanded Tregs Another strategy involves the **adoptive transfer** of Tregs that have been expanded ex vivo to restore immune tolerance. This approach leverages the ability to isolate Tregs from a patient, expand them

in the laboratory, and reintroduce them into the patient's body to suppress autoimmune responses. [54]

Mechanism: Adoptively transferred Tregs are expected to migrate to sites of inflammation, such as the kidneys, where they can suppress autoreactive T cells and inflammatory cytokine production. This approach offers the potential to directly increase the Treg population in lupus nephritis patients. [55]

Preclinical Studies: In lupus-prone mice, the adoptive transfer of ex vivo expanded Tregs has been shown to reduce kidney inflammation and improve renal outcomes. It was demonstrated that adoptively transferred Tregs were capable of homing to the kidneys and suppressing local immune responses, leading to decreased proteinuria and improved kidney histology. [56]

Modulating the Th17/Treg Axis The imbalance between **Th17 cells** and **Tregs** in lupus nephritis provides another therapeutic target. Strategies that either suppress Th17 activity or enhance Treg function may help restore immune homeostasis and protect against renal damage. [57]

Blocking IL-17 Signaling: Since Th17 cells promote kidney inflammation through the production of **IL-17**, therapies that target the IL-17 pathway could reduce inflammation in lupus nephritis. Inhibitors of IL-17 or its receptor are currently being investigated in preclinical and clinical studies for their potential to alleviate kidney inflammation and slow disease progression [58]

Enhancing Treg Function: In addition to IL-2-based therapies, other approaches aim to boost Treg function by modulating the pathways that control their suppressive activity. For example, **TGF-β signaling** is crucial for maintaining Treg stability and function, and therapies targeting this pathway could further enhance Treg-mediated suppression in lupus nephritis [59]

Targeting Co-Stimulatory Molecules Treg activity is influenced by the interaction of co-stimulatory molecules, such as **CTLA-4** and **PD-1**, with their ligands on antigen-presenting cells. Manipulating these pathways to enhance Treg function is another potential therapeutic approach in lupus nephritis. [60,61]

CTLA-4 Agonists: CTLA-4 is expressed on Tregs and plays a key role in their suppressive function by inhibiting the activation of effector T cells. Agonists that enhance CTLA-4 signaling may boost Treg activity and reduce kidney inflammation in lupus nephritis. Experimental studies have shown that CTLA-4-Ig (abatacept) can attenuate lupus nephritis in animal models by enhancing Treg function and reducing pro-inflammatory cytokine production [62]

PD-1 Agonists: Similarly, **programmed death-1 (PD-1)** is another checkpoint molecule expressed on Tregs that regulates their activity. PD-1 agonists have been investigated as a means to promote Treg function and reduce autoimmunity in SLE, including lupus nephritis [63]

Response to Immunosuppressant Treatment

Regulatory T cells (Tregs), a specialized subset of T lymphocytes, play a pivotal role in maintaining immune homeostasis and preventing autoimmunity. Their suppressive function is crucial in modulating the intensity of immune responses, and their abundance and activity significantly impact the efficacy and side effects of immunosuppressive therapies. Understanding the intricate relationship between Tregs and immunosuppressant response is therefore essential for optimizing treatment strategies in various autoimmune and inflammatory diseases. [63]

One key aspect of this correlation lies in the differential response of Tregs to various immunosuppressants. Some agents, such as calcineurin inhibitors (cyclosporine and tacrolimus), primarily target activated effector T cells, leaving Tregs relatively unaffected or even enhancing their suppressive activity in certain contexts. This selective targeting contributes to the effectiveness of these drugs in suppressing inflammation while potentially minimizing immunosuppression-related complications. Conversely, other immunosuppressants, like glucocorticoids, can exert a broader suppressive effect on both effector and regulatory T cells, leading to a more profound, albeit potentially risky, level of immune modulation. [64]

The impact of immunosuppressive treatment on Treg numbers and function varies significantly depending on the disease context and the specific therapeutic regimen employed. In some autoimmune disorders, such as rheumatoid arthritis, depletion of Tregs is observed, contributing to the uncontrolled inflammatory response. Immunosuppressive therapy in these cases may aim to restore Treg numbers or enhance their suppressive capacity, thereby restoring immune balance and alleviating symptoms. However, in other conditions, such as transplant rejection, excessive Treg activity might be detrimental, leading to immune tolerance to the transplanted organ. [65]

The precise mechanisms through which immunosuppressants influence Treg function are complex and multifaceted. Direct effects on Treg signaling pathways, indirect effects through modulation of other immune cells, and alterations in the cytokine milieu all contribute to the observed changes in Treg activity and abundance. Furthermore, the interplay between various immunosuppressants and their impact on Tregs can be synergistic or antagonistic, depending on the specific combination used. Research into these complex interactions is critical for developing more tailored and effective treatment strategies. [65]

Furthermore, the baseline Treg frequency and suppressive capacity before initiating immunosuppressant therapy can predict the response to treatment. Patients with lower Treg numbers or impaired Treg function may experience less favorable outcomes, potentially requiring higher doses or more aggressive immunosuppression, leading to an increased risk of adverse events. Conversely, patients with robust Treg populations may respond well to lower doses, reducing the risk of opportunistic infections and other side effects. [66]

Monitoring Treg numbers and functionality during immunosuppressive therapy provides valuable insights into treatment efficacy and potential risks. Changes in Treg populations can serve as biomarkers to predict response, guide dosage adjustments, and prevent adverse events. Regular monitoring allows clinicians to tailor treatment strategies to maintain optimal therapeutic efficacy while minimizing immunosuppression-related complications. This personalized approach represents a significant advance in improving the management of autoimmune and inflammatory diseases. [67]

The correlation between Tregs and immunosuppressant response extends beyond simple numerical changes. The functional capacity of Tregs, specifically their ability to suppress effector T cell activity, is also crucial. Even if Treg numbers remain stable during treatment, impairments in their suppressive function can compromise treatment effectiveness. Therefore, assessing both Treg numbers and functional activity is essential for comprehensive evaluation of immunosuppressant response. [68].

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