

A major factor in the pathophysiology of systemic sclerosis is the imbalance between T helper 17 and regulatory T cell subsets.

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ABSTRACT

The skin and internal organs might develop fibrosis, inflammation, and vasculopathy as a result of the uncommon autoimmune illness known as systemic sclerosis (SSc). The exact etiopathogenesis of SSc is yet unknown. Nonetheless, it is widely known that T cells with an abnormal immunological response play a crucial role in SSc. It has recently been discovered that subsets of T cells called regulatory T (Treg) and helper T (Th17) cells, which produce IL-17, are essential. the pathophysiology of SSc. Generally speaking, Treg cell subsets have an immunosuppressive role and oppose the immunological performance of Th17 cells, whereas Th17 cell subsets upregulate inflammation, fibrosis, and autoimmunity, which are prevalent in SSc. Recent research has indicated that Th17/Treg cell imbalance and aberrant functioning may be involved with SSc. Consequently, In order to provide new insights into the possibility of targeting the Th17/Treg balance as a potential therapy for SSc treatment in the near future, this review aims to summarize the current understanding of the critical cytokines and signaling pathways that are involved in Th17/Treg differentiation and functions, as well as their roles in the pathogenesis of SSc.

Keywords: Th17 cellss , Regulatory T cell , Autoimmune disease , Immunomodulation , Systemic sclerosis.

INTRODUCTION

An autoimmune connective tissue disease with a high death

rate is systemic sclerosis (SSc). In many non-fatal instances, the illness affects a patient's ability to function and their quality of life as They experience a variety of severe and incapacitating symptoms [1]. Widespread fibrosis, inflammation, and vascular abnormalities of the skin and internal organs, such as the heart, kidneys, lungs, and gastrointestinal system, are characteristics of sickle cell disease (SSc) [2, 3]. Numerous molecular and biological processes, including endothelial cell death, mesenchymal transition, fibrogenic extracellular matrix (ECM) buildup, and autoantibodies, are responsible for connecting these three pathogenetic processes [3]. Skin tightening and Raynaud's phenomenon are common symptoms of SSc, and they frequently begin in the extremities, particularly the skin on the fingers and toes. Based on the degree of fibrosis and the autoantibody profile, two subtypes of SSc—limited cutaneous SSc and diffuse cutaneous SSc—are diagnosed; the diffuse subgroup is more likely to die. While scientists concur that a particular genetic background plus environmental circumstances might produce immune system abnormalities and inflammatory responses, the full pathophysiology and etiology of sickle cell disease remain unclear.

Syphilis (SSc) is classified as an autoimmune illness and shares characteristics with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), dermatomyositis, bullous disorders, and other autoimmune diseases, including the dysregulation of innate and adaptive immunity and the presence of autoantibodies [1,4]. Important autoantibodies against the angiotensin II type I receptor (AT1R) are generated in SSc. and the endothelin-1 type A receptor (ETAR), which connects the control of angiogenesis to the collagen synthesis of skin fibroblasts [1].

T cells are recognized to be important in the pathophysiology of both innate and adaptive immunity. T cells can be divided into three subsets based on the tasks they perform: the regulatory T (Treg), helper T (Th), and cytotoxic T cell (CTL). The Th cell subgroup, whose cells display the surface marker CD4, has been shown to control the adaptive immune responses. The two most prevalent subgroups of Th cells, Th1 and Th2, have different immunological characteristics. When antigen-presenting cells (APCs) are active, IL-12 co-stimulates naïve Th cells to develop into Th1 cells. Th1 cells secrete IFN- γ , which stimulates the antigen processing pathways, further differentiating Th1 subsets and inhibiting the formation of

other patterns of cytokines. In the meantime, IL-4 suppresses other Th cell subsets and guides naïve Th cells' development into Th2 cells, encouraging the latter's growth. The main cytokines produced by Th2 cells are IL-4, IL-10, IL-13, and IL-5 [5,6]. Like other autoimmune conditions, the Immune system dysregulation, which includes SSc, was traditionally thought to be caused by an imbalance or alternating pattern of Th1 and Th2 subsets [5,7–14]. New research, however, points to the growing significance of other T cell subsets in SSc and other autoimmune disorders, including Th17 and Treg cells.

Th17 subsets drive SSc pathogenesis by cytokine-related secretion Th17 cells secrete

IL-17, a pro-inflammatory cytokine that is characteristic of Th17 cells whose development is mostly facilitated by IL-6 [15,16]. Caused by various cytokines, Th17 effector cells (Teff17) and Th17 regulatory cells (Treg17) are the two functionally separate populations of Th17 cells. In addition to secreting IL-22 and granulocyte-macrophage colony-stimulating factor (GM-CSF), Teff17 cells exhibit pathogenic properties. In the meanwhile, Treg17 cells have been discovered to be protective and regulatory, generating IL-10 and IL-21, and their development is controlled by the signal transducer and STAT 3 is an activator of transcription [17–20]. The cytokine family known as IL-17 is multifunctional; among its many actions are the induction of tissue-damaging chemicals and inflammation. Because Th17 cells have a pleiotropic effect on fibroblasts, keratinocytes, endothelial cells, neutrophils, and memory T cells, they play a significant role in mediating tissue inflammation and autoimmunity [21]. Th17 cells and IL-17 are essential for defense against parasites, extracellular microorganisms, and fungus, as well as in rheumatoid arthritis (RA), granulomatosis with polyangiitis (GPA), SLE, and other autoimmune and chronic illnesses Myasthenia gravis (MG), multiple sclerosis (MS), and other conditions [7,9,22–27].

Th17 cells and the cytokines they produce—IL-17, IL-21, and IL-22—have garnered a lot of attention lately due to their involvement in SSc. Many research teams have noted that, in comparison to healthy donors, SSc patients' peripheral blood or skin have higher concentrations of Th17 cells and their byproducts [8,13,27–37]. According to certain research, the presence of Th17 cell subsets in lung impairment in both mouse models and human SSc patients is correlated with disease activity and collagen overproduction [8,31,35,38]. IL-17 A, the primary Th17 production, has several, profound effects [5]. Skin vascular smooth muscle cells (DVMSCs) have been observed to proliferate, synthesize, and migrate in response to IL-17 A isolated from SSc patients via the extracellular signaling cascade including signal-regulated protein kinases (ERK) [39, 40]. Furthermore, three pro-inflammatory chemokines—monocyte chemotactic protein

(MCP)-1, IL-8, and matrix metalloproteinases (MMP)-1—are impacted by IL-17A [41]. It's interesting to note that IL-17A appears to express less in localized scleroderma and appears to rise specifically in SSc skin. [33].

IL-17 A/Th17 cells have been shown to have inconsistent roles in fibrosis (Table 1) [32, 34, 41–48]. According to certain research, SSc-related IL-17 A/Th17 cells triggered the production and release of type I collagen to encourage the fibrosis of the skin and lungs of mice with SSc, and mice lacking IL-17A showed a protective effect [34, 42]. Nevertheless, several study found that IL-17 A/Th17 cells were shown to reduce the differentiation of fibroblasts into myofibroblasts and the production of type I collagen by dermal fibroblasts in both healthy individuals and SSc patients; they also reported that increased Th17 cell counts may be related to autoimmunity rather than a mechanistic relationship with fibrosis [32,41,46]. The reason behind the IL-17 A/Th17 cells' wildly divergent behavior in various circumstances is yet unknown, though. The fibrotic manifestation in SSc is thought to be caused by pro-fibrotic pathways mediated by other cells and chemicals, even if IL-17 A/Th17 cells may exhibit some degree of anti-fibrotic activities.

In addition to the IL-17 clan, more members of Cytokines produced from Th17 also have clear correlations with SSc. One important pro-inflammatory cytokine in the skin that is generated by a lot of Th cells—including Th17—because of its increased capacity to eradicate bacteria and produce chemokines (MCP-1 and IL-8) and cytokines (TNF, IL-1, and IL-12) [5,49]. There is a relationship between the severity of early SSc skin lesions and IL-21 [30]. Studies have demonstrated that patients with sickle cell disease (SSc) had elevated levels of circulating IL-17 and IL-23 [28, 31, 37]. However, a different group has discovered that serum IL-21 is raised while IL-23 is decreased, in addition to IL-17 [35]. Either way, it is undeniable that these cytokines produced from Th17 are important in SSc.

Additionally, it has been documented that the CCR6 gene polymorphisms, a surface marker of Subsets of Th17 cells have been linked to an increased risk of SSc [50]. The aforementioned findings all support the critical roles played by Th17 cells in both the early and late stages of SSc, contributing to targeted organ damage.

fibrous tissue, autoimmune, and inflammation. One may summarize the pathophysiology of SSc by saying that Th17 cell subsets mostly promote the disease.

Researchers found that Th17 cell differentiation is influenced by increased IL-1 β and IL-6 release in IL-33-matured dendritic cells [51]. It has been found that Th17 cell differentiation from naïve T cells and IL-17 production are downregulated by TLR7 signaling [52].

Th17 differentiation was induced by retinoic acid-related orphan receptor (ROR) γ activity through I κ B kinase (IKK) α -dependent phosphorylation of S376, whereas IKK α -independent S484 phosphorylation exhibits inhibition [53]. The differentiation, proliferation, and function of SSc Th17 cells may be influenced by changes in cytokines, signaling pathways, or protein phosphorylations, according to these recent findings (Fig. 1).

In the pathophysiology of SSc, impaired Treg cell subsets lost their immunosuppressive.

The subgroup of T lymphocytes known as Treg cells is identified by the surface expression of CD25 (IL-2R α), CTLA-4 (cytotoxic T-lymphocyte antigen), and Foxp-3 (fork head box protein), a transcription factor crucial to the growth and survival of Treg cells [5].

Because they modulate allergy and autoimmune responses by decreasing different immunity cell subsets, such as T cells, B cells, natural killer cells, monocytes/macrophages, and dendritic cells, Treg cells are necessary to maintain immunological homeostasis and avoid autoimmune disease, both in vivo and off-line. Through cytokine production and cellular interactions with substances that are membrane-bound, Treg cells contribute to both innate and adaptive immunity [5,54–59]. The Treg cells secrete three primary cytokines that have anti-inflammatory properties: TGF- β , IL-10, and IL-35.

The primary criteria used to categorize distinct Treg cell subset groups are their phenotypic characteristics or places of origin. In the earliest stages of life, natural Treg (nTreg) cells are created after emerging from the thymus undergoes negative selection, which is succeeded by suitable activation of T-cell receptors (TCRs) in the presence of an unusual cytokine milieu, like Foxp3. On the other hand, naïve T cells undergo lifelong differentiation into inducible Treg (iTreg) cells in secondary lymphoid organs when TGF- β is stimulated when pro-inflammatory cytokines are not present [6,60]. Additionally, TGF- β helps to prevent inflammation by additionally preventing the generation of cytokines and T cell division [6].

The loss or malfunction of Treg cells is thought to be a significant factor in autoimmune illnesses, including SLE, RA, ankylosing spondylitis, type 1 diabetes (T1D), RA, and others, because of their critical involvement in innate and adaptive immunity [23,56,58,61–67,62].

Regarding SSc, certain research examining the flow of Treg cells subsets have produced varying Treg cell frequency values. When functional impairment occurred, the amount of Treg cells in peripheral blood either decreased, increased, or exhibited no discernible changes at all.

in the last ten years when compared to healthy controls

(Table 2) [29,36,68–75].

The two forms of immune responses that result in the varied Treg cell numbers, morphologies, and activities are what cause Treg cells to behave differently in peripheral blood and determine whether or not the discovery of circulating Treg cells is significant in SSc. Increased lymphocyte apoptotic vulnerability and CD4+T cell proliferation were linked to a more aggressive immunological profile with high Treg cell counts. This led to diffuse cutaneous SSc, lung involvement, and active illness. Conversely, restricted cutaneous SSc is caused by a decrease in circulating Treg cells, CD4+T cell proliferation, and lymphocyte death linked to a progressive rise in naïve T cells. features of an alternative immune response that is distinct from those of other autoimmune illnesses [29,76]. Based on the expression of Foxp3 and CD45RA, circulating Treg cells can be divided into three types: FrI, FrII, They express CD4+CD25+Foxp3highCD45RA+, CD4+CD25highFoxp3highCD45RA-, and CD4+CD25+Foxp3lowCD45RA-, in that order. As does FrIII. It's interesting to note that whereas immunosuppressive FrIs and FrIIs are both reduced in SSc, the increased fraction of Treg cells in peripheral blood are FrIIIs, which do not exhibit functional suppression [74].

Research on skin-specific Treg cells may help to clarify their relevance in SSc since it has been confirmed that these cells exist in secondary lymphoid organs in addition to circulation [77]. Treg cells in human skin were identified as effector memory cells, or mTreg cells, based on their morphological and functional characteristics. They localize mostly to hair follicles, remain in situ localized, accumulate over time, exhibit distinct TCRs, CD45RO, and markedly elevated levels of BCL-2, CTLA-4, CD25, ICOS, and CD27 [78].

While there is ongoing debate on the prevalence of peripheral Treg cells in SSc, experts appear to agree that cutaneous Treg cells in SSc skin lesions, there was a decrease in both the population and the immunosuppressive ability [72,79].

It has been found that Th2-derived cytokines, such as IL-4 and IL-13, which are involved in fibrosis and autoimmunity, can be produced by Treg cells in SSc skin [80]. Furthermore, certain soluble substances in SSc plasma linked to altered TGF- β production and CD69 surface expression are likely responsible for the malfunctioning of Treg cells [68].

According to research conducted by our team, SSc patients have The frequency of Treg cells in CD4+ T cells and the aberrant expression and methylation status of Foxp3 have been connected. This suggests that higher levels of methylation of the Foxp3 mRNA and Foxp3 regulatory sequences have an inverse correlation [73]. Furthermore, Foxp3 expression has been linked to both diffuse and active types of SSc [29], which suggests that the pathophysiology of SSc may involve functional and numerical abnormalities in

suppressive Treg cells. Furthermore, the modification of Treg linked with the activity and severity of SSc [69], regardless of what was circulating in the patients or in the skin lesions.

A critical role for the mismatch between Th17 and Treg cells in SSc

Multiple cells and their balances play a complex role in the pathogenesis of SSc, and these processes appear to be more important than the structural or molecular abnormalities of individual T cell subsets [13].

In addition to the canonical Th1/Th2 balancing alternation, the Th17/Treg imbalance has recently attracted a lot of attention. The distinction between the Th17 and Treg lineages is relevant. Peripheral naïve T cells produce Foxp3 only in response to TGF- β , a strong regulatory cytokine that regulates lymphocyte proliferation, differentiation, and survival to preserve tolerance [81,82]. Antigen-activated naïve T cells produce Foxp3 and ROR γ t, a Th17 lineage-specific transcription factor, in the presence of TGF- β ; however, Foxp3 counteracts the effects of ROR γ t [83,84]. IL-6, IL-21, and IL-23 are necessary for the production of Th17 cells from these ROR γ t + Foxp3⁺ cells, whereas retinoic acid and IL-2 are required for the differentiation of Treg cells [5,29,85–88]. IL-6 has a variety of biological activities and impacts on the regulation of the immune system, hematopoiesis, inflammation, and carcinogenesis. As said, Foxp3 can prevent ROR γ t's transcriptional activation at the mutual progenitor of Th17 and Treg cells, which increases the proliferation of Treg cells. When IL-6 is present, this inhibition can be reversed, which encourages Th17 cell development [87,89]. Conversely, it is hypothesized that IL-6 inhibits Treg cell differentiation linked to their alternation [90]. Because Th17 and Treg cell differentiation has such profound impacts, IL-6 upsets their equilibrium. Furthermore, it has been discovered that IL-23 stimulates Th17 cell growth and development and can be generated at low doses.

IL-6 or IL-21, in addition to TGF- β [88,91]. Th17 and Treg cells may interact reciprocally through Foxp3 and ROR γ t's hostile struggle under the effect of those potent cytokines.

Furthermore, according to certain research, some Treg cells may be able to develop into Th-17 cells, which produce IL-17, as a result of their cytokine milieu [55,74,92–96]. Despite the possibility that these IL-17-producing Treg cells will continue to suppress the immune system, Treg cell plasticity leads to pro-inflammatory and autoimmune behaviors [92,96]. However, it doesn't appear that any research has indicated that Th17 cell subsets have the same function transforming into Treg cells. Furthermore, the flexibility of Treg cells is associated with both epigenetic programming and gene expression [85,93]. It has been shown that upsetting the Th17/Treg equilibrium in

The development of autoimmune-related illnesses such as SLE, RA, primary immune thrombocytopenia (ITP), connective tissue diseases-associated pulmonary arterial hypertension (CTD-aPAH), and HIV infections may be significantly influenced by peripheral blood. Additionally, it has been linked to disease activity and severity [9,23,55,64,97–99]. Further, since research on IL-6 indicate a link between SSc activity and disability [100], it can be assumed that IL-6 mediates the Th17/Treg balance based on the overexpression of Th17 cells and the inhibition of Treg cells.

Studies have also demonstrated Th17's functional and numerical deficiencies. and Treg cells coexisting in SSc and raising the Th17/Treg cell ratio, indicating that the immune response in SSc is biased toward the development or expansion of Th17 cells, which results in the fibrosis, vascular anomalies, and pro-inflammation [13, 36, 74].

Additionally, it has been discovered that SSc is associated with Treg cells that have the ability to release IL-17 [74].

Th17 cells secrete IL-17, IL-21, IL-22, and other cytokines, as was previously described. They can influence various immune cells and promote the creation of collagen and extracellular matrix (ECM), as well as the migration of dermal vascular smooth muscle cells (DVMSCs) and the differentiation of endothelium into myofibroblasts, which may also produce excessive amounts of ECM. These actions have a tight connection to fibrosis and persistent inflammation in the skin, blood vessels, SSc, as well as interior organs. Normal Treg cells and the substances they produce, like TGF- β , IL-10, and IL-35, help to keep the immune system in balance and stop inflammation; however, SSc Treg cells, which have defects in their numbers or functions, may encourage the growth of immunological responses that are adaptable to antigens [101]. Moreover, Treg cells in SSc differentiate into Th2-like cells to stimulate fibroblasts and increase the deposition of collagen and extracellular matrix [80]. Defective Treg cells in SSc thereby worsen the fibrotic and inflammatory process that leads to visceral, vascular, and cutaneous damage.

Consequently, the increased Th17/Treg ratio seen in SSc patients indicates the improvement of Th17 function and the reduction of Treg repression, which leads to the differentiative and functional antagonism of the Th17 and Treg cell lineages. It causes extensive tissue damage in SSc by continuous inflammation, microangiopathy, and widespread fibrosis. Studies on the processes underlying the Th17/Treg balance have been conducted.

Within living things. It has been discovered that Notch signaling in dendritic cells plays a role in the balance of Th17 and iTreg cells and is directly regulated by Rbpj protein transcription [102]. According to some studies, α -ketoglutaric acid can upregulate Treg cells and limit the differentiation of

Th17 cells by increasing Foxp3 expression and inhibiting the activity of transcription factor ROR γ t [103]. Further research is necessary to determine the roles that Notch signaling and the glutamate-dependent metabolic pathway play in Th17/Treg balance and SSc pathogenesis.

CONCLUSIONS

An essential step in the pathophysiology of SSc is aberrant T-cell homeostasis, and a Th17/Treg imbalance seems to be significant. Th17 cells function as effector cells displaying their pro-inflammatory and pro-fibrotic properties. Treg cells, on the other hand, fend off the inflammatory and fibrotic processes in SSc. Recent research has confirmed that these two T cell subsets alternate either alone or together. An imbalance between Th17 and Treg cells has a major effect on SSc pathogenesis because of their antergic immunological activities and interaction, which were previously highlighted. Studies on this topic have been scarce, which is far from sufficient given that the disease's trajectory is still unknown. As of yet, there is no effective treatment for SSc. Therapeutic strategies linked to Th17 and Treg cell subsets are under study in light of the Th17/Treg imbalance, and there are numerous theories focused on the alternation of Th17 or Treg cells. For example, because the Th17/Treg ratio is biased in favor of Th17 cells, which block pro-in-Th17 differentiation is fueled by inflammatory cytokines such IL-6, IL-1 β , and IL-21, which may be more successful in reestablishing the Th17/Treg balance. Regarding Th17-related tactics, medications that focus on the important Th17 cytokine production pathways, such as IL-17, are being studied [104]. Furthermore, it has been shown that immunotherapy directed against IL-17 and IL-23 is beneficial for a number of immune-mediated inflammatory conditions and may be applied to SSc [105]. It is still unclear if Treg cell therapy can be truly useful in treating SSc, despite a number of animal trials and a few clinical research demonstrating its efficacy [106]. It should be mentioned that segmentation may occur in unidirectional therapy procedures, resulting in lower safety levels and additional restrictions. of the Th17 and Treg cell imbalance in SSc being more significant than individual T cell subsets. Treatments that focus on diverting the Maintaining the Th17/Treg balance or modulating both of these T cell subsets might be more important. Blocking IL-6 is thought to be beneficial in treating experimental autoimmune models because it affects the Th17/Treg cell balance [107,108]. Furthermore, it is possible to restore the T17/Treg balance with extracorporeal photochemotherapy (ECP) and endurance training. Patients may be more receptive to these treatments due to their noninvasiveness and convenience [109, 110]. Treg and Th17 cells differ and serve different purposes,

making them agonistically competitive. In the presence of TGF- β , antigen-activated naïve T lymphocytes express Foxp3, which can do the following: preventing ROR γ t's transcriptional activation. These Th17/Treg cells differentiate from ROR γ t(+) Foxp3(+) cells based on the local cytokine environment. Th17 cells release IL-17, IL-21, IL-22, and other cytokines to aid in the synthesis of SSc during pathogenesis. of collagen and extracellular matrix (ECM), DVS MC movement, endothelium development into myofibroblasts, and their impact on various immune cells. Treg cell abnormalities in SSc, such as decreased deficiency, malfunction, and differentiation into Th2-like cells, may lessen their ability to suppress Th17 and other immune cells and encourage the production of autoimmune antibodies. In SSc, the aforementioned pathways are all involved in the chronic inflammation and fibrosis of the skin, blood vessels, and internal organs. As a result, the Th17/Treg cell balance is skewed in favor of Th17 cell subsets, which leads to a number of SSc pathogenic processes.

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