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Systemic Sclerosis and the Immune System: From Pathways to Targets

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Abstract
Systemic sclerosis is a rare connective tissue disorder characterized by a widespread thrombotic microangiopathy, excessive deposition of extracellular matrix components in the skin and internal organs causing systemic fibrosis, associated to immune dysfunction affecting both innate and adaptive immunity. The immune dysregulation appears earlier in the course of the disease, and the innate immunity components seem to react to vascular antigens released following endothelial cells apoptosis, thus initiating the adaptive immunity. Via a cytokines network, the immune system provides a profibrotic environment in which fibroblasts thrive with excess secretion of extracellular matrix components. Once activated, the adaptive immunity acts as an amplifier of these disorders whether by sustaining the pro-fibrotic environment (by T helper 2 cells), promoting auto-antibodies secretion (by B Cells), or via disruption of suppressive cells (regulatory T cells). The intricacy of these immunological aspects offers an explanation as to why classical immunosuppressors fall short when it comes to managing systemic sclerosis, asserting the need for newer and more specific molecules.

Keywords: Systemic Sclerosis, Immune Dysfunction, Innate Immunity, Adaptive Immunity, Immunotherapeutic Perspectives

Introduction

Systemic sclerosis (SSc) is a rare autoimmune connective tissue disease, affecting mainly women between 40 and 60 years, characterized by excessive fibrogenesis, widespread microangiopathy, and immune dysfunction. Skin thickening is a hallmark feature of SSc that allows us to classify patients into diffuse cutaneous SSc and limited cutaneous SSc with different degrees of internal organ involvement and thus associated with different complications and prognosis [1, 2].

Signs of immune dysregulation seemingly appear during the early stages of SSc, evidenced by the presence of cutaneous mononuclear cells infiltrates and abnormal production of autoantibodies preceding skin fibrosis [3]. This dysfunction involves both the effectors of innate and adaptive immunity with alternations affecting their surface molecules, signaling pathways and cytokine secretions [4].

The purpose of this review is to highlight the major immunological dysfunctions in systemic sclerosis and their contribution to fibrogenesis and vascular damage, including the potential therapeutic targets in light of recent advances.

Immune functions and endothelial dysfunctions

The intertwined relationship between the endothelial system and the immune system makes it hard to establish a clear chronological order of the pathological events during SSc.

Endothelial cells' (EC) apoptosis is among the first manifestation reported in the early stages of the disease [5]. This apoptosis is thought to be behind both *structural* vascular alterations - involving angiogenesis and vasculogenesis- and *functional* ones affecting the regulation of inflammatory response, vasomotion and coagulation. This results in a widespread thrombotic microangiopathy with aberrant vascular remodeling, especially in small and medium-sized vessels, bringing about the classical manifestations of the disease such as Raynaud's syndrome, pulmonary hypertension and scleroderma renal crisis [5].

EC apoptosis is also associated with an increase in pro-inflammatory cytokines secretion during this stage. The recruited white cells engulf the apoptotic cells and act as antigen-presenting cells to initiate the adaptive immune response with vascular antigen as targets, thus amplifying the vascular damage [6]. Furthermore, the apoptotic ECs can also activate the alternative complement pathway and coagulation cascade, altering the endothelium's antithrombotic properties and consequently exacerbating the ischemic phenomena [7].

To date, an exact trigger for the EC apoptosis is yet to be identified, however several factors have been proposed: Genetic, toxic, infectious, autoimmune and metabolic.

Role of the innate immunity

Although the role of B and T cells seems more prominent, innate immunity components are a key element in the pathogenesis of SSc, as they are involved in the recognition of EC antigens, initiation of the adaptive immune response and of the inflammatory cascades.

Macrophages are very versatile cells whose properties may change depending on their cytokine micro-environment with two main subsets of opposite characteristics; **M1** profile induced by Interferon γ (IFNγ) and Tumor necrosis factor α (TNFα), and **M2** profile activated by T_H2 cytokines such as IL-4 and IL-13 [8, 9]. According to a recent study, the pro-fibrotic M2 profile is predominant in SSc patient's sera and thought to be the result of activation by soluble factors in local microenvironment [10]. This profile has been known to increase the synthesis of Transforming growth factor β (TGFβ) and induce the differentiation of fibroblasts into myofibroblasts - cells specialized in tissue repair - therefore promoting the fibrosing processes compatible with SSc clinical features [11, 12].

This activation most likely results from the recognition by the Toll-like receptor (TLR) receptors of DAMPs (Damage-associated molecular patterns) released following ECs' apoptosis. These receptors can be found on the surface of macrophages and dendritic cells and are highly involved in the initiation of the innate immune response as well as the development of antigen-specific acquired immunity. Moreover, some TLR subsets expressed on the surface of fibroblasts, namely TLR4 and TLR8, appear to be involved in fibrogenesis by promoting the production of TGFβ and tissue inhibitors of metalloproteinase (TIMPs) during SSc [13, 14].

Dendritic cells (DCs), as the most potent antigen-presenting cells (APC) of the immune system, play a pivotal role in initiating the adaptive response. During SSc, these cells are responsible for DAMPs recognition, their presentation to adaptive immunity effectors and cytokine secretion. They can also deviate naïve T cells' differentiation to a profibrotic T helper 2 (T_H2) profile following their activation via TLR4, or to a pro-inflammatory T helper 1 (T_H1) profile which increases the production of IL-6 or TNFα especially in the early stages of the disease [15, 16].

Role of the adaptive immunity

T cells

T cells infiltrates can be detected in the skin of scleroderma patients long before the appearance of the histological signs of cutaneous fibrosis, acting on both fibroblasts and ECs [17].

In general, T cells' activation can be either **specific** (also known as antigenic activation) or **non-specific** via cytokines. The mechanisms underlying their activation in SSc are always a topic of debate. On one hand, their activation by chemokines produced by fibroblasts was detected in SSc patients [18]. On the other hand, the existence of monoclonal expansion of αβ-T cells (or oligoclonal if several antigens) which has been reported in these patients, is usually a sign of an antigenic activation while the exact triggering factors of this response remain unknown [19].

Once activated, the T cells' profile was found to vary according to the stage of the disease, systemic involvement and sampling site [4]. And so, a predominance of T_H2 cytokine profile (e.g. IL-4, IL-13) has been observed in peripheral blood samples and cutaneous infiltrates in patients with lung fibrosis and diffuse forms [17, 20, 21], while a T_H1 profile (e.g. IL-12 and IFN-γ) has been associated with a long duration of the disease [22], which could explain the improvement of skin thickening in later stages (Fig 1).

However, as recent studies showed, these weren't the only abnormalities within the T cell population. An imbalanced ratio between T helper 17 (T_H17) and regulatory T cells (Treg) subsets was found in SSc sera with high T_H17 and low Treg levels, with IL-17 secreting cells being more abundant in the skin and blood of these patients [23]. Moreover, functional alterations in Treg cells were reported to display either a loss of their suppressive functions by a diminished CD69 [24] or Foxp3 expression [25], or a conversion into a T_H2-like profile in the skin of SSc patients, allowing them to produce significant amounts of IL-4 and IL-13, thus promoting the fibrotic processes [26].

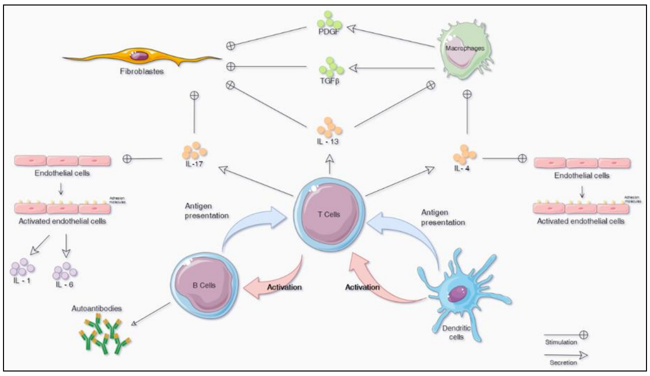

Fig 1: T cells roles during systemic sclerosis

B Cells

The existence of hypergammaglobulinemia and the overexpression of the CD19 marker on its surface are usually a sign of B cell's activation, both of which were reported during SSc [27]. This activation may be triggered by the recognition of vascular antigens following apoptotic ECs' phagocytosis by macrophages and DCs or, the post-apoptotic release of cell contents, where B cells will also act as APC.

This results in the production of a wide variety of auto-antibodies (auto-Abs). Anti-EC Ab stimulates the expression of adhesion molecules and the secretion of IL-1 by EC, facilitating the recruitment and adhesion of leukocytes and consequently perpetuating the apoptotic processes that led to their synthesis in the first site [28, 29]. Apoptotic nuclear components such as DNA topoisomerase I can bind to fibroblasts, leading to their activation and adhesion in the presence of anti-topoisomerase I Ab [30]. Other released components include centromeres, RNA polymerases, PM-Scl and some RNP units, although Abs targeting these antigens seem to have no pathological role [31]. Other auto-Abs seem particularly involved in systemic fibrogenesis, either by stimulating the production of extracellular matrix components or by inhibiting their degradation. For instance, anti-fibroblast Abs, found mainly in the diffuse form, promotes fibroblast activation to a pro-inflammatory phenotype, boosting the release of IL-1 and IL-6 [32]. Anti-fibrillin I Ab can act on fibroblasts via TGF-β [33], whereas anti-PDGF Abs stimulate collagen production and increase the release of reactive oxygen species (ROS) known to have adverse biological effects [34]. Anti-MMP Abs are able to inhibit matrix metalloproteases, a family of proteases that are greatly involved in the degradation of extracellular matrix proteins among other functions, amplifying the pathological fibrosing processes [35]. Lastly, elevated levels of auto-Abs against angiotensin II type 1 receptors and anti-endothelin type A receptor -which bound to their respective receptors on CE - were reported in SSc patients and were significantly associated to the progression and mortality of the disease [36], suggesting a potential role in the development of the disease.

Cytokines and systemic sclerosis

The term "cytokines" refers to a family of small proteins (5-20 kDa) that are significantly involved – among other roles- in cell's signaling, particularly as immunomodulating agents. These include interleukins (IL), chemokines, interferons and the TNF family, and they are produced by a broad range of cells primarily by immune system cells (B and T Cells, macrophage), ECs and fibroblasts.

Several cytokines have been tightly associated with the pathogenesis of SSc, chiefly the Transforming Growth Factor-β (TGF-β). This cytokine -which is produced by T cells, fibroblasts and macrophages- promotes the synthesis of collagen and proteoglycans, and limits their degradation by inhibiting the production of metalloproteinases or by promoting that of their inhibitors. Moreover, TGFβ can also make fibroblasts more resistant to apoptosis and drive their differentiation into myofibroblasts [37]. Interestingly, it is the overexpression of TGF-β receptors on the surface of fibroblasts rather than its hypersecretion that is considered responsible for the excessive production of extracellular matrix components in scleroderma patients, since TGF-β levels aren't high in SSc patients [38, 39].

High levels of IL-4, IL-13 and IL-17 -produced by T_H2 cells and mast cells - were reported in the skin and serum of SSc patients since the 90s [40]. IL-4 promotes the proliferation of fibroblasts, the synthesis of TaGF-β, and the inhibition of the anti-fibrotic effects of IFN-γ, in addition to its role in upregulating the expression of adhesion molecules in endothelial cells [17]. IL-13 boosts the production of TGF-β and PDGF by macrophages, or via a TGF-β-independent mechanism [27]. In SSc patients, not only IL-13 levels were elevated in comparison to healthy people [41], recent studies showed that CD8+ T cells mediated fibrosis via the secretion of this cytokine [42]. Finally, IL-17 stimulates the production of TGF-β and the release of pro-inflammatory cytokines - including IL-6 and IL-1- as well as the expression of adhesion molecules in both ECs and fibroblasts, thus enhancing the fibrotic process [43].

Fibroblasts also participate in this "cytokine network" by secreting pro-inflammatory cytokines and chemokines, such as TNF-α and Monocyte chemoattractant protein 1 (MCP-1), as they promote mononuclear cells recruitment, their migration across vascular walls and the induction of cutaneous infiltrates [44]. Furthermore MCP-1 has been recognized to drive T cells activation toward a T_H2 profile [45] as well as collagen synthesis via the production of TGF-β and IL-4 [19].

Despite the predominance of T_H2 profile, T_H1 cytokines were also shown to play an important role in the pathogenesis of SSc, notably IL-1 that will stimulate collagen synthesis through the production of IL-6 and PDGF [46]. PDGF are considered as the main neuroectodermal and mesenchymal tissue growth factors, and their dysregulation has been linked with pathological conditions, including atherosclerosis, pulmonary hypertension and systemic fibrosis [47]. During SSc, PDGF are detected at high levels with aberrant expression of their receptors (PDGFRs) on the surface of ECs and fibroblasts [48]. These alterations amplify TGF-β effects on fibroblasts and stimulate the expression of PDGFRs, creating a positive feedback loop that favors the proliferation, migration, contraction and apoptosis resistance of myofibroblasts [49].

CTGF (Connective Tissue Growth Factor) intervenes mainly in the late stage of SSc. In normal circumstances, CTGF is produced by ECs and fibroblasts and is normally involved in the regulation of angiogenesis and wound healing under the control of TGF-β. During SSc, fibroblasts produce a high level of CTGF induced by either TGFβ and TGF-β-independent mechanism, causing endothelial dysfunction, aberrant fibroblast growth and excessive secretion of collagen [50].

To exert their effects, these cytokines depend on the JAK-STAT signaling pathway, which is the main signaling system for a wide range of cytokines and growth factors. This pathway combines: A **receptor** that binds the cytokines, a **Janus kinase** (JAK), and a **signal transducer and activator of transcription proteins** (STATs) which in its phosphorylated form acts as a transcription factor to produce the cell's effects mediated by different cytokines. Recent studies gave evidence of high concentration of phosphorylated STAT3 in the skin of SSc patients. This accumulation was induced in a TGFβ-dependent manner, with p-STAT3 acting as its intracellular mediator for its pro-fibrotic effects - mainly inducing fibroblasts' differentiation into myofibroblasts and stimulating collagen production [51]. JAK2, one of the key regulators of STAT3 phosphorylation, was also increased in SSc fibroblast compared to healthy individuals, acting both as down-stream mediator for TGFβ, but may act as an amplifier of its expression in these patients [52], suggesting it as a potential candidate for targeted therapies of SSc.

Autoantibodies and systemic sclerosis

Clinical significance of auto-antibodies

Auto-antibody screening is of great importance when it comes to SSc diagnosis and management, with their inclusion in the 2013 ACR / EULAR SSC Classification Criteria [53]. The close relationship between the auto-Abs, internal organ involvement and the disease progression makes it possible to assess the disease stage and to establish a prognosis earlier through auto-Ab screening, allowing for a better management (Table 1). Currently their mere association with the Raynaud's phenomenon and puffy fingers is sufficient to diagnose patients with a very early stage of SSc [54].

Auto-antibody's pathogenicity

During SSc, auto-Abs target a heterogeneous group of antigens: Nuclear (topoisomerase I, centromeres, RNA polymerases,), cytoplasmic (mitochondria, ANCA), cellular (fibroblasts, endothelial cells) and extracellular (Fibrillin I, MMP...).Several elements argue in favor of the pathogenicity of the autoantibodies during SSc, such as their specificity, their presence in the majority of patients, their positivity at the beginning of the disease, as well as their associations to specific clinical phenotypes. However, the nature of this pathogenicity remains controversial.

In connection with this, four criteria must be met: Their existence before the onset of the disease; the positivity in most patients; the access to their antigenic target and the ability to trigger the disease of interest in an animal model following a passive transfer [31]. In the case of SSc, the antigens targeted by the auto-Abs are -by definition- sequestered inside the nucleus and inaccessible to circulating Abs, and up to now, the reproduction of a satisfactory animal model is yet to be achieved by the passive transfer of these auto-Abs [31, 55]. On the other hand, Abs targeting non-nuclear antigens, such as anti-fibroblasts or anti-ECs or anti-MMP Ab were indeed found to be involved in the perpetuation of the inflammatory and fibrotic phenomena but their presence seems to be the consequence rather than the cause of the immune dysfunctions [55].

Additionally, the existence of the ANA-negative SSc, a rare form, is yet another argument against the pathogenicity of these antibodies. This diagnosis is made when a patient has enough criteria to be classified as SSc but negative for known SSc-related auto-Abs. These patients have less vascular involvement, diffuse interstitial lung disease and pulmonary hypertension, but they're more likely to develop digestive disorders than subjects with auto-Abs [56], suggesting the existence of other factors eluding their detection by current means.

Systemic sclerosis and microchimerism

Microchimerism is defined as the stable presence of a small number of cells from a genetically different individual. It can be observed during pregnancy following two-way cell transfer between the mother and the fetus, or after a transplantation or blood transfusion, and it has been proposed as a potential trigger for autoimmune diseases [57].

Several studies have suspected the role of microchimerism in the development of SSc, taking into account the close similarities with graft-versus-host disease, including skin disorders and autoimmune manifestations [58], even if the later doesn't share SSc endothelial abnormalities [59]. This hypothesis is further supported by the high prevalence of SSc in females compared to their male counterparts and by the high level of fetal cells in the cutaneous lesions reported in SSc patients in comparison to healthy subjects [60].

Immunotherapeutic perspectives of Systemic Sclerosis

Due to the multifactorial aspects of SSc, non-selective immunosuppressive drugs - including cyclophosphamide, azathioprine and mycophenolate mofetil - remain the main molecules used in the treatment of skin thickening and active diffuse interstitial lung disease. However, these immunosuppressants appear to have little effect on the progression of the disease and their long-term use is not without a risk, hence the need to develop safer and more effective treatment options, either by targeting specific organ involvement (lung, kidney, skin..) or the specific processes involved in the disease (excessive fibrogenesis, widespread microangiopathy, and immune dysfunction) [61–64].

The use of polyvalent intravenous immunoglobulins, characterized by their ability to bind to circulating autoantibodies and B cell's surface immunoglobulins, seems to inhibit IL-4 and TGFβ in SSc-mice, and was shown to improve skin and joint involvement in SSc patients [61, 62]. A similar effect was also reported after the use of monoclonal antibodies, whether they were directed against B cells (Rituximab) [65], T cells (Basiliximab) [66], APC (Abatacept) [67], IL (Tocilizumab) [68] or TGF-β (Fresolimumab) [69].

A new family of immunosuppressants known as proliferation signal inhibitors, most notably Sirolimus (Rapamycin), was shown to limit T and B cell responses to cytokine's production and other activation stimuli. Recent studies have reported an improvement in skin thickening in SSc patients, and with minimal toxicity compared to methotrexate [70, 71]. However, given the size of the sample further studies are needed to better evaluate its efficacy and side effects.

In the same vein, JAK2-STAT3 inhibitors, which showed their efficacy in other autoimmune diseases, are currently under assessment for a potential benefit on SSc. A study carried out by Chakraborty *et al*. showed that the pharmacological inhibition of this pathway made fibroblast less sensitive to the pro-fibrotic effects of TGF-β, thus improving sclerosis in experimental models [51]. A potential candidate is the Tofacinib, an inhibitor of JAK1 and JAK3 approved in the treatment of rheumatoid arthritis and psoriasis. This JAK-inhibitor not only had potent antifibrotic effects in animal models [72], it also improved skin sclerosis and musculoskeletal involvement in SSc patients, with a satisfactory safety [73]. Another candidate appears to be ruxolitinib, a JAK1/2 inhibitor used in the treatment of polycythemia vera and myelofibrosis, which significantly improved skin sclerosis in a large cohort but with no effect on lung involvement [74].

And lastly the use of autologous stem cell transplantation is also considered as a potential treatment, and very promising for patients with poor prognosis, with an improvement in skin thickness and lung function, as well as a reduction in overall mortality [75].

Conclusion

The dysfunction of the immune system is a key element in the pathogenesis of SSc.

After their recruitment, innate immune cells are not only responsible for the recognition and presentation of vascular antigens and initiation of the adaptive immunity response (Disruption of immune tolerance), they can also intervene in the genesis of a profibrotic microenvironment, either via M2 macrophage cytokine secretions (IL-4) or via the ability of dendritic cells to promote T_H2 activation.

During SSc, the profile of T cell (proinflammatory T_H1 / profibrotic T_H2) will vary depending on the stage of the disease, systemic involvement and sampling site. Acting as modulators of the inflammatory response, the T cells promote macrophage activation, expression of EC adhesion molecules and B cell activation, which in response produces auto-antibodies, hallmarks of SSc and potential maintainers of pathological processes.

The intricate relationship between the immune system and the endothelial system, as well as the multifactorial aspects of the immune dysfunction explain the difficulty of SSc management. On one hand, non-selective immunosuppressive drugs with their ability to act on several targets at once remain the first-line of treatment, especially when it comes to skin thickening and diffuse interstitial lung disease. On the other hand, their adverse effects as well as their weak effect on the progression of the disease call for the development of new therapies that are more targeted, more effective and less toxic.

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