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Review article

Update on the etiopathogenesis of systemic sclerosis

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ABSTRACT

Systemic Sclerosis (SSc) is an autoimmune disease of multifactorial etiology, triggered by a combination of genetic and environmental factors. Its varied clinical expression results from the complex physiopathogenic interaction of three main elements: proliferative vasculopathy, immune dysregulation and abnormal deposition and remodeling of the extracellular matrix (ECM), of which the characteristic disease fibrosis is the result. Early physiopathogenic events appear to be endothelial injury and imbalance in vascular repair with the activation of endothelial cells, the immune system and platelets, with the release of multiple mediators such as TH2 proinflammatory cytokines and growth factors, triggering a sequence of simultaneous or cascading events that involve several intracellular signaling pathways.

The most important result of these events is the hyperactivation of fibroblasts, the main effector cells of fibrosis, which will then produce large amounts of ECM constituents and secrete multiple growth factors and cytokines that perpetuate the process. In this article we review the main factors potentially involved in the etiology of SSc and reexamine the current knowledge about the most important mechanisms involved in the development of lesions that are characteristic of the disease. A better understanding of these physiopathogenic mechanisms will help identify potential therapeutic targets, which may result in advances in the management of this complex and debilitating disease.

Atualização na etiopatogênese da esclerose sistêmica

Palavras-chave:
Esclerose sistêmica
Etiopatogênese
Sistema imune
Angiopatia
Matriz extracelular

RESUMO

A Esclerose Sistêmica (ES) é uma doença autoimune de etiologia multifatorial, desencadeada pela combinação de fatores genéticos e ambientais. Sua variada expressão clínica resulta da complexa interação fisiopatogênica de três elementos principais: a vasculopatia proliferativa, a desregulação imunológica e a deposição e remodelamento anormais da matriz extracelular (MEC), da qual resulta a fibrose característica da doença. Eventos fisiopatogênicos precoces parecem ser a lesão endotelial e o desequilíbrio no reparo vascular, com a ativação de células endoteliais, do sistema imune e das plaquetas, com a liberação de múltiplos mediadores, como as citocinas proinflamatórias TH2 e os fatores de cresci-

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mento, desencadeando uma sequência de eventos simultâneos ou em cascata que envolve diversas vias de sinalização intracelular. O resultado mais importante desses eventos é a hiperativação dos fibroblastos, as principais células efetoras da fibrose, as quais passam a produzir grandes quantidades de constituintes da MEC e a secretar múltiplos fatores de crescimento e citocinas que perpetuam o processo. Neste artigo apresentamos uma revisão dos principais fatores potencialmente implicados na etiologia da ES e revisitamos os conhecimentos atuais sobre os mais importantes mecanismos envolvidos no desenvolvimento das lesões características da doença. O melhor entendimento desses mecanismos fisiopatogênicos possibilita identificar potenciais alvos terapêuticos, o que pode resultar em avanços no manejo dessa complexa e debilitante doença.

Introduction

Systemic sclerosis (SSc) is a connective tissue disease of autoimmune origin, characterized by vascular alterations and progressive skin and visceral fibrosis affecting mainly the lungs, gastrointestinal tract, heart, and kidneys.[1] The disease is extremely heterogeneous in its phenotypic expression, and its prognosis is determined by the predominant clinical manifestations, especially regarding visceral involvement.[2-4]

Despite advances in knowledge about the mechanisms responsible for the disease onset, there is still a lack of understanding regarding the pathogenic process is initiated and undergoes intensification in each subgroup of patients, leading to different clinical expressions. As in other autoimmune diseases, especially those that are not organ specific, it is known that the process results from the interaction of multiple factors, both individual and those related to the surrounding environment.[5]

However, the mechanisms that trigger the disease in genetically susceptible individuals have not yet been elucidated. In this article, the main factors potentially implicated in the etiopathogenesis of SSc are reviewed, as well as the current knowledge on the most important mechanisms involved in the development of SSc characteristic lesions, and the potential treatments directed at molecular and cell targets that have emerged from recent research are listed.

SSc etiology: environmental factors

In the great majority of cases, SSc is considered to be idiopathic. However, in some situations, environmental factors likely play an important role in its development. These associations have been recognized for many decades, and the most important are those related to exposure to silica and organic solvents. The combined relative risk estimate (CRRE) for silica, calculated in a meta-analysis, was 3.20 (95% CI: 1.89-5.43) for men. Regarding exposure to organic solvents, the CRRE found in a meta-analysis was 2.91 (95% CI: 1.60-5.30),[6] and, according to another more recent meta-analysis,[7] the latter is a factor associated with increased risk of SSc in men.

The possible association between silicone breast implants and connective tissue disorders, especially scleroderma, has been the subject of great controversy, generated by case reports that suggested this association.[8] However, a meta-analysis[9] and a recent and comprehensive systematic review[10] of the available epidemiological evidence did not confirm such association.

Other environmental factors that have been implicated in the etiology of SSc are exposures to infectious agents, especially viruses. Among them, parvovirus B19 is an example of a very prevalent infection in patients with SSc.[11] Regarding the Epstein-Barr virus, it has been demonstrated that specific adaptive immunity against the virus (the activation of suppressor T lymphocytes) was deficient in scleroderma patients.[12] Cytomegalovirus (CMV) infects endothelial cells and monocytes, leading to the production of profibrotic cytokines, causing vascular lesions and activating fibroblasts, and may therefore trigger pathogenic processes associated with SSc development.[13]

An association between positivity to anti-CMV antibodies and prevalence of specific autoantibodies in patients with SSc has been reported.[14] These data suggest an association between infectious and environmental factors and the disease, but more studies are still necessary to determine the possible causal role of external agents in triggering SSc.

SSc etiology: hormonal and genetic factors

Considering the marked predominance of SSc in women,(7:1) a hypothesis was raised that hormonal factors are relevant to the disease development. However, this has not been proven. For instance, an increased incidence of the disease in women who use oral contraceptives has not been observed.[15]

Among the host factors involved in the etiopathogenesis of autoimmune diseases, genetic susceptibility is perhaps the most relevant, and therefore has been the target of extensive research. In SSc, as in almost all other systemic rheumatic diseases, polymorphisms of the main histocompatibility system (human leukocyte antigen [HLA]) have been associated to the disease development, with the main associations being with class II HLA antigens.

A recent study involving a fairly significant sample showed a positive association of haplotypes HLA-DRB1_1104, DQA1_0501, DQB1_0301 and, in contrast, the protective factor of haplotypes HLA-DRB1_0701, DQA1_0201, DQB1_0202, and DRB1_1501 in whites and Hispanics with SSc; however, in blacks, the association was with HLA-DRB1_0804, DQA1_0501, and DQB1_0301 alleles.[16] Moreover, the association of the HLA system with autoantibody specificity in SSc has also

been studied. The same abovementioned study demonstrated the association of anti-Scl70 antibodies with HLADPB1_1301 antigens, of anti-centromere antibodies (ACA) with HLADQB1_0501 and DQB1_26, and of anti-RNA polymerase antibodies with HLA-DRB1_0404, DRB1_11, and DQB1_03 alleles(16), which illustrates the multiple influences that this gene system can exert on SSc and its clinical and immunological profile.

Many other genes have been implicated in SSc susceptibility, mostly those encoding proteins responsible for the regulation and transduction of signals that comprise the autoimmunity and inflammation mechanisms involved in the pathogenesis of SSc. One of the main associations found in different populations was with the gene encoding for the signal transducer and activator of transcription 4 (STAT4),[17] which promotes the differentiation of type-1 T helper lymphocytes and negatively regulates the Th2 type.

The association of B-cell scaffold protein with ankyrin repeats (BANK1), which binds the B-cell receptor to intracellular signaling proteins such as kinases,[18] and with the interferon regulatory factor five (IRF-5), regulator of transcription of type I interferon genes, were also confirmed.[19] Moreover, positive associations have also been reported of SSc with candidate interleukin 23 (IL-23R) receptor genes involved in expression of the IL-23, a cytokine which expands the population of TH17 lymphocytes, but SSc has only been associated with positivity to anti-scleroderma 70 (anti-Scl70) autoantibody, and it acts as a protective factor in relation to pulmonary hypertension.[20] Another gene related to SSc susceptibility is the connective tissue growth factor (CTGF), which induces cell proliferation, increasing production of ECM and chemotaxis of mesenchymal cells.[21]

Recently, it has been observed that interactions between genes are also important, such as the apparent additive effect in SSc exerted by the simultaneous presence of STAT4, IRF-5, and BANK1 on the susceptibility and the development of the diffuse clinical form and pulmonary fibrosis.[17,22] Another interesting finding was the sharing of genetic risk factors between different autoimmune diseases, exemplified by the protein tyrosine phosphatase 22 (PTPN22) non-receptor gene, involved in SSc susceptibility[23] as well as in diabetes mellitus type I,[24] systemic lupus erythematous (SLE),[25] and rheumatoid arthritis (RA).(25) Other shared genes, such as BANK1, IRF5, and STAT4 have also been reported as involved in SLE and RA susceptibility.[26-28]

Another genetic factor of SSc susceptibility was recently demonstrated in white European populations.[29] It is the macrophage migration inhibitory factor (MIF)-173, a cytokine with immunoregulatory functions and a mediator of innate and adaptive immunity, which has been implicated in the pathogenesis of vasculopathy in SSc.(30) In addition to the association with susceptibility, the MIF-173C allele was associated with the diffuse form of the disease.[29]

Physiopathogenic mechanisms of systemic sclerosis

The current accumulated knowledge regarding the physiopathogenesis of SSc derives from extensive research in different areas, and indicates that the pathological process arises from the complex interrelation between three main components: vascular dysfunction, innate and adaptive immunity dysregulation, and excess activation of fibroblasts and related cells, which culminates in the development of fibrosis (Fig. 1).[31]

Proliferative vasculopathy

The occurrence of Raynaud's phenomenon in almost all patients with SSc, with high severity in many of them, demonstrates the importance of vasculopathy in the pathogenic context of the disease. It is believed that the vasculopathy may originate after injury and activation of endothelial cells by unknown factors.[32] The endothelial activation has been demonstrated in several studies that detected high plasma levels and increased expression of von Willebrand factor, intercellular adhesion molecules, endothelin-1, and thrombomodulin, which also represent evidence of excessive apoptosis of endothelial cells.[33-35]

Chronic endothelial injury results in platelet adhesion and activation of the fibrinolytic system, as well as in increased vascular permeability and leukocyte adhesion to the vascular wall.[34] Increased levels of endothelin-1, a potent vasoconstrictor, have been detected in plasma and bronchoalveolar lavage fluid of patients with SSc.[36] This protein is responsible for increasing leukocyte adhesion to the endothelium, promoting migration and proliferation of smooth muscle cells into the intima layer of vessels and activating fibroblasts.

This process promotes the synthesis and deposition of ECM molecules, leading to fibrosis with loss of elasticity and progressive reduction of the vascular lumen, causing progressive tissue necrosis and hypoxia.[37]

Tissue hypoxia promotes angiogenesis (formation of new vessels from remaining functional vessels) and vasculogen-

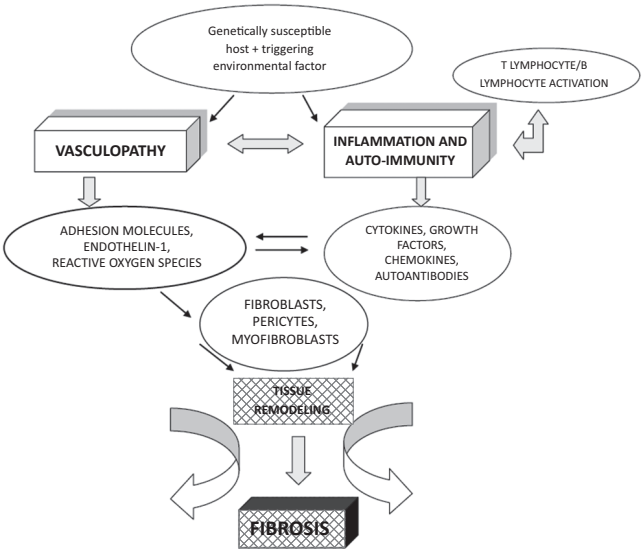

Fig. 1 – Physiopathogenic mechanisms of systemic sclerosis: the interaction between vasculopathic, inflammatory, and autoimmune factors lead to hyperactivation of effector cells and production of tissue fibrosis.

esis (formation of new vessels from endothelial progenitor cells),[38] in order to restore cell oxygen supply. Due to multiple causes not yet understood, these processes are deficient in SSc, and there is an imbalance between angiogenic and angiostatic factors and ineffective vascular repair.[39-40]

The result is the formation of morphologically aberrant and dysfunctional capillaries, which can be viewed in the nailfold capillaroscopy examination. It is now known that tissue hypoxia present in SSc plays an important pathogenic role in the disease through different factors, such as the production of hypoxia-induced factor (HIF-1), whose production and deficient regulation is ineffective in restoring normal blood pressure levels of oxygen. This deficiency creates a vicious circle, with increased activation of immune cells, increased activation of fibroblasts, increased levels of transforming growth factor β (TGFβ), and ECM deposition, which in turn aggravate the hypoxic environment. Furthermore, the increase in oxidative stress caused by hypoxia has a proinflammatory and profibrotic effect, exerted by reactive oxygen species (ROS).[41]

An additional factor that contributes to microvasculopathy in SSc is the pericytes, cells very close to the endothelium that normally inhibit cell migration and vascular proliferation. These cells are hyperplastic and hyperactivated in SSc, inhibiting the process of angiogenesis and transdifferentiating into myofibroblasts, producing excess ECM, which accumulates in the perivascular area and aggravates the proliferative vasculopathy of the disease.[38] Table 1 summarizes the most relevant physiopathological events in relation to SSc vasculopathy.

Autoimmunity and inflammation

Another important factor implicated in the pathogenesis of SSc is the involvement of both humoral and cellular immune system, whose mediators are the connection between vascular disease and tissue fibrosis, as they are involved in both processes.[32] The involvement of the humoral immune system is demonstrated by the presence of B lymphocyte infiltrates with expression of chronic activation markers (CD19, CD85), which have been detected in patients with SSc skin using DNA microarray techniques.[42] The homeostasis of circulating B lymphocytes is altered, expanding the population of non-activated cells (naïve) and reducing the number, but increasing the activation of memory B cells.[43] This knowledge has led to the use of therapies directed against B cells (monoclonal antibodies belimumab and rituximab) in the treatment of patients with SSc, as well as to the blocking of the costimulation between the latter and T lymphocytes.[44]

Table 1 – Physiopathogenesis of vasculopathy in systemic sclerosis.

Effector cells	Physiopathogenic processes	Molecules involved
Endothelial cells Smooth muscle cells of vessels Pericytes	• Lesion and apoptosis of endothelial cells • Oxidative stress • Increased vascular permeability • Platelet activation and thrombosis • Structural vasculopathy (progressive reduction of vascular caliber due to hypertrophy and fibrosis) Impaired neovascularization	• Von Willebrand factor • HIF-1 • Endothelin- 1 • VCAM-1 • ELAM-1 • VEGF • Reactive oxygen species • Cytokines

The specific autoantibodies, which represent one of the attributes of the disease, characterize its clinical forms and have important prognostic associations; they are the most obvious expression of the humoral immune system involvement in the etiopathogenesis of SSc. The main autoantibodies whose pathogenic potential has been established, in addition Scl70 and ACA, are those directed against endothelial cells and against the platelet-derived growth factor (PDGF) receptor.[32]

ACA are characteristic of limited SSc, which is generally more benign than the diffuse form, but is associated with later development of pulmonary hypertension, one of the most severe complications of the disease, as well as digital ulcers and important gastrointestinal involvement. Patients with limited SSc may have anti-Th/To antibodies (more frequent in men, with interstitial pulmonary involvement and earlier mortality),[45] anti-PM/Scl antibodies (associated with myositis, calcinosis, acro-osteolysis and interstitial lung disease),[46] and the anti-U1RNP antibodies (that characterize overlapping forms between SSc, SLE, and myositis).[47]

Conversely, the presence of anti-Scl-70 is associated with the diffuse form of SSc, with interstitial pulmonary involvement and increased risk of renal crisis, especially in the early years of the disease. Musculoskeletal complications, such as flexion contractures of the fingers, are common and very disabling.[47] More rarely, the anti-RNA polymerase III (POL3) antibodies occur in the diffuse form, whose patients have a high frequency of renal crisis, rapidly progressive skin fibrosis, and little pulmonary and gastrointestinal involvement.[48] The diffuse form can also show the presence of anti-U3RNP (fibrillarin), which is more common in black individuals and has worse prognosis, with severe pulmonary fibrosis, arterial pulmonary hypertension, pigmentation alterations, and joint contractures.[49]

The pathogenic role of cell immunity, represented mainly by T lymphocytes, is evidenced in SSc by the increase in endothelial transmigration of T CD4 + cells originating from perivascular inflammatory infiltrates and oligoclonal activation of these cells, resulting in profibrotic cytokine production.[50] The oligoclonal activation of T-lymphocytes was demonstrated by the increased levels of soluble IL-2 receptor in the serum of SSc patients, which showed a strong association with skin involvement (Rodnan skin score) in the disease.[51]

The predominant production of these cytokines (IL-4, IL-5, IL-6, IL-10, IL-13, and monocyte chemoattractant protein-1 [MCP-1]) results from an imbalance between the profiles of T helper type 1 (TH1) and type 2 (TH2) cells, derived from TH2- cells, which is the predominant profile in SSc

and promotes worsening of tissue fibrosis.[52] Current knowledge allows for the inference that the processes triggered by profibrotic cytokines derived from the interaction between T lymphocytes and fibroblasts play a key role in the development of fibrosis (Table 2).

Development of fibrosis: fibroblast activation

The third key pathogenic mechanism involved in SSc, and the most representative of the disease, is fibrosis, which lends its name to the disease and affects the skin, lungs, heart, digestive tract, kidneys, and musculoskeletal system. The extent of skin fibrosis is associated with mortality by SSc, as recently demonstrated both in the European and Brazilian populations.[3-4]

Fibrosis results from complex interactions between multiple concurrent or cascading processes, in which dozens of cell mediators, cytokines and their receptors, chemokines, growth factors, and intracellular signaling molecules are present (Table 3). The result of this interaction is the excessive production and accumulation of insoluble material in the tissues that constitutes the ECM. Fibrillar collagens types I and II, type VII collagen, and elastin and fibrillin fibrils are mainly found in ECM, as well as enzymes that promote the production of collagen crosslinks.[53]

Regarding fibrosis cell mediators, the fibroblast is the cell primarily responsible for the production and remodeling of the ECM, and its main physiological importance lies in the healing process of connective tissue injuries, having a self-limited action, depending on the injury extent.[53] In SSc, as in other fibroproliferative diseases, there is a state in which the fibroblast is permanently hyperactivated, with altered expression of genes that determine ECM overproduction.

In SSc, one of the mechanisms responsible for this hyperactivation is the mechanotransduction abnormality, in which fibroblasts and myofibroblasts would be able to perceive tensional forces and change their intracellular signaling in response, leading to altered homeostasis and remodeling of the ECM.[54] In addition to the fibroblasts, myofibroblasts also participate in the process of fibrosis formation in SSc. These contractile and ECM-producing cells originate from the transdifferentiation of fibroblasts, epithelial cells, and pericytes.[55] Unlike the normal healing process, in which myofibroblasts occur only transiently in granulation tissue, in SSc these cells become permanent, producing areas of fibrosis with contracture of the ECM.[56]

The bone marrow also contributes to the increase of the amount of profibrotic cells, with the release of pluripotent mesenchymal cells and fibroblast progenitors (fibrocytes). The latter physiologically replenish the population of fibroblasts maintaining tissue homeostasis, but they also exert a pathogenic role in SSc. Fibrocyte precursors migrate and accumulate in tissues by gradient of chemokine receptors (CRs), such as CCR3, CCR5, and CXCR4.[32] These receptors and their ligands have been found at high levels in the skin of patients with SSc.[57] Furthermore, tissue-infiltrating fibrocytes have also been implicated in the pathogenesis of pulmonary fibrosis disease.[58]

The main effector proteins involved in the fibrosis mechanisms in SSc are the cytokines, chemokines, and the family of ECM growth factors, which induce fibrogenic cell response by increasing the expression of genes encoding ECM constituents.[59] Profibrotic cytokines play a pathogenic role in SSc. The best-known and most often studied cytokine regarding its mechanisms in fibrosis is IL-4, which stimulates the synthesis of TGFβ and CTGF; it also promotes the migration, proliferation, and synthesis of collagen by fibroblasts. High levels of IL-4 were found in serum and tissues of patients with SSc, and a larger number of T cells that produce this cytokine were detected in these patients.[60-61] It is also known that IL-13 induces the expression of type I collagen gene and that its levels are elevated in patients with SSc, but its possible role in the induction of fibrosis is not well established.[60] Very recently, a study found increased levels of IL-6 in serum and tissues of patients with diffuse SSc, which was associated with more severe skin involvement and increased mortality after three years,[62] suggesting that IL-6 antagonism would be a promising therapeutic target in this situation.

Perhaps the most important of all effector proteins of fibrosis is TGFβ, considered to be the orchestrator of the phys-

Table 2 – Autoimmunity and inflammation in the pathogenesis of systemic sclerosis.

Effector cells	Physiopathogenic processes	Molecules involved
T Lymphocytes B Lymphocytes	• General and local activation of T and B lymphocytes, oligoclonal expansion • Transendothelial migration of CD4+ activated T lymphocytes • Production and release of pro-fibrotic autoantibodies and cytokines	• Autoantibodies (anti-PDGF, anti-endothelial cells, anti-Scl70, anti-centromere) • Profibrotic cytokines: IL-4, IL-6, IL-10, IL-13 • IL-2 receptor

Table 3 – Physiopathogenesis of fibrosis in systemic sclerosis.

Effector cells	Physiopathogenic processes	Molecules involved
Fibroblasts Myofibroblasts Pericytes Smooth muscle cells of vessels Fibrocytes (bone marrow)	• Differentiation and trans-differentiation of fibroblasts • Excessive synthesis of ECM (mainly collagen fibers) • Tissue remodeling • Reduction in ECM resorption	• Growth factors (TGFβ and TGFβRII, CTGF, PDGF, EGR-1) • Chemokines (CRs, MCP-1) • Intracellular signaling molecules (SMADs, tyrosine-kinases, MAPK-, GNK-, BMPs, EGR-1, Wnt-β-catenin • Nuclear hormone receptors (PPAR-ϒ) • Endothelin- 1

iological process of tissue repair and known to be involved in the development of pathological fibrosis, as in SSc.[59] TGFβ is produced by fibroblasts, T cells, monocytes, and platelets, and it is released as a latent complex that is activated by tissue injury to its biologically active form within the ECM, exerting its function by binding to a specific receptor (TGFβRII) on the surface of different cell types.[37]

After this binding, an intracellular signaling cascade starts, which results in the expression of target genes such as type I collagen, CTGF, and plasminogen activator inhibitor-1, among others.[63] The main control of TGFβ intracellular signaling system is exercised by the SMAD system (SMAD2 and SMAD3 activators, as well as endogenous inhibitor SMAD7 and its cofactors), whose dysregulation results in increased fibrogenesis, a phenomenon already demonstrated in SSc.[64] Recently, other regulatory mechanisms of TGFβ were studied and their importance was demonstrated in the pathogenesis of SSc, such as c-Abl kinase (c-Abelson, a tyrosine kinase implicated in the pathogenesis of chronic myeloid leukemia), a potent regulator of the TGFβ-induced profibrotic response in fibroblasts.[65]

Imatinib, an inhibitor of c-Abl, reduces fibrotic responses in animal models and have shown to be promising in the treatment of patients with SSc.[44,66] Also relevant as mediators of profibrotic cell response to TGFβ are genes from the early growth response (EGR) family, particularly EGR-1, whose expression is induced by chemical or mechanical tissue injury and whose levels are elevated in skin lesions of SSc, as demonstrated in a murine model of bleomycin-induced scleroderma.[67]

Another relevant mechanism in the process of fibrosis that has recently been demonstrated, but whose role still requires elucidation, is the Wnt-β-catenin, an important intracellular signaling pathway in the embryonic period during organogenesis whose posterior and aberrant reactivation is associated with disease (cancer, for instance) by increasing fibroblast activity and promoting transdifferentiation. In biopsies of scleroderma patients, this pathway was activated and found responsible for significant production of fibrosis and lipoatrophy.[68]

In addition to TGFβ, other growth factors are important in the pathogenesis of SSc, such as CTGF, whose effects are similar to those of TGFβ and whose levels are increased in lesions of patients with SSc. Its expression is stimulated by TGFβ itself, by hypoxia, and by ET-1.[37] PDGF is produced by fibroblasts, platelets, macrophages, and endothelial cells, with important mitogen and chemoattractant activity for fibroblasts, inducing their production of collagen, fibronectin, and proteoglycans, and the release of profibrotic mediators IL-6 and MCP-1. This is another growth factor implicated in the interaction with TGFβ and CTGF, which was detected at high levels in the lungs of patients with SSc.[69]

In addition to all the aforementioned mechanisms, which help to promote excessive fibrogenesis, in SSc there are also abnormalities in the physiological counterregulation systems that normally prevent the occurrence of fibrosis. This was demonstrated in the case of SMAD7, signaling molecules that exert an antifibrotic role through negative regulation of TGFβ action.[64]

Searching for antifibrotic mechanisms that could be explored for therapeutic purposes in SSc, the peroxisome proliferator activated receptor-gamma (PPAR-ϒ) was identified. This molecule is a key hormonal nuclear receptor in lipid and glucose metabolism, which has been increasingly associated with ECM remodeling and fibrosis, capable of modulating TGFβ signaling and mesenchymal cell plasticity. It was found that this receptor is involved in an important antifibrotic mechanism, and its expression and activity were found to be reduced in patients with SSc.[70] Natural or synthetic PPAR-ϒ agonists, such as the antidiabetic drugs pioglitazone or rosiglitazone, or tissue stimulation of its expression could, therefore, play a role in the treatment of fibrosis. Table 3 summarizes the elements involved in the physiopathological process of establishment fibrosis in SSc.

In spite of the fact that SSc is considered to be incurable, in recent years intensive research has led to the identification of antifibrotic cellular and molecular targets and the development of therapeutic options directed against them. Table 4 lists some treatments aimed at targets (mostly discussed above) that have emerged from *in vitro* studies, animal models, and early trials in humans.[44] A better understanding of the physiopathological mechanisms of SSc has shed light on the factors that most likely initiate the process and lead to its perpetuation.

Considering that the vascular lesion and its defective repair are known early events, it is possible that the clinical expression of the disease depends more on the magnitude of vascular changes and its chronicity than on the triggering event itself.[41] Therefore, efforts are needed in order to diagnose the early establishment of vasculopathy and to institute treatment in order to halt the progression of the process. In addition, the elucidation of the molecular mechanisms involved in SSc may contribute to the identification of other potential targets to be assessed in the search for more specific and effective treatments for this severe and debilitating disease.

Table 4 – Therapies directed against targets in systemic sclerosis.

Therapeutic target	Drugs (available or in development)
• Intracellular Molecules	
PPARϒ, Notch	Rosiglitazone, inhibitors of the Notch signaling pathway
• Cytokines, growth factors, chemokines, intracellular signaling pathways	
MCP-1/CCR2	CCR2 inhibitors (PF-04136309, BMS-741672, MLN1202)
TGFβ, CTGF, IL-13, IL-6	Monoclonal antibodies (CAT-192, FG3019, QAX576, tocilizumab)
Chemokines (CXCL12, CCL4)	CXCR4, CCR2 inhibitors
Wnt signaling pathway	PRI-724 inhibitors, resveratrol
• Blocking of the coagulation system activation	
Thrombin	Inhibitor: dabigatran
• Therapies directed against T and B cells	
T/B co-stimulation	Abatacept (CTLA4-Ig)
CD20, BAFF (BlyS)	Monoclonal antibody (rituximab, belimumab)

Conflicts of interest

The authors declare no conflicts of interest.

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