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Review

Systemic sclerosis: Recent insights

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ABSTRACT

Systemic sclerosis is an orphan connective tissue disease characterized by alterations of the microvasculature, disturbances of the immune system and massive deposition of collagen and other matrix substances in the skin and internal organs. A major achievement of the recent years has been the validation of new classification criteria, allowing earlier diagnosis and earlier treatment of systemic sclerosis, before irreversible fibrosis and organ damage appeared ("window of opportunity"). Raynaud's phenomenon is usually the first sign of the disease and is considered as the main sentinel sign for the identification of very early systemic sclerosis. Systemic sclerosis is clinically heterogeneous and disease course remains unpredictable. Its prognosis depends on cardiopulmonary involvement and recent studies aim to identify serum or genetic biomarkers predictive of severe organ involvement. Moreover, the prospective follow-up of large cohorts has provided and will offer critical material to identify strong prognostic factors. Whereas the outcomes of vascular manifestations of the disease has been recently improved due to targeted therapy, recent data have highlighted that mortality has not changed over the past 40 years. This reflects the absence of efficacy of current available drugs to counteract the fibrotic process. Nevertheless, several targeted immunity therapies, commonly with proven efficacy in other immune diseases, are about to be investigated in systemic sclerosis. Indeed, promising results in small and open studies have been reported. This article deals with recent insights into classification criteria, pathogenesis, organ involvements, outcome and current and possible future therapeutic options in systemic sclerosis.

1. Classification of systemic sclerosis

A major achievement of the recent years has been the validation of new ACR/EULAR classification criteria for systemic sclerosis (SSc) (Table 1) [1]. These criteria were developed because the 1980 ACR classification criteria lacked sensitivity for diagnosis, particularly in cases of early SSc and limited cutaneous SSc (lcSSc). Sensitivity and specificity in the validation sample were, respectively, 0.91 and 0.92 for the new criteria, which contrasts with the 0.75 and 0.72 values for the 1980 ACR classification criteria.

These new criteria should allow for more patients to be classified as having SSc, particularly those with the lcSSc and early SSc and therefore, recruit such patients in clinical trials. This is of major interest, since recent data suggest that there could be a "window" of opportunity to treat patients, before irreversible fibrosis develops. Potential new therapies should be assessed in patients with early SSc, which is now made easier thanks to these criteria.

2. Recent insights in pathogenesis

SSc is characterized by microvascular abnormalities, immune activation with autoimmunity and then fibroblastic activation leading to fibrosis.

2.1. Vasculopathy

Early vascular events include endothelium's dysfunction and injury with apoptosis of endothelial cells. The molecular mechanisms underlying early pathogenic changes in endothelial cells remain unclear. A recent study showed that down-regulation of the transcription factor GATA-6 in endothelial cells represented a key pathological event during development of pulmonary arterial hypertension (PAH) [2]. It was suggested that reduction of GATA-6 occurs before vessel occlusion and may reflect an early phase of endothelial cell activation and/or dysfunction during PAH. Furthermore, mice knockout for GATA-6 in endothelial cells spontaneously developed features of PAH.

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Table 1
The American College of Rheumatology/European League Against Rheumatism criteria for the classification of systemic sclerosis[a] [1].

Item	Sub-item(s)	Weight/score[b]
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints *(sufficient criterion)*	–	9
Skin thickening of the fingers *(only count the higher score)*	Puffy fingers	2
	Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints)	4
Fingertip lesions *(only count the higher score)*	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia	–	2
Abnormal nailfold capillaries	–	2
Pulmonary arterial hypertension and/or interstitial lung disease *(maximum score is 2)*	Pulmonary arterial hypertension	2
	Interstitial lung disease	2
Raynaud's phenomenon	–	3
SSc-related autoantibodies (anticentromere, anti-topoisomerase I [anti-Scl-70], anti-RNA polymerase III) *(maximum score is 3)*	Anticentromere	3
	Anti-topoisomerase I	3
	Anti-RNA polymerase III	3

SSc: systemic sclerosis.

[a] These criteria are applicable to any patient considered for inclusion in a systemic sclerosis study. The criteria are not applicable to patients with skin thickening sparing the fingers or to patients who have a scleroderma-like disorder that better explains their manifestations (e.g., nephrogenic sclerosing fibrosis, generalised morphea, eosinophilic fasciitis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft-versus-host disease, and diabetic cheiroarthropathy).

[b] The total score is determined by adding the maximum weight (score) in each category. Patients with a total score of ≥ 9 are classified as having definite systemic sclerosis.

New data were recently published regarding the key role of the vascular endothelial growth factor (VEGF) in SSc-vasculopathy. First, the late capillaroscopic pattern characterized by a severe vasculopathy with extensive avascular areas is associated with increased VEGF levels [3]. Furthermore, VEGF may act as a molecular link between vasculopathy and fibrosis, as it was suggested by two recent studies [4,5]. Indeed, in two mouse models of SSc, using VEGF mono and double transgenic mice, Maurer et al. showed that VEGF dose-dependently exerts strong profibrotic effects [4]. These profibrotic effects were accompanied by a vasculopathy with an increase in vessel wall thickness, which is a classical feature of SSc-microangiopathy.

In another study, key features of SSc-PAH were reproduced in a mouse model (TβRIIΔκ-fib) following inhibition of VEGF [5]. This model is characterized by a ligand-dependent up-regulation of transforming growth factor β (TGF-β) signaling and reproduces fibrotic features of SSc, underlining the link between TGF-β and VEGF signaling.

There is also impairment in compensatory mechanisms for vascular damage and chronic hypoxia, which are angiogenesis (compensatory growth of new vessels from existing vessels) or vasculogenesis (*de novo* formation of new vessels). The role of VEGF in the impairment in angiogenesis was supported by one study, demonstrating an inverse gene-dosing effect on the efficacy of angiogenesis between VEGF mono and double transgenic mice [4]. Another study suggested that the loss of the expression of the endothelial cell-derived factor EGFL7 in endothelial cells and their progenitors might play a role in SSc-vasculopathy and contribute to impaired angiogenesis and vasculogenesis [6]. It was also recently suggested that *in vivo* neovascularization capacity of endothelial progenitor cells was defective in SSc-patients, contributing to defective vasculogenesis [7].

2.2. Dysimmunity

Regarding genetic factors, the most consistent data have identified genes involved in autoimmunity. Several of these genes are already well-established risk factors for other autoimmune diseases, raising the concept of shared autoimmunity [8,9]. This is a major step forward and some genes are robustly associated with the disease or some subsets; this might suggest that shared therapies could be of help in various autoimmune diseases but it also suggests that post-genomic data are required to better establish the role of these genes on the fibrotic propensity that characterizes SSc. Two studies have demonstrated the contribution of two immune genes (i.e. CD226 and STAT4) in SSc-pathogenesis and dermal fibrosis in vivo [10–12]. In another study, targeting IL-6 by both passive and active immunization strategies prevented the development of inflammatory driven dermal fibrosis [13].

A new hypothesis has been proposed concerning the pathogenesis of SSc [14]. SSc would be in some cases a paraneoplastic syndrome, initiated by exposure to a foreign tumoral antigen that cross-reacts with endogenous molecules. This is a stimulating new area of interest which fits well with all the developments of the immune control of neoplasia and that will deserve further confirmative studies.

2.3. Fibrosis

Fibrosis is the clinical hallmark of SSc and may be exacerbated by the failure of intrinsic mechanisms that normally constrain fibroblast activation (e.g. the nuclear receptor PPAR-γ). Moreover, intrinsic alterations in SSc-fibroblasts resulting from epigenetic changes have been identified, such as DNA methylation changes and altered microRNA expression that might contribute to the persistent activated phenotype of fibroblasts [15].

3. Prognosis of systemic sclerosis

SSc is the most severe connective tissue disease (CTD). The standardized mortality ratio has been estimated to 3.5, as compared to age and sex-matched population in a meta-analysis [16]. Mortality has not significantly changed over the past 40 years, reflecting the insufficient efficacy of available therapies. Causes of death were studied in the EUSTAR cohort including 5860 SSc-patients in 2010 [17]. Deaths were in 55% of the cases SSc-related and in 41% of the cases SSc-unrelated. Among SSc-related deaths, 35% were secondary to lung fibrosis, 26% to PAH, 26% to heart involvement (heart failure or arrhythmias) and 4% to scleroderma renal crisis (SRC), whereas unrelated SSc-causes included infections (33%), neoplasia (31%) and cardiovascular diseases (29%). SSc-patients have an increased risk of cancer [18]. However, absolute risk is relatively low. Patients with anti-RNA polymerases III seem to have a higher risk of cancer in close temporal relationship to onset of SSc, which suggests a paraneoplastic phenomenon in this