Presse Med. 2014; 43: e267–e278

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Quarterly Medical Review

Pathophysiology of systemic sclerosis: State of the art in 2014

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Available online: 29 August 2014

In this issue

Summary

Major work has been done in order to improve the understanding of systemic sclerosis (SSc) pathogenesis. A number of new experimental models have been set up, that should help to understand the disease pathogenesis and test new therapeutic targets. Reactive oxygen species represent a hallmark of the pathogenesis of SSc, both at the fibroblast and at the endothelial cell levels. Although a large number of genetic studies have been conducted, it is still difficult to identify a genetic background specific to SSc, and the major progress in this setting is probably the identification of an interferon signature. Besides endothelial cells and fibroblasts, major development has been made in the understanding of the role of B cells and autoantibodies in the pathogenesis of SSc. Plasmacytoid dendritic cells seem to play a major role in the pathogenesis of SSc through the secretion of CXCL4, although these data will need to be confirmed in the near future.

Systemic sclerosis (SSc) is a rare connective tissue disease characterized by vascular involvement responsible for vascular hyperactivity and remodeling, together with fibroblasts activation and extra-cellular matrix synthesis [1].
SSc mostly occurs in females (3 to 8 females for 1 male). Its prevalence varies between 30 and 240 per million inhabitants, being higher in North America and Australia than in Japan [2]. In Europe, the prevalence varies between 50 and more than 150, with 158 per million in France [3]. Reports of sporadic clusters of higher prevalence suggest the existence of environmental risk factors, but only silica and solvents exposure have been consistently associated with SSc [2].
Patients with SSc are usually classified into two main groups, according to the extent of skin involvement: limited SSc (lSSc), with skin involvement essentially limited to the hands and face; and diffuse SSc (dSSc), with skin involvement proximal to the elbows and knees. In patients with

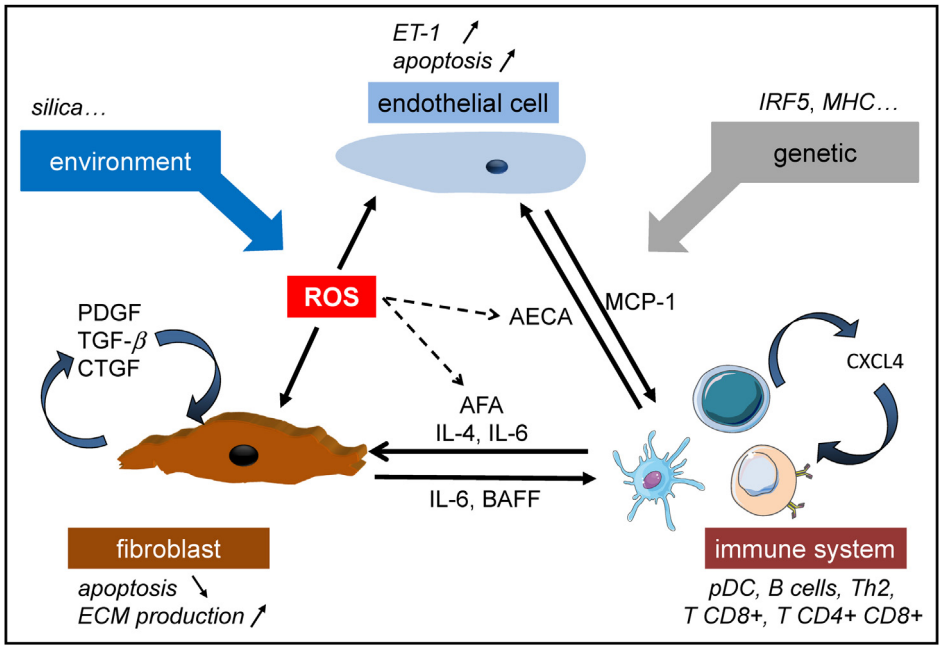

FIGURE 1

Key elements in the pathophysiology of systemic sclerosis

Dotted arrow: possible modulation; Solid arrow: activation.

AECA: anti-endothelial cell antibodies; AFA: anti-fibroblast antibodies; BAFF: beta cell activated factor; CTGF: connective tissue growth factor; ECM: extracellular matrix; ET-1: endothelin-1; IL: interleukin; IRF-5: interferon response factor 5; MCP-1: monocyte chemotactic protein 1; MHC: major histocompatibility complex; pDC: plasmacytoid dendritic cells; PDGF: platelet derived growth factor; ROS: reactive oxygen species; TGF-β: transforming growth factor beta.

lSSc, visceral involvement is rare, whereas patients with dSSc more frequently experience visceral involvement [4]. It is essential to distinguish between limited and diffuse SSc in order to elucidate the pathophysiology of the disease, since distinct mechanisms probably contribute to the occurrence of the two forms of the disease.

In recent years, significant progress has been made in the understanding of mechanisms contributing to the occurrence of vasculopathy and fibrosis, both in human samples and animal models. However, experimental models, although very useful, do not allow to characterize all the mechanisms at play in SSc, contributing to explain why we are still lacking a universal treatment of SSc. In this review article, we will provide the reader with an overview of the pathogenesis of SSc, with emphasis of recent acquisitions in the field *(figure 1)*.

Environmental factors

A number of environmental factors that may contribute to the occurrence of SSc have been identified. Various activities, including manufacturing and rural activities have been associated with the occurrence of SSc, notably the exposure to silica, dust and hydrocarbons [2]. The first reports of the association between silica and SSc were made in limited numbers of patients [5] followed by retrospective comparative studies, which confirmed that exposure to silica conferred a high risk to develop SSc [6]. Odds Ratio of 3.93 (1.84–8.54) [7] and 5.57 (1.69–18.37) [8] were calculated in studies conducted in Australia and France, respectively, leading a number of countries including France, Germany, Canada and South Africa to consider SSc as an occupational disease. In addition to silica, case control studies pointed out that past exposure to solvents was associated with SSc [5], with discrepancies among studies regarding the types of solvents involved and/or patient gender. Thus, paint thinner or removers, mineral spirits, trichloroethylene, trichloroethane, perchloroethane, gasoline, aliphatic hydrocarbons, halogenated hydrocarbons, benzene, toluene or xylene-solvents have been proposed as the most at risk solvents, although discrepancies were identified among studies. Nietert et al. found that SSc males were more frequently exposed to organic solvents (in particular trichloroethylene) than controls (OR 2.9 [1.1–7.6]), which was not the case for females [9]. In a recent meta-analysis of the literature, the occurrence of SSc was associated with increased ORs for silica, chlorinated solvents, trichloroethylene and welding fumes for male patients, aromatic solvents and ketones for female patients and white spirit for both [10]. Several others toxic