Pathologie Biologie 63 (2015) 61–68

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

Review

Cellular and molecular mechanisms in the pathophysiology of systemic sclerosis

Mécanismes cellulaires et moléculaires dans la physiopathologie de la sclérodermie systémique

T. Hua-Huy, A.T. Dinh-Xuan *

UPRES-EA 2511, laboratoire de physiologie respiratoire, hôpital Cochin–Paris Centre, Assistance publique–Hôpitaux de Paris, université Paris-Descartes, Sorbonne Paris-Cité, 27, rue du Faubourg-Saint-Jacques, 75679 Paris cedex 14, France

ARTICLE INFO

Article history:
Received 5 August 2014
Accepted 6 March 2015
Available online 25 March 2015

Keywords:
Systemic sclerosis
Pathophysiology
Fibrosis
Endothelial dysfunction
Inflammation
Oxidative stress

Mots clés :
Sclérodermie systémique
Physiopathologie
Fibrose
Dysfonctionnement endothélial
Inflammation
Stress oxydatif

ABSTRACT

Fibrosis is characterized by disproportionate accumulation of collagens and other extracellular matrix substances, resulting in organ dysfunction and failure. In systemic sclerosis, cellular and molecular mechanisms involved in the pathophysiology of fibrosis are highly complex and yet barely understood. Anatomopathological findings showed the coexistence of patchy inflammatory cell infiltration, microvascular injuries, and fibrotic foci. One of the most commonly accepted hypotheses considers endothelial activation as the triggering phenomenon inducing inflammatory and autoimmunity activation. The resulting cytokines and autoantibodies production accelerates the proliferating rate of normal fibroblasts and their transformation into myofibroblasts, leading to diffuse fibrosis. This review aims to focus on cellular and molecular mechanisms implicated in the fibrogenesis of systemic sclerosis.
© 2015 Elsevier Masson SAS. All rights reserved.

RÉSUMÉ

La fibrose est caractérisée par une accumulation excessive de collagène et d'autres substances de la matrice extracellulaire qui entraînent un dysfonctionnement des organes atteints. Dans la sclérodermie systémique, les mécanismes cellulaires et moléculaires impliqués dans la physiopathologie de la fibrose sont très complexes et ne sont que partiellement connus. Les examens anatomopathologiques ont montré la coexistence de foyers inflammatoires disséminés et de lésions microvasculaires, intercalés des foyers fibrosants contenant des myofibroblastes. L'une des hypothèses contemporaines considère l'activation des cellules endothéliales comme le phénomène initiateur, capables d'induire l'inflammation et l'auto-immunité dont les cytokines et les auto-anticorps résultant contribuent à stimuler les fibroblastes normaux en les transformant en myofibroblastes, responsables de la fibrose diffuse. Cette revue se propose de faire le point sur les mécanismes cellulaires et moléculaires de la fibrogénèse dans la sclérodermie systémique.
© 2015 Elsevier Masson SAS. Tous droits réservés.

1. Introduction

Systemic sclerosis (SSc) is a heterogeneous multisystem connective tissue disease with autoimmune component of unknown origin, characterized by microvascular lesions, inflammation, and immune system activation, leading to progressive fibrosis of conjunctive tissues of the skin and internal organs. Visceral dysfunction including the lungs, the kidneys, the heart, and the gastrointestinal tract represents the essential risk factor of morbidity and mortality related to the disease [1].

It is not easy to carry out reliable worldwide epidemiological studies on SSc, as clinical presentation is heterogeneous and can highly vary among patients [2]. The available data indicate a prevalence ranging from 30 to 300 cases per 1 million persons

* Corresponding author.
E-mail address: anh-tuan.dinh-xuan@cch.aphp.fr (A.T. Dinh-Xuan).

http://dx.doi.org/10.1016/j.patbio.2015.03.003
0369-8114/© 2015 Elsevier Masson SAS. All rights reserved.

[3,4], and an incidence ranging from 0.2 to 2.2 cases per 1 million persons per year [4]. Women are at much higher risk for scleroderma than men [3,4], and the worldwide prevalence appears to be higher in North America and Australia as compared to Europe and Japan [4]. Cumulative survival of SSc has significantly improved since the early 1970s [5]. However, lung involvements still remain a major cause of concern as pulmonary fibrosis and pulmonary arterial hypertension are now becoming the two leading causes of death [6].

The pathophysiology of SSc is very complex and incompletely known. However, histological and cellular abnormalities have been well-described, implicating endothelial cells, fibroblasts, and cells of the immune systems such as monocytes/macrophages and lymphocytes [1,7–10]. The dysfunctions of these cells explained a number of clinical signs of the disease. Cellular injuries (Fig. 1) are characterized by the pathological triad [1], including:

- endothelial dysfunction that appears to be initiator;
- immune system disorders with B and T lymphocytes activation, responsible for overproduction of cytokines, growth factors, and autoantibodies, as well as a chronic infiltration by monocytes/macrophages and T lymphocytes in the altered tissues;
- progressive fibrosis of the skin and multiple internal organs resulting from previously described events.

2. Vascular injuries and endothelial dysfunction

Vascular injury, in particular endothelial cells activation, is one of the earliest events occurring in the natural history of SSc as illustrated by Raynaud's phenomenon and digital ulcers in patients with SSc [3]. These vascular lesions might result from direct or indirect effects of anti-endothelial cell antibodies (AECA) whose serum levels are usually increased in SSc patients [11].

Endothelial dysfunction also promotes vasoconstriction by inducing the synthesis and secretion of endogenous vasoconstrictors (e.g. endothelin-1) and reducing those of endothelial vasodilators such as nitric oxide (NO) and prostacyclin. This phenomenon leads to vasoconstriction and altered tissue oxygenation, consequent hypoxia stimulates VEGF production [11]. Increased synthesis of angiogenic factors followed by the decrease of endothelial progenitor cells during the SSc development leads to vascular bed rarefaction, digital ulcers appearance, and consequent arterial pulmonary hypertension [12].

Endothelin-1 plays a key role in the fibrogenesis of SSc by inducing fibroblasts proliferation [13] and their differentiation into myofibroblasts [14]. ET-1 has the same fibrogenic effects of TGF-β by stimulating CTGF secretion, responsible for collagen production [15]. Treatment by Bosentan, a non-selective antagonist of ET-A and ET-B receptors, can prevent pulmonary fibrosis in the rats intoxicated by bleomycin [16]. However, this molecule could not improve significantly exercise capacity in patients with SSc-related ILD [17].

Vascular injuries induce a coagulation/fibrinolysis imbalance and illicit in situ tissue thrombin release. Thrombin provokes fibroblasts proliferation [18] and their transformation into myofibroblasts in the lungs [19].

3. Inflammation and immune system activation

Inflammation and immune system activation play an important role in the fibrogenesis of SSc, linking endothelial lesions to tissue fibrosis [20].

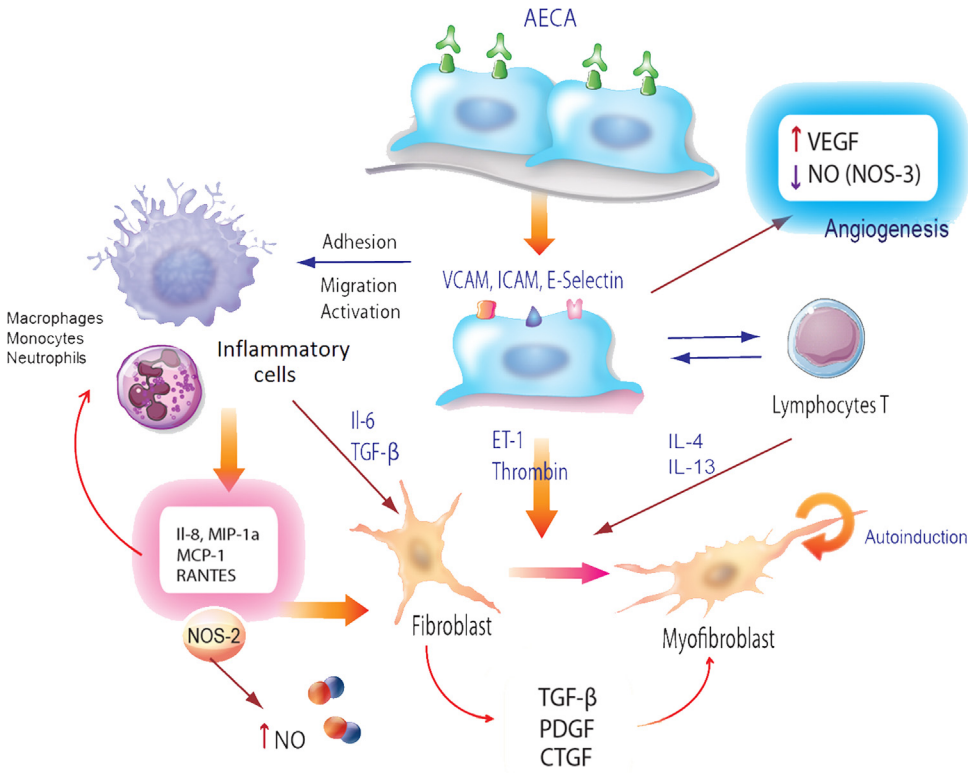

Fig. 1. Cellular and molecular mechanisms in the fibrogenesis of systemic sclerosis. Anti-endothelial cells antibodies (AECA) induce endothelial activation which promotes inflammation and autoimmunity. Inflammatory cells increase the synthesis and secretion of several pro-inflammatory and profibrotic cytokines that stimulate the transformation of fibroblasts into myofibroblasts, responsible for the progressive systemic fibrosis. VCAM-1: vascular cell adhesion molecule-1; ICAM-1: intercellular adhesion molecule-1; VEGF: vascular endothelial growth factor; NO: nitric oxide; NOS-2: inducible NO synthase; NOS-3: endothelial NO synthase; ET-1: endothelin-1; IL-4-6, -8, -13: interleukin-4, -6, -8, -13; MIP-1a: macrophage inflammatory protein-1-alpha; MCP-1 (CCL2: chemokine ligand 2): Monocyte chemoattractant protein-1; Rantes (CCL5: chemokine ligand 5): regulated on activation normal T cell expressed and secreted; TGF-β: transforming growth factor-beta; PDGF: platelet-derived growth factor; CTGF: connective tissue growth factor.

Download English Version:

https://daneshyari.com/en/article/4135873

Download Persian Version:

https://daneshyari.com/article/4135873

Daneshyari.com