Updates on the pathophysiology of systemic sclerosis

Systemic sclerosis (SSc) is a heterogeneous connective tissue disease with autoimmune component, inflammation, and progressive fibrosis of conjunctive tissues of the skin and internal organs. Lung involvements are a major cause of concern as pulmonary fibrosis and pulmonary arterial hypertension are now the two leading causes of death in SSc patients. Understanding the pathological mechanisms will help to discover innovative therapeutics for the disease.

The pathophysiology of SSc is very complex and incompletely known. It is characterized by various histological and cellular abnormalities, including endothelial cells, fibroblasts, and cells of the immune systems such as monocytes/macrophages, dendritic cells (DCs), and lymphocytes (Fig. 1).

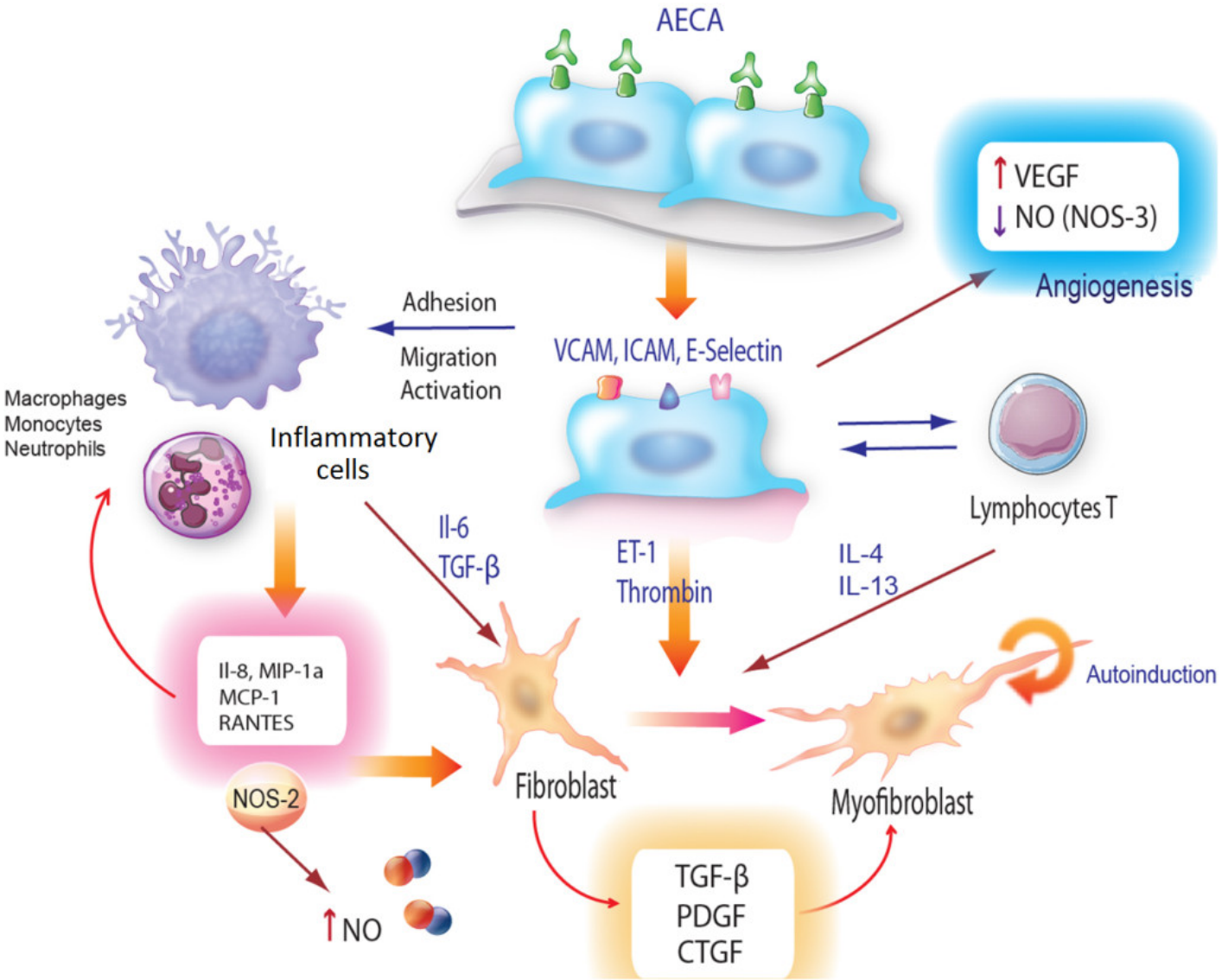

Fig. 1. Cellular and molecular mechanisms in the fibrogenesis of systemic sclerosis
Anti-Endothelial Cells Antibodies (AECA) induce endothelial activation which promotes inflammation and autoimmunity. Inflammatory cells increase the synthesis and secretion of several pro-inflammatory and pro-fibrotic cytokines that stimulate the transformation of fibroblasts into myofibroblasts, responsible for the progressive systemic fibrosis.
Abbreviations: 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 ChemoattractantProtein-1; RANTES (CCL5: Chemokine ligand 5):Regulated on Activation, Normal T cell Expressed and Secreted; TGF-?: Transforming Growth Factor-Beta; PDGF: Platelet-Derived Growth Factor; CTGF: Connective Tissue Growth Factor.

Early endothelial dysfunction appears to be the triggering factor, with endothelial activation induced by anti-endothelial cells antibodies. Endothelial dysfunction promotes vasoconstriction by increasing the synthesis of endogenous vasoconstrictors (e.g. endothelin-1) and reducing endothelial vasodilators such as nitric oxide and prostacyclin. Vasoconstriction alters tissue oxygenation and the resulting hypoxia stimulates VEGF production, followed by the decrease of endothelial progenitor cells. Cytokines derived from endothelial dysfunction (e.g. endothelin-1 and thrombin) exert direct fibrogenic effects by enhancing the proliferation and transformation of fibroblasts into myofibroblasts.

Mediators	Role in fibrogenesis
CTGF	Regulation of fibroblast proliferation and migration
ET-1	Regulation of ECM production and contraction
FGF	Regulation of fibroblast growth
IL-1	Inflammatory mediator
IL-4	Regulation of collagen synthesis
IL-6	Regulation of α-SMA expression in myofibroblasts
IL-10	Anti-inflammatory mediator; lymphocyte B proliferation
IL-12	Regulation of collagen synthesis
IL-13	Induction of TGF-β
IL-17	Fibroblast proliferation
MCP-1	Inflammatory mediator; regulation of collagen synthesis
MCP-3	Regulation of collagen synthesis
PDGF	Induction of TGF-β receptor expression; Recruitment of progenitor cells and fibroblasts
TGF-β	Extracellular matrix (ECM) synthesis; Fibroblast proliferation, activation, and migration
TNF-α	Lymphocyte recruitment, pro-inflammatory et anti-fibrotic effects

Tab. 1. Cytokines and chemokines involved in the fibrogenesis of systemic sclerosis
Abbreviations: TGF-?: Transforming Growth Factor-Beta; CTGF: Connective Tissue Growth Factor;

PDGF: Platelet-Derived Growth Factor; FGF: Fibroblast Growth Factor; ET-1: Endothelin-1; IL-1, -4, -6, -10, -12, -13, -17: Interleukin-1, -4, -6, -10, -12, -13, -17; ?-SMA: alpha-smooth muscle actin; MCP-1 (CCL2: Chemokine ligand 2) or MCP-3 (CCL7: Chemokine ligand 7): Monocyte ChemoattractantProtein-1ou-3; TNF-?: Tumor Necrosis Factor-alpha.

Pulmonary inflammation is characterized by infiltration of inflammatory cells (such as T lymphocytes, macrophages, neutrophils, eosinophils, and mast cells) in alveolar spaces and pulmonary interstitial tissues. These inflammatory cells induce pulmonary fibrosis by the production of soluble mediators capable of initiating and aggravating local inflammation, and subsequently activating resident fibroblasts. Increasing number of chemokines and cytokines implicated in the fibrogenesis of SSc is summarized in Table 1. The most important molecules are MCP-1, IL-4, IL-6, IL-13, and TGF-?.

In the lungs, alveolar macrophages and dendritic cells cooperate at the alveolar-capillary barrier to sample air-borne and blood-borne materials to set the threshold and the quality of the immune response. Recent studies have suggested a pivotal role of dendritic cells in the pathophysiology of lung involvement in SSc by unravelling the relationship between the induction of type I interferon and chemokine CXCL4 with disease manifestations of systemic sclerosis, including lung fibrosis and pulmonary hypertension.

Data from the medical literature suggest an orientation of the cytokine profile in favour of Th2 orientation. Th2-cytokines production is usually increased in the skin and in the BAL fluids of patients with SSc. These cytokines may account for the main pathological processes in SSc, namely endothelial cell activation, inflammation, autoantibody production, and fibrosis. Auto-antibodies are useful for clinical diagnosis of SSc and provide evidence of B cells activation in SSc. However, their pathophysiological roles and prognostic significance in the SSc-related pulmonary fibrosis remained questioned.

Fibroblasts isolated from skin lesions of patients with SSc have a constitutively activated myofibroblast-liked phenotype, augmenting their capacity of collagen synthesis. Multiple origins of SSc myofibroblasts were recently discovered, including pericytes in the vessel walls, adventitial fibroblasts, bone marrow-derived fibrocytes, epithelial and endothelial cells. Several cytokines, chemokines, and growth factors contribute to fibroblasts activation, myofibroblasts formation, and accumulation in the fibrotic foci in SSc (Tab. 1). More recent molecular mechanisms involve the Notch family protein, the ?-catenin/Wnt pathway, and the lipoic acid. Oxidative stress via reactive oxygen species (ROS) formation also plays a crucial role in fibroblast activation in SSc. PDGF-induced ROS secretion may promote the proliferation and activation of SSc fibroblasts in human SSc. ROS generation in healthy mice caused inflammation, autoimmune activation, and disseminated fibrosis resembling to human features of SSc.

In summary, multiple interactive signalling pathways in different types of cells implicated in the pathophysiology of SSc is the basis of all current and incoming therapeutic options, including anti-inflammatory, immunosuppressive, and anti-fibrotic strategies.

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