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Cytokines in Systemic Sclerosis: Focus on IL-17

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1. Introduction

Systemic sclerosis (SSc) is an autoimmune disease characterized by progressive sclerosis of the skin and internal organ dysfunction. Cytokine production and release are key events in SSc pathogenesis as they are involved in T and B cell activation leading to inflammation, auto-antibodies production, microvascular damage and fibrosis (Katsumoto et al. 2011). The Th1/Th2/Th17/Treg balance is one of the hallmarks of SSc pathogenesis, as the Th2 and Th17 cytokines response leads to tissue fibrosis, whereas Th1 and Th17 cytokines promote inflammation in SSc patients. In our previous review, we analyzed the relationship between cytokine release and SSc pathogenesis, based on experimental and clinical data. We concluded that circulating or in situ cytokine levels could be assessed as diagnostic and prognostic markers in SSc patients (Baraut et al. 2010).

The precise pathogenesis of SSc is still poorly understood. The use of microarray technology showed significant differences of gene patterns in skin biopsies from diffuse scleroderma (dSSc) and limited scleroderma (lSSc) patients, which also differed from normal controls (Milano et al. 2008). An immune signaling cluster was evidenced, suggestive for a role of B and T cells in SSc pathogenesis. Interleukin IL-1α, IL-4, tumor necrosis factor-α (TNF- α), connective tissue growth factor (CTGF), and transforming growth factor-β (TGF-β) have been identified as some relevant genes related to SSc disease. More recently, major contributions were made by experiments using genome-wide screening technology, which identified specific nucleotide polymorphisms (SNPs) in relevant genes related to SSc disease, including genes coding for cytokines and growth factors (Agarwal et al. 2008). The first genome-wide association study (GWAS), performed in Korean patients and confirmed in US Caucasians population, indicated that specific SNPs of HLA-DPB1 and/or DPB2 were strongly associated with SSc patients who had anti-DNA topoisomerase I or anticentromere autoantibodies (X. Zhou et al. 2009). More recently, a larger GWAS identified a new susceptibility locus for SSc susceptibility, previously found in systemic lupus erythematosus, at CD247 (T cell receptor T3 zeta chain). The role of Major Histocompatibility complex (MHC), Interferon regulatory factor 5 (IRF5) and STAT4 gene regions as SSc genetic risk factors has also been confirmed in this recent GWAS study (Radstake et al. 2010). GWAS approaches have identified multiple genetic

markers related to innate and adaptive immunity as SSc susceptibility, such as HLA class II, STAT-4, IRF5, B cell scaffold protein BANK1, B lymphocyte kinase (BLK), Tumor necrosis factor ligand super-family member 4 (TNFSF4) and CD247 genes (Romano et al. 2011). However no GWAS have been preformed to clarify the role of genes involved in vascular and fibrotic processes in SSc susceptibility.

2. Th17 lineage differentiation

The identification of a new subset of inflammatory T cells distinct from Th1 and Th2 cells, so-called Th17 T cells, secreting interleukin IL-17A/F, IL-21 and IL-22, which play a major role in inflammation, has significantly improved our understanding of autoimmune diseases. Th17 cell differentiation can be induced by the combination of TGF-β and IL-6 or IL-21 (Dong 2008). IL-1 also plays a crucial role in early Th17 cell differentiation (Chung et al. 2009). Moreover, development and propagation of the Th17 lineage requires IL-1, IL-6, IL-23, and TGF-β stimulation, whereas Th17 differentiation is inhibited by IFN-γ and IL-4 (Harrington et al. 2005). The pro-inflammatory cytokine IL-23 is involved in Th17-mediated immune pathology since IL-23-deficient (p19−/−) mice contain very few Th17 cells and are protected from autoimmune diseases such as experimental autoimmune encephalomyelitis (EAE) and collagen-induced arthritis. However IL-23 is not required for the differentiation of Th17 from naïve CD4 T cells. Several transcription factors have been shown as critical regulators of Th17 cell differentiation (Dong 2011). STAT3 has been reported to be a crucial component of IL-6 and IL-21-mediated Th17-cell regulation. Moreover, STAT3 deficiency greatly decreased the expression of RORγt and RORα, transcriptions factors that drives Th17-cell lineage differentiation. RORγt and RORα overexpression are induced by TGFβ or IL-6 and promote Th17-cell differentiation. Both transcription factors RORγt and RORα have a synergistic effect in promoting Th17-cell differentiation and have similar and redundant functions. Furthermore, Smad2 was reported by several groups to positively regulate Th17 cell differentiation and Th17 immune response *in vivo* during pathogen infection or in autoimmune disease (Malhotra et al. 2010) (Martinez et al. 2010) (Takimoto et al. 2010). Smad2 might be a co-factor for RORγt to mediate the expression of Th17-specific genes (Martinez et al. 2010). In addition to the ROR, STAT and Smad factors, interferon-regulatory factor 4 (IRF4) was recently shown to be essential for Th17-cell differentiation upstream of RORγt (Brüstle et al. 2007). Other transcription factors such as the aryl hydrocarbon receptor (AHR), Batf (member of AP-1 transcription factor family), IκBζ (encoded by the Nfkbiz gene) have recently been shown to be required for Th17 cell development (Dong 2011).

Differentiation of Th17 and regulatory T cells, both of which depend on TGF-β, shares a reciprocal regulation. In relation with tolerance induction, TGF-β is able to increase Foxp3 levels and reduces IL-23R expression shifting the differentiation of Th cells from Th17 towards regulatory T cells (L. Zhou et al. 2008). Foxp3 interacts with RORs and recruits histone deacetylases to Th17-specific genes, thus inhibiting the transcriptional activity of RORγt genes (X. O. Yang et al. 2008). Although Foxp3 has a strong inhibitory role in Th17 differentiation, IL-6 has been found to down-regulate Foxp3 expression in TGFβ-induced and thymically derived Treg cells and together with IL-1, to upregulate Th17-specific gene expression (X. O. Yang et al. 2008) (L. Xu et al. 2007).

In addition to Th17 cells, a wide variety of T cells also produce IL-17A and IL-17F: cytotoxic CD8+ T cells (Tc17), distinct populations of γδT (γδ-17) cells, NKT (NKT-17) cells, neutrophils, monocytes and lymphoid tissue inducer (LTi)-like cells (Iwakura et al. 2011).
NKT-17 and γδ-17 cells rapidly produce IL-17A and IL-17F in response to pro-inflammatory cytokine stimulation and may therefore provide an essential initial source of these two cytokines. In contrast to naive $CD4^+$ and $CD8^+$ T cells, IL-23 and IL-1 can directly induce γδ-17 cell development in the absence of IL-6 and TCR ligation because they constitutively express IL-23R, IL-1R, and RORγt.
Th17 which is a distinct lineage of T cells bridging the innate and adaptive immunity, is characterized by expression of the transcription factors RORγt and RORα, as well as the surface markers CCR4, CCR6 and IL-23R, the production of the potent proinflammatory molecules IL-17, IL-17F, IL-21, IL-22, IL-26 and G-CSF as well as the chemokine CCL20. However, the mechanisms underlying the generation of these cells *in vivo* remain incomplete.

3. Th17 involvement in inflammation and fibrosis

Th17 effectors, IL-17A/F, IL-21 and IL-22, encompass both pro-inflammatory and pro-fibrotic characteristics, suggesting that this cell type may act as an intermediate between the Th1 and Th2 lineages. Indeed, IL-17 has been shown to enhance the secretion of the pro-inflammatory and pro-fibrotic cytokines IL-6 and IL-8 from fibroblasts (Fossiez et al. 1996). Both IL-17 and IL-22 are mainly produced by Th17 cells and promote production of antimicrobial peptides (Liang et al. 2006) constituting thereby a link between innate and adaptive responses (Stockinger et al. 2007).
Several studies have shown implication of Th17 cytokines in rheumatoid arthritis, asthma, psoriasis, multiple sclerosis, systemic lupus erythematous, inflammatory bowel disease, graft versus host (GVH), autoimmune diabetes, Sjogren's syndrome, autoimmune thyroid diseases and thrombocytopenia (Stockinger & Veldhoen 2007) (Hemdan et al. 2010). Th17 cells have been implicated as the pivotal driving force of autoimmune inflammation in several animal models of human autoimmune diseases, including autoimmune colitis (Elson et al. 2007), experimental autoimmune encephalomyelitis (Langrish et al. 2005), collagen-induced arthritis (CIA) (Nakae et al. 2003), and rat adjuvant-induced arthritis (AIA) (Bush et al. 2002).
It has been demonstrated that IL-17A and IL-17F contribute to rheumatoid arthritis (RA) pathogenesis by inducing specific expression patterns in RA synovial fibroblasts (Fossiez et al. 1996). They enhance their response by stabilizing mRNA of IL-6 and IL-8 cytokines (Hot & P. Miossec 2011) and enhancing IL-17RA and IL-17RC receptor expression (Zrioual et al. 2008) in the presence of TNFα. They contribute to the inflammatory cell accumulation by increasing migration, chemokine gene expression (CXCL12 and its receptor CXCR4, CCL20) and invasiveness of synoviocytes (K.-W. Kim et al. 2007) (Hirota et al. 2007). Moreover, they induce up-regulation of RANKL, an important positive regulator of osteoclastogenesis (Kelchtermans et al. 2009). They contribute to disease chronicity by inhibiting synoviocyte apoptosis (Toh et al. 2010). Finally, they enhance metalloprotease secretion, such as MMP-1, -2, -9 and -13 leading to cartilage damage (Moran et al. 2009). A recent study demonstrated that Th17 cells mediate inflammation at very early stages of RA development and progression (Leipe et al. 2010). They showed an impaired inhibition of Th17 cell development in RA leading to increased frequencies of Th17 cells together with enhanced production of IL-17.

Recently, a role of IL-17 in SSc pathogenesis has been shown. First, Kurasama et al. demonstrated that IL-17 is overproduced by T cells from the peripheral blood and fibrotic lesions of the skin and lungs in SSc patients (Kurasawa et al. 2000). They reported that IL-17 also enhances the proliferation of fibroblasts and induces the expression of adhesion molecules and IL-1 production in endothelial cells *in vitro*, while no collagen stimulation was observed. This study also demonstrated that IL-17 overproduction was involved in the early stage of SSc pathogenesis. Consistent with this report, another study showed that IL-17 production was transiently increased in the earlier phase of the disease (Murata et al. 2008). More recently, Radstake et al. described increase levels of activated $CD4^+$ cells in SSc patients compared to healthy controls and $CD4^+$ lymphocytes (activated or not) highly expressed the IL23R, which was associated with a higher IL-17 expression. They also observed increased levels of IL-6, IL-23 and IL-1α cytokines in SSc patients, which all induced IL-17 production (Radstake et al. 2009). Furthermore, IL-21 cytokine, which is mainly produced by Th17 and NK cells, potentiates Th17 inflammatory response via stimulation of IL-23 receptor expression and Treg inhibition. IL-21 can also regulate the Th1/Th2 response and Ig production (Wurster et al. 2002). It has been demonstrated that cell adhesions molecules such as L-selectin and ICAM-1 were able to regulate Th2 and Th17 cell accumulation into the skin and lung, leading to the development of fibrosis, whereas P-selectin, E-selectin, and PSGL-1 regulated Th1 cell infiltration, resulting in the inhibition of fibrosis (Yoshizaki et al. 2010).

4. IL-17 and auto-immunity

Distinct from its pro-inflammatory effects, IL-17 promotes autoimmune disease by enhancing formation of spontaneous germinal centers (GCs), as shown by autoimmune BXD2 recombinant inbred mouse strain which spontaneously develop glomerulonephritis and erosive arthritis. These mice express more IL-17 than wild-type counterparts and show spontaneous development of GCs by retaining B cells and promoting CD4 T-cell and B-cell interactions, resulting in increased autoimmune antibodies (Hsu et al. 2008). Furthermore, long-lasting apoptosis-resistant Th17 cells activate B cells and their immunoglobulin production mediated by IL-21.

Effects of IL-17 on B-cell activation and antibody production have been also described recently. Milovanovic and colleagues' study showed that IL-17A enhances IgE production (Milovanovic et al. 2010). Indeed, depletion of Th17 cells *in vitro* from allergic patients' blood cells induced a decrease in IgE production; addition of IL-17A in the depleted cultures reversed IgE reduction. In this study, PBMC cultures were stimulated with IL-17 + IL-4, this leading to memory B-cell activation, IgE class switching and differentiation into plasma cells.

Interestingly, a novel population of CD4 memory T cells (Th17/Th2) that produce both IL-17 and IL-4 has recently been described (Cosmi et al. 2010). IL-17 and IL-4-coproducing CD4 T cells were increased in the circulation of patients with severe asthma. This could explain the relationship between Th17 cells and increased IgE levels observed in this disease.

Moreover, the gene encoding for IL-23 receptor has been identified as a susceptibility gene for SSc development, and IL-23R polymorphisms are associated with anti-

topoisomerase-I positivity and lower frequency of pulmonary hypertension (Agarwal et al. 2009).

5. IL-17 and tolerance

Th17 and Treg differentiations are interconnected as previously introduced upper. Indeed, naïve T cells can differentiate into Treg cells in response to TGF-β, whereas in the presence of TGF-β plus IL-6/IL-21, they will differentiate into Th17 lineage (Bettelli et al. 2006). Treg and Th17 cells are reciprocally regulated via the induction of the transcription factors Foxp3 and RORγt, respectively, together in the presence of low or high levels of IL-6. The increase in IL-6 production inhibits Th1 and Treg cells and with low TGF-β levels promotes differentiation of Th17 cells with a regulatory function. They still need support of IL-23 to attain their full effectors' potency with capacity to produce IL-22, CXC chemokines, antimicrobial peptides and IL-21. The present literature clearly indicates that IL-6 and IL-21 play a major role in dictating how the immune response will be dominated by pro-inflammatory Th17 cells or by protective Treg.

6. IL-17 measurement in SSc serum before and after HSCT

Autologous hematopoietic stem cell transplantation (HSCT) has been shown as a promising treatment modality for severe and refractory autoimmune disorders, especially in diffuse systemic sclerosis (Farge et al. 2002). Our data and others demonstrate that HSCT induced a significant, progressive and sustained reduction of the modified Rodnan skin score (mRSS) throughout follow-up, 4 years (M48) after HSCT (Vonk et al. 2008). In this context, we analysed the IL-17 profile before and up to 4 years after HSCT and its potential correlation with skin involvement in patients treated for diffuse systemic cutaneous sclerosis (SSc). Our results showed that IL-17 levels were significantly higher in SSc compared to control sera from healthy donors (106.7±33.7pg/ml (n=16) *vs* 24.2±8.6pg/ml (n=6), $p<0.05$) (Fig.1). IL-17 levels observed in SSc patients were similar to those observed in psoriasis patients (137.8±70.5/ml (n=3)). In regards to HSCT follow-up, serum IL-17 levels were measured at 6, 12, 24, 36, 48 months after HSCT in SSc patients. As compared to initial levels, IL-17 levels were reduced at M6 (39.3±17.6pg/ml), but not significantly because of the wide-range of inter-individual variations (Fig.2). A progressive recovery was observed throughout follow up to 183.9±63.7pg/ml 4 years (M48) after HSCT (Fig.2). This observation confirmed the involvement of IL-17 in the pathogenesis of SSc and the efficacy of HSCT to down-regulate IL-17 initially levels. The increase observed after 6 months after HSCT cannot be involved in the fibrotic process since we observed reduction of Rodnan skin score throughout follow-up. More patients treated by HSCT must be further investigated during long-term follow-up to conclude about IL-17 involvement and cellular origin of this cytokine in the immune reconstitution. Our previous report showed that 4 years after HSCT, pro-fibrotic (VEGF, MCP1) and Th2 (IL-6, IL-8,) cytokines were significantly decreased and associated with the progressive and sustained reduction of the Rodnan skin score (Michel et al. 2011 submitted). That cytokine changes coincided with increasing numbers of reemerging CD3+ CD4+ T cells and memory CD4+CD45RA+RO-CD4+ T cells in SSc patients. It might be suggested that IL-17 progressive increase observed after HSCT could be due to an active and efficient immune reconstitution.

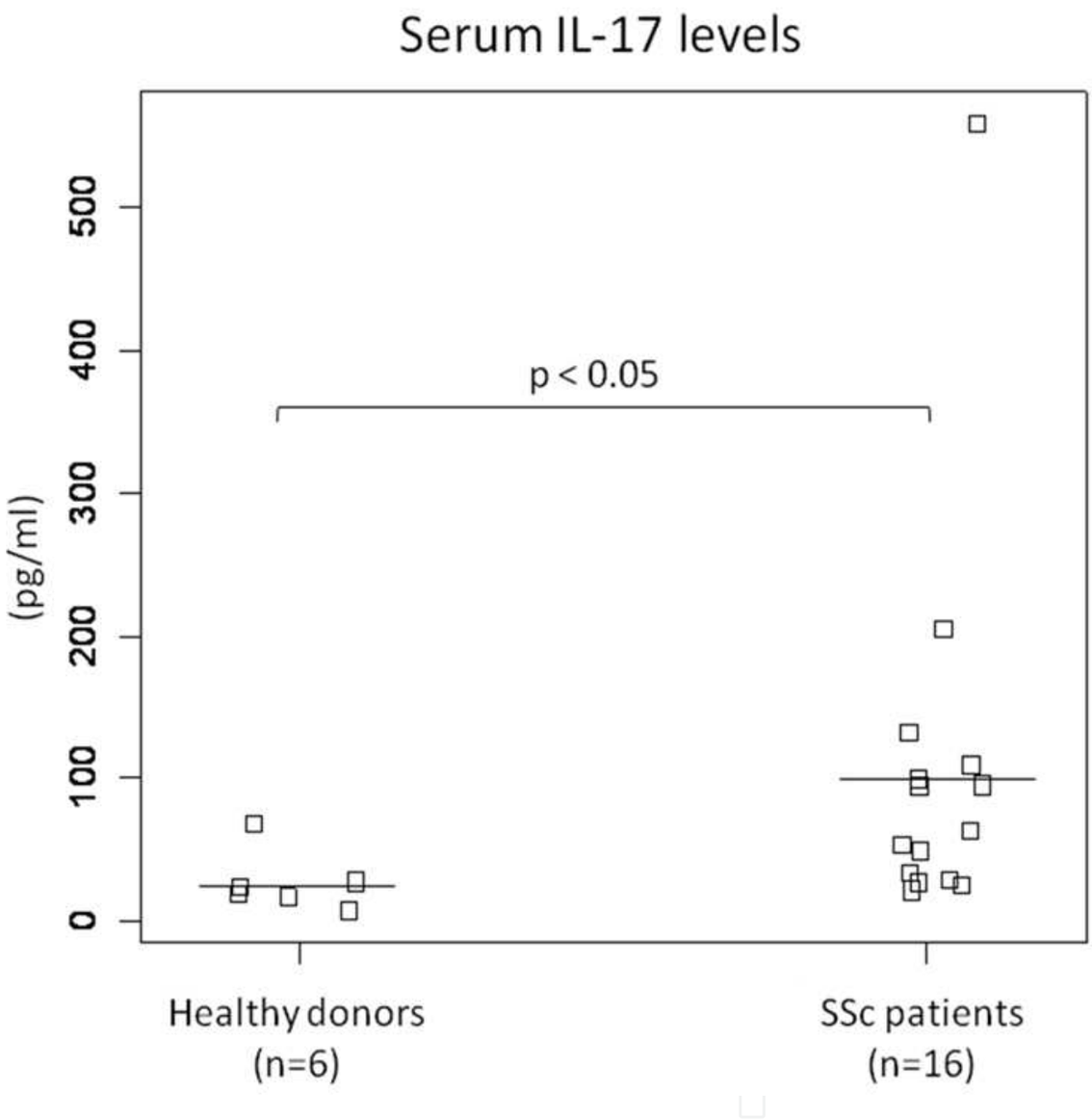

Fig. 1. Serum levels of interleukin 17 (IL-17) in patients with systemic sclerosis (SSc) and healthy donors

Serum levels of IL-17 were determined by a specific ELISA (R&D Systems Inc., Minneapolis, MN, USA) in patients with systemic sclerosis (SSc) and healthy donors. Data are presented as dot plots and the lines indicate the mean values. IL-17 levels are expressed in pg/ml.

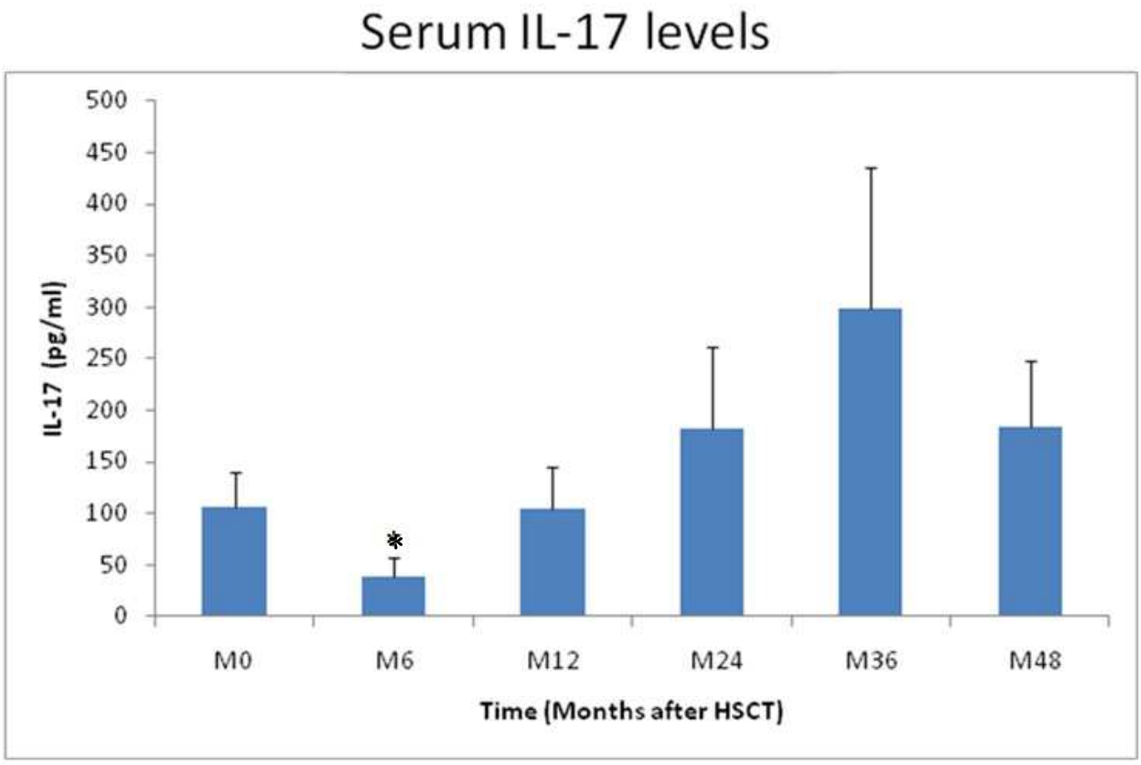

Fig. 2. Serum interleukin 17 (IL-17) levels in SSc patients after HSCT

Serum interleukin 17 (IL-17) levels at M0 and following HSCT (M: month) in 6 patients with systemic sclerosis (SSc). Mean (±SD) levels of IL-17 detected in the serum by ELISA assay are expressed in pg/ml.
*p<0.05, significant difference between mean levels at M6 compared with basal level detected at M0.

7. Conclusion

Th17 cells have been implicated as the pivotal driving force of autoimmune inflammation and fibrosis in several animal models and autoimmune diseases. Several studies showed that circulating and *in situ* IL-17 levels are up regulated in SSc patients. It is well known that IL-17 plays a major role in the pathogenesis of SSc through its involvement in the inflammation process, the fibrosis and the auto-antibody production, as confirmed by our present data.

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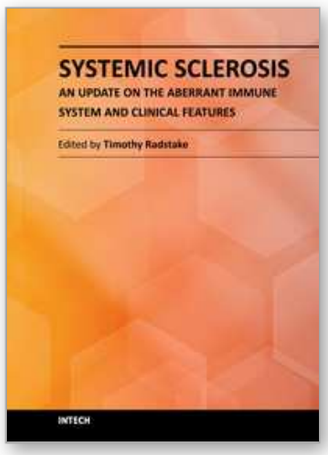

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Systemic sclerosis (SSc), or often referred to as Scleroderma (tight skin), is characterized by an exaggerated formation of collagen fibers in the skin, which leads to fibrosis. Accumulating evidence now points toward three pathological hallmarks that are implicated in Ssc, the order of which has yet to be determined: endothelial dysfunction, autoantibody formation, and activation of fibroblasts. This current book provides up-to-date information on the pathogenesis and clinical features of this severe syndrome. It is our hope that this book will aid both clinicians and researchers in dealing with patients with this clinical syndrome. In addition, we hope to shed more light on this rare and severely disabling syndrome, ultimately leading to better research and successful therapeutic targeting.

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