# EULAR 2018 - Systemic Sclerosis Highlights - Basic Science

## A EUSTAR Young Investigator Group Report

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A large number of exciting abstracts foccusing on basic science in the field of systemic sclerosis (SSc) were presented at the EULAR 2018 meeting. This article presents a summary of small selection of excellent work presented at the meeting.

Exploring the genetic component in SSc, López-Isac E et al identified twelve new loci that reached genome-wide significance level, from a large cohort comprising a total of 26 679 genome-wide genotyped individuals of European ancestry. The identified loci associate with SSc susceptibility and are involved in the pathogenesis of the disease, some of them correlating with expression quantitative trait loci (eQTLS) [1].

In the field of transcriptomics, Rudnik M et al analyzed RNA sequencing from circulating CD14+ monocytes in limited and diffuse SSc patients and in healthy donors. The authors identified 123 deregulated genes (CCL3, CD14, IL27, MMP17) in SSc subgroups, with a close clustering within SSc subgroups and separation from healthy controls (HC). Pathway analysis revealed associations with fibrosis mechanisms including antigen presentation, MIF-induced immune responses, TGF-β, NOTCH and WNT signalling pathways, reinforcing the relevant role of circulating monocytes in the mechanisms of fibrosis [2].

The immune cell signatures of circulating blood cells in SSc has also been examined using mass cytometry and transcritpomic analysis. A significant decrease in the frequencies of Va7.2+CD161+mucosal associated invariant T cells (MAIT) and an increase in total B cells was found in SSc patients, compared with HC. Transcriptome analysis of B and T cells showed a decrease in genes related to survival, and an increased expression of apoptotic genes in CD4+, CD8+ T and MAIT cells from SSc patients, suggesting an underlying dysfunction of these cells that requires further characterization in future studies [3].

Analyzing apoptosis and the role of microRNA (miRs), namely miR-125b in SSc, Kozlova A et al examined its expression in fibroblasts from SSc patients. miR-125b expression was downregulated in SSc, specially in dermal fibroblasts. BAK1, BMF and BBC3, that are part of the BCL2 apoptosis pathway, were identified as predicted targets of miR-125b. Furthermore, miR-125b knockdown upregulated these genes, resulting in an increased apoptosis in transfected cells, while overexpression of miR-125b resulted in decreased apoptosis. These results sugest that MiR-125b downregulation increases apoptosis in dermal fibroblasts, being a compensatory strategy against excessive fibrosis in SSc [4].

A number of studies explored pathways of fibrosis. CXCL4 has been previously identified in SSc, correlating with skin and lung fibrosis [5]. Marut W et al further explored the role of CXCL4 in fibrosis developement in both human cells and in CXCL4 knockout mice models. CXCL4 induced the expression of myofibroblast markers αSMA and SM22α, and collagen synthesis in human dermal fibroblasts, endothelial cells, and pericytes. The expression of CXCL4 was increased in both the bleomycin mouse model and in the Chronic Graft-versus-Host Disease (cGvHD) model. In CXCL4-/- mice there was less skin, lung and cardiac fibrosis compared with wild type mice. These results can support a potential role for neutralising CXCL4 as a novel therapeutic strategy [6].

Further exploring the Wnt pathway and its regulation, Daoussis D et al analyzed the expression of Dickkopf-1 (Dkk-1), a soluble inhibitor of the Wnt pathway, that is absent from clinically involved SSc skin. Its expression was determined in clinically uninvolved skin from SSc patients and in skin from very early SSc. There was a high immunoexpression of Dkk-1 in the skin of HC. Clinically uninvolved scleroderma skin and skin from very early disease at the edematous phase, prior to skin thickening, displayed a weak Dkk-1 immunoreactivity in basal cells of the epidermis and in the fibroblasts of the dermis, compared with HC, indicating that the Wnt pathway may also be involved in early disease stages prior to the established fibrosis [7].

Studying the transforming growth factor-β (TGF-β)-induced JAK2/STAT3 signalling, Zehender A et al examined the role of SHP2, a ubiquitous tyrosine phosphatase. siRNA-mediated knockdown of SHP2 and pharmacological inhibition of SHP2 abrogated the profibrotic effects of TGF-β in human SSc fibroblasts. SHP2 dephosphorylates JAK2 at the inhibitory Y570 site to promote TGFβ-dependent activation of JAK2 and its downstream mediator STAT3, confirming the role of SHP2 as a molecular checkpoint of (TGF-β)-induced JAK2/STAT3 signalling [8].

Analyzing the relevance of respiratory chain dysfunction and reactive oxygen species (ROS) in fibrosis, namely in the lung, Jaeger et al. studied the presence of somatically acquired mutations in mitochondrial DNA (mtDNA) in lung biopsies from patients with interstitial lung disease (ILD) - SSc and idiopathic interstitial pneumonitis patients, versus HC. The authors confirmed the important role of mtDNA-mutations and respiratory chain dysfunction as a trigger and perpetuator of ROS formation in both forms of ILD. The expression of malondialdehyde (marker of ROS formation) was increased in ILD, as well as the proportion of mtDNA containing the pathogenic common deletion, with a decrease of mtDNA-

encoded cytochrome c-oxidase activity compared with controls [9].

Further work on the potential pathogenic role mechanisms of autoantibodies directed against angiotension II receptor I (AT1R) was reported [10]. Yue X et al investigated the role of AT1R in the pathogenesis of SSc in mice. Immunization with human AT1R induced the production of autoantibodies against this receptor in mice, and induced a SSc-like disease with perivascular infiltrates, skin fibrosis and pulmonary inflammation with autoantibody deposition in the lung. This work enhances the pathogenic role of autoimmunity to AT1R, and provides a novel mouse model for SSc [11].

Exploring angiogenesis disturbances in SSc, Romano E et al examined the Slit2/Robo4 axis in SSc, giving its capacity of inhibition of VEGF-mediated endothelial cell migration and tube formation. Circulating Slit2 levels were significantly increased in SSc and in VEDOSS patients compared with HC. Slit2 and Robo4 expression was also higher in clinically affected skin and cultured microvascular endothelial cells (MVECs) from both SSc groups. Cell viability, wound healing capacity and in vitro angiogenesis were severely compromised in SSc-MVECs and were significantly ameliorated by both Slit2 neutralisation and Robo4 gene silencing [12].

Recent interest in the role of plasmocitoyd dendritic cells (pDCs) in the pathogenesis of SSc was deepened by Marut W et al who explored pathways underlying pDC aberrancies in SSc. RUNX3 is known to be a key regulator of DC development and function. Low RUNX3 expression was found in SSc patients compared with HC. The authors identified three pathways that underly a low RUNX3 expression in SSc: a higher methylation status of the RUNX3 gene; the presence of SNP rs6672420 in the RUNX3 promoter region; and hypoxia, as pDC cultured in hypoxic conditions showed a significantly lower RUNX3 expression. Moreover, using the SSc bleomycin mouse model, specific delection of RUNX3 led to an increase in both skin inflammation and fibrosis [13].

In another work on pDCs, Kioon Ah et al, assessed the ability of SL-410, a biologic target therapy directed to the IL-3 receptor (CD123) to deplete pDCs from SSc patients. In this study, SL-410 effectively deplected pDCs in both SSc and HC and lead to a significant reduction in CpG-induced IFN-α secretion. Accordingly to the conclusions of this study a clinical trial is being planned for SL-410 as a novel teraphy, targeting pDCs in SSc [14].

Considering the previously reported effects of abatacept in skin fibrosis in mouse models [15], Boleto G et al explored the effect of abatacept, using two pre-clinical mouse models: cGvHD with gastrointestinal disease, and Fra2 mouse model characterized by lung fibrosis and pulmonary vascular remodelling. Abatacept led to a decreased inflammatory infiltrate in cGvHD mice, and to a decrease in lung fibrosis and in fibrogenic markers such as MCP1, osteopontin and M1 and M2 macrophage expression in lesional lungs of Fra2 mice. Furthermore, a reduction of right ventricular systolic pressure was observed in abatacept Fra2 treated mice compared with controls. These results offer further support the role of abatacept for treatment of internal organ involvement in SSc [16].

Conclusions

This is only a small selection of the many valuable works on basic science in the field of SSc presented in 2018 EULAR meeting. It has to be taken into account that the selection presented here is inherently subjective and will inadvertently omit important research findings. Nonetheless, we hope that these highlights will be of interest to all the investigators dedicated to undertanding the pathogenesis of SSc.

**References**


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