using qPCR assays across treatment groups for Co1, SMA and CTGF. Gene expression data (qPCR) confirmed protein expression. Genome-wide RNAseq analysis identified an S100A4 activated signature in NF overlapping the hallmark gene expression signature of SScF. The differentially expressed genes (FDR<0.001 and FC>1.5) induced in NF by S100A4, were also constitutively overexpressed, and downregulated by AX-202, in SScF (Figure 1A). Pathway mapping of these S100A4 dependent genes in SSc showed the most significant enriched Kegg pathways (FDR<0.001) were regulation of stem cell pluripotency (4.6-fold) and metabolic pathways (1.8-fold) (Figure 1B).

Conclusions: Our data confirm that S100A4, supporting a profibrotic role for S100A4 in fibroblast activation in SSc and suggest that serum level may be a biomarker of major organ manifestations and disease severity. This study supports examining the therapeutic potential of targeting S100A4 in SSc are warranted.

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BIOSAMPLES FROM VEISSO PATIENTS SHOW CLASSIC PATHOLOGICAL SIGNS OF SCLERODERMA:OPPORTUNITY FOR A BIOLOGICAL DIAGNOSIS OF DISEASE

Keywords: Systemic sclerosis, Autoantibodies, Cytokines and chemokines

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Background: The five-year analysis of the EUSTAR multicentre prospective study for Very Early Diagnosis Of Systemic Sclerosis (VESSOS) has recently indicated that RP patients with one more VEISSOS criteria have an increased risk of SSc progression, indicating a window of opportunity for early detection of SSc and clinical and therapeutic intervention. Furthermore, it warrants further evaluation of VEISSOS biosamples to enhance our understanding of SSc pathogenesis.

Objectives: Here we aimed to determine whether sera, skin or dermal fibroblasts cultured from VEISSOS patients showed any biological hallmark of SSc.

Methods: Sixty-four VEISSOS sera samples were tested for expression of IFN inducible chemokines (CXCL9,10 and 11 and CCL2, 8 and 19) and biomarker of extracellular matrix turnover (ELF test), 3mm skin biopsies were taken from the forearms from 11 skin biopsies from the forearm of VEDOSS patients and 5 healthy controls and 6 SSc patients. Biopsies was subjected to histology analysis, including haematoxylin and eosin (H&E) and masson trichrome (MT) staining and immunohistochemical analysis using antibodies for CD45+ cells to assess the density of CD45+. Semi-quantitative analysis of histopathological difference to HC. Skin biopsies from VEDOSS patients showed evidence of a profibrotic profile in their sera, skin biopsies and fibroblast level. Our findings provide compelling evidence supporting a profibrotic role of IFN induction in mediating the fibrotic process. Thus, further analyses of fibroblasts induced greater gel contraction compared to HC.

Results: Sera from VEISSOS patients showed significantly higher IFN-inducible chemokines compared to HC and an intermediate levels compared to SSc (Mean (STDEV) Hc= 4.69(0.29) vs. VEISSOS= 4.93 (0.39); SSc= 5.30 (0.54)). ELF score was within normal range for most patients with VEISSOS and showed no statistic difference to HC. Skin biopsies from VEISSOS patients showed evidence of fibrosis and increased collagen bundles within the dermis evidenced in H&E and MT staining and immunohistochemical staining (IHC) for CD45, pSMA and pMTX. In addition, 7 VEISSOS, 5 SSc patients, along with 2 healthy control and 3 SSc, were used to expand fibroblasts cell lines. mRNA and protein were isolated from primary fibroblasts and processed for RT-qPCR and western blotting analyses and compared to HC. Alexander's test was used to evaluate: phenotype; expression of MF biomarkers (collagen, elastin and CTGF). The effect of the normal/fibrotic ECMs on the following parameters of naïve DF triggered by TGF-α/β3 integrin are expressed on the TH receptor that binds T3 and especially T4. The TH binding sites are located proximal to the RGD binding site, MF also express high levels of the pro-fibrotic miRNA-21, which regulates the TGF-β pathway and the level of DIO3 enzyme, which degrades T3. T3 attenuates fibrotic processes. Since high levels of αvβ3 integrin are expressed by MF in the fibroitic sites and the TH binding site of αvβ3 is close to the RGD recognition site, MF expresses high levels of the integrin αvβ3. Interestingly, αvβ3 is a special integrin since it also serves as a membrane thyroid hormone (TH) receptor that binds T3 and especially T4. The TH binding sites are located proximal to the RGD binding site.

Conclusion: Although pilot in nature, this study suggests that patients with no clinical signs of skin fibrosis in their forearms already show biomarker signs of SSc both in their sera, skin biopsies and fibroblast level. Our data indicate that skin thickening is a late manifestation of SSc pathogenesis and early window of opportunity of patients with VEISSOS could be targeted for immune intervention and antifibrotic intervention.

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STIFFNESS INDUCED PROGRESSION OF FIBROSIS BY SORBIN AND SH3 DOMAIN-CONTAINING PROTEIN2 IN SYSTEMIC SCLEROSIS

Keywords: -omics, Systemic sclerosis, Skin
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Background: Persistently activated fibroblasts status leads to progressive extracellular matrix (ECM) deposition and tissue remodeling. The hallmark of systemic sclerosis (SSc) is collagen accumulation in organs, mainly in skin and lung. Despite intensive progress in understanding disease occurrence, SSc remains an intriguing disease with unknown pathology and high mortality. Sorbin and SH3 domain-containing protein2, encoded by SORBS2 is a key member of the sorbin homology family of adapter and scaffold proteins. Recent studies suggest that SORBS2 plays a role in cardiac disease, unknown pathology and high mortality. Sorbin and SH3 domain-containing protein2, encoded by SORBS2 is a key member of the sorbin homology family of adapter and scaffold proteins.

Methods: To identify molecules specifically upregulated in persistently activated fibroblasts, human fibroblasts were chronically stimulated with TGF-β and analyzed by RNA-sequencing. To evaluate the functional implication of tissue elasticity on the transcription of fibroblasts, multwell stiffness assays were performed. SORBS2 expression was further analyzed in skin samples of patients with SSc and murine models of fibrosis. Fibroblast specific SORBS2 knockout mice were challenged with bleomycin to induce skin and lung fibrosis. Further specific readouts like collagen content, skin thickness, myofibroblast count, CT scans were performed.

Results: Upon chronic TGF-β stimulated human normal skin fibroblasts we identified SORBS2, as significantly upregulated molecule. SORBS2 is implicated in cytoskeletal organization, cell adhesion and different signaling pathways. Moreover, extracellular stiffness induced upregulation of SORBS2 mRNA level in fibroblasts. Deletion of SORBS2 in fibroblasts led to a change of the diameter of collagen fibers and modified the elastic index of the tissue. SORBS2 expression is not only elevated in different animal models of fibrosis, but also in fibrotic skin samples of SSc patients. SORBS2 knockout mice (KO) developed significantly less skin fibrosis upon bleomycin challenge in comparison to wild type mice (WT), as assessed by measurement of dermal thickness, myofibroblast counts and hydroxyproline content. Col1a1, Col1a2 and expression of αSMA were significantly lower in SORBS2 KO mice in comparison to SORBS2 WT mice. Similarly, fibroblast specific knockout of SORBS2 showed protective effects in bleomycin induced lung fibrosis. CT scans of the lungs showed statistically significant less fibrotic changes in SORBS2 KO mice in comparison to wild type mice.

Conclusion: SORBS2 is engaged in a vicious circle of fibrosis. Triggered by chronic TGF-β stimulation, SORBS2 is further upregulated by the increasing stiffness of the extracellular matrix. This leads to persistently high levels of SORBS2 resulting into further production of ECM products. Deleting SORBS2 has potent antifibrotic effects in animal models of skin and lung fibrosis. As most of the currently used therapeutic approaches are focussed on early stages of the disease, SORBS2 might be an interesting new therapeutic target in established stages of SSc.

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AUTOANTIBODIES AGAINST FIBROBLAST GROWTH FACTOR (FGF-2), PLACENTAL GROWTH FACTOR (PLGF) AND BETA-ADRENERGIC RECEPTOR 1 (ADRB1) IN AN ALTERED NETWORK OF AUTOANTIBODIES IN SYSTEMIC SCLEROSIS

Keywords: Biomarkers, Systemic sclerosis, Autoantibodies