of whom 7 had pulmonary arterial hypertension (PAH). The patients were divided according to high (n=8)/low (n=12) T3 levels into 2 groups and the difference in circulating miRNA-21 levels between the groups was evaluated.

Results: Fibrotic-ECMs generated by TGFβ-triggered DF had higher levels of collagen-I and TGFβ in comparison to normal ECM. In comparison to the normal ECM, the fibrotic-ECM increased the followings in the DF: 1) ability to liberate TGFβ from the ECM by increasing MMP-9 activity and αv expression. 2) TGFβ activation and differentiation to MF evidenced by increased expression of phospho-Smad3, αSMA, collagen, and elastin, and increased proliferation. 3) Expression of αvβ3, miRNA-21 and Dio3 (all changes in 1-3: 24-123%, p<0.05).

The addition of tetrac to DF cultured on fibrotic-ECM downregulated cell proliferation, collagen, elastin and αSMA expression to the levels found in DF cultured on normal ECM. Furthermore, it reduced αvβ3, miRNA-21, and Dio3 levels. Accordingly, decreased miRNA-21 levels were found in the high T3 SS group, compared to the low T3 group that contained all the PAH patients (p<0.05). Conclusion: Our results demonstrated the existence of a vicious cycle: TGFβ-triggered DF produced a fibrotic-ECM that promoted bystanders’ DF differentiation to MF. Using this model, we demonstrated that tetrac binding to αvβ3 integrin inhibited the differentiation of DF to MF, and their ability to activate the αvβ3/miRNA-21/Dio3/T3 pathway. These results suggest that the thyroid hormone binding site of αvβ3 may be a potential target for the treatment of fibrosis.

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POS0149

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, however there is no available data about its role in fibrotic conditions.

Objectives: We aimed to investigate the role of SORBS2 in the pathogenesis of SSc.

Methods: To identify molecules specifically upregulated in persistently activated fibroblasts, human fibroblasts were chronically stimulated with TGFβ1 and analyzed by RNA-sequencing. To evaluate the functional implication of tissue elasticity on the transcription of fibroblasts, multiwell 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 TGFβ stimulation of 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 TGFβ 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. Deletig 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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POS0148

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
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Background: Systemic sclerosis (SSc) is a chronic inflammatory disorder characterized by tissue fibrosis and autoimmunity. The pathogenesis remains incompletely understood.

Methods: We performed a genome-wide association study (GWAS) that included 53 patients with SSC and 1086 healthy controls. We investigated associations of known autoantibodies to FGF-2, PLGF and ADRB1 with SSc.

Results: We identified new associations of autoantibodies against FGF-2, PLGF and ADRB1 with SSc. The strongest association was with ADRB1 (OR=3.6, 95% CI 1.7-7.4), followed by PLGF (OR=1.9, 95% CI 1.2-3.1) and FGF-2 (OR=1.9, 95% CI 1.2-3.0).

Conclusion: Our findings suggest an altered network of autoantibodies in SSc, including ADRB1, PLGF and FGF-2, which may represent novel therapeutic targets.
Background: Autoantibodies (ab) against G-protein coupled receptors (GPCR), such as ab against angiotensin II receptor type 1 (AT1R), endothelin receptor type A (ETAR) or CX3 chemokine receptor 3 and 4 (CXC3/4) may contribute to the pathogenesis of systemic sclerosis (SSc) [1]. AT1R- and ETAR-ab are associated with SSc-related mortality and CXC3/4- ab predict a deteriorating pulmonary fibrosis [2,3].

Objectives: We aim to identify new ab targets and ab discriminating healthy controls (HC) from SSc patients or SSc clinical phenotypes, organ involvements and therapy.

Methods: Serum ab levels against a panel of GPCR, GF and GFR were measured by ELISA in SSc (n=177) and compared to HC (n=88). Gender matched and age adjusted data were screened for univariate differences of ab levels in clinical phenotypes, explored for multivariate predictive performance of ab levels by a random-forest classifier and tested for differences of ab correlations.

Results: In SSc ab levels against 19 targets were higher compared to HC. Abs against fibroblast growth factor-2 (FGF-2), beta-adrenergic receptor 1 (ADRB1), and placental growth factor (PIGF) discriminated best SSc patients from HC. Multivariate predictions supported the ranking value of FGF-2 and ADRB1-ab for SSc and abs against ADRB1/2, muscarinic receptor 1 (M1R) and alpha-adrenergic receptor 2 ADRA2 for diffuse cutaneous SSc (dSSc) versus limited cutaneous SSc (lSSc). Ab levels were denser and stronger correlated in SSc than in HC (figure 1), suggesting a disturbed regulation of ab with a prominent role of autoregulatory ab. Abs against fibroblast growth factor-2 (FGF-2), beta-adrenergic receptor 1 (ADRB1), and muscarinic receptor 1 (M1R) showed poor accuracy.

Conclusion: SSc is characterized by both quantitative and qualitative alterations in ab levels and ab correlations. This study reveals ab against FGF-2, ADRB1 and PIGF to be new biomarkers of SSc. Alterations within these ab correlation networks could help to identify pathways promoting SSc and its clinical manifestations.

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Figure 1. Different univariate correlations between abs in HC and SSc. The correlations of the ab concentrations are generally increased in SSc compared to HC. Largest accumulated differences are found for ETAR, VEGFA, AT1R and EGFR as indicated by the covered degrees in the circle. Dark bands depict significant differences after FDR-correction (p < 0.05)

Conclusion: SSc is characterized by both quantitative and qualitative alterations in ab levels and ab correlations. This study reveals ab against FGF-2, ADRB1 and PIGF to be new biomarkers of SSc. Alterations within these ab correlation networks could help to identify pathways promoting SSc and its clinical manifestations.

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