epigenetic control of autophagy might thus be a novel approach to ameliorate fibrotic tissue remodeling.

References:

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SAT0285

VISUALISATION OF THE ACTIVE CALCIFICATION PROCESS WITH 18-F SODIUM FLUORIDE PET/CT IN LIMITED CUTANEOUS SYSTEMIC SCLEROSIS WITH CALCINOSIS CUTIS IS FEASIBLE: A PILOT STUDY


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Background: Calcinosis cutis is a major daily challenge to patients with long-standing systemic sclerosis (SSc), negatively affecting their quality of life. Unfortunately, treatment options are very limited due to lack of understanding of the pathogenic process. Currently, calcinosis cutis is only detected at its irreversibly end-stage. Early detection of calcinosis cutis could putatively allow early disease-modifying interventions and monitor treatment effects.

Objectives: The aim of the current study is to assess the feasibility of visualising “active” micro-califications with 18-F Sodium Fluoride (NaF) PET scanning, compared to low-dose CT in patients with clinically overt calcinosis cutis.

Methods: This was a cross-sectional, observational, pilot study. All patients met 2013 ACR/EULAR criteria for SSc. Patients underwent a whole body NaF PET/low-dose CT scan, scanned 90 minutes post-injection. (Sub)cutaneous calcifications were described and assessed on NaF PET, which was compared to CT images by two independent investigators.

Results: A total of 10 female patients with limited cutaneous SSc [median age 56 years (IQR 52-66), median disease duration 17 years (8-19), PAH 10%, ILD 20%] were included, and compared to 10 controls [70 years (65-73)]. NaF uptake showed normal distribution throughout the skeletal bones, arterial tree, and visceral organs, which was comparable between patients and controls. Additionally, NaF uptake was visible in the skin of all SSc patients, but in none of the controls. Cutaneous NaF uptake largely correlated with clinical calcifications. Most common sites of cutaneous NaF uptake were the fingers (6 patients) and knees (7 patients). Only 5% of the NaF positive lesions were not accompanied by visible calcifications on CT. Furthermore, of all calcified lesions seen on CT, 51% showed uptake on NaF PET. Small lesions (<1cm), were generally only visible on CT, due to lower resolution of NaF PET.

Conclusion: Imaging of “active” calcinosis cutis in limited cutaneous systemic sclerosis is feasible using NaF PET scanning. Most clinically overt calcifications and half of those seen on CT were positive for NaF uptake. Whether these “active” calcifications behave differently in terms of faster progression, clinical complaints, and infection risk, and whether these are potentially suitable for disease modifying interventions is subject to future study.

SAT0286

BIOLOGICAL CORRELATES OF RADIOGRAPHIC FEATURES OF INTERSTITIAL LUNG DISEASE IN SYSTEMIC SCLEROSIS: AN IN DEPTH ANALYSIS OF BRONCHOALVEOLAR PROTEINS OF SCLERODERMA LUNG STUDY I PARTICIPANTS

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Background: Systemic sclerosis-related interstitial lung disease (SSc-ILD) involves a combination of inflammation, fibrosis and vascular pathology that is typically assessed on CT imaging as a mixture of ground-glass opacification (GGO) and fibrotic changes. We hypothesized that proteins recovered from bronchoalveolar lavage (BAL) could be used to probe the underlying pathobiology associated with GGO and fibrotic changes.

Objectives: (1) To assess the relationship between 68 unique BAL proteins measured in participants of Scleroderma Lung Study (SLS) I and radiographic and physiologic measures of ILD. (2) To identify inter-correlations among specific proteins to enlighten our understanding of how specific biological pathways contribute to SSC-ILD.

Methods: Bronchoscopy was performed on 144 of the 158 participants in SLS I with 103 BAL samples available for analysis. BAL was lyophilized, concentrated 10X and used in a multiplex protein analysis for 68 different cytokines, chemokines and other factors. Kendall tau correlations were performed to assess the relationship between individual proteins and baseline measures of pulmonary function and quantitative CT scores for fibrosis, GGO and total ILD. Those proteins found to correlate significantly with at least 2 clinical measures of ILD were entered into a cluster analysis with inter-correlations expressed as a heatmap.

Results: Significant correlations were observed between fibrosis scores and several biologic pathways including pro-fibrotic factors (transforming growth factor beta [TGF-B], platelet-derived growth factor [PDGF]), proteins involved in tissue remodeling (Matrix metallopeptidase [MMP]-1,8,9; Hepatocyte growth factor [HGF]), and those involved in monocyte/macrophage migration and activation (Monocyte chemoattractant protein [MCP]-1,3; macrophage colony-stimulating factor [MCSF]). These same pathways correlated with the diffusing capacity for carbon monoxide (DLCO). In contrast, GGO scores correlated primarily with immune and inflammatory mediators (Interleukin [IL]-5,13,15, IL-1 receptor antagonist and interferon gamma) with only limited overlap to proteins that related to fibrosis. Vascular endothelial growth factor (VEGF) levels were lower in patients with more extensive GGO, fibrosis and diffusion impairment, suggesting that vascular changes are a central feature of SSC-ILD. Specific proteins were highly correlated with one another in a pattern suggesting biologically-related networks (Figure) that might provide additional insight regarding disease pathogenesis.

Fig. 1 Clinical calcinosis cutis with corresponding images of 18F-NaF PET/CT-scan
Conclusion: Combining a diverse analysis of BAL proteins with the rich dataset available from SSc-ILD patients participating in SLS 1, the study findings suggest the involvement of distinct biologic pathways, inter-related networks, and specific biologic signatures associated with unique radiographic features of IILD. The relationship of these factors to other SSc disease features, patient outcomes and as predictors of treatment responses will be studied in future analyses.

References:

Figure. Correlation heatmap of BAL proteins associated with at least 2 clinical measures of ILD in SSc patients. Absolute correlations are depicted, and darker colors signify stronger correlations.

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SAT0287

AMPLIFICATION OF THE PRO-FIBROTIC JAK2-STAT3 SIGNALING AXIS BY TGFβ-INDUCED EPIDEMIC SILENCING OF SOCS3

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Background: Tissue fibrosis caused by a pathological activation of fibroblasts is a major hallmark of systemic sclerosis (SSc). Epigenetic gene silencing of anti-fibrotic genes is thought to play a central role to establish the persistently activated phenotype of fibroblasts independent of external stimuli such as TGFβ, which has been identified as key-mediator of fibroblast activation.

Objectives: The aims of the present study were to investigate whether the aberrant activation of JAK2-STAT3 signaling in fibroblasts might be caused by epigenetic silencing of SOCS expression and whether re-establishment of the endogenous, SOCS-dependent control of JAK/STAT signaling may prevent aberrant fibroblast activation and ameliorate tissue fibrosis.

Methods: The methylation status of SOCS3 in fibroblasts was evaluated by methylation-specifc PCR and MeDIP assays. 5-aza-2-deoxycytidine (5-aza) and siRNA was used to inhibit DNA methyltransferases (DNMTs) in vitro and in vivo. Knockdown and overexpression experiments served to analyze the mechanism of action in cultured fibroblasts. Fibroblast-specific knock out mice were additionally used to analyze the role of SOCS3 and DNMTs in vivo. Results: Chronically increased levels of TGFβ reduced the expression of SOCS3 in normal fibroblasts to a level also found in SSc fibroblasts. Consistently, the expression of SOCS3 was severely downregulated in skin of SSc patients compared to healthy individuals with only minor differences between limited and diffuse cutaneous SSc. Methylation analyses demonstrated a prominent promoter hypermethylation of SOCS3 in SSc fibroblasts and in normal fibroblasts exposed to persistently high levels of TGFβ. Increased DNMT activity and a time-dependent induction of DNMT3A and DNMT1 expression upon chronic exposure to TGFβ resulted in promoter hypermethylation of SOCS3. Knockdown of SOCS3 induced an SSC-like phenotype in normal dermal fibroblasts with increased activation of JAK2-STAT3 signaling, enhanced expression of myofibroblast markers, increased collagen release, and an aggrivated experimental tissue fibrosis with increased activation of JAK2-STAT3 signaling. This effect was mimicked by overexpression of mutant JAK2 with mutations in the SOCS3 binding motif. Vice versa, forced overexpression of SOCS3 reduced TGFβ-mediated fibroblast activation and ameliorated the endogenous activation of SSc fibroblasts. Pharmacological inhibition or selective knockdown of DNMTs restored the normal expression of SOCS3, reduced fibroblast activation and collagen release, blocked STAT3-responsive transcription, and exerted potent antifibrotic effects in bleomycin- and TBNРІRII-induced dermal fibrosis. In addition, treatment with 5-aza or knockdown of either DNMT1 or DNMT3A induced regression of established fibrosis.

Conclusion: These findings identify a novel pathway of epigenetic imprinting of fibroblasts in fibrotic disease with translational implications for the development of new targeted therapies in fibrotic diseases. We demonstrate that chronic activation of TGFβ signaling in diseased tissues perturbs the epigenetic control of STAT signaling by DNMT-induced silencing of SOCS3 expression. Our data might thus strengthen the scientific rational for targeting DNA methylation in fibrotic diseases.

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SAT0288

CHARACTERIZATION OF ANTI-AMINOACYL TRNA SYNTHETASE AUTOANTIBODIES IN PATIENTS WITH IDIOPATHIC INFLAMMATORY MYOPATHIES

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Background: Idiopathic inflammatory myopathies (IIM) are rare chronic inflammatory diseases associated with high mortality and morbidity [1]. One subgroup of IIM, anti-synthetase syndrome (ASS), is characterized by the presence of autoantibodies that target aminoacyl tRNA synthetases (aaRS), together with specific clinical manifestations such as myositis, interstitial lung disease (ILD), arthritis, mechanic's hand, Raynaud's syndrome and fever [2]. The most common anti-aaRS autoantibody, anti-Jo1 targeting histidyl tRNA synthetase (HisRS), is present in up to 20-30% of patients with IIM, and up to 90% of patients with myositis and ILD [3, 4]. Besides Jo1, there are today seven other identified autoantigens of systemic sclerosis (US8247389, EP2331143). Consultant of: Consultancy fees from Actelion, Acceleron Pharma, AnMar, Bayer, Baecon Discovery, Blade Therapeutics, Boehringer, CSL Behring, Catienon, ChemobAb, Curzon Pharmaceuticals, Ergonex, Galapagos NV, GSK, Glenmark Pharmaceuticals, Inventiva, Italfarmaco, iOvi, medac, Medscape, Mitsubishi Tanabe Pharma, MSD, Roche, Sanofi and UCB, Speakers bureau: Pfizer fees from Actelion, Bayer, Boehringer Ingelheim, Medscape, Pfizer and Roche, Georg Schett Speakers bureau: AbbVie, BMS, Celpgene, Janssen, Eli Lilly, Novartis, Roche and UCB, Jörg Distler Grant/research support from: Boehringer Ingelheim, Consultant of: Boehringer Ingelheim, Paid advisor for: Boehringer Ingelheim, Speakers bureau: Boehringer Ingelheim

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