phenotype exhibited by functionally adapted, exhausted T cells in response to chronic stimulation.

Conclusion: Overall this study provides an in depth analysis of systemic immunome in SSC, highlighting role of inflammation and chronic stimulation mediated "premature senescence" of immune cells, with implications to delineate mechanism of pathogenesis and identify diagnostic/therapeutic targets.

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THU0343

PU.1 INHIBITOR DB1976 CONTROLS FIBROBLAST POLARIZATION IN SYSTEMIC SCLEROSIS AND LEADS TO REGRESSION OF FIBROSIS IN DIFFERENT MODELS OF ORGAN FIBROSIS

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Background: Persistent activation of fibroblast with excessive release of extracellular matrix is a hallmark of systemic sclerosis (SSc). Fibroblasts can either acquire a "pro-fibrotic" phenotype with excessive matrix production or a "pro-inflammatory" phenotype with releasing of matrix-degrading enzymes and subsequent tissue destruction. Despite these well-characterized phenotypic differences, the molecular mechanisms that drive polarization of fibroblasts into these two functionally opposing phenotypes remain enigmatic.

Objectives: We aimed to evaluate the transcriptional network that promotes the extracellular matrix-producing fibrotic fibroblast fate.

Methods: We investigated the transcriptional network that induces the pro-fibrotic phenotype of fibroblasts by in silico and immunofluorescence analyses of human fibrotic skin, lung, liver and kidney, and performed functional assays to address the fibrogenic potential of fibroblasts in vitro and in several mouse models of systemic sclerosis. The heterocyclic diamidine DB1976 was used as new therapeutic compound to induce regression of fibrosis.

Results: We identified the ETS transcription factor PU.1 as molecular checkpoint for acquisition of a "pro-fibrotic" phenotype of fibroblasts. Our data demonstrate that expression of PU.1 is effectively silenced in fibroblasts during tissue homeostasis. When the epigenetic control of PU.1 is lost and PU.1 expression is induced, fibroblasts differentiate into a fibrotic phenotype that includes the transcription of numerous pro-fibrotic mediators. PU.1 polarized resting fibroblasts and even repolarized extracellular matrix-degrading inflammatory fibroblasts to an extracellular matrix-producing fibrotic phenotype. PU.1 is associated with a network of pro-fibrotic factors including members of the TEAD-HIPPO, canonical TGF- β -SMAD and AP1 signaling pathways. Other transcription factors with fibrotic abilities, such as SNAI2 and myocyte enhancer factor (MEF) 2, bind in close vicinity to PU.1-binding sites within the genome and contribute to the recruitment of the transcription machinery that drives the switch towards the fibrotic phenotype. PU.1 has a major coordinating role within this complex network of transcription factors in fibroblasts, as the inactivation of PU.1 alone is sufficient to prevent fibrotic polarization in vitro and in vivo. Finally, we investigated pharmacological targeting of PU.1 as a

potential strategy to prevent uncontrolled fibrotic tissue remodelling. DB1976 showed anti-fibrotic effects in vivo in various fibrosis models and across several organs. Treatment with DB1976 not only prevented bleomycin-mediated skin fibrosis, but also induced regression of pre-established fibrosis, and was well tolerated.

Conclusion: These findings suggest that PU.1 inhibition may represent a novel and effective therapeutic approach to treat a wide range of fibrotic diseases. Inactivation of PU.1 effectively reverted the fibrotic phenotype of fibroblasts to a resting state and induced the regression of tissue fibrosis.

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THU0344

A PILOT STUDY ASSESSING THE EFFECT OF AIR POLLUTION ON EXTRACELLULAR VESICLES IN SYSTEMIC SCLEROSIS

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Background: Systemic sclerosis (SSc) is a severe autoimmune disease characterized by a progressive multi-organ fibrosis. The identification of specific diagnostic and prognostic biomarkers remains an unmet need. Over the past few years, it has been suggested that extracellular vesicles (EVs) and environmental toxicants, such as particulate matter (PM), may have an important role in the pathogenesis of autoimmune diseases. At present, no data are available on the impact of PM exposure on EVs from patients with SSc.

Objectives: Our aim was to evaluate the effects of PM with aerodynamic diameter $\leq 10 \mu\text{m}$ (PM₁₀) and $\leq 2.5 \mu\text{m}$ (PM_{2.5}) on EVs in SSc and osteoarthritis (OA) as control.

Methods: Plasma EVs were analyzed by Nanosight and flow cytometry after labeling with the following markers: CD14 (monocyte), CD61 (platelet), CD25 (T-reg), human endogenous retrovirus w (HERV-w), human leukocyte antigen G (HLA-G). Demographic and clinical data were collected for each patient. Plasma EV concentrations were measured in SSc and OA patients and were analyzed by generalized linear regression models. Daily PM concentrations, estimated by Regional Environmental Protection Agency at municipality resolution, were used to assign short-term exposure (mean of the 7 days preceding the evaluation) to each study subjects.

Results: 12 consecutive patients with limited cutaneous SSc (11 female, median age 66.8, median disease duration 12.3, 7 anti-centromere positive, median mRSS 3.5) and 12 patients with OA (median age 67.1, median disease duration 9.3, 8 female) were enrolled. The increase of PM_{2.5} led to a decrease of HERV-w+ microvesicles (MV) in both SSc ($\beta = -0.10$; $p = 0.01$) and OA ($\beta = -0.09$; $p = 0.01$) and of HLA-G+ ($\beta = -0.11$; $p < 0.01$) only in SSc. Similar results were observed analyzing PM₁₀ exposure. Analysis of EVs concentration according to their dimensions showed a negative association in the size range of exosomes (63-

92nm) in SSc compared to OA ($p < 0.05$) and in the range of MV (230-510 nm) (figure below). Finally, we observed a positive association between HLA-G+ with Erythrocyte Sedimentation Rate (ESR) ($\beta = 0.34$; $p < 0.01$).

Abstract THU0344 – Figure 1

Conclusion: In our study, limited cutaneous SSc showed different EVs concentrations from controls: SSc tends to have less exosomes and more MV than OA. Moreover, environmental stimuli (e.g. PM exposure) are confirmed to be able to influence HERV-w+ MV release both in SSc and controls. Finally, in SSc patients PM exposure could significantly alter the release of HLA-G+ MV that has been correlated to the process of self-tolerance maintenance. Further studies are required to fully unlock the role of PM and EVs in SSc.

Disclosure of Interests: None declared

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THU0345 TEXTURE-BASED RADIOMICS FEATURES DISCRIMINATE DIFFERENT STAGES OF EXPERIMENTAL INTERSTITIAL LUNG DISEASE

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Background: Interstitial lung disease (ILD) is a life-threatening complication of systemic sclerosis (SSc). There is an unmet need for validated, routinely available biomarkers for disease staging and individualized patient stratification. In that respect, high-resolution computed tomography (HRCT), routinely performed in the work-up of SSc-ILD patients, has great potential as a source for non-invasive imaging biomarkers. Recently, radiomics, the quantitative extraction of hundreds of radiologic image features, has emerged as a powerful tool for biomarker research and precision medicine approaches; however, so far, it has been applied predominantly in oncology.

Objectives: To evaluate the performance of CT-based radiomics for disease detection, staging and as surrogate marker for tissue pathophysiology in the model of bleomycin (BLM)-induced lung fibrosis.

Methods: To mimic different stages of SSc-ILD, small-animal CT imaging was performed at days 3, 7, and 14 after instillation of BLM or saline solution, respectively (n=5-6 mice/group). Trained observers manually segmented the left and right mouse lungs in the CT images, and 154 radiomics features were extracted including 17 histogram- and 137 texture-based features using the in-house developed software Z-Rad (Python 2.7). To link the radiomics features with the underlying pathophysiology, Pearson correlation analysis between radiomics and histological features (Ashcroft score, Sirius red and CD45 staining positivity) was performed.

Results: CT imaging visualized morphological changes of the lung architecture in BLM-treated mice, as evidenced by a time-dependent increase of grey areas on chest CT images and a gradual increase in tissue density on density-masked lungs. Accordingly, 6 out of 17 classical histogram

features (e.g. mean CT density, skewness and kurtosis) precisely distinguished diseased from healthy mice with area under the curve values (AUCs) of >0.87 ($p < 0.05$) and thus detected lung remodelling. However, histogram-based features failed to differentiate between the different time points and thus stages of experimental lung fibrosis as investigated by receiver operating characteristic curve analysis and by hierarchical clustering. In contrast, 59 out of 137 texture-based radiomics features, including features describing image homogeneity or contrast detected ILD and distinguished the different stages with excellent accuracy (AUCs >0.84 ; $p < 0.05$) thus outperforming the classical histogram features.

In addition, texture-based, but not histogram-based features were associated ($R^2 > 0.5$, $p < 0.05$) with histological parameters, thereby possibly reflecting changes in lung (micro-)architecture, which may result from both inflammatory and/or fibrotic changes.

Conclusion: If confirmed in human SSc-ILD, texture-based radiomics features have great potential to provide biological and stage-specific quantitative information on lung (micro-)architecture and thus could serve as quantitative imaging biomarkers for guided decision making in SSc-ILD.

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THU0346 EVALUATION OF A NOVEL PARTICLE-BASED ASSAY FOR DETECTION OF MYOSITIS SPECIFIC ANTIBODIES

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Background: Myositis specific antibodies (MSA) represent important diagnostic tools and also help stratify idiopathic inflammatory myositis (IIM) patients with particular clinical features, treatment responses, and disease outcomes. Standardization of MSA detection is of high importance because these antibodies also have the potential to be used in classification criteria.

Objectives: The objective of this study was to evaluate the clinical performance of a novel particle based multi-analyte technology (PMAT) for the detection of MSA as an aid in the diagnosis and also in the differentiation of IIM subtypes.

Methods: The study included 464 patient samples collected at Hospital Vall d'Hebron, Autonomous University of Barcelona, most of whom had a diagnosis of IIM (n=264). As controls, samples from patients with myositis like conditions (ML, n=20), rheumatoid arthritis (RA, n=33), systemic lupus erythematosus (SLE, n=40), Sjögren's syndrome (SjS, n=25), infectious diseases (ID, n=40) and healthy individuals (HI, n=42) were included. All samples were tested using a novel fully automated particle-based multi-analyte technology (PMAT, Inova Diagnostics, research use only; Jo-1, PL-7, PL-12, EJ, Mi-2b, NXP2, SAE, TIF1y, MDA5, HMGCR, SRP) which utilizes paramagnetic particles with unique signatures and a digital interpretation system.