(p=0.018). The rs4938573 risk allele decreased enhancer (p=0.043) and promoter (p=0.024) activity. While rs7117261 or rs4938573 were not reported in eQTL databases, GTex data reported rs57494551 as an eQTL that alters *DDX6* expression in whole blood (p=1.8E-7). Additionally, these functional SNPs have been associated with looping events to several proximal promoters in nearby genes in immune cells.

Conclusion: SS and SLE have similar genomic architecture across the *DDX6-CXCR5* risk interval. Multiple variants in the credible set exhibited allele specific changes in protein binding, as well as modified enhancer activity, promoter activity or both. Ongoing studies will use Cas9 in EBV B cells to determine which other loci are within the local regulatory network.

Disclosure of Interests: Mandi M Wiley: None declared, Bhuwan Khatri: None declared, Kandice L Tessneer: None declared, Michelle L Joachims: None declared, Anna M Stolarczyk: None declared, Astrid Rasmussen Speakers bureau: Novartis, ThermoFischer, Simon J. Bowman Consultant of: Astrazeneca, Biogen, BMS, Celgene, Medimmune, MTPharma, Novartis, Ono, UCB, xtl-bio, Glapagos, Speakers bureau: Novartis, Lida Radfar: None declared, Roald Omdal: None declared, Marie Wahren-Herlenius: None declared, Blake M Warner: None declared, Torsten Witte: None declared, Roland Jonsson: None declared, Maureen Rischmueller: None declared, Patrick M Gaffney: None declared, Judith A. James Grant/research support from: Progentec Diagnostics, Inc, Consultant of: Abbvie, Novartis, Jannsen, Lars Ronnblom Grant/research support from: AZ, Speakers bureau: AZ, R Hal Scofield Grant/research support from: Pfizer, Xavier Mariette: None declared, Wan-fai Ng: None declared, Kathy L Sivils: None declared, Gunnel Nordmark: None declared, Betty Tsao: None declared, Christopher Lessard: None declared

DOI: 10.1136/annrheumdis-2020-eular.3935

OP0140 DYSREGULATED EXPRESSION OF THE LONG NON-CODING RNA, LINC01871, IMPLICATED IN SJÖGREN'S SYNDROME PATHOGENESIS

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Background: Sjögren's syndrome (SS) is a chronic, heterogenous autoimmune disease characterized by inflammatory destruction of the exocrine glands. Long non-coding RNAs (lncRNAs) have emerged as a functionally diverse class of non-protein coding RNA (ncRNA) with increasing implications in interferon signaling, immune cell regulation, and autoimmune disease pathology. The potential role of lncRNAs in SS pathogenesis is unknown.

Objectives: To identify and characterize candidate lncRNAs with potential relevance to SS pathology.

Methods: RNA-seq was used on whole blood from SS patients (n=30 antibody negative (Ro^-); n=27 antibody positive (Ro^+)) and healthy controls (HC, n=27) to identify differentially expressed (DE) lncRNAs (log2 fold change (FC) ≥ 2 or ≤ 0.5; p_{adj} <0.05). Bioinformatic and pathway analyses were used to predict lncRNA function. *In vitro* time course experiments in HSB2 T cell lymphoblasts stimulated with PMA/Ionomycin (PMA/I) or type I interferon (IFN) were used to assess biological relevance. *LINC01871* function was further investigated by RNA-seq on a single cell clone of HSB2 with confirmed CRISPR-targeted *LINC01871* deletion (*LINC01871*$^{-/-}$).

Results: We identified a total of 1054 unique DE ncRNAs between Ro^+, Ro^- and/or a combined analysis relative to HC; of these, 45 (1 long intergenic ncRNA (lincRNA), 1 antisense, 43 pseudogenes) were overexpressed in all 3 SS subsets. To begin investigating the function of the previously undescribed lincRNA, *LINC01871* (SS^{Ro-}: FC=2.85; p_{adj}=1.1x10^{-4}), we performed a correlation analysis of the SS^{Ro-} transcriptome, which found several co-expressed protein coding RNAs involved in immune regulation (*THEMIS*, *TBX21*, *IL10RA*, *IL2RB,* among many others). Similarly, Ingenuity Pathway Analysis of the SS transcriptome compared to HC, as well as several gene ontology enrichment analyses of publicly available RNA expression correlation databases, identified shared immune-related pathways including cytotoxic T cell, natural killer cell, and T cell regulation. To further study the role of *LINC01871* in cytotoxic T cells, we used qRT-PCR to resolve the effects of PMA/I or type I IFN stimulation on *LINC01871* expression in the T lymphoblastoid HSB2 cells. *LINC01871* expression was downregulated after PMA/I stimulation, but unchanged with type I IFN stimulation. To explore the regulatory function of *LINC01871* in T cells, we targeted *LINC01871* in HSB2 cells using CRISPR. To this end, we generated a single cell *LINC01871*$^{-/-}$ clone with no RNA expression by qPCR and confirmed homozygous deletion using DNA sequencing. RNA-seq analysis of *LINC01871*$^{-/-}$ compared to unmodified HSB2 cells identified 1166 DE transcripts. Pathway analyses clustered the DE transcripts into similar immune regulatory, cytotoxic and T cell pathways identified in SS^{Ro-} whole blood RNA-seq and publicly available RNA-seq databases. Further, several prominent T cell regulatory transcripts that exhibited correlated upregulation with *LINC01871* in SS^{Ro-} whole blood RNA-seq also demonstrated downregulation after *LINC01871* deletion: *CD109* (FC=-9.7; p_{adj}=5.3x10^{-16}), *IL22* (FC=-8.1; p_{adj}=7.6x10^{-11}), *PDCD1* (FC=-6.2; p_{adj}=1.1x10^{-6}), *THEMIS* (FC=-3.8; p_{adj}=2.7x10^{-165}) and *TBX21* (FC=-2.1; p_{adj}=3.3x10^{-25}).

Conclusion: LncRNAs are emerging as important regulators of immune function with increasing evidence of autoimmune disease relevance. Here, we leveraged RNA-seq, extensive bioinformatic data, and CRISPR technology to identify and functionally characterize *LINC01871* as a potential mediator of the dysregulated T cell inflammatory response pathways implicated in SS pathogenesis.

Disclosure of Interests: Michelle L Joachims: None declared, Bhuwan Khatri: None declared, Kandice L Tessneer: None declared, Anna M Stolarczyk: None declared, Graham B Wiley: None declared, Astrid Rasmussen Speakers bureau: Novartis, ThermoFischer, Joel Guthridge Grant/research support from: Xencor, Bristol Myers Squibb, DXterity, Judith A. James Grant/research support from: Progentec Diagnostics, Inc, Consultant of: Abbvie, Novartis, Jannsen, R Hal Scofield Grant/research support from: Pfizer, Kathy L Sivils: None declared, Indra Adrianto: None declared, Christopher Lessard: None declared

DOI: 10.1136/annrheumdis-2020-eular.3950

OP0141 HIGH DIMENSIONAL ANALYSIS REVEAL A NETWORK OF CERTAIN TRANSCRIPTION FACTORS THAT LINK VASCULOPATHY AND ORGAN FIBROSIS IN SYSTEMIC SCLEROSIS

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Background: Since vascular manifestations such as Raynaud's phenomenon often precede the onset of other clinical manifestations of systemic sclerosis (SSc), the identification of pathways linking vasculopathy to organ fibrosis might thus provide important insights into early disease mechanisms and allow early targeted intervention for both fibrotic and vascular events.

Objectives: In this study we performed high dimensional (HD) analyses to identify mediators that link vasculopathy to organ fibrosis.

Methods: HD techniques including RNA-seq, ChIP-seq, ATAC-seq and FISH-seq have been performed to identify mediators in vessels and fibrotic lesions of human skin samples of SSc patients and healthy volunteers. In addition, murine skin and lung tissue samples were analyzed by multi-channel immunofluorescence (IF) and confocal laser scanning microscopy. Microvascular endothelial cells, smooth muscle cells and fibroblasts have been further processed to address their functional attributes with regard to their proliferative, migratory and chemotactic capacity. In vivo models and *ex vivo* mouse fetal metatarsal assays were performed to study fibrotic and angiogenic processes.

Results: Bioinformatic HD analyses revealed the ETS transcription factor PU.1 as molecular checkpoint of a network of factors that drive matrix production and fibrotic imprinting in SSc. Within this network ATF3 was significantly upregulated in fibroblasts of skin biopsies of SSc patients and of various organs of fibrosis models. ATF3 deficiency ameliorated fibrosis in various mouse models. Notably, ATF3 was significantly upregulated in vascular cells of fibrotic tissues of SSc patients. Multi-channel IF and confocal laser scanning microscopy of skin and lung biopsies of SSc patients revealed an increased expression of ATF3 especially in microvascular endothelial cells and smooth muscle cells. ATF3 overexpression in smooth muscle cells led to an extensively enhanced proliferation and increased migratory capacity whereas endothelial cells showed a SSc-like phenotype with reduced proliferation and migration. After ATF3 overexpression, tube formation capacity was completely altered as assessed by cumulative tube length, tube numbers and capillary sprouting. To investigate vessel outgrowth from a different perspective, we used the *ex vivo* fetal mouse metatarsal assay. ATF3 knockout mice showed a completely altered angiogenic response as assessed by tube length, number of branches and number junctions compared to wildtype controls.

Conclusion: We identified PU.1 and ATF3 as key factors in disturbed vasculature and endogenous activated fibroblasts suggesting this axis as a potential therapeutic target intervening both fibrotic and vascular manifestations.

Disclosure of Interests: Charles Gwellem Anchang: None declared, Bettina Matalobos Lawaree: None declared, Stefanie Weber: None declared, Simon Rauber: None declared, Thomas Wohlfahrt: None declared, Markus Luber:

Ann Rheum Dis: first published as 10.1136/annrheumdis-2020-eular.3950 on 2 June 2020. Downloaded from http://ard.bmj.com/ on September 28, 2023 by guest. Protected by copyright.