($p=0.018$). 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 rs7494551 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 Tessner: 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, xtlbio, Glapagos, Speakers bureau: Novartis, Lida Radfar: None declared, Røld 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, Janssen, 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 Sivits: None declared, Gunnell 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

M. L. Joachims¹, B. Khatri¹, K. L. Tessner¹, A. M. Stolarczyk¹, G. B. Wiley¹, A. Rasmussen¹, J. Guthridge¹, J. A. James¹, R. H. Scofield², K. L. Sivits¹, I. Adrianto³, C. Lessard¹. ¹Oklahoma Medical Research Foundation, Oklahoma City, United States of America; ²University of Oklahoma, Oklahoma City, United States of America; ³Henry Ford Health System, Detroit, United States of America

Background: Sjögren's syndrome (SS) is a chronic, heterogeneous 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 ($\log_2$ fold change (FC) ≥ 2 or ≤ 0.5 ; $p_{\text{adj}} < 0.05$). 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 (lncRNA), 1 antisense, 43 pseudogenes) were overexpressed in all 3 SS subsets. To begin investigating the function of the previously undescribed lncRNA, *LINC01871* (SS^{Ro}: FC=2.85; $p_{\text{adj}}=1.1 \times 10^{-4}$), 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; $p_{\text{adj}}=5.3 \times 10^{-16}$), *IL22* (FC=-8.1; $p_{\text{adj}}=7.6 \times 10^{-11}$), *PDCD1* (FC=-6.2; $p_{\text{adj}}=1.1 \times 10^{-6}$), *THEMIS* (FC=-3.8; $p_{\text{adj}}=2.7 \times 10^{-165}$) and *TBX21* (FC=-2.1; $p_{\text{adj}}=3.3 \times 10^{-25}$).

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 Tessner: 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, Janssen, R Hal Scofield Grant/research support from: Pfizer, Kathy L Sivits: 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

C. G. Anchang¹, B. Matalobos Lawaree¹, S. Weber¹, S. Rauber¹, T. Wohlfahrt¹, M. Luber¹, A. Kreuter², G. Schett¹, J. Distler¹, A. Ramming¹. ¹Department of Internal Medicine 3 - Rheumatology and Immunology, Friedrich-Alexander University (FAU) Erlangen-Nürnberg and Universitätsklinikum Erlangen, Erlangen, Germany; ²Department of Dermatology, Venereology and Allergy, HELIOS St. Elisabeth Klinik Oberhausen, University Witten-Herdecke, Oberhausen, Germany, Oberhausen, Germany

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:

None declared, Alexander Kreuter: None declared, Georg Schett Speakers bureau: AbbVie, BMS, Celgene, Janssen, Eli Lilly, Novartis, Roche and UCB, Jörg Distler Grant/research support from: Boehringer Ingelheim, Consultant of: Boehringer Ingelheim, Paid instructor for: Boehringer Ingelheim, Speakers bureau: Boehringer Ingelheim, Andreas Ramming Grant/research support from: Pfizer, Novartis, Consultant of: Boehringer Ingelheim, Novartis, Gilead, Pfizer, Speakers bureau: Boehringer Ingelheim, Roche, Janssen
DOI: 10.1136/annrheumdis-2020-eular.5745

OP0142

FIBROBLAST GROWTH FACTOR RECEPTOR 3 REGULATES THE ACTIVITY OF PROFIBROTIC CYTOKINE AND GROWTH FACTOR PATHWAYS TO DRIVE FIBROBLAST ACTIVATION AND TISSUE FIBROSIS IN SYSTEMIC SCLEROSIS

D. Chakraborty¹, H. Zhu^{2,3}, A. Juengel⁴, L. Summa², Y. N. Li², C. Bergmann², A. E. Matei², T. Trinh-Minh², C. W. Chen², C. Dees², A. Ramming², G. Schett², O. Distler⁴, J. Distler². ¹Friedrich-Alexander University (FAU) Erlangen-Nürnberg and Universitätsklinikum Erlangen, ²Department of Internal Medicine 3 - Rheumatology and Immunology, Erlangen, Germany; ³Friedrich-Alexander University (FAU) Erlangen-Nürnberg and Universitätsklinikum Erlangen, Department of Internal Medicine 3 - Rheumatology and Immunology, Erlangen, Germany; ⁴Xiangya Hospital, Central South University, Department of Rheumatology, Changsha, Hunan, China; ⁵University of Zurich, Zürich, Switzerland

Background: Fibroblast growth factor receptor 3 (FGFR3) is a member of the family of different fibroblast growth factor receptors with several ligands called fibroblast growth factors (FGFs) in humans. Each FGFR has different isoforms resulting from natural alternative splice variants. Upon binding FGF ligands, fibroblast growth factor receptors (FGFRs) trigger various intracellular signaling pathways to regulate important biological processes. Systematic evaluation of FGF/FGFR signaling in the context of SSc has not been performed so far.

Objectives: The aim of this study was to characterize FGFR3/FGF9 signaling in the context of fibroblast activation and to evaluate FGFR3 as a potential molecular target for antifibrotic treatment in SSc.

Methods: Differential expression profiling of dermal cells from SSc patients and healthy volunteers were performed employing GEArray cDNA microarray. Real-time PCR, Western Blot, immunohistochemistry and immunofluorescence were done in skin tissues and fibroblasts from SSc patients. Selective inhibitors in conjunction with genetic knockdown and knockout strategies were used to target FGFR3 signaling *in vitro* and in mouse models of SSc: skin fibrosis induced by bleomycin and by overexpression of a constitutively active transforming growth factor receptor 1 (TBR) and tight skin-1 (TSK) mice. Affymetrix gene arrays in dermal fibroblasts from mice with constitutive FGFR3 signaling and mice lacking FGFR3.

Results: Expression of FGFR3, specifically the isoform FGFR3IIIb and its ligand FGF9, was significantly upregulated in the dermis and dermal fibroblasts of SSc patients as compared to healthy volunteers. Furthermore, an increase of FGFR3 IIIb/FGF9 expression comparable to that in SSc fibroblasts could also be obtained by stimulating normal healthy dermal fibroblasts with transforming growth factor (TGFβ) *in vitro* and in mice constitutively overexpressing active TGFβ receptor type I.

Transcriptome profiling, *in silico* analysis and functional experiments revealed that FGFR3 synergistically induces multiple profibrotic pathways including Endothelin-, Interleukin-4- and CTGF-signaling in a CREB-dependent manner. FGFR3 exerts profibrotic effects by modulating phosphorylation of CREB by ERK-, AKT-, CAMK2- and p38-kinases. Activation of FGFR3 in healthy or SSc dermal fibroblasts by stimulation with recombinant FGF9 was sufficient to induce resting fibroblast-to-myofibroblast differentiation along with increased collagen secretion and alpha-SMA production.

Genetic knockout of Fgfr3 abrogates myofibroblast differentiation *in vitro* and ameliorates skin fibrosis in TSK and TBR mice and in bleomycin-induced fibrosis. Further confirming the translational potential of these findings in the preclinical models of SSc, we demonstrate that pharmacological inactivation of FGFR3 by PD173074 could induce the regression of experimental fibrosis *in vitro* and in bleomycin-challenged, TSK and TBR mice.

Conclusion: Our findings characterize FGFR3 as an upstream regulator of a network of profibrotic mediators in SSc and thus, we could demonstrate successfully that the targeted inhibition of FGFR3 could inhibit multiple signaling pathways *in vitro* and ameliorated fibrosis in different preclinical models of SSc. These findings may have direct translational implications as FGFR3 inhibitors are currently in development.

Disclosure of Interests: Debomita Chakraborty: None declared, Honglin Zhu: None declared, Astrid Juengel: None declared, Lena Summa: None declared,

Yi-Nan Li: None declared, Christina Bergmann: None declared, Alexandru-Emil Matei: None declared, Thuong Trinh-Minh: None declared, Chih-Wei Chen: None declared, Clara Dees: None declared, Andreas Ramming: None declared, Georg Schett Speakers bureau: AbbVie, BMS, Celgene, Janssen, Eli Lilly, Novartis, Roche and UCB, Oliver Distler Grant/research support from: Grants/Research support from Actelion, Bayer, Boehringer Ingelheim, Competitive Drug Development International Ltd. and Mitsubishi Tanabe; he also holds the issued Patent on mir-29 for the treatment of systemic sclerosis (US8247389, EP2331143)., Consultant of: Consultancy fees from Actelion, Acceleron Pharma, AnaMar, Bayer, Baecon Discovery, Blade Therapeutics, Boehringer, CSL Behring, Catenion, ChemomAb, Curzon Pharmaceuticals, Ergonex, Galapagos NV, GSK, Glenmark Pharmaceuticals, Inventiva, Italfarmaco, IQvia, medac, Medscape, Mitsubishi Tanabe Pharma, MSD, Roche, Sanofi and UCB, Speakers bureau: Speaker fees from Actelion, Bayer, Boehringer Ingelheim, Medscape, Pfizer and Roche, Jörg Distler Grant/research support from: Boehringer Ingelheim, Consultant of: Boehringer Ingelheim, Paid instructor for: Boehringer Ingelheim, Speakers bureau: Boehringer Ingelheim
DOI: 10.1136/annrheumdis-2020-eular.2915

Vasculitis

OP0143

CANCER IN GIANT-CELL ARTERITIS PATIENTS: A LARGE NATIONWIDE STUDY

N. Ben-Shabat¹, L. Dar^{2,3}, S. Tiosano^{2,3}, A. Watad^{1,2,3}, D. Comanesther⁴, A. Cohen⁴, H. Amital^{1,2,3}. ¹Tel-Aviv University, Sackler Faculty of Medicine, Tel-Aviv, Israel; ²Sheba Medical Center, Medicine B, Ramat-Gan, Israel; ³Sheba Medical Center, The Zabudowicz Center for Autoimmune Diseases, Ramat-Gan, Israel; ⁴Clalit Health Services, Chief Physician's Office, Tel-Aviv, Israel

Background: The association between giant-cell arteritis (GCA) and malignancy is controversial.

Objectives: To assess malignancy rates and risk in GCA patients in a large-scale population-based study.

Methods: We utilized the medical database of Clalit-Health-Services for this retrospective cohort study. Follow-up was from January 1, 2002 and continued until death or end of follow-up on September 1, 2018. Incident GCA patients were compared with age-and-sex-matched controls. Hazard-ratios for subtypes of malignancies were obtained by the Cox proportional-hazard model, adjusted for socio-demographic variables and cancer risk factors.

Results: The study population included 7,213 GCA patients and 32,987 age- and sex-matched controls who were not diagnosed with the disease. The mean age of GCA diagnosis was 72.3±9.9 years (median 73.1 years) and 69.1% were women. At Kaplan-Meier survival analysis, assessing cumulative cancer-free survival in GCA patients and controls, GCA patients had worse curve than controls (chi-squared = 49.84; degrees of freedom = 1; p < 0.0001; Figure 1). At the cox-survival analysis adjusted for age, sex, SES and cancer risk factors GCA patients showed increased risk for overall cancer (HR 1.29 [95%CI 1.20-1.39]),

Table 1. Cox survival analysis assessing crude and adjusted hazard for cancer in GCA patients compare to controls

Type of malignancy	Adjusted HR	
	HR	95% CI
Any malignancy	1.29	1.20, 1.39
Oropharyngeal cancer	0.96	0.69, 1.35
Thyroid cancer	1.20	0.66, 2.16
Breast cancer	0.93	0.75, 1.14
Lung cancer	1.26	0.99, 1.59
Esophagus cancer	1.86	0.93, 3.75
Stomach Cancer	0.61	0.37, 0.98
Colorectal Cancer	1.12	0.93, 1.36
Liver and bile ducts cancer	1.06	0.69, 1.62
Kidney cancer	1.60	1.15, 2.23
Bladder cancer	1.15	0.88, 1.50
Uterus cancer	0.85	0.55, 1.30
Cervical cancer of the uterus	0.45	0.37, 1.46
Ovary Cancer	0.96	0.58, 1.59
Prostate Cancer	1.07	0.80, 1.43
Sarcoma	2.14	1.41, 3.24
Melanoma	1.11	0.80, 1.55
Acute Leukemia	1.81	1.06, 3.07
Chronic Leukemia	1.82	1.19, 2.77
Myelodysplastic syndrome	1.84	0.94, 3.60
Hodgkin's Lymphoma	2.42	1.12, 5.20
Non-Hodgkin's Lymphoma	1.66	1.21, 2.29
Multiple Myeloma	2.40	1.63, 3.53