had consultancy relationship with and/or has received research funding from the following companies in the area of potential treatments for systemic sclerosis and its complications in the last three years: Research Grants: Kymera, Mitsubishi Tanabe, Boehringer Ingelheim, Przemyslaw Blyszczuk. None declared, Gabriela Kania: None declared.

DOI: 10.1136/annrheumdis-2023-eular.4605

POS0626
PERTURBED LIPID METABOLISM IS A CENTRAL METABOLIC REPROGRAMMING HUB IN SYSTEMIC SCLEROSIS

Keywords: Systemic sclerosis, -omics, Skin

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Background: Perturbed cellular metabolism has been increasingly associated with fibroblast activation in fibrosis. A deeper understanding of metabolic rewiring might help to unravel the interplay between the metabolic and fibrotic pathways in systemic sclerosis (SSc).

Objectives: We aimed to identify transcriptomic alterations in metabolic pathway-related genes in fibrotic SSc skin and unravel whether fibroblasts could contribute to the perturbed skin metabolic networks in SSc.

Methods: We integrated transcriptomic microarray data from skin (clinically affected forearm and non-affected back skin) of 76 SSc patients and 26 healthy controls (HC, forearm skin) from three distinct cohorts (GSE:45485, 59785, 92853/32413). Differentially expressed (DE) genes (FDR<0.05) between healthy and SSc skin were identified using the limma package. The supervised gene set enrichment analysis (GSEA) was based on DE genes using the clusterProfiler package, focusing on metabolic pathways. Transcriptional changes in skin in response to the TGFβ-induced changes in transcriptomes of primary human skin fibroblasts, measured by RNA-seq and scRNA-seq. For these experiments, cultured healthy skin fibroblasts were treated or not with TGFβ for 24h.

Results: Pathway enrichment analysis of DE gene in skin transcriptomes identified multiple alterations of metabolic pathways in SSc skin (Figure 1A) compared to healthy skin, pointing to enhanced pyrimidine/folate metabolism and suppressed lipid metabolism in SSc skin. Steroid hormone biosynthesis (AKR1, DHR51, CYP1A2, SULT2B1, HSD1, EHTM2, HSD11B2), fatty acid synthesis (FASN1, FADS1, FADS2, ELOVL, SCD5, PTP), and fatty acid degradation (ACAT1, ACADS, ACSA1/2, ACDAM, ACSL5) were the main downregulated lipid metabolism pathways in SSc skin, particularly in patients with the inflammatory intrinsic gene expression subset. The latter changes were detected in the affected and non-affected SSc skin, suggesting that altered lipid metabolism is a generalized feature of the SSc skin. Furthermore, pathway enrichment analysis of TGFβ-induced transcriptional changes in skin fibroblasts, as detected by RNA-seq and scRNA-seq, suggested that TGFβ-driven reprogramming could significantly contribute to the lipid metabolism perturbations in SSc skin (Figure 1B, C). Specifically, STRING analysis revealed that TGFβ suppressed metabolic networks of glycero sphingolipids, arachidonic acid, and fatty acids in cultured skin fibroblasts (Figure 1D).

Conclusion: Our data suggest perturbed lipid metabolic networks in SSc skin and identify skin fibroblasts, exposed to profibrotic milieu, as likely contributors to the altered lipid metabolism in SSc. These results might pave the way to a deeper understanding of the interplay between the metabolic and fibrotic pathways in SSc. Integrating these data with future metabolomic and single-cell studies could accelerate the discovery of potential metabolic targets in SSc.

Acknowledgements: We would like to acknowledge Foundation for Research in Rheumatology (FOREUM) and University Medical Centre Ljubljana for financial support.

Disclosure of Interests: Blaž Burja: None declared, Hubert Rehrauer: None declared, Dominique Paul: None declared, Michael Whitfield: None declared, Matija Tomsic: None declared, Ziga Rotar: None declared, Mark Robinson: None declared, Oliver Distler Speakers bureau: Bayer, Boehringer Ingelheim, Janssen, Medscape, Consultant for: 4P-Pharma, Abbvie, Acceleron, Alcimed, Altavant Sionces, Amgen, AnaMar, Arxx, AstraZeneca, Baecon, Blade, Bayer, Boehringer Ingelheim, Corbus, CSL, Behring, Galapagos, Glenmark, Horizon, Inventiva, Kymera, Lupin, Miltten Biotec, Mitsubishi Tanabe, MSD, Novartis, Prometheus, Redxpharma, Roivant, Sanofi and Topadur, Grant/research support from: Kymera, Mitsubishi Tanabe, Boehringer Ingelheim, Katja Lakota: None declared, Mojca Frank Bertonec: None declared.

DOI: 10.1136/annrheumdis-2023-eular.4637

POS0627
BLOOD-BASED PROTEIN BIOMARKERS ARE ASSOCIATED WITH SUBCLINICAL CARDIOVASCULAR ABNORMALITIES AS DEFINED BY CARDIOVASCULAR MAGNETIC RESONANCE IMAGING IN SYSTEMIC SCLEROSIS (SSC) PATIENTS

Keywords: Biomarkers, Systemic sclerosis, Cardiovascular disease

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Background: Systemic sclerosis-primary heart involvement (SSc-pHI) accounts for up to one-third of SSc-related deaths and clinically apparent pHi portends poor outcome. Early detection of SSc-pHi is therefore crucial. We have previously shown cardiovascular magnetic resonance (CMR)-detected subclinical myocardial abnormalities. Identifying robust blood biomarkers of SSc-pHi would facilitate diagnostic testing, help to resolve the biological mechanisms underpinning SSc-pHi and potentially identify new targets for drug development.

Objectives: To identify protein biomarkers associated with subclinical cardiovascular abnormalities as defined by CMR measures in SSc patients, and predominantly inflammatory and cardiometabolic pathways implicated.

Figure 1. A) Enriched metabolic pathways in SSc skin compared to healthy skin based on DE gene expression. Downregulated GO biological processes in TGFβ-treated cultured healthy skin fibroblasts based on RNAseq (B) and scRNAseq (C) analyses. D) STRING pathway enrichment analysis of downregulated genes (RNA-Seq) linked to lipid metabolism in TGFβ-stimulated skin fibroblasts.