of Rheumatology, University Medical Centre Ljubljana, Ljubljana, Slovenia;

⁴Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

Background: Immunopathology of giant cell arteritis (GCA) results from dysregulated interactions between arterial wall-resident non-immune cells, e.g. vascular smooth muscle cells (VSMCs), and components of the immune system [1]. In spite of several efforts at identifying microRNAs (miRNAs) implicated in the pathogenesis of GCA, the overall information on miRNA involvement in GCA and its related arterial fibro-sclerotic alterations remains scarce.

Objectives: To analyze miRNA expression and identify target genes of dysregulated miRNAs in temporal arteries from GCA patients, and to determine their association with GCA-associated arterial wall remodeling.

Methods: The study included formalin-fixed, paraffin-embedded temporal artery biopsies (TABs) from 71 clinically diagnosed treatment-naïve patients fulfilling the ACR 1990 classification criteria, and 22 non-GCA subjects (control group). Of GCA patients, 54 histologically positive and 17 histologically negative TABs were included. miRNA expression profiling was performed with quantitative real-time PCR (qPCR)-based miRNA PCR panels and qPCR. The miRDB database and STRING protein-protein network analysis were used for identification of miRNA gene targets and their pathway enrichment analysis, respectively.

Results: Of 356 detected miRNAs, we determined significant under-expression of 78 and significant over-expression of 22 miRNAs (≥ 2 -fold; $p < 0.05$) in TAB-positive GCA arteries compared to non-GCA controls, pointing to a strong dysregulation of miRNA expression in inflamed GCA arteries. Several dysregulated miRNAs targeted genes involved in the ubiquitin-proteasome system and the RNA silencing complex, suggesting a novel role of these pathways in GCA. qPCR validation confirmed a 1.9–14.2-fold ($p < 0.001$) over-expression of “pro-synthetic” (miR-21-3p/-21-5p/-146a-5p/-146b-5p/-424-5p) and 3.4–9.4-fold ($p < 0.001$) under-expression of “pro-contractile” (miR-23b-3p/-125a-5p/-143-3p/-143-5p/-145-3p/-145-5p/-195-5p/-365a-3p) VSMC phenotype-associated regulatory miRNAs in TAB-positive GCA arteries. These miRNAs targeted gene pathways involved in the arterial remodeling and regulation of the immune system, and their expression significantly correlated with the extent of intimal hyperplasia in TABs from GCA patients ($p \leq 0.015$). Additionally, the expression of miR-21-3p/-21-5p/-146a-5p/-146b-5p/-365a-3p differentiated TAB-negative GCA arteries from non-GCA temporal arteries, making these miRNAs potential biomarkers of GCA.

Conclusion: Our study demonstrated an extensive dysregulation of arterial miRNA networks in GCA, favoring the pathogenic switch in the VSMC phenotype and associated intimal hyperplasia. We identified several miRNAs, which could represent potential novel GCA biomarkers. Furthermore, our results imply that the ubiquitin-proteasome system and the RNA silencing complex are targets of dysregulated arterial miRNA networks in GCA lesions, providing new insight into the complexity of GCA pathogenesis.

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THU0007

INDIVIDUALIZED PATHWAY ANALYSIS FROM WHOLE BLOOD TRANSCRIPTOMIC IN SSC PATIENTS DEMONSTRATES UNIQUE CORRELATIONS WITH DISEASE SEVERITY

C. Bellocchi^{1,2}, M. Rossato³, G. Barturen⁴, G. Segatto¹, B. Vigone¹, Z. Makowska⁵, A. Buttgerit⁵, M. Kerick⁶, M. Alarcon-Riquelme⁴, J. Martin Ibanez⁶, L. Beretta¹. ¹Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Scleroderma Unit, Milano, Italy; ²University of Milan, Department of Clinical Sciences and Community Health, Milano, Italy; ³University of Verona, Department of Biotechnology, Verona, Italy; ⁴GENYO, Center for Genomics and Oncological Research: Pfizer, University of Granada, Andalusian Regional Government, Granada, Spain; ⁵Bayer AG, Berlin, Germany; ⁶Institute of Parasitology and Biomedicine López-Neyra, IPBLN-CSIC, Granada, Spain

Background: Genome-wide gene expression profiles and pathways analysis may help to discover deregulated processes underlying the pathogenesis of complex diseases or their phenotypic expression. Little or nothing is currently known about pathways associated with disease severity and damage in SS.

Objectives: To perform a whole blood transcriptome analysis and to characterize the individualized functional pathways associated with disease severity scores in SSc patients via a discovery and replication strategy.

Methods: Whole blood samples were collected in RNA stabilizers from a discovery and a replication cohort of 67 and 34 patients, respectively. RNAseq

data were generated by Illumina sequencing in two independent experiments pathways analysis was conducted according to the Functional Analysis of Individual Microarray Expression (FAIME) protocol (1). FAIME scores from Reactome pathways were correlated with the Scleroderma Clinical Trial Consortium Damage Index (SCTC-DI) total scores or with each of its two components (mortality and morbidity) as calculated from regression coefficient previously published (2). A non-parametric partial correlation analysis correcting the results for the use of steroids, immunosuppressants and disease duration was performed. Results independently associated with damage in both cohorts at the 0.1 level after 1000-fold permutation-testing were considered as significant and replicated.

Results: A total of 1116 pathways were analyzed. None of them was associated in both cohorts with the total SCTC-DI; similarly, no association was found with the SCTC mortality component. On the contrary, 26 pathways showed an independent and replicated association with the SCTC morbidity component, including platelet degranulation, the transcriptional activity of SMAD2/SMAD3, Toll Like Receptor 2 (TLR2) cascade and related intracellular signaling events involving MyD88, IRAK and NF- κ B, and the deregulation of selected transcription factors (TFAP2, E2F6).

Conclusion: Selected molecular events involving the innate immune system, signaling and platelet metabolism are associated with the morbidity component of the SCTC-DI in SSc patients, reflecting an irreversible loss of function in several organs and apparatus. The sensitivity of these associations to individual change in accrual damage is to be determined.

References:

- [1] PMID: 22291585; (2) PMID: 30928903

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THU0008

DEVELOPMENT OF A NOVEL TRANSLATIONAL IN SILICO INDICATION DISCOVERY FRAMEWORK: EXEMPLIFIED BY THE CLINICAL COMPOUND CENERIMOD

D. Hartl¹, M. Keller¹, A. Klenk¹, M. Murphy¹, M. Martinic¹, G. Pierlot¹, P. Groenen¹, D. Strasser¹. ¹Idorsia Pharmaceuticals Ltd, Allschwil, Switzerland

Background: To explore the full therapeutic spectrum of a drug it is crucial to consider its potential effectiveness in all diseases. Serendipitous clinical observations have often shown that approved drugs and those in development to be efficacious in indications different to those originally tested for. Traditional approaches to match a drug candidate with possible indications are mostly based on matching drug mechanistic knowledge with disease pathophysiology. Proof-of-concept trials or elaborate pre-clinical studies in animal models do not allow for a broad assessment due to high costs and slow progress. Gene expression changes in patients or animal models represent a good proxy to comprehensively assess both disease and drug effects. Furthermore, this data type can be integrated with a plethora of publicly available data.

Objectives: Generation of a novel in silico framework to support the selection and expansion of potential indications which associate with a compound or approved drug. The framework was exemplified by the clinical compound cenerimod, a potent, selective, and orally active sphingosine-1-phosphate receptor 1 modulator (Piali et al., 2017).

Methods: A total of ~13'000 public patient gene expression datasets from ~140 diseases were evaluated against cenerimod gene expression data generated in mouse disease models. To improve comparability of studies across platforms and species, computer algorithms (neural networks) were trained and employed to reduce noise within the data sets and improve signal. The predicted response to cenerimod for individual patients was contrasted against clinical patient characteristics.

Results: The neural network algorithm efficiently reduced experimental noise and improved sensitivity in the gene expression data. The results predicted cenerimod to be efficacious in several auto-immune diseases foremost SLE. Additionally, focused analysis on individual patients rather than disease cohorts revealed potential determinants predictive of maximal clinical response, with the highest predicted clinical response for cenerimod in patients with severe inflammatory endotype and/or high SLE Disease Activity Index (SLEDAI).

Conclusion: Combining preclinical compound data with the wealth of public disease gene expression data, provides great potential to support indication