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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

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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 SSC.

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

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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

selection. The novel in silico framework identified SLE as a prime potential indication for cenerimod and supported the cenerimod phase 2b clinical trial in patients with SLE (CARE study, NCT03742037).

References:

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THU0009 SYSTEMIC DEREGULATION OF LONG NON-CODING RNAs IN PATIENTS WITH SYSTEMIC SCLEROSIS AND THEIR ASSOCIATION WITH REGULATORS OF FIBROSIS.

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Background: Microvascular dysfunction is one of the major clinical challenges in systemic sclerosis (SSc) and mesenchymal transformation of the major event for microvascular dysfunction. Recent studies have shown epigenetic regulation of long non coding RNAs (lncRs) in different disease pathophysiology.

Objectives: To study the differential expressions of lncRs in patients with SSc and to study their associations with regulatory molecules of fibrosis

Methods: Peripheral Blood were collected from 15 diffused cutaneous SSc patients (dSSc) [ACR, 2013] and 10 age-sexes matched healthy controls. RNA was isolated from the peripheral blood & cDNAs were prepared and the Relative mRNA expressions were measured with respect to an endogenous control gene by real-time PCR. Protein expressions were measured by ELISA.

Results: Increased expression of MEG3, MALAT1 and NEAT1 (3.5, 3, 4fold respectively) has been found in SSc patients with respect to healthy individuals and they are mutually correlated (MEG3 and NEAT1: $r=0.9$, $p<0.0001$; MALAT1 and NEAT1: $r=0.7$, $p<0.0001$; MEG3 and MALAT1 $r=0.7$, $p<0.0001$). The expression of NEAT1 is significantly higher ($p=0.0009$) in case patients with disease duration (DD) >5 years compare to the patients with DD≤5 years. No significant difference was found in the expression of MEG3 and MALAT1 between these two subpopulations. Modified Rodnan's skin score (mRDSS): the clinical parameter of measuring fibrosis, was significantly up regulated ($p=0.004$) in patients with long disease duration (>5 years) and also have a positive correlation with DD ($r=0.2$, $p=0.2$) and the regulatory RNAs: MEG3 ($r=0.4$, $p=0.003$), MALAT1 ($r=0.2$, $p=0.2$), and NEAT1 ($r=0.3$, $p=0.009$).

The master regulator of fibrosis TGFβ which is significantly up regulated at both transcriptional ($p<0.0001$) and translational ($p=0.0009$) level has significant positive correlation with MEG3 ($r=0.3$, $p=0.02$), MALAT1 ($r=0.5$, $p=0.0005$), and NEAT1 ($r=0.3$, $p=0.006$). MEG3, MALAT1 and NEAT1 also have significant high correlation ($r=0.7$, $p<0.0001$; $r=0.6$, $p<0.0001$ and $r=0.7$, $p<0.0001$ respectively) with αSMA: the marker of fibroblast activation and the collagen-1 ($r=0.3$, $p=0.03$; $r=0.3$, $p=0.03$ and $r=0.3$, $p=0.03$ respectively).

In multivariate analysis MEG3 and NEAT1 together could explain 37.5% variability of fibrotic marker and NEAT1 alone could explain 35.5% of the same.

Conclusion: mRDSS probably does not reflect the underlying fibrotic process occurring sub-clinically, as no significant correlation was observed either with the disease duration or with the pro-fibrotic molecules (TGFβ, αSMA, and collagen1). The strong inter-correlation of NEAT1, MALAT1 and MEG3 suggest that any one of them might well be studied as specific marker of sub-clinical fibrosis. The long non coding RNAs (MALAT1, MEG3, NEAT1) better reflects the sub-clinical fibrosis occurring in the patients, suggested by strong correlation with fibrotic markers (TGFβ, αSMA, collagen1). The linear regression values suggest that NEAT1 could be an important biomolecule in SSc pathogenesis.

References:

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THU0010 GENES ASSOCIATED WITH NUCLEOTIDE OLIGOMERIZATION DOMAIN-LIKE RECEPTOR SIGNALING PATHWAY ARE UPREGULATED IN CUTANEOUS LUPUS ERYTHEMATOSUS

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Background: Cutaneous Lupus Erythematosus (CLE) is a disfiguring autoimmune skin disorder with several subtypes: discoid lupus, subacute cutaneous lupus, and acute cutaneous lupus. CLE is associated with defects in the adaptive immune system, and, at times, systemic involvement. The innate immune system is likely involved as seen in the presence of interface dermatitis, which is observed in viral exanthems, and improvement of CLE using inhibitors to membrane-bound Pattern Recognition Receptors.

Objectives: Compare the expression of genes associated with the innate immune system in active CLE skin lesions of different subtypes compared to normal skin controls.

Methods: Five datasets selected from the Gene Expression Omnibus (GEO) were analyzed using GEO2R to compare the gene expressions between different subtypes of CLE. Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) database, Gene Card, and Kyoto Encyclopedia of Genes and Genomes (KEGG) Pathway analysis were used to identify the interaction and function of specific genes.

Results: There were a total of 147 CLE skin samples and 52 normal controls. Genes associated with the Nucleotide-Binding Oligomerization Domain-Like Receptor (NLR) signaling pathway were upregulated in CLE skin samples (adjusted p-value < 0.001). Five genes associated with the NLR signaling pathway, STAT1, OAS1, OAS2, OAS3, and AIM2, were found to be upregulated in skin samples of CLE patients in all datasets, regardless of type, compared to normal controls in all datasets. These five genes are associated with transcription activation, regulation of viral infection, and interferon response.

Conclusion: Genes associated with the NLR signaling pathway are upregulated in the skin lesions of CLE patients compared to normal controls, supporting the role of the innate immune system in CLE. Further validation studies using experimental methods are needed.

References:

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THU0011 ANALYSIS OF METABOLIC STATUS IN CYBRIDS REVEALED IMPAIRED METABOLIC FLEXIBILITY IN OA PROCESS.

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Background: There are several metabolic pathways involved in cell metabolism, including glycolysis, tricarboxylic acid (TCA) cycle and fatty acid (FA) oxidation. Metabolic flexibility has previously described as the ability to respond or adapt to changes in metabolic demand; assessed by the ability to switch from fat to carbohydrate oxidation. In the last years there is a growing interest to assess the influence of metabolic flexibility, as a mechanism to explain how lipids can accumulate in the tissue. During OA, it has been established a relationship between mitochondrial dysfunction and cellular damage due to impairments in mitochondrial function and metabolic flexibility. Several studies have suggested that fatty acids may play an important role in OA development and progression.

Objectives: The aim of this work was to examine the differences in glucose and fatty acid metabolism, with special focus on metabolic flexibility, in cybrids from healthy (N) or OA donors.