Background: Immuno-pathology 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-naive 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 dysregulation of miRNA expression in inflamed GCA arteries. qPCR validation confirmed a 1.9–14.2-fold (p < 0.001) over-expression of several miRNAs (miR-23b-3p/-125a-5p/-143-3p/-145-5p/-146-5p/-365a-3p) in TAB-positive GCA arteries. These miRNAs targeted gene pathways involved in the arterial remodeling and regulation of the immune system, and their expression was significantly correlated with the extent of intimal hyperplasia in TABs from GCA patients (p ≤ 0.015). Additionally, the expression of miR-21-3p/-21-5p/-146a-5p/-146b-5p/-365a-3p decreased in 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.

References:

Acknowledgments: This work was supported by the Slovenian Research Agency [research core funding No. P3-0054].

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2020-eular.2282
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).


Disclosure of Interests: None declared

References:

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 was 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, ST14, 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.

Disclosure of Interests: None declared

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 micovascular dysfunction. Recent studies have shown epigenetic regulation of long non coding RNAs (IncRs) in different disease pathophysiology.

Objectives: To study the differential expressions of IncRs 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. 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).

Disclosure of Interests: None declared

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=0.7, p<0.0001; MALAT3 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 (mRSS): 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=0.02) and the regulatory RNAs: MEG3(r=0.4, p=0.003), MALAT1(r=0.2, p=0.02), and NEAT1(r=0.3, p=0.009).

Conclusion: mRSS 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=0.0006). MEG3, MALAT1 and NEAT1 also have significant high positive correlation with DD(r=0.7, p<0.0001; r=0.6, p<0.0001 and r=0.7,p<0.0001 respectively) with sSMA: the marker of fibroblast activation and the collagen-I (r=0.3, p=0.03; r=0.3, p=0.03 and r=0.3,p=0.03 respectively).

Disclosure of Interests: None declared

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