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


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THU0010 GENES ASSOCIATED WITH NUCLEOTIDE OXIDATION DEFICIENCY—SIMILARITY SIGNALING PATHWAY ARE UPREGULATED IN CUTANEOUS LUPUS ERYTHEMATOSUS

I. Calderón1, R. Mina2,1

SCDS, Cincinnati, United States of America; 1University of Cincinnati, Cincinnati, United States of America

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, STI1, 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:

Disclosure of Interests: None declared

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THU0009 SYSTEMIC Deregulation of Long Non-Coding RNAs in Patients with Systemic Sclerosis and Their Association with Regulators of Fibrosis.

D. Bhattacharjee1, S. Chatterjee1, S. Misra1, A. Saha1, P. Sinhamahapatra1

Department of Pharmacy, University of Oslo, Oslo, Norway

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, MALAT1and NEAT1 (3.5, 3, 4 fold 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; MALAT1and NEAT1: r=0.7, p<0.0001; MEG3 and MALAT1: r=0.7, p<0.0001).

Conclusion: Genes associated with the NLR signaling pathway are 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.

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2020-eular.5320

References:

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

A. Dalmaz-Fernandez1, J. Lund2, T. Hermida Gómez2, M. E. Vazquez Mosquera1, I. Rego-Perez1, F. J. Blanco1, M. Fernandez-Moreno1,2,3

1Grupo de Investigación en Reumatología. Instituto de Investigación Biomédica de A Coruña (INIBIC), Complexo Hospitalario Universitario de A Coruña (CHUAC), A Coruña, Spain; 2Section for Pharmacology and Pharmaceutical Biosciences, Department of Pharmacy, University of Oslo, Oslo, Norway; 3Centro de Investigación Biomédica en Red, Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN), Madrid, Spain

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 cyprids from healthy (N) or OA donors.

Disclosure of Interests: None declared

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References:
Methods: Cybrids were developed using 143B.TK Rho-0 cell line (nuclear donor) and platelets (mitochondrial donors) from healthy (N) and OA donors. Glucose and FA metabolism were measured using D-[14C(U)]glucose and [1-14C] oleic acid respectively. Metabolic flexibility was evaluated by co-culturing with glucose and oleic acid acutely by using inhibitors against glucose and FA oxidation. 20μM UK5099 and 10μM etomoxir, respectively. Incorporation of FA into lipid droplet (LD) was evaluated by thin layer chromatography and LD were stained by LDS40 and analyzed by confocal microscope and flow cytometry. Mitochondrial dynamics was measured by real-time PCR method. Percentage of mitochondrial Anion Superoxide (O$_2^-$) production was evaluated incubating cells with Mitosox® using Flow Cytometer. Appropriate statistical analyses were performed with GraphPad Prism v6.

Results: There were no changes in basal glucose metabolism between cybrids. N cybrids had higher acid-soluble metabolites, reflecting incomplete FA oxidation than OA cybrids. Comparing glucose and FA metabolism showed that both types of cybrids preferred to oxidize glucose. Co-culturing with glucose and Oleic acid, increased total cellular uptake and oxidation of glucose in N compared to basal condition (Figure-1) and in this condition the OA cybrids showed an increase in mitochondrial O$_2^-$ production. Inhibition of FA oxidation by etomoxir increased complete glucose oxidation of N cybrids but not in OA cybrids that had a preference to oxidize oleic acid compared to basal condition. Gene expression of mitofusin-2 (MFN2) was higher in N than OA cybrids under inhibiting conditions. Combine these data indicate that N cybrids are more metabolically flexible and have better adaptative response than OA. Cybrids presented different lipid distribution patterns. Lipid droplet (LD) formation increased in both groups incubated in presence of FA. Furthermore, N cybrids showed less LD formation than OA.

Conclusion: The results indicated that cybrids from OA patients had reduced metabolic flexibility compared to N cybrids. These results enhance our understanding of the mitochondria metabolism in OA, suggesting a mitochondrial dysfunction and impairment of metabolic flexibility during the OA process.

Figure 1. Effect of oleic acid in glucose metabolism. A. Scheme of substrate oxidation protocol: cybrids were cultured for 48 h in DMEM-glucose and glucose metabolism was evaluated using D-[14C(U)]glucose. B. Effect of 100 μM oleic acid compared to 5.5 mM glucose (basal) on glucose metabolism in N and OA cybrids. Values are presented as mean ± SEM relative to basal. * N versus OA cybrids (p<0.05, unpaired t test); b versus basal (lh p=0.05, paired t test).

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Table 1. Binary regression model comparing progressors pool vs. no-progress

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CI: confidence interval; OR: Odd Ratio; *: statistical significance declared at P ≤ 0.05