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).

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Disclosure of Interests: Dominik Hartl Shareholder of: Idorsia shares, Employee of: Idorsia employee, Marcel Keller Shareholder of: Idorsia options/shares, Employee of: Idorsia employee, Axel Klenk Shareholder of: Idorsia option/shares, Employee of: Idorsia employee, Mark Murphy Shareholder of: Idorsia shares and stock options, Employee of: Idorsia employee, Marianne Martinic Shareholder of: Idorsia options/shares, Employee of: Idorsia employee, Gabin Pierlot Shareholder of: Idorsia options/shares, Employee of: Idorsia employee, Peter Groenen Shareholder of: Idorsia options/shares, Employee of: Idorsia employee, Daniel Strasser Shareholder of: Idorsia options/shares, Employee of: Idorsia employee

DOI: 10.1136/annrheumdis-2020-eular.3520

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-I ($r=0.3$, $p=0.03$; $r=0.3$, $p=0.03$ 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.

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Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2020-eular.5486

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.

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Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2020-eular.6159

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.

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-[1-¹⁴C(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 LD540 and analyzed by confocal microscope and flow cytometry. Mitochondrial dynamics was measured by real-time PCR method. Percentage of mitochondrial Anion Superoxide (O₂⁻) 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 β-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 O₂⁻ 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

Figure -1. Effect of oleic acid in glucose metabolism. A. Scheme of substrate oxidation protocol: cybrids were cultured for 48 h in DMEM-glu/ole and glucose metabolism was evaluated using D-[1-¹⁴C(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 (bb p≤0.01, paired t test).

Disclosure of Interests: Andrea Dalmao-Fernandez: None declared, Jenny Lund: None declared, Tamara Hermida Gómez: None declared, Maria Eugenia Vazquez Mosquera: None declared, Ignacio Rego-Perez: None declared, Francisco J. Blanco Grant/research support from: Sanofi-Aventis, Lilly, Bristol MS, Amgen, Pfizer, Abbvie, TRB Chemedica International, Glaxo SmithKline, Archigen Biotech Limited, Novartis, Nichi-iko pharmaceutical Co, Genentech, Janssen Research & Development, UCB Biopharma, Centrexion Therapeutics, Celgene, Roche, Regeneron Pharmaceuticals Inc, Biohope, Corbus Pharmaceutical, Tedec Meiji Pharma, Kiniksa Pharmaceuticals, Ltd, Gilead Sciences Inc, Consultant of: Lilly, Bristol MS, Pfizer, Mercedes Fernandez-Moreno: None declared

DOI: 10.1136/annrheumdis-2020-eular.3620

THU0012

IMPACT OF RS12107036 POLYMORPHISM OF TP63 ON THE RISK OF RAPID PROGRESSIVE OSTEOARTHRITIS OF THE KNEE. DATA FROM THE OSTEOARTHRITIS INITIATIVE

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Background: There is a need to identify patients with the rapid progressive phenotype of Osteoarthritis (RPOA) to include them in clinical trials and to implement prevention strategies. During the last years, nuclear single nucleotide polymorphisms (SNPs) were associated with susceptibility and progression of the disease, but not with the rapid progression phenotype.

Objectives: Analyze the influence of previously knee OA-associated nuclear SNPs on the risk of RPOA in patients of the OAI.

Methods: Caucasian patients from the OAI were selected and assigned into three different groups (N=252/group) based on the following criteria:

A.rapid progressors; baseline KL grade 0-1 in at least one knee and increase up to KL≥ 3 during a 48-month period; or baseline KL grade 2 in at least one knee and increase up to KL 4 or total knee replacement during the follow-up.

B.no-rapid progressors; baseline KL grade 0-1 in at least one knee and increase up to KL 2 during 48-month period; or baseline KL grade 2 in at least one knee and increase up to KL 3 during the follow-up.

C.no-progressors; KL grade 0-2 at baseline in at least one knee and bilaterally stable during 48-month period.

Groups were re-categorized into two groups: non-progressors and progressors (pooling A and B). Nuclear SNPs were previously assigned by mini-sequencing techniques. Preliminary chi-square analyses and binary and multinomial logistic regression models adjusted by gender, age, body mass index (BMI), contralateral OA, previous injury in target knee and WOMAC pain, were performed with IBM SPSS Statistics v24.

Results: We analyzed the effect of 7 SNPs that had been strongly associated with knee OA susceptibility in different GWAS studies: rs11177, rs4730250, rs11842874, rs12107036, rs8044769, rs10948172 and rs143383. Chi-square analyses only showed differences in the frequency distribution of rs12107036 between groups (p=0,028), being the GG genotype over-represented in the rapid progressors group and the AA genotype in the non-progressors group (Figure 1). The binary logistic regression showed that G allele was significantly over-represented in the (pooled) progressors group when compared with non-progressors (p=0,008) (Table 1). And the multinomial logistic regression showed that, in

Figure 1. Frequency distribution of the rs12107036 genotypes among the different progression groups

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

Variables	p-value	OR	C.I. 95%	
			Min.	Max.
Age	0,217	1,012	0,993	1,030
Sex (Female)	0,000 [#]	2,049	1,478	2,842
BMI	0,000 [#]	1,085	1,044	1,127
Contralateral OA (Yes)	0,044 [#]	1,400	1,009	1,942
Previous Injury (Yes)	0,002 [#]	1,723	1,223	2,429
WOMAC pain	0,003 [#]	1,102	1,033	1,177
rs12107036 G (Yes)	0,008 [#]	1,682	1,148	2,463

CI: confidence interval; OR: Odd Ratio; [#]: statistical significance declared at P ≤ 0.05