subtypes is jointly associated with RNA transcripts or FAIME scores with strong differences in relation to the geographical origin of samples; neutrophils emerged as the major determinant of gene expression in SSC-whole-blood samples.

Conclusion: We discovered a set of differentially expressed genes and pathways that could be validated in two independent sets of SSC patients highlighting a number of deregulated molecular processes that have relevance for the pathogenesis of autoimmunity and SSC.

Figure:

Acknowledgments: This work was supported by EU/EFPIA/Innovative Medicines Initiative Joint Undertaking PRECISESADS grant No. 115565.

Disclosure of Interests: Lorenzo Beretta Grant/research support from: Pfizer, Guillermo Barturen: None declared, Barbara Vigone: None declared, Chiara Bellocchi: None declared, Nicolas Hunzelmann: None declared, Ellen Delanghe: None declared, László Kovács: None declared, Ricard Cervera: None declared, Maria Gerosa: None declared, Rafaela Ortega Castro: None declared, Isabel Almeida: None declared, Divi Cornec: None declared, Carlo Chizzolini Consultant of: Boehringer Ingelheim, Roche, Jacques-Olivier Pers: None declared, Zuzanna Makowska Employee of: Bayer AG, Anne buttgereit Employee of: Bayer AG, Ralf Lesche Employee of: Bayer, Martin Kerick: None declared, Marta Alarcon-Riquelme: None declared, Javier Martin Ibanez: None declared

DOI: 10.1136/annrheumdis-2020-eular.3788

OP0138

CLUSTERIN ASSOCIATES WITH DISEASE MECHANISMS AND INFLAMMATION IN MYOSITIS PATIENTS

T. Kropacková^{1,2}, L. Vernerová¹, H. Štorkánová^{1,2}, V. Horvathová^{1,2}, M. Vokurková¹, M. Klein^{1,2}, S. Oreska^{1,2}, M. Špiritović¹, B. Heřmáňková³, K. Kubínová^{1,2}, L. Andres Cerezo¹, O. Kryštůfková^{1,2}, H. Mann^{1,2}, J. Ukropec⁴, B. Ukropcová⁴, J. Zámečník⁵, M. Tomčík^{1,2}, J. Vencovský^{1,2}, L. Šenolt^{1,2}.

¹Institute of Rheumatology, Prague, Czech Republic; ²First Faculty of Medicine, Charles University, Department of Rheumatology, Prague, Czech Republic; ³Faculty of Physical Education and Sport, Charles University, Department of Physiotherapy, Prague, Czech Republic; ⁴Biomedical Research Center, Slovak Academy of Sciences, Institute of Experimental Endocrinology, Bratislava, Slovakia (Slovak Republic); ⁵2nd Medical School and University Hospital Motol, Charles University, Department of Pathology and Molecular Medicine, Prague, Czech Republic

Background: Idiopathic inflammatory myopathies (IIM, myositis) are a heterogeneous group of autoimmune muscle disorders characterized by skeletal muscle weakness and damage, inflammation and extramuscular manifestations. Recent findings suggest that immunological as well as nonimmunological processes, such as endoplasmic reticulum stress, hypoxia, mitochondrial and metabolic dysfunction are involved in the pathogenesis of IIMs [1]. Clusterin (CLU) has been reported to play a protective function in the development of tissue injury, inflammation and autoimmunity, and is involved in the maintenance of immune homeostasis [2].

Objectives: This study aimed to explore a potential involvement of the circulating and skeletal muscle expression of CLU in pathogenic mechanisms of IIM.

Methods: A total of 85 IIM patients and 86 healthy controls (HC) were recruited. In addition, 20 IIM patients and 21 HC underwent a muscle biopsy. Circulating concentrations of CLU were measured by ELISA. Serum cytokine profile of patients and HC was assessed by Cytokine 27-plex Assay. Immunohistochemical localisation of CLU was assessed in 10 IIM and 4 control muscle tissue specimens. The expression of CLU and myositis related cytokines in muscle tissue was determined by real-time PCR.

Results: We observed a significant increase of circulating CLU in all IIM patients compared to HC (86.2 (71.6-99.0) vs. 59.6 (52.6-68.4) µg/mL, $p < 0.0001$). Moreover, CLU serum levels were positively correlated with myositis disease activity assessment (MYOACT) ($r = 0.337$, $p = 0.008$), myositis intention-to-treat activity index (MITAX) ($r = 0.357$, $p = 0.004$) and global disease assessment evaluated

by physician ($r = 0.309$, $p = 0.015$). In addition to that, a multivariate redundancy analysis revealed a combined effect of serum CLU and cytokine profile (represented by cytokines and chemokines known to be involved in IIM) on disease activity measures. In muscle tissue, CLU mRNA was significantly increased in IIM patients compared to controls ($p = 0.032$) and correlated with IL-1β ($r = 0.489$, $p = 0.034$), IL-6 ($r = 0.581$, $p = 0.009$), TNF ($r = 0.485$, $p = 0.035$) and PGC-1α ($r = 0.709$, $p = 0.001$) mRNA. Immunohistochemistry revealed CLU accumulation in the cytoplasm of regenerating myofibers.

Conclusion: Our results show an up-regulation of clusterin in circulation and skeletal muscle of IIM patients that associates with disease activity and inflammation, and its specific expression in regenerating myofibers. Based on our data and the known cytoprotective function of CLU we suggest an attempt of the organism to limit further muscle damage induced by myositis disease mechanisms.

References:

- [1] Ernste FC, Reed AM. Idiopathic inflammatory myopathies: current trends in pathogenesis, clinical features, and up-to-date treatment recommendations. *Mayo Clin Proc.* 2013;88:83-105.
- [2] Savkovic V, Gantzer H, Reiser U, Selig L, Gaiser S, Sack U, et al. Clusterin is protective in pancreatitis through anti-apoptotic and anti-inflammatory properties. *Biochem Biophys Res Commun.* 2007;356:431-7.

Acknowledgments: This work was supported by GAUK 534217 and the Ministry of Health of the Czech Republic grants nr. 16-33746A and 16-33574A.

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2020-eular.6237

OP0139

FUNCTIONAL EVALUATION OF THE SJÖGREN'S SYNDROME AND SYSTEMIC LUPUS ERYTHEMATOSUS DDX6-CXCR5 RISK INTERVAL

M. M. Wiley¹, B. Khatri¹, K. L. Tessner¹, M. L. Joachims¹, A. M. Stolarczyk¹, A. Rasmussen¹, S. J. Bowman², L. Radfar³, R. Omdal⁴, M. Wahren-Herlenius⁵, B. M. Warner⁶, T. Witte⁷, R. Jonsson⁸, M. Rischmüller⁹, P. M. Gaffney¹, J. A. James¹, L. Ronnblom¹⁰, R. H. Scofield³, X. Mariette¹¹, W. F. Ng¹², K. L. Sivils¹, G. Nordmark¹⁰, B. Tsao¹³, C. Lessard¹. ¹Oklahoma Medical Research Foundation, Oklahoma City, United States of America; ²University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom; ³University of Oklahoma, Oklahoma City, United States of America; ⁴University of Bergen, Bergen, Norway; ⁵Karolinska Institute, Stockholm, Sweden; ⁶National Institute of Dental and Craniofacial Research, Bethesda, United States of America; ⁷Hannover Medical School, Hannover, Germany; ⁸Haukeland University Hospital, Bergen, Norway; ⁹University of Adelaide, Adelaide, Australia; ¹⁰Uppsala University, Uppsala, Sweden; ¹¹Université Paris-Saclay, Le Kremlin Bicêtre, France; ¹²NHR Biomedical Research Centre, Newcastle upon Tyne, United Kingdom; ¹³Medical University of South Carolina, Charleston, United States of America

Background: Sjögren's Syndrome (SS) and Systemic Lupus Erythematosus (SLE) are distinct chronic, complex autoimmune diseases with shared characteristics such as autoantibodies, heightened interferons, and polyarthritis. SS and SLE genome-wide association studies (GWAS) report strong associations with the DDX6-CXCR5 risk interval. DDX6 suppresses interferon stimulated gene expression and CXCR5 regulates T cell functions implicated in autoimmunity.

Objectives: To identify functional variants that impact regulation in the DDX6-CXCR5 interval.

Methods: Fine-mapping was done using ImmunoChip data from 3785 SLE, 1916 SS cases and 6893 population controls of European ancestry that were imputed and tested for SNP-trait association. Bayesian statistics assigned posterior probabilities to SNPs and defined a credible set of risk variants. Bioinformatic analyses further prioritized variants with predicted functionality. Electrophoretic mobility shift assays (EMSAs) and luciferase expression were used to validate predicted SNPs in EBV transformed B (EBV B) cells.

Results: While some differences were observed, the overall SS and SLE association signals were similar. SNP-SS rs9736016 near CXCR5 and SNP-SLE rs76409436 near DDX6 were the most significant but did not show evidence of functionality. Bayesian statistics defined credible sets of variants in strong D' in common between both SS and SLE. Bioinformatics analyses (Haploreg, RegulomeDB, ENCODE data, etc) further refined the credible set and identified 5 common SNPs with strong evidence of functionality in immune cell types: rs4938572, rs4936443, rs57494551, rs7117261 and rs4938573. EMSAs showed a significant increase in protein binding to the risk allele of rs57494551 ($p=0.0001$), rs7117261 ($p=0.0001$) and rs4938573 ($p=0.0003$), but not the others, using nuclear lysates from EBV B cells. Luciferase vectors with a minimal promoter or no promoter were used to test for enhancer or promoter activity, respectively. To this end, the rs57494551 risk allele exhibited a significant increase in enhancer activity ($p=0.0001$). In contrast, the rs7117261 risk allele decreased enhancer activity