Results: 345 samples were obtained from patients in remission. 28.6% of the patients in *clinical remission on treatment* (requiring clinical SELENA-SLEDAI = 0, positive anti-dsDNA antibodies and/or C3 decrease and prednisone intake 1 – 5 mg/day) had an abnormal serum IFN α level, compared to 6.5% of the patients in *complete remission on treatment* (requiring clinical SELENA-SLEDAI = 0, no anti-dsDNA antibodies nor C3 decrease and prednisone intake 1 – 5 mg/day). In patients in remission, high serum IFN α levels at baseline were associated in multivariable analysis with the positivity of anti-dsDNA Abs (HR 3.4 [95%CI 1.6-7.2], $p=0.0001$) and anti-RNP Abs (HR 3.2 [95%CI 1.5-6.8], $p=0.0002$). In patients in remission, high serum IFN α level at baseline was a significant and independent risk factor of lupus flare (HR=4.8 [95%CI 2.3-9.7], $p<0.0001$). Low C3 was also associated with the risk of relapse with a HR=3.2 [95%CI 1.4-7.0], $p=0.005$, but positive anti-dsDNA Abs was not (HR=1.8 [95%CI 0.9-3.6], $p=0.1$). **Conclusion:** A large number of SLE patients in remission display abnormal levels of serum IFN α . Abnormal levels of serum IFN α in patients in remission were significantly associated with positive anti-dsDNA and anti-RNP Abs and were an independent predictive biomarker of lupus flare in the following year. Adding serum IFN α to the routine laboratory assessments perform in patient in remission could help clinicians to identify a subgroup of SLE patient clinically in remission but serologically active and at higher risk of relapse.

REFERENCES:

- [1] Mathian A, et al. Monitoring disease activity in systemic lupus erythematosus with single-molecule array digital ELISA quantification of serum interferon- α . *Arthritis Rheumatol* Hoboken NJ. 2018 Dec 3;
- [2] Vollenhoven R, et al. A framework for remission in SLE: consensus findings from a large international task force on definitions of remission in SLE (DORIS). *Ann Rheum Dis*. 2017 Mar 1;76(3):554–61.

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2019-eular.5640

THU0228

EXPRESSION OF APOBEC FAMILY MEMBERS AS REGULATORS OF ENDOGENOUS RETROELEMENTS AND MALIGNANCY IN SYSTEMIC LUPUS ERYTHEMATOSUS AND SJÖGREN'S SYNDROME

Clio Mavragani^{1,2,3,4}, Kyriakos Kirou¹, Adrianos Nezos², Surya V. Seshan⁵, Teresa Wild⁶, Sharon M. Wahl⁶, Haralampos M. Moutsopoulos⁷, Mary K. Crow¹. ¹Hospital for Special Surgery, Weill Cornell Medical College, Mary Kirkland Center for Lupus Research, New York, United States of America; ²Medical School, National and Kapodistrian University of Athens, Department of Physiology, Athens, Greece; ³Medical School, National and Kapodistrian University of Athens, Department of Pathophysiology, Athens, Greece; ⁴Joint Academic Rheumatology Program, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece; ⁵Weill Cornell Medical College, Department of Pathology, New York, NY, United States of America; ⁶National Institute of Dental and Craniofacial Research (NIDCR), NIH, Bethesda, MD, United States of America; ⁷Academy of Athens, Athens, Greece

Background: Activation of type I and II interferon (IFN) pathways contributes to the pathogenesis of systemic autoimmune diseases. We have previously shown increased expression of the LINE-1 (L1) endogenous retrotransposon in systemic lupus erythematosus (SLE) kidneys and in minor salivary glands (MSG) from primary Sjögren's syndrome patients (SS) that strongly correlates with IFN α expression in the same tissues. Moreover, an imbalance between type I and II IFNs in SS salivary gland tissues has been related to non-Hodgkin's lymphoma (NHL) development. Members of a family of retroviral resistance factors (APOBECs) have been implicated in L1 control and are regulated by both type I and II IFNs.

Objectives: We investigated whether these mechanisms are involved in the response to inappropriate expression of L1 retroelements in primary SS and SLE, as well as in SS related lymphomagenesis.

Methods: MSG and kidney biopsy specimens were obtained from 41 patients with primary SS and 23 patients with SLE, respectively. Peripheral blood mononuclear cells (PBMC) and sera were also collected from 73 SLE patients. Relative mRNA expression was quantified by real-time polymerase chain reaction for full-length L1 transcripts, along with members of the APOBEC family [APOBEC3A, APOBEC3B, APOBEC3G, AID (activation-induced cytidine deaminase)] and IFN α and γ transcripts. Type I IFN activity was assessed in lupus plasma by a reporter cell assay. The induction of APOBEC3A and B by IFN α in healthy control PBMCs was also assessed.

Results: APOBEC3A, previously implicated in control of endogenous retroelements, was increased in SS MSG and lupus nephritis kidney tissues and in SLE PBMC and strongly correlated with L1 retroelement expression in both SS and SLE tissues. APOBEC3A was also associated with IFN α mRNA expression in SS MSG tissues and lupus kidneys and with type I IFN activity in lupus plasma. While APOBEC3A expression was induced by IFN α , such a relationship was not observed with APOBEC3B. Moreover, a strong correlation was detected between AID and APOBEC3G with IFN γ expression in SS MSG tissue, a relationship particularly relevant to development of NHL.

Conclusion: Increased expression of APOBEC3A reflects a host-intrinsic and IFN α -dependent mechanism regulating potentially harmful L1 retroelements in patients with SS and SLE. Moreover, IFN γ -related induction of APOBEC3G, together with AID, might contribute to SS-related lymphomagenesis by increasing mutational load or epigenetic alterations. These data reveal a previously unappreciated role of APOBEC family proteins in the pathogenesis of autoimmune disorders.

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2019-eular.6152

THU0229

AMPHIREGULIN ATTENUATES LUPUS NEPHRITIS VIA SUPPRESSION OF PRO-INFLAMMATORY T-CELL FUNCTIONS IN AN ANIMAL MODEL OF SLE

Simon Melderis¹, Matthias Warkotsch¹, Julia Hagenstein¹, Georg Hermstadt¹, Gisa Tiegs², Oliver Steinmetz¹. ¹University Medical Center Hamburg-Eppendorf, III. Department of Medicine, Hamburg, Germany; ²University Medical Center Hamburg-Eppendorf, Experimental Immunology and Hepatology, Hamburg, Germany

Background: Amphiregulin (AREG) is a member of the epidermal growth factor (EGF) family and plays a role in development, tissue homeostasis and tumorigenesis. Recently, however, AREG has also emerged as novel player in immunity. Interestingly, AREG expression was shown to be one of the most highly upregulated transcripts in peripheral blood leukocytes of patient with systemic lupus erythematosus (SLE) [1]. The functional role of AREG in SLE, and inflammation in general, remains unclear to date and both, pro- and anti-inflammatory functions have been postulated [2, 3].

Objectives: Our aim was to investigate the role of AREG in the mouse model of pristane induced lupus (PIL) with particular focus on lupus nephritis (LN). We further wanted to identify target cells and mechanisms by which AREG exerts its immunomodulatory effects.

Methods: PIL was induced in AREG knock-out (KO) mice and wild type controls. Animals were sacrificed at pre-specified time points. Renal histology, immune complex deposition, leukocyte influx and mRNA expression levels were analyzed. Furthermore, broad in vivo and in vitro analyses of renal and systemic immune responses were carried out.

Results: Renal AREG mRNA expression significantly increased during development of LN, indicating functional relevance. Indeed, lupus nephritis was significantly aggravated in AREG-KO mice both at early (9 months) and later (12 months) stages after PIL induction. In line with this, we noted an increased deposition of immune complexes and renal influx of pro-inflammatory leukocytes (CD3⁺ T-cells, macrophages and neutrophils). In addition, we found the CD4⁺ T-cells of AREG-KO mice to have a more pro-inflammatory phenotype with significantly increased production of pro-inflammatory cytokines (IFN γ and IL-17A) both in ex-vivo culture, as well as FACS-analyses of nephritic kidneys. Mechanistically, we found that AREG treatment of spleen cell cultures potently suppressed cytokine production. More detailed evaluation by further in-vitro studies indicated, that AREG can directly suppress cytokine production by effector CD4⁺ T-cells as well as enhance the suppressive capacity of FoxP3⁺ regulatory T-cells (Tregs).

Conclusion: These data show that AREG has a protective role on development of LN induced by pristane, which might be therapeutically exploited. Our results further suggest, that direct effects on CD4⁺ T-effector cells, as well as indirect effects via Tregs, are two mechanisms by which AREG exerts its protective role.

REFERENCES:

- [1] Ishii, T., et al., *Isolation and expression profiling of genes upregulated in the peripheral blood cells of systemic lupus erythematosus patients*. *DNA Res*, 2005. 12(6): p. 429-39.
- [2] Kefaloyianni, E., et al., *ADAM17 substrate release in proximal tubule drives kidney fibrosis*. *JCI Insight*, 2016. 1(13).
- [3] Zaiss, D.M., et al., *Amphiregulin enhances regulatory T cell-suppressive function via the epidermal growth factor receptor*. *Immunity*, 2013. 38(2): p. 275-84.

Disclosure of Interests: None declared
DOI: 10.1136/annrheumdis-2019-eular.2264

THU0230 TNF- α PROMOTER POLYMORPHISMS (G-308A AND G-238A) ARE ASSOCIATED WITH SUSCEPTIBILITY TO SLE: A HOSPITAL-BASED CASE-CONTROL INVESTIGATION

MOHAPATRA DEBASISH¹, Rina Tripathy², Aditya Kumar Panda³, Manoj Kumar Parida¹, Saumya Ranjan Tripathy⁴, Bidyut Kumar Das⁵. ¹S.C.B. MEDICAL COLLEGE, Cuttack, Medicine, Cuttack, India; ²S.C.B. Medical College, Biochemistry, Cuttack, India; ³Khallikote University, Life Sciences, Brahmapur, India; ⁴S.C.B. Medical college, Cuttack, Rheumatology, Cuttack, India; ⁵S.C.B. Medical college, Medicine, Cuttack, India

Background: Tumour necrosis factor- α (TNF- α) is a proinflammatory cytokine associated with various autoimmune disorders¹. High levels of TNF- α has been reported in systemic lupus erythematosus (SLE)². Two functional common polymorphisms (G-238A and G-308A) at promoter region of TNF- α gene have been linked to SLE susceptibility in different populations^{3,4}.

Objectives: To investigate association of TNF- α (G-238A and G-308A) polymorphisms with susceptibility/resistance to SLE.

Methods: A total of 102 female SLE patients and 112 age and sex matched healthy controls were enrolled in the study. Patients were examined in detail, physical findings recorded and SLEDAI 2K calculated to assess disease severity. TNF- α polymorphisms (G-238A & G-308A) were typed by polymerase chain reaction and restriction length polymorphism (PCR-RFLP). Plasma level of TNF- α was quantified by ELISA. Statistical analysis was carried out using GRAPH PAD PRISM -7.01.

Results: Mean age of SLE patients and healthy controls was 27.84 $\pm$ 8.83 and 29.56 $\pm$ 5.48 years, respectively. At the time of enrolment, mean disease duration of patients was 2.07 $\pm$ 1.13 years. The mean SLEDAI 2K of patients was 16.07 $\pm$ 7.66. The prevalence of heterozygous mutant and minor allele of TNF- α (G-238A) polymorphisms were significantly higher in SLE patients compared to healthy controls (GA: P=0.04, OR=2.16; A: P=0.02, OR: 2.09). Furthermore, heterozygous (GA) and minor allele (A) of TNF- α (G-238A) polymorphism were associated with susceptibility to lupus nephritis (GA: P=0.02, OR=2.89; A: P=0.001, OR: 2.92). SLE patients displayed higher levels of plasma TNF- α compared to healthy controls. Although the prevalence of heterozygous mutant and minor allele of TNF- α (G-308A) polymorphism was higher in SLE patients, it was not statistically significant. TNF- α (G-238A and G-308A) variants were associated with higher plasma TNF- α in both SLE patients and healthy control. However, no significant association was observed on distribution of TNF- α polymorphisms (G-238A and G-308A) with severity of disease activity of SLE patients.

Conclusion: The results of the present study demonstrate that TNF- α (G-238A) variant is associated with higher plasma TNF- α level and increased susceptibility to development of SLE and lupus nephritis.

REFERENCES:

- [1] Aggarwal BB, Gupta SC, Kim JH. Historical perspectives on tumor necrosis factor and its superfamily: 25 years later, a golden journey. *Blood*. 2012;119(3):651–665.
- [2] Studnicka-Benke A, Steiner G, Petera P, Smolen JS. Tumour necrosis factor alpha and its soluble receptors parallel clinical disease and autoimmune activity in systemic lupus erythematosus. *Br J Rheumatol*. 1996;35(11):1067–1074.
- [3] D'Alfonso S, Colombo G, Della Bella S, Scorza R, Momigliano-Richiardi P. Association between polymorphisms in the TNF region and systemic lupus erythematosus in the Italian population. *Tissue Antigens* 1996;47(6):551–555.
- [4] Lee YH, Harley JB, Nath SK. Meta-analysis of TNF-alpha promoter-308 A/G polymorphism and SLE susceptibility. *Eur J Hum Genet*. 2006;14:364–371.

Disclosure of Interests: None declared
DOI: 10.1136/annrheumdis-2019-eular.5559

THU0231 GELSOLIN A NEW BIOMARKER OF DISEASE ACTIVITY IN SLE PATIENTS ASSOCIATED WITH HDL-C

Sandra Parra^{1,2}, Mercedes de Las Heras³, Pol Herrero⁴, Nuria Amigó⁵, Esperanza Garcés¹, Josepa Girona³, Xavier Correig³, Nuria Canela⁴, Antoni Castro^{1,2}. ¹"Sant Joan" University Hospital, Internal medicine department. Autoimmune diseases unit, Reus, Spain; ²Institut Investigacions Sanitàries Pere i Virgili, Reus, Spain; ³Universitat Rovira i Virgili, Unitat de Recerca de Lipids i Arteriosclerosis (URLA), Reus, Spain; ⁴Universitat Rovira i Virgili, Centre for Omic Science, Joint Unit, Reus, Spain; ⁵Universitat Rovira i Virgili, Department of Electronic Engineering, Reus, Spain

Background: Recent proteomics techniques have demonstrated that high-density lipoprotein (HDL) associated proteins are involved in functions related to systemic inflammatory and immune responses in several pathological conditions, including autoimmune diseases. HDL undergoes structural and functional modifications in systemic lupus erythematosus (SLE) patients.

Objectives: To identify potential biomarkers of disease activity analyzing the proteome of HDL particles from SLE patients in clinical remission and when they develop a flare compared to a healthy control group.

Methods: Quantitative proteomic analyses of purified HDL were performed using Tandem Mass Tag (TMT) isobaric tag-labeling and nanoLC-Orbitrap (nLC-MS/MS) from 9 SLE patients in clinical remission when they developed a flare and from 9 healthy controls (9-9-9). We verified the identified proteins by Western blot and ELISA in a cohort of 104 SLE women patients, 46 healthy women and 14 SLE patients when developed a flare.

Results: A total of 83 proteins associated with HDL were identified. We found 17 proteins with a significant fold-change (>1.1) compared with their levels in control patients. In lupus patients experiencing a flare compared with those in remission, we identified 4 proteins with a significant fold-change (C4, Indian Hedgehog protein, S100A8 and gelsolin). Plasma Gelsolin (pGSN) levels were decreased in the 104 SLE patients (176.02 (74.9) mcg/l) compared with the control group (217.13(86.7)mcg/l); p = 0.005 and when they developed a clinical flare (104.84(41.7)mcg/l); p = 0.002). pGSN levels were associated with HDL-c levels (r = 0.316, p < 0.001). Antimalarial treated patients showed significant higher levels of pGSN (214.56(88.94)mcg/l respect 170.35(66.36) mcg/l); p = 0.017.

Conclusion: The proteome cargo from HDL differentiates SLE patients from healthy controls. HDL from SLE patients carries proteins that are involved in the activation of the immune system. Decreased pGSN are associated with clinical disease activity in SLE patients. Antimalarial treatment and HDL-c are associated with higher levels of pGSN in SLE patients. pGSN is a potential biomarker of disease activity in SLE patients.

Disclosure of Interests: None declared
DOI: 10.1136/annrheumdis-2019-eular.5958

THU0232 DIFFERENTIAL METHYLATION OF IL8 AND TISSUE FACTOR PROMOTER IN ANTIPHOSPHOLIPID SYNDROME

Markos Patsouras, Karagianni Panagiota, Paraskevi Kogionou, Panayiotis Vlachoyiannopoulos. National and Kapodistrian University of Athens, Pathophysiology, Athens, Greece

Background: Antiphospholipid syndrome (APS) is an autoimmune thrombophilia characterized by recurrent thromboembolism and/or pregnancy morbidity in the presence of Antiphospholipid antibodies mainly anti- β 2glycoprotein I (anti- β 2GPI), which lead to monocyte and endothelial cell activation and subsequent tissue factor and proinflammatory cytokine expression such as IL-6 and IL-8 (1). Epigenetics describes changes in gene expression without alterations in the genomic sequence. Methylation of DNA at CpG islands by adding a methyl group to the nucleotide cytosine, is one of main epigenetic mechanisms.

Objectives: To explore the possible differential methylation of IL8 and Tissue Factor (F3) gene promoters, which are critical for the pathophysiology of APS.

Methods: Whole blood and serum were isolated from 27 APS patients and 25 healthy donors (HDs). Human umbilical vein endothelial cells (HUVECs) and peripheral blood monocytes were isolated from 3 HDs. Anti- β 2GPI IgG was isolated and pooled from 8 APS patients. HUVECs and monocytes were stimulated with a mixture of IgG, β 2GPI and CXCL4. Then mRNA was isolated and qPCR was performed for the assessment of IL8 and tissue factor (F3) gene expression. Whole blood DNA from APS patients and HDs, and DNA from the *in vitro* experiments was isolated and bisulphite treated. The methylation of 1CpG in the