thrombolytic pathways, the induction of DAH by pristane was unaffected by the absence of plasminogen activator inhibitor1 or tissue plasminogen activator, suggesting that protection is related to the action of Serp-1 on macrophage function.

Conclusions Serp-1 blocks pristane-induced lung hemorrhage by enhancing LXR-regulated M2 macrophage polarization and Klf4-regulated IL-10 production. In view of the similarities between DAH in pristane-treated mice and SLE patients, clinical trials of Serp-1 for DAH in SLE may be warranted. Since Serp-1 treatment increases expression of the reverse cholesterol transporter ABCA1, it also may have beneficial effects on atherosclerosis in SLE patients. Supporting the feasibility of future clinical studies in SLE, Serp-1 treatment reduced myocardial damage in patients with acute coronary syndrome.

Acknowledgments This work was supported by NIH grant R01-AR44731. We are grateful to Dr. Alexandra Lucas (Arizona State University) for providing recombinant Serp-1 protein.

702 PRISTANE INDUCED LUPUS IN HDAC6-MICE

Christopher M Reilly. *Edward Via College of Osteopathic Medicine, Blacksburg, Virginia, USA*

10.1136/lupus-2021-lupus21century.37

Background We and others have reported that selective histone deacetylase 6 (HDAC6) inhibition decreases inflammation in a variety of animal models including inflammatory arthritis and lupus. In this study, we explored whether HDAC6 gene deletion could affect pristane-induced lupus.

Methods C57BL/6 (w.t.) and HDAC6$^{-/-}$ C57BL/6 mice were given 0.5 ml of pristine intraperitonealy (ip) at 3 months of age. Injection of pristane induces a lupus-like syndrome whose pathogenesis implicates the secretion of type I IFN by CD11b (+) Ly6C(high) inflammatory monocytes in a TLR7-dependent fashion. Two weeks after pristane administration the mice were euthanized and assessed for various parameters of inflammation. At termination of the experiment, serum, peritoneal macrophages, and splenic tissue was collected and evaluated.

Results The pristine treated animals euthanized showed diffuse alveolar hemorrhage, both w.t. and knock-outs. At sacrifice, spleens were significantly larger in the HDAC6$^{-/-}$ mice compared to the w.t. pristine mice, however when compared to body weights there was not a significant difference. Flow cytometry did not indicate any differences in T cell or B cell populations. Sera IL-12, IL-6, TGF-β, IL-10, and TNF-α were comparable in the w.t. and the knock-out animals treated with pristine. Peritoneal recruitment of CD11b(+) Ly6C(high) inflammatory monocytes in HDAC6$^{-/-}$ mice was significantly increased compared to the w.t. mice. Evaluation of the transcripts for several IFN inducible genes revealed significantly increased IRF-7 expression in the HDAC6$^{-/-}$ mice however lower expression of IFN β and IRF-9.

Conclusions Taken together, our results show that in early lupus induction with pristine, HDAC6 gene deletion alters monocyte activation and differentially regulates IFN inducible genes.

800 – Pharmacoepidemiology

801 FACTORS ASSOCIATED WITH SLE FLARES AFTER HCQ TAPER, DISCONTINUATION OR MAINTENANCE IN THE SLICC INCEPTION COHORT: LOWER EDUCATION LINKED WITH HIGHER FLARE RISK

[1]Celline C Almeida-Brasil, [2]John G Hanly, [3]Murray B Urowitz, [4]Ann E Clarke, [5]Rosalind Ramsey-Goldman, [6]Caroline Gordon, [7]Michelle A Petri, [8]Ellen M Ginzler, [9]Daniel J Wallace, [10]Sang-Cheol Bae, [11]Juanita Romero-Diaz, [12]Mary Anne Dooley, [13]Christine A Peschken, [14]David A Isenberg, [14]Anisur Rahman, [15]Susan Manzi, [16]Soren Jacobsen, [17]Sam Lim, [18]Ronald van Vollenhoven, [19]Ola Nived, [19]Andreas Jonsen, [20]Diane L Kamen, [21]Cynthia Aranow, [22]Guillermo Ruiz-Irastorza, [3]Jorge Sanchez-Guerrero, [3]Dafna D Gladman, [23]Paul R Fortin, [24]Graciela S Alarcón, [25]Joan T Merrill, [26]Kenneth C Kalunian, [27]Manuel Ramos-Casals, [28]Kristjan Steinsson, [29]Asad Zoma, [30]Anca Askanase, [31]Munther A Khamashta, [32]Ian Bruce, [33]Murat Inanc, [1]Sasha Bernatsky*. *[1]Research Institute of the McGill University Health Centre, Canada; [2]Queen Elizabeth II Health Sciences Centre, Canada; [3]University of Toronto, Canada; [4]University of Calgary, Canada; [5]Northwestern University, USA; [6]Institute of Inflammation and Ageing of the University of Birmingham, UK; [7]Johns Hopkins University School of Medicine, USA; [8]SUNY Downstate Medical Center, USA; [9]Cedars-Sinai Medical Centre, USA; [10]Hanyang University Hospital for Rheumatic Diseases, South Korea; [11]Instituto Nacional de Ciencias Médicas y Nutrición, Mexico; [12]UNC Kidney Centre, USA; [13]University of Manitoba, Canada; [14]University College London, UK; [15]Allegheny Health Network, USA; [16]Rigshospitalet, Denmark; [17]Emory University School of Medicine, USA; [18]University of Amsterdam, Netherlands; [19]Lund University, Sweden; [20]Medical University of South Carolina, USA; [21]Feinstein Institute for Medical Research, USA; [22]Hospital Universitario Cruces, Spain; [23]Université Laval, Canada; [24]University of Alabama at Birmingham, USA; [25]Oklahoma Medical Research Foundation, USA; [26]UC San Diego School of Medicine, USA; [27]Universitat de Barcelona, Spain; [28]Landspitali University Hospital, Iceland; [29]Hairmyres Hospital, UK; [30]Columbia University Medical Centre, USA; [31]St Thomas' Hospital, UK; [32]University of Manchester, UK; [33]Istanbul University, Turkey*

10.1136/lupus-2021-lupus21century.38

Background Hydroxychloroquine (HCQ) is a cornerstone treatment of systemic lupus erythematosus (SLE). We compared time to flare in SLE patients discontinuing/reducing HCQ versus those maintaining their dose, and identified factors associated with time to flare.

Methods We analyzed prospective data from the Systemic Lupus International Collaborating Clinics (SLICC) cohort, which includes SLE patients from 33 sites in Europe, Asia, and North America, enrolled within 15 months of diagnosis and followed annually (1999-2019). We identified patients with HCQ reduction/discontinuation, regardless of disease activity. We evaluated person-time that patients contributed on their initial dose ('maintenance'), comparing this to person-time contributed after a first dose reduction, and person-time after a first HCQ discontinuation. We estimated time to first flare, defined as either subsequent need for therapy augmentation (steroids or other immunomodulators), increase of ≥4 points in the SLE Disease Activity Index-2000 (SLEDAI-2K) or hospitalization for SLE. We estimated crude flare rates for each sub-cohort and hazard ratios and 95% confidence intervals (CIs) for various demographic and clinical factors potentially associated with flare risk in the reduction and discontinuation sub-cohorts, as well as comparator maintenance sub-cohorts (matched for time on HCQ to the reduction and discontinuation sub-cohorts).

Results We studied 1460 SLE patients (90% women, 52% Caucasian) on HCQ. Of these, 592 subsequently reduced HCQ at any point, while 407 discontinued HCQ at any point. The crude flare rate for the HCQ reduction sub-cohort was 42.3 per 100 person-years (95% CI 38.6, 46.4), versus 35.6 (95% CI 32.4, 39.1) in the matched maintenance sub-cohort. In the discontinuation sub-cohort, the crude flare rate

Abstract 801 Table 1 Adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) for SLE flare across sub-cohorts

Characteristics at time zero	Sub-cohort I, HCQ reduced	Maintenance (matched to I)	Sub-cohort II, HCQ discontinued	Maintenance (matched to II)
	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)
Male sex	1.04 (0.74, 1.45)	0.93 (0.68, 1.29)	0.94 (0.62, 1.42)	0.88 (0.61, 1.27)
Non-Caucasian race/ethnicity	1.19 (0.94, 1.51)	1.01 (0.81, 1.26)	0.95 (0.69, 1.29)	1.18 (0.91, 1.54)
Age at SLE diagnosis, years	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)	0.99 (0.98, 1.00)	1.01 (1.00, 1.02)
No post-secondary education	1.04 (0.85, 1.28)	1.16 (0.95, 1.43)	**1.40 (1.07, 1.83)**	0.90 (0.70, 1.15)
Geographic location				
North America	Reference	Reference	Reference	Reference
Europe	1.16 (0.91, 1.48)	1.10 (0.87, 1.40)	1.03 (0.76, 1.39)	1.05 (0.80, 1.37)
Asia	**0.69 (0.51, 0.93)**	0.87 (0.61, 1.23)	0.68 (0.46, 1.02)	**0.66 (0.43, 0.99)**
SLE duration	1.02 (0.98, 1.06)	1.00 (0.96, 1.04)	0.99 (0.95, 1.04)	0.99 (0.95, 1.03)
SLEDAI-2K $\geq$ 4	1.15 (0.94, 1.41)	1.17 (0.94, 1.44)	1.18 (0.90, 1.54)	1.17 (0.92, 1.48)
Renal damage	0.90 (0.60, 1.37)	0.99 (0.62, 1.59)	0.81 (0.55, 1.21)	0.82 (0.48, 1.39)
Body mass index	1.02 (1.00, 1.04)	1.00 (0.98, 1.01)	0.99 (0.97, 1.02)	0.99 (0.97, 1.01)
Smoker	1.07 (0.85, 1.35)	0.98 (0.78, 1.22)	0.95 (0.72, 1.25)	1.09 (0.83, 1.43)
Prednisone	**1.63 (1.28, 2.09)**	**2.03 (1.59, 2.59)**	**1.79 (1.31, 2.44)**	**2.39 (1.79, 3.19)**
Immunosuppressive	**1.60 (1.28, 2.00)**	**2.34 (1.87, 2.92)**	**1.48 (1.09, 2.01)**	**2.42 (1.86, 3.16)**
Biologics	0.67 (0.36, 1.24)	0.88 (0.47, 1.67)	0.63 (0.32, 1.26)	0.94 (0.45, 1.98)

was 43.1 (95% CI 38.3, 48.4), versus 34.2 (95% CI 30.6, 38.2) in the matched maintenance sub-cohort. Table 1 shows the factors associated with time to flare within each sub-cohort. The hazard ratios are adjusted by all variables in the table. Prednisone or immunosuppressive use at time-zero was associated with higher flare risk in all analyses. Lower education was associated with higher risk of SLE flares among patients who discontinued HCQ. There was a trend across sub-cohorts for lower flare risk among patients from Asia, versus North America.

Conclusions Compared to HCQ maintenance, crude flare rates were numerically higher after HCQ taper/discontinuation. SLE patients on prednisone or immunosuppressives were at higher risk for flare in all groups. The association between lower education and higher SLE flare risk was most clearly seen upon discontinuation of HCQ, suggesting this as a particularly vulnerable group.

Acknowledgements This research was supported by the Canadian Institutes of Health Research (CIHR).

900 – Nucleic acids in SLE

901 AUTOANTIBODY-MEDIATED IMPAIRMENT OF DNASE1L3 ACTIVITY IN SPORADIC SYSTEMIC LUPUS ERYTHEMATOSUS

[1]Johannes Hartl, [1]Lee Serpas, [1]Yueyang Wang, [2]Claudia Bracaglia, [3]Stefano Volpi, [4]Gregg J Silverman, [4]Robert M Clancy, [4]Peter M Izmirly, [4]Jill P Buyon, [1,4]Boris Reizis*. *[1]Department of Pathology, NYU Grossman School of Medicine, New York, NY, 10016, USA; [2]Division of Rheumatology, IRCCS Ospedale Pediatrico Bambino Gesù, 00165, Rome, Italy; [3]UOSD Centro per le Malattie Autoinfiammatorie e Immunodeficienze, IRCCS Istituto Giannina Gaslini and DINOGMI, Università degli Studi di Genova, Genoa, Italy; [4]Division of Rheumatology, Dept. of Medicine, NYU Grossman School of Medicine, New York, NY, 10016, USA*

10.1136/lupus-2021-lupus21century.39

Background Antibodies to double-stranded DNA are prevalent and pathogenic in systemic lupus erythematosus (SLE), particularly in patients with lupus nephritis. However, the physical nature and regulation of cell-free DNA (cfDNA) that becomes antigenic in SLE is poorly understood. Null mutations in the secreted DNase DNASE1L3 cause human monogenic SLE with anti-dsDNA autoreactivity, whereas a hypomorphic variant of DNASE1L3 is associated with SLE and other autoimmune diseases. We sought to characterize the role of DNASE1L3 in the regulation of cfDNA and its relevance for sporadic forms of SLE that are not associated with DNASE1L3 variants or mutations.

Methods Activity of DNASE1L3 in the plasma of SLE patients was measured using a novel assay based on the digestion of intact cell nuclei. Antibodies to DNASE1L3 were measured using a novel ELISA with recombinant DNASE1L3 as an antigen. The fraction of microparticle-associated cell-free DNA was measured using differential centrifugation followed by genomic qPCR. Antibodies to DNASE1L3-sensitive antigens on microparticles were measured by flow cytometry using tissue culture-derived microparticles digested with recombinant DNASE1L3.

Results More than 50% of sporadic SLE patients with nephritis manifested reduced DNASE1L3 activity in circulation. This reduced activity was associated with the presence of neutralizing autoantibodies to DNASE1L3, but not to its close homolog DNASE1. Patients with reduced DNASE1L3 activity had normal total plasma cfDNA levels but showed accumulation of cfDNA in circulating microparticles released from apoptotic cells. Microparticle-associated cfDNA contained a higher fraction of longer polynucleosomal cfDNA fragments, which bound autoantibodies with higher affinity than mononucleosomal fragments and were stronger inducers of type I interferon. Autoantibodies to DNASE1L3-sensitive antigens on microparticles were prevalent in SLE nephritis patients and correlated with the accumulation of cfDNA in microparticles and with disease severity. DNASE1L3-sensitive antigens on microparticles included DNA-associated proteins such as HMGB1, a known self-antigen in SLE

Conclusions Our results suggest that autoantibody-mediated impairment of DNASE1L3 activity is a common non-genetic mechanism facilitating anti-dsDNA autoreactivity in patients with severe sporadic SLE. In particular, it leads to the