S4D:6 SLE COMPRISES FOUR IMMUNE-PHENOTYPES, WHICH DIFFER REGARDING HLA-DRB1 AND CLINICAL ASSOCIATIONS

[1]LM Diaz Gallo, [1]E Lundström, [1]V Oke, [2]K Elvin, [3]YL Wu, [1]J Gustafsson, [4]A Jönsen, [5]D Leonard, [1]A Zickert, [5]G Nordmark, [4]AA Bengtsson, [5]J Sandling, [5]L Rönnblom, [1]I Gunnarsson, [3]CY Yu, [1]L Padyukov, [1]E Svenungsson. *[1]Department of Medicine, Rheumatology Unit, Karolinska Institutet/Karolinska University Hospital, Stockholm, Sweden; [2]Department of Clinical Immunology and Transfusion Medicine, Unit of Clinical Immunology, Karolinska Institutet/Karolinsk, Stockholm, Sweden; [3]The Research Institute at Nationwide Childrens Hospital, Columbus, Ohio, USA; [4]Department of Clinical Sciences, Section of Rheumatology, Lund University, Skåne University Hospital, Lund, Sweden; [5]Department of Medical Sciences, Section of Rheumatology, Uppsala University, Uppsala, Sweden*

10.1136/lupus-2018-abstract.25

SLE is a heterogeneous disease including diverging clinical symptoms, autoantibodies and genetic susceptibility. Hitherto unrecognised patterns may define sub-phenotypes with different pathogenesis and specific treatment needs. Based on autoantibody profile we therefore investigated phenotypic clusters and explored cluster associations with clinical manifestations and one of the most important genetic risk factors for SLE, HLA-DRB1 alleles.

908 SLE Caucasian patients and 3654 age- gender- and ethnicity-matched healthy controls (HC) were included. We determined the occurrence of 13 autoantibodies: dsDNA, nucleosomes, ribosomal P, RNP68, RNPA, Sm, Sm/RNP, SSA52, SSA60, SSB, aCL-IgG/IgM and aB2GP1. HLA-DRB1 typing was performed by sequence-specific primer polymerase chain reaction assay. Cluster analysis was done using Gower distance matrix, followed by partition around medoids cluster calculation and Silhouette metric for number of clusters validation. Chi-square test, odds ratios (OR), 95% confidence intervals and false discovery rate p value (p) were calculated for the association tests.

Four clusters were defined based on autoantibody occurrence.

1. 29%, dominated by anti–SSA52/60/SSB positivity is strongly associated with HLA–DRB1*03 when compared to HC (4.1 [3.4–4.9] p=6.4E–56) and other clusters (OCs) (2.9[93.3–3.6] p=1.1E–19). Discoid lesions were more common vs OCs (1.8[1.3–2.6] p=0.02).
2. 29%, dominated by anti–SmRNP/Sm/DNA/RNPA/RNP68/ nucleosome, was specifically associated with HLA–DRB1*15 when compared to HC (1.7[1.6–2.1] p=5.7E–6) and other clusters (1.5[1.1–1.9] p=0.01). Nephritis was common vs OCs (1.9[1.4–2.7) p=2.E–03)
3. 24%, dominated by anti–B2GP1/aCL–IgG/IgM, was associated with HLA–DRB1*04 when compared with other clusters (1.8[1.4–2.4] p=2E–4). More thrombotic events vs OCs were observed in this group (1.84 [1.3–2.6] p=0.01)
4. 18% was negative for the 13 tested autoantibodies and was not associated with any specific HLA–DRB1 alleles and it was not associated as risk factor for any of the evaluated clinical manifestations.

We demonstrate that immune-phenotypes/clusters in SLE can fit into a frame of HLA-DRB1 alleles and that the overall association between SLE and HLA-DRB1*03 and HLA-DRB1*15 seems to be driven mainly by clusters 1 and 2, respectively. We also confirm previous observations that autoantibody clusters associate with clinical symptoms. We believe that these results could be used to redefine SLE, determine predictive biomarkers and inclusion criteria for clinical trials.

S4D:7 NEXT GENERATION SEQUENCING IN HEMATOPOIETIC PROGENITORS OF MURINE SLE MODEL REVEALS ABERRANT REGULATION OF CEBP/A EXPRESSION

[1]M Grigoriou, [1]P Verginis, [2]C Nikolaou, [3]P Pavlidis, [4]E Dermitzakis, [5]G Bertsias, [1,6]D Boumpas, [1]A Banos. *[1]Biomedical Research Foundation of the Academy of Athens, Greece; [2]Department of Biology, University of Crete, Heraklion, Crete, Greece; [3]Institute of Molecular Biology and Biotechnology-FORTH, Heraklion, Crete, Greece; [4]Department of Genetic Medicine and Development, Medical School, University of Geneva, Geneva, Switzerland; [5]Medical School, University of Crete, Heraklion, Crete, Greece; [6]Joint Academic Rheumatology Program, Medical School, National and Kapodistrian University of Athens, Greece*

10.1136/lupus-2018-abstract.26

Background and purpose All blood cell lineages that have implicated to the pathogenesis of SLE originate from the Hematopoietic Stem Cells (HSCs). Studying HSCs may help to dissect fundamental immune aberrations in SLE and elucidate the HSC contribution to the pathogenesis of the disease.
Materials and methods HSCs were isolated from either healthy C57/BL6 or NZBxNZW/F1 lupus-prone mice bone marrow. The selection markers used are Lin-Sca-1+c-Kit+for LSK compartment that encompasses both long- and short-term HSCs as well as multipotent progenitors (MPP). Flow cytometry cell sorting of LSK was used for enumeration, RNA extraction, qPCR and cell cultures. Paired-end RNA-sequencing analysis was performed by the Illumina HiSeq 2000 platform.
Results We found significantly increased numbers of LSK in the BM of lupus NZBxNZW/F1 mice with established disease as compared to pre-diseased NZBxNZW/F1 mice in combination with evidence of them exiting the latent state and progression of cell cycle and aberrant differentiation with skewing towards the myeloid lineage. Transcriptome analysis revealed 800 differentially expressed genes (DEGs) ($FC>1.5$, $q<0.05$) in diseased lupus mice compared to pre-diseased with enrichment in transcription factors involved in hematopoiesis, regulation of immune responses and HSC function/homeostasis. We selected Cebpα (FC −0,88) -a master regulator of myeloid differentiation, self-renewal and resistance to stress-induced apoptosis of HSCs- for further investigation. qPCR analysis showed decreased Cebpα expression during the progression of the disease in SLE but increased Cebpα in aged healthy C57/BL6 mice. *In vitro* stimulation with IFNα decreased Cebpα expression in lupus -but not in healthy LSK. Serum from pre-diseased NZBxNZW/F1 decreased Cebpα expression only in pre-diseased LSK. Experiments to reverse Cebpα downregulation (using lenti-virus and modifiers of the metabolomics) are in progress.
Conclusions HSC RNA-seq analysis suggests both intrinsic and extrinsic influences resulting in downregulation of Cebpα in murine lupus. SLE HSCs have pronounced expansion, enhanced proliferation and aberrant differentiation -in part due to the effects of IFNα. Together these results suggest a decreased capacity of lupus HSCs to respond to stressors which may account for the cytopenias and the infections in SLE.

Lupus Sci Med: first published as 10.1136/lupus-2018-abstract.25 on 21 March 2018. Downloaded from http://lupus.bmj.com/ on February 26, 2024 by guest. Protected by copyright.