LO-035 THE EFFECTS AND MOLECULAR MECHANISMS OF TRAF5 ON PULMONARY ARTERY ENDOTHELIAL CELLS IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS ASSOCIATED PULMONARY ARTERIAL HYPERTENSION

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Background Pulmonary arterial hypertension (PAH) is one of the most important complications that seriously threatens the prognosis of patients with systemic lupus erythematosus (SLE). We aim to investigate candidate biomarkers and targeted therapy for the early diagnosis and timely treatment of SLE-PAH patients.

Methods 1) In order to screen susceptible genes of SLE-PAH, a number of 150 peripheral blood from SLE-PAH patients were subject to whole-exome sequencing (WES), and genome-wide association study (GWAS) was performed by comparing with 934 healthy controls.

2) The transcriptional expression levels of the above screened genes on peripheral blood of SLE-PAH patients were examined by RT-qPCR for further validation.

3) Intervention experiments on pulmonary artery endothelial cells (PAEC) were performed to figure out the potential pathogenesis of the selected gene in vitro. RNA-seq and gene ontology were applied to identify downstream pathways.

4) Established by pristane injection and hypoxia induction, SLE-PAH mice model was established. Pulmonary arterial pressure (PAP) was measured by right heart catheterization with/without tail-intravenous injection of therapeutic vectors.

Results 1) The tumor necrosis factor receptor-associated factor 5 (TRAF5) was identified as a susceptible gene of SLE-PAH based on WES and GWAS.

2) The significant reductions of TRAF5 on transcriptional level in peripheral blood of SLE-PAH patients were identified, indicating clinical diagnosis values.

3) Knockdown of TRAF5 significantly increased early apoptosis of PAEC and triggered the pathogenesis of PAH through distinct pathways.

4) SLE-PAH mouse model was successfully established since they showed phenotypes of lupus and the mean PAPs were measured as over 40mmHg. Tail-intravenous injection of TRAF5-overexpression vector attenuated PAH phenotypes.

Conclusions Lack of TRAF5 triggers the pathogenesis of PAH in SLE patients through inducing abnormal apoptosis of PAEC. TRAF5 is a susceptible gene of SLE-PAH and it could be a candidate biomarker for diagnosis and therapy for SLE-PAH patients.

LO-036 INHIBITION OF TRANSCOLBALAMIN2 OVEREXPRESSION AMELIORATED RENAL INJURY IN SYSTEMIC LUPUS ERYTHEMA VIA REDUCING PATHOGENIC TFH AND B CELL INFILTRATION

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Background Transcolbalamin2 (TCN2) is a vitamin B12 transport plasma protein that facilitates cellular uptake of cobalamin. TCN2 deficiency displays a metabolic disorder with immunodeficiency disease. However, its functions in autoimmunity diseases remain unknown. We attempt to investigate the effects of TCN2 on immune cells in systemic lupus erythema (SLE).

Methods TCN2 expression change in SLE was detected by analyzing our RNA-seq data and microarray from the GEO database and further examined by qPCR. TCN2-KO mice were developed and induced to lupus via pristane injection. The anti-dsDNA and urine protein level, skin, and renal involvement were assessed by ELISA, urine-protein test strips, hematoxylin-eosin (HE), PAS, and immunofluorescent staining. The frequency of immune cells in blood and kidney was investigated via flow cytometry.

Results We identified increased TCN2 expression in the blood and kidneys of SLE and confirmed upregulated expression of TCN2 in CD19+ B cells and CD4+ T cells in lupus patients and lupus-like mice compared to healthy controls. Then we successfully knocked out TCN2 in C57B/L6. Further studies demonstrated that downregulated expression of TCN2 ameliorated lupus symptoms, which displayed lower dsDNA levels, miler urine protein, and less mesangial hypercellularity and IgG deposition in the glomerulus. Flow cytometry results showed that inhibition of TCN2 remarkably reduced the frequency of B cells and CXCR5+ ICOS+ Tfh cells in the spleen and kidney of lupus-like mice.

Conclusions These results substantiate the involvement of TCN2 in SLE development. Inhibition of TCN2 overexpression alleviated renal injury by reducing Tfh and B cell infiltration. Our findings imply that cobalamin metabolism might be associated with aberrant germinal center responses and provide a novel target for SLE treatment.

Concurrent session 10: immune cells

LO-037 ALTERED PERIPHERAL NON-CLASSIC MONOCYTE AND NKT COUNTS AND CD8+ TCR DIVERSITY OF SYSTEMIC LUPUS ERYTHEMATOSUS IDENTIFIED VIA INTEGRATED HIGH-DIMENSIONAL FLOW CYTOMETRY, CYTOF, METABOLIC PROFILING AND TCR CLONALITY ANALYSES

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Background The phenotypic, signaling and metabolic diversities of leucocytes of systemic lupus erythematosus (SLE) impede comprehensive identification of immunopathologically-relevant alterations in leucocytes associated with active SLE. We aimed to identify these alteration signatures in leucocytes from patients with active SLE by an integrated platform comprising high-dimensional flow cytometry, cytometry by time of flight (CyTOF) and RNA sequencing (RNA-seq).

Methods Peripheral blood mononuclear cells (PBMCs) of SLE patients and healthy subjects were subjected to high-dimensional flow cytometry and CyTOF for studying alterations of myeloid cells and lymphocytes. Bulk RNA-seq was conducted for 8 sorted cell populations. Data were subjected to integrative analyses with Cytozoom that identified cellular signatures of active SLE. Differences in T-cell and B-cell receptor