Results Tregs from SLE patients showed a significantly reduced number, elevated apoptosis rates, and impaired suppressive capacity compared with NCs. The increased Tregs apoptosis was negatively correlated with the total number of Tregs and positively correlated with disease activities. Microarray profiles of Tregs from SLE subjects reveal a cellular response that could make the cells sensitive to apoptosis, partially due to the stress responses, DNA-damaging, and cytokine stimulation.

Conclusions This global picture of pathway-specific expression signatures is a step further dissecting Treg cells defects in the pathogenesis of SLE, and may shed light on the newly therapeutic strategies towards the aberrant Treg apoptosis and reconstruction of SLE immune homeostasis.

Background and aims The aim of this study was to assess the peripheral immune cell phenotypes in a correlation with clinical findings in patients with systemic lupus erythematosus (SLE).

Methods Peripheral blood mononuclear cells were obtained from 143 SLE patients and 26 healthy donors (HD). Circulating B, T and dendritic cells were defined based on flow cytometric analysis for human immune system termed “the Human Immunology Project” proposed by the National Institutes of Health (NIH) and the Federation of Clinical Immunology Societies (FOCIS).

Results The proportions of CD3+CD4+CXCR5+ICOS+ T follicular helper (Tfh) cells, but not CD3+CD4+CXCR3+CCR6+Th1 and CD3+CD4+CXCR3CCR6+Th17 cells, were higher in SLE than the HD. The proportions of CD19+CD20+IgD+CD27+ central memory B cells and CD19+CD20+IgD+CD27+ central memory B cells and CD19+CD20+IgD+CD27+ central memory B cells and CD19+CD20+IgD+CD27+ central memory B cells and CD19+CD20+IgD+CD27+ central memory B cells and CD19+CD20+IgD+CD27+ central memory B cells and CD19+CD20+IgD+CD27+ central memory B cells. Th17 and Th17, Treg and Tfh, Th1 and Th17, Treg and Tfh, Th17 cells only showed positive correlation with the proportion of plasmablast (r=0.24, p=0.02).

Conclusions Peripheral immuno-phenotyping confirmed the importance of Tfh-plasmablasts axis in patients with SLE, i.e., activation of Tfh cells correlated with autoantibody production while plasmablast did with disease activity of SLE. Our findings supported the relevance of Tfh-plasmablasts axis as a potential therapeutic target for SLE.
RESPONSE GENE TO COMPLEMENT-32 PROMOTES MICROMANAGING LUPUS NEPHRITIS: MIR17

Methods We traced the evolution of two anti-Ro52 autoantibodies isolated from circulating IgG-switched memory B-cells from a mother of two children with cardiac neonatal lupus. Each antibody was expressed as its immune form or pre-immune ancestor by reverting somatic mutations to germline sequence. Antibody reactivity against autoantigens Ro52, Ro60, La and dsDNA were tested by ELISA.

Results Both anti-Ro52 autoantibodies utilised the same heavy and light chain genes (IGHV3-23 and IGLV1-44) but represented distinct clones based on differing complementarity determining region sequences. Anti-Ro52 autoantibodies exhibited a low frequency (3%-4%) of somatic mutations compared to the average rate of 8% in healthy switched memory B-cells. In contrast to other pathogenic autoantibodies, the pre-immune (germlined) anti-Ro52 autoantibodies showed specific binding to Ro52. However, Ro52 reactivity was higher for the mutated post-immune antibodies compared to their pre-immune counterparts demonstrating that autoreactivity was enhanced by affinity maturation.

Conclusions These data demonstrate that Ro52 reactivity is an intrinsic property of the germline antibody repertoire in a mother of children affected by neonatal lupus and indicate defects in central and peripheral tolerance pathways allowing propagation of pathogenic autoantibodies.

Background and aims Response Gene to Complement (RGC) –32 plays an important role in cell cycle activation. Our prior studies showed that RGC-32 promotes Th17 differentiation of CD4 T cells. We used wild-type (WT) and RGC-32 knockout (KO) mice to determine whether lack of RGC-32 impairs B cell differentiation and activation and alters autoantibody parameters in the chronic graft versus host disease (cGVHD) model of lupus.

Methods TLR-dependent and T dependent B cell differentiation to plasma cells (PC) was induced with LPS and with IFN-γ. cGVHD was induced with LPS and with IRF4 and Prdm1 mRNA expression were found

Conclusions These results suggest that expression of RGC-32 in B cells is critical for optimal GC proliferation, PC differentiation and autoantibody production in a murine model of lupus. These data support the idea that RGC-32 blockade has the potential to attenuate autoimmune parameters of cGVHD and possibly reverse abnormalities in the T and B cell that contribute to lupus pathogenesis.

Background and aims Regulatory T (Treg) cells play a critical role in maintaining self-tolerance and controlling the magnitude of physiologic immune response. The Treg transcription factor forkhead box P3 (Foxp3) works in concert with other co-regulator molecules including Eos to determine suppressive phenotype of Treg. We identified miR17-92 cluster targeting Eos through bioinformatics approaches.

Methods We generated T-cell-specific miR-17–92 null (mir17–92 -/-) mice by mating mir17-92floxed/floxed mutants to CD4-Cre+ transgenic mice. Treg from mir17-92 -/- mice will be isolated, followed by suppression assay to evaluate the role of the miR-17–92 cluster in Treg function. We applied pristane to induce lupus nephropathy in wild type and mir17-92 -/- mice. We examined the up-stream promoter region of miR-17–92 for binding sites of down-stream mediators of IL-6 signalling, verified by chromatin immunoprecipitation assay.

Results The inflammatory cytokine IL-6 unregulated miR17-92 through HIF-1, MiR17-92 cluster, actively suppressed Eos expression. Knockdown of miR17-92 in Treg enhanced their suppressive activity. Mir17-92 T cell specific deficiency mitigated pristane induced-lupus nephropathy associated with diminished Th17 cells and autoantibody. Moreover, histological analysis revealed a lower mean renal histopathology score and less complement deposition. Ectopic expression of miR-17 downmodulated the suppression functions of Tregs and provided Treg with partial effector activity via the derepression of cytokine genes.

Conclusions Our studies suggest that miR17-92 modulates Treg cell function by targeting Eos and potentially additional Foxp3 co-regulators, unveiling the future therapeutic potential of microRNA manipulation in lupus nephritis.