

foetuses exposed to maternal anti-Ro52 autoantibodies. Recent studies investigating other pathogenic autoantibodies (anti-interferon, anti-desmoglein) report that they arise as a result of somatic mutation. The aim of this study was to determine how anti-Ro52 autoantibodies originate.

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 allow propagation of pathogenic autoantibodies.

55 RESPONSE GENE TO COMPLEMENT-32 PROMOTES PLASMA CELL DIFFERENTIATION AND ENHANCES LUPUS-LIKE CHRONIC GRAFT VERSUS HOST DISEASE

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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 autoimmune 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 CD40mAb plus IL-4. cGVHD was induced with 100×10^6 Bm12 splenocytes injected into WT or RGC-32 KO recipients.

Results RGC-32 KO B cells failed to differentiate normally to PC as demonstrated by a 2-fold reduction in PC numbers generated after stimulation and impaired upregulation of Prdm1 and IRF4 mRNA. RGC-32 transcripts were upregulated in spleen cells from cGVHD mice and protein expression was detected in B cells and germinal centre (GC) cells. RGC-32 KO hosts displayed an attenuated autoimmune phenotype as demonstrated by decreased production of anti-dsDNA autoantibodies and proliferation of germinal centre B cells. In

addition a decreased number of IgG anti-dsDNA secreting PC and 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.

56 MICROMANAGING LUPUS NEPHRITIS: MIR17–92 MODULATES REGULATORY T CELL ACTIVITY BY TARGETING FOXP3 CO-REGULATORS

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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 *mir17-92* flox/flox 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 compliment 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.

57 A HIGHER FREQUENCIES OF T HELPER 22 CELLS IN PATIENTS WITH NEW ONSET ACTIVE SYSTEMIC LUPUS ERYTHEMATOSUS

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Background and aims This study is aimed at elucidating the potential role of Th22 cells in patients with SLE.