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.

RESPONSE GENE TO COMPLEMENT-32 PROMOTES A HIGHER FREQUENCIES OF T HELPER 22 CELLS IN MICROMANAGING LUPUS NEPHRITIS: MIR17-92

Methods To induce lupus nephropathy in wild type and RGC-32 KO mice. Treg from mice infected with LPS and with TLR-dependent and T dependent B cell differentiation and activation and alters autoimmune parameters in the chronic graft versus host disease (cGVHD) model of lupus.

Results Both RGC-32 KO and WT B cells failed to differentiate normally to Th17 cells and autoantibody. Moreover, histological analysis revealed a lower mean renal histopathology score and less complement deposition. Ecotropic 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.

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

Methods We generated T-cell-specific miR-17–92 null (mir17–92–/−) mice by mating mir17–92floxfloxb/c mice 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 upstream promoter region of miR-17–92 for binding sites of downstream 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. Ecotropic 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.