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Immunological Analysis of Discordant Monozygotic Twins Reveals a Role for T-follicular Helper Cells in IgA Nephropathy

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Objectives : IgA nephropathy (IgAN), a common form of glomerulonephritis, is caused by deposition of IgA1 immune complexes in the glomerulus. The mechanism of the excess IgA1 production in IgAN is unclear and one proposed mechanism has been the dysregulation of B-cell-T-cell interactions.
Methods : We studied IgAN, Lupus Nephritis (LN), polycystic kidney disease (PKD) patients, healthy controls (HC), and 5 pairs of monozygotic twins discordant for IgAN, using multi-parameter flow cytometry and antibody repertoire sequencing.
Results : IgAN patients had a 3.6-fold increase in the IgA antibody secreting cells compared to HC and PKD patients, that correlated with elevated serum concentrations of IgA and IgA1. Analysis of the (T-follicular Helper) T_{FH}-like cells revealed a significant increase in the Th17 T_{FH}-like cells in the peripheral blood of IgAN patients compared to HC and PKD patients. The T_{FH}-like cell ratio of Th2 cells + Th17 cells / Th1 cells was significantly increased in IgAN patients compared to HC and PKD patients, indicating a skewing towards the T-helper cell population supporting antibody production. Autologous co-culture experiments of the T_{FH}-like cells with naïve B-cells demonstrated an elevated IgA production from cells derived from IgAN patients (45.5±18.2 ng/ml) compared to HC, LN and PKD patients (27.8±8.9, 25.7±5.4, and 27.2±8.4 ng/ml, respectively). Co-culture experiments in cells derived from IgAN discordant monozygotic twins, demonstrated cells derived from the IgAN twins yielded significantly higher IgA production compared to the cells from the healthy twins. In addition, T_{FH}-like cells derived from the IgAN twins significantly increased IgA production in the naïve B-cells from their corresponding healthy twin (38.5±9.3 ng/ml). T_{FH}-like cells derived from the healthy twins only elicited a baseline IgA production from naïve B-cells from their corresponding IgAN twins (22.5±8.9 ng/ml).
Conclusions : Our data demonstrates an essential interaction of naïve B-cells and T_{FH}-like cells in the increased generation of IgA in IgAN.