

Are IgG autoantibodies a key pathogenic trigger in IgAN?

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IgA Nephropathy (IgAN) is the most common cause of primary glomerulonephritis worldwide, being especially prevalent in East Asian populations. The condition is characterised by the deposition of undergalactosylated IgA1 (ug-IgA1) containing immune complexes in the glomeruli [1], leading to mesangial cell proliferation, extracellular matrix synthesis, interstitial fibrosis and ESRD in 30% of patients within 20 years of diagnosis. The biological processes which lead to IgAN are unclear. According to a multi-hit hypothesis for the pathogenesis of IgAN; circulating IgA1 with reduced galactose in the glycans attached to the hinge region (ug-IgA1) bind to autoantibodies and form circulating immune-complexes (IC) which deposit in the glomeruli and cause renal injury. In support of this theory, significantly higher levels of circulating ug-IgA1 are seen in serum from IgAN patients and IgA1 isolated from renal tissue from IgAN patients showed reduced galactosylation. However not all IgAN patients have IgG deposited in their glomeruli. Previously, serum levels of IgG autoantibodies which bind ug-IgA1 were measured using an ELISA based method employing an IgA1 hinge region with the galactose moieties enzymatically removed as the capture antibody [2]. In this study, we used a more physiological relevant capture antibody to measure levels of circulating IgG molecules which bind to ug-IgA1 to investigate the importance of anti ug-IgA1 IgG in the pathogenesis of IgAN.

Methods: Serum from 48 patients with biopsy proven IgAN, and 50 healthy subjects (HS) were analysed for the levels of ug-IgA1, IgA-IgG IC and IgG against ug-IgA1 using in-house ELISA based methods. Ug-IgA1 was measured using biotinylated Helix pomatia (HPA) lectin and IgA-IgG IC were captured using an (Fab')₂ antihuman IgA and detected with an antihuman IgG-HRP. The IgG which binds ug-IgA1 was measured using a novel ELISA based method with ug-IgA1 isolated from serum from a patient with marked mesangial IgA deposition, IgG and C3 deposition and an RPGN as the capture antibody and an (Fab')₂ antihuman IgG-HRP detection antibody. Biopsy data from the IgAN patients were analysed for glomerular IgG deposition. Statistical analysis was performed using Student's t test and Spearman's correlation.

Results: Serum from IgAN patients contained significantly higher levels of ug-IgA1 compared with HS (P=0.0018). However no correlation was observed between this ug-IgA1 and levels of IgG autoantibodies in IgAN. Additionally, the levels of IgG autoantibodies did not correlate with circulating IgA-IgG IC levels nor IgG deposition on kidney biopsy in IgAN and IgG autoantibody levels were no different between IgAN and HS.

Discussion: Evidence suggests that ug-IgA1 containing immune complexes deposited in the glomeruli in IgAN originate from the systemic compartment thus, investigating the levels of ug-IgA1, antibodies which bind this aberrantly galactosylated IgA1 and IgA-IgG IC in serum give an insight into the importance of these molecules in IgAN. The lack of correlation between levels of circulating ug-IgA1, IgG molecules which bind ug-IgA1 and IgA-IgG IC raises doubts about the importance of these antibodies in the pathogenesis of IgAN.