Glomerular disease

**Sugars and immune complex formation in IgA nephropathy**

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*In vitro* evidence suggests that immune complex formation in IgA nephropathy is determined by the sugar content of the IgA1 hinge region. The absence of galactose residues at the IgA1 hinge seems to render the IgA molecule immunogenic and results in the production of anti-IgA IgG autoantibodies.

Mesangial deposition of IgA is the principal trigger for the development of glomerulonephritis in IgA nephropathy (IgAN). Recurrence of IgA deposition in the majority of recipients of renal allograft suggests that this IgA is derived from a circulating pool of pathogenic IgA molecules. Serum levels of IgA do not correlate, however, with disease activity or severity, which gave rise to the belief that only a small percentage of serum IgA carries IgAN pathogenic potential.\(^1\) Two of the principal factors thought to contribute to IgA pathogenic potential are the composition of *O*-linked sugars in the IgA1 hinge region and the variable propensity of IgA1 to form large immune complexes and.\(^2\) Hitoshi Suzuki and colleagues present evidence that the composition of IgA1 hinge region sugars directly influences immune complex formation by determining the immunogenicity of the IgA1 molecule and the generation of anti-IgA1 IgG autoantibodies.\(^3\)
IgA1 is one of the very few serum proteins to possess O-linked sugars. The fact that these O-linked sugars are clustered within a relatively short segment of the IgA1 protein backbone (the so-called hinge region) means they might have a considerable effect on IgA1 function. Furthermore, the composition of O-glycans can vary widely among IgA1 molecules, which results in a variety of IgA1 O-glycoforms with potentially different biological characteristics. Suzuki et al. have obtained in vitro data showing that IgG produced by B cells isolated from patients with IgAN binds poorly galactosylated IgA1 and is capable of triggering the formation of IgA1-IgG immune complexes. The researchers suggest that the anti-IgA1 IgG autoantibodies they identified in the serum of patients with IgAN are the principal driver for IgA-immune complex formation in IgAN.

An increase in the proportion of serum IgA molecules that are poorly O-galactosylated has been one of the most consistent findings in studies of IgAN over the past decade. Perhaps more importantly, mesangial IgA eluted directly from glomeruli comprises predominantly these poorly galactosylated IgA1 O-glycoforms, which strongly implicates the composition of glycans in IgA1 hinge region in the mechanism of mesangial IgA1 deposition. Consistent with these observations, poorly galactosylated IgA1 O-glycoforms are more likely to bind to mesangial matrix proteins and activate mesangial cells and complement than their heavily galactosylated counterparts. Evidence from Suzuki et al. suggests also that hinge region O-glycans protect IgA1 from recognition by the immune system and that IgA1 O-glycoforms with low levels of galactose have increased immunogenic potential.
Why patients with IgAN have excess amounts of poorly galactosylated IgA1 O-glycoforms in their serum remains unknown. A number of explanations have been put forward, including an enzymatic defect in IgA1 O-glycosylation that is at least in part inherited. One alternative explanation is that poorly O-galactosylated IgA1 is in fact ‘normal’ IgA that should have been secreted at mucosal surfaces but has mistakenly found its way into the circulation. In fact, the pattern of O-glycosylation is different between mucosal and serum IgA1 in the same individual and IgA1 directed against mucosal pathogens is poorly O-galactosylated compared with IgA1 against systemic antigens. These findings combined with reduced IgA1-secreting plasma cell numbers at mucosal sites and increased numbers in the bone marrow in patients with IgAN suggests that in these patients there is a shift in IgA production from mucosal to systemic sites. The result of this shift is secretion into the circulation of high levels of mucosal-type (poorly galactosylated) IgA1 molecules with biological properties ill-suited to the systemic circulation.

Irrespective of the reasons for the high circulating levels of poorly galactosylated IgA1 O-glycoforms, little data exist to explain why IgG autoantibodies should develop in IgAN. One intriguing possibility put forward by Suzuki and colleagues is that anti-IgA1 IgG autoantibodies could in fact be antibodies specific for bacterial and viral surface glycoproteins and that recognition of poorly galactosylated IgA1 O-glycoforms by IgG is an unfortunate incident of ‘molecular mimicry’. Such a link between microbial infection and IgA immune complex formation might help explain the association of mucosal infection with macroscopic hematuria in IgAN. During a normal response to infection, serum levels of microbial-specific IgG rise, a proportion of this IgG will be specific for microbial cell surface sugars. In individuals with
persistently high serum levels of poorly galactosylated IgA1 $O$-glycoforms, a sudden rise in glycan-specific IgG might therefore precipitate IgA immune complex formation. A sudden increase in immune complex levels might then lead to rapid glomerular IgA deposition, mesangial cell and complement activation and glomerular hematuria. An increase in circulating IgA immune complex levels has been reported during episodes of macroscopic hematuria.\(^9\)

With the identification and characterization of anti-IgA1 IgG autoantibodies we have a better appreciation of the interrelationship between IgA1 $O$-glycosylation and immune complex formation in IgAN. However, to fully understand the implications of these data, the pathogenic importance of IgA1–IgG immune complexes in IgAN must be clarified. The relative paucity of mesangial IgG staining in most biopsy series of IgAN does raise questions over the pathological role \textit{in vivo} of such complexes. Suzuki \textit{et al.} have already suggested that measurement of anti-IgA IgG autoantibodies might in the future be the basis of a non-invasive diagnostic test for IgAN. They have also published work supporting an ELISA-based method of measuring the proportion of serum IgA that is poorly galactosylated, and an assay combining both of these measurements could be a powerful diagnostic tool for IgAN.\(^{10}\) However, studies need to confirm these findings in different patient cohorts and need to validate the diagnostic specificities, sensitivities and predictive values of these assays. Finally, convincing evidence that IgG-driven IgA immune complex formation has a pathological role \textit{in vivo} in IgAN needs to be presented.

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Competing interests
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