Is sialylation of IgA the agent provocateur of IgA nephropathy?*

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Review of field

Altered O-glycosylation of IgA1 has been recognized as a potentially pathogenic abnormality in IgAN for ∼20 years [1]. The 17-amino acid hinge region of IgA1 can carry from 0 to 6 O-glycan moieties, each of which is relatively short and simple sugar chain, but there are up to six different potential forms [2]. The variability in the number and location of occupied O-glycosylation sites, and the different possible forms of each of these chains (Figure 2) result in a vast array of potential IgA1 O-glycoforms, and this immense diversity has hindered the precise structural definition of the abnormality in IgAN.

O-Glycosylation is a post-translational modification effected by a series of O-glycosyltransferases that are highly specific in respect to the acceptor and donor sugars and the linkage between them (Figure 1). Alterations in the expression or activity of one or more of these O-glycosyltransferases may underlie abnormal IgA1 O-glycosylation in IgAN, but the available evidence to date has been inconclusive or conflicting [3–6]. The confusion partly arises from studies being carried out on mixed cell populations: even isolated B cells contain variable proportions of cells differing in maturity, activation status and Ig isotype production, all of which are likely to influence expression of O-glycosyltransferases.

In this paper, Suzuki and colleagues have established IgA1-secreting EBV-transformed B cell lines derived from the peripheral blood of patients with IgAN and controls. As each of these cell lines is a clone, this has provided them with sufficient cells and IgA1 of a single type for detailed characterization of O-glycosyltransferases and IgA1 O-glycosylation. Previous studies have shown that patients with IgAN are able to produce normally O-glycosylated proteins [7–9], and do not have a global defect in the enzymes involved. Therefore, abnormally glycosylated IgA1 may arise from specific subpopulations of IgA1-producing B cells in IgAN. Suzuki and colleagues have established IgAN B cell lines producing such abnormal IgA1, and carried out a series of elegant experiments comparing these cells and their products to those from healthy subjects. In this way, they have shown that the abnormality in IgAN takes the form of premature sialylation of the core N-acetylgalactosamine moiety, preventing its more usual galactosylation and resulting in truncated O-glycan chains. This is clearly associated with increased gene expression and activity of one of the sialyltransferases, ST6GalNAcII and downregulation of the O-galactosylating enzyme C1GalT1 and its chaperone protein Cosmc.

The results of this study shed new light on this important pathogenic feature of IgAN, and highlight ST6GalNAcII as a novel target of interest. We now need to understand the factors that govern expression and activity of O-glycosyltransferases as it is apparent from this study that subtle changes in the balance between them have important consequences. Our group has found that IgAN B cells produce normally O-galactosylated IgD [8], suggesting that the O-glycosyltransferase imbalance does not appear until a later stage of B cell maturation, after class-switching to IgA1. Furthermore, the shift in relative expression of ST6GalNAcII and C1GalT1 and consequent production of IgA1 with truncated O-glycans may be normal in certain immunological situations. We have shown that both IgAN patients and healthy subjects produce such ‘abnormal’ IgA1 in response to the mucosal antigen Helicobacter pylori, whereas IgA1 antibodies to tetanus toxoid are heavily O-galactosylated in both IgAN and controls. This implies that B cell populations possessing the ability to produce IgA1 with alternative O-glycoforms exist in IgAN and in healthy subjects. Suzuki et al. have shown that the O-glycosyltransferase expression of blood-derived EBV cell lines correlates with serum IgA1 O-glycosylation of the same subject, providing a new in vitro system in which to study the factors

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**Clinical implications**

Suzuki and colleagues have identified and characterized B cell subsets that generate IgA1 O-glycoforms that are widely accepted to have an important pathogenic role in IgA immune complex formation in IgAN [10]. What remains unknown is the origin of these B cells and why in IgAN they appear in the circulation in increased numbers. Undergalactosylation and increased sialylation of IgA1 is a normal feature of IgA1 directed against mucosal antigens and this raises the possibility that the cells identified by Suzuki and colleagues are mucosally derived trafficking lymphocytes [9,11]. While undergalactosylated and sialylated IgA1 may confer an advantage at mucosal surfaces,
when present in the circulation it appears that they promote the formation of immune complexes with a propensity for mesangial deposition. The association between mucosal infections and IgAN has been established for many years but the precise link between the mucosal IgA immune system and mesangial IgA deposition has remained elusive. There is however an increasing body of evidence supporting the displacement of mucosally primed B cells to systemic sites in IgAN. This might be explained by defects in the expression of cell surface homing receptors by trafficking lymphocytes [12–15]. What is needed now is precise immunophenotyping of the IgA1-committed B cells isolated and studied by Suzuki and colleagues so that we can trace their origins and understand how they arrived in the circulation in IgAN. Pinpointing the origins of these B cells will not only get us closer to understanding the fundamental immune processes operating in IgAN but also provide novel therapeutic targets in a disease currently bereft of any form of specific treatment.

**Take home message**

B cells programmed to sialylate IgA1 early in post-translational glycosylation (which therefore preclude the addition of galactose) may be the architects of IgA immune complex formation in IgA nephropathy.

**Conflict of interest statement.** None declared.

**References**


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