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 a 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 populations: even isolated B cells contain variable proportions of cells differing in maturity, activation status and populations: even isolated B cells contain variable proportions of cells differing in maturity, activation status and populations: even isolated B cells contain variable proportions of cells differing in maturity, activation status and populations: even isolated B cells contain variable proportions of cells differing in maturity, activation status and populations: even isolated B cells contain variable proportions of cells differing in maturity, activation status and populations: even isolated B cells contain variable proportions of cells differing in maturity, activation status and populations: even isolated B cells contain variable proportions of cells differing in maturity, 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**Fig. 1.** O-glycosylation of IgA1. The O-linked sugars of IgA1 are attached to serine or threonine residues in the IgA1 hinge region that lies between the CH1 and CH2 domains of the α1 heavy chain. The hinge region is made up of 17 amino acids, of which at least six are O-linked glycosylation sites. The O-linked sugar chains are core 1 structures based on N-acetylgalactosamine (GalNAc) in O-linkage with serine (usually) or threonine. This core GalNAc is usually further extended with galactose (Gal) in the β1,3 configuration or sialic acid (N-acetylneuraminic acid, NeuNAc) in an α2,6 configuration.

**Fig. 2.** The major O-glycan forms of human IgA1. The IgA1 O-glycans are all based on a core 1 structure with N-acetylgalactosamine (GalNAc) units in O-linkage with serine or threonine. This may occur alone or may be extended with sialic acid in α2,6-linkage with GalNAc or β1,3-linked galactose (Gal). Further extension with sialic acid (NeuNAc) in α2,3-linkage with Gal can also occur.

underlying the presence of pathogenic IgA1 in the circulation in IgAN.

**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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