Mutant mice provide new insight into the role of (mis-)glycation in IgA nephropathy and other glomerular diseases*

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In the 24 October 2006 issue of PNAS, Alexander and colleagues [1] describe the results of a systematic search for thrombocytopenic mice generated by large-scale mutagenesis. Amongst 3523 mice, one pedigree indeed exhibited ~50% reduction in platelet counts. Apart from thrombocytopenia, the only other notable feature of these mice was prominent renal disease (albuminuria/proteinuria, glomerulosclerosis and tubulointerstitial inflammatory infiltration) leading to uraemia and death at around 200 days after birth. This renal disease was not immune mediated, since it persisted in mutant mice crossed to B- and T-cell deficient mice and since no glomerular immune deposits were detected. Serum IgA levels were normal.

The genetic defect in the above mice was identified as a point mutation in the enzyme core1-β1,3-galactosyltransferase, C1GalT1 (EC 2.4.1.122). This led to minimal (<5%) residual enzymatic activity. However, the small amount of enzyme activity that was preserved related to preserved interaction of mutated C1GalT1 with its chaperone C1GalT2, also known as Cosmc. Reduced C1GalT1 enzyme activity resulted in the appearance of the Tn-antigen on various proteins, most prominently glycoprotein Ib-α on platelets and aminopeptidase N as well as podocalyxin in kidneys.

Core1-β1,3-galactosyltransferase and IgA nephropathy

Human IgA1, the main isoform deposited in the mesangium of patients with IgA-nephropathy (IgAN) and Henoch–Schoenlein purpura (HSP), is an unusual serum protein, since it is O-glycosylated. The O-glycans, located in the hinge region of IgA1, are based on a core N-acetylgalactosamine (GalNAc) linked to serine and/or threonines of the protein. The core is extended by galactose to form Galβ1,3GalNAc, and this in turn may be covered with α2,6 and/or α2,3 sialic acid. Thus IgA1 can consist of a number of different glycoforms (Figure 1).

In patients with IgAN and HSP, circulating and mesangial IgA1 has abnormal O-linked hinge-region sugars with reduced galactosylation and sialylation [2–4]. The basis for the reduced galactosylation may be linked to a B cell-restricted reduction of C1GalT1 activity [5], although the enzyme exhibits widespread expression with a predominance in kidney, heart, placenta and liver [6]. However, there is no evidence for reduced C1GalT1 activity in non-lymphocyte cell types in IgAN [7]. Furthermore, IgD (the only other O-glycosylated immunoglobulin isotype in humans), does not share the O-glycan abnormality seen in IgA1 in IgAN [8]. This indicates that the mechanism responsible is restricted to particular B-cell subsets and is possibly related to the stage of development of an immune response.

The altered glycosylation has been suggested to induce mesangial IgA1 deposition by predisposing to the formation of circulating IgA1-immune complexes, or by directly modifying IgA1 interactions with matrix proteins and mesangial cell and/or monocyte Fc receptors. It may also impair IgA1 clearance, by inhibiting IgA1 interactions with hepatic IgA receptors.

So why do the mice not develop IgAN but some other glomerular disease? Rodent studies cannot assist our understanding of the role of undergalactosylated IgA, aberrant function of C1GalT1 and Cosmc, since rodent IgA does not contain a hinge region. Whereas C1GalT1 knock-out mice are not viable, it is
noteworthy that genetic deletion of another galactosyltransferase member in mice, namely β1,4-galactosyltransferase-I, resulted in glomerulosclerosis that was linked to increased levels of polymeric IgA [9], and there is recent evidence that cell surface β1,4-galactosyltransferase-I may also act as a human mesangial cell IgA receptor [10]. Thus, the study of Alexander et al. is an important step in better understanding the non-IgA related role(s) of this enzyme in renal disease.

**What are the potential clinical implications?**

The role of altered glycosylation in glomerular disease and proteinuria, apart from IgAN, is largely uncharted territory. In this respect, both misglycated glomerular proteins found in the study of Alexander et al. [1], namely aminopeptidase N and podocalyxin, may be of considerable interest. Injection of an antibody to another aminopeptidase, namely aminopeptidase A, resulted in a membranous nephropathy-like picture in mice [11] and intraperitoneal injection of sialidase into mice induced heavy proteinuria, which was linked at least in part to removal of sialic acid from podocalyxin on the foot processes of podocytes [12]. Therefore, altered glycosylation of both aminopeptidase N and podocalyxin due to reduced C1GalT1 might contribute to an altered function of these two molecules in the glomerular barrier and thus in proteinuria. The work of Alexander et al. lays the basis for a potentially much wider role of aberrant glycosylation in the pathogenesis of IgAN and other progressive glomerular diseases. If the above sequence can indeed be verified and confirmed in humans, then therapeutic intervention at the level of C1GalT1 might result in a novel approach to proteinuric glomerular diseases.

**Take-home-message**

Dysregulated activity of C1GalT1 in patients with IgAN and HSP results in pathogenic under-galactosylation of IgA but might also impair the normal function of other important molecules constituting the glomerular capillary wall, such as aminopeptidase N and podocalyxin (Figure 2).

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**References**


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