**microRNA-Induced IgA Nephropathy**

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IgA nephropathy (IgAN) is the most common GN in the world. Prevalence of IgAN is extremely high, noted in 30%–40% of renal biopsies in Asian countries and South Europe. In Japan, the Renal Biopsy Registry compiles information from >1500 cases a year, among which the most frequent pathologic diagnosis is IgAN at 30%.2 Glomerular IgA deposition is observed in 16% of zero-hour biopsies, and IgA nephropathy with C3 deposition and macrophage infiltration is surprisingly observed in 1.6% of healthy donors’ kidneys.3 Thirty percent of IgAN cases resolve spontaneously, 30%–40% smolder, and 30% progress to ESRD within 20–30 years.4,5

Over the last decade, the etiology of IgAN at the molecular level has been thoroughly investigated, resulting in a proposed four-step mechanism.6,7 First, the aberrantly galactosylated IgA1 with the hinge region O-glycans is generated in patients with IgAN. Second, antibodies against the aberrantly galacosylated IgA1 are produced. Third, immune complexes of IgA1-IgA or IgA1-IgG are generated. Fourth, the immune complexes bind to mesangial cells through the transferrin receptor (CD71). Complement activation occurs in response to immune complex deposition, leading to mesangial proliferation and eventually glomerulosclerosis.

The first step of aberrant galactosylation at the hinge region of IgA1 was extensively studied during the last decade. The heavy chain of IgA1 contains an 18 amino acid hinge region that is rich in serine and threonine residues. Six O-linked saccharides containing N-acetylgalactosamine are added in a post-translational manner. Galactose is added to the saccharides containing N-acetylgalactosamine by core 1,3-galactosyltransferase 1 (C1β3GALT1). The role of miRNA in the kidney is revealed not only in normal kidney development and homeostasis of electrolytes but also in the induction of kidney diseases.14 Upregulation of miR-192 is associated with diabetic nephropathy, which regulates Smad-interacting protein-1, transforming growth factor-β1 (TGFβ), and δ1-crystallin enhancer binding protein, leading to enhanced fibrosis of the kidney in a diabetic rodent. In addition, TGFβ increases miRNA-148b and vice versa, resulting in a positive feedback system. miR-17 is also reported to target polycystic kidney disease (PKD2) and interfere with the function of a post-transcriptional regulator (Bicc1) of PKD2 at the 3’-untranslated region of mRNA encoding PKD2, which in turn enhanced translation of PKD2. Given the compromised Bicc1, the increase in PKD2 causes the development of a PKD-like phenotype. In IgAN, the level of miR-141, miR-205, and miR-192 in the kidneys increases, whereas the level of miR-200 decreases.15 These microRNAs are not investigated in the present study.
The unresolved question regarding the etiology of IgAN is whether the undergalactosylation of O-glycan in IgA1 caused by miR-418b results from a hereditary defect. As mentioned above, the SNP 1365A/G variant is associated with the genetic susceptibility to IgAN. By contrast, IgD, which has five O-glycan moieties at the hinge region, is more heavily galactosylated but less sialylated than IgA1 in IgAN.\textsuperscript{16} Galactosylation of O-glycan of IgA1 and IgD is completed by C1β3GALT1 at the Golgi apparatus, suggesting a different regulation of C1β3GALT1 activity on IgA1 and IgD in B cells. It is unlikely that the genetic upregulation of miR-418b in all B cells fully accounts for the undergalactosylation.

Do B cells modify the O-glycosylation of IgA1 at the hinge region after class switch through miR-418b induction? IgA1 O-glycosylation varies according to different immune responses, and patients with IgAN and healthy subjects produce the full spectrum of IgA1 and IgD in IgAN.\textsuperscript{16} The Th2 cytokine, IL-4,\textsuperscript{18} in this step, miR-418b may be induced by the Th2 cytokine. The induction of miRNA has been observed in transplant kidneys; a cluster of miRNA was induced in kidney grafts with acute rejection.\textsuperscript{19}

Taken together, the following hypothesis may be generated: a combination of genetic susceptibility to C1β3GALT SNP 1365G and enhanced miR-418b induction by infection or immunologic stimuli may cause IgAN by increasing C1β3GALT activity in B cells, particularly derived from tonsils.

New finding of miRNA-418b regulation regarding C1β3GALT expression in IgAN will open new avenues for treatment of IgAN. Anti-miRNA therapy holds promise for the treatment of hepatitis C, cardiovascular diseases, metabolic diseases, inflammatory diseases, and fibrosis of the organs.\textsuperscript{20} Development of a new therapy for targeting miR-418b is attractive and potentially applicable to patients with IgAN. Effective distribution of inhibitor to B cells will be a key step for clinical use.

DISCLOSURES

None.

REFERENCES


See related article, “Abnormal miR-148b Expression Promotes Aberrant Glycosylation of IgA1 in IgA Nephropathy,” on pages 814–824.