microRNA-Induced IgA Nephropathy

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IgA nephropathy (IgAN) is the most common GN in the world.1 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 hour-zero 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 generated. 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 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 N-acetylgalactosamine by core β1,3-galactosyltransferase 1 (C1β3GALT1).

There are three hypotheses to explain the blocking of galactosylation of the N-acetylgalactosamine residue on the hinge region of IgAN. First, α 2,6-sialyltransferase is excessively activated and sialic acid is attached to N-acetylglactosamine, skipping galactose. Second, activity of C1β3GALT1 is attenuated, resulting in decreased galactose at O-glycan. Third, the stability of C1β3GALT is decreased by the reduction in its chaperone (Cosmc).

Decreased activity of C1β3GALT1 was reported in freshly isolated and immortalized B cells from patients with IgAN.5,9 The level of mRNA encoding C1β3GALT1, but not Cosmc, is low in tonsillar B lymphocytes in IgAN.10 The aberrant galactosylation at the hinge region of IgA1 in IgAN may be inheritable in that a higher IgA1 level with poor galactosylation is observed in first-degree relatives. Mutation of the Cosmc gene may account for the low activity of C1β3GALT1, but no evidence for the mutation was detected in patients with familiar IgAN.

In this issue of JASN, Serino et al.11 report a comprehensive microarray screening of miRNA in IgAN and reveal a novel pathophysiological mechanism whereby the microRNA miR-418b regulates the levels of mRNA encoding C1β3GALT1 in IgAN patients. The miR-418b binds to the 3'-untranslated region of C1β3GALT mRNA and breaks it down. The expression level of C1β3GALT mRNA is inversely correlated with the expression level of miR-418b in IgAN patients. The C1β3GALT1 single nucleotide polymorphism (SNP) variant is associated with genetic susceptibility to IgAN.12,13 miR-418b binding to the C1β3GALT1 mRNA can be modulated by SNP (rs1047763) 1365G/A. The 1365G enhances binding of miR-418b and 1365A weakens it. The level of miR-418 expression is significantly higher in IgAN than Henoch-Schonlein purpura nephritis (HSPN), suggesting the pathophysiology of HSPN may differ from that of IgAN. The authors also show a potential treatment for IgAN using a miR-418b inhibitor that normalizes the galactosylation of IgA1 from patient B cells that reduces the aberrant galactosylation of IgA1.

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 (TFGβ), and δ1-crystallin enhancer binding protein, leading to enhanced fibrosis of the kidney in a diabetic rodents. 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 kidney 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.\(^6\) Galactosylation of O-glycan of IgA1 and IgD is completed by C1\(\beta\)3GALT1 at the Golgi apparatus, suggesting a different regulation of C1\(\beta\)3GALT1 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 O-glycoforms.\(^7\) C1\(\beta\)3GALT is downregulated by the Th2 cytokine, IL-4.\(^8\) 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.\(^9\)

Taken together, the following hypothesis may be generated: a combination of genetic susceptibility to C1\(\beta\)3GALT SNP 1365G and enhanced miR-418b induction by infection or immunologic stimuli may cause IgAN by increasing C1\(\beta\)3GALT activity in B cells, particularly derived from tonsils.

New finding of miRNA-418b regulation regarding C1\(\beta\)3GALT1expression 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.\(^10\) 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.