Fatal Attraction: Immunoglobulin A and the Glomerular Mesangium

Jürgen Floege
Division of Nephrology, Medizinische Klinik II, Rheinisch Westfälische Technische Hochschule University Hospital Aachen, Aachen, Germany

JASN 30: 1139–1141, 2019.
doi: https://doi.org/10.1681/ASN.2019040373

The defining feature of IgA nephropathy (IgAN) is glomerular mesangial deposition predominantly of IgA and here, mostly of dimeric and polymeric IgA_1. It has long been discussed whether the deposited IgA carries any antigenic specificity and whether this might yield clues to the pathogenesis of the disease. In this issue of *JASN*, Wehbi *et al.*[1] have new insight into this question by studying affinity maturation of IgA and its relationship to mesangial IgA deposition.

In the process of affinity maturation, B cells, activated by follicular helper T cells, continuously improve the binding of their antibodies after antigen exposure, in particular on repeated exposure.[1] In simple terms, affinity maturation is the consequence of two principles. First, continuous mutation of antigen binding sequences of the IgA genes, which requires the DNA editing enzyme activation-induced cytidine deaminase (AID), generates antibodies with new binding specificity and affinity. Second, another principle then is "selection of the fittest" B cells, in which the many B cell clones must compete for help from the follicular helper T cells. These T cells present antigen to the B cells, and only those clones with high-affinity antibodies to the antigen receive signals that favor their survival, whereas low-affinity B cells are deleted.

In their study, Wehbi *et al.*[1] used transgenic mice overexpressing human IgA_1. In the presence of AID (*i.e.*, in mice with preserved affinity maturation), mesangial IgA and complement C3 deposits as well as mild mesangioproliferative disease developed with age. No proteinuria, hematuria, or renal failure was noted. In the absence of AID, mice expressed human IgA_1 carrying nonmutated, nonaffinity matured variable domains. In these mice compared with AID wild-type mice, mesangial IgA and C3 deposits increased as did mesangial expansion. Renal failure developed, but again, it was in the absence of significant proteinuria or hematuria. The authors conclude that IgA-related nephrotoxicity involves IgA produced by innate-like B cells rather than high-affinity maturated IgA antibodies.

Although indeed, polymeric IgA may exhibit different capacities to inflict glomerular damage depending on affinity maturation, the alternative hypothesis is that glomerular damage is a function of the abundance of polymeric IgA. Thus, in the mice with present AID, IgA levels in serum increased four- to sevenfold with age, whereas serum IgA levels increased by about 50-fold in AID-deficient mice.[1] This study thereby extends a number of mouse models of glomerular IgA deposition and variable degrees of renal damage (Table 1). All of these, when examined, exhibited moderately to massively elevated IgA serum levels, much higher than the mild about twofold elevation in serum IgA that is observed in about one half of patients with IgAN.[2]

Another important observation in the study of Wehbi *et al.*[1] is that serum IgA, even in the mice with pronounced renal damage, did not exhibit an altered glycosylation, in particular reduced galactosylation. In human primary IgAN, most mesangial IgA_1 exhibits an undergalactosylated hinge region.[3] This galactose-deficient IgA is now believed to be a major contributor to the pathogenesis of IgAN, although its serum levels are only mildly elevated and normal in about 50% of patients with IgAN.[4] The IgA_1 hinge region is unique to humans and higher monkeys, and even small monkeys, like the Brazilian marmoset, no longer have a hinge-containing IgA molecule. In addition to other differences in the IgA system, this has severely hampered the development of good preclinical models of human IgAN. Therefore, the remarkable observation in the study of Wehbi *et al.*[1] is that human IgA_1 without any obvious glycation defect can induce glomerular damage as long as serum levels are high enough or it is not affinity maturated. Similarly, a second important observation in that study is that human IgA_1 induced glomerular damage independent of CD89, a presumed IgA receptor.[5] In a previous study, human CD89 overexpression on macrophages/monocytes as opposed to neutrophils in the work by Wehbi *et al.*[1] induced overt disease with hematuria and proteinuria in mice transgenic for human IgA_1.[5]

Therefore, my conclusion from all of these data is that markedly elevated human or murine polymeric IgA in serum can induce glomerular IgA deposits in mice, a case of "fatal attraction." If the same is true in humans, it could explain why glomerular IgA deposits have been detected in 5% of random German autopsies[6] and 15% of Japanese donor kidneys before transplantation,[7] even in the absence of any known cause of

Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Prof. Jürgen Floege, Division of Nephrology, Rheinisch Westfälische Technische Hochschule University Hospital Aachen, Pauwelsstrasse 30, D-52057 Aachen, Germany. Email: juergen.floege@rwth-aachen.de

Table 1. Mouse models with an IgA nephropathy–like disease manifestation

Model	Glomerular IgA Deposits (Species)	Total IgA Levels in Blood	GFR	Proteinuria	Hematuria	Glomerular Pathology
Present study[1]						
AID wild-type mice	++ (Human)	↑ about fivefold	Normal	None	None	Mild mesangial expansion and C3 deposition
AID-deficient mice	+++ (Human)	↑ about 50-fold	Reduced	None	None	Mesangial expansion and C3 deposition
Mice expressing human IgA_1 and CD89	+++ (Human)	↑ >100-fold	Mildly reduced	+	++	Mesangial expansion and C3 deposition
High-IgA mice	+++ (Mouse)	↑ up to fourfold	Reduced	+	None	Mesangial expansion and C3 deposition
β-1,4-galactosyl-transferase–deficient mice	++ (Mouse)	↑ up to tenfold	No data	++	+	Mesangial expansion and C3 deposition
CD37-deficient mice	+++ (Mouse)	↑ up to 15-fold	Normal	None	None	Mesangial expansion and hypercellularity; no data on C3
BAFF transgenic mice	+++ (Mouse)	↑ up to 50-fold	ESRD at 17 mo	++	+++	Mesangial matrix expansion; no data on C3; little C4
Uteroglobin-deficient mice	+++ (Mouse)	No data	No data	No data	+++	Mesangial matrix expansion and C3 deposition
LIGHT transgenic mice	+++ (Mouse)	↑ 30- to 40-fold	No data	++	+	Mesangial matrix expansion and C3 deposition
MBP20 peptide fusion protein	+++ (Mouse)	No data	No data	(+)	++	Mesangial matrix expansion and proliferation and C3 deposition
Monoclonal IgA from Peyer patch hybridomas of vomitoxin-exposed mice	++ (Mouse)	↑ two- to four-fold	No data	No data	+	Normal mesangium, C3 deposition

AID, activation-induced cytidine deaminase. Modified from ref. 9, with permission.

secondary IgAN.[8] What requires more systematic study is the relative contribution of elevated polymeric serum IgA versus particular features, in particular galactosylation patterns, of circulating IgA in inducing IgAN or an IgAN-like disease. Thus, Table 1 shows that experimental IgA-associated glomerular damage can develop without hematuria, an almost universal finding in human primary IgAN, or proteinuria, and in particular, only rare models seem to lead to ESRD. In addition, in the study of Wehbi *et al.*[1] as in several other studies, no electron microscopy was performed, and we are left to speculate whether the glomerular localization of IgA or IgA complexes, be it mesangial or capillary, affects disease manifestations, such as hematuria or proteinuria. Indeed, in a previous study,[5] mice overexpressing human IgA_1 only had endocapillary IgA_1 deposits but did not have mesangial injury or kidney dysfunction, and only sCD89 coinjection or coexpression induced mesangial IgA_1 deposits, hematuria, and proteinuria.

A final good illustration of why we need to better understand the "fatal attraction" of IgA for the mesangium is liver disease: IgAN is detected in 9%–25% of patients receiving a kidney biopsy at the time of a liver transplantation, and patients with liver cirrhosis exhibit two- to fourfold increases in serum IgA levels, including elevated polymeric IgA and undergalactosylated IgA.[8] However, in contrast to primary IgAN, the mesangial IgA deposits in liver cirrhosis did not stain with an antibody specific for the galactose-deficient IgA_1 hinge region,[3] mesangial proliferation is less prominent, and serum IgA_1 from patients with liver cirrhosis was less potent in inducing proliferation of human mesangial cells *in vitro*.[8] All of the above are calls for efforts to identify subtypes of what we collectively call IgAN. Better understanding of these different pathomechanisms may allow us to clarify why patients have radically different clinical courses ranging from inert glomerular IgA deposits with little or no clinical manifestations to rapidly progressive IgAN quickly resulting in ESRD.

DISCLOSURES

None.

REFERENCES

1. Wehbi B, Oblet C, Boyer F, Huard B, Druilhe A, Paraf F, et al.: Mesangial deposition can strongly involve innate-like IgA molecules lacking affinity maturation. *J Am Soc Nephrol* 30: 1238–1249, 2019
2. van der Boog PJ, van Kooten C, de Fijter JW, Daha MR: Role of macromolecular IgA in IgA nephropathy. *Kidney Int* 67: 813–821, 2005
3. Suzuki H, Yasutake J, Makita Y, Tanbo Y, Yamasaki K, Sofue T, et al.: IgA nephropathy and IgA vasculitis with nephritis have a shared feature involving galactose-deficient IgA1-oriented pathogenesis. *Kidney Int* 93: 700–705, 2018
4. Yasutake J, Suzuki Y, Suzuki H, Hiura N, Yanagawa H, Makita Y, et al.: Novel lectin-independent approach to detect galactose-deficient IgA1 in IgA nephropathy. *Nephrol Dial Transplant* 30: 1315–1321, 2015

5. Berthelot L, Papista C, Maciel TT, Biarnes-Pelicot M, Tissandie E, Wang PH, et al.: Transglutaminase is essential for IgA nephropathy development acting through IgA receptors. *J Exp Med* 209: 793–806, 2012
6. Waldherr R, Rambausek M, Duncker WD, Ritz E: Frequency of mesangial IgA deposits in a non-selected autopsy series. *Nephrol Dial Transplant* 4: 943–946, 1989
7. Suzuki K, Honda K, Tanabe K, Toma H, Nihei H, Yamaguchi Y: Incidence of latent mesangial IgA deposition in renal allograft donors in Japan. *Kidney Int* 63: 2286–2294, 2003
8. Saha MK, Julian BA, Novak J, Rizk DV: Secondary IgA nephropathy. *Kidney Int* 94: 674–681, 2018
9. Suzuki H, Suzuki Y: Murine models of human IgA nephropathy. *Semin Nephrol* 38: 513–520, 2018

See related article, "Mesangial Deposition Can Strongly Involve Innate-Like IgA Molecules Lacking Affinity Maturation," on pages 1238–1249.

A "Set Point" for Water Homeostasis Disturbed with Altered Kidney Transplantation Outcome

Daniel G. Bichet
Research Center, Hôpital du Sacré-Coeur de Montreal, Departments of Medicine, Pharmacology and Physiology, University of Montreal and Nephrology Service, Montreal, Quebec, Canada

JASN 30: 1141–1143, 2019.
doi: https://doi.org/10.1681/ASN.2019050472

Mazloum *et al.*[1] performed a water-loading test in 1258 kidney transplant recipients 3 months after transplantation. A total of 163 healthy kidney donors served as controls. Plasma sodium slope was flatter during the waterload test in kidney transplant patients, and a steeper plasma sodium reduction, that is hyponatremia, was associated with mortality, allograft lost, and lower GFR.

These interesting results need to be confirmed in other kidney transplantation centers, but they suggest water-loading could be a useful clinical surveillance tool. The waterload test done by the Necker team consists of water administered orally at 6 ml/kg of water over 30 minutes, followed by 150 ml of water every hour. It is different from the classic test, 20 ml/kg body wt of water load administered intravenously, which is used to assess, for example, hyponatremic cirrhotic patients or patients with suspected syndrome of inappropriate antidiuretic hormone secretion.[2,3] This modified "Necker" waterload is likely to represent the day-to-day changes in plasma sodium observed in real life in kidney transplant recipients, many of whom are accustomed to restricting their water intake during hemodialysis prior to transplantation.

Oral administration of water is better understood from a physiologic point of view since recent optogenetic experiments have demonstrated how thirst and arginine-vasopressin (AVP) producing neurons perceive an oral water intake.[4] AVP or copeptin measurements were not done by Mazloum *et al.*,[1] but it reasonable to postulate that high AVP and copeptin levels not suppressed by hyponatremia would be observed in kidney transplant recipients, especially those with poorer outcomes. This result would favor an extrarenal explanation of the osmoregulatory defect. Alternatively, normal suppression of AVP/copeptin by hyponatremia would indicate an intrarenal defect; that is, less water presented to the collecting duct, therefore a reduced possibility to excrete urine with a low osmolality.

Measurements of suppressed levels of plasma AVP are not simple since there is large intra- and inter-assay variability (around 20%) for plasma vasopressin levels between 0.5 and 1.0 pg/ml.[5] Copeptin is the C-terminal fragment of the AVP prohormone. It is released in equimolar amounts with AVP in response to osmotic stimulation and its measurement is likely more robust than that of AVP.[6] Plasma copeptin of $<$25 pmol/L have been observed in normal subjects for plasma sodium $<$140 mEq/L.[7] Measurement of copeptin is established as an important tool to differentiate polyuric disorders, but the use of copeptin in the evaluation and treatment of the hyponatremic osmoregulatory defects is not considered to have diagnostic value.[6,8]

What do these findings mean for clinical practice? High AVP/copeptin may be associated with hyperfiltration and has been postulated to induce a progressive deterioration of kidney function (well reviewed by Bankir *et al.*[9]). As a consequence, a modest increase in water intake could be hypothesized to be of value in transplant recipient patients demonstrating a defect in water-load excretion. Nevertheless, the CKD Water Intake Trial conducted in patients with CKD stage 3, coaching to increase water intake compared with coaching to maintain the same water intake, did not significantly slow the decline in kidney function after 1 year.[10] A mean water intake from 0.43 to 1.35 L/d has been found to decrease plasma copeptin levels in normal subjects.[11] In summary, at this point we do not know if AVP is elevated in those kidney transplant patients with abnormal waterload. Data from recent publications do not demonstrate an eGFR benefit of an increased water intake. We are therefore left with an abnormal set-point for water homeostasis as a clinical biomarker of a severe outcome in kidney transplantation. Clearly the interesting results of Mazloum and coauthors raise important questions that will require further study.

Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Dr. Daniel G. Bichet, Research Center, Hôpital du Sacré-Coeur de Montreal, University of Montreal and Nephrology Service, 5400 Gouin Ouest, Montreal, QC H4J 1C5, Canada. Email: daniel.bichet@umontreal.ca