Membranous nephropathy: integrating basic science into improved clinical management

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Idiopathic membranous nephropathy (INM) remains a common cause of the nephrotic syndrome in adults. The autoimmune nature of IMN was clearly delineated in 2009 with the identification of the glomerular-deposited IgG to be a podocyte receptor, phospholipase A2 receptor (PLA2R) in 70% to 75% of cases. This anti-PLA2R autoantibody, predominantly the IgG4 subclass, has been quantitated in serum using an enzyme-linked immunosorbent assay and has been used to aid diagnosis and monitor response to immunosuppressive therapy. In 2014, a second autoantigen, thrombospondin type 1 domain–containing 7A (THSD7A), was identified. Immunostaining of biopsy specimens has further detected either PLA2R or THSD7A antigen in the deposited immune complexes in 5% to 10% of cases autoantibody seronegative at the time of biopsy. Therefore, the term IMN should now be superseded by the term primary or autoimmune MN (AMN) (anti-PLA2R or anti-THSD7A positive) classifying ~80% to 90% of cases previously designated IMN. Cases of secondary MN associated with other diseases show much lower association with these autoantibodies, but their true incidence in secondary cases still needs to be defined. How knowledge of the autoimmune mechanism and the sequential measurement of these autoantibodies is likely to change the clinical management and trajectory of AMN by more precisely defining its diagnosis, prognosis, and treatment is discussed. Their application early in the disease course to new and old therapies will provide additional precision to AMN management. We also review innovative therapeutic approaches on the horizon that are expected to lead to our ultimate goal of improved patient care in A(I)MN.

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Idiopathic membranous nephropathy (IMN) remains one of the most common causes of nephrotic syndrome in adults and one of the leading known causes of end-stage renal disease.[1,2] Reported variation in incidence may reflect specific country/physician indication for kidney biopsy but could as well be real differences related to the population's socioeconomics, ethnicity, or environment.[3] What does seem likely, given the advances in the both the understanding of the autoimmune nature of the disease and improvements in conservative management as well as more specific therapeutic options, is that the natural IMN history, classically the rule of thirds (one third spontaneous remission, one third persistent proteinuria and one third progressive renal failure), has altered.[4,5]

Although the incident biopsy rate of IMN in the North American population has changed little, as evidenced by data over the past 30 years from the Toronto Glomerulonephritis Registry, despite widened population ethnicity (Table 1),[6] there has also been minimal change in numbers from the dominant Caucasian population served by the Mayo Clinic[7] and the Scottish Renal Association, Renal Biopsy Registry.[8] In all instances, IMN remains near the top of the list of the most common incident GN variants.[5,9,10] What has changed is that the average age at presentation has increased by approximately 2 decades and when combined with the global issue of obesity, increases the risks of our current therapeutic options and brings into focus the need for more precise management tools and more specific therapies now potentially offered by our new understanding of the nature of the pathobiology of the disease.

The new biology of autoimmune disease

Discovery of the specific autoimmune mechanism and autoantigen phospholipase A2 receptor. IgG antibody has been associated with the glomerular lesion of IMN since the 1960s, but the autoimmune nature of the antibody specificity was not determined until 2009 with the identification of phospholipase A2 receptor (PLA2R) on podocytes as the target antigen in >70% of cases.[11] Sera from IMN patients with active disease was found to contain a circulating autoantibody, predominantly of the IgG4 subclass, that reacted by Western blotting on high molecular protein bands only on unreduced sodium dodecylsulfate gels. Analysis of relevant protein bands by mass spectrometry identified PLA2R as the target antigen. The PLA2R gene had previously been cloned[12] but in the context of studies on the PLA2 enzyme not MN.

Table 1 | Trends in Toronto Glomerulonephritis Registry: 1975–2015[a]

	1975–1979	1980–1984	1985–1989	1990–1994	1995–1999	2000–2004	2005–2011	2012–2015[a]	Total
MN	134	172	171	164	129	138	230	168	1306
MPGN	99	67	33	46	37	22	34	N/A	329
FSGS	141	164	163	239	311	318	338	288	1962
IGA	129	215	227	262	309	299	349	286	2076
LUPUS	170	191	143	174	136	130	262	N/A	1206
Vasculitis	29	66	76	93	76	87	152	N/A	579

FSGS, focal segmental glomerulosclerosis; IGA, IgA nephropathy; MN, membranous nephropathy; MPGN, membranoproliferative glomerulonephritis; N/A, not available.
[a]In 5-year blocks (4-year block, 2012–2015).

Genetics of idiopathic (A)MN. Initially, IMN was associated with human leukocyte antigen (HLA) DR,[13] then, with the advent of molecular typing, DQA1.[14] The first DQA1 in IMN reported in 2011 confirmed DQA1 and identified PLA2R as the second gene with strong interaction between these 2 genes, supporting genetic susceptibility in a high percentage of previously defined IMN.[15] Sequencing of the PLA2R gene in 100 IMN cases identified no amino acid changes in the structure specific to MN.[16] A recent combined approach using a denser single nucleotide polymorphism dataset based on the 1000 Genomes Project of genotype imputation, genome-wide association study, and human leukocyte antigen imputation investigated the genetic IMN risk variants in a more comprehensive way[17] but found no other significant loci linked to IMN and no sex-specific links to explain the male predominance. Evidence from both lines of investigation of antibody specificity and genome-wide association study confirms PLA2R as the major autoimmune antigen in IMN.

The nature of PLA2R. The antigen PLA2R belongs to the mannose receptor structural family consisting of the mannose receptor, DEC205, Endo180, and FcRY.[18] The main function of the human receptor remains undefined. It is assumed to be a receptor for human PLA2 based on structural homology to rodent and rabbit homologues that show high affinity binding for their homologous PLA2 ligands.[19] However, there is no published evidence of direct binding of human PLA2 by human PLA2R. Indeed, there is evidence that human sPLA2-1B and sPLA2-IIA do not bind human PLA2R.[20] The true ligand may be a rare PLA2 species or even another protein.

PLA2R, like its family member FcRY, displays a pH-induced structural change in shape, but there is no evidence that it is important for autoantibody binding.[21] Other members of the mannose receptor family bind type IV collagen, but the evidence of PLA2R doing so is controversial.[22,23] The Manchester model of PLA2R, accurate to 20 Å, shows a compact N-terminal ring formed by the ricin domain with a C-terminal tail of CTLD4-8 domains.[24] The dominant epitope recognized by anti-PLA2R is present in the N-terminal ricin domain. The synthetic peptide containing a linear sequence and disulfide-linked ring retains the ability to interact with the autoantibody with high affinity. The affinity of anti-PLA2R antibodies to the ricin epitope is very high at 1×10^{-10}M, which has possible implications for clinical interpretation of anti-PLA2R positivity status. Some patients who are low producers of antibody may appear to be seronegative until the antibody has saturated the PLA2R binding sites on podocytes and only then become seropositive. In practical terms, the high affinity of anti-PLA2R means that PLA2R tissue positivity (PLA2R antigen in the glomerular basement membrane immune complexes) can account for 80% to 90% of cases, including those showing low or even absent seropositivity.[25]

Two other domains in PLA2R, namely, CTLD1 and CTLD7, have been identified as targets for some anti-PLA2R antibodies,[26] but these seem to appear only consequent to the development of autoantibodies to the dominant ricin epitope and are likely to represent epitope spreading as the immune response to PLA2R matures over time. Although autoantibodies to the N-C3 fragment[27] probably describe those to the ricin and CTLD1 domains, this must be tested in much larger prospective studies as must the clinical utility of antidomain epitopes in characterizing the maturity of the immune response to PLA2R.

Other target antigens. In 2014, a second autoantigen, thrombospondin type 1 domain–containing 7A (THSD7A), was described in A(I)MN accounting for perhaps 5% of cases.[28] Initially, it was reported that patients are either seropositive for anti-PLA2R or anti-THSD7A but not for both antigens, but a few cases of dual antibody positivity on renal biopsy staining have recently been identified.[29] The genetic susceptibility to anti-THSD7A MN has not yet been determined, but the very strong association of HLA DQA1 pathologic allele in biopsy-proven A(I)MN suggests a common HLA gene in anti-PLA2R and anti-THSD7A MN, but in the latter, single nucleotide polymorphisms in THSD7A versus PLA2R will be the marker of involvement. That 10% to 20% of A(I)MN cases are anti-PLA2R and anti-THSD7A seronegative raises the possibility that other autoantigen-autoantibody systems may exist. Cytoplasmic antigens (e.g., alpha enolase, aldose reductase, and superoxide dismutase) have been proposed as candidates[30,31] but have not been widely confirmed.

The interaction of complement and autoantibodies

The role of complement in inducing proteinuria in experimental MN models has long been clear,[32,33] and in human studies, urinary C5b-9 complexes appeared as a possible biomarker of disease activity.[34–37] Recently, there have been new insights that support a potentially significant role in human IMN but are currently based on complement