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Narrative Review

Membranous Nephropathy: A Journey From Bench to Bedside

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Lessons from an animal model that faithfully resembles human membranous nephropathy (MN) have informed our understanding of the pathogenesis of this organ-specific autoimmune disease and common cause of nephrotic syndrome. After it was established that the subepithelial immune deposits that characterize experimental MN form in situ when circulating antibodies bind to an intrinsic podocyte antigen, it was merely a matter of time before the human antigen was identified. The M-type phospholipase A_2 receptor 1 (PLA_2R) represents the major target antigen in primary MN, and thrombospondin type 1 domain-containing 7A (THSD7A) was more recently identified as a minor antigen. Serologic tests for anti-PLA_2R and kidney biopsy specimen staining for PLA_2R show >90% specificity and 70% to 80% sensitivity for the diagnosis of primary MN in most populations. The assays distinguish most cases of primary MN from MN associated with other systemic diseases, and sequential anti-PLA_2R titers are useful to monitor treatment response. A positive pretransplantation test result for anti-PLA_2R is also helpful for predicting the risk for posttransplantation recurrence. Identification of target epitopes within PLA_2R and the genetic association of primary MN with class II major histocompatibility and *PLA2R1* variants are 2 additional examples of our evolving understanding of this disease.

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In the late 1970s, 2 groups of investigators, one based in the Netherlands and the other in Boston, MA, were studying Heymann nephritis, a rat model of experimental membranous nephropathy (MN), and made an observation that changed our understanding about the pathogenesis of MN.[1-3] Until that time, it was believed that all forms of immune-complex glomerulonephritis (ie, those characterized by granular immune deposits on immunofluorescence [IF] and electron densities on electron microscopy) were due to circulating immune complexes passively trapped in glomeruli. However, the new work conclusively showed that the deposits in experimental MN formed in situ when circulating immunoglobulin G (IgG) antibodies bound to a yet to be characterized intrinsic glomerular antigen.[3] Although the location of the intrinsic antigen on the glomerular capillary wall was not defined, we speculated that it might be a component of the visceral epithelial cell (podocyte) surface.[1] Some years later, a confluence of studies from several groups identified megalin, a large transmembrane protein member of the low-density lipoprotein receptor family, as the intrinsic antigen and showed that it is expressed on the soles of podocyte foot processes, where it can be engaged by circulating IgG antibodies.[4-8] This finding led to a search for anti-megalin antibodies in patients with MN, which proved futile: human podocytes do not express megalin, although it is abundant in the human proximal tubular brush border.[8] This, and the failure by several investigators to identify another candidate podocyte antigen, created some doubt about whether the in situ paradigm established in Heymann nephritis also applied to human MN. This doubt was finally dispelled in 2002: interest in the identity of one or more podocyte antigens in human MN was rekindled when Debiec et al[9] described a remarkable case of neonatal MN in which transplacental passage of anti-neutral endopeptidase (NEP) antibodies from a presensitized NEP-deficient mother bound to NEP on the baby's podocytes.

MN is a common cause of nephrotic syndrome in adults, with a peak occurrence in decades 5 to 6, although the age range of onset is broad.[10] Most cases (~80%) are primary (formerly called idiopathic MN), but MN may be secondary to systemic lupus erythematosus (class V lupus nephritis), infection

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with hepatitis B virus or other agents, solid cancers, and various drugs or toxins. MN may also occur as the result of an alloimmune response, for example, de novo MN after kidney transplantation and during chronic graft-versus-host disease after allogeneic stem cell transplantation, and also as neonatal MN, as noted previously. Primary MN is an organ-specific autoimmune disease. The characteristic pathologic features are a noninflammatory glomerular lesion with glomerular basement membrane thickening (often seen as spike-like extrusions or craters in the glomerular basement membrane) on Jones silver stain, granular capillary wall deposits of IgG and complement on IF, and subepithelial immune deposits on electron microscopy with extensive podocyte foot-process effacement. Primary MN may be distinguished from secondary MN by its predominant IgG4 and absent C1q. The clinical course is variable, with spontaneous remission reported in up to one-third of cases and progression to end-stage renal disease (ESRD) in a similar number. Recurrence of primary MN after kidney transplantation is common and may lead to transplant loss, as we discuss later.

In 2009, we reported on the identification of the M-type phospholipase A_2 receptor (PLA_2R) as a major target antigen in human primary MN.[11] This finding followed several years of experimentation with extracts of normal human glomeruli and MN patient sera using Western blotting and mass spectrometry and the serendipitous discovery that human MN autoantibodies only recognize the antigen PLA_2R under nonreducing conditions (ie, the epitope[s] identified by anti-PLA_2R are conformation dependent). Our initial studies also showed that PLA_2R is expressed on podocytes and that anti-PLA_2R autoantibodies are present in a high proportion of, but not all, cases of primary MN; are predominantly of the IgG4 subclass (as is true of the immune deposits from which they can be eluted); are uniquely present in primary and not secondary MN; and are correlated with disease activity. As in the Heymann nephritis model, we also found that the distribution of PLA_2R shifted to become readily detectable in immune deposits in primary but not secondary MN (Fig 1), a finding that has been adopted by nephropathologists to define PLA_2R-associated MN.[12,13] Interestingly, our initial studies identified another putative antigen in a small number of anti-PLA_2R–negative cases that ultimately proved to be a second podocyte antigen: thrombospondin type 1 domain-containing 7A (THSD7A).[14] Like PLA_2R, THSD7A is expressed on podocytes and redistributes to form the subepithelial immune deposits.[14,15] It may account for up to 5% of cases of primary MN in Western countries, but has been reported in 9.1% of Japanese patients with primary MN, with an equal prevalence among women and men[16] (Box 1).

Our 2009 report[11] stimulated renewed interest in primary MN and led to the development of diagnostic tests, investigation of the genetic basis of MN, and exploration of the target epitope(s). As commercial immunoassays for anti-PLA_2R become more widely used and more nephropathologists perform immunostaining of kidney biopsy specimens for PLA_2R, the value for these tests will become increasingly clear for the diagnosis and treatment of primary MN, the exclusion of secondary causes (especially cancer), and the prediction of posttransplantation recurrence. In this review, we focus on developments since the initial discovery of PLA_2R as a major target antigen in primary MN. The reader is referred elsewhere for updated discussions of the treatment of MN.[17-19]

Are the Available Serum Assays for Anti-PLA_2R Sensitive and Specific in Predicting Primary MN?

Anti-PLA_2R antibody has proved to be a valuable biomarker for the diagnosis of primary MN. It is also useful for monitoring disease activity and predicting

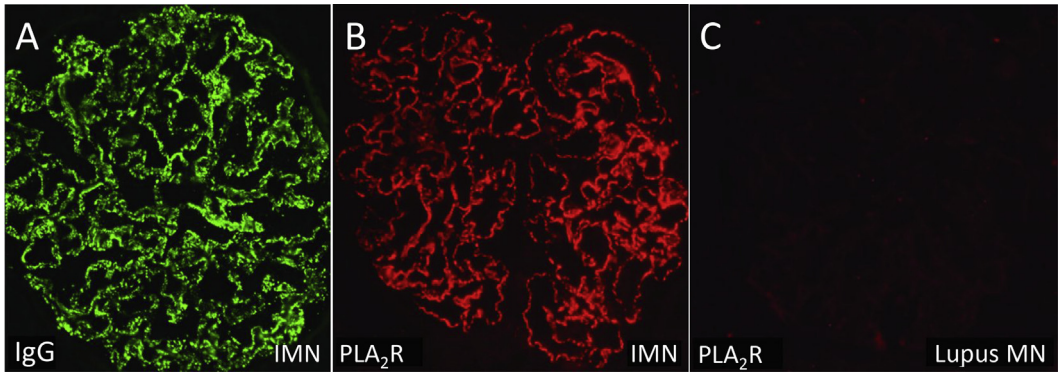

Figure 1. Immunofluorescence micrographs of kidney biopsy specimens from patients with (A, B) primary membranous nephropathy (MN) and (C) membranous lupus nephritis stained for (A) immunoglobulin G (IgG) and (B, C) phospholipase A_2 receptor (PLA_2R). Note the bright staining for PLA_2R in immune deposits in primary MN but not in lupus MN. Abbreviation: IMN, idiopathic membranous nephropathy.