Recent Advances and Prognosis in Idiopathic Membranous Nephropathy

Paul E. Segal and Michael J. Choi

Idiopathic membranous nephropathy (MN) is one of the most common causes of nephrotic syndrome. Recently, progress has been made in understanding the pathogenesis of idiopathic MN with the finding of M-type phospholipase A2 receptor (PLA2R) antibodies in the serum and immune complexes of glomeruli in the majority of adult idiopathic MN patients. In the future, the detection of M-type PLA2R antibodies may help distinguish patients with primary MN who require aggressive immunosuppressive therapy from those with secondary disease. Levels of circulating antibody to this receptor may help in monitoring disease activity and in gauging response to therapy, as changes in antibody levels may precede changes in proteinuria. The degree of renal dysfunction or change in renal function over time and the level of persistent proteinuria are key prognostic factors in the decision to initiate therapy in idiopathic MN patients. Although spontaneous remissions occur in ~30% of patients, partial and complete remissions help to define the clinical course of an individual patient.

Key Words: Proteinuria, Membranous nephropathy, Podocyte, Subepithelial deposits

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Idiopathic membranous nephropathy (MN) remains one of the most common causes of adult nephrotic syndrome, accounting for ~30% of biopsy cases, with up to one-third of patients progressing to ESRD. Idiopathic MN resembles the rat model of passive Heymann nephritis in which subepithelial immune deposits are formed against a target antigen located on the podocyte. These immune complex deposits activate the terminal complement pathway, leading to the assembly of C5b-9 membrane attack complex, which then inserts into the podocyte plasma membrane, creating the characteristic changes of proteinuria and glomerular basement membrane (GBM) expansion.[1] However, megalin, the target antigen identified in animal models, is not expressed on human podocytes.[2] This has led researchers to search for other potential target antigens in an attempt to understand the pathogenesis of MN and use antibody levels to these target antigens as biomarkers to gauge disease activity.

Role of the Phospholipase A2 Receptor (PLA2R)

Beck and colleagues, using kidneys from deceased transplant donors, performed Western blotting on protein extracts from normal human kidneys using serum from patients with idiopathic MN and detected a 185-kD glycoprotein present in 70% (26 of 37 patients) of MN patients.[3] This glycoprotein was not found using serum from patients with secondary MN, other glomerular diseases, or normal control subjects. Mass spectroscopy subsequently identified this protein as the M-type PLA2R, a type 1 transmembrane receptor of the mannose receptor family, which is highly expressed on the surface of glomerular podocytes. Podocytes are the only glomerular cells that express PLA2R, although PLA2R also is found in the lungs and on leukocytes. Anti-PLA2R IgG autoantibodies from patients with idiopathic MN were found to consist primarily of IgG4, the most abundant immunoglobulin subclass found in idiopathic MN immune deposits, with a smaller component of IgG1. PLA2R and IgG4 colocalized within subepithelial immune deposits in patients with idiopathic MN. Although classically IgG4 only minimally activates the complement, it is conceivable that for full expression of the pathologic glomerular changes, concomitant production of IgG1 autoantibodies is required. Alternatively, the mannose lectin or alternative pathways of complement activation associated with IgG4 may be involved. These antibodies from patients with idiopathic MN only recognize a conformation-dependent epitope. Binding of circulating antibodies to the PLA2R antigen on the podocyte surface generates subepithelial deposits in situ, which are not found in secondary causes of MN or other autoimmune diseases. After podocyte injury, exposure of cryptic epitopes may allow for the process of epitope spreading, where the immune response to non-PLA2R podocyte antigens may allow for cross-linkage by antibodies and play an active role in complement activation and proteinuria.[4]

Stanescu and colleagues recently have identified 2 risk alleles associated with idiopathic MN in whites: Human leukocyte antigen (HLA)-DQA1 (chromosome 6p21) and PLA2R1.[5] Interestingly, HLA-DQA1 showed a higher risk association than PLA2R1. Perhaps conformational changes of the HLA molecule alter the specificity of antigen presentation, making individuals with this HLA type

From Division of Nephrology, Johns Hopkins University School of Medicine, Baltimore, MD.

Address correspondence to Paul E. Segal, DO, Division of Nephrology, Johns Hopkins Bayview Medical Center, Johns Hopkins University School of Medicine, 301 Mason Lord Drive, Suite 2500, Baltimore, MD 21224. E-mail: psegal2@jhmi.edu

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more susceptible to autoantibody formation than those with PLA2R.

There is uncertainty with declaring PLA2R as the putative target antigen for MN. Circulating anti-PLA2 antibodies were not identified in 30% of idiopathic MN patients with significant proteinuria. Perhaps the current assay for detection of circulating anti-PLA2 antibodies may lack optimal sensitivity. Another possibility is that idiopathic MN may be a heterogeneous disease with various phases of immunologic activity. Alternatively, other potential target antigens, including aldose reductase, anti-manganese superoxide dismutase, and α-enolase, may be involved in the pathogenesis of MN.

Debiec and Ronco assessed the presence of PLA2R antibody in both serum and glomerular deposits of 42 consecutive patients and found that the absence of circulating PLA2R autoantibody does not rule out a diagnosis of PLA2R-related MN, as PLA2R immune deposits were found in glomeruli.[6] There were also 3 patients with high circulating PLA2R antibody levels without glomerular immune deposits, implying that either these antibodies were not causing disease or that the epitopes were poorly accessible in tissue. Beck and Salant proposed that the presence of detectable circulating anti-PLA2 antibodies defines the immunologically active phase of idiopathic MN, and that residual proteinuria may not represent ongoing disease activity, as subepithelial deposits take time to resorb. Proteinuria in idiopathic MN patients without detectable antibody may also result from cumulative structural damage to podocytes.[7] There is a linear correlation between anti-PLA2R antibody levels and degree of proteinuria, with, on average, 2 to 3 g of proteinuria in those MN patients with absent antibody levels. The recent identification of anti-PLA2R autoantibodies before and after transplantation in a case of recurrent MN provides further proof of a potential causative role, and may allow the clinician to identify a subgroup of individuals with potential risk of recurrence in the transplant.[8] However, further studies assessing donor and recipient PLA2R genotype, HLA, the composition of immune deposits, and detailed analysis of PLA2R antibody levels are needed to determine the role of anti-PLA2R antibodies in renal transplantation; nevertheless, the identification of anti-PLA2R antibodies should not preclude transplantation.

The absolute specificity of PLA2R antibodies for ruling out secondary causes of MN remains somewhat controversial, as these antibodies were detected in some patients with hepatitis B, systemic lupus erythematosus (SLE), malignancy, and sarcoidosis.[9,10] PLA2R is likely a major target antigen in the pathogenesis of MN; however, further studies are required to fully elucidate its role and that of PLA2R antibody levels in determining immunologic activity and prognosis.

CLINICAL SUMMARY

- The M-type phospholipase A2 receptor, expressed on glomerular podocytes, has been identified as a major antigen in idiopathic MN, occurring in up to 70% of patients, and antibodies to the PLA2R may be associated with the disease.
- Approximately 30% of patients with idiopathic MN undergo spontaneous complete remission within 5 years.
- Creatinine clearance and the degree of proteinuria over 6 months classify patients with idiopathic MN into low, moderate, and high risk for progressive CKD and help guide the decision to start immunosuppressive therapy.
- Superimposed FSGS is common in patients with idiopathic MN, but the severity and chronicity of glomerular and tubulointerstitial lesions on renal biopsy do not preclude response to therapy.

Alternative PLA2R Target Antigens

There are other possible antigens involved in the pathogenesis of MN. Prunotto and colleagues used a proteomic approach to identify anti-aldose reductase and anti-manganese superoxide dismutase IgG4 in the sera and glomeruli of patients with idiopathic MN and found levels significantly increased compared with normal subjects and patients with focal glomerulosclerosis (FSGS).[11] These antibodies also were eluted from the glomeruli of 3 patients with MN, and they colocalized with both antigens and C5b-9 in electron-dense glomerular immune deposits. These antibodies were not eluted from the biopsy specimens with other forms of glomerulonephritis. The authors hypothesized that oxidative stress may induce glomerular expression of these antigens, with antibody formation playing a role in onset or maintenance of MN.

Bruschi and colleagues detected specific IgG1 and IgG4 reacting with podocyte α-enolase eluted from microdissected glomeruli, and confocal and immune electron microscopy showed colocalization of α-enolase with IgG4 and C5b-9 in immune deposits.[12] Serum levels of anti-α-enolase IgG4 were found to be elevated in 33 of 131 (25%) untreated MN patients. However, anti-α-enolase antibody levels did not correlate with pretreatment proteinuria or serum creatinine levels in these patients. Ronco and Debiec[13] recently developed a sensitive enzyme-linked immunosorbent assay using recombinant human neutral endopeptidase (NEP), which revealed low levels of anti-NEP antibodies in a substantial portion of adult patients with idiopathic MN. NEP has been shown to be a target antigen in alloimmune antenatal MN in mothers deficient in NEP.

Recently food proteins have been proposed as putative triggering agents for a wide variety of autoimmune diseases, including celiac disease, multiple sclerosis, rheumatoid arthritis, and type 1 diabetes mellitus. Debiec and colleagues used enzyme-linked immunosorbent