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## Idiopathic membranous nephropathy and anti-phospholipase A2 receptor antibodies

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Membranous nephropathy (MN) is a glomerular disease due to subepithelial immune deposits and local complement activation resulting in podocyte injury and proteinuria. Patients with idiopathic (but not secondary) MN had circulating autoantibodies, predominantly of the IgG4 subclass, directed against M-type phospholipase A2 receptor (PLA2R) located on podocytes. It is also possible that the binding of anti-PLA2R antibodies to PLA2R on podocytes could alter receptor function resulting in podocyte dysfunction.

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### Editorial

Membranous nephropathy (MN) is a glomerular disease due to subepithelial immune deposits and local complement activation resulting in podocyte injury and proteinuria (1). With a peak incidence in the fourth and fifth decades, MN is more prevalent in men than women. Proteinuria, often in the nephrotic range, is the hallmark of MN. Microscopic hematuria and hypertension are present in approximately 50% and 25-50% of patients, respectively. In approximately 75% of cases, MN is idiopathic because no obvious cause can be identified. Im-

munohistologically, MN is characterized by subepithelial deposition of predominantly IgG, complement C3 and terminal complement complex C5b-9, also known as membrane attack complex. Ultrastructural examination reveals subepithelial electron-dense deposits and foot process effacement of podocytes. The clinical course of idiopathic MN is quite variable. Spontaneous resolution occurs in up to one third of the patients; in another third, proteinuria persists for years while solute clearance remains unaffected; the final third demonstrates a progressive decline in renal function over time. Predictors of poor renal outcome are advanced age, male gender, heavy

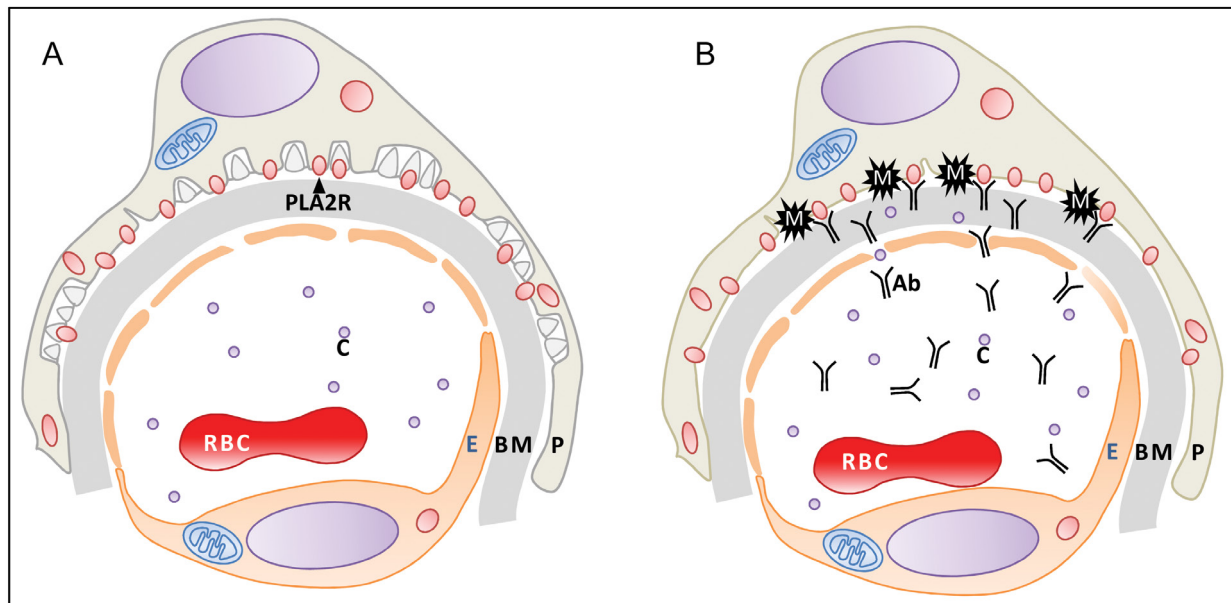
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proteinuria, hypertension, glomerulosclerosis, interstitial fibrosis, and renal insufficiency at presentation. Anti-proteinuria strategies, including inhibition of the renin-angiotensin system, are recommended for all patients with MN. Immunosuppressive therapy is reserved for those who demonstrate predictors of poor renal outcome.

Idiopathic MN is considered an autoimmune disease targeting podocytes. The exact etiology and pathogenesis of idiopathic MN are incompletely understood. Although Heymann nephritis in the rat has served as an excellent model to dissect the mechanisms involved in MN, attempts to demonstrate megalin on podocytes and circulating anti-megalyn antibodies in human idiopathic MN have failed. Recent investigations have shed some light on the pathogenesis of idiopathic MN. Beck and colleagues have shown that 70% of patients with idiopathic (but not secondary) MN had circulating autoantibodies, predominantly of the IgG4 subclass, directed against M-type phospholipase A2 receptor (PLA2R) located on podocytes (2). Furthermore, they showed that subepithelial immune deposits contained IgG4 and PLA2R. In addition, the presence of circulating anti-PLA2R antibodies correlated with disease activity. Ardalan and colleagues found a similar prevalence for circulating anti-PLA2R antibodies among Iranian patients with idiopathic MN (3). They detected anti-PLA2R antibodies in sera from 74% (17/23) of patients with idiopathic MN and in none from seven control cases, including two with secondary MN. They also examined a possible correlation between the level of circulating anti-PLA2R antibodies and the degree of proteinuria. Although there seemed to be a trend for a direct correlation, it did not reach statistical significance, likely due to the small sample size.

It is worth mentioning that it remains to be

seen how the binding of anti-PLA2R antibodies to PLA2R causes podocyte injury and proteinuria in idiopathic MN. The preponderance of evidence drawn from experiments using Heymann models of MN indicated that subepithelial immune deposits provoke local complement activation and podocyte injury. It is conceivable that the binding of anti-PLA2R antibodies to PLA2R could activate complements (Figure 1). In fact, complement C3 and membrane attack complex were present in subepithelial immune deposits in 80% and 50% of patients with idiopathic MN, respectively (4). Subepithelial immune deposits in idiopathic MN contain predominantly IgG4 and small amounts of IgG1 (5). IgG4 has a low or negligible affinity for the versatile pattern recognition molecule of the classical pathway C1q (6). Therefore, IgG4 does not activate complements through the classical pathway effectively. IgG1, however, has a strong affinity for C1q and can induce complement activation. It is also possible that the binding of anti-PLA2R antibodies to PLA2R on podocytes could alter receptor function resulting in podocyte dysfunction. PLA2R is a transmembrane receptor for secreted PLA2 (sPLA2), which catalyzes the hydrolysis of phospholipids to fatty acids and lysophospholipids (7). PLA2R might be involved in removal and inactivation of sPLA2 from biological fluids (7). PLA2R could also mediate receptor-dependent actions of sPLA2 such as those involved in cell proliferation and inflammation (7). Considering the presence of a multitude of sPLA2 isoforms that exhibit distinct distribution patterns and enzymatic specificities, the physiological roles of sPLA2 are rather complex and context-dependent. Ardalan et al. also demonstrated a direct correlation between anti-PLA2R and anti-sPLA2 antibodies in the sera from Iranian patients with idiopathic MN. This intriguing finding



**Figure 1. Anti-phospholipase A2 receptor antibodies and idiopathic membranous nephropathy.** A peripheral capillary loop from a normal glomerulus is shown (A). The basement membrane separates endothelium from podocyte. Phospholipase A2 receptors (PLA2R) are localized on podocyte foot processes. In idiopathic membranous nephropathy, autoantibodies bind to PLA2R and activate complements resulting in the formation of membrane attack complex and podocyte injury (B). Ab, anti-PLA2R antibodies; BM, basement membrane; C, complements; E, endothelial cell; M, membrane attack complex; P, podocyte; RBC, red blood cell.

needs confirmation and raises the possibility that sPLA2 could be involved in the pathogenesis of idiopathic MN.

### Authors' contributions

AN wrote the manuscript. AA made substantial contributions to conception and design as well as revised the manuscript critically for important intellectual content.

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### Conflict of interest

The authors declare no conflicts of interest.

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