New insights into the pathogenesis of membranous nephropathy

Membranous nephropathy (MN) is a leading cause of nephrotic syndrome in adults. The target of injury in MN is the glomerular visceral epithelial cell or podocyte, a highly specialized and terminally differentiated cell that rests on the outside of the glomerular basement membrane. Proteinuria follows the formation of subepithelial deposits, which is associated with podocyte flattening and effacement. With time, there is thickening of the glomerular basement membrane (GBM) due to an increase in the accumulation of extracellular matrix protein synthesis by podocytes.

In an attempt to develop specific therapy for MN, researchers have focused on the rat model of passive Heymann nephritis, because it closely resembles many of the features of the human disease [1]. Because the presence of subepithelial deposits suggested to researchers early on that MN is an immune-mediated disease, the first area of search was to identify the antigen(s) responsible for the membranous lesion. After many years, Kerjaschki, Farquhar and others have identified the antigen as the Megalin-receptor associated protein complex in experimental MN [2]. However, at this time the identification of the human antigen remains elusive. A second major area of research has been the recognition that antibody binding to the membranous antigen activates complement, leading to the insertion of C5b-9 (membrane attack complex) into the podocyte plasma membrane [3]. Over the past 10 years studies have clearly documented a critical role for C5b-9-induced podocyte injury leading to the development of proteinuria.

The third area of research is to delineate the mechanisms underlying the podocyte’s response to C5b-9 injury, which include hypertrophy, matrix production, and the maintenance of a well-differentiated and quiescent phenotype, and to determine how these events translate into proteinuria and progressive glomerulosclerosis. In this regard, Cybulsky and colleagues have provided new insights into the regulation of phospholipase A₂ (PLA₂) in the podocytes in response to C5b-9-induced injury [4]. Previous studies showed that C5b-9 activates the release of oxidants in passive Heymann nephritis, and that treating these animals with antioxidants significantly reduces the proteinuria [5]. Proteinuria may also be due to a C5b-9 induced increase in specific proteinases (gelatinase and metalloproteinase-9) [6]. The characteristic thickening of the glomerular basement membrane in MN is due to the accumulation of extracellular matrix proteins. Studies have shown that specific isoforms of transforming growth factor-β (TGF-β) and their receptors are potential mediators of matrix accumulation in Heymann nephritis [7]. In contrast to the mesangial and endothelial cells, podocytes do not readily undergo proliferation in response to immune-mediated injury, but rather hypertrophy. The apparent inadequate proliferative response may underlie the development of progressive glomerulosclerosis in certain forms of glomerular disease. Recent studies have shown that the expression of specific cell cycle proteins are altered following C5b-9 attack on podocytes in vitro and in vivo, and that these prevent the proliferative response of podocytes to C5b-9-mediated injury [8, 9].

There is a growing body of literature showing that the response to C5b-9 injury is not merely due to the creation of holes in the cell membrane, but rather are due to the activation of specific signal pathways. Thus, sublytic C5b-9 activates the phospholipase C, protein kinase C and extracellular signal-regulated kinase-2 signal pathways [10]. Why did Cybulsky et al study phospholipase A₂ (PLA₂) [4], an enzyme that releases free arachidonic acid from phospholipids? Arachidonic acids are precursors for the synthesis of eicosanoids (prostaglandins, thromboxanes, leukotrienes), which are increased in the passive Heymann nephritis model. Furthermore, inhibiting specific eicosanoids has confirmed their role in the development of proteinuria and increased intraglomerular pressures in MN [11–15]. In their current study, Cybulsky and colleagues show that cytoplasmic PLA₂, but not the soluble PLA₂ isoform, was activated by C5b-9 in podocytes in culture, and also in the glomeruli of rats with experimental membranous nephropathy [4]. This was not associated with an increase in gene expression for either the cytoplasmic or soluble PLA₂ isoforms. This study thus provides further insights into the complexities of C5b-9-induced injury to podocytes, and also into the pathogenesis of MN. Perhaps reducing phospholipase activity may be another potential way of interrupting...

**Key words:** podocyte, membranous nephropathy, C5b-9, complement, glomerular epithelial cell.

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the disease process in patients with membranous nephropathy.

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