Why study membranous nephropathy in rats?

Membranous nephropathy (MN) is an important cause of nephrotic syndrome and end-stage renal disease in adults. The current treatment of this disease remains inadequate and nonspecific. To design more rational therapy, it would be useful if we really understood basic disease pathophysiology. Since only limited information can be obtained from the direct study of diseased humans, animal models are very helpful in our capacity to understand pathogenesis. In the case of MN, we are fortunate to have the accurate Heymann nephritis (HN) experimental MN model in rats, which has been studied for almost 45 years.

What has the HN model taught us about the pathogenesis of MN? Initially, it was considered to be a disease in which circulating immune complexes accumulated in the subepithelial space. It later became clear that antibodies were directed against intrinsic podocyte antigens, such as the rat megalin–receptor associated protein (RAP) complex, and that these antibodies progressively accumulated over time to form the typical subepithelial immune complexes. Complement activation by these podocyte-associated immune complexes was required for proteinuria to occur [1]. The classic study of Cybulsky et al [2] showed that activation of C5b-9 was pathogenic and that the podocyte was the focus of injury in experimental MN. Subsequently, Kerjaschki et al [3] directly visualized the insertion of C5b-9 into podocytes.

The concept that podocyte abnormalities could lead to proteinuria underwent a resurgence with the discovery of the podocyte protein nephrin, which is mutated in congenital nephrotic syndrome [4]. Since then, a great deal of effort has gone into defining the composition and architecture of the podocyte slit diaphragm, and how genetic abnormalities of slit diaphragm proteins can lead to altered glomerular permselectivity [5]. It is likely that acquired abnormalities of slit diaphragm proteins will have similar consequence to these inherited conditions, which is now an area of active research [6].

What happens to the slit diaphragm in HN? Early ultrastructural studies clearly showed that the slit diaphragm was altered in HN [7]. With the recent discovery of a number of podocyte proteins, it has become possible to be more specific about slit diaphragm events occurring in HN. In previous work from the Salant lab [8], the quantity of glomerular nephrin was reduced as the disease advanced, which corresponded with its altered distribution. Examining ZO-1- and CD2-associated proteins that were not appreciably changed in HN showed that this was not ubiquitous to all slit diaphragm proteins.

In this issue of Kidney International, Saran et al [9] have gone one step further to define events occurring in the slit diaphragm in HN. Here they have shown that the redistribution and loss of nephrin requires complement activation. The presence of subepithelial immune complexes was not sufficient to induce these abnormalities alone—an intact complement system was necessary. Furthermore, this reduced nephrin was attributable to a diminished pool of nephrin associated with actin. Importantly, by studying early events, they were able to provide evidence that the alteration in actin-associated nephrin was a cause of proteinuria and not simply an effect of the proteinuria.

Thus, the current paradigm for the pathogenesis of HN has antibodies to podocyte proteins, such as to the megalin-RAP complex, accumulating over time in subepithelial immune deposits. Once a threshold amount of antibody has accumulated [10], productive complement activation ensues, leading to C5b-9 insertion into the podocyte plasma membrane. Such C5b-9 insertion can have a number of effects on the podocyte, including the activation of specific signal pathways [11]. Relevant to the slit diaphragm, there are several possible effects of C5b-9, including ATP depletion, altered phosphorylation state of nephrin, and a primary defect in podocyte actin. Irrespective of exact mechanism, the C5b-9–mediated dissociation of nephrin from actin, its redistribution and loss potentially into the urine [12] are associated with disruption of slit diaphragms and consequent proteinuria.

What is the relevance of HN in rats to MN in humans? Clearly, the subepithelial deposits in human MN contain immune complexes; the specific antigens, be they intrinsic podocyte proteins or extrinsic to the podocyte, have been elusive. There is evidence that nephrin quantity is reduced in MN [13, 14], comparable to what has been shown in HN. Perhaps of greatest importance to clinicians concerns the C5b-9–mediated pathogenesis of HN. Because the evidence was so compelling that C5b-9 was relevant in rats, a multicenter study using a humanized anti-C5 monoclonal antibody [15] has been completed. Although there was no effect apparent in a short-term study over 16 weeks, encouraging results were seen with the one-year open-label extension of this study. For example, the two nephrotic patients enrolled from our site at the University of Chicago have gone into complete...
remission with anti-C5 treatment, and this has extended beyond cessation of therapy. If these data stand up to more careful study, we will have in hand a specific means of treating human MN. This will have made the 45 years of studying HN useful.

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