In Search of the Elusive Membranous Nephropathy Antigen

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Work on the Heymann nephritis model of experimental membranous nephropathy (MN) in rats in the Couser and Hoedemaeker labs in the late 1970s established that the characteristic subepithelial immune deposits form in situ [1–3]. The target antigen gp330/megalin was subsequently identified by Kerjaschki and Farquhar [4, 5] and shown to reside on rat podocytes; however, megalin is not expressed on human podocytes. Nonetheless, more recent observations by Debiec et al. [6, 7] in an alloimmune form of neonatal MN in babies born to mothers with a homozygous deficiency of neutral endopeptidase (NEP) validated the in situ paradigm in human MN. The mothers were sensitized to NEP by a previous pregnancy and developed circulating anti-NEP alloantibodies that crossed the placenta and bound to NEP on the babies' podocytes.

With this background we embarked on a search for the target antigen in idiopathic MN using patient sera and proteins extracted from glomeruli isolated from normal human donor kidneys that were unsuitable for transplantation. On Western blot analysis we found that sera from almost 70% of patients with idiopathic MN – but not secondary (lupus and hepatitis B) MN, other proteinuric diseases, or normal controls – had circulating antibodies to a reduction-sensitive glycoprotein that is expressed on normal human podocytes. One might ask: why aren't 100% positive? It could be the technical limitations of the assay, or that idiopathic MN might not be a uniform disease and may have different antigens. The possibility that

I favor is that antibodies may wax and wane with disease activity during the clinical course, and the presence of proteinuria in MN does not necessarily imply immunological activity.

Another interesting finding is that most of the reactivity to the MN antigen resides in the IgG4 subclass. This is significant because most of the immunoglobulin that is deposited in the glomeruli of patients with MN is IgG4. However, the serum of several patients also has lesser amounts of IgG1 reactivity to the antigen. This is noteworthy because we believe that the podocyte injury that occurs in MN is complement-mediated [8, 9], and IgG4 does not fix complement; however, IgG1 does. We have also obtained repeat samples from a few patients with MN and found that the presence of the antibodies corresponds to disease activity in that they disappear during drug-induced or spontaneous remission and reappear with relapse. These findings have clear implications for the diagnosis of idiopathic MN and for monitoring the response to treatment.

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References

- 1 Couser WG, Steinmuller DR, Stilmant MM, Salant DJ, Lowenstein LM: Experimental glomerulonephritis in the isolated perfused rat kidney. *J Clin Invest* 1978;62:1275–1287.
- 2 Van Damme BJ, Fleuren GJ, Bakker WW, Vernier RL, Hoedemaeker PJ: Experimental glomerulonephritis in the rat induced by antibodies directed against tubular antigens. V. Fixed glomerular antigens in the pathogenesis of heterologous immune complex glomerulonephritis. *Lab Invest* 1978;38:502–510.
- 3 Couser WG, Salant DJ: In situ immune complex formation and glomerular injury. *Kidney Int* 1980;17:1–13.
- 4 Kerjaschki D, Farquhar MG: The pathogenic antigen of Heymann nephritis is a membrane glycoprotein of the renal proximal tubule brush border. *Proc Natl Acad Sci USA* 1982;79:5557–5561.
- 5 Kerjaschki D, Farquhar MG: Immunocytochemical localization of the Heymann nephritis antigen (GP330) in glomerular epithelial cells of normal Lewis rats. *J Exp Med* 1983;157:667–686.
- 6 Debiec H, Guignon V, Mougnot M, Decobert F, Haymann JP, Bensman A, Deschenes G, Ronco PM: Antenatal membranous glomerulonephritis due to anti-neutral endopeptidase antibodies. *N Engl J Med* 2002;346:2053–2060.
- 7 Debiec H, Nauta J, Coulet F, van der Burg M, Guignon V, Schurmans T, de Heer H, Soubrier F, Janssen F, Ronco PM: Role of truncating mutations in MME gene in fetomaternal allo-immunization and antenatal glomerulopathies. *Lancet* 2004;364:1252–1259.
- 8 Salant DJ, Belok S, Madaio MP, Couser WG: A new role for complement in experimental membranous nephropathy in rats. *J Clin Invest* 1980;66:1339–1350.
- 9 Cybulsky AV, Quigg RJ, Salant DJ: Experimental membranous nephropathy redux. *Am J Physiol* 2005;289:F660–F671.