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Commentary

Membranous Nephropathy: The Journey Continues …

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With the discovery of the phospholipase A_2 receptor (PLA_2R) and thrombospondin type-1 domain-containing 7A (THSD7A) as target antigens in 80% of patients with primary membranous nephropathy clinical and experimental research as well as patient management can be better adapted to the pathophysiology of the disease (Beck et al., 2009; Tomas et al., 2014). This is still not possible in the remaining 20% of patients, in whom no pathogenic antibodies or pathophysiologic disease mechanisms are known. It is probable, that in these patients different antibodies and pathophysiologic mechanisms lead to the development of membranous nephropathy. In some of those patients another underlying disease may be the first step in initiating the disease. Thus, a better understanding of the pathophysiology is needed. In the case presented by Buelli et al. the authors investigate possible mechanisms how an underlying disease, in this case IgG4-related disease, might lead to the development of membranous nephropathy (Buelli et al., 2015). They show that circulating IgG4 anti-carbonic anhydrase II antibodies can bind to carbonic anhydrase II on the podocyte surface. In cultured podocytes, IgG4 leads to a podocytic stress reaction and externalization of SOD2 which could serve as neoantigen under *in vivo* conditions. Should this hypothesis in fact apply, it could explain another mechanism of disease induction in human membranous nephropathy. Furthermore, the presented data in this study support the hypothesis that neoantigens may develop during the course of membranous nephropathy, which would add to the observations made by Murtas et al. earlier (Murtas et al., 2012).

The pathophysiology of membranous nephropathy has drawn the interest of clinical, histological and experimental research over many years. The potential role of the immune system in the development of this disease was assumed more than 50 years ago, when IgG was detected in the glomerular basement membrane in patients with membranous nephropathy (Mellors et al., 1957). Findings in the rat model of Heymann's nephritis further strengthened the hypothesis of membranous nephropathy being an antibody-mediated autoimmune disease (Heymann et al., 1959). The question which mechanism leads to subepithelial immune complex formation in humans, whether it is the re-formation of circulating immune complexes or the *in situ* formation by binding of circulating antibodies to a target antigen on the podocyte surface remained a matter of discussion for many years. A first confirmation that *in situ* immune complex formation is induced by binding of circulating antibodies to a podocytic antigen and leads to the development of membranous nephropathy in humans came in 2002 (Debiec et al., 2002). Transplacental transport of antibodies against neutral endopeptidase from the mother to the fetus led to membranous nephropathy in the newborn. However, antibodies to neutral endopeptidase were not found to be responsible for the initiation of membranous nephropathy in adults. The major breakthrough in elucidating the pathophysiology of membranous nephropathy came with the identification of the PLA_2R as the target antigen in 70% of patients with membranous nephropathy (Beck et al., 2009). Circulating PLA_2R antibodies bind to the podocytic PLA_2R antigen leading to immune deposit formation and membranous nephropathy. While confirming the *in situ* formation of immune complexes in these patients, these findings lead to more questions about the genesis of membranous nephropathy, most importantly, how the disease develops in PLA_2R antibody negative patients. In some of these patients, THSD7A was identified as the podocytic target antigen with circulating antibodies against THSD7A (Tomas et al., 2014). These findings show that more than one podocytic antigen exists, and circulating antibodies against these antigens lead to membranous nephropathy. It is now clear that membranous nephropathy may have different pathologic backgrounds in individual patients.

The understanding how the disease develops is of outmost importance in order to develop new, specific treatment options. This is also important in patients with membranous nephropathy, who are negative for PLA_2R and THSD7A antibodies. In some cases membranous nephropathy is associated with other diseases; however, the association of the diseases might be coincidental and even in the cases of "true" secondary membranous nephropathy, very little data exist on how the underlying disease leads to formation of immune deposits. The work of Buelli et al. elucidates a possible mechanism of disease development in patients with IgG4-related disease and membranous nephropathy. The hypothesis of the authors suggests a two-step model of disease induction, where an antibody-independent or an antibody-induced podocytic lesion associated with IgG4-related disease results in the formation of podocytic neoantigens. These findings are important in

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several aspects and might have an impact on patient management, should they be confirmed *in vivo*. First, they shed more light on the relationship of IgG4-related disease to membranous nephropathy, suggesting that the two diseases are not merely coincidental. At the same time, this work points to another key question in the field: what is the role of these neoantigens in disease development, perpetuation or remission? This is important for patient care, because it may lead to the development of more specific treatment options and new biomarkers for disease activity and treatment response. To confirm such a hypothesis future studies will need to show that circulating antibodies against SOD2 are in fact present and persist in patients with membranous nephropathy and how they relate to disease activity over time. The clinical experience of patients with PLA_2R-associated membranous nephropathy already shows that the discovery of this antigen affects patient care (Hoxha et al., 2014). Further research on the pathomechanisms of membranous nephropathy should thus also focus on the aim to achieve tailored treatment options, addressing the issue of the need of an immunosuppressive therapy, versus supportive treatment without immunosuppression, which still has a number of severe side effects.

Disclosure

The authors declare no conflicts of interest.

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