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EDITORIAL COMMENTARY

(T-) Regulation of Immunity in Membranous Nephropathy

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Idiopathic membranous nephropathy (IMN), an important etiology of nephrotic syndrome in adults, is uncommon in childhood. Histologically, the entity is characterised by stiffening of the glomerular capillary walls due to formation of immune complexes, visible as 'spikes and craters' in the glomerular basement membrane on special stains, linear IgG deposits on immunofluorescence, and subepithelial deposits on electron microscopy. Our understanding of the pathophysiology of the condition has evolved considerably in the last two decades [1]. The Heymann nephritis rat model of the 1970s adequately mimicked human MN, but the implicated antigen, namely megalin (or LRP2), is not expressed in human podocytes. In 2002, the rare entity of neonatal MN was ascribed to alloimmunization of pregnant women who are congenitally deficient in neural endopeptidase (a membrane-bound zinc metalloproteinase) following exposure to the paternally derived placental antigen: placental transfer of maternal antibodies to the fetus was followed by *in situ* immune complex formation in the fetal/neonatal podocytes [2]. The identification, in 2009, of phospholipase A2 receptor (PLA2R), a podocyte transmembrane glycoprotein, as the key antigen evoking an autoimmune response, heralded a radical transformation in the management of MN [3]. Additional antigens were subsequently identified, including NEL-like protein 1 (NELL1), thrombospondin type 1 domain-containing 7A (THSD7A) and protocathedrin 7 (PCDH7) in adult-onset MN, sometimes associated with malignancy; semaphorin 3b (SEMA3B) in childhood-onset MN; and exostosin (EXT1, EXT2) and neural cell adhesion molecule 1 (NCAM1) in type V lupus nephritis. This led to the proposal of an antigen-based management algorithm that allows specific diagnosis and has implications for targeted treatment and outcomes [4].

The key pathophysiological mechanism of MN is that antigens expressed in the podocyte trigger humoral immune responses associated with increased B cells and follicular helper T (Tfh) cells, which interact in the germinal center of lymph nodes to induce differentiation of B cells into high-affinity antibody-producing plasma cells [5]. While the precise reasons for loss of tolerance to self-antigens remain unclear, review of evidence supports a dysregulated immunological milieu in patients with MN [6]. Autoantibodies in primary MN are primarily of the IgG4 subclass, potentially due to Th2-mediated IL-4 production [5]. Loss of tolerance to podocyte antigens such as PLA2R may follow loss of thymus-derived podocyte antigen-specific T regulatory cells (Tregs) [7]. Abnormal increases in B regulatory, Tfh and autoreactive plasma cells, along with reduced number and function of Tregs, play important roles in the generation and maintenance of autoantibodies in IMN [7, 8]. Therapy with rituximab is shown to increase Tregs and may predict treatment response [9].

In an article published in this issue of the Journal, the authors describe the immune phenotype of adult patients with MN associated with anti-PLA2R antibodies [10]. The authors found higher proportions of B cells, Tfh and Tregs in patients with MN, compared to healthy controls. This was associated with increased Tfh expression of programmed cell death protein-1 (PD-1) and reduced expression of cytotoxic T-lymphocyte associated protein-4 (CTLA-4) and interleukin-2 receptor (IL-2R). While most of these findings confirm current understanding about the T-cell dysregulation in MN, the finding of an increased proportion of Treg is unexpected. The manuscript requires readers to have a detailed understanding of T cell biology in autoimmunity, for which they are directed to recent reviews [5, 11]. The report lacks information of B cell subsets, levels of intracellular expression of cytokines and FoxP3, changes in levels of other cytokines, and changes in immune phenotype in response to therapy. A more focused approach, associated with clear research questions providing tangible clinical insights, is

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essential for bench research to contribute meaningfully to bedside practice. Finally, MN is chiefly an adulthood disease that may not evoke much interest among pediatricians, towards whom this journal is directed. Additional challenges are expected in examining the immune basis of childhood-onset MN, which is almost always diagnosed following immunosuppression with prednisolone for nephrotic syndrome. Prospective larger studies are required which explore the immune phenotypes of MN in adults and children in context of the antigen-based classification and response to targeted immunosuppression.

Declarations

Conflict of Interest The authors declare no conflict of interest.

References

1. Radhakrishnan Y, Zand L, Sethi S, Fervenza FC. Membranous nephropathy treatment standard. Nephrol Dial Transpl. 2024;39:403–13.
2. Debiec H, Guigonis V, Mougenot B, et al. Antenatal membranous glomerulonephritis due to anti-neutral endopeptidase antibodies. N Engl J Med. 2002;346:2053–60.
3. Beck LH Jr, Bonegio RG, Lambeau G, et al. M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. N Engl J Med. 2009;361:11–21.
4. Sethi S, Beck LH Jr, Glassock RJ, et al. Mayo Clinic consensus report on membranous nephropathy: proposal for a novel classification. Kidney Int. 2023;104:1092–102.
5. Zhao Q, Dai H, Liu X, et al. Helper T cells in idiopathic membranous nephropathy. Front Immunol. 2021;12:665629.
6. Ronco P, Beck L, Debiec H, et al. Membranous nephropathy. Nat Rev Dis Primers. 2021;7:69.
7. Rosenzwajg M, Languille E, Debiec H, et al. B- and T-cell subpopulations in patients with severe idiopathic membranous nephropathy may predict an early response to rituximab. Kidney Int. 2017;92:227–37.
8. Ramachandran R, Kaundal U, Girimaji N, et al. Regulatory B cells are reduced and correlate with disease activity in primary membranous nephropathy. Kidney Int Rep. 2020;5:872–8.
9. Roccatello D, Sciascia S, Di Simone D, et al. New insights into immune mechanisms underlying response to rituximab in patients with membranous nephropathy: a prospective study and a review of the literature. Autoimmun Rev. 2016;15:529–38.
10. Xu L, Tayier D, Yang S, Zhang X, Lu C. Follicular helper T cells and follicular regulatory T cells involved in immune disorders of idiopathic membranous nephropathy. Indian J Pediatr. 2023. https://doi.org/10.1007/s12098-023-04815-2.
11. Qi J, Liu C, Bai Z, Li X, Yao G. T follicular helper cells and T follicular regulatory cells in autoimmune diseases. Front Immunol. 2023;14:1178792.