New target antigens in Membranous Nephropathy: Beyond PLA2R

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Membranous nephropathy (MN) is an autoimmune disease resulting from deposition of IgG-target antigen immune-complexes along the subepithelial region of the glomerular basement membrane (GBM). From a relatively unknown etiology not so long ago, to the discovery of PLA2R and THSD7A in 2009 and 2014, and to the more recent explosion of target antigen discovery, MN has undergone rapid advances.

Discovery of newer antigens used laser microdissection of PLA2R-negative MN glomeruli from formalin fixed paraffin embedded tissue followed by mass spectrometry to study the proteomic profile and identify unique glomerular protein(s). The assumption was that the unique protein (target antigen) would stand out since substantial amounts of the protein was likely present as it lined the entire glomerular capillary walls. This was followed by immunohistochemistry (IHC) and confocal microscopy to localize the unique glomerular protein/antigen along the GBM, and finally western blot analysis to the unique protein using IgG extracted from the frozen tissue remnant and/or serum to detect corresponding antibodies to the unique protein thus establishing that the unique protein was indeed the target antigen. Using this methodology, seven new target MN antigens- EXT1/2, NELL1, SEMA3B, PCDH7, FAT1, NDNF, and PCSK6 (2019-2023) have been identified. Each of these new MN represents a distinct disease entity with different clinical and pathologic findings. The role of mass spectrometry for accurate diagnosis of MN cannot be overemphasized. Finally, any classification of MN should be based on the "antigens" detected. In this lecture, the discovery and clinicopathologic findings of the new MN target antigens are discussed.