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**Recent topics on novel antigens of membranous nephropathy:
including a study of NELL1- and EXT1-associated membranous
nephropathy in the Hokkaido area**

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The discovery of specific antigens of membranous nephropathy (MN), including the discovery of PLA2R in 2009 and THSD7A in 2014, was followed by the discovery of many antigens including Exostosin 1/2 (EXT1/2), Neural epidermal growth factor-like 1 protein (NELL1), SEMA3B, NCAM1, PCDH1, HTRA1 and TGFBR3. As of 2021, almost the entire spectrum of antigens of MN has been elucidated. NELL1-associated MNs are thought to be mainly primary MNs, but some of them are associated with cancer, and EXT1/2-associated MNs are associated with autoimmune diseases and lupus nephritis class V. There have been few reports from East Asia on these novel antigens of MN, and the clinicopathological picture remains unclear. We have received a large number of kidney biopsy specimens from the Hokkaido area. To determine the frequency of NELL1- and EXT1-associated MNs in Hokkaido, we performed immunohistochemical studies of PLA2R, THSD7A, NELL1, and EXT1 in MNs diagnosed at our hospital. Of the 107 MNs in the NELL1-MN discovery cohort, 43 (40%) were PLA2R-positive, 14 (13%) were NELL1-positive, 12 (11%) were THSD7A-positive, and 5 (5%) were EXT1-positive. The male-to-female ratio of NELL1-associated MNs was 11:5, and the mean age of the patients was 74.6 years, mean sCr was 1.09 mg/dL, and mean urinary protein was 7.8 g/gCr. Eleven patients had diabetes mellitus and 3 patients had malignancies. The IgG subclasses in immunofluorescence (IF) were IgG1 dominant in 12 cases and IgG1 co-dominant in 4 cases. In the EXT1-MN discovery cohort, among 120 MNs, 6 (5%) were EXT1-positive. Among 30 cases of lupus nephritis class V, 2 cases (6.7%) were EXT1-positive. Among the patients with EXT1-related MNs, 75% were female, and the mean age was 44.4 years, mean sCr was 0.67 mg/dL, and the mean urinary protein was 4.3 g/gCr. Autoimmune disease was present in 75% of the patients, and IgG subclasses in IF were IgG1 dominant in 87.5% of the patients.

In summary, NELL1 was the second most common MN antigen, and some of the cases of NELL-related MNs were associated with malignancy. EXT1 was frequently found in MN in women with autoimmune diseases.

In this lecture, I would like to introduce some recent papers on MN in addition to the above studies at our institution.