UKE Paper of the Month July 2016

Journal of Clinical Investigation 2016 2016 Jul 1;126(7):2519-32. (PMID 27214550)

Autoantibodies against thrombospondin type 1 domain-containing 7A induce membranous nephropathy

Nicola M. Tomas*, Elion Hoxha*, Anna T. Reinicke, Lars Fester, Udo Helmchen, Jens Gerth, Friederike Bachmann, Klemens Budde, Friedrich Koch-Nolte, Gunther Zahner, Gabriele Rune, Gerard Lambeau, Catherine Meyer-Schwesinger#, Rolf A.K. Stahl#
*,# authors contributed equally

ABSTRACT:
Membranous nephropathy (MN) is the most common cause of nephrotic syndrome in adults, and one-third of patients develop end-stage renal disease (ESRD). Circulating autoantibodies against the podocyte surface antigens phospholipase A2 receptor 1 (PLA2R1) and the recently identified thrombospondin type 1 domain-containing 7A (THSD7A) are assumed to cause the disease in the majority of patients. The pathogenicity of these antibodies, however, has not been directly proven. Here, we have reported the analysis and characterization of a male patient with THSD7A-associated MN who progressed to ESRD and subsequently underwent renal transplantation. MN rapidly recurred after transplantation. Enhanced staining for THSD7A was observed in the kidney allograft, and detectable anti-THSD7A antibodies were present in the serum before and after transplantation, suggesting that these antibodies induced a recurrence of MN in the renal transplant. In contrast to PLA2R1, THSD7A was expressed on both human and murine podocytes, enabling the evaluation of whether anti-THSD7A antibodies cause MN in mice. We demonstrated that human anti-THSD7A antibodies specifically bind to murine THSD7A on podocyte foot processes, induce proteinuria, and initiate a histopathological pattern that is typical of MN. Furthermore, anti-THSD7A antibodies induced marked cytoskeletal rearrangement in primary murine glomerular epithelial cells as well as in human embryonic kidney 293 cells. Our findings support a causative role of anti-THSD7A antibodies in the development of MN.

STATEMENT:
Autoantibodies have long been assumed to play a causative role in the development of human membranous nephropathy. This is, however, the first time that experimental evidence actually proves this concept by fullfilling all steps of Koch's postulates.

BACKGROUND:
This work was performed in the III. Medizinische Klinik, Section for Nephrology, in the group of the head of the department, Rolf A.K. Stahl. Strong cooperation with other UKE and non-UKE institutes were the prerequisite for the high impact of this work. The first and last authors have strong research interest in the molecular fundament as well as the clinical predictors of membranous nephropathy.
These studies were supported by grants from the Deutsche Forschungsgemeinschaft, KFO 228 (STA-193/9-2) and the Sonderforschungsbereich 1192 (projects B1, B2, and B3).