UKE Paper of the Month Februar 2023

The classical pathway triggers pathogenic complement activation in membranous nephropathy

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ABSTRACT:

Membranous nephropathy (MN) is an antibody-mediated autoimmune disease characterized by glomerular immune complexes containing complement components. However, both the initiation pathways and the pathogenic significance of complement activation in MN are poorly understood. Here, we show that components from all three complement pathways (alternative, classical and lectin) are found in renal biopsies from patients with MN. Proximity ligation assays to directly visualize complement assembly in the tissue reveal dominant activation via the classical pathway, with a close correlation to the degree of glomerular C1q-binding IgG subclasses. In an antigen-specific autoimmune mouse model of MN, glomerular damage and proteinuria are reduced in complement-deficient mice compared with wild-type littermates. Severe disease with progressive ascites, accompanied by extensive loss of the integral podocyte slit diaphragm proteins, nephrin and neph1, only occur in wild-type animals. Finally, targeted silencing of C3 using RNA interference after the onset of proteinuria significantly attenuates disease. Our study shows that, in MN, complement is primarily activated via the classical pathway and targeting complement components such as C3 may represent a promising therapeutic strategy.

STATEMENT:

This translational study for the first time demonstrates that the classical pathway of complement is the main driver of complement activation in membranous nephropathy and a pathogenic disease driver.

BACKGROUND:

This work was performed at the UKE and is the result of a long-standing collaboration between the groups of Nicola Tomas, III. Department of Medicine, and Thorsten Wiech, Institute of Pathology, Section Nephropathology. The project was funded by the DFG as part of the Emmy Noether Research Group “Molecular mechanisms of membranous nephropathy” and the Collaborative Research Center 1192 “Immune-mediated kidney diseases”.