UKE Paper of the Month December 2025

Autoantibody-triggered podocyte membrane budding drives autoimmune kidney disease

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Cell 2025, ahead of print

ABSTRACT:

Chronic kidney disease affects 1 in 10 people worldwide, with damage to specialized blood filter cells of the kidney, called podocytes, playing a critical role. In membranous nephropathy (MN), a major cause of nephrotic syndrome, circulating autoantibodies attack transmembrane proteins on podocyte foot processes (FPs), damaging the kidney's filtration barrier. Our study shows that these autoantibodies trigger the formation of antigen-autoantibody aggregates on the podocyte FP plasma membrane. These aggregates bud off as stalked vesicles, termed autoimmunoglobulin-triggered extracellular vesicles (AIT-EVs), which are released into the urine. AIT-EVs carry disease-causing autoantibodies, their target antigens, essential FP proteins, and disease-associated stressors representing a mechanism for removing immune complexes (ICs) and waste. However, their excessive release leads to FP effacement and podocyte dysfunction. In MN patients, urinary AIT-EVs correspond to the diagnostic glomerular urinary-space aggregates. Enriching AIT-EVs enables detection and monitoring of pathogenic autoantibodies, suggesting a non-invasive approach for autoimmune kidney disease diagnosis.

STATEMENT:

The study identifies autoimmunoglobulin-triggered extracellular vesicles (AIT-EVs) as a previously unrecognized, central pathomechanism in membranous nephropathy (MN). Disease-causing autoantibodies directed against podocyte foot process proteins induce the formation of immune complex aggregates at the cell membrane, which are shed into the urine as stalked vesicles, thereby enabling the removal of stressors from the basal extracellular space and the cytoplasm of podocytes. However, increased AIT-EV release is associated with membrane loss and consequent podocyte injury. Histopathologically, urinary AIT-EVs correspond to the diagnostic immune complex aggregates found in the glomerular urinary space in MN. Their targeted enrichment from urine enables sensitive autoantibody detection and disease monitoring in autoimmune kidney diseases. This establishes AIT-EVs as a new disease-defining vesicle class, introduces a new conceptual framework and highlights AIT-EVs as a non-invasive, disease-specific platform with translational relevance.

BACKGROUND:

This work was conducted at the Institute of Cellular and Integrative Physiology as part of the PhD thesis of Karen Lahme under the supervision of Prof. C. Meyer-Schwesinger. The study involved collaborations with several UKE departments, the LIV and CSSB (for imaging), and Asklepios Clinic Barmbek (for patient samples), as well as national research partners (Prof. L. Fester originally from Neuropathology

(UKE) now Neuropathology Bonn for EM analyses; K. Surmann, S. Michalik and U. Völker Greifswald, proteomic analyses). Funding was mainly provided by the DFG: SFB 1192, Heisenberg ME2018/5-1 and research grants ME2018/8-1, 9-1, 10-1.