THSD7A-associated membranous nephropathy involves both complement-mediated and autonomous podocyte injury

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Backgrounds: As a distinctive subtype in the serology-based classification of membranous nephropathy (MN), thrombospondin type 1 domain containing 7A (THSD7A)-associated MN has attracted increasing interest because THSD7A is expressed in preclinical species, facilitating the study of its role in MN. This study aimed to establish models of THSD7A-associated MN by using a commercial antibody. The potential pathomechanisms and the therapeutics efficacy of repository corticotropin injection (RCI) were tested in this model.

Methods: Primary mouse podocytes were cultured in regular complete medium containing complements or in medium pre-heated to inactivate heat-labile complements, followed by exposure to a rabbit anti-THSD7A antibody. In vivo, mice were injected with the anti-THSD7A antibody and treated

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with RCI or vehicle. To deplete complement, some mice were treated with cobra venom factor (CVF). Podocyte injury and glomerular disease was evaluated.

Results: After anti-THSD7A antibody insult, mice developed massive proteinuria, concomitant with histologic lesions of glomerular injury, including epimembranous or intramembranous electron-dense deposits in glomeruli as well as variable podocyte foot process effacement, reminiscent of glomerular ultrastructural changes in human MN. Complement depletion with CVF only partially attenuated proteinuria and glomerular injury, suggesting that complement-independent pathomechanisms also contribute. Consistently, in primary podocytes, exposure to the anti-THSD7A antibody caused evident podocytopathic changes, such as disruption of the actin cytoskeleton integrity, podocyte hypermobility, oxidative stress and apoptosis. These signs of podocyte injury were preserved, although to a lesser extent, following complement inactivation, denoting an autonomous podocytopathic activity of this antibody. As an FDA-approved treatment option for primary nephrotic glomerulopathies including MN, RCI appeared to be beneficial in this model.

Conclusions: Both complement-dependent and autonomous podocytopathy are involved in the mouse model of THSD7A-associated MN, which could be attenuated by RCI. This model, based on the use of a commercially available anti-THSD7A antibody, could be an important tool for MN research.

Keywords: Thrombospondin Type 1 Domain Containing 7A, Membranous Nephropathy, Complement, Autonomous Podocytopathy

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