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Thrombospondin Type-1 Domain-Containing 7A in Idiopathic Membranous Nephropathy

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ABSTRACT: Background: Idiopathic membranous nephropathy is an autoimmune disease. In approximately 70% of patients, it is associated with autoantibodies against the phospholipase A2 receptor 1 (PLA2R1). Antigenic targets in the remaining patients are unknown. Methods: Using Western blotting, we screened serum samples from patients with idiopathic membranous nephropathy, patients with other glomerular diseases, and healthy controls for antibodies against human native glomerular proteins. We partially purified a putative new antigen, identified this protein by means of mass spectrometry of digested peptides, and validated the results by analysis of recombinant protein expression, immunoprecipitation, and immunohistochemical analysis. Results: Serum samples from 6 of 44 patients in a European cohort and 9 of 110 patients in a Boston cohort with anti-PLA2R1-negative idiopathic membranous nephropathy recognized a glomerular protein that was 250 kD in size. None of the serum samples from the 74 patients with idiopathic membranous nephropathy who were seropositive for anti-PLA2R1 antibodies, from the 76 patients with other glomerular diseases, and from the 44 healthy controls reacted against this antigen. Although this newly identified antigen is clearly different from PLA2R1, it shares some biochemical features, such as N-glycosylation, membranous location, and reactivity with serum only under nonreducing conditions. Mass spectrometry identified this antigen as thrombospondin type-1 domain-containing 7A (THSD7A). All reactive serum samples recognized recombinant THSD7A and immunoprecipitated THSD7A from glomerular lysates. Moreover, immunohistochemical analyses of biopsy samples from patients revealed localization of THSD7A to podocytes, and IgG eluted from one of these samples was specific for THSD7A. Conclusions: In our cohort, 15 of 154 patients with idiopathic membranous nephropathy had circulating autoantibodies to THSD7A but not to PLA2R1, a finding that suggests a distinct subgroup of patients with this condition.

STATEMENT: *The work published in this article represents a major breakthrough in the understanding of membranous nephropathy, an autoimmune renal disease with potential poor outcome for affected patients. Importantly, our results have an immediate impact on clinical procedures as we describe a new and highly specific serum biomarker for the diagnosis of this disease. Moreover, this work opens a new field in the research of membranous nephropathy as it enables pathophysiological and mechanistic studies in animals.*

BACKGROUND: This work was performed in the research group of Prof. Dr. Rolf A.K. Stahl, head of Nephrology (UKE) and initiator of the project. Prof. Stahl's research group focuses on clinical and molecular investigation of membranous nephropathy and has published a high number of articles in this field over the last years. All UKE authors in this publication have a strong interest in this area. This project was supported by the Deutsche Forschungsgemeinschaft. This study combined expertise from three international laboratories. Besides the group of Prof. Stahl, the groups of Dr. Gérard Lambeau, France, and Dr. David Salant, USA, were involved.