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2019 Annual Report

UAB SCHOOL OF MEDICINE

The University of Alabama at Birmingham

Pivotal Role Found for IgG Autoantibodies in IgA Nephropathy

IgA nephropathy is the most common primary glomerular disease—which reduces the kidney's ability to maintain a balance of specific substances in the blood stream—in the world. The disease is believed to be caused by IgA-containing immune complexes formed in the blood that ultimately deposit in the glomeruli, the filtering units of the kidneys. This IgA is characteristically deficient in certain sugars called galactose. The level of galactose-deficient IgA is elevated in the blood of patients with IgA nephropathy and is thought to trigger the production of IgG autoantibodies. These IgG autoantibodies bind the galactose-deficient IgA to form immune complexes. Some of these complexes ultimately deposit in the kidneys and induce injury. When kidney glomeruli become damaged by the pathogenic complexes, the kidneys leak blood and protein into the urine and ultimately can lose their ability to remove waste from the blood, leading to progressive chronic kidney disease.

In IgA nephropathy kidney biopsies, IgA is the main immunoglobulin detected in the glomeruli by a clinical test called routine immunofluorescence. That test fails to detect immunoglobulin IgG, the autoantibody component of the pathogenic complexes, in 50-80% of cases. Additionally, the specificity of this deposited IgG against the galactose-deficient IgA has never been established.

A study by UAB researchers published in October 2019 in the *Journal of the American Society of Nephrology* largely validates the hypothesis that the IgG autoantibody is a crucial part of the pathogenic immunodeposits in glomeruli of patients with IgA nephropathy. The researchers hypothesized that the IgA was blocking the IgG from being detected in routine immunofluorescence microscopy, say co-corresponding authors Dana Rizk, M.D., professor in the Division of Nephrology, and Jan Novak, Ph.D., professor in the Department of Microbiology. When a different reagent, a small nanobody that detects the very end of the IgG molecule, was used, IgG was detected in all biopsy specimens, including those that did not show IgG by routine immunofluorescence. Moreover, a highly sensitive confocal microscopy showed co-localization of the IgA and IgG in glomerular deposits of the biopsy-tissue specimens.

Furthermore, UAB researchers extracted IgG from IgA nephropathy biopsies as well as from biopsies with other forms of glomerular diseases (primary membranous nephropathy and lupus nephritis). They confirmed that the IgG from IgA nephropathy kidney tissue is an autoantibody specific for galactose-deficient IgA, whereas such autoantibody was not found in the biopsies with the two other forms of glomerular diseases. The study, Novak and Rizk say, supports the multi-hit hypothesis of IgA nephropathy pathogenesis.

"These results reveal, for the first time, that IgA nephropathy kidney biopsies, with or without IgG by routine immunofluorescence, contain IgG autoantibodies specific for galactose-deficient IgA," say Novak and Rizk. "These findings support the importance of these autoantibodies in the pathogenesis of IgA nephropathy.

"These IgG autoantibodies specific for galactose-deficient IgA1 are present also in blood of patients with IgA nephropathy, and the autoantibody levels predict disease progression. Thus, we could potentially measure these autoantibodies in blood to identify patients who could benefit from a future disease-specific therapy, or monitor patients for responses to the therapy. Better understanding of these autoantibodies can help us develop new, disease-specific treatments for IgA nephropathy."

Co-authors of the study include Manish Saha and Bruce Julian, M.D., in the Division of Nephrology; Stacy Hall, Rhubell Brown, and Zhi-Qiang Huang, M.D., in the Department of Microbiology; and Huma Fatima, M.D., and Lea Novak, M.D., in the Department of Pathology. Novak and Julian designed the study. – *Jeff Hansen*