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The role of fumarate in the progression of membranous nephropathy: metabolomics analysis and its in-vitro validation.

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Objectives: Although pathognomonic antigens such as phospholipase A2 receptor (PLA2R) and thrombospondin type 1 domain-containing 7A (THSD7A) identified in membranous nephropathy (MN), the levels of their corresponding autoantibodies do not always predict the long-term prognosis or treatment response. We aimed to figure out biomarkers predicting the prognosis and treatment response using metabolomics analysis of urine samples.

Methods: Urine samples at the time of kidney biopsy were obtained from patients with MN (n=76), minimal change disease (MCD) (n=74) and healthy controls (n=82). Metabolic profiles of the urines were analyzed by using the 800-MHz NMR-based method. An *in-vitro* validation study was performed using primary-cultured human podocytes treated with IgG purified from an MN patient with high PLA2R level. To characterize the role of fumarate, we conducted lentivirus-mediated fumarate hydratase activation *in-vitro*.

Results: On the basis of metabolomics findings, *in-vitro* experiments using primary-cultured human podocytes were performed to validate the metabolomics analysis. Western blotting was performed using the lysates from the podocytes with purified IgG from a PLA2R-associated MN patient (MN-IgG). There was a 185-kD protein band which indicates the expression of PLA2R on the podocytes and PLA2R Ag-Ab interaction following treatment of the MN-IgG. In *in-vitro* experiments, the MN-IgG, but not control-IgG, increased fibronectin and SNAIL, and decreased ZO-1, WT-1 and fumarate hydratase, an enzyme that catalyzes fumarate. Meanwhile, lentivirus-mediated fumarate hydratase activation significantly abrogated the MN-IgG mediated changes in the protein expressions.

Conclusions: These findings suggest that fumarate might play an important role in the progression and disease activity of MN via the regulation of podocyte integrity and renal fibrosis.