TRANSCRIPTIONAL ANALYSIS OF IgA NEPHROPAHY BIOPSIES: TOWARDS A MOLECULAR CLASSIFICATION

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IgA nephropathy (IgAN) is defined by histopathological features. It is currently unclear if a single or multiple pathogenetic mechanisms are activated in IgAN. Genome wide expression profiles of micro-dissected IgAN and living donor (LD) renal biopsies were generated to define IgAN transcriptional-associated pathways and molecular subgroups.

Renal biopsies from LD (n=6) and patients with IgAN (n=27) were collected from an international multi-center cohort. Affymetrix genechips were processed separately from glomeruli and tubulointerstitium, and analyzed using a customized data processing pipeline (www.GenePattern.org).

Unsupervised hierarchical clustering segregated controls and IgAN biopsies. Using a Ridge regression analysis, candidate markers defined with a FDR below 5% significantly predicted GFR-MDRD in the tubulointerstitium compartment. Within the IgAN cohort, two subgroups of IgAN patients were defined: one with a fingerprint related to the control group and one with a distinct signature. Analyzing the mRNA and associated pathways responsible for this segregation, Integrin signaling was a top scoring canonical pathway mainly activated in the IgAN group 2 vs. the group 1. GFR-MDRD was significantly lower in group 2 vs. group 1; whereas proteinuria was increased. The segregation observed in IgAN patients was validated by testing a second IgAN cohort (n=14) using a custom array platform.

Gene expression profiles of IgAN biopsies can segregate subgroups based on molecular pathways associated with disease subtypes, which might provide a novel type of information for defining molecular targets and predicting disease course.