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Nephrotic syndrome: Predicting and defining therapeutic outcomes by systems biology omics approaches

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Statement of the Problem: Nephrotic syndrome (NS) is a kidney disease characterized by proteinuria, edema and increased risk for complications such as infection, acute kidney injury, thrombosis and dyslipidemia. Glucocorticoids (GC) induce remission of NS in most children, though ~20% present with or develop GC resistance. The predictive biomarkers and molecular basis for differences in GC efficacy between steroid-sensitive (SSNS) and steroid resistant (SRNS) children remain largely unknown. This study seeks to determine the predictive biomarkers and mechanisms responsible for differential responses to GC in children with SSNS and SRNS.

Methodology & Theoretical Orientation: Paired plasma samples and total mRNA from leukocytes were collected at presentation (P) and 6-8 weeks later after the first course of GC therapy (F) from children with SSNS (n=30) and SRNS (n=15). Transcriptome profile was generated by deep RNA seq and differentially expressed genes identified by volcano plotting followed by extreme learning machine algorithm. The plasma samples were enriched for low-abundant serum proteins and analyzed by LCMS for generation of proteomics profile. Broad spectrum HNMR data were acquired, binned, and concentration fit for metabolomics analyses. Cytokine profile was generated using a 27-cytokine panel on immulite system.

Findings: Each sample produced ~100 million sequence reads of ~50 bases/read by RNAseq. Transcriptome profile could identify 15,418 genes after filtering, 28 of which were differentially expressed at presentation and 84 upon treatment between SSNS and SRNS. Curation of 215 identified proteins in the samples resulted in 13 predictor and 67 steroid resistance defining markers following Wilcoxon and Mann-Whitney testing. Metabolites most perturbed by treatment included lipoproteins, adipate, tyrosine, valine, alanine, glutamine, glucose, pyruvate and creatine. These could be differentiated in SSNS but not SRNS. Also, elevated malonate levels increased the odds of GC response. Cytokine profile was also altered in the two patient population specifically for IL-8, RANTES and PDGF.

Conclusion & Significance: Different omics approaches could identify candidate biomarkers that can differentiate between the SSNS and SRNS groups at baseline and after treatment.

Biography

Shipra Agrawal is an Investigator in the Center for Clinical and Translational Research at The Research Institute at Nationwide Children's Hospital and a Research Assistant Professor in the Department of Pediatrics at The Ohio State University College of Medicine. She is trained in Molecular, Cellular and RNA Biology and mechanistic aspects of human diseases and her research interests have both basic and translational components with a committed focus on kidney disease. Her basic research direction is the identification and modulation of molecular signaling pathways involved in glomerular and podocyte biology and injury, which can potentially translate into novel therapeutic targets for nephrotic syndrome and other glomerular diseases. Her additional translational research focus is on the identification of biomarkers to predict and define steroid resistance in nephrotic syndrome. Her contributions have been published in high impact journals: *NEJM, JBC, KI, JASN, HMG, AJHG, JVirol, Virology* and *NRN*.

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