

Integrative Omics for Identifying Dysfunctional Pathways in CKD



Adrienne Tin^{1,2} and Morgan E. Grams^{1,2,3}

¹Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA; ²Welch Center for Prevention, Epidemiology, Clinical Research, Baltimore Maryland, USA; and ³Division of Nephrology, Department of Medicine, Johns Hopkins School of Medicine, Baltimore, Maryland, USA

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The mechanisms underlying chronic kidney disease (CKD) remain poorly understood, and treatments to prevent or forestall CKD progression are limited. Precision medicine aims to change this. Advances in high-throughput technologies have already led to the discovery of important genes, metabolites, and proteins implicated in CKD.^{1,2} On its own, however, a single omic technique may offer only a narrow window into the exceedingly complex pathophysiology of CKD. By integrating multiple omic studies, such as genetics, epigenetics, gene expression, metabolomics, proteomics, and microbiome profiling, we may be able to achieve sufficient understanding of the dysfunctional biological pathways to identify novel prevention and therapeutic targets.

In this issue of *Kidney International Reports*, Øvrehus and colleagues³ report on a proof-of-concept study that links gene expression from kidney biopsy

specimens of patients with hypertensive nephrosclerosis with targeted quantification of urine metabolites in a second set of patients with long-standing hypertension and evidence of estimated glomerular filtration rate decline. They found that gene expression profiles were significantly different in diseased kidneys, with underexpression of amino acid-related processes, fatty acid oxidation, and gluconeogenesis, and upregulation of various inflammatory pathways. The authors followed up on the amino acid findings with the quantification of 47 amino acids or related compounds in urine, 31 of which were reliably measured. There was a trend toward lower urine amino acid levels in the 62 patients with presumed hypertensive nephropathy compared with the 33 without, but the differences in median values were not statistically significant. Eight of the top 15 metabolites were then evaluated in a third study, with replication in direction for 7. The metabolites that showed the strongest differences between patients with presumed hypertensive nephropathy and those without included glycine, serine, tyrosine,

dopamine, phenylalanine, and alanine.

Previous studies have also suggested that plasma and urinary amino acid concentrations are altered in CKD. Whereas many metabolites tend to be higher in CKD, likely owing to decreased renal clearance, certain amino acids are lower. Patients receiving hemodialysis in particular have low levels of many amino acids.⁴ Lower amino acid levels have been associated with incident CKD and CKD progression.^{5,6} The kidney has a recognized role in the catabolism and synthesis of several amino acids, including the breakdown of glutamine to ammonia and glutamate, and the conversion of citrulline to arginine, phenylalanine to tyrosine, and glycine to serine.⁷ However, lower amino acid levels in CKD may be the result of not only kidney dysfunction in amino acid metabolism, but also poor nutritional intake and impaired gut absorption. Metabolite association studies are limited in that they cannot provide direct evidence of the concurrent biological processes in the kidney.

The integration of gene expression with metabolite measures can provide additional clues for causal inference; in this case, whether the kidney itself is a cause of lower urine amino acid levels in patients with CKD. Øvrehus and colleagues³ demonstrated that kidneys afflicted by hypertensive nephrosclerosis had lower expression of genes involved in cellular amino acid catabolic and metabolic processes than normal kidneys based on Gene Ontology terms. These results in kidney gene expression, the process by which information in the genome is used to generate functional products that determine cell behavior,

Correspondence: Adrienne Tin, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, 21212, USA. E-mail: atin1@jhu.edu

directly implicate dysregulation of amino acid metabolism in the kidney in CKD.

Gene expression has been used elsewhere in the study of the biology underlying CKD. The kidney expression of *SLC7A9*, which encodes an amino acid transporter, positively associates with estimated glomerular filtration rate and negatively associates with fibrosis.⁸ This finding was extended by a metabolite-gene association study, which identified a genetic variant at *SLC7A9* as associated with higher urinary lysine levels and lower risk of CKD.⁵ However, it is worth noting that gene expression is an intracellular process and thus specific to a cell. Gene expression in tissues with heterogeneous cell types may obscure signals from specific cells.

Recently, technology has enabled the study of gene expression at a more granular level, from tissue down to a single cell.¹ Single-cell transcriptional profiling in mice has been used to generate an atlas of kidney cell types, and suggests that gene expression in a single cell type may have a distinct role in the development of a specific phenotype.⁹ Qiu and colleagues¹ used these principles to follow up on the genome-wide significant locus Disabled homolog 2 (*DAB2*), an adaptor protein in the transforming growth factor beta pathway. By integrating kidney tissue compartment-specific

expression quantitative trait loci in humans and single-cell RNA sequencing in the mouse, they demonstrated that the allele associated with lower estimated glomerular filtration rate in *DAB2* (rs11959928) was associated with higher *DAB2* gene expression in the human kidney tubule but not in the glomerulus. Mice with a tubule-specific *Dab2*-knockout were less susceptible to kidney injury and developed less fibrosis compared with wild-type mice, suggesting a role in CKD development for *DAB2*.¹

The National Institute of Diabetes and Digestive and Kidney Diseases has also lent support to an integrative omics approach. With funding for the Nephrotic Syndrome Study Network, Cure Glomerulonephropathy, and the Kidney Precision Medicine Project, the ultimate goal is to augment understanding of the heterogeneous group of etiologies underlying CKD and to develop and implement targeted solutions to improve patient well-being. The collaborative effort by Øvrehus and colleagues,³ using 3 distinct cohorts and different biospecimen types, is a step in this direction.

DISCLOSURE

All the authors declared no competing interests.

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