HelmholtzZentrum münchen
German Research Center for Environmental Health

Scientific Highlight October 2015

☒ co-ordinated with the Director of the Institute / Research Unit

Institute of Bioinformatics and Systems Biology (IBIS) (Metabolomics Group)

PSP-Element:
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Title of the highlight:
Using multi-omics data for better understanding and identifying early decline of kidney function and predicting human kidney allograft status

Keywords:
chronic kidney disease; kidney transplantation; allograft rejection; multi-omics data; metabolome- and genome-wide associations study;

Central statement of the highlight in one sentence:
Metabolite profiles together with other omics data from population-based and clinical cohorts provide mechanistic insights and potential novel markers of early decline of kidney function and allow prediction of human kidney allograft status.

Text of the highlight:
Chronic kidney disease (CKD) affects approximately 10% of the population in western countries and is characterized by a major decline of the kidneys' filtration and detoxification capabilities. Diabetes patients with a long history of the disease have a particularly high risk to develop end stage renal disease (ESRD), in which hemodialysis and kidney transplantation with its risk of allograft rejection remain as the only treatment options. Despite the high prevalence and increasing incidence of CKD, the underlying pathophysiologic mechanisms are not fully understood. Moreover, serum creatinine, the metabolite that is currently used as diagnostic marker of CKD, indicates disease only after 50% of kidney function has been lost and is also dependent on other factors such as muscle mass.
Today, high-throughput metabolomics techniques give access to a wide range of blood and urine metabolites, of which many are synthesized, metabolized, or cleared from the body by the kidneys. Impaired kidney function is therefore expected to largely influence the homeostasis of these metabolites, which can, in turn, include potential new markers of kidney function improving early and reliable diagnosis of CKD. Analyzing blood levels of almost 500 metabolites in

more than 1,700 individuals from the general population identified six metabolites that showed particularly strong association with kidney function while lacking some of the disadvantages of creatinine. At the same time, two of these metabolites, namely C-mannosyltryptophan and pseudouridine were also good measures of kidney function decline in the general population over a period of seven years and of disease progression in CKD patients.

Besides their role as potential biomarkers, the highlighted metabolites share a link to glycosylation, an important mechanism of so-called post-translational modifications, which have numerous structural and functional implications on proteins. Further mechanistic insights can be gained by combining the results from metabolite analysis with data from other omics technologies and body fluids. In the largest genome-wide scan of genetic influences on metabolite levels in urine, we found genetic variants, which have previously been associated with higher risk of CKD, to also correlate with higher concentrations of various N-acetylated compounds both in blood and urine. As two of the six metabolites that were linked to CKD were N-acetylated amino acids, these findings suggest an important role of post-translational N-acetylation, a mechanism of detoxification, in kidney disease. For *myo*-inositol, which was also among the six CKD related metabolites, the same study identified a genetic variant that indicates less effective re-absorption of this compound by the kidneys of carriers.

As we could also show recently, the combination of data from various omics layers can not only improve our understanding of how genetic risk factors are involved in the development of kidney disease but can also improve prediction of allograft status in ESRD patients after transplantation and thus potentially avoid biopsies. Investigating the levels of 749 metabolites in 1516 urine samples from 241 patients after kidney transplantation, a metabolite signature consisting of ratios that include 3-sialyllactose, xanthosine, quinolinate and an unnamed compound best differentiated between cases with and without acute cellular rejection. Combining this metabolite signature with a previously reported urinary signature of transcripts further enhances the specificity and sensitivity of the prediction yielding a receiver 84% and 90%, respectively.

Thus, on the one hand measurement of blood C-mannosyltryptophan and pseudouridine concentrations might improve future prediction of early kidney function decline compared to creatinine based diagnosis allowing early treatment and prevention of complications and disease progression to end stage renal disease with the need of kidney transplantation. On the other hand, non-invasive diagnose of acute cellular rejection of kidney allografts through the measurement of four metabolites and three transcripts could save costs and complications caused by biopsies (estimated 21$ in the US) currently used to monitor allograft status. Assays for exact and reliable measurement of these markers are under active development.

Publication:

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- Raffler J, Friedrich N, Arnold M, Kacprowski T, Rueedi R, Altmaier E, Bergmann S, Budde K, Gieger C, Homuth G, Pietzner M, Römisch-Margl W, Strauch K, Völzke H, Waldenberger M, Wallaschofski H, Nauck M, Völker U, **Kastenmüller G*,** Suhre K. Genome-Wide Association Study with Targeted and Non-targeted NMR Metabolomics Identifies 15 Novel Loci of Urinary Human Metabolic Individuality. PLoS Genet. 2015 Sep 9;11(9):e1005487.

• Suhre K, Schwartz JE, Sharma VK, Chen Q, Lee JR, Muthukumar T, Dadhania DM, Ding R, Ikle DN, Bridges ND, Williams NM**, Kastenmüller G**, Karoly ED, Mohney RP, Abecassis M, Friedewald J, Knechtle SJ, Becker YT, Samstein B, Shaked A, Gross SS, Suthanthiran M*. Urine Metabolite Profiles Predictive of Human Kidney Allograft Status. J Am Soc Nephrol. 2015 Jun 5. pii: ASN.2015010107. [Epub ahead of print]

Taking account of the HMGU mission:
Chronic kidney disease is a frequent complication of diabetes with diabetic nephropathy being the most common cause of end stage renal disease, which may require hemodialysis or even kidney transplantation. Our studies do not only help to understand the pathophysiological mechanisms underlying kidney disease but also contribute to the improvement of early diagnoses and prediction of allograft rejection after transplantation.

The internal HMGU co-operation partners with whom the highlight was compiled, if appropriate:
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