Urinary metabolites give new clues to kidney transplant tolerance

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Kidney transplantation is the treatment of choice for patients with end-stage kidney disease. While the procedure is very successful in the first years following transplantation, long-term rejection of allografts remains a major problem despite immunosuppression and a further difficulty is the worldwide shortage of organs suitable for transplant. There is therefore a tremendous need to identify new therapeutic pathways that could be targeted to improve the long-term survival of kidney transplants. The study published in this issue of *eBioMedicine* by Colas et al. takes a novel approach to understanding operational tolerance by performing urinary metabolomic profiling, using ultrahigh performance liquid chromatography with high resolution mass spectrometry. The results identify a urinary metabolomic signature in a cohort of spontaneously tolerant kidney transplant recipients.[1]

This unique cohort is defined by the stable and acceptable function of their allografts in the absence of immunosuppressive treatments.[2] To date the mechanisms underlying such tolerance have not been fully elucidated despite data indicating distinct immunological modifications in the operationally tolerant group (eg in regulatory B and T follicular helper lymphocytes[3,4] and the recent observation of a specific proteobacteria urinary profile).[5] In the current study, the following groups were compared: healthy volunteers, spontaneously tolerant allograft recipients, patients treated by minimum immunosuppression, patients considered stable on the basis of graft function and treated by conventional immunosuppression and patients with subclinical antibody mediated rejection (scABMR).

First, a total of 2700 urinary metabolites were examined by unsupervised clustering. This distinguished the metabolome of healthy volunteers and of tolerant patients from the other transplant patient groups. Second, the metabolomic signature of spontaneously tolerant patients revealed by twelve leading ions was specific and distinct from that of the other transplant recipient groups. Finally, the profile of the spontaneously tolerant cohort selectively implicated the kynurenine metabolic pathway and was associated with elevation of three tryptophan-derived urinary metabolites.

The scABMR group was included only in the first stage of non-supervised clustering analysis and could not be distinguished from other patient groups, this is likely to be due to including too low a number of scABMR patients to allow delineation. Future studies will be needed to investigate this important patient group.

The results of this study are exciting for several reasons, monitoring kidney transplant survival currently requires regular biopsies and although the shortcomings of analysis of biopsies have been underlined, a non-invasive molecular method that is accurate, easy to perform and inexpensive to implement has not yet been developed. The urinary metabolome is particularly pertinent with regard to allograft monitoring, not only because of the non-invasive nature of the procedure but also because urine is a direct product of the kidney transplant. There have been reports of urinary studies identifying selective metabolomic profiles in allograft rejections following kidney transplantation and previous studies have revealed panels of metabolites that could diagnose T cell mediated rejection (TCMR) from non-TCMR with a high degree of specificity. Blydt-Hansen et al. analysed 134 urinary metabolites and revealed a panel of ten that identified TCMR with high specificity.[6] Sigdel et al compared biopsy-matched urine samples from 310 pediatric renal transplant recipients and reported encouraging results since a series of eleven metabolites specifically associated with acute rejection and 4 metabolites distinguished BK viral nephritis from acute rejection.[7] Nissaisorakarn identified a four-metabolite panel and this was further improved upon by combination of the four metabolites with a three-gene signature.[8]

However, this is the first report of urinary metabolomic data from a cohort of spontaneously tolerant patients. A high overall number of metabolites were detected and the results represent a new step in pinpointing metabolic pathways involved in spontaneous tolerance. These data also pave the way for future studies enhancing or disrupting these pathways to allow their evaluation as targets for new therapies potentially leading to tolerance in kidney transplant recipients in general. It is interesting to note that the metabolites identified indicate pathways that have already been implicated in immune regulation and indeed in

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transplant tolerance such as the enzyme indole 2,3-diamine oxygenase (IDO) in a murine transplant model.[9] Moreover, higher urinary IDO levels were detected in stable pediatric transplant patients compared with healthy volunteers.[10]

In summary, the study by Colas et al. provides data from a particularly interesting patient cohort that are likely to lead to larger and multicentric studies. Such studies will fully elucidate the degree to which urinary metabolite profiles may distinguish different clinical groups of kidney transplant patients. They will also highlight pathways implicated in spontaneous tolerance that could be exploited to develop new treatments for the vast majority of non-tolerant transplant patients.

Declaration of interests

The author declares no conflict of interest.

References

1 Colas L, et al. Urinary metabolomic profiling from spontaneous tolerant kidney transplanted recipients shows enrichment in tryptophan-derived metabolites. *eBioMedicine*. 2022. https://doi.org/10.1016/j.ebiom.2022.103844. In press.

2 Brouard S, et al. The natureal history of clinical operational tolerance after kidney transplantation through 27 cases. *Am J Transplant*. 2012;12(12). https://doi.org/10.1111/j.1600-6143.2012.04249.x.

3 Newell KA, et al. Identification of a B cell signature associated with renal transplant tolerance in humans. *J Clin Investig*. 2010;120(6). https://doi.org/10.1172/JCI39933.

4 Chenouard A, et al. Renal operational tolerance is associated with a defect of blood Tfh cells that exhibit impaired B cell help. *Am J Transplant*. 2017;17(6). https://doi.org/10.1111/ajt.14142.

5 Colas L, et al. Unique and specific Proteobacteria diversity in urinary microbiota of tolerant kidney transplanted recipients. *Am J Transplant*. 2020:(1):20. https://doi.org/10.1111/ajt.15549.

6 Blydt-Hansen TD, et al. Urinary metabolomics for noninvasive detection of borderline and acute T Cell–mediated rejection in children after kidney transplantation. *Am J Transplant*. 2014;14(10). https://doi.org/10.1111/ajt.12837.

7 Sigdel TK, et al. Targeted urine metabolomics for monitoring renal allograft injury and immunosuppression in pediatric patients. *J Clin Med*. 2020:(8):9. https://doi.org/10.3390/jcm9082341.

8 Nissaisorakarn V, et al. Urine biomarkers informative of human kidney allograft rejection and tolerance. *Hum Immun*. 2018;79(5). https://doi.org/10.1016/j.humimm.2018.01.006.

9 Sucher R, et al. IDO and regulatory T cell support are critical for cytotoxic T lymphocyte-associated Ag-4 Ig-mediated long-term solid organ allograft survival. *J Immunol*. 2012;188(1). https://doi.org/10.4049/jimmunol.1002777.

10 Al Khasawneh E, et al. Stable pediatric kidney transplant recipients run higher urine indoleamine 2, 3 dioxygenase (IDO) levels than healthy children. *Pediatr Transplant*. 2014;18(3). https://doi.org/10.1111/petr.12232.