UKE Paper of the Month September 2023

An integrated organoid omics map extends modeling potential of kidney disease

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ABSTRACT:

Kidney organoids are a promising model to study kidney disease, but their use is constrained by limited knowledge of their functional protein expression profile. Here, we define the organoid proteome and transcriptome trajectories over culture duration and upon exposure to TNFα, a cytokine stressor. Older organoids increase deposition of extracellular matrix but decrease expression of glomerular proteins. Single cell transcriptome integration reveals that most proteome changes localize to podocytes, tubular and stromal cells. TNFα treatment of organoids results in 322 differentially expressed proteins, including cytokines and complement components. Transcript expression of these 322 proteins is significantly higher in individuals with poorer clinical outcomes in proteinuric kidney disease. Key TNFα-associated protein (C3 and VCAM1) expression is increased in both human tubular and organoid kidney cell populations, highlighting the potential for organoids to advance biomarker development. By integrating kidney organoid omic layers, incorporating a disease-relevant cytokine stressor and comparing with human data, we provide crucial evidence for the functional relevance of the kidney organoid model to human kidney disease.

STATEMENT:

This is indeed an important UKE study as it takes the non-animal ("3R UKE") approach to kidney research to a new level. Organoids have the potential to model human disease in complex organs including the kidney. However, their function largely depend on the proteins expressed, as well as the dynamic responses towards inflammatory stimuli. This is the first time that a comprehensive atlas of human kidney organoids was generated, showcasing cell-type responses, secretome and protein dynamics, and direct relevance to patients with proteinuric kidney disease. The generated map on both proteome and single-cell transcriptome level map extends organoid modelling potential, but also shows limitations of this model system that will be able to guide future research.

BACKGROUND:

The work was led by Dr. Moritz Lassé who has been at the UKE since 2021. The main work was performed at the III. Department of Medicine in the group of Markus Rinschen. The focus of the group is molecular deciphering and functional analysis of kidney disease on proteome and metabolome level. It was part of the work put forward in the SFB1192, projects B1, B2, B6, B8, B9, B10 and C1. This work was performed jointly with Jennifer Harder's group at the Department of Nephrology, University of Michigan, Ann Arbor, with contributions from scientists at Aarhus University, Denmark.