Abstract Hilmar Stolte Preis 2020 - Amrei Maxi Mandel

Title: Comparative transcriptomics of different mouse models of cystic kidney disease

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Introduction and Aim:
Cystic kidney diseases (CKD) encompass a variety of hereditary diseases that lead to cyst development and eventually end stage renal disease. CKD show a broad range of clinical variability, but the underlying molecular mechanisms are poorly understood. It has been suggested that cystogenic processes share partially overlapping pathological mechanisms because CKD-associated proteins co-localize at the primary cilium, which is thought to play a central pathogenic role. With our study, we aim to shed light on the transcriptional changes preceding and accompanying cyst growth, which may facilitate the establishment of curative treatment for the severe CKD.

Method:
This project compared the nephronophthisis models FVB/NJ-Invs^{inv} and C57BL/6J-Nek8^{jck}, and the autosomal dominant polycystic kidney disease model C57BL/6J-Pkd1$^{tm1.1Pcha}$. The timepoints of analysis were matched for the stage of disease, including a timepoint preceding cyst development. The kidneys were collected at P0 and P7 for Invs^{inv}, at P5, P10, and P15 for Nek8^{jck}, and at P10, P20, and P30 for Pkd1$^{tm1.1Pcha}$ and homogenized in Trizol. Total RNA was prepared, and samples were sent for bulk mRNA sequencing. Additionally, we snap-froze kidneys in liquid nitrogen for nuclei preparation and single-cell RNA sequencing (in progress).

Results:
mRNA sequencing revealed differential gene expression for Invs^{inv} and Pkd1$^{tm1.1Pcha}$ mice; these were comparable between the two models and included gene sets previously known to be affected in CKD. However, the analysis of the Nek8^{jck} mRNA data did not show any differentially expressed genes for the first timepoints and few for the last. Analyzing the gene sets of the Invs^{inv} mouseline, we saw mainly inflammation as being positively, and especially mitochondrial gene sets as being negatively enriched. In contrast, mitochondrial gene sets were positively enriched for the early Pkd1$^{tm1.1Pcha}$ timepoints, as well as translation and protein synthesis associated gene sets. A small overlap between Invs^{inv} P0 and Pkd1$^{tm1.1Pcha}$ P10 encompassed positively regulated inflammatory gene sets, and majorly transmembrane transport associated negatively regulated gene sets.

Conclusion:
Despite the genetic, phenotypic, and pathological differences among CKD, some alterations overlap that may be promoting cyst development. By conducting mRNA seq of three CKD mouse models, we were able to compare and analyze the data of the Invs^{inv} and the Pkd1$^{tm1.1Pcha}$ mice. We could show that a common feature in pre-cystic stages is the positive enrichment of genes associated with inflammation, cancer and cell cycle. Negatively enriched were gene sets related to ion transport across membranes, mirroring the extent of kidney damage occurring already in the early stages of CKD. With our single-cell RNA-seq data, we aim to include the third mouseline Nek8^{jck} in our analysis. Moreover, we plan to decipher a cyst-driving cell lineage and aim to provide more specific insights into potential cyst causing pathways.