Molecular signaling of flow-mediated electrolyte handling in the kidney

Scientific context

The kidneys filter our blood and principally remove excess fluid and waste products generated during our metabolism. Generally, the kidneys reabsorb 95% of the electrolytes contained in the pro-urine after glomerular filtration. The pro-urine flows through the renal tubule, which in turn contain dedicated tight junction proteins, ion channels and transporters contributing to renal electrolyte handling. The *PKD1* gene encodes polycystin-1 (PC1), a mechanosensor of pro-urine flow, which triggers intracellular responses upon pro-urine flow sensing. Mutations in *PKD1* lead to autosomal dominant polycystic kidney disease (ADPKD), which is one of the most common inherited renal diseases accounting for 7 to 10% of all patients on renal replacement therapy. ADPKD is characterized by increased cell proliferation, fluid accumulation and altered extracellular matrix synthesis, resulting in renal cyst formation.

Project background

Patients with ADPKD present electrolyte disturbances. However, when these imbalances are detected in cystic ADPKD, it is not possible to discern the exact cause (cyst formation, reduced glomerular filtration, PC1 defective flow sensing, etc.). However, in the last year, we have identified that changes in the electrolyte reabsorption precede cystic formation and decreased renal function. Thus, the absence of PC1 is potentially the cause for the electrolyte disturbances.
Along the nephron there are ion channels and transporters responsible for the reabsorption of valuable ions from the pro-urine. Specifically, the distal convoluted tubule (DCT) is the main nephron segment important for the fine-tuning of final Ca^{2+} and Mg^{2+} reabsorption. However, the functional regulation of Ca^{2+} and Mg^{2+} channels/transporters due to flow sensing by PC1 remains largely unknown.

Aims and Research Questions

Our aim is to decipher the PC1-mediated molecular mechanisms controlling ion channels/transporters involved in Ca^{2+} and Mg^{2+} reabsorption. Moreover, changes due to PC1 absence, following initial steps of ADPKD, will be addressed. Based on the previous facts, we would like to investigate whether:
1) Activation of PC1 by flow leads to a modulated uptake of Ca^{2+} and Mg^{2+} from the pro-urine?
2) Following, what molecular pathway of PC1 activation is involved in affecting the activity of Ca^{2+} and Mg^{2+} transporters?

What will you do?

You will investigate the function of PC1 on ion channels/transporters. This will include the use of renal cell models, in combination with microfluidics technology to mimic pro-urine flow. Moreover, you will measure effects of flow on transepithelial electrolyte transport via the following techniques:

- electrolyte measurements (radioactive and stable isotopes)
- western blotting
- qPCR
- localization study (confocal microscopy)
- cell surface biotinylation

These techniques will be performed under the supervision of an experienced postdoc. In addition, you will be in charge of the design and analysis of your experiments, with the appropriate coaching. By the end of the internship, you will be able to provide the molecular explanation for electrolyte imbalances in pre-cystic stages of ADPKD.

Contact

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