Not just waste: urinary ATP and intercellular communication along the nephron

Scientific context

The kidney plays a major role in maintaining the electrolyte homeostasis (i.e. Na^+, K^+, Ca^{2+}, Mg^{2+}). Alterations of this balance frequently underlie disease states like renal lithiasis, cardiac arrhythmias, development of seizures, etc. In order to maintain electrolyte levels within the physiological range, the kidney has several control mechanisms to properly face changes in dietary food and fluid intake as well as changing needs of the whole body. Among them, autocrine and paracrine signaling have been described to play a role in electrolyte handling in the kidney.

Project background

Besides its well-known role as high energy molecule, ATP has been reported to function as an extracellular messenger mediating communication between different cell types. In this regard, ATP can be released to the extracellular space of a cell upon sensing a given stimulus. Previously we have observed changes in ATP release in renal cells that were exposed to variable fluid flow to induce so-called fluid shear stress (simulating differences in pro-urine flow, for example, due to variable water intake). Following, ATP can reach a target cell resulting in changes in particular cellular processes. Specifically, purinergic receptors have been demonstrated to be activated by ATP in the kidney and associated with disease states like chronic kidney disease. To date, the molecular mediators of ATP release (i.e. membrane channels) in response to variable pro-urine flow and the molecular signaling of this process are not known. Moreover, whether released ATP can reach downstream nephron segments and has an impact on the electrolyte handling has not been investigated yet.

Research Questions and Aim

Therefore, our aim is to elucidate which molecular players are involved in ATP signaling along the nephron in response to variable pro-urine flow, how they are regulated and whether this regulation has an impact on the renal electrolyte handling. The following points will be addressed:

1- Investigate the participation of different ATP channels (i.e. connexins, pannexins) in the release of ATP by kidney tubular cells in response to variable fluid shear stress. And assess the regulation (gene and protein expression, localization, transport activity) of the responsible entity.

2- Study the effects of proximally released ATP (i.e. upstream in the nephron) on distal cells. And investigate the role of different purinergic receptors and their effect on the transepithelial electrolyte transport.

What will you do?

You will culture kidney cell lines of different nephron segments in microfluidics chambers allowing the co-culture of different cell types, which will be used to measure transepithelial ion transport and assess signaling and regulation by various techniques, like:

- cell culture
- electrolyte measurements (radioactive and stable isotopes)
- western blotting
- qPCR
- immunocytochemistry (confocal microscopy)
- pharmacological inhibition

During your internship, you will work with a team of experienced postdocs and PhD candidates who will guide you through the planning and execution of your experiments, data analysis and presentation.

Contact

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