How does CNNM2 regulate magnesium (Mg2+)-transport in the kidney?

Background

Magnesium is the most prevalent divalent cation in the human body and is required for many physiological processes, such as DNA repair/synthesis, neuronal signal transduction, muscle contraction, and many more. The kidney is the organ that is largely responsible for Mg2+ homeostasis by regulating the reabsorption of Mg2+ from the pro-urine. Approximately 10% of the Mg2+ is actively reabsorbed in the latter segments of the nephrons: the distal convoluted tubule (DCT). When Mg2+ is taken up by the cell, this needs to be transported towards the blood compartment. However, this process is largely not understood.

We have identified CNNM2 as an important player at regulating Mg2+ towards the blood. This is a transmembrane protein expressed at the basolateral side of the cells in the DCT. Mutations in this gene have been found causative for hypomagnesaemia, a condition in which the Mg2+ serum levels are <0.7mM. This causes a range of symptoms; muscle cramps, seizures, and cardiac arrhythmia. In addition, a GWA-study has linked CNNM2 to hypertension, attributing the protein a role in blood pressure regulation. Although it has become clear that CNNM2 is involved in the regulation of Mg2+-transport, the mechanism underlying this remains unclear.

Aim and research question

In order to study the mechanisms by which CNNM2 regulates Mg2+-homeostasis on a molecular and physiological level, we want to establish multiple models to address these questions accordingly. Firstly, we want to generate a CNNM2 KO cell line using CRISPR/Cas9 technology. By designing specific small guide RNA's, we can specifically target and modify our gene of interest. Using this model, we can, for example, study the specific protein interactions between CNNM2 and potential candidate interactors. Moreover, this cell model could aid in the investigation of the role of CNNM2 in blood pressure regulation.

In addition, we have mice which are heterozygous for CNNM2. These mice exhibit lowered serum magnesium levels, but further characterisation needs to be done. We designed a study in which we will challenge the mice with a magnesium-deprived -and -rich diet and assess the phenotype caused by the diets

- How does CNNM2 regulate Mg2+ extrusion to the blood compartment?
- How do mutations affect the function of the CNNM2 regarding Mg2+-handling?
- What might be the mode of action by which CNNM2 influences blood pressure regulation?
- What are the effects of a magnesium-deprived and -rich diet on CNNM2+/- mice regarding serum magnesium levels?

Internship and techniques

Our department offers an environment to perform high-quality research that includes both basic and translational aspects of biomedical science. Here, you will be part of a professional and diverse group consisting of PhD students, post-doctoral researchers and other students. Under supervision of your PhD-student, you will have your own project in which you will formulate your research question and design and perform your own experiments accordingly.

Techniques that can be used during your internship:

- Cell culture and transfection
- CRISPR/Cas9 technology
- RNA studies (Real-time quantitative PCR)
- Protein studies (Co-immunoprecipitation, cell surface biotinylation and Western Blot)
- Cloning, PCR, and bacterial transformation
- 25Mg2+ uptake assays
- Imaging techniques (live imaging, immunocyto/histochemistry)

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