Fishing for function: characterization of renal electrolyte handling in health and disease with the zebrafish model

Clinical relevance

Electrolyte imbalances are a common symptom manifested by hospitalized patients. Electrolyte imbalances resulting in disturbed electrolyte concentrations in serum arise from genetic and drug-induced renal disorders involving a variety of defects in filtration and tubular transport processes. Low serum electrolyte concentrations can cause a wide variety of features including serious cardiac, metabolic and neurological disorders. The present project will decipher new genes involved in thick ascending limb of Henle's loop (TAL) and/or distal convoluted tubule (DCT) electrolyte reabsorption, and will establish their physiological relevance *in vivo* in health and disease. This knowledge is key to elucidate the genetic etiology of drug-induced and inherited electrolyte imbalances, to identify the link between electrolyte imbalances and chronic diseases, and to design potential treatments for hospitalized patients since new targets for drug development will be established. The development of drugs targeting TAL and/or DCT electrolyte transport genes will be an effective treatment to restore electrolyte homeostasis. Additionally, when the genetic etiology of inherited and acquired renal electrolyte transport disorders is established, clinicians will profit from the new zebrafish model of electrolyte imbalance generated in the present project.

Background

The TAL and DCT are crucial nephron segments for the transport of electrolytes from the urine towards the circulation. These segments play a major role in determining serum and urine electrolyte levels and thereby the disorders associated to disturbed serum/urine electrolyte concentrations. As a result, mutations affecting genes expressed in the TAL and DCT are linked to clinically-low serum electrolyte levels. Exome sequencing in patients with electrolyte imbalances have yielded candidate genes expressed in the TAL and DCT that encode proteins that may be related to renal TAL and/or DCT electrolyte handling. In this project, the function of these genes will be elucidated.

Goals

In this internship, we aim to find whether there is a causal relation between the patient(s) phenotype and the candidate gene(s) obtained from exome sequencing analysis. In this sense, we want to answer the following scientific questions:

- Can we detect defects in the renal handling of electrolytes when knocking down exome sequencing candidates in the zebrafish model?
- Are the renal functions elucidated with the zebrafish model extrapolable to human disease?

Techniques you will learn

This internship will allow you to learn and apply several techniques such as:

- Knockdown of gene expression using antisense oligonucleotides
- Qualitative analyses of morphological phenotypes denoting defects in kidney function in morphant (knockdown) and control zebrafish
- Electrolyte analyses in zebrafish larvae
- RNA isolation, cDNA synthesis and gene expression analyses by RTqPCR

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