The Role of the FGF23-Klotho Axis in Uremic Media Calcification

Summary
Philipp Eller, Institute of Internal Medicine, Intensive Care Unit, Medical University of Graz

Supervisor:
Prof. Dr. Philipp Eller

Availability:
This position has been occupied.

Offered by:
Medical University of Graz

Application deadline:
Applications are accepted between February 01, 2017 00:00 and March 19, 2017 23:59 (CEST)

Description

Background:
The massive burden of cardiovascular disease in chronic kidney disease and diabetes mellitus is strongly associated with extensive media calcification, reduced vascular compliance, left ventricular hypertrophy, and sudden cardiac death. Media sclerosis and media calcification are regulated by a complex interaction of systemic and local triggers of vascular calcification such as hyperphosphatemia and hyperglycemia, but also critically dependent on diverse physiological protectors from vascular calcification such as fetuin A or vitamin K [1-4]. These triggers and protectors modulate the phenotype of vascular smooth muscle cells, which they are not terminally differentiated cells. In this manner they can eventually react to stress, inflammation or injury by transdifferentiating from contractile to proliferative and/or osteoblastic phenotypes. FGF23 has also been implicated to play a key role in the development of uremic media calcification, since it is upregulated by phosphate intake and leads to hyperphosphaturia by binding to Klotho on tubular epithelial cells. Increased FGF23 levels have been detected in chronic kidney disease (CKD) patients. They increase with the CKD stage and correlate significantly with vessel calcification and cardiovascular mortality.

Hypothesis and Objectives:
We postulate that the FGF23-Klotho axis plays a central role in the phenotypic modulation of vascular smooth muscle cells. Preliminary data from our lab indicate that FGF23 signalling is not only essential for phosphorus hemostasis, but also an important trigger for inflammation in chronic kidney disease. The main objective of this project is to analyse the diverse effects of the FGF23 signalling and to interfere with its various receptors in order to prevent chronic inflammation and concomitant media calcification.

Methodology:
The PhD candidate will learn how to induce and to evaluate an in vivo murine model of uremic media calcification using histology, molecular biology, mass spectrometry and vascular wire myography, respectively [1-3]. The FGF23-Klotho Axis will be evaluated in vivo by using blocking antibodies. The PhD student will furthermore perform primary cell culture experiments and investigate the role of FGF23 –Klotho in these cells by performing knock-down experiments. Ultimately we aim to modulate the vascular smooth muscle cell behaviour and thus prevent/treat media sclerosis and media calcification that are associated with heavy burden of morbidity and mortality in patients suffering from diabetes mellitus or end-stage renal disease.

References:


To get more information or to apply online, visit https://mug.glowbase.com/positions/66 or scan the code on the left with your smartphone.