Medical University of Graz

Vascular autophagy in hypertension and kidney disease

Summary

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Supervisors:	Prof. Dr. Simon Sedej Mahmoud Abdellatif
Availability:	This position is available.
Offered by:	Medical University of Graz
Application deadline:	Applications are accepted between August 03, 2022 00:00 and September 20, 2022 23:59 (Europe/Zurich)

Description

Background: Human life expectancy has dramatically increased across the globe, significantly shifting the demographic profile towards an elderly population. In our aging societies, vascular diseases are the major cause of morbidity and mortality. Amongst these, hypertension is the leading risk factor. Although a great majority of patients with hypertension receive regular pharmacological therapies, only a third show controlled blood pressures. Thus, more efforts are needed to achieve better management of hypertension. Autophagy, which is an essential process for maintaining health by recycling damaged cellular components, is altered during vascular aging and hypertension. However, whether autophagy is directly involved in blood pressure regulation remains to be determined.

Hypothesis and Objectives: we speculate that autophagy is required for vascular homeostasis. To test this hypothesis, we will assess the vascular phenotype of genetically engineered mice that mimic human hypertension and kidney diseases- these mice will have either enhanced or reduced autophagy.

Methodology: Mice lacking autophagy globally or specifically in vascular smooth muscle or endothelial cells will be generated. Autophagy-deficient and WT mice will be subjected to hypertension and/or vascular calcification using established models in the presence or absence of autophagy inducers, like spermidine. Measurements of vascular calcification and autophagic flux will be complemented by high-resolution micro-CT and computational 3D reconstruction analysis of the vascular tree to visualize the heart, kidney, and their microcirculation. Vascular function (wire myography) and remodeling (histology, gene/protein expression) will be analyzed. Kidney function will be assessed by glomerular filtration rate (GFR) measurements, serum urea and proteinuria. Cardiac phenotyping will include echocardiography, invasive hemodynamics, as well as in vivo energy metabolism and polyamine flux using state-of-the art metabolomics and fluxomics, respectively. The selected PhD candidate will closely work with other fellows who will be recruited as part of the MedUniGraz first Flagship Project: Vascular health in aging and disease (Vasc-Health). Additionally, the recruited PhD student will have the opportunity to perform parts of the study abroad in close collaboration with renowned international research groups.

References:

1. Abdellatif *et al*. Fine-Tuning Cardiac Insulin-Like Growth Factor 1 Receptor Signaling to Promote Health and Longevity. **Circulation** (2022)
2. Abdellatif *et al*. Autophagy in Cardiovascular Aging. **Circulation Research** (2018)
3. Frauscher *et al*. Autophagy Protects From Uremic Vascular Media Calcification. **Frontiers in Immunology** (2018)

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4. Eisenberg & Abdellatif *et al*. Cardioprotection and Lifespan Extension by the Natural Polyamine Spermidine. **Nature Medicine** (2016)

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