Medical University of Graz

Mimicking caloric restriction against cardiometabolic decline in aging and related heart failure

Summary

Simon Sedej, Division of Cardiology and Center of Medical Research, Medical University of Graz

Supervisor:	Prof. Dr. Simon Sedej
Availability:	This position is available.
Offered by:	Medical University of Graz
Application deadline:	Applications are accepted between August 18, 2021 00:00 and October 04, 2021 23:59 (Europe/Zurich)

Description

Background:

Aging and associated obesity are major risk factors contributing to the development of heart failure with preserved ejection fraction (HFpEF) – a burgeoning public health problem and one of the greatest challenges in cardiovascular and geriatric medicine – for which no lifesaving therapies exist (1). Considering that HFpEF is a systemic metabolic disease linked with impaired myocardial relaxation (i.e., diastolic dysfunction), targeting the communication between the heart and adipose tissue may have a therapeutic value to prevent cardiometabolic decline in aging and associated HFpEF. We recently discovered that selected caloric restriction mimetics (CRMs) restore metabolic perturbations, reduce obesity, and improve diastolic dysfunction, at least in part, through increased autophagy and deacetylation of the proteins regulating the mechanoelastic properties of cardiomyocytes (2,3). However, CRMs may also exert their salutary effects by promoting lipid homeostasis through the manipulation of lipolysis. Atglistatin is an adipose triglyceride lipase inhibitor that effectively protects against obesity by lowering circulating free fatty acids (4), which have the potential to exert lipotoxic effects, especially in the heart whose oxidative capacity declines with age.

Hypothesis and Objectives:

We hypothesize that pharmacological inhibition of lipolysis through atglistatin is capable of alleviating the HFpEF phenotype. Our aims are to (i) determine HFpEF-related changes in lipolysis in adipose tissue and cardiac muscle, and (ii) delineate protective cardiac and metabolic effects of atglistatin by assesing the impact of lipolysis manipulation on the pathogenesis of HFpEF at the molecular, cellular and tissue to organismal levels. Our objective is to uncover the mechanisms by which atglistatin improves the crosstalk between the heart and adipose tissue and, thus, attenuates the development of metabolic impairments that directly contribute to HFpEF.

Methodology:

To study the consequences on the cardiometabolic health-protective capacity of atglistatin, the PhD student will employ clinically relevant HFpEF and genetically-modified animal models. She/he will learn and apply state-of-the-art *in vivo* cardiac and metabolic phenotyping, ranging from high-precision cardiac evaluation using non-invasive echocardiography and intra-cardiac catheterization as well as serial insulin and glucose tolerance testing, indirect calorimetry to exercise tolerance testing. These experiments will be coupled to mass spectrometry-based metabolome and lipidome analysis of the myocardium, adipose tissue and plasma of atglistatin-treated animals. Biochemical and molecular biology assays in relevant tissues such as determination of autophagic flux, mitochondrial respiration, oxidative stress, inflammatory markers, and blood and plasma parameters will provide key insights into the processes to test whether rescuing the cardiometabolic HFpEF phenotype via atglistatin depends on autophagy or other mechanisms. The PhD student will have the opportunity to perform part of the study in close collaboration with renowned Austrian and international research groups.

References:

- Dunlay, S. M., Roger, V. L. & Redfield, M. M. Epidemiology of heart failure with preserved ejection fraction. *Nature Reviews Cardiology* 14, 591–602 (2017).
- Abdellatif, M. *et al.* Nicotinamide for the treatment of heart failure with preserved ejection fraction. *Science Translational Medicine* 13, (2021).

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- Eisenberg, T. *et al.* Cardioprotection and lifespan extension by the natural polyamine spermidine. *Nature Medicine* 22, 1428–1438 (2016).
- Schweiger, M. *et al.* Pharmacological inhibition of adipose triglyceride lipase corrects high-fat diet-induced insulin resistance and hepatosteatosis in mice. *Nature Communications* 8, 14859 (2017).