Medical University of Graz

Targeting Excitation-Transcription Coupling for Managing Hypertensive Cardiomyopathy

Summary

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Supervisors:	PD Dr. Gunther Marsche Dr. Senka Holzer
Availability:	This position is available.
Offered by:	Medical University of Graz
Application deadline:	Applications are accepted between February 10, 2020 00:00 and March 30, 2020 23:59 (Europe/Zurich)

Description

Background: Hypertensive cardiomyopathy or pathophysiological changes in myocardial structure and function caused by hypertension is a growing clinical problem due to the ageing population and a lack of curative therapies. The onset of the disease is often clinically silent, progressing over time to therapy-resistant symptomatic forms. Existing therapeutic concepts are, therefore, symptom-oriented and tailored for advanced stages of cardiac remodeling. Understanding molecular processes driving early hypertension-induced changes may improve diagnosis and treatment options.

Recent evidence positions changes in Ca^{2+} cycling as an early promoter of cardiac remodeling *via* Ca^{2+}-mediated regulation of transcription. The enzyme Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) has a central role in this process, as it can translate fine changes in Ca^{2+} fluxes into altered gene expression. However, the specific regulation of this so-called excitation-transcription coupling in hypertensive cardiomyopathy is unclear.

Hypothesis and Objectives:

This project aims to provide a comprehensive, in-depth characterization of the CaMKII-mediated transcription in hypertensive cardiomyopathy at the molecular, cellular and whole organism level. We will follow the hypothesis that (1) changes in Ca^{2+}-mediated transcriptional activity are causally involved in the initiation and progression of hypertensive cardiomyopathy and (2) heart-specific targeting of the altered transcription *via* inhalation of CaMKII inhibitory peptide-loaded nanoparticles can halt disease progression or even delay its manifestation.

Methodology: We will primarily employ various techniques for assessing cardiac structure and function *in vivo* (blood pressure and hemodynamic pressure-volume measurements, transthoracic echocardiography) and *in vitro* (isolation of adult ventricular myocytes, subcellular Ca^{2+} imaging, purification of cardiomyocyte nuclei, electron microscopy, protein detection assays and immunofluorescence).

With our multidisciplinary approach, a wide range of state-of-the-art techniques and invaluable access to human myocardium, we expect to acquire better understanding of hypertension-related cardiac pathophysiology and provide the necessary preclinical evidence to support future translational and clinical studies employing peptide-loaded nanocarriers as a remedy for treating cardiomyopathies of different etiologies.

References:

1. **Ljubojevic S**, Radulovic S, Leitinger G, Sedej S, Sacherer M, Holzer M, Winkler C, Pritz E, Mittler T, Schmidt A, Sereinigg M, Wakula P, Zissimopoulos S, Bisping E, Post H, Marsche G, Bossuyt J, Bers DM, Kockskämper J, Pieske B. Early remodeling of perinuclear Ca^{2+} stores and nucleoplasmic Ca^{2+} signaling during the development of hypertrophy and heart failure. *Circulation*. 2014 Jul 15;130(3):244-55. doi: 10.1161/CIRCULATIONAHA.114.008927.
2. **Ljubojevic S**, Bers DM. Nuclear calcium in cardiac myocytes. *J Cardiovasc Pharmacol*. 2015 Mar;65(3):211-7. doi: 10.1097/FJC.0000000000000174. Review.

3. Bers DM. Calcium cycling and signaling in cardiac myocytes. *Annu Rev Physiol.* 2008;70:23-49. doi: 10.1146/annurev.physiol.70.113006.100455. Review.
4. Mishra S, Gray CB, Miyamoto S, Bers DM, Brown JH. Location matters: clarifying the concept of nuclear and cytosolic CaMKII subtypes. Circ Res. 2011 Dec 9;109(12):1354-62. doi: 10.1161/CIRCRESAHA.111.248401.