Medical University of Graz

Comprehensive analysis of CaMKII-mediated inflammatory signaling in cardiac (patho)physiology

Summary

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Supervisor:	Dr. Senka Holzer
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: Inflammation is an established driver of adverse cardiac remodeling after acute myocardial infarction in humans and experimental animal models. Ischemic interventions lead to necrotic cell death and release of damage-associated molecular patterns, factors that signal cell damage and induce expression of proinflammatory chemokines and cytokines. However, emerging evidence demonstrates that nonischemic conditions such as atherosclerosis, atrial fibrillation (AF) and heart failure (HF) are also associated with increases in inflammatory genes and immune cell accumulation in the heart. How proinflammatory responses are elicited in nonischemic heart disease which is not—at least initially—associated with cell death is one of the most critical unanswered question in cardiovascular biology.

Activation of Ca2+/calmodulin-dependent protein kinase II (CaMKII) is the early promoter of cardiac remodelling via transducing stress signals to gene reprogramming in the process termed excitation-transcription coupling (ET-coupling).1,2 In line with this, recent evidence showed that CaMKII triggers inflammatory gene expression and activation of the NOD-like receptor pyrin domain-containing protein 3 (NLPR3) inflammasome in cardiomyocytes,3 while increased assembly of NLPR3 inflammasome on hyperacetylated mitochondria has been identified as a key driver of HF pathogenesis.4 Furthermore, our latest work showed that CaMKII is critically involved in the upregulation of interleukin 6 receptor (IL6R) signaling in cardiomyocytes upon tachycardia- and hypertension-induced cardiac stress.5

Hypothesis and Objectives: In this project we will further follow the hypothesis that cardiomyocytes are an initiating site of inflammatory gene expression in response to nonischemic stress. Specifically, this project aims to (1) reveal specific CaMKII-dependent sites and molecular mechanisms of inflammatory signaling activation within cardiomyocytes,

(2) their effects on immune cells recruitment and (3) their contribution to overall functional vulnerability of the heart in conditions of tachycardia, hypertension and AF. Finally, we will test the possibility that pharmacological interventions targeting CaMKII signaling axis could serve

as potential treatment for alleviating increased inflammatory response and structural and functional remodeling of the heart.

Methodology: We will employ various techniques for assessing cardiac structure and function *in vivo* (blood pressure and transthoracic echocardiography) and *in vitro* (isolation of adult ventricular myocytes, live-cell subcellular Ca2+ imaging, proximity ligation assays and immunocytochemistry, purification of cardiomyocyte nuclei, MS-based CaMKII interactome analyses, electron microscopy, single cell RNA sequencing and standard qRT-PCR and protein detection assays). With our multidisciplinary approach, a wide range of state-of-the-art techniques and invaluable access to human myocardium with various degrees of cardiac pathologies, we expect to acquire a better understanding of CaMKII-mediated inflammatory signaling in cardiac (patho)physiology and provide substantial preclinical evidence to support future translational and clinical studies targeting identified signaling cascades as a remedy for treating cardiac remodeling of different etiologies.

References:

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2. Ljubojevic-Holzer S et al., *Circ Res*. 2020. doi: 10.1161/CIRCRESAHA.120.316947.
3. Suetomi T et al., *Circulation*. 2018. doi: 10.1161/CIRCULATIONAHA.118.034621.
4. Deng Y et al., *Circ Res*. 2021. doi: 10.1161/CIRCRESAHA.120.317933.
5. Matzer I et al., *Biomedicines*. 2022. doi: 10.3390/biomedicines10071648.