Role of endothelial cells in development of post-inflammatory dilated cardiomyopathy

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Popular science summary:

Inflammation of the myocardium, termed myocarditis, is a progressive heart disease, which either resolves without serious complications or is followed by development of dilated cardiomyopathy (DCM) phenotype. Due to limited ability to perform endomyocardial biopsies, non-specific symptoms or asymptomatic disease course, myocarditis is very likely an underdiagnosed cause of heart failure, and sudden death. DCM is a cardiac condition in which the left ventricle is enlarged, dilated and weak, and can't effectively pump the blood. Transition of myocarditis to DCM is associated with cardiac pathological tissue remodelling resulting in fibrotic lesions and hypertrophic (enlarged in size) cardiomyocytes. These changes are usually irreversible and progressive. The mechanisms controlling these pathogenic processes remain, however, obscure and treatment options are limited. Due to the COVID-19 pandemic and the fact that SARS-CoV-2 virus often cause cardiac injury in infected patients, it is expected that the number of patients with post-inflammatory heart disease will likely rise in the near future.

In this project, we will address the role of cardiac microvascular endothelial cells (CMVECs) in development of post-inflammatory DCM. Coronary microvasculature plays a pivotal role in physiological processes such as blood supply, nutrient delivery, metabolic homeostasis and prevention of thrombotic events as well as represents a highly selective permeability system that controls entry of blood proteins and cells into the tissue. Activation of CMVECs in myocarditis has been linked with their increased interaction with inflammatory cells and with development of coronary microvascular dysfunction. Our preliminary data from mouse model of experimental autoimmune myocarditis (EAM) confirmed activation of CMVECs at the inflammatory phase of the disease. Now, we plan to perform in vitro and in vivo experiments to prove, whether or not, activated CMVECs modulate fibrotic and hypertrophic processes in the heart by cellular cross-talk with cardiac fibroblasts and cardiomyocytes. The project is planned as a three-step approach: In the first step, we will identify novel biomarkers and active biomolecules produced by CMVECs in response to pro-inflammatory and pro-fibrotic stimuli. In the second step, we will evaluate effect of pre-activated CMVECs on profibrotic response of cardiac fibroblasts and hypertrophic response of cardiomyocytes. In the last step, by using specific transgenic mice and the EAM model, we will address the relevance of pro-fibrotic TGF-beta signalling on endothelial cells for development of acute myocarditis and post-inflammatory DCM.

Currently, there is no effective treatment against immunofibrotic cardiac diseases due to insufficient understanding of immune-induced pathogenic processes in the heart. Elucidation the role of immune-activated microvascular cells in post-inflammatory DCM would substantially broaden our current knowledge on the pathophysiology of inflammatory heart diseases. Identification of the respective mediators would open new perspectives for development of novel treatment strategies against immunofibrotic heart diseases in the future.