Molecular mechanisms of cardiac microvascular endothelial cell activation by autoreactive CD4$^+$ T lymphocytes and inflammatory myeloid cells

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Popular science summary

Inflammation of the myocardial tissue called myocarditis is an inflammatory disease of the myocardium caused by different infectious and non-infectious triggers. In 10-20% of diagnosed cases, myocarditis progresses into inflammatory dilated cardiomyopathy, a chronic inflammatory process resulting in progressively impaired contractility, tissue remodelling, ventricular dilatation and heart failure. Inflammatory dilated cardiomyopathy is the leading cause of heart failure cases in patients below the age of forty. 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, sudden death and chronic dilated cardiomyopathy. In most of the cases myocarditis is caused by viral or protozoan infections, but autoimmune mechanisms are critically involved in development and progression of the disease. It is known from mouse models as well as from clinical observations that heart-specific autoreactive CD4$^+$ T lymphocytes are critically involved in the development of myocarditis. Though the autoreactive CD4$^+$ T cells mediate myocarditis, the majority of inflammatory cells in the myocardium represent cells of the myeloid lineage.

Mechanisms controlling development and progression of inflammatory heart diseases are poorly understood. It is well recognized that microvascular endothelial cells control entry of leukocytes into the tissue. However, surprisingly little is known about activation of coronary microvasculature by autoreactive CD4$^+$ T cells in myocarditis. During the effector response, CD4$^+$ T lymphocytes produce a variety of proinflammatory cytokines including TNF-alpha, which is well known cytokine activating endothelial cells. Furthermore, CD4$^+$ T lymphocytes can secrete extracellular vesicles, which represent another class of cell-to-cell mediators with immunomodulatory properties. Two major research aims are proposed in this project. The first aim is to understand molecular mechanisms by which CD4$^+$ T cells, CD4$^+$ T cell-derived extracellular vesicles as well as inflammatory myeloid cells activate cardiac microvascular endothelial cells and affect endothelial barrier function. The aim of the second part of this project is to elucidate how TNF-alpha produced by CD4$^+$ T lymphocytic and myeloid compartments (by using the specific Cre-lox mice, which allow to suppress TNF-alpha production in specific cell lines) contributes to development and progression of experimental autoimmune myocarditis in mouse model.

Elucidation of mechanisms, by which heart-reactive CD4$^+$ T cells and inflammatory myeloid cells control adhesive properties and permeability of the coronary microvascular barrier will substantially broaden our current knowledge on the physiopathology of inflammatory heart diseases. We believe that our study on the role of extracellular vesicles will contribute to identification of novel inflammatory mediators and signalling pathways. Recognition of novel targets will open new perspectives for development of innovative treatment strategies against inflammatory-mediated heart diseases in the future. Furthermore, elucidation of cell type specific role of TNF-alpha in autoimmune myocarditis will shed more light on the actual contribution of TNF-alpha to cardiac immunopathology. Summarizing, we hope that the proposed project will significantly contribute to better understanding of cardiac pathophysiology and will provide answers to some of the important and internationally competitive questions in cardiology.