Title: **Role of autophagy in experimental autoimmune myocarditis**

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Popular science summary

Inflammation of the myocardial tissue called myocarditis is an inflammatory disease of the myocardium caused by various infectious and non-infectious triggers. Some myocarditis patients progress into dilated cardiomyopathy, a condition characterized by tissue remodelling, ventricular dilatation and heart failure. The mechanisms controlling these pathogenic processes remain, however, obscure and treatment options rather limited. In humans, myocarditis is often caused by cardiotropic 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.

Our data from mouse model of experimental autoimmune myocarditis (EAM) show high activity of autophagy in inflammatory cells during the acute phase of myocarditis. Autophagy is a general term for degradation of cellular components (from proteins to organelles) inside the cell through the action of lysosomes. This is a common cellular adaptation to stress conditions, such as nutrient depravation, but also to inflammatory response. So far, however, very little is known about the role of autophagy in EAM, and the existing data are contradicting.

We hypothesize that autophagy-dependent processes significantly contribute to the pathophysiology of the disease. In order to understand contribution of autophagy to development of myocarditis and DCM, we propose a multifaceted study based on mouse model of EAM. In our study we aim 1) to identify cell populations with increased autophagic activity in hearts during myocarditis, 2) to address treatment with pharmacological modulators of autophagy on disease development and progression, 3) to address effect of genetic deficiency of autophagic gene Atg5 in myeloid lineage and 4) to define the role of autophagy in adhesion of myeloid cells to activated cardiac microvascular endothelial cells. We hypothesize that blockage of autophagy may successfully limit expansion of disease-inducing heart-reactive CD4+ T cells during early stage of EAM. On the other hand, during transition from myocarditis to DCM, autophagy may control production of proinflammatory and profibrotic mediators by inflammatory cells and therefore serve as cardioprotective mechanism.

Understanding the role of autophagy in myocarditis may have important therapeutic implications. Autophagy inhibitors chloroquine and hydroxychloroquine are well-tolerated FDA-approved drugs that have been used for many years in the treatment of patients with malaria or with rheumatic disorders. Similarly, pro-autophagic agent resveratrol is used as a nutritional supplement. In this project, effect of pharmacological autophagy modulators will be complemented with studies using the specific genetic tools and cutting-edge technologies. Thus, use of combined approaches, as presented in this proposal, will allow to identify the role of autophagy and autophagy-associated processes in myocarditis and in post-inflammatory dilated cardiomyopathy. Summarizing, with the support from the National Science Centre Poland, we will be able to answer some of the important and internationally competitive questions in cardiology and set the basis for future therapies.