Mitochondrial targets of flozins in endothelial cells - a new approach to the prevention, diagnosis and therapy of heart failure

Cardiovascular diseases, particularly heart failure (HF), are the leading causes of death in developed countries. The early stage HF involves dysfunction in both large and small blood vessels, leading to disease progression and reduced oxygen supply to the myocardium. Two primary factors contributing to this are 1) obstructive atherosclerosis in arteries with lipid plaque deposition and 2) microvascular dysfunction associated with structural and functional changes in smaller blood vessels. Dysfunction of the endothelium, a single layer of cells lining the blood vessels, underlies both these conditions occurring earlier than damage to heart myocytes during HF. Thus, investigating endothelial dysfunction (ED) mechanisms should be a primary goal for the prevention and treatment of HF and many other cardiovascular pathologies.

Recent evidence indicates that function of blood vessels depends on mitochondria in endothelial cells. Endothelial mitochondria are an engine for energy production in the form of adenosine triphosphate (ATP), which favors 1) the synthesis of nitric oxide (NO), a key modulator of vascular tone, and 2) formation of new vessels. Thus, enhancing endothelial function through bioenergetics modulation may delay HF progression.

Lately, it has been shown that flozins (sodium-glucose cotransporter 2 inhibitors, SGLT2i), a new group of antidiabetic drugs, reduce cardiovascular mortality regardless of the presence of diabetes. However, the mechanisms of their beneficial effects are not fully understood. Apart from lowering blood glucose levels by inhibiting its renal reabsorption, flozins may reveal a sodium transport-dependent effect and improve the energy metabolism in cardiomyocytes. However, the effects and mechanisms of their action on endothelium remain unclear.

This project aims to investigate how flozins affect the bioenergetics and functions of endothelial cells, and whether targeting these processes may be beneficial in the prevention and treatment of macro- and microcirculatory dysfunction, delaying the progression of HF and supporting cardiac regeneration.

The study will include patients with HF as well as experimental cell culture and animal models. Research techniques, including analytical, microscopic, and molecular will be used to assess the effects and mechanisms of flozins. Patients with HF before and after 3 months of therapy with flozins will be assessed for macro- and microcirculatory function and condition of the vascular endothelium using a non-invasive skin fluorescence test combined with the analysis of circulating parameters of oxidative stress as well as endothelial and mitochondrial dysfunction. These interdisciplinary studies will be conducted by a research team from the Medical University of Gdansk, Postgraduate Education Center in Warsaw and University of Gdansk, in cooperation with the National Institute of Cardiology in Warsaw, Federico II University of Naples, and University of Grenoble.

The knowledge gained during the project will provide unique information on basic aspects of endothelial bioenergetics together with highlighting therapeutic targets delaying the development of HF and supporting cardiac regeneration. The proposed research will indicate new drugs as candidates for targeting endothelial mitochondria. Moreover, the development of a non-invasive approach to assess the condition of the endothelium will allow for early diagnosis and monitoring of HF and many other endothelium-dependent pathologies.