Sphingosine kinase 1 as a modulator of vascular function – mechanisms and therapeutical opportunities

Essential hypertension is one of the diseases of affluence and a major risk factor for cardiovascular diseases. It is a complex disease, which means that a number of factors, both genetic and environmental, influence its development and progress. Research on the causes and possible therapeutic targets for the treatment of hypertension have been conducted for many years and resulted in inventions of various drugs. However, there is an ongoing need for accurate understanding of the basis of the hypertension development in order to develop more effective forms of therapy. Basic research, i.e. research on the mechanisms of biological phenomena, are often carried out in animal models and are prerequisite for further translational research aiming to apply discoveries made in the treatment of human diseases.

Research, carried out in our laboratory in recent years, suggest an extremely complex mechanism of hypertension. Using mouse model of the disease we have identified many genes and biological pathways altered in hypertension. Such observations are not a proof for causality of relationships between these genes and hypertension because these may be a simple result of blood pressure raise. Advanced bioinformatical analysis of pathways altered in hypertension allowed us to identify sphingosine kinase 1 (Sphk1), which level and activity are significantly elevated in the mouse model of hypertension. Sphk1 synthesizes sphingosine-1-phosphate, which acts in blood vessels through specific receptors. Moreover, genetically modified strain of mouse that does not express *Sphk1* (i.e. *Sphk1*$^{-/-}$), developed significantly less severe hypertension as compared to wild type mice. This observation, confirmed by other scientific teams, shows that Sphk1 may be one of the genes causally related to hypertension. Interestingly, *Sphk1*$^{-/-}$ mice were characterized by the impairment of another important vascular parameter called “function of endothelium”, which is the innermost layer of the vessel having a direct contact with blood. In light of our research we believe that Sphk1 plays an important role not only in the endothelium, but also in the next layer of the vessel, i.e. smooth muscle cells. In order to thoroughly investigate this phenomenon we propose to create and examine mouse strains that do not express *Sphk1* specifically in endothelial or smooth muscle cells. This will help to establish an exact role of Sphk1 in these 2 layers of the vessel. Moreover, we are planning to examine effects of pharmacological modulators of Sphk1 pathway (e.g. inhibitor of Sphk1) on the development of hypertension in mice. Such study will help to identify potentially effective substance for antihypertensive treatment. In the last stage of our research, we plan to check whether results of previous experiments translate into human cells. We propose to establish relationships between plasma level of sphingosine-1-phosphate and clinical parameters of cardiovascular function in a group of approximately 130 subjects. We also plan to describe effects of pharmacological modulators of Sphk1 pathway on human endothelial and smooth muscle cell cultures *in vitro*.

In summary, proposed project aims to examine function of Sphk1 in the vascular system and to describe the mechanisms of its action. The project also fits into the efforts of other scientific groups, which have recently started to describe novel relationships between Sphk1 and cardiovascular system. Joint research effort may result not only in the description of novel molecular mechanisms of hypertension, but also in creation of effective therapeutic trials in human hypertension. Importantly, one of Sphk1 pathway modulators, a drug called Fingolimod, has been recently approved for the treatment of multiple sclerosis in humans. This is a result of longstanding research, focused on this substance, and gives a hope that Sphk1 pathway may be an effective therapeutical target in other complex diseases, including essential hypertension.