

Popular science summary of the project.

The role of MOTS-c peptide in the regulation of adrenal cortex physiological function

MOTS-c is a newly discovered bioactive peptide composed of 16 amino acids. It is secreted into the circulation and thus acts as a hormone. It has been proven so far that MOTS-c regulates important physiological functions. Among others, it affects insulin sensitivity and energy homeostasis. It has been shown that the administration of MOTS-c inhibits the development of obesity in mice. Interestingly, unlike other genes, the gene encoding MOTS-c is not located within the DNA of the nucleus but originates from the mitochondrial DNA sequence. Mitochondria also occur abundantly within the adrenal cortex, where they participate in the biosynthesis of aldosterone and cortisol - the main adrenocortical hormones. These hormones play an important role in the regulation of several physiological processes. Among other, they are a strong inhibitor of the immune response, they participate in response to stress, play an important role in the regulation of blood pressure and act in the opposite way to insulin; thus they participate in the regulation of metabolism. The physiological levels of adrenocortical hormones are precisely regulated, and any disturbance of this regulation leads to serious health implications. The excess of adrenal hormones leads to the development of Cushing's syndrome, which is also manifested by the development of obesity. In contrast, adrenal hormone deficiency leads to the development of Addison's disease, characterized by, inter alia, loss of appetite and weight. Studies of recent years have shown that the levels of adrenal hormones can also be controlled by a number of bioactive peptides, which in the future may become the target for the development of new drugs or therapies related to adrenal dysfunction. Our preliminary research allows us to assume that MOTS-c can be included in such a group of peptides. The proposed project concerns issues not yet discussed by other scientists. The implementation of research tasks proposed in the project will focus on the determination of the MOTS-c effect on the biosynthesis of adrenal steroid hormones using in vitro models (primary adrenal cell cultures, freshly isolated adrenocortical cells, adrenal fragments) as well as by activation of the hypothalamic-pituitary-adrenal axis. In addition, it is planned to determine the intracellular mechanism activated by MOTS-c. For this reason, a number of experiments will be conducted using specific pharmacological inhibitors of signalling pathways relevant for adrenal function. It is also planned to conduct an analysis of the MOTS-c effect on the adrenocortical cells proliferation. The potential clinical value of the obtained results will be verified by determination of the MOTS-c expression in normal and highly aggressive human adrenal carcinomas with reference to the collected clinical data.

We plan to use a range of modern molecular biology techniques, including the determination whole transcriptome modulation (about 30,000 genes) using microarray approach and visium spatial transcriptomics technology allowing to visualize individual transcripts on adrenal histological slices.