

The human life span has dramatically increased over several decades, and the quality of life has been considered to be equally important. Diet and physical activity are factors that could influence both life span and quality of life. Excessive consumption of foods and reduced physical activity is thought to be largely attributable to the current obesity epidemic. Moreover, obesity may lead to the development of diabetes type 2 (DM2), which accounts for 90% of diabetes cases reported around the world. **As obesity and diabetes emerge throughout the globe, the WHO recognizes both disorders as the biggest public health problem.** Besides primary metabolic health problems occurring in people with obesity and diabetes, there are numerous secondary problems, including memory loss and Alzheimer's disease. Above abnormalities could be related to alterations in functions of the brain structure called the hippocampus. The hippocampus is responsible for learning and memory and is a very plastic brain structure, where generation of new neurons in adult life occurs in a process called neurogenesis. It was shown that diet and exercise affect adult hippocampal neurogenesis. In obese and diabetic patients, beneficial effects of physical activity were revealed. Benefits observed upon physical exercise were not only in weight loss but also improved cognitive functions in patients. Physical activity is considered as a beneficial therapy in cases of obesity and diabetes type 2. Despite of a growing body of data on beneficial effects of physical activity, the underlying mechanism(s) remains to be elucidated. Recent findings have shown that physical activity (voluntary running) causes functional changes in the muscle and modulates the epigenetic patterns, especially DNA methylation signature. Over weeks during physical activities (e.g., running) substances released from the muscle, including cathepsins B, irisin, and interleukin-6, travel to the blood and later to the brain. In the brain, those substances can stimulate the production of new neurons in the hippocampus, improving learning and memory.

**Thus, the main goal of this project is to gain new knowledge about protective and therapeutic effects of physical activity towards mechanism(s) responsible for disruptions of hormonal and metabolic profiles, muscle physiology and hippocampal functions in diet-induced obesity.**

We will employ an innovative approach by using the cafeteria diet (CAF) model, in which rats are fed high-fat and high-sugar food products reflecting what people commonly consume. The CAF diet has a high energy value and is highly palatable, which increases animals' tendency to overconsumption and the development of obesity. We will explore both short-term (protective) and long-term (therapeutic) effects of physical activity (running) in obese rats. We hypothesize that CAF diet-induced obesity leads to alterations of transcriptomic profiles (RNA-seq) in the muscle and the brain **via epigenetic mechanisms** (WGBS, ATAC-seq), and that substances released by the exercising muscle (e.g., higher cathepsin B, higher irisin, but lower IL-6) improve, at least partially, neurogenesis in the hippocampus and thus learning and memory.

We will use various methods: immunohistochemistry, Western blots, ELISA, RIA, electrophysiology, epigenetic omics methods (WGBS, RNA-seq, ATAC-seq), and behavioral tests (Novel Object Recognition – NOR and Morris Water Maze MWM).

**The project proposes a novel multi-organ omics approach to comprehensively study effects of physical activity by integrating physiological processes occurring in the muscle, blood and brain. We expect that findings of the proposed work will reveal the epigenetic mechanism(s) behind the therapeutic effects of physical activity on hippocampal and muscle functions, metabolic, hormonal, and behavioral outcomes. Understanding mechanisms underlying the development of obesity, when these changes might still be reversed by interventions incorporating physical activity, is important for rehabilitation, decrease in disease burden, mortality, and improving the quality of life of patients.**