Project 1.5. Determination of the impact of the ERK3/MK5 pathway on the development of metabolic diseases

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Background:

Storage and degradation of triglycerides from lipid droplets (in the process of lipolysis) is the key evolutionary adaptation to cope with the prolonged periods of fasting. However, the induction of uncontrolled lipolysis in adipocytes independently of the nutritional demand of the organism is an event contributing to the development of multiple metabolic diseases including cancer-associated cachexia (CAC), obesity, and type 2 diabetes (T2D). In multiple types of cancers, CAC is the direct cause of death of the patients. Obesity and associated diabetes also result in decreased life span and life quality. Therefore, there is an urgent need to develop anti-cachexic and anti-obesity therapies.

In our previous studies, we identified that atypical member of Mitogen-Activated Protein Kinase (MAPK), extracellular regulated kinase 3 (ERK3), and its interaction partner, MAPK-activated protein kinase 5 (MK5) promote lipolysis in adipocytes of mice and humans. The same complex of kinases regulates energy dissipation by adipocyte, another key event evoked during cachexia and suppressed in the course of obesity. Within the course of this project we will investigate the role of ERK3/MK5 signaling pathway on the development of metabolic diseases.

Aim:

In the framework of this project, we will test the impact of the ERK3/MK5 complex of kinases on the development of both, CAC and obesity, and investigate underlying molecular events regulated by these kinases. For this purpose, we will utilize cell biology and biochemical approach as well as mouse models of CAC and obesity in which we will ablate or increase the signaling via the ERK3/MK5 complex using genetic and pharmacological means.