Description for general public

Every human body consists of more than 30 trillion highly organized units, commonly known as cells. Every single cell is able to produce its own energy from nutrients, synthesize molecules necessary to perform its duties, and dispose unnecessary or damaged proteins. These functions are provided by numerous cellular structures called organelles and complexes. Energy is produced by organelles called mitochondria. They function like batteries, because they convert energy from one form to another: food nutrients to ATP, the main currency of cellular energy. Because of their key functions mitochondria are among the first part of the cell to become dysfunctional, especially in metabolically active tissues requiring high amounts of cellular energy like the brain, heart and muscles.

In addition to the energy production cells require also constant cleaning of damaged or abnormally modified proteins. This is crucial biological process ensured by the Ubiquitin Proteasome System (UPS). The accumulation of abnormal or unwanted proteins may perturb cellular functions. The proteins destined for the degradation by the proteasome are marked with small tag called ubiquitin. Ubiquitin tagging is reversible and special deubiquitinase proteins are used for this purpose.

Mitochondria and UPS dysfunction are pathological features being considered as a “central point” for neurodegeneration, a process which ultimately leads to irreversible neuronal damage and death. The most common examples of neurodegenerative diseases include Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis and Huntington's disease. Mechanistic understanding of the interplay between mitochondria and UPS and their common implication in neuropathology is still fragmented. Our project is focused on one particular UPS component, deubiquitinase UCH-L1. This protein has been described to be present mainly outside the mitochondria but our unpublished data showed that UCH-L1 is partially located to this organelle and its abundance in the dysfunctional mitochondria is reduced. Increasing literature data indicate the link of UCH-L1 to neurodegeneration however the relationship of UCH-L1 to pathophysiological processes related to neurodegenerative diseases, such as mitochondrial impairment remains unknown.

In the presented project we plan to perform three main research tasks. First we would like to find mitochondrial proteins that bind to UCH-L1. We will pay special attention to the proteins reported in literature as related to neurodegeneration and reported to be localized in the mitochondria. This will allow us to reveal a wide array of novel interactors leading to a much greater understanding of UCH-L1 function in the mitochondria. Second, we would like to describe mechanisms responsible for UCH-L1 trafficking to the mitochondria and the role of UCH-L1 in these important organelles. To this end, we will remove UCH-L1 and we will observe by different methods what happen to the mitochondria and to the proteins identified as binding partners of UCH-L1. In the last task we will overproduce UCH-L1 in the cells with dysfunctional mitochondria and we will assess if UCH-L1 will be able to rescue these dysfunctional mitochondria.

Neurodegenerative diseases have a major impact at professional, social and family level of patients and can ultimately lead to a complete inability to carry out any type of everyday activity. According to World Health Organization (WHO) as life expectancy increases, the number of people affected by this group of diseases will continue to increase. Our studies will enrich our basic understanding but can also form a basis for designing therapies that target specific interactions of disease-specific protein with mitochondria.