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Mitochondrion is a cellular compartment commonly known as “the power plant” of cells. To fulfill its various functions, these organelles need more than one thousand cellular proteins. Yet, the majority of mitochondrial proteins are synthesized outside mitochondria in the cytosol and thus must be transported into mitochondria with the help of other proteins forming import machines. Dysfunctional mitochondrial protein import machines cause mitochondrial malfunctions, but also accumulation of precursor proteins in the cytosol. Cellular consequences of such precursor over-accumulation stress remained elusive. Our group has discovered the role of the cytosolic degradation machinery in precursors’ clearance and the mechanism called the UPRam that protects the cell from stress caused by mistargeted mitochondrial precursor proteins accumulating in the cytosol. These processes pinpoint an important crosstalk between the state of mitochondria and regulatory mechanisms responsible for maintaining the cellular protein homeostasis.

In this project, using simple model organisms, such as yeasts and worms, in addition to mammalian cells, we will undertake multidisciplinary approaches based on biochemistry, molecular cell biology and systems biology. Our efforts will be concentrated to identify and characterize the mechanisms of both, degradation of mistargeted mitochondrial proteins and the regulation of degradation machinery observed in the UPRam. We also aim to uncover biological consequences of these mechanisms, which are critical for homeostasis, survival and ageing at the cellular and organismal level.

Both mitochondrial dysfunction and cellular protein homeostasis failure are commonly implicated in many degenerative and age-related diseases in humans. The newly discovered mechanism may represent the missing link between the processes underlying degenerative pathologies, and may provide new strategies to maintain cellular survival and to preserve organismal fitness over time.