To degrade or not to degrade

–waste management in neurodegeneration

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Neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease and other dementias are rated by the World Health Organisation (WHO) among the main causes of global disease burden and although these diseases have been known for a long time, there is to date no cure available. A factor that most of these diseases share is the disturbed waste-management of cells in the brain.

In order for cells to function properly, waste, in the form of damaged proteins and other elements of the cells has to be managed and disposed. For this, cells have developed two different pathways: The ubiquitin-proteasome-system (UPS) and autophagy. The UPS shreds small proteins into their building blocks, allowing the recycling of these for other cellular needs. Autophagy is required to dispose larger amounts of waste, such as organelles and big protein complexes. During autophagy, substrates become packed into a double-membrane structure that is called autophagosome and functions as the garbage bag of the cell. In the autophagosomes the substrates are transported to lysosomes, specific compartments of the cell that break down waste and recycle its components. An important function of autophagy is the production of cellular energy by recycling of unwanted proteins e.g. during starvation to ensure cell survival. Autophagy is also activated when organelles of the cell are damaged and threaten to cause cell death.

Mitochondria are the power-houses of the cell and produce most of the cellular energy. To maintain their integrity and the cellular energy homeostasis, damaged mitochondria need to be disposed. This is done via mitophagy, a substrate specific type of autophagy.

Both, the UPS and autophagy depend on the small signalling molecule ubiquitin, which becomes attached to substrates as a tag for their destruction. Ubiquitin plays an important role in many cellular processes and its amount in the cell is limited, making ubiquitin recycling a crucial mechanism. The removal of ubiquitin-tags from substrates is done by specific proteins called deubiquitylating enzymes (DUBs). For the UPS, the involvement of DUBs to recycle ubiquitin has been demonstrated. However, in autophagy, the fate of ubiquitin is largely unknown.

In this study, we investigated the involvement of one specific DUB in starvation induced autophagy and in the removal of damaged mitochondria. We analysed the fate of ubiquitin during starvation induced autophagy and determined whether the absence of the DUB affects this fate. Furthermore, we demonstrate that this DUB is also involved in mitophagy. We found that an inactive form of the DUB affects the recruitment of specific autophagy-related proteins during mitophagy while the depletion of the DUB interfered in parts with the destruction of the mitochondria.

The results of this study will help to further characterize and understand the molecular mechanisms of autophagy. Additional studies on this topic will provide crucial insights into the development of neurodegenerative disorders and potential drug targets.

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