When a lack of sugar drives cells to eat themselves

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Autophagy is the recycling process by which our cells keep themselves young. They continually break down and renew small parts of themselves in a kind of self-digestion; this helps to counteract harmful deposits which may form. Autophagy – Greek for "to eat oneself" – is stimulated particularly in hunger situations and when there is an energy shortfall. A team of researchers headed by Professor Tassula Proikas-Cezanne at the University of Tübingen's Interfaculty Institute for Cell Biology (IFIZ) has now discovered a molecular signaling circuit which regulates autophagy. In this process, WIPI proteins act as scaffolds, connecting the signal-directed initiation of autophagy with the subsequent breaking-down of cellular material. The findings were made in collaboration with Professor Boris Macek of the Proteome Center Tübingen and have been published in the latest editon of *Nature Communications*.

Professor Tassula Proikas-Cezanne and her team discovered the family of WIPI proteins several years ago. The researchers are now investigating the various functions of the four types of WIPI proteins (WIPI1-4). They discovered that when there is a lack of sugar – in other words, energy – in the cell, a direct signal is sent via the WIPI4 protein to regulate the extent of the breakdown process. That process is initiated by the WIPI1 and WIPI2 proteins and continued by the WIPI3 and WIPI4 proteins. The researchers also believe that the WIPI3 protein acts as an additional regulator of lysosomes to prevent anabolic pathways of the cell during the autophagy process. The four WIPI proteins act as platforms for multiple protein-protein and protein-lipid interactions which the Tübingen researchers identified, as well as the protein kinases

NUAK2 and BRSK2 to control WIPI4. Explaining the molecular processes of autophagy in such detail enables the researchers to better understand how a lack of sugar reinforces cellular autophagy.

The new findings may be used to better understand the faulty regulation of autophagy which underlies many age-related diseases. This in turn may lead to the development of new approaches to treatment, allowing doctors to specifically influence autophagy in age-related conditions such as diabetes mellitus, cancer, and a number of neurodegenerative disorders.

More information: Daniela Bakula et al. WIPI3 and WIPI4 β-propellers are scaffolds for LKB1-AMPK-TSC signalling circuits in the control of autophagy, *Nature Communications* (2017). DOI: 10.1038/NCOMMS15637

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