Membrane Remodeling in Autophagy and its involvement in neurodegeneration

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The cells of our body are constantly generating waste including aggregated proteins and non-functional or superfluous cellular components. Autophagy is a cellular recycling system that collects such waste, enclose it within membranes called phagophores and transport it to lysosomes for degradation. The unique feature of autophagy is that it can degrade any cargo, independently of size and shape. However, if cells are challenged by cytotoxic stress or starvation, they generate phagophores which sequester cytoplasm randomly.
We recently identified a protein coat that assembles on the outside of phagophores. We predict that the coat stabilizes the phagophore membrane and guides its expansion such that a complete, spherical autophagosome will be generated. Sealing of these phagophores generate autophagosomes that contain their cargo within the lumen. The mechanism of phagophore shaping, the composition of the coat and its structure are currently unknown.
In the proposed project, the membrane coat will be investigated in living cells using a combination of biophysical techniques. The composition of the coat will be studied by fluorescence lifetime imaging (FLIM) to reveal interactions and binding efficiencies of coat components and their distance to each other. Our unique confocal microscope is equipped with a FLIM module including a pulsed white light laser. Furthermore, shaping of the membrane will be investigated by correlative light electron microscopy (CLEM).
Neural cells are very vulnerable to perturbations of autophagy. In many neurodegenerative diseases such as Alzheimer's disease, protein aggregates accumulate in such cells due to a reduced autophagic activity. We found that theses protein aggregates are surrounded by phagophores that are decorated with the autophagic coat. Understanding its composition and its molecular function will allow us to improve its assembly, which will lead to an enhanced autophagic activity that degrades such toxic protein aggregates to rescue neurons.