Ph.D. projects in progress

1.

Mentor: Gábor Juhász

Doctoral school: University of Szeged, Faculty of Science and Informatics, Doctoral School of Biology

Ph.D. student: Hussein Abuammar

Title of the research topic: Lysosomal activation and a possible role of calcium starvation-induced autophagy

Description of the research topic: Autophagy is a highly conserved self-degradation process in eukaryotes and essential to maintain cellular homeostasis. Autophagosome-lysosome fusion as well as lysosomal degradation of cargo are critical steps in this pathway. Dystrophic neurites of Alzheimer's Disease (AD) patients accumulate autophagosomes and autolysosomes containing undegraded cargo. The lysosomal proton pump V-ATPase is necessary for lowering lysosomal pH, a prerequisite for the degradation of autophagosomal cargo by acidic hydrolases. Decreased V-ATPase activity causing elevated lysosomal pH and degradation defects are observed in aged brains and adult-onset neurodegeneration disorders, including AD and certain forms of Parkinson's Disease. Hence, lysosomal Ca2+ homeostasis is clearly important in context of disease progression.

My aims are: 1. Studying the role of intracellular Ca2+ in control of autophagosome-lysosome fusion. I am studying changes in Ca2+ levels during autophagosome-lysosome fusion. For this purpose, I generated a lysosomal-targeted TRPML1-GCaMP reporter which is being tested during autophagy induction. I am also testing the possibility that lysosomal calcium efflux during autophagy can influence the recruitment of endolysosomal fusion factors. 2. Determining the regulation of the lysosomal proton pump v-ATPase during autophagy. Maintaining an acidic pH inside lysosomes costs a lot of energy (in the form of ATP) to run the V-ATPase proton pump, which is why only few lysosomes are highly acidic and therefore active in fed, growing human HeLa and HEK 293 cells. I will investigate whether V-ATPase activity during autophagy induction is due to lysosomal calcium changes.

2.

Mentor: Hajnalka Laczkó-Dobos

Doctoral school: University of Szeged, Faculty of Science and Informatics, Doctoral School of Biology

Ph.D. student: Asha Kiran Maddali

Title of the research topic: Regulatory roles of lipids during autophagy

Description of the research topic: Macroautophagy (hereafter autophagy) is a self-eating process in the eukaryotic cells, during which damaged, obsolete cytoplasmic components and even intracellular pathogens are removed and degraded in lysosomes. Misregulation of autophagy can lead to a broad range of neurological disorders (such as, Parkinson, Alzheimer, and Huntington), aging and cancer. Autophagy is one of the rapidly exploring fields, however comprehensive molecular level understanding is still elusive. This process undergoes several steps: initiates with phagophore formation and matures into autophagosomes by their membrane expansion and closure. These membranes are unique and composed majorly of lipids and less membrane proteins compared to membranes of other cell organelles. Although mounting evidence in this area has comprehensively addressed autophagy related proteins and their role in orchestrating autophagy, knowledge is still incomplete about autophagosomal lipid composition and lipid-protein interactions in regulating autophagy. Therefore, we study "Regulatory roles of lipids during autophagy". Comprehensively we study the interplay between autophagic membrane lipids and autophagy related proteins, therefore it is important to get a detailed lipid map of autophagic membranes. Combination of biochemical, biophysical, molecular and cell biological methods are applied throughout our investigations. The obtained lipidomic data will serve as a basis for further lipid-protein in vitro interaction studies. By taking in vitro results as reference, certainly we pursue in vivo studies that can attain by creating various lipid mutants and follow how autophagic proteins incorporate into autophagic membranes by utilizing microscopic methods. In future, our obtained results potentially contribute to the research community to understand the lipid profile of autophagic membranes and their interactions with autophagic proteins. This may contribute to the therapeutic modulation of autophagy, by developing new possible drugs and agents.

3.

Mentor: Gábor Juhász

Doctoral school: University of Szeged, Faculty of Science and Informatics, Doctoral School of Biology, Genetics education programme

Ph.D. student: Enikő Lakatos

Title of the research topic: Investigating the function of Drosophila sorting nexins in endosomal trafficking

Description of the research topic: Organelles of eukaryotic cells represent an intricate network the members of which are connected with each other either via vesicular transport processes or permanent physical contacts. Significance of the latter type of organellar communication (the so-called membrane contact sites) has only been recognized in the last decade. The complex, dynamic endomembrane system plays a pivotal role in normal cell physiology and its proper function requires the concerted action of several proteins. Main research focus of our group is the investigation of genes and proteins involved in vesicular trafficking routes chanelling to the lysosomes, the central degradative organelles of cells. Members of the Sorting nexin (Snx) protein family play important roles in numerous points of the endolysosomal system. All Snx proteins contain the lipid-binding PX-domain that enables

them to associate with organellar membranes where they utilize other protein domains to take part in versatile molecular events. However, exact cellular functions of many Snx proteins are currently unknown, and importantly, some of these proteins are involved in the pathogenesis of human diseases. Most of the Sorting nexins are evolutionarily conserved, offering the possibility to investigate their functions in model organisms. We use various fruitfly tissues to study the molecular functions of the less well-characterized Snx proteins in the endolysosomal system. Our current focus is on the investigation of the function of Snx25, a known membrane contact site protein, which is involved in a human hereditary neurodegenerative disease. Our results show that the mutation of the fruitfly counterpart of this gene leads to severe defects in the endosomal maturation process of the highly endocytic larval nephrocytes. However, the exact mechanism of this phenomenon is currently not known. Besides investigating the role of Snx25 in the endosomal system, we aim to understand the function of a currently uncharacterized sorting nexin Snx21, int he same context.