Graduate School of Biomedical Sciences

The Graduate School of Biomedical Sciences
Cancer Biology

Announces the PhD Thesis Defense of

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Identification of a myotubularin-related phosphatase that regulates autophagic flux and lysosome homeostasis

Wednesday, June 24, 2020 at 2:00 p.m. Via Zoom Meeting

Macroautophagy (autophagy) is a vesicle trafficking process that targets cytoplasmic cargoes to the lysosome for degradation and underlies multiple human disorders. Pioneering work in *Saccharomyces cerevisiae* defined the core autophagy machinery, but animals possess autophagy regulators that were not identified in yeast. Autophagic flux occurs when autophagy rate increases or decreases in response to various cellular cues, such as nutrient availability. Indeed, dysregulated autophagy rates contribute to disease, making autophagy-modulation a therapeutic avenue to treat cancer, neurodegenerative disorders, and other diseases.

To identify novel regulators of autophagy in animals, I investigated autophagy in the context of animal development using *Drosophila*. In my dissertation, I screened for phosphoinositide phosphatases that influence autophagy, and identified *CG3530/dMtmr6*, a previously uncharacterized phosphatase. CG3530/dMtmr6 is homologous to the human MTMR6 subfamily of myotubularin-related 3-phosphoinositide phosphatases. I showed that dMtmr6 functions as a regulator of autophagic flux in multiple *Drosophila* cell types, and the MTMR6 family member *MTMR8* functions similarly in autophagy of higher animal cells. Decreased *dMtmr6* function resulted in autophagic vesicle accumulation, lysosome biogenesis, and impaired both fluid phase endocytosis in the fat body and phagocytosis in embryonic macrophages. Additionally, *dMtmr6* is required for development and viability in *Drosophila*. In human cells, lysosome homeostasis requires both the MTMR8 PH domain and catalytic cysteine residue, but only the PH domain is required to maintain autophagic flux. Collectively, this work identified a role for dMtmr6 and MTMR8 in autophagic flux and lysosome homeostasis.

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