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Autophagy: From Model Systems to Therapeutic Opportunities
Poster Abstract

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Rab3GAP-Rab18 module: a novel regulator of autolysosome maturation

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Autophagy is a conserved lysosomal degradation pathway in eukaryotes. During autophagy dispensable or aberrant organelles are sequestered into double-membraned autophagosomes that eventually fuse with lysosomes. Inside the newly formed autolysosomal lumen, the cargo is degraded and the resulting monomers are subsequently recycled. Thus, this process is essential for cellular homeostasis and autophagy dysfunction is linked to several diseases such as neurodegeneration, cancer and aging. Autophagosome-lysosome fusion is a key step of autophagy, however our knowledge about its genetic regulation is still limited. During the autophagic process, the cellular endomembrane system undergoes extensive transformation. Small GTPases of the Rab protein family are major regulators of membrane dynamics. The nucleotide bound state of Rab proteins is dependent of several cofactors, including the activator GEFs (guanine nucleotide exchange factor) and inactivator GAPs (GTPase-activating protein). Our research focuses on the complex of Rab3GAP2 and Rab3GAP1 proteins. The Rab3GAP1/2 complex is a multi-modal Rab cofactor as on one hand it can function as a GAP for Rab3, but on the other hand it can also act as a GEF for Rab18. In our study we found that the loss of Rab3GAP2 inhibits autophagic degradation in *Drosophila melanogaster*. In addition, we showed that loss of Rab3GAP2 leads to the severe alteration of lysosome morphology and function associated with autophagosome accumulation. Knocking down Rab18 inhibits autophagy in a similar way to Rab3GAP2. Finally, we found that aged Rab3GAP2 mutants show neuromuscular dysfunction, which is a well-known consequence of an autophagy defect. Taken together, our results suggest that the Rab3GAP-Rab18 module acts as a novel regulator of autolysosome maturation.

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