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### Abstract

#### **Role of Small GTPases In Autophagy. The Rab3GAP-Rab18 module.**

Autophagy which means 'self-eating', is an evolutionarily conserved degradation pathway in eukaryotes. During this process, superfluous or aberrant organelles are sequestered into a doublemembrane vesicle, called autophagosome, that eventually fuses with the lysosome, so in that way the enclosed contents can be degraded and the resulting macromolecules can be recycled. This process is essential for cellular homeostasis and it's disfunction is linked to several diseases and to aging as well.

However, autophagosome-lysosome fusion is a key step of autophagy, our knowledge about its genetic regulation is still limited. During the autophagic process the cellular endomembrane system undergoes extensive transformation. Membrane dynamics is mainly regulated by small GTPases of the Rab protein family. Rabs are switch-like proteins which have a GTP bound active and a GDP bound inactive conformation. This nucleotide binding status is dependent of the presence of activating and inactivating cofactors, GEFs (guanine nucleotide exchange factor), and GAPs (GTPase-activating protein) respectively.

Our research focuses on the Rab3GAP2 protein that forms a heterodimeric complex with Rab3GAP1. Rab3GAP1/2 complex is multi-modal Rab cofactor as it can function as a GAP for Rab3, but it can also act as a GEF for Rab18. During our study in *Drosophila melanogaster*, we found that the loss of Rab3GAP2 inhibits autophagic degradation. In addition, with light and electron microscopy we showed that in Rab3GAP2 loss of function mutant cells, the lysosomal system is disorganized, and autophagosomes accumulate due to impaired fusion events. We also found that silencing the Rab18 gene inhibits autophagy in a similar way to Rab3GAP2. These results suggest, that the Rab3GAP-Rab18 module represents a novel regulatory step in autophagosomelysosome fusion. Our aim is to discover the exact mechanism by which these proteins regulate this essential step of autophagy.