

Hungarian Molecular Life Sciences 2019
Poster Abstract

P-130

Rab3GAP-Rab18 module promotes autolysosome maturation through Atg14-PI3K complex

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Autosomal recessive mutations of the RAB18, RAB3GAP1 and RAB3GAP2 genes are associated with Warburg Micro Syndrome, a hereditary neuromuscular disorder. The genetic background of the disease is well known, however our current knowledge of the exact pathomechanism is still limited. The Rab3GAP complex, consisting of Rab3GAP1 and 2, serves as a guanine exchange factor, therefore as activator for Rab18. In our study we found that loss of the Rab3GAP-Rab18 module leads to perturbed autolysosome maturation and morphology and impaired autophagic degradation. Despite the absence of the Rab3GAP-Rab18 module, cells were able to maintain the early but not late endosomal compartments and exhibited partial failure in the delivery of the lysosomal hydrolase Cathepsin L. We also demonstrate that Rab18 interacts with the Atg6 subunit of the Atg14 containing PI3K complex and loss of Atg14 results in similar phenotype to Rab3GAP-Rab18 module lacking cells. Finally, we show that Rab3GAP mutant *Drosophila* is useful as a model for Warburg Micro Syndrome, as aged flies' climbing abilities were compromised and this defect is likely due to impaired autophagy in the thoracic muscles. Our study suggests that defect in autolysosomal maturation and autophagic degradation in muscle cells may contribute to the onset of Warburg Micro Syndrome.

Keywords: *Rab18, Rab3GAP, Warburg Micro Syndrome, autophagy*