

Potential new regulatory points of lysosomal exocytosis in *Drosophila melanogaster*

Fanni Keresztes^{1,2}, Ramóna Gálíková¹, Tünde Mónika Balog¹, Győző Szenci³, Szabolcs Takáts³, Tibor Kovács¹

¹ Eötvös Loránd University, Department of Genetics, Budapest, Hungary

² Eötvös Loránd University, Doctoral School of Biology, Budapest, Hungary

³ Eötvös Loránd University, Department of Anatomy, Cell and Developmental Biology, Budapest, Hungary

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As we age, the efficiency of autophagy gradually declines. However, autophagy is an essential degradation process in the cells to maintain homeostasis by removing damaged particles or organelles to keep neurons healthy. Numerous methods exist to increase autophagy: we can induce the formation of more autophagic structures or help the fusion steps of the vesicles. But what if the degradation is still inefficient, furthermore, toxic components from dysfunctional cell organelles accumulate in the autolysosome? In this presented study we aimed to induce anterograde transport to increase lysosomal exocytosis. Therefore, the elimination of the potentially harmful and damaged components could facilitate the rescue of the cells.

Previously we studied Arl8 which is a small GTPase protein localized in the membrane of lysosomes. It interacts with HOPS complex, thereby mediates endosome-lysosome and autophagosome-lysosome fusion steps. It also connects with kinesin-1 and plays a crucial role in anterograde transport. Moreover, it supports the transport of presynaptic vesicles, their neurotransmission and biogenesis.

Our results revealed that the neuronal activation of the small GTPase protein Arl8 elongates lifespan, improves reaction time of the animals and enhances autophagy. Therefore, we aimed to find activation points, which regulate the Arl8 protein. GTPase activating proteins (GAPs) are enzymes that inactivate the small GTPase proteins by inducing the hydrolysis of GTP. By silencing GAPs, we are able to increase the activity of Arl8. Our hypothesis involves the silencing of specific GAPs to activate Arl8, increase anterograde transport, which enhances lysosomal exocytosis.

During our studies we investigated various tissues: adult nervous system, larval fat body and salivary glands as well. We can conclude that the silencing of specific GAP enzymes influences the number and location of Arl8 positive lysosomal structures. During microscopy experiments we found that many GAP silencing contribute to peripheral accumulation of lysosomal vesicles. It seems like we could successfully increase lysosomal exocytosis by inducing the anterograde transport of the vesicles. A couple of GAP silencing increased the activity of Arl8 in the nervous system, therefore, improving the climbing ability of older animals and elongated lifespan. In addition, they also increased the efficiency of autophagy.

In the future, the results obtained can contribute to the development of drug molecules, which can facilitate the survival of senescence neurons.