Role of RUFY4 in autophagy and immunity

Autophagy is a crucial process for survival of individual cells as well as whole organisms. Autophagy enables cells to digest parts of its cytoplasm or even whole organelles to get energy during starvation, dispose of its damaged components, or fight intracellular infections. The same process is used in dendritic cells for regulation of adaptive immunity by delivering intracellular proteins for presentation on MHC class II (type 2 cross-presentation). Such an important process needs to be tightly controlled. One of the newly discovered regulators of autophagy is Rufy4 (RUN and FYVE domain containing protein 4). It is the only positive regulator of autophagy expressed only in a subset of immune cells, mainly in dendritic cells treated by IL-4, alveolar macrophages, and neutrophils.

To explore the molecular mechanism of function of Rufy4, we created a mouse model expressing truncated form of Rufy4 in dendritic cells and alveolar macrophages. This isoform of Rufy4, which can be naturally expressed by alternative splicing, lacks a functional RUN domain that is important for vesicular transport. We also cloned this isoform as well as other mutated forms of Rufy4 to dissect its function in cell cultures.

Rufy4 increases the autophagy flux in cells by an unknown mechanism. We discovered that Rufy4 is interacting with autophagosome-lysosome fusion machinery, but is not degraded by autophagy. Interestingly, Rufy4 is recruited to the mitochondria upon stimulation by LPS. Rufy4 may also be involved in formation of an autophagosomes, presumably by its FYVE domain, which can bind phosphatidylinositol 3-phosphate. We also plan functional tests with bacterial infection and induction of asthma in our mouse model.

Together these data should describe molecular mechanisms of regulation of autophagy by Rufy4 and indicate possible role of Rufy4 in asthma, immune modulation and infections of the dendritic cells.

Keywords : Rufy4, autophagy, mitochondria
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