RUN and FYVE domain-containing protein 4 enhances autophagy and lysosome tethering in response to Interleukin-4

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In addition to removing defective proteins or deteriorated subcellular organelles, autophagy is key to eliminate parasitic microbes in response to a variety of stress and metabolic changes. Most of our current knowledge about autophagy regulation was obtained through the study of starvation induced-autophagy in yeast. This process is used to recycle cellular material upon acute lack of nutrients. Autophagy is conserved among species and this pioneering work has served as a blue-print for chartering the molecular basis of autophagic processes in higher eukaryotes; however, little is known about the existence of cell – or tissue-specific factors controlling autophagy in multicellular organisms in other circumstances than amino acid starvation. Few are the molecules involved with the autophagic process that display cell – or tissue – specific expression. The groups of Philippe Pierre and Evelina Gatti have unraveled the positive regulatory role on autophagy of RUFY4 (RUN and FYVE domain containing 4), which is expressed in subsets of immune cells, including dendritic cells (DCs). DCs orchestrate the eradication of pathogens by coordinating the action of the different cell types involved in microbe recognition and destruction during the immune response. To fulfill this function, DC display particular regulation of their endocytic and autophagy pathways in response to the immune environment. Autophagy flux is down-modulated in DCs upon microbe sensing, but is remarkably augmented, when cells are differentiated in the presence of the pleiotropic cytokine IL4 (interleukin 4). From gene expression studies aimed at comparing the impact of IL4 on DC differentiation, the iBiMED researchers identified RUFY4, as a novel regulator that augments autophagy flux and, when overexpressed, induces drastic membrane redistribution and strongly tethers lysosomes. RUFY4 is therefore one of the few known positive regulators of autophagy that is expressed in a cell specific manner or under specific immunological conditions associated with IL4 expression, such as allergic asthma. The study of RUFY in the future might help to understand the role of autophagy in allergic asthma and potentially other types of lung inflammation.

FIGURE 1
Rufy4 facilitates STX17 or WIPI2 recruitment on phagophore via its RUN domain to concentrate these molecules and favor autophagosome formation

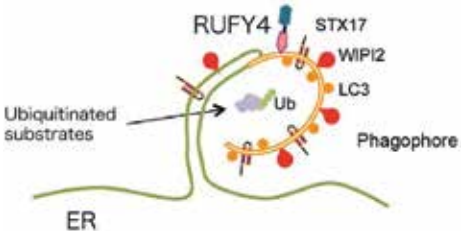

FIGURE 2
Interaction between Rufy4 and RAB7 or HOPS induces autophagosome and lysosome tethering?