Control of lysosomal biogenesis and Notch-dependent tissue patterning by components of the TFEB-V-ATPase axis in Drosophila melanogaster

In vertebrates, TFEB (transcription factor EB) and MITF (microphthalmia-associated transcription factor) family of basic Helix-Loop-Helix (bHLH) transcription factors regulates both lysosomal function and organ development. However, it is not clear whether these 2 processes are interconnected. Here, we show that Mitf, the single TFEB and MITF ortholog in Drosophila, controls expression of vacuolar-type H+--ATPase pump (V-ATPase) subunits. Remarkably, we also find that expression of Vha16-1 and Vha13, encoding 2 key components of V-ATPase, is patterned in the wing imaginal disc. In particular, Vha16-1 expression follows differentiation of proneural regions of the disc. These regions, that will form sensory organs in the adult, appear to possess a distinctive endo-lysosomal compartment and Notch (N) localization. Modulation of Mitf activity in the disc in vivo alters endo-lysosomal function and disrupts proneural patterning. Similar to our findings in Drosophila, in human breast epithelial cells we observe that impairment of the Vha16-1 human ortholog ATP6V0C changes the size and function of the endo-lysosomal compartment and that depletion of TFEB reduces ligand-independent N signaling activity. Our data suggest that lysosomal-associated functions regulated by the TFEB-V-ATPase axis might play a conserved role in shaping cell fate.

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