Title:	The small GTPase Arl8b regulates assembly of the mammalian HOPS complex on lysosomes
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Keywords:	Arl8b hVps41 Lysosome Mammalian HOPS complex SKIP
Issue Date:	2015
Publisher:	Company of Biologists Ltd
Citation:	Journal of Cell Science, 128 (9) pp. 1746-1761
Abstract:	The homotypic fusion and protein sorting (HOPS) complex is a multi-subunit complex conserved from yeast to mammals that regulates late endosome and lysosome fusion. However, little is known about how the HOPS complex is recruited to lysosomes in mammalian cells. Here, we report that the small GTPase Arl8b, but not Rab7 (also known as RAB7A), is essential for membrane localization of the human (h)Vps41 subunit of the HOPS complex. Assembly of the core HOPS subunits to Arl8b- and hVps41-positive lysosomes is guided by their subunit–subunit interactions. RNA interference (RNAi)-mediated depletion of hVps41 resulted in the impaired degradation of EGFR that was rescued upon expression of wild-type but not an Arl8b-binding-defective mutant of hVps41, suggesting that Arl8b-dependent lysosomal localization of hVps41 is required for its endocytic function. Furthermore, we have also identified that the Arl8b effector SKIP (also known as PLEKHM2) interacts with and recruits HOPS subunits to Arl8b and kinesin-positive peripheral lysosomes. Accordingly, RNAi-mediated depletion of SKIP impaired lysosomal trafficking and degradation of EGFR. These findings reveal that Arl8b regulates the association of the human HOPS complex with lysosomal membranes, which is crucial for the function of this tethering complex in endocytic degradation.
URI:	https://jcs.biologists.org/content/128/9/1746 (https://jcs.biologists.org/content/128/9/1746) http://hdl.handle.net/123456789/3049 (http://hdl.handle.net/123456789/3049)
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