Title:	Identification of SNAREs that interact with mammalian HOPS complex to mediate late endosome-lysosome fusion.
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Keywords:	Biology Proteins HOPS (Homotypic fusion and vacuole Protein Sorting) Endosome-Lysosome Fusion
Issue Date:	8-Jul-2015
Publisher:	IISER M

Abstract:	Eukaryotic cells dynamically communicate with their extracellular environment that involves a constant uptake and degradation of cargo, such as nutrients, in the lysosomes. The dynamic fusion and fission events that drive cargo transport to lysosomes are regulated by protein machineries such as small GTPases, tethering factors like HOPS (Homotypic fusion and vacuole Protein Sorting) complex and SNAREs (soluble N-ethylmaleimide-sensitive factor (NSF) attachment protein receptor). Human HOPS complex is a six subunit tethering factor, conserved from yeast to mammals, that has been shown to mediate cargo trafficking to lysosomes. Previous studies suggest that Vps33 subunit of yeast HOPS complex interacts with vacuolar SNAREs such as Vam3, Vam7 and Nyv1 to mediate homotypic fusion at the vacuole/lysosome. However, little is known about the SNAREs that function in conjunction with mammalian HOPS complex to mediate late endosome-lysosome fusion. In this study, we have characterised mammalian SNARE proteins that partially localize to lysosomes, namely, VAMP7, Syntaxin7, Syntaxin8, and Vti1b. Using yeast two-hybrid assays, we have tested interaction of these SNAREs with all the six subunits of the HOPS complex. No direct binding with any of the HOPS subunits was found in this assay, suggesting that probably more than one subunit of HOPS complex is required for interaction with SNAREs. Further identification of the SNARE proteins will be carried out using tandem affinity pull down approaches using Vps41 and Vp33a subunits as bait proteins. Confocal microscopy analysis indicates that target membrane associated SNARE Vti1b co localizes with hVps41 subunit of HOPS complex. Depletion of Vps41 subunit results in severely dispersed staining of Vti1b that continues to colocalize with lysosomal marker LAMP1. Furthermore, Vti1b co localizes with other SNAREs such as Syntaxin7, Syntaxin8 and VAMP7 suggesting that they could be the potential SNAREs forming a quaternary complex that mediates membrane fusion at the lysosomes.
URI:	http://hdl.handle.net/123456789/483 (http://hdl.handle.net/123456789/483)
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