Metazoan cell biology of the HOPS tethering complex

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Membrane fusion with vacuoles, the lysosome equivalent of the yeast *Saccharomyces cerevisiae*, is among the best understood membrane fusion events. Our precise understanding of this fusion machinery stems from powerful genetics and elegant in vitro reconstitution assays. Central to vacuolar membrane fusion is the multi-subunit tether the HOMotypic fusion and Protein Sorting (HOPS) complex, a complex of proteins that organizes other necessary components of the fusion machinery. We lack a similarly detailed molecular understanding of membrane fusion with lysosomes or lysosome-related organelles in metazoans. However, it is likely that fundamental principles of how rabs, SNAREs and HOPS tethers work to fuse membranes with lysosomes and related organelles are conserved between *Saccharomyces cerevisiae* and metazoans. Here, we discuss emerging differences in the coat-dependent mechanisms that govern HOPS complex subcellular distribution between *Saccharomyces cerevisiae* and metazoans. These differences reside upstream of the membrane fusion event. We propose that the differences in how coats segregate class C Vps/HOPS tethers to organelles and domains of metazoan cells are adaptations to complex architectures that characterize metazoan cells such as those of neuronal and epithelial tissues.

Fundamental Insights from the Yeast *Saccharomyces cerevisiae*

The HOPS complex was originally discovered in the yeast *Saccharomyces cerevisiae*.

Genetic screens in *S. cerevisiae* for mutant strains deficient in the localization of lysosomal enzymes revealed phenotypes in vacuole morphology and vacuolar protein secretion.¹⁻⁴ The gene products of these strains came to be referred to as the vacuole protein sorting (Vps) proteins.³ Vps mutant strains were classified as class A–F based on vacuolar characteristics and morphology.^{1,3} Among those are the class B and C Vps genes, which encode subunits of the HOPS complex. Class B Vps strains were characterized by fragmentation of vacuoles³ and class C Vps strains were characterized by the absence of any visible vacuolar compartment.³ The class B proteins Vps39 and Vps41 and the class C proteins Vps11, Vps16, Vps18, and Vps33 assemble in a hexameric complex referred as the HOMotypic fusion and Protein Sorting (HOPS) complex (Fig. 1).⁷⁻⁹ The class C proteins Vps11, Vps16, Vps18, and Vps33 assemble in an additional hexameric complex with the Vps3 and Vps8 subunits referred as the class C core vacuole/endosome tethering complex (CORVET, Fig. 1).^{10,11} In the HOPS complex the class B and C subunits play specific roles in the tethering, docking, and fusion stages of membrane fusion.^{3,5,8,9,11-15} A similar function is performed by the class C Vps proteins present in the CORVET complex.^{10,11} For outstanding reviews please refer to Nickerson et al.,¹² Wickner,¹⁶ Brocker et al.,¹⁵ and Epp et al.¹⁷

Elegant studies by Ostrowicz and Plemel lead to a model for HOPS complex organization.^{5,6} In this model, the class C subunits reside as an extended core of the complex with Vps33 interacting with membrane SNAREs while

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Figure 1. Organization of the class C Vps proteins into the multisubunit tethers HOPS and CORVET. Diagrams depict the proposed architecture of the HOPS and CORVET complexes based on studies in *S. cerevisiae*^{5,6} and a putative organization of HOPS complexes in metazoans. Class C Vps subunits are represented by gray spheres and class B Vps subunits are diagrammed as green and blue spheres, CORVET-specific subunits are depicted by purple spheres. At least four HOPS complexes could exist defined by Vps33a and Vps33b isoforms and the binding of SPE-39 to Vps33 isoforms. The existence of the mammalian CORVET complex has not been documented yet. It may be possible that Vps33a and Vps33b isoforms and the binding of SPE-39 to Vps33 isoforms may define similarly diverse CORVET complexes.

the class B subunits Vps39 and Vps41 interact with the Rab7-GTPase at the apposed membrane.^{5,6} This organization of HOPS complex subunits fits with the known functions of individual subunits. The core subunit Vps33 is a member of the Sec1/Munc18 protein family.¹⁸⁻²⁰ Interactions of Vps33 with t-SNAREs through the Sec1/MUNC18 domain may have a role in the recognition of target-specific SNAREs, thereby aiding in trans-SNARE pairing or, may inhibit non-specific trans-SNARE pairs.²¹ The class B HOPS subunits Vps39 and Vps41 have specificity for interaction with the Rab7 *S. cerevisiae* homolog Ypt7. In *S. cerevisiae*, the HOPS subunit Vps39 has been shown to interact with Ypt7. Though Vps39 was originally proposed to serve as the GEF for this vacuolar Rab Ypt7, recent studies in vivo suggest Vps39 is not the Rab7 GEF.^{9,22,23} Instead, the dimeric Mon1-Ccz1 complex is the Rab7/Ypt7 GEF.²⁴ The subunit Vps41 has also been shown to directly bind Ypt7 and act as the effector for Ypt7 in vacuolar tethering events.^{12,25} In addition to interactions with the Rab7 homolog, Vps41 has also been shown to interact with the vesicle adaptor AP-3 in *S. cerevisiae*.^{23,26-28}

Metazoan Mutations in HOPS Subunits Reveal Diverse Functions of the HOPS Complex

S. cerevisiae studies have been instrumental in understanding the role HOPS subunits have in regulating tethering, SNARE pair formation, and fusion of organelles with the vacuolar compartment.^{1,3-5,7-9,12-15,26-42} Metazoan genetic deficiencies are consistent with the role of the HOPS complex in the delivery of vesicle contents to lysosomes and lysosome-related organelles. However, the existence of HOPS subunit isoforms, metazoan-specific HOPS subunits, such as SPE-39, as well as partially overlapping distribution or function of HOPS subunits along the endocytic route suggest a more complex picture in metazoans than in yeast.⁴³⁻⁴⁷

Vps33 exists as two isoforms (a and b) encoded by different genes in *C. elegans*, *Drosophila melanogaster* and *Homo sapiens*. Vps33A and Vps33B are not redundant in *Drosophila* suggesting distinct tissue and possibly organellar functions.⁴⁸ Moreover, the Hermansky-Pudlak syndrome (HPS) and Arthrogyroposis, Renal Dysfunction and Cholestasis (ARC), affecting Vps33a and Vps33b respectively, further support

this idea in mammals. HPS is characterized by oculocutaneous pigment dilution, prolonged bleeding, and pulmonary fibrosis.⁴⁹⁻⁵¹ Symptoms of HPS arise from defects in sorting to lysosomes and lysosome-related organelles such as the melanosome and platelet dense granules.^{49,50,52} In humans, a subset of HPS patients displays mutations to the gene encoding the β subunit of AP-3.^{53,54} Models for HPS have been discovered in mouse and *Drosophila*.^{53,54} In mice, mutations to the genes that encode the clathrin adaptor AP-3 subunits AP-3 β 1 and AP-3 δ 1 as well as the class C HOPS subunit Vps33a result in decreased coat color, prolonged bleeding, and defects in lysosomal protein targeting.^{49,52,55,56} *Drosophila* homologs of class B and C HOPS subunits Vps33a, Vps41, Vps18, and adaptor protein AP-3 subunits also result in pigmentation defects.^{48,52,57-61} Importantly, mammalian phenotypes in AP-3 and Vps33a deficiencies are distinct from those of patients carrying mutations in Vps33b, a defect that leads to the ARC syndrome. ARC results from mutations to the gene responsible for encoding the class C HOPS subunit Vps33b or the Vps33b-interacting protein SPE-39, which is absent in yeast.^{46,62,63} SPE-39 is also referred as VIPAR in *Homo sapiens*, a nomenclature that we have disputed.^{62,64} In *Drosophila* SPE-39 is known as Vps16b⁶⁵ despite evidence indicating that SPE-39 possesses unique domains not present in Vps16.^{45,46} SPE-39 robustly immunoprecipitates Vps16,⁴⁶ thus suggesting that rather than a Vps16 isoform, SPE-39 is an additional component of class C Vps complexes such as HOPS and a putative mammalian CORVET complex (Fig. 1). Patients with ARC syndrome display a variety of phenotypes including severe contracture of joints referred to as arthrogyroposis, defects in renal function, cholestasis, bleeding disorders, dry, thickened, scaly or flaky skin referred to as ichthyosis, defects in metabolic absorption, absence or severe size decrease of the corpus callosum and defective organization of the anterior horn of the spinal cord.^{62,63,66-84} Importantly, severe joint contracture in patients with ARC syndrome results from a neurological defect as opposed to

muscular defects.^{63,75,80} Analysis of ichthyosis in ARC patients suggests defects in lamellar body secretion as shown by increased amounts of lamellar granules in patients with ARC syndrome by electron microscopy.^{68,69,72} Kidney epithelial cells and hepatocytes show a loss of apically targeted proteins.⁷¹ All of these phenotypes are consistent with a role for Vps33b and SPE-39 in regulation of lysosome-related organelles and secretion in polarized mammalian cell types. Thus, differences between HPS and ARC phenotypes affecting isoforms of class C Vps proteins may reflect differential tissue distribution of Vps33 isoforms. Alternatively, Vps33 isoforms expressed in the same cell may mediate either distinct tethering events between organelles and target membranes whose identities are specified by Vps33a, Vps33b, and SPE-39 and/or differences in cargoes trafficked by SPE-39-, Vps33a-, or Vps33b-dependent mechanisms.

Signaling receptors are attractive cargo candidates for explanation of phenotypic differences in HPS and ARC patients. For example, epidermal growth factor and Notch receptor degradation are impaired in HOPS complex deficiencies.^{46,85} Notch signaling is critical for embryonic development of neural and epidermal tissues and in the adult Notch modulates synaptic plasticity.^{86,87} Notch regulation could contribute to the severe neuronal and neuromuscular symptoms in patients with ARC syndrome. In the canonical Notch signaling pathway, Notch binds extracellular ligands and undergoes cleavage at the extra- and intracellular domains.^{85,86} Following cleavage, the intracellular domain is transported to the nucleus where it regulates gene expression.^{85,86} In addition, there is an endosomal pathway for Notch activation where Notch receptor is internalized in the absence of extracellular ligand.⁸⁵ Internalized Notch is targeted into intraluminal vesicles in multi-vesicular bodies where receptor degradation terminates signaling.⁸⁵ However in the endosomal pathway, which is AP-3- and HOPS-dependent, Notch is sorted away from intraluminal vesicles and remains at the multi-vesicular body limiting membrane for delivery to lysosomes where the intracellular domain undergoes cleavage and translocates to the

nucleus.^{85,86} The proposed role of HOPS subunits in this study was in regulating the fusion of late endosomes with the lysosome.⁸⁵ Such a model is consistent with the presence of HOPS in late endosomes, as demonstrated in yeast⁸⁸ and mammalian cells (see below). In such a model an AP-3 pool localized to incoming vesicles would encounter HOPS complexes present in late endosomes resulting in fusion of AP-3 vesicles with late endosomes (see Fig. 2A).^{28,88,89} An alternative yet not exclusive view, considers that since HOPS and AP-3 interact^{28,47,88-90} and AP-3 and HOPS are present in vesicle carriers⁴⁷ (Fig. 2B), perhaps the HOPS complex subunits may regulate Notch receptor sorting away from multivesicular bodies, to AP-3-HOPS clathrin-coated vesicles for delivery to lysosomes.

Comparative Cell Biology of *S. cerevisiae* and Metazoan HOPS-Coat Interactions

The role of HOPS in the membrane fusion event itself is well understood in *S. cerevisiae* thanks to in vitro vacuole fusion assays.¹⁶ However, a comparable assay in a metazoan system does not yet exist, limiting our ability to draw parallels with *S. cerevisiae*. Thus, we limit our discussion to HOPS subcellular localization and HOPS-coat interactions where information allows a preliminary comparison between unicellular and multicellular eukaryotes. The *S. cerevisiae*'s HOPS subunits are localized to the vacuolar compartment.^{28,31,36,40,41,91} HOPS complex subunits have not been identified at the Golgi or endosomal intermediates in *S. cerevisiae*.²⁸ Thus, it is postulated that in *S. cerevisiae*, cytosolic HOPS complex cycles on and off the target membrane.²³ In contrast with this unique localization of HOPS in yeast, metazoan cells yield a different localization of HOPS subunits.^{46,47,92,93} Vps class C proteins Vps11, 16 and 18 colocalize with early and late endosome compartment markers in mammalian cells.^{92,94} This observation is consistent with the HOPS complex interaction with mammalian late endosomal SNARE syntaxin-7 and Rab7.^{92,95} However, some studies indicate that the class C Vps proteins Vps11, 16, 18, and 33b as well as the

HOPS subunits Vps39 and Vps41 mostly localize to early endosomes but minimally with late endosomal and lysosomal markers.^{47,93} These data suggest that additional mechanisms beyond what is present in yeast have evolved to localize HOPS complexes to diverse endosomal compartments in metazoans.

The different HOPS localization patterns observed in *S. cerevisiae* and mammals could be due to changes in the organization of AP-3 trafficking mechanisms that evolved concurrent with multicellularity. In *S. cerevisiae*, the adaptor AP-3 recruits cargoes at the Golgi compartment for inclusion into vesicles that will be targeted to the vacuole, whereas in mammals, AP-3 functions at the early endosome for vesicle formation.⁹⁶⁻¹⁰⁰ Unlike mammals, *S. cerevisiae* AP-3 does not bind clathrin and clathrin is not required for the proper localization of AP-3 cargoes.^{97,100,101} In contrast, clathrin does bind AP-3 and clathrin-coated vesicles contain AP-3 subunits in mammals.^{90,102-105}

Early studies of HOPS subunits suggested interaction of AP-3 with the HOPS subunit Vps41 in *S. cerevisiae*.^{26,27} Direct interaction of the ear domain of AP-3 with Vps41 was presumed to occur with the isolated Vps41 subunit and not with the entire HOPS complex.^{26,27} These findings suggested that Golgi-derived AP-3 vesicles would require Vps41 as a coat complex in lieu of clathrin in *S. cerevisiae*.²⁶ However, elegant experimentation by Angers et al.²⁸ indicate AP-3 interacts with the whole hexameric HOPS complex rather than with the isolated Vps41 subunit. Furthermore, they showed that HOPS subunits are not associated with the Golgi, where *S. cerevisiae* AP-3 vesicle formation occurs, or on AP-3 vesicular intermediates.²⁸ Instead the results by Angers et al. as well as Cabrera et al. suggested a model where coated or partially coated AP-3 vesicles reached a vacuole decorated with HOPS complexes. Interestingly, the AP-3 cargo kinase Yck3 phosphorylates the HOPS subunit Vps41, present at the vacuole, making HOPS permissive to bind AP-3 in the vesicle. It is at the vacuole that an AP-3-HOPS interaction materializes as a step of the membrane tethering-fusion process (Fig. 2A).^{28,88}

Figure 2. Models of HOPS complex localization to early and late endosome/lysosome compartments. (A) HOPS complex localization to late endosome/lysosomes is specified by the properties of the late endosome/lysosomal membrane. HOPS complexes cycle on and off of the late endosome/lysosomal membrane. Interactions between coat and HOPS occur at the fusion stage where an incoming coated vesicle encounters the acceptor membrane that already contains the HOPS tether. (B) In a second model of HOPS complex localization, the HOPS complex is incorporated into newly forming vesicles at the donor endosome by interactions with, but not restricted to, the coat. A coated vesicle delivers the HOPS complex to a late endosome/lysosomal compartment. Coats confer information to vesicles for specific fusion with target organelles by inclusion of tethers and at the vesicle formation stage in this second model of HOPS localization.

Like in *S. cerevisiae*, mammalian AP-3 and HOPS complexes interact.^{47,90} However, the temporal and spatial organization of mammalian AP-3 and HOPS complex interactions differ from yeast in the following ways:

(A) HOPS subunits interact and colocalize on early endosomes with the coats, AP-3 and clathrin;⁴⁷

(B) HOPS subunits co-fractionate with clathrin-coated vesicles;⁴⁷

(C) HOPS subunits localize to endosomal compartments in a clathrin-dependent manner as revealed by chemical-genetic perturbation of clathrin;⁴⁷

(D) HOPS subunits are distributed in a polarized manner by clathrin-dependent mechanism.⁴⁷

The basic tenet of HOPS complex localization to the yeast vacuole is that it occurs through recruitment from the cytoplasm directly to the vacuolar membrane

(Fig. 2A). This model supports class B and C Vps HOPS subunits localization exclusively to the vacuole in *S. cerevisiae*. However, this model is not sufficient to explain the clathrin-dependent subcellular localization of HOPS complexes in mammalian cells.⁴⁷ Thus, we propose a novel and complementary model of class B and C Vps HOPS subunit localization in mammalian cells (Fig. 2B). In this model, HOPS localizes to early endosomes at sites of vesicle formation. HOPS complex subunits are included in clathrin-coated membranes as cargoes for traffic to the late endosome/lysosome or polarized domain of cells, such as those found in epithelial and neuronal cells (Fig. 2B).

The prevailing notion is that coats recruit target-specific cargoes for inclusion into vesicles destined for its target.¹⁰⁶ However, how does a vesicle “know” its target location?¹⁰⁷ Coats could confer

information to vesicles for specific fusion with target organelles by inclusion of tethers and SNAREs at the vesicle formation stage (Fig. 2B). This view is not represented in canonical models of vesicle-mediated membrane traffic that have conceptually segregated vesicle formation from vesicle fusion machineries for analytical purposes.¹⁰⁶ Our work demonstrated that tethers, such as the HOPS complex, are located on coated vesicles. These findings provide a mechanism for target recognition by coupling the vesicle formation and fusion machineries (Fig. 2B). In addition, coat-tether associations would provide a coat-dependent vesicular mechanism governing organelle-specific tether localization and delivery. These principles may be universal as suggested by the interaction between the coat COPII and the tether TRAPP1 in coated vesicles targeted from the ER to the Golgi complex.¹⁰⁸

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References

1. Banta LM, Robinson JS, Klionsky DJ, Emr SD. Organelle assembly in yeast: characterization of yeast mutants defective in vacuolar biogenesis and protein sorting. *J Cell Biol* 1988; 107:1369-83; PMID: 3049619; DOI: 10.1083/jcb.107.4.1369.
2. Robinson JS, Klionsky DJ, Banta LM, Emr SD. Protein sorting in *Saccharomyces cerevisiae*: isolation of mutants defective in the delivery and processing of multiple vacuolar hydrolases. *Mol Cell Biol* 1988; 8:4936-48; PMID: 3062374.
3. Raymond CK, Howald-Stevenson I, Vater CA, Stevens TH. Morphological classification of the yeast vacuolar protein sorting mutants: evidence for a prevacuolar compartment in class E vps mutants. *Mol Biol Cell* 1992; 3:1389-402; PMID: 1493335.
4. Wada Y, Anraku Y. Genes for directing vacuolar morphogenesis in *Saccharomyces cerevisiae*. II. VAM7, a gene for regulating morphogenic assembly of the vacuoles. *J Biol Chem* 1992; 267:18671-5; PMID: 1526999.
5. Ostrowicz CW, Brocker C, Ahnert F, Nordmann M, Lachmann J, Peplowska K, et al. Defined subunit arrangement and rab interactions are required for functionality of the HOPS tethering complex. *Traffic* 2010; 11:1334-46; PMID: 20604902; DOI: 10.1111/j.1600-0854.2010.01097.x.

6. Plemel RL, Lobingier BT, Brett CL, Angers CG, Nickerson DP, Paulsel A, et al. Subunit organization and Rab interactions of Vps-C protein complexes that control endolysosomal membrane traffic. *Mol Biol Cell* 2011; 22:1353-63; DOI: 10.1091/mbc.E10-03-0260.
7. Nakamura N, Hirata A, Ohsumi Y, Wada Y. Vam2/Vps41p and Vam6/Vps3p are components of a protein complex on the vacuolar membranes and involved in the vacuolar assembly in the yeast *Saccharomyces cerevisiae*. *J Biol Chem* 1997; 272:11344-9; PMID: 9111041; DOI: 10.1074/jbc.272.17.11344.
8. Seals DF, Eitzen G, Margolis N, Wickner WT, Price AA. Ypt/Rab effector complex containing the Sec1 homolog Vps33p is required for homotypic vacuole fusion. *Proc Natl Acad Sci USA* 2000; 97:9402-7; PMID: 10944212; DOI: 10.1073/pnas.97.17.9402.
9. Wurmser AE, Sato TK, Emr SD. New component of the vacuolar class C-Vps complex couples nucleotide exchange on the Ypt7 GTPase to SNARE-dependent docking and fusion. *J Cell Biol* 2000; 151:551-62; PMID: 11062257; DOI: 10.1083/jcb.151.3.551.
10. Markgraf DF, Ahnert F, Arlt H, Mari M, Peplowska K, Epp N, et al. The CORVET subunit Vps8 cooperates with the Rab5 homolog Vps21 to induce clustering of late endosomal compartments. *Mol Biol Cell* 2009; 20:5276-89; PMID: 19828734; DOI: 10.1091/mbc.E09-06-0521.
11. Peplowska K, Markgraf DF, Ostrowicz CW, Bange G, Ungermann C. The CORVET tethering complex interacts with the yeast Rab5 homolog Vps21 and is involved in endo-lysosomal biogenesis. *Dev Cell* 2007; 12:739-50; PMID: 17488625; DOI: 10.1016/j.devcel.2007.03.006.
12. Nickerson DP, Brett CL, Merz AJ. Vps-C complexes: gatekeepers of endolysosomal traffic. *Curr Opin Cell Biol* 2009; 21:543-51; PMID: 19577915; DOI: 10.1016/j.ceb.2009.05.007.
13. Sato TK, Rehling P, Peterson MR, Emr SD, Class C. Vps protein complex regulates vacuolar SNARE pairing and is required for vesicle docking/fusion. *Mol Cell* 2000; 6:661-71; PMID: 11030345; DOI: 10.1016/S1097-2765(00)00064-2.
14. Wang T, Ming Z, Xiaochun W, Hong W. Rab7: role of its protein interaction cascades in endo-lysosomal traffic. *Cell Signal* 2011; 23:516-21; PMID: 20851765; DOI: 10.1016/j.cellsig.2010.09.012.
15. Bröcker C, Engelbrecht-Vandre S, Ungermann C. Multisubunit tethering complexes and their role in membrane fusion. *Curr Biol* 2010; 20:R943-52; PMID: 21056839; DOI: 10.1016/j.cub.2010.09.015.
16. Wickner W. Membrane fusion: five lipids, four SNAREs, three chaperones, two nucleotides, and a Rab, all dancing in a ring on yeast vacuoles. *Annu Rev Cell Dev Biol* 2010; 26:115-36; PMID: 20521906; DOI: 10.1146/annurev-cellbio-100109-104131.
17. Epp N, Rethmeier R, Kramer L, Ungermann C. Membrane dynamics and fusion at late endosomes and vacuoles - Rab regulation, multisubunit tethering complexes and SNAREs. *Eur J Cell Biol* 2011; 90:779-85; PMID: 21683469; DOI: 10.1016/j.ejcb.2011.04.007.
18. Cai H, Reinisch K, Ferro-Novick S. Coats, tethers, Rab, and SNAREs work together to mediate the intracellular destination of a transport vesicle. *Dev Cell* 2007; 12:671-82; PMID: 17488620; DOI: 10.1016/j.devcel.2007.04.005.
19. Jahn R, Sudhof TC. Membrane fusion and exocytosis. *Annu Rev Biochem* 1999; 68:863-911; PMID: 10872468; DOI: 10.1146/annurev.biochem.68.1.863.
20. Waters MG, Hughson FM. Membrane tethering and fusion in the secretory and endocytic pathways. *Traffic* 2000; 1:588-97; PMID: 11208146; DOI: 10.1034/j.1600-0854.2000.010802.x.
21. Carr CM, Rizo J. At the junction of SNARE and SM protein function. *Curr Opin Cell Biol* 2010; 22:488-95; PMID: 20471239; DOI: 10.1016/j.ceb.2010.04.006.
22. Peralta ER, Martin BC, Edinger AL. Differential effects of TBC1D15 and mammalian Vps39 on Rab7 activation state, lysosomal morphology, and growth factor dependence. *J Biol Chem* 2010; 285:16814-21; PMID: 20363736; DOI: 10.1074/jbc.M110.111633.
23. Angers CG, Merz AJ. New links between vesicle coats and Rab-mediated vesicle targeting. *Semin Cell Dev Biol* 2011; 22:18-26; PMID: 20643221; DOI: 10.1016/j.semedb.2010.07.003.
24. Nordmann M, Cabrera M, Perz A, Brocker C, Ostrowicz C, Engelbrecht-Vandre S, et al. The Mon1-Ccz1 complex is the GEF of the late endosomal Rab7 homolog Ypt7. *Curr Biol* 2010; 20:1654-9; PMID: 20797862; DOI: 10.1016/j.cub.2010.08.002.
25. Brett CL, Plemel RL, Lobinger BT, Vignali M, Fields S, Merz AJ. Efficient termination of vacuolar Rab GTPase signaling requires coordinated action by a GAP and a protein kinase. *J Cell Biol* 2008; 182:1141-51; PMID: 18809726; DOI: 10.1083/jcb.200801001.
26. Darsow T, Katzmann DJ, Cowles CR, Emr SD. Vps41p function in the alkaline phosphatase pathway requires homo-oligomerization and interaction with AP-3 through two distinct domains. *Mol Biol Cell* 2001; 12:37-51; PMID: 11160821.
27. Rehling P, Darsow T, Katzmann DJ, Emr SD. Formation of AP-3 transport intermediates requires Vps41 function. *Nat Cell Biol* 1999; 1:346-53; PMID: 10559961; DOI: 10.1038/14037.
28. Angers CG, Merz AJ. HOPS interacts with Apl5 at the vacuole membrane and is required for consumption of AP-3 transport vesicles. *Mol Biol Cell* 2009; 20:4563-74; PMID: 19741093; DOI: 10.1091/mbc.E09-04-0272.
29. Banta LM, Vida TA, Herman PK, Emr SD. Characterization of yeast Vps33p, a protein required for vacuolar protein sorting and vacuole biogenesis. *Mol Cell Biol* 1990; 10:4638-49; PMID: 2201898.
30. Bugnicourt A, Froissard M, Sereti K, Ulrich HD, Haguenaer-Tsapir R, Galan J-M. Antagonistic roles of ESCRT and Vps class C/HOPS complexes in the recycling of yeast membrane proteins. *Mol Biol Cell* 2004; 15:4203-14; PMID: 15215319; DOI: 10.1091/mbc.E04-05-0420.
31. Cabrera M, Ostrowicz CW, Mari M, LaGrassa TJ, Reggiori F, Ungermann C. Vps41 phosphorylation and the Rab Ypt7 control the targeting of the HOPS complex to endosome-vacuole fusion sites. *Mol Biol Cell* 2009; 20:1937-48; PMID: 19193765; DOI: 10.1091/mbc.E08-09-0943.
32. Gerhardt B, Kordas TJ, Thompson CM, Patel P, Vida T. The vesicle transport protein Vps33p is an ATP-binding protein that localizes to the cytosol in an energy-dependent manner. *J Biol Chem* 1998; 273:15818-29; PMID: 9624182; DOI: 10.1074/jbc.273.25.15818.
33. Hickey CM, Stroupe C, Wickner W. The major role of the Rab Ypt7p in vacuole fusion is supporting HOPS membrane association. *J Biol Chem* 2009; 284:16118-25; PMID: 19386605; DOI: 10.1074/jbc.M109.000737.
34. Iwaki T, Osawa F, Onishi M, Koga T, Fujita Y, Hosomi A, et al. Characterization of vps33+, a gene required for vacuolar biogenesis and protein sorting in *Schizosaccharomyces pombe*. *Yeast* 2003; 20:845-55; PMID: 12868054; DOI: 10.1002/yea.1011.
35. Laage R, Ungermann C. The N-terminal domain of the t-SNARE Vam3p coordinates priming and docking in yeast vacuole fusion. *Mol Biol Cell* 2001; 12:3375-85; PMID: 11694574.
36. LaGrassa TJ, Ungermann C. The vacuolar kinase Yck3 maintains organelle fragmentation by regulating the HOPS tethering complex. *J Cell Biol* 2005; 168:401-14; PMID: 15684030; DOI: 10.1083/jcb.200407141.
37. McVey Ward D. hVPS41 is expressed in multiple isoforms and can associate with vesicles through a RING-H2 finger motif. *Exp Cell Res* 2001; 267:126-34; PMID: 11412045; DOI: 10.1006/excr.2001.5244.
38. Poupon V, Stewart A, Gray SR, Piper RC, Luzio JP. The role of mVps18p in clustering, fusion, and intracellular localization of late endocytic organelles. *Mol Biol Cell* 2003; 14:4015-27; PMID: 14517315; DOI: 10.1091/mbc.E03-01-0040.
39. Starai VJ, Hickey CM, Wickner W. HOPS proof-reads the trans-SNARE complex for yeast vacuole fusion. *Mol Biol Cell* 2008; 19:2500-8; PMID: 18385512; DOI: 10.1091/mbc.E08-01-0077.
40. Wang L. Hierarchy of protein assembly at the vertex ring domain for yeast vacuole docking and fusion. *J Cell Biol* 2003; 160:365-74; PMID: 12566429; DOI: 10.1083/jcb.200209095.
41. Wang L, Seeley ES, Wickner W, Merz AJ. Vacuole fusion at a ring of vertex docking sites leaves membrane fragments within the organelle. *Cell* 2002; 108:357-69; PMID: 11853670; DOI: 10.1016/S0092-8674(02)00632-3.
42. Cowles CR, Snyder WB, Burd CG, Emr SD. Novel Golgi to vacuole delivery pathway in yeast: identification of a sorting determinant and required transport component. *EMBO J* 1997; 16:2769-82; PMID: 9184222; DOI: 10.1093/emboj/16.10.2769.
43. Sriram V, Krishnan KS, Mayor S. deep-orange and carnation define distinct stages in late endosomal biogenesis in *Drosophila melanogaster*. *J Cell Biol* 2003; 161:593-607; PMID: 12743107; DOI: 10.1083/jcb.200210166.
44. Swetha MG, Sriram V, Krishnan KS, Oorschot VM, Ten Brink C, Klumperman J, et al. Lysosomal membrane protein composition, acidic pH and sterol content are regulated via a light-dependent pathway in metazoan cells. *Traffic* 2011; 12:1037-55; PMID: 21535339; DOI: 10.1111/j.1600-0854.2011.01214.x.
45. Zhu GD, L'Hernault SW. The *Caenorhabditis elegans* spe-39 gene is required for intracellular membrane reorganization during spermatogenesis. *Genetics* 2003; 165:145-57; PMID: 14504223.
46. Zhu GD, Salazar G, Zlatich SA, Fiza B, Doucette MM, Heilman CJ, et al. SPE-39 family proteins interact with the HOPS complex and function in lysosomal delivery. *Mol Biol Cell* 2009; 20:1223-40; PMID: 19109425; DOI: 10.1091/mbc.E08-07-0728.
47. Zlatich SA, Tornieri K, L'Hernault SW, Faundez V. Clathrin-dependent mechanisms modulate the subcellular distribution of class C Vps/HOPS tether subunits in polarized and nonpolarized cells. *Mol Biol Cell* 2011; 22:1699-715; PMID: 21411634; DOI: 10.1091/mbc.E10-10-0799.
48. Akbar MA, Ray S, Krämer H. The SM protein Car/Vps33A regulates SNARE-mediated trafficking to lysosomes and lysosome-related organelles. *Mol Biol Cell* 2009; 20:1705-14; PMID: 19158398; DOI: 10.1091/mbc.E08-03-0282.
49. Bonifacio JS. Insights into the biogenesis of lysosome-related organelles from the study of the Hermansky-Pudlak syndrome. *Ann N Y Acad Sci* 2004; 1038:103-14; PMID: 15838104; DOI: 10.1196/annals.1315.018.
50. Pierson DM, Ionescu D, Qing G, Yonan AM, Parkinson K, Colby TC, et al. Pulmonary fibrosis in hermansky-pudlak syndrome: a case report and review. *Respiration* 2006; 73:382-95; PMID: 16490934; DOI: 10.1159/000091609.
51. Hermansky F, Pudlak P. Albinism associated with hemorrhagic diathesis and unusual pigmented reticular cells in the bone marrow: report of two cases with histochemical studies. *Blood* 1959; 14:162-9; PMID: 13618373.

52. Huizing M, Boissy RE, Gahl WA. Hermansky-Pudlak syndrome: vesicle formation from yeast to man. *Pigment Cell Res* 2002; 15:405-19; PMID: 12453182; DOI: 10.1034/j.1600-0749.2002.02074.x.
53. Di Pietro SM, Dell'Angelica EC. The cell biology of Hermansky-Pudlak syndrome: recent advances. *Traffic* 2005; 6:525-33; PMID: 15941404; DOI: 10.1111/j.1600-0854.2005.00289.x.
54. Wei ML. Hermansky-Pudlak syndrome: a disease of protein trafficking and organelle function. *Pigment Cell Res* 2006; 19:19-42; PMID: 16420244; DOI: 10.1111/j.1600-0749.2005.00289.x.
55. Swank RT, Novak EK, McGarry MP, Rusiniak ME, Feng L. Mouse models of Hermansky Pudlak syndrome: a review. *Pigment Cell Res* 1998; 11:60-80; PMID: 9585243; DOI: 10.1111/j.1600-0749.1998.tb00713.x.
56. Suzuki T, Oiso N, Gautam R, Novak EK, Panthier J-J, Suprabha PG, et al. The mouse organellar biogenesis mutant buff results from a mutation in *Vps33a*, a homologue of yeast *vps33* and *Drosophila* carnation. *Proc Natl Acad Sci USA* 2003; 100:1146-50; PMID: 12538872; DOI: 10.1073/pnas.0237292100.
57. Mullins C, Hartnell LM, Bonifacino JS. Distinct requirements for the AP-3 adaptor complex in pigment granule and synaptic vesicle biogenesis in *Drosophila melanogaster*. *Mol Gen Genet* 2000; 263:1003-14; PMID: 10954086; DOI: 10.1007/PL00008688.
58. Mullins C, Hartnell LM, Wassarman DA, Bonifacino JS. Defective expression of the $\mu 3$ subunit of the AP-3 adaptor complex in the *Drosophila* pigmentation mutant carmine. *Mol Gen Genet* 1999; 262:401-12; PMID: 10589826; DOI: 10.1007/s004380051099.
59. Sevrioukov EA, He JP, Moghrabi N, Sunio A, Kramer H. A role for the deep orange and carnation eye color genes in lysosomal delivery in *Drosophila*. *Mol Cell* 1999; 4:479-86; PMID: 10549280; DOI: 10.1016/S1097-2765(00)80199-9.
60. Shestopal SA, Makunin IV, Belyaeva ES, Ashburner M, Zhimulev IF. Molecular characterization of the deep orange (dor) gene of *Drosophila melanogaster*. *Mol Gen Genet* 1997; 253:642-8; PMID: 9065698; DOI: 10.1007/s004380050367.
61. Warner TS, Sinclair DA, Fitzpatrick KA, Singh M, Devlin RH, Honda BM. The light gene of *Drosophila melanogaster* encodes a homologue of VPS41, a yeast gene involved in cellular-protein trafficking. *Genome* 1998; 41:236-43; PMID: 9644832.
62. Cullinane AR, Straatman-Iwanowska A, Zaucker A, Wakabayashi Y, Bruce CK, Luo G, et al. Mutations in *VIPAR* cause an arthrogryposis, renal dysfunction and cholestasis syndrome phenotype with defects in epithelial polarization. *Nat Genet* 2010; 42:303-12; PMID: 20190753; DOI: 10.1038/ng.538.
63. Gissen P, Tee L, Johnson CA, Genin E, Caliebe A, Chitayat D, et al. Clinical and molecular genetic features of ARC syndrome. *Hum Genet* 2006; 120:396-409; PMID: 16896922; DOI: 10.1007/s00439-006-0232-z.
64. L'Hernault SW, Faundez V. On the endosomal function and gene nomenclature of human SPE-39. *Nat Genet* 2011; 43:176; PMID: 21350494; DOI: 10.1038/ng.0311-176.
65. Pulipparacharuvil S, Akbar MA, Ray S, Sevrioukov EA, Haberman AS, Rohrer J, et al. *Drosophila* Vps16A is required for trafficking to lysosomes and biogenesis of pigment granules. *J Cell Sci* 2005; 118:3663-73; PMID: 16046475; DOI: 10.1242/jcs.02502.
66. Kim SM, Chang HK, Song JW, Koh H, Han SJ. Agranular platelets as a cardinal feature of ARC syndrome. *J Pediatr Hematol Oncol* 2010; 32:253-8; PMID: 20224444; DOI: 10.1097/MPH.0b013e3181c3a8d0.
67. Arhan E, Yusufoglu AM, Sayli TR. Arc syndrome without arthrogryposis, with hip dislocation and renal glomerulocystic appearance: a case report. *Eur J Pediatr* 2009; 168:995-8; PMID: 18972129; DOI: 10.1007/s00431-008-0860-5.
68. Bull LN, Mahmoodi V, Baker AJ, Jones R, Strautnieks SS, Thompson RJ, et al. VPS33B mutation with ichthyosis, cholestasis, and renal dysfunction but without arthrogryposis: incomplete ARC syndrome phenotype. *J Pediatr* 2006; 148:269-71; PMID: 16492441; DOI: 10.1016/j.jpeds.2005.10.005.
69. Choi H-J, Lee M-W, Choi J-H, Moon K-C, Koh J-K. Ichthyosis associated with ARC syndrome: ARC syndrome is one of the differential diagnoses of ichthyosis. *Pediatr Dermatol* 2005; 22:539-42; PMID: 16354257; DOI: 10.1111/j.1525-1470.2005.00135.x.
70. Cullinane AR, Straatman-Iwanowska A, Seo JK, Ko JS, Song KS, Gizewska M, et al. Molecular investigations to improve diagnostic accuracy in patients with ARC syndrome. *Hum Mutat* 2009; 30:E330-7; PMID: 18853461; DOI: 10.1002/humu.20900.
71. Gissen P, Johnson CA, Morgan NV, Stapelbroek JM, Forshaw T, Cooper WN, et al. Mutations in VPS33B, encoding a regulator of SNARE-dependent membrane fusion, cause arthrogryposis-renal dysfunction-cholestasis (ARC) syndrome. *Nat Genet* 2004; 36:400-4; PMID: 15052268; DOI: 10.1038/ng1325.
72. Hershkovitz D, Mandel H, Ishida-Yamamoto A, Chefetz I, Hino B, Luder A, et al. Defective lamellar granule secretion in arthrogryposis, renal dysfunction, and cholestasis syndrome caused by a mutation in VPS33B. *Arch Dermatol* 2008; 144:334-40; PMID: 18347289; DOI: 10.1001/archderm.144.3.334.
73. Jang JY, Kim KM, Kim G-H, Yu E, Lee J-J, Park YS, et al. Clinical characteristics and VPS33B mutations in patients with ARC syndrome. *J Pediatr Gastroenterol Nutr* 2009; 48:348-54; PMID: 19274792; DOI: 10.1097/MPG.0b013e31817fcb3f.
74. Taha D, Khider A, Cullinane AR, Gissen P. A novel VPS33B mutation in an ARC syndrome patient presenting with osteopenia and fractures at birth. *Am J Med Genet A* 2007; 143A:2835-7; PMID: 17994566; DOI: 10.1002/ajmg.a.32051.
75. Eastham KM, McKiernan PJ, Milford DV, Ramani P, Wyllie J, van't Hoff W, et al. ARC syndrome: an expanding range of phenotypes. *Arch Dis Child* 2001; 85:415-20; PMID: 11668108; DOI: 10.1136/ad.85.5.415.
76. Jang WY, Cho TJ, Bae JY, Jung HW, Ko JS, Park MS, et al. Orthopaedic manifestations of arthrogryposis-renal dysfunction-cholestasis syndrome. *J Pediatr Orthop* 2011; 31:107-12; PMID: 21150740; DOI: 10.1097/BPO.0b013e3182032c83.
77. Parsch K, Pietrzak S. Arthrogryposis multiplex congenita. *Orthopade* 2007; 36:281-92; PMID: 17323063; DOI: 10.1007/s00132-007-1044-0.
78. Abu-Sa'da O, Barbar M, Al-Harbi N, Taha D. Arthrogryposis, renal tubular acidosis and cholestasis (ARC) syndrome: two new cases and review. *Clin Dysmorphol* 2005; 14:191-6; PMID: 16155421; DOI: 10.1097/00019605-200510000-00005.
79. Tekin N, Durmus-Aydogdu S, Dinleyici EC, Bor O, Bildirici K, Aksit A. Clinical and pathological aspects of ARC (arthrogryposis, renal dysfunction and cholestasis) syndrome in two siblings. *Turk J Pediatr* 2005; 47:67-70; PMID: 15884633.
80. Hayes JA, Kahr WH, Lo B, Macpherson BA. Liver biopsy complicated by hemorrhage in a patient with ARC syndrome. *Paediatr Anaesth* 2004; 14:960-3; PMID: 15500499; DOI: 10.1111/j.1460-9592.2004.01301.x.
81. Howells R, Ramaswami U. ARC syndrome: an expanding range of phenotypes. *Arch Dis Child* 2002; 87:170-1; PMID: 12138079; DOI: 10.1136/ad.87.2.170-c.
82. Horslen SP, Quarrell OW, Tanner MS. Liver histology in the arthrogryposis multiplex congenita, renal dysfunction, and cholestasis (ARC) syndrome: report of three new cases and review. *J Med Genet* 1994; 31:62-4; PMID: 8151641; DOI: 10.1136/jmg.31.1.62.
83. Denecke J, Zimmer KP, Kleta R, Koch HG, Rabe H, August C, et al. [Arthrogryposis, renal tubular dysfunction, cholestasis (ARC) syndrome: case report and review of the literature]. *Klin Padiatr* 2000; 212:77-80; PMID: 10812557; DOI: 10.1055/s-2000-9656.
84. Abdullah MA, Al-Hasnan Z, Okamoto E, Abomelha AM. Arthrogryposis, renal dysfunction and cholestasis syndrome. *Saudi Med J* 2000; 21:297-9; PMID: 11533803.
85. Wilkin M, Tonggok P, Gensch N, Clemence S, Motoki M, Yamada K, et al. *Drosophila* HOPS and AP-3 complex genes are required for a Deltex-regulated activation of notch in the endosomal trafficking pathway. *Dev Cell* 2008; 15:762-72; PMID: 19000840; DOI: 10.1016/j.devcel.2008.09.002.
86. Lai EC. Notch signaling: control of cell communication and cell fate. *Development* 2004; 131:965-73; PMID: 14973298; DOI: 10.1242/dev.01074.
87. Pierfelice T, Alberi L, Gaiano N. Notch in the vertebrate nervous system: an old dog with new tricks. *Neuron* 2011; 69:840-55; PMID: 21382546; DOI: 10.1016/j.neuron.2011.02.031.
88. Cabrera M, Langemeyer L, Mari M, Rethmeier R, Orban I, Perz A, et al. Phosphorylation of a membrane curvature-sensing motif switches function of the HOPS subunit Vps41 in membrane tethering. *J Cell Biol* 2010; 191:845-59; PMID: 21079247; DOI: 10.1083/jcb.201004092.
89. Anand VC, Daboussi L, Lorenz TC, Payne GS. Genome-wide analysis of AP-3-dependent protein transport in yeast. *Mol Biol Cell* 2009; 20:1592-604; PMID: 19116312; DOI: 10.1091/mbc.E08-08-0819.
90. Salazar G, Zlatich S, Craige B, Peden AA, Pohl J, Faundez V. Hermansky-Pudlak syndrome protein complexes associate with phosphatidylinositol 4-kinase type II alpha in neuronal and non-neuronal cells. *J Biol Chem* 2009; 284:1790-802; PMID: 19010779; DOI: 10.1074/jbc.M805991200.
91. Nakamura N, Hirata A, Ohsumi Y, Wada Y. Vam2/Vps41p and Vam6/Vps39p are components of a protein complex on the vacuolar membranes and involved in the vacuolar assembly in the yeast *Saccharomyces cerevisiae*. *J Biol Chem* 1997; 272:11344-9; PMID: 9111041; DOI: 10.1074/jbc.272.17.11344.
92. Kim BY, Kramer H, Yamamoto A, Kominami E, Kotsaka S, Akazawa C. Molecular characterization of mammalian homologues of class C Vps proteins that interact with syntaxin-7. *J Biol Chem* 2001; 276:29393-402; PMID: 11382755; DOI: 10.1074/jbc.M101778200.
93. Richardson SC, Winistorfer SC, Poupon V, Luzio JP, Piper RC. Mammalian late vacuole protein sorting orthologues participate in early endosomal fusion and interact with the cytoskeleton. *Mol Biol Cell* 2004; 15:1197-210; PMID: 14668490; DOI: 10.1091/mbc.E03-06-0358.
94. Chirivino D, Del Maestro L, Formstecher E, Hupe P, Raposo G, Louvard D, et al. The ERM proteins interact with the HOPS complex to regulate the maturation of endosomes. *Mol Biol Cell* 2011; 22:375-85; PMID: 21148287; DOI: 10.1091/mbc.E10-09-0796.
95. Caplan S, Hartnell LM, Aguilar RC, Naslavsky N, Bonifacino JS. Human Vam6p promotes lysosome clustering and fusion in vivo. *J Cell Biol* 2001; 154:109-22; PMID: 11448994; DOI: 10.1083/jcb.200102142.
96. Piper RC, Bryant NJ, Stevens TH. The membrane protein alkaline phosphatase is delivered to the vacuole by a route that is distinct from the VPS-dependent pathway. *J Cell Biol* 1997; 138:531-45; PMID: 9245784; DOI: 10.1083/jcb.138.3.531.

97. Stepp JD, Huang K, Lemmon SK. The yeast adaptor protein complex, AP-3, is essential for the efficient delivery of alkaline phosphatase by the alternate pathway to the vacuole. *J Cell Biol* 1997; 139:1761-74; PMID: 9412470; DOI: 10.1083/jcb.139.7.1761.
98. Peden AA, Rudge RE, Lui WY, Robinson MS. Assembly and function of AP-3 complexes in cells expressing mutant subunits. *J Cell Biol* 2002; 156:327-36; PMID: 11807095; DOI: 10.1083/jcb.200107140.
99. Robinson MS. Adaptable adaptors for coated vesicles. *Trends Cell Biol* 2004; 14:167-74; PMID: 15066634; DOI: 10.1016/j.tcb.2004.02.002.
100. Cowles CR, Odorizzi G, Payne GS, Emr SD. The AP-3 adaptor complex is essential for cargo-selective transport to the yeast vacuole. *Cell* 1997; 91:109-18; PMID: 9335339; DOI: 10.1016/S0092-8674(01)80013-1.
101. Vowels JJ, Payne GS. A dileucine-like sorting signal directs transport into an AP-3-dependent, clathrin-independent pathway to the yeast vacuole. *EMBO J* 1998; 17:2482-93; PMID: 9564031; DOI: 10.1093/emboj/17.9.2482.
102. Borner GH, Harbour M, Hester S, Lilley KS, Robinson MS. Comparative proteomics of clathrin-coated vesicles. *J Cell Biol* 2006; 175:571-8; PMID: 17116749; DOI: 10.1083/jcb.200607164.
103. Peden AA, Oorschot V, Hesser BA, Austin CD, Scheller RH, Klumperman J. Localization of the AP-3 adaptor complex defines a novel endosomal exit site for lysosomal membrane proteins. *J Cell Biol* 2004; 164:1065-76; PMID: 15051738; DOI: 10.1083/jcb.200311064.
104. Theos AC, Tenza D, Martina JA, Hurbain I, Peden AA, Sviderskaya EV, et al. Functions of adaptor protein (AP)-3 and AP-1 in tyrosinase sorting from endosomes to melanosomes. *Mol Biol Cell* 2005; 16:5356-72; PMID: 16162817; DOI: 10.1091/mbc.E05-07-0626.
105. Dell'Angelica EC, Klumperman J, Stoorvogel W, Bonifacino JS. Association of the AP-3 adaptor complex with clathrin. *Science* 1998; 280:431-4; PMID: 9545220; DOI: 10.1126/science.280.5362.431.
106. Bonifacino JS, Glick BS. The mechanisms of vesicle budding and fusion. *Cell* 2004; 116:153-66; PMID: 14744428; DOI: 10.1016/S0092-8674(03)01079-1.
107. Behnia R, Munro S. Organelle identity and the signposts for membrane traffic. *Nature* 2005; 438:597-604; PMID: 16319879; DOI: 10.1038/nature04397.
108. Lord C, Bhandari D, Menon S, Ghassemian M, Nycz D, Hay J, et al. Sequential interactions with Sec23 control the direction of vesicle traffic. *Nature* 2011; 473:181-6; PMID: 21532587; DOI: 10.1038/nature09969.