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Lysosome-Related Organelles: Driving post-Golgi compartments into specialisation

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Abstract

Some cells harbor specialised lysosome-related organelles (LROs) that share features of late endosomes/ lysosomes but are functionally, morphologically, and/or compositionally distinct. Ubiquitous trafficking machineries cooperate with cell type-specific cargoes to produce these organelles. Several genetic diseases are caused by dysfunctional LRO formation and/or motility. Many genes affected in these diseases have been recently identified, revealing new cellular components of the trafficking machinery. Current research reveals how the products of these genes cooperate to generate LROs and how these otherwise diverse organelles are related by the mechanisms through which they form.

Introduction

Specific cell types often require unique organelles to effect cell type-specific functions. One class of such organelles is called LROs based on their shared compositional and physiological features with lysosomes (Table 1). LROs comprise a heterogeneous set of organelles, most of which undergo secretion from their respective cell type. Although similar in some respects to regulated secretory granules, such as insulin or zymogen granules of the endocrine and exocrine pancreas, LROs are distinguished by the primary source of their membrane and lumenal contents: whereas classic secretory granules form directly from the *trans* Golgi network (TGN), some or all LRO contents derive from the endosomal system. Furthermore, LROs may be collectively altered by related heritable diseases (see below). Most LROs contain lysosomal proteins and a low lumenal pH. Some resemble lysosomes morphologically with electron-dense protein deposits and/or intraluminal membranes, and are accessible to endocytic traffic. Other LROs, however, present entirely novel morphological features as a product of their unique cargo, such as the proteinaceous fibrils of melanosomes, the proteinaceous tubules of Weibel-Palade bodies (WPBs), and the lipid swirls within lamellar bodies [1,2] (Figure 1).

The existence of such varied yet apparently related organelles raises a number of questions. Do all LROs share a common biogenetic pathway? The answer appears to be no. Some LROs, often referred to as secretory lysosomes, are thought to be wholly transformed lysosomes that act as dual-functional organelles, carrying out both specialised and universal functions [3,4].

Other LROs, such as melanosomes, WPBs, and platelet dense granules, appear to co-exist with bona fide late endosomes (LE)/lysosomes and thus must derive separately from other endocytic and biosynthetic organelles[5,6]. Some, like WPBs, appear to be “secretory granule-like” in that significant (but not all) content derives directly from the TGN (see below). The formation and maintenance of LROs that co-exist with lysosomes presents novel challenges to the host cell. If they are distinct, how are resident proteins sorted among the tissue-specific and conventional endosomal organelles? Are ubiquitous sorting pathways subverted for use by specialised organelles or are there also sorting pathways unique to LROs?. This review will highlight recent advances in defining biogenetic mechanisms of these LROs, with a special focus on melanosomes and WPBs.

Generation of LROs requires multiple structural changes and sorting events

Functional LROs are generated by a multistep process in which an immature organelle forms and then subsequently matures by acquiring additional cargo and effector proteins (Figure 2). Pre-melanosomes and immature WPBs (iWPBs) are characterised by the presence in their lumen of Pmel17-containing amyloid-like fibrils [7,8] or von Willebrand Factor (VWF)-containing tubules[9], respectively. Similar morphological features are generated in non-specialised cell types by heterologous expression of Pmel17 [10] or VWF [11], and require proteolytic maturation of the respective proprotein [12,13]. In both cases the hallmark morphological transformation is critical to function; altering shape from cigar-like to spherical reduces WPB haemostatic function [14], and melanocytes with morphologically altered melanosomes (e.g. from *silver* mice) show decreased viability [15].

How are these morphogenetic transformations regulated? Interestingly, whereas the Pmel17 protomers in premelanosomes originate from within early endosomal intermediates, iWPBs emerge, like secretory granules, from the TGN, emphasizing the diverse origins of immature LROs. Within endosomes, Pmel17 is sorted to intraluminal vesicles that form by invagination of the limiting membrane; this process is essential for the proteolytic maturation of Pmel17 and subsequent fibril formation, and is solely dependent on its luminal domain, contrasting with cytoplasmic ubiquitin-dependent sorting of other intraluminal membrane proteins [16]. Once segregated from endocytic cargo, the Pmel17 “primed” organelle is fully competent to recruit additional melanosomal cargo (e.g., melanogenic enzymes) and to mature, while recruiting effectors for movement to the cell periphery (e.g., Rab27a) [17]. In a parallel yet distinct sequence of events, WPBs form at the TGN, presumably driven by formation of VWF tubules. The nascent iWPB then recruits the inflammation-initiating leukocyte receptor P-selectin before budding [18,19]. A second wave of membrane protein recruitment is marked by the accumulation of CD63, Rab27 and Rab3D [11,18,20]. The recruitment of Rab27 to WPBs is a cell type-independent, maturation-dependent and cargo-driven event. Although such sequential maturation events are best defined for melanosomes and WPBs, they likely represent a general paradigm for LROs as highlighted by the activation-induced recruitment of Rab27a and other effectors to cytolytic granules [21].

LRO dysfunction in disease

Important in identifying LROs as related organelles was the discovery that subsets of this varied group are dysfunctional in a cluster of genetic diseases, including Chediak-Higashi syndrome (CHS), Griscelli syndrome (GS) and Hermansky-Pudlak syndrome (HPS). Information on these can be found via the HPS database (<http://liweilab.genetics.ac.cn/HPSD/HPSD.htm>). Additional disease states affecting LRO function are being identified [22,23].

Patients suffering from these syndromes present with one or more of the following symptoms: decreased pigmentation of the skin and eyes (partial albinism); immunodeficiency and inflammatory problems; bleeding disorders; neurological disorders; and lung fibrosis. Whilst

some of these clinical features can be straightforwardly ascribed to defects in particular organelles - *e.g.* melanosomes, cytolytic granules, dense granules, and lamellar bodies, additional organelles involved in these processes are also likely impaired. For example, the neurological defects observed in some of these patients might reflect defective generation and function of a subset of synaptic vesicles that appear to form directly from endosomes [24,25]; the immunodeficiencies may reflect defects not only in cytolytic function but also in LROs within antigen presenting cells; and the bleeding diathesis may in part reflect malformation of endothelial WPBs. Despite these unknowns, the genes mutated in these syndromes encode proteins that play key roles in lysosome and LRO biogenesis and/or motility (Table 2). The challenge has been to define where and how these proteins act and cooperate to deliver specialised cargo to LRO.

LRO Biogenesis

The gene affected in CHS (and the corresponding mouse *beige* mutation in mouse) was one of the first to be mapped and encodes a ~ 400 kDa protein called Lyst (Lysosomal trafficking regulator) or CHS1p. Its function, however, remains unknown. Dominant negative approaches suggest a potential role in phosphoinositide metabolism [26]. Proteomic analysis of giant lysosomes purified from beige mouse liver revealed variations in composition relative to normal lysosomes, but the relevance of such changes is not yet clear [27].

In contrast, studies on HPS genes and their corresponding mouse models (Table 2) have greatly accelerated our understanding of LRO formation [28]. Some of the defective genes encode subunits of evolutionarily conserved protein complexes already known to regulate protein traffic. For example, mouse HPS models include mutations in the δ and β subunits of AP-3 (known to regulate lysosomal transport), the rab geranyl geranyl transferase α subunit (required for prenylation of rab proteins), and the Vps33a subunit of VpsC (vacuolar protein sorting C complex, which binds to endosomal SNAREs - [29]). Other mapped genes encode novel proteins that are not conserved in unicellular organisms and that largely lack known structural or functional domains other than small predicted coiled-coil regions. These ubiquitously expressed proteins assemble into 3 different complexes called BLOCs (Biogenesis of Lysosome-related Organelles Complexes): BLOC-1, BLOC-2, BLOC-3 [30].

AP-3 localises to clathrin coated buds on early endosomes of HepG2 cells and melanocytic cells, cell types that lack and harbor LRO, respectively [31,32]. This distribution may explain the retention of a known AP-3 cargo, tyrosinase, in endosomes in AP-3-deficient melanocytes, suggesting that AP-3 functions in cargo sorting from endosomes to LRO (*e.g.* melanosome) [32]. Consistently, RNAi-mediated depletion of AP-3 in human umbilical vein endothelial cells (HUVECs) interferes with delivery of CD63 to maturing WPBs [18]. Additional relevant AP-3-dependent cargo in melanocytes, HUVECs, or other LRO have yet to be determined. Moreover, despite clear functional consequences of AP-3 loss in platelets and CTLs [33], the exact role of AP-3 in these cells remains unknown.

The BLOCs are the most enigmatic HPS genes, since their subunits lack clear functional domains [30]. The different BLOCs are thought to play distinct roles in LRO development based on the different coat color phenotypes in mice, likely reflecting different degrees of melanosome malformation, with BLOC-1 mutants being the most severely hypopigmented and BLOC-3 mutants the least. BLOC-1 and BLOC-2 each localise to a distinct tubular early endosomal sub-domain in melanocytes at steady state, separate from the AP-3-enriched endosomal buds, suggesting distinct roles in endosomal function [34]. Consistently, BLOC-1 components bind in vitro to endosomal SNARE proteins syntaxin 13 [35] and SNAP-25 [36], and BLOC-1-deficient fibroblasts mis-sort endosomal SNAREs [37]. Importantly, BLOC-1-deficient melanocytes accumulate melanogenic enzymes, including a fraction of tyrosinase

and essentially all Tyrp1 (a tyrosinase-related protein), in early endosomes [38]. The data suggest a model in which BLOC-1 facilitates targeting of melanogenic enzymes and SNARE proteins from early endosomes to melanosomes (or other LRO). BLOC-2 also appears to act in the same pathway, likely downstream of BLOC-1 [38]. By contrast, AP-3 appears to act in a different early endosome-to-melanosome pathway, since only tyrosinase - but not Tyrp1 - is mistargeted in AP-3-deficient cells [32,38]. Despite the different phenotypes of HPS model melanocytes, and a distinct localisation on endosomal subdomains, BLOC-1 appears to physically interact with both BLOC-2 and AP-3 [34,37]. The functional significance of these interactions is unclear, but the increased association of AP-3 with membranes of BLOC-1-deficient fibroblasts suggests that BLOC-1 may regulate dissociation of AP-3 from endosomal membranes [34]. BLOC-3 appears to function independently of AP-3 and the other BLOCs. BLOC-3 localises to melanosomes and vesicles close to the Golgi [39]. Its function in membrane trafficking is not clear, although melanocytes from HPS-1 patients display increased autophagy [40]. Alternatively, altered lysosomal distribution in BLOC-3-deficient fibroblasts suggests a potential role in lysosome motility [41]. How these roles are linked is not yet understood.

Additional genes that regulate LRO biogenesis through post-Golgi traffic have emerged through analysis of other mouse coat colour mutants, gene inactivation or proteomics. Targeted inactivation of AP-1 by RNAi in HUVEC abolishes the formation of early WPBs from the TGN [42]. In melanocytes, AP-1 may function to facilitate AP-3-independent trafficking from endosomes of tyrosinase [32], and perhaps Tyrp1 [43], to the melanosome by a still undefined route. Analysis of the coat colour mutant 'chocolate' (*cht*) identified the cell type-specific small Rab GTPase, Rab38, as another gene involved in the regulation of pigmentation [44]. Rab38 expression is restricted to limited tissues including skin melanocytes, RPE and lung; the closely related Rab32 is also distributed in limited tissues, including melanocytes and platelets. In melanocytes, Rab38 and Rab32 localise to pigmented melanosomes and tubules possibly of endosomal origin [45]. Melanosomes in *cht* melanocytes are largely normal, but inactivation of Rab32 in these cells impairs localisation of both Tyrosinase and Tyrp1, demonstrating that both Rabs are functionally redundant regulators of melanosomal protein trafficking [45]. Ubiquitous rab proteins also appear to regulate LRO biogenesis. Rab11-positive endosomal tubules and vesicles are closely apposed to cytolytic granules in human primary cytotoxic T cells, and Rab11 is recruited to the CTL granules upon contact with target cells [21]. These observations imply that CTL granule maturation requires fusion with Rab11-containing endosomes. Finally there is evidence for a role for Rab3D in controlling WPB exocytosis [20].

Rab proteins and LRO Motility

Failures of LRO motility underlie GS and corresponding mouse models (Table 2). Genetic, cellular and biochemical analyses of melanocytes in this disease revealed the requirement for a motor (myosin Va) to be recruited to melanosomes by the concerted action of a Rab (Rab27a), and a Rab effector (melanophilin) to coordinate melanosome translocation to the cell periphery for their ultimate transfer to keratinocytes [17,46]. A similar complex with a different motor (myosin VIIa) and Rab27a effector (MyRip) regulate diurnal light cycle-dependent melanosome motility in mouse retinal pigment epithelia [47] and [57]). By contrast to these clear functions in melanosome motility, Rab27a plays distinct roles in regulating the activity of other LRO and secretory granules, often in conjunction with alternative effectors [3,48]. Rab27a regulates secretion of CTL and mast cell granules, at least in part through its effector Munc13-4, a member of the Sec1/Munc18 family of putative SNARE regulatory proteins that is mutated in a sub-class of patients suffering from hemophagocytic lymphohistiocytosis [49,50]. In dendritic cells, Rab27a functions with yet different effectors to dock a LRO-like organelle to phagosomes, regulating antigen presentation [51]. Precisely how Rab27a regulates

effector function in these different settings remains to be determined. It is also unclear how are Rab27a and its effectors are recruited to LROs. Recruitment of Rab27a to WPB appears to be cargo-driven and maturation-dependent [11] possibly to avoid premature release of incompletely processed cargo. In CTLs, Rab27a is recruited to cytolytic granules from an endosomal intermediate upon stimulation triggered by a target cell [21]. In addition to Rab27a, other Rab proteins regulate LRO motility in apparently different ways. For example, Rab8 regulates motility of mature melanosomes along actin filaments [52] and Rab7 facilitates movement of early melanosomes along microtubules through its effector, RILP [53]. How the differential recruitment of Rab proteins to maturing LRO is regulated and the signal for recruitment is not yet clear.

Conclusions and perspectives

The formation of LROs illustrates the complexity of the endocytic and biosynthetic pathways of specialised cells and highlights the importance of analysing these cells to better understand the role of membrane trafficking components and to unravel novel regulatory mechanisms. For example, the role of Rab27a has moved beyond LROs to many different secretory organelles [48], and other Rabs are being found to control motility of ubiquitous organelles e.g. [54]. Recent studies on CTLs revealed that cytolytic granule polarisation at the immunological synapse is controlled by centrosome delivery to the plasma membrane [55], raising the possibility that regulated motility and/or secretion of other organelles may also exploit a similar mechanism.

LRO are often considered as one class, but it is becoming increasingly evident that despite common determinants and shared protein sorting machineries, the cellular mechanisms involved in their biogenesis and/or secretion may be differentially adapted from ubiquitous trafficking components. Many questions then remain regarding why and how the different trafficking machineries cooperate in generating LROs. For example, what specifies BLOC or AP-3 function in specialised cell types? Do they interact with tissue-specific effectors? How are Rab proteins differentially recruited to and released from LRO, and how are their effectors chosen at particular sites? How do luminal contents such as VWF translate organelle maturation to the cytosolic face of the organelle membrane to regulate cargo recruitment and motility? Answers to these questions will assuredly come from further analysis of diseases affecting LROs and the proteins and lipids with which the disease gene products interact. It will also be necessary to re-evaluate the subcompartmentation of the endosomal and biosynthetic system of the highly specialised LRO host cells, and better define the heterogeneity of all LRO. A greater understanding of these specialised systems will not only provide us with great insight into general membrane dynamics, but also lead us toward the development of effective treatments of LRO-related diseases.

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Footnotes

** {Michaux, 2006 #2} The physiological function of von Willebrand's factor depends on its tubular storage in endothelial Weibel-Palade bodies.

This paper combines fluorescence and electron microscopy analyses of vWF conformation and WPB shape with flow chamber and in vivo measurements of platelet recruitment to demonstrate that the packaging of vWF into long tubules is essential for both driving the shape of the WPB and their haemostatic function. The paper is important in demonstrating that form follows function for this organelle.

** {Lui-Roberts, 2005 #4} An AP-1/clathrin coat plays a novel and essential role in forming the Weibel-Palade bodies of endothelial cells

Using electron and fluorescence microscopy analyses of human umbilical vein endothelial cells, this paper shows that newly forming WPB are extensively coated with clathrin and AP-1. Using siRNA to deplete AP-1, AP-1 is shown to be required for both secretagogue-responsive vWF secretion and the formation of WPB. The paper is novel in showing that clathrin/ AP-1 coats are needed at the TGN to form a secretory organelle.

* {Harrison-Lavoie, 2006 #3} P-selectin and CD63 use different mechanisms for delivery to Weibel-Palade bodies

This paper provides evidence that at least two waves of membrane protein recruitment are required in forming WPBs, one of which uses AP-3. The paper also uses electron microscopy analyses of cells expressing a P-selectin-horseradish peroxidase chimera to directly show incorporation of P-selectin into a forming organelle at the TGN.

** {Theos, 2006 #29} A novel pathway for sorting to intraluminal vesicles of multivesicular endosomes involved in organelle morphogenesis

Delivery into the internal vesicles of MVBs is generally dependent on the conserved ESCRT machinery. Analysis of the melanosomal protein Pmel17 in this paper uncovers an alternative Hrs and Tsg101-independent pathway for MVB sorting that requires a luminal determinant.

* {Theos, 2005 #14} Functions of AP-3 and AP-1 in tyrosinase sorting from endosomes to melanosomes

This paper provides evidence that AP-3 and AP-1 are involved in sorting tyrosinase from endosomes to melanosomes in seemingly redundant sorting pathways. The AP-3 pathway is shown to avert loss of tyrosinase to internal vesicles of MVBs..

** {Jancic, 2007 #55} Rab27a regulates phagosomal pH and NADPH oxidase recruitment to dendritic cell phagosomes

This paper shows that dendritic cells derived from Rab27a mutant ashken mice show increased phagosome acidification and antigen degradation, causing a defect in antigen cross presentation. Enhanced acidification results from a delay in the recruitment to phagosomes of a subset of "inhibitory lysosome-related organelles" containing the membrane subunits of NOX2. The Rab27a-dependent recruitment of these to phagosomes continuously limits acidification and degradation of ingested particles in dendritic cells, thus promoting antigen cross presentation.

** {Wasmeier, 2006 #28} Rab38 and Rab32 control post-Golgi trafficking of melanogenic enzymes

This manuscript makes use of melanocytes from a natural Rab38 mutant mouse line and siRNA approaches to reveal a redundant role for two tissue-specific Rab proteins (Rab38 and Rab32) in regulating transport of melanogenic enzymes to melanosomes. Cells deficient in both Rab32 and Rab38 show severe defects in pigment formation.

** {Menager, 2007 #27} Secretory cytotoxic granule maturation and exocytosis require the effector protein hMunc13-4.

This manuscript provides evidence that Rab27a and Rab11 are recruited to cytolytic granules only after stimulation triggered by a target cell. The authors propose that the cytotoxic function of lymphocytes requires the cooperation of two types of organelles: the Rab27a-Rab11--containing lysosomal cytotoxic granule and the Rab11-containing endosomal 'exocytic vesicle'. Independently of Rab27a, hMunc13-4 mediated the assembly of Rab11(+) recycling and Rab27(+) late endosomal vesicles, constituting a pool of vesicles destined for regulated exocytosis.

** {Setty, 2006 #9} BLOC-1 is required for cargo-specific sorting from vacuolar early endosomes toward lysosome-related organelles

This manuscript shows that melanocytes from BLOC-1-deficient mouse HPS models fail to export Tyrp1 from early endosomes toward melanosomes, and that BLOC-2 functions in the same pathway. The results indicate that melanosome maturation requires at least two cargo transport pathways directly from early endosomes to melanosomes, one mediated by AP-3 and another by BLOC-1 and BLOC-2, that are deficient in several forms of HPS.

* {Di Pietro, 2006 #12} BLOC-1 interacts with BLOC-2 and the AP-3 complex to facilitate protein trafficking on endosomes

Using a combination of biochemical, morphological and genetic approaches the authors show that BLOC-1 interacts with AP-3 and with BLOC-. In addition it is shown that BLOC-1 and BLOC-2 localize mainly to early endosome-associated tubules.

* {Salazar, 2006 #1327} BLOC-1 complex deficiency alters the targeting of Adaptor Protein complex-3 cargoes

The authors show that purified AP-3-coated vesicles from PC12 cells contain BLOC-1, and that similar cargoes - including selected endosomal SNARE proteins - are mislocalized fibroblasts deficient in AP-3 or BLOC-1. With Di Pietro et al., these papers suggest that AP-3 and BLOC-1 function together to regulate transport of certain cargoes.

Abbreviations

AP, Adaptor protein Complex; BLOC, Biogenesis of Lysosome related Organelle Complex; LRO, Lysosome Related Organelle; MVB, Multi Vesicular Body; SNARE, Soluble NSF Attachment Protein Receptor; TGN, *trans* Golgi network; Tyrp, Tyrosinase Related Protein; VWF, von Willebrand Factor; WPB, Weibel Palade Bodies; iWPB, immature WPB.

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Figure 1.
LROs display different morphological features
A: Melanosomes; B: Azurophilic granules; C: Cytolytic granules; D: MHC class II compartments (Here MIICs are immunogold labeled for MHC class II molecules); E: Weibel Palade Bodies

Figure 2.

Comparative biogenesis of Melanosomes and Weibel-Palade Bodies

This figure shows both the differences; origin in the TGN versus origin in the EE for these two organelles, and the similarities; continued receipt of content after initial formation (Tyrosinase versus CD63), and recruitment of Rabs. The overall image of a complex, multi-stage, gradual transformation of a post-Golgi (TGN versus EE) organelle into an LRO is similar for both. Gold coating, AP-1; Purple coating, AP-3; Grey coating on stage I melanosome, bilayered clathrin/Hrs coat. TGN, Trans-Golgi Network; EE, early endosome; MVB, multivesicular body/Late endosome; Tyr, Tyrosinase. Typr1, Tyrosinase Related Protein-1

Table 1

Examples of Lysosome Related Organelles, their host cells and their functions

Organelle	Tissue distribution	Physiologic function
Lytic granules	Cytotoxic T lymphocytes, NK cells	Destruction of virally-infected or cancerous target cells
Dense granules	Platelets, megakaryocytes	Release of ATP, ADP, serotonin and calcium for blood clotting
α granules	Platelets, megakaryocytes	Fibrinogen and von Willebrand factor release for platelet adhesion and blood clotting
Basophilic granules	Basophils, mast cells	Triggered release of histamines, other inflammatory stimuli
MHC class II compartments	Antigen presenting cells (dendritic cells, B lymphocytes, macrophages)	Processing and presentation of antigens to CD4 ⁺ T lymphocytes for immune regulation
Lamellar bodies	Lung epithelial type II cells	Storage and secretion of surfactant for lung function
Weibel-Palade bodies	Endothelial cells	Storage and regulated release of haemostatic and pro-inflammatory factors into blood
Melanosomes	Melanocytes, retinal and iris pigment epithelial cells	Melanin synthesis, storage, and transfer
Osteoclast granules	Osteoclasts	Bone resorption and remodeling
Pigment granules	Drosophila melanogaster eye cells	Eye pigmentation
<i>Acrosomes</i>	<i>Sperm cells</i>	<i>Fertilization, fusion of sperm and egg</i>
<i>Fat Storage Organelle</i>	<i>C Elegans</i>	<i>Fat storage</i>
<i>Inhibitory lysosomes</i>	<i>Dendritic cells</i>	<i>Control the pH of the phagosome</i>

Table adapted from Marks and Seabra (NRMC, 2001)

* In italics; organelles that can also be considered LROs [51,56,57]

Table 2
Diseases of intracellular traffic affecting LROs and mutant genes

Griscelli Syndrome		
Gene / Protein	Mouse model	Human Disease
Rab27a	<i>ashen</i>	GS1
Myosin V	<i>dilute</i>	GS2
Melanophilin	<i>leaden</i>	GS3
Chediak-Higashi Syndrome		
Gene / Protein	Mouse model	Human Disease
CHS1/ Lyst	<i>beige</i>	CHS
Hermansky-Pudlak Syndrome		
Gene / Protein	Mouse model	Human Disease
β 3A δ	<i>AP-3</i> [*] <i>pearl</i>	HPS2
	<i>mocha</i>	
Pallidin Cappuccino Muted BLOS3a Dysbindin	<i>BLOC-1</i> ^{**} <i>pallid</i>	HPS8 HPS7
	<i>cappuccino</i>	
	<i>muted</i>	
	<i>reduced pigmentation</i>	
HPS3 HPS5 HPS6	<i>BLOC-2</i> <i>cocoa</i>	HPS3 HPS5 HPS6
	<i>ruby-eye-2</i>	
	<i>ruby eye</i>	
HPS1 HPS4	<i>BLOC-3</i> <i>pale ear</i>	HPS1 HPS4
	<i>light ear</i>	
Vps33a	<i>VpsC complex</i> ^{***} <i>buff</i>	****
Rabggtb	<i>Rab geranylgeranyl transferase II complex</i> <i>gunmetal</i>	

Table adapted from Marks and Seabra (NRM, 2001)

* Other components not represented among natural disease models are μ 3A and either σ 3A or σ 3B ; in a neuronal isoform, β 3B and μ 3B substitute for the ubiquitous β 3A and μ 3A subunits.

** Other components not represented among natural disease models are Snapin, BLOS1 and BLOS2.

*** Also called HOPS (homotypic protein sorting complex), the VpsC complex contains additional core subunits Vps11, Vps16 and Vps18.

**** Rabggtb is an additional subunit.