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The road to LROs: insights into lysosome-related organelles from Hermansky-Pudlak syndrome and other rare diseases

Shanna L. Bowman[1,2,4], **Jing Bi-Karchin**[1,2,4], **Linh Le**[1,2,3,4], and **Michael S. Marks**[1,2,5]

[1]Dept. of Pathology & Laboratory Medicine, Children's Hospital of Philadelphia Research Institute, Philadelphia, PA 19104

[2]Dept. of Pathology & Laboratory Medicine and Dept. of Physiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104

[3]Cell and Molecular Biology Graduate Group, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104

Abstract

Lysosome-related organelles comprise a diverse group of cell type-specific, membrane-bound subcellular organelles that derive at least in part from the endolysosomal system but that have unique contents, morphology, and functions to support specific physiological roles. They include melanosomes that provide pigment to our eyes and skin, alpha and dense granules in platelets and lytic granules in cytotoxic T cells and natural killer cells that release effectors to regulate hemostasis and immunity, and distinct classes of lamellar bodies in lung epithelial cells and keratinocytes that support lung plasticity and skin lubrication. The formation, maturation and/or secretion of subsets of lysosome-related organelles are dysfunctional or entirely absent in a number of hereditary syndromic disorders, including in particular the Hermansky-Pudlak syndromes. This review provides a comprehensive overview of lysosome-related organelles in humans and model organisms and presents our current understanding of how the products of genes that are defective in heritable diseases impact their formation, motility and ultimate secretion.

Keywords

Hermansky-Pudlak syndrome; Chediak-Higashi syndrome; BLOC-1; BLOC-2; BLOC-3; AP-3; RAB32; RAB38; RAB27A; Griscelli syndrome; VPS33A; VPS33B; HOPS; melanosome; Weibel-Palade body; alpha granule; dense granule; lamellar body

Introduction

The endolysosomal system in metazoans consists of a complex web of interconnected compartments and membranes that, in all cell types, serve an astoundingly large array of functions including nutrient uptake, metabolic control, signaling, pathogen destruction,

[5]To whom correspondence should be addressed: Michael S. Marks, Ph.D., Dept. of Pathology & Laboratory Medicine, Children's Hospital of Philadelphia, 816G Abramson Research Center, 3615 Civic Center Blvd., Philadelphia, PA 19104, Tel: 215-590-3664, marksm@pennmedicine.upenn.edu.

[4]These authors contributed equally to this work.

innate immunity, and others.[1,2] The endolysosomal system is highly plastic, allowing specific cell types to adapt it to serve their special needs. For example, phagocytic cells coopt the recycling endosomal system to provide the membrane needed to engulf large particles[3,4], polarized cells diversify the endosomal system to accommodate sorting among topologically distinct plasma membrane domains[5], and adipocytes and muscle cells adapt recycling endosomes to generate reservoirs from which glucose transporters can be rapidly deployed to the plasma membrane upon insulin signaling.[6-8]

Research over the last 15-20 years has revolutionized our understanding of endosomal system adaptation towards a distinct end - the formation of cell type-specific organelles known as lysosome-related organelles (LROs).[9-11] LROs are named as such because of their primary derivation from the endosomal system, their variable content of lysosomal proteins, and often an acidic phase during their life cycle – requiring the activity of the vacuolar ATPase.[12] However, they encompass a broad array of structures with distinct morphologies and functions that are unique to the physiology of their host cell (Table 1, Figure 1).[9,10] These structural and functional features are conferred by the unique cell type-specific contents of each LRO, which are specifically sorted to nascent LROs during their formation. While some LROs, such as immature cytolytic granules of resting cytotoxic T cells (CTLs), double as the host's lysosomes[13] (T cell activation induces granule maturation by fusion with recycling endosomes[14]), others such as melanosomes, Weibel-Palade bodies and platelet dense and alpha granules coexist with bona fide endolysosomes in their particular cell type.[15,16] The host cell types for the latter LRO class therefore require a dedicated system(s) by which LRO contents are segregated from cargoes destined to classical endolysosomes. In addition, most (if not all) LROs are regulated secretory organelles, and secretion at the proper time is critical for LRO function. For example, the contents of cytolytic granules must only be directed towards a target cell following immune recognition, and contents of platelet alpha and dense granules must only be released upon platelet activation at sites of vascular damage. Thus, proper regulation of the biogenesis, maintenance/protection from degradation, and secretion of LROs is necessary for normal physiological function.

Progress in understanding both the formation and secretion of LROs has been greatly accelerated by the study of syndromic human genetic disorders – and their animal models – in which these processes are disrupted in many LRO-generating cell types. Biogenetic disorders include the Hermansky-Pudlak syndromes (HPS), Chediak-Higashi syndrome (CHS), the arthrogryposis, renal dysfunction and cholestasis (ARC) syndromes, and gray platelet syndrome (GPS). Secretory disorders include the Griscelli syndromes (GS) and familial hemophagocytic lymphohistiocytosis (FLH) types 3-5. Each of these monogenic disorders impacts the function of a group of LROs[a], resulting in loss of function in such diverse physiological systems as immunity, neurology, pigmentation, hemostasis, and others. For example, oculocutaneous albinism and excessive bleeding and bruising in HPS patients are due to impaired biogenesis of pigment cell melanosomes and platelet dense granules, respectively.[17,18]

[a]GPS is unique among these syndromes in that it appears to impact only alpha granule biogenesis in megakaryocytes and platelets.

Over the last 10-15 years, functional analyses of HPS genes and their products in particular have enlightened molecular pathways required for content delivery and function of melanosomes, dense granules, lung lamellar bodies, and several organelles in innate and adaptive immune cell types. This review will focus primarily on the roles of HPS gene products and their associated proteins in LRO biogenesis at the level of human disease, model organisms, and cell culture systems. We will briefly touch upon how the other syndromic diseases mentioned above are similarly providing new insights into LRO biogenesis, positioning and secretion, and then provide some perspectives on future studies.

LROs vs. secretory granules and secretory lysosomes

How are LROs defined and distinguished from classical secretory granules? Most experts agree that LROs derive a substantial component of their contents from the endolysosomal system, including either late endosomes, early endosomes, or both (Figure 2). By contrast, secretory granules derive most of their contents from the Golgi complex. However, the line between LROs and classical secretory granules can be blurred. For example, Weibel-Palade bodies - cigar-shaped regulated secretory organelles in endothelial cells that package and store von Willebrand factor (vWF) for stimulated secretion – have long been considered LROs[10], but immature Weibel-Palade bodies bearing polymerized vWF bud directly from the trans Golgi network[19] and later fuse with endosomal membranes bearing CD63 and P-selectin.[20] By contrast, large dense core granules have long been considered classical secretory granules but have some features of LROs, such as the requirement for complexes that are defective in several HPS subtypes for their proper formation[21-23] and the recruitment of ectopically expressed LRO cargos.[24] In this review, we define LROs broadly as cell type-specific organelles for which at least some functionally or structurally significant components derive from the endolysosomal system, and/or for which their biogenesis, motility or secretion requires effectors that are disrupted in LRO diseases described here (HPS, GPS, GS, ARC or FLH) or their homologues in model systems (Table 1). This inclusive definition would encompass organelles such as cytolytic granules that have been referred to as “secretory lysosomes”[25,26], but would exclude actual lysosomes (which can also be secreted under some conditions but which are not cell type-specific[27,28]). Note that this definition might also encompass certain types of synaptic vesicles in neurons (Table 1), but due to the complexity of the neuronal system we have chosen not to cover this topic extensively in this review.

The Hermansky-Pudlak syndromes

HPS is a group of syndromic disorders characterized in all cases by varying degrees of oculocutaneous albinism, with concomitant visual impairment and susceptibility to skin cancer, and by excessive bleeding and bruising that can, under some conditions such as childbirth or surgery, become life-threatening.[29] HPS is rare in the general population (incidence estimated at 1:1,000,000), but is particularly prevalent in certain populations due to founder effects; for example, HPS1 is estimated to afflict ~1:1800 individuals in Puerto Rico.[29] Albinism reflects defects in the biogenesis of melanosomes in melanocytes of the skin, hair and choroid of the eye and in pigment epithelial cells of the retina, iris and ciliary body of the eye. Bleeding and bruising reflects absence of detectable dense granules in

platelets. Patients with the most common HPS subtypes (HPS1 and HPS4) additionally suffer from a progressive lung fibrosis that is typically lethal without a lung transplant within the 4th or 5th decade of life. The primary insult responsible for lung fibrosis appears to be defects in the biogenesis of lamellar bodies, which are LROs in alveolar type II (AT2) cells responsible for surfactant synthesis and secretion.[30-32] Consequent inflammatory sequelae, which likely result from reduced surfactant levels, initiate and expand the fibrotic response.[33,34] A subset of HPS1 and 4 patients also suffer from granulomatous colitis (a type of inflammatory bowel disease), the etiology of which is currently unknown. HPS2 and HPS10 patients also suffer from lung disease[35,36], but additionally suffer from recurrent bacterial and viral infections due to impaired immune responses.[36-40] The molecular basis for the impaired immune response will be discussed later in this review.

HPS can be caused by inactivating mutations in any of at least 10 different genes in humans. All of these genes encode subunits of four obligate multi-subunit protein complexes: adaptor protein-3 (AP-3) and the **b**iogenesis of **l**ysosome-related **o**rganelles **c**omplex (BLOC)-1, −2 and −3 (Table 2, highlighted in gray, yellow, green and blue). LRO biogenesis in model organisms is also disrupted by mutations in the same genes and in genes encoding additional BLOC-1 subunits, as well as additional genes; these include genes encoding the Rab GTPase targets of BLOC-3 function (RAB32 and RAB38) and subunits of the homotypic fusion and vacuole protein sorting (HOPS) and the class c core vacuole/endosome tethering (CORVET) complexes (Table 2; HOPS/CORVET subunits highlighted in orange). The phenotype in mice with BLOC or AP-3 subunit mutations is remarkably similar to that of HPS patients. In almost all cases, disease results from nonsense mutations that ablate production of an intact subunit and that thereby (1) disrupt formation of the entire complex with which the subunit is associated, and (2) destabilize the remaining subunits. For example, mutations in HPS4 destabilize both HPS4 and HPS1 and result in a loss of BLOC-3 function.[41] A substantial fraction of HPS patients lack identifiable mutations within these 10 genes, suggesting that mutations in additional genes may also cause the disease.[29]

As discussed further below, the protein complexes that are disrupted in HPS each participate in a discrete step of membrane trafficking required for LRO biogenesis or for additional functions in cell types that lack LROs (Figure 3). Not all steps appear to be equally required for minimally functional LRO biogenesis in each cell type, resulting in the differences in the disease spectrum of patients with mutations in distinct HPS genes. However, the disease spectrum is nearly identical in patients with mutations in different components of the same protein complex - e.g. the disease spectrum in HPS3, HPS5 and HPS6 patients, all with mutations in BLOC-2 subunits, is very similar.[42-44] For this reason, HPS is best understood in the context of BLOC-1, BLOC-2, BLOC-3 or AP-3 disease rather than in the context of each individual gene product.

Model systems for LRO biogenesis

Rodents.

The laboratory mouse has been perhaps the most informative for the study of HPS and LRO biogenesis, in large measure due to both (1) the similarity of HPS disease in humans to the phenotype of orthologous mutations in mice[45,46], and (2) the availability of models for all

HPS subtypes. The latter reflects the impact of HPS on mouse coat color and the ease with which spontaneous coat color mutants can be detected and propagated.[47,48] Such spontaneous mutations have given rise to at least 15 HPS models in the mouse including correlates of all of the human HPS variants and mutants in genes encoding two additional BLOC-1 subunits (Muted[49,50] and Cappuccino[51]), the HOPS/ CORVET subunit VPS33A[52], the Rab geranylgeranyltransferase II subunit RGGTA[53], and the plasma membrane cysteine/ glutamate transporter SLC7A11.[54] In addition, the *Chocolate* mouse bears a mutation in *Rab38* and has pigmentation and lung defects – but curiously no platelet defect.[55-57] By contrast, the *Ruby* mutation in *Rab38* in Fawn-hooded and Tester-Moriyama rats is associated with classical hypopigmentation, bleeding diathesis and lung dysfunction.[58,59] Notably, immortalized melanocyte cell lines[60,61] from each of the mouse HPS models (see http://www.sgul.ac.uk/depts/anatomy/pages/Dot/Cell%20bank%20holdings.htm) and engineered HPS models in an AT2 cell line[62] provide excellent tools for analyses of cell type-specific effects of HPS subtypes.

Zebrafish.

The zebrafish *Danio rerio* harbors a number of unique LROs, including melanosomes in skin melanophores and retinal pigment epithelia, notochord vacuoles, and lamellar body-like surfactant storage organelles at the caudal tip epithelium of the swimbladder. Melanophores are epidermal cells in fish and amphibians that, like melanocytes in mammals, generate melanosomes in which melanin is synthesized. However, unlike mammalian melanocytes, they respond more rapidly to external stimuli either by accumulating pigment granules in the cell center or by dispersing them to the cell periphery.[63,64] The retinal pigment epithelia in zebrafish is structured similarly to that in mammals and also harbors melanosomes, and defects in their melanization are easy to spot even in embryos. Zebrafish and mammals share most of the genes known to regulate melanosome biogenesis and motility, and altered pigmentation has been observed in zebrafish with mutations in genes encoding subunits of BLOC-1, BLOC-2, and HOPS[65-69], as well as an unidentified gene in the *fade* mutant.[70] Mutations in numerous additional pigment cell-specific genes, such as PMEL (responsible for the amyloid matrix upon which melanins deposit in melanosomes) and SLC24A5 (a transporter that is defective in oculocutaneous albinism type 6) have also been identified in zebrafish, but will not be discussed further here.

The notochord vacuole is a fluid-filled organelle that takes up most of the volume of the inner cells at the center of the notochord and that provides rigidity to the notochord during development. As for other LROs, notochord vacuole biogenesis and maintenance require the HOPS complex, the small GTPase RAB32A, and the vacuolar proton-ATPase[71], as well as the homologue of the mammalian lysosomal scavenger receptor LIMP2/ SCARB2.[72] The swimbladder is an air-filled organ that inflates and deflates to regulate buoyancy, and is a valued model system for lung development and surfactant formation. Mutations in the BLOC-1 and BORC subunit, BLOS1, result in a defective swimbladder. This appears to reflect a requirement for BLOS1 in activating a transcriptional network for the surfactant system, which is critical to swimbladder function.[65] It is not clear whether this reflects a primary defect in BLOC-1, BORC or both (see discussion of BLOC-1 and BORC below).

Xenopus tropicalis.

X. tropicalis harbors retinal pigment epithelia and melanophores similar to those in zebrafish. Recent identification of an HPS6 (BLOC-2 subunit) mutant with reduced pigmentation in the retina and body suggests that this organism may provide another model for LRO biogenesis.[73]

Drosophila melanogaster.

The *D. melanogaster* eye (as for eyes of other insects) consists of approximately 800 individual units called ommatidia, within which pigment granules are generated in primary pigment cells near the cornea and secondary pigment cells that surround the retinular cells along the length of the ommatidia.[74] These cells make two classes of pigment: brown ommochrome and red pteridines. Defects in the formation of pigment granules lead to changes in eye color from the normal brownish red to a variety of colors. Eye color mutants in *D. melanogaster* have been described for over a century, and many reflect mutations in conserved genes required for pigment granule biogenesis. For example, mutations in any of the four subunits of AP-3[75-79] result in a similar phenotype with a reduction in the number and size of the pigment granules and loss of both ommochrome and pteridine pigments. RNAi depletion of BLOC-1 subunits[80], the *pink* mutation in the orthologue to the HPS5 subunit of BLOC-2[81], the *lightoid* mutation in a Rab32/38 orthologue and the *claret* mutation in its putative guanine nucleotide exchange factor[82], and mutations in the Vps16, Vps33, Vps18 and Vps41 subunits of HOPS[83-87] all cause altered eye color due to malformation of pigment granules. The availability of these models allows for relatively easy testing of genetic interactions among these and other genes. For example, pigmentation defects due to BLOC-1 deficiency could be partially offset by overexpression of Rab11, a Rab GTPase that controls endosomal recycling.[80]

D. melanogaster and other insects may have additional LROs in other tissues. The zinc concentration in zinc storage granules of principal cells in the Malpighian tubules, the major zinc reservoir in *D. melanogaster*, is sensitive to mutations in genes encoding subunits of AP-3, BLOC-2, and HOPS as well as the Rab32/38 orthologue *lightoid*[88], suggesting that the zinc storage granules are LROs. In addition, the mucin-containing glue granules of larval salivary glands have features of LROs and are sensitive to mutations in the AP-3-associated type II phosphatidylinositol-4-kinase and in AP-1, a complex similar to AP-3.[89,90]

Caenorhabditis elegans.

Gut granules in *C. elegans* - and likely in other nematodes - are LROs that are sites of fat storage in intestinal cells and contain birefringent, autofluorescent material.[91,92] The accumulation of this material requires a number of gut granule membrane proteins, including the ABC transporters PGP-2[92], MRP4 (a homologue of mammalian MRP4 that might localize to platelet dense granules) and WHT-2.[93] Like many LROs in mammalian cells, gut granules contain some lysosomal membrane proteins and co-exist with lysosomes.[91] Proper gut granule formation requires homologues to components of the mammalian HPS complexes AP-3, BLOC-1 and HOPS, as well as the RAB32/38 family member, GLO-1.[91,94,95]

The biogenesis of gut granules in *C. elegans* and of LROs such as melanosomes in mammals share striking features but a few intriguing differences. Like for melanosomes in melanocytes, distinct cargoes show differential requirements for BLOC-1 and AP-3 for sorting to gut granules.[95] Moreover, a homologue of the LYST (Lysosomal Trafficking regulator) protein that is deficient in CHS, LYST-1, is required for proper gut granule morphogenesis, although the effects of *lyst-1(−)* mutations (increased number but smaller gut granules) are opposite to that observed for LROs from CHS models.[96] On the other hand, in *C. elegans* lacking BLOC-1 subunits, gut granule cargoes are mislocalized to the plasma membrane and lysosomes rather than primarily to early endosomes like in BLOC-1-deficient melanocytes.[95] In addition, the BORC subunit, KXD1, which is partially required for melanosome and platelet dense granule biogenesis, is not required for gut granule formation. However, another gene product with a similar KxDL motif may function in gut granule formation[95], suggesting that differential protein components in different cell types, tissues, or organisms may function in the biogenesis of distinct LROs.

Dictyostelium discoideum.

The slime mold *D. discoideum* is a simple eukaryote with a small genome and well-developed secretory and endocytic pathways.[97] Because it is highly phagocytic and easy to manipulate genetically, *D. discoideum* has been used as a model system to dissect lysosomal secretion defects such as those in CHS.[98] *D. discoideum* harbor LROs called post-lysosomes that are equivalent to secretory lysosomes in mammalian cells and that undergo regulated secretion in response to stimuli such as starvation. Post-lysosomes derive from classical lysosomes that are accessed by internalized extracellular material, are enriched in the vacuolar proton ATPase, and are highly acidic.[99] Over time, however, they lose their acidity and mature into post-lysosomes that can be stimulated to fuse with the plasma membrane, releasing undigested material to the extracellular space.[100] The post-lysosomes are distinguished from traditional lysosomes by their neutral pH, absence of vacuolar proton ATPase[99,101], enrichment in cargoes P80 (a transmembrane protein that mediates copper transport)[102] and AmtA (Ammonium transporter A)[103], and association with cytoskeleton markers such as vacuolin[104], coronin[104-106], WASH[105], and F-actin.[104,107] The biogenesis of post-lysosomes in *D. discoideum* shares similarities with the biogenesis of mammalian LROs. For example, *D. discoideum* cells require AP-3 for post-lysosome secretion, for proper endosomal recycling of membrane proteins, and for endosomal sorting of the vSNARE, VAMP7.[108-110] More strikingly, *D. discoideum* has served as an outstanding model to understand the function of LYST. Two LYST homologues, lvsA and lvsB, regulate the endocytic pathway at different stages. lvsA is necessary for the proper organization of the early endocytic and phagocytic system and for phagocytosis, whereas lvsB is necessary for the maturation of post-lysosomes; lvsB mutants have fewer, larger post-lysosomes that are more acidic and constitutively secrete lysosomal enzymes. There is debate as to whether this reflects a role for lvsB in negatively regulating fusion of post-lysosomes with early endosomes or in supporting transfer of endocytosed material from lysosomes to post-lysosomes.[111-113] Supporting the former, lvsB appears to dampen Rab14 function in lysosomal fusion. The *D. discoidium* Rab14 homologue - which is normally restricted to lysosomes - was also present in post-lysosomes in lvsB mutant cells, and expression of a dominant negative Rab14 suppressed the lvsB phenotype.[114,115] These observations support

the notion that lvsB and LYST function to prevent fusion among endolysosomal organelles and LROs.

Tetrahymena thermophila.

The ciliated protist *T. thermophila* harbors a secretory organelle called the mucocyst, which stores mucins in paracrystalline arrays that are secreted in response to extracellular stimuli.[116,117] Mucocysts have some functional similarities to dense core secretory vesicles in animals, and mucocyst formation requires effectors that are similar to components required for mammalian lysosome and LRO biogenesis. For example, cargo sorting to mucocysts and consequent mucocyst formation, maturation, and secretion require SOR4 (a Vps10/sortillin family member)[118], AP-3[119] and the Qa SNARE protein, STX7L, a homologue of the mammalian Syntaxins 7 and 13 that are involved in lysosome and LRO formation, respectively.[119] Mucocyst formation also requires some components of the *T. thermophila* CORVET complex[120], which in other organisms shares its core subunits with HOPS. Interestingly, HOPS-specific subunits of yeast and mammalian HOPS and CORVET complexes were lost during evolution to *T. thermophila*, whereas genes encoding the CORVET VPS8 subunit expanded to six paralogs. One of these paralogs is required for mucocyst formation and colocalizes with the Rab7 late endosome/lysosome marker, rather than endosomes like CORVET[120], suggesting that the specificity of these complexes for different organelles has changed throughout evolution.

Bombyx mori.

If LROs are defined by the requirement for HPS-associated protein complexes, the silkworm appears to have two LROs. The *B. mori* larval integument is opaque due to the presence of urate granules, and impairment of urate granule biogenesis results in translucency. *B. mori* larvae with mutations in subunits of the HPS-associated BLOC-1 and BLOC-2 are translucent[121-124], suggesting that these granules are LROs. In addition, riboflavin accumulation in needle-like granules in the Malpighian tubules has been observed to be reduced in mutants with translucent skin, including mutants in BLOC1 and BLOC2 subunits and in ABC transporters w-3 and Bm-brown that are homologous to the Drosophila white gene[125] and brown gene[126], respectively. These organelles and their control by BLOC-1 subunits are conserved in other silkworms such as *Samia ricini*.[127]

HPS-associated protein complexes

AP-3.

The heterotetrameric adaptor proteins (AP) are a family of related complexes that function as coats for sorting of integral membrane protein cargoes within the endomembrane system. They engage and accumulate cargoes on a source membrane by binding to sorting signals located in the cargo cytoplasmic domains, and recruit an outer coat and/or other accessory proteins to generate transport carriers that facilitate cargo delivery to their destinations. Five AP complexes are known[128]; AP-1, AP-2 and at least a cohort of AP-3 employ clathrin as an outer coat, while AP-4 and AP-5 do not. AP-2 primarily functions at the plasma membrane and plays an important role in clathrin-mediated endocytosis, whereas the other APs mediate trafficking among the TGN and endolysosomal compartments.[128-130] Genetic analyses in

multiple organisms show that AP-3 plays a unique role in cargo sorting to LROs, and mutations in the genes encoding two AP-3 subunits in humans cause rare forms of HPS (Table 2).[131,132]

AP-3 subunits—AP-3, like the other APs, is a stable heterotetramer and consists of the four adaptin subunits δ, β3, μ3, and σ3.[133] The genes that encode these subunits are highly conserved throughout eukaryotic evolution with orthologues from yeast to humans.[133,134,135,136] In mammals, each of the β3, μ3, and σ3 subunits has two variants. The δ, β3A and μ3A subunits are ubiquitously expressed in most/all tissues and cells, and assemble with either of the ubiquitously expressed and functionally redundant σ3A or σ3B subunits to form the AP-3A complex.[137] Expression of the β3B and μ3B subunits is restricted to neuronal cells, forming (with δ and either σ3A or σ3B) the neuronal AP-3B complex that functions in cargo sorting to synaptic vesicles.[138] Mutations in the genes encoding the ubiquitous δ or β3A subunit in humans lead to HPS10 or HPS2, respectively, and mutations in orthologous subunits in numerous model organisms lead to defects in LRO biogenesis and, in some cases, in cargo sorting to lysosomes.[36,139] Indeed, the identification of mutations in the *AP3B1* gene (encoding β3A) in HPS2 and the *pearl* mouse, and in the *Ap3d* gene (encoding δ) in the *mocha* mouse represented the first link between HPS and defective membrane trafficking in the endolysosomal system in mammals.[131,132,140]

AP-3 is a coat protein.—Although the yeast AP-3 appears to function in protein sorting from the Golgi[141] and initial observations suggested a similar function for mammalian AP-3[142,143], it is now well-accepted that AP-3 functions primarily from early endosomes in mammals.[144,145] AP-3 is recruited to membranes at least in part by association with the small GTPase Arf1[142,146,147] and possibly phosphatidylinositol-3-phosphate.[148] The μ3A subunit of AP-3 recognizes tyrosine-based sorting signals in the cytoplasmic domain of cargo proteins destined for lysosomes or LROs[149,150], while the interface of the σ and δ subunit hemicomplex binds to dileucine-based sorting signals[151-153]; the corresponding components of AP-1 and AP-2 recognize similar signals, with some complex-specific preferences based on sequence and context.[135,149,154,155] Like AP-1 and AP-2, AP-3 associates with clathrin and is enriched in clathrin-coated buds on endosomes.[144,145,147,156] This cohort of AP-3 is necessary for transport of specific cargoes to late endosomes or lysosomes in cells that lack LROs and to melanosomes in melanocytes.[144,145] Unlike AP-1 and AP-2, however, AP-3 is not enriched in clathrin-coated vesicle fractions from cells[142], and a β3A chain lacking a clathrin binding site is able to fully restore AP-3 function in diverting LAMP1 from the plasma membrane.[157] While these data can be explained by a weak association with clathrin mediated by multiple binding sites, a pool of membrane-associated AP-3 lacking clathrin is readily detectable by microscopy[142-145], and acute depletion of clathrin light chains did not disrupt AP-3 vesicle formation in PC12 cells.[158] This suggests that AP-3 might function in both clathrin-dependent and -independent pathways.

AP-3-dependent cargo sorting in LRO biogenesis.—The function of AP-3 in LRO biogenesis is best exemplified by its role in protein sorting to maturing melanosomes (Figure 3, step 1). A critical cargo for AP-3 in pigment cells is tyrosinase (TYR), an integral

membrane protein that catalyzes the limiting steps in melanin synthesis. TYR bears a di-leucine-based sorting signal in its C-terminal cytoplasmic domain that is necessary for transport to maturing melanosomes (or to lysosomes upon ectopic expression in other cell types[24,159,160]) and is capable of binding AP-3 as well as AP-1 and AP-2.[145,161] TYR is enriched in early endosome-derived vesicles that are coated with AP-3 and clathrin, and is depleted from melanosomes and enriched in late endosomes and lysosomes of AP-3-deficient melanocytes from HPS-2 patients or *pearl* mice.[145,162] These data suggest that TYR is sorted by AP-3 from early endosomes into vesicles destined for melanosomes (Figure 3). Intriguingly, a superficially similar dileucine-based sorting signal in another melanosomal protein, TYR related protein 1 (TYRP1)[163], does not engage AP-3 and TYRP1 is not as grossly missorted in AP-3-deficient melanocytes.[145,162] Moreover, a small cohort of TYR is properly sorted to melanosomes in AP-3-deficient melanocytes, likely by engaging with AP-1.[145,164] This suggests that there are multiple pathways by which cargoes are sorted to melanosomes, including AP-3-dependent and -independent pathways (Figure 3). Lastly, a cohort of AP-3 interacts physically with BLOC-1[165,166], which – as discussed further below – is essential for a second cargo transport pathway. In neurons, BLOC-1 and AP-3 appear to function largely in tandem to sort specific cargoes into synaptic vesicles[138,166], and accordingly, melanosome sorting of another pigment cell-specific protein, OCA2, requires both AP-3 and BLOC-1.[154,167] This implies a potential dual role for AP-3 in multiple sorting pathways in melanocytes.

AP-3 functions in cargo sorting not only for melanosome biogenesis, but also for the formation of other LROs. In model organisms, AP-3 is required for the generation of gut granules in *C. elegans*[91], mucocysts in *T. thermophila*[119], post-lysosomes in *D. discoideum*[109], and eye pigment granules in *D. melanogaster*[77,143]. In mammals, AP-3 plays an essential role in sorting cargoes such as the zinc transporter ZnT-3, the GABA transporter and SNARE proteins into synaptic vesicles in neurons.[132,138,168,169] Consequently, animals or individuals lacking both AP-3A and AP-3B (e.g. by loss of the δ chain in mocha mice or HPS10 patients) suffer from neuronal deficiencies.[36,169-171] Excessive bleeding and bruising due to platelet storage pool deficiency, which results from defective or absent dense granules in platelets, is also associated with loss of AP-3 in HPS2 and 10 and their mouse models[172,173], but relevant cargos have not yet been identified.

AP-3 function in the lung and hematopoietic cells.—Besides albinism and excessive bleeding, HPS2 patients uniquely suffer from a number of additional serious symptoms. Like patients with BLOC-3 disease, HPS2 patients suffer from interstitial lung disease and pulmonary fibrosis, likely due to an initial defect in the maturation of lamellar bodies in AT2 cells.[30,33,174-176] To date, one AP-3-dependent cargo of lamellar bodies has been identified: PRDX6, a non-integral membrane member of the peroxiredoxin family of redox proteins, which is targeted to lamellar bodies in association with the AP-3 engaged transmembrane protein LIMPII/SCARB2.[177] Additional AP-3-dependent lamellar body cargoes are likely to exist. AP-3-deficient patients and the *pearl* and *mocha* mouse models also suffer from recurrent bacterial and viral infections[36,39,40,173,178-181] due to critical roles of AP-3 in various immune responses. Increased susceptibility to viral infections likely reflects impaired natural killer cell and cytolytic T cell activity due to defective polarization

and decreased perforin content of cytolytic granules[36,37,39], as well as impaired type I interferon responses from plasmacytoid dendritic cells (pDCs) due to a failure to deliver viral nucleotide sensing toll-like receptors, TLR7 and TLR9, to a signaling LRO in these cells (Table 1).[182,183] AP-3 controls a different TLR trafficking step in conventional DCs (cDCs), facilitating the recruitment of TLR4 and likely other TLRs to maturing phagosomes following uptake of bacteria and other large particles. Reduced TLR recruitment to phagosomes in AP-3-deficient mice and HPS2 patients results in impaired proinflammatory signaling by bacterial stimuli and reduced antigen presentation of phagocytosed antigens to CD4+ T cells, with consequent skewing of CD4+ T cell responses toward the Th2 lineage and altered cDC maturation and chemokine responses.[184,185] Additionally, AP-3 plays a role in dampening autophagic responses to pathogenic bacteria in cDCs. This has an important impact on clearance of inflammasomes, which are large cytoplasmic complexes that are assembled following a variety of cytoplasmic inflammatory stimuli and consist of many copies of nucleotide binding domain leucine rich repeat containing proteins (NLRs), inflammatory caspases, and the scaffold protein ASC. Inflammasomes process pro-IL-1 family cytokines to their mature form. Inflammasomes in AP-3-deficient cDCs are more rapidly consumed by autophagy than in control cDCs, leading to impaired inflammasome activity, consequent reduced local IL-1β and IL-18 secretion, and increased susceptibility of AP-3-deficient mice to pathogenic bacterial infection.[186] AP-3 also regulates the trafficking of CD1b (in humans) and CD1d (in mice) to lysosomal compartments to acquire glycolipid antigens. Consequently, presentation of glycolipid antigens to NKT cells is impaired and NKT cell numbers are reduced in HPS2 patients and mouse models, also contributing to susceptibility to certain bacterial infections.[181,187-189] Lastly, cyclic neutropenia has been observed in HPS2 patients and a dog model of AP-3 deficiency, and sorting of neutrophil elastase to primary granules and proper processing to the mature form require AP-3.[190,191] Whether this reflects a direct interaction of a cytoplasmic sequence on a transmembrane form of elastase as proposed[190] or an effect of AP-3 on a transmembrane carrier of elastase, as for PRDX6 in lung AT2 cells, remains unclear.

BLOC-1.

BLOC-1 subunits and HPS models.—BLOC-1 contains eight subunits: BLOS1, BLOS2, BLOS3[192,193], cappucino[51,194], muted[50], pallidin[50,195,196], snapin[193,197], and dysbindin.[198-200] The human gene names for each subunit are referred to as *BLOC1S1-8*. Each of the subunits is small (136 to 351 amino acids) and lacks obvious homology domains other than predicted short coiled coil regions. Mutations in the genes that encode dysbindin, BLOS3 and pallidin have been identified in patients with HPS subtypes HPS7, HPS8 and HPS9, respectively.[200-208] These patients tend to have mild HPS disease with no obvious immunologic or lung impairment. Five HPS mouse models exist[49,193,194,209-211] and are the most severely hypopigmented of the HPS models[212] (by contrast, skin and hair pigmentation in human HPS7-9 patients is less obvious than in other HPS variants). BLOC-1 homologues have also been described in non-mammalian model organisms. Gut granule formation in *C. elegans* and synaptic vesicle recycling in *D. melanogaster* neurons require BLOC-1[80,95,213], and in the silkworm, *Bombyx mori*, a mutation in the *muted* ortholog causes translucent larval skin.[124] In addition, in zebrafish BLOS1 regulates formation of melanophore and iridiphore pigment organelles and surfactant storage organelles in the swimbladder.[65]

Interestingly, the BLOS1, BLOS2 and snapin subunits are shared with the distinct BLOC One Related Complex (BORC)[214], which will be briefly discussed later. Some of the effects of mutations in the genes encoding these subunits might reflect defects in BLOC-1, BORC, or both.

BLOC-1 function in cargo transport carrier formation.—The role of BLOC-1 in LRO biogenesis has been most clearly elucidated in cultured melanocytes from mouse HPS models. BLOC-1 is required to deliver a cohort of transmembrane protein cargoes that are involved in melanin synthesis, including TYRP1, OCA2, ATP7A and a small subset of TYR, from early endosomes to melanosomes via tubular transport carriers[154,164,165,215,216] (Figure 3, step 2). These transport carriers have features of recycling endosomes[164,217-219], and BLOC-1 regulates the formation of similar tubular carriers for endosomal recycling in HeLa cells.[217,218] The fact that these carriers in melanocytes are co-opted specifically for melanosome cargo delivery suggests that they reflect a cell type specialization of the recycling endosomal machinery, perhaps through regulation by as yet undefined cell type-specific components such as Rab proteins. Because TYR is primarily trafficked to melanosomes via a separate AP-3-dependent vesicular pathway[145,162,215,216], TYR is only mildly mislocalized in BLOC-1 deficient melanocytes. However, TYR activity in melanosomes is essentially absent in BLOC-1-deficient cells due at least in part to depletion of ATP7A, an ATP-dependent copper transporter that is required for import of the essential TYR cofactor copper into melanosomes[216], and of OCA2, a pigment cell-specific chloride channel that is required to neutralize acidic early stage melanosomes, both of which are prerequisites for TYR activity.[154,220] Similarly, BLOC-1 physically interacts with ATP7A and affects copper homeostasis in neuronal cells.[221] A third set of cargoes, MART1 and dopachrome tautomerase (DCT), are delivered directly to melanosomes from the Golgi apparatus through a BLOC-1- and AP-3-independent but RAB6-dependent pathway[222] (Figure 3, step 3). BLOC-1 is ubiquitously expressed, and roles for BLOC-1 in endosomal trafficking have been identified in other cell types. For example, in HeLa cells BLOC-1 facilitates transferrin cycling through classical recycling endosomes[218], and in neurons BLOC-1 and AP-3 collaborate to mediate cycling of cargoes between endosomes and synaptic vesicles and may differentially regulate synaptic vesicle trafficking in different brain regions.[138,166,170,223]

BLOC-1 and cytoskeletal interactions.—BLOC-1 localizes to and is required for formation of the endosomal tubular transport carriers that fuse with melanosomes to deliver cargo[164,165,218,224] (Figure 3). Negative stain EM structures of recombinant BLOC-1 suggest that BLOC-1 subunits form a flexible linear chain[225], which could be consistent with BLOC-1 interactions with curved, tubulating membranes. In melanocytes and HeLa cells, BLOC-1 associates with the kinesin-3 motor, KIF13A, perhaps linking membrane tubules to the microtubule cytoskeleton, and promotes actin rearrangements to stabilize and elongate tubules, and in HeLa cells (but perhaps not in melanocytes) to sever them.[217,218] Some of these interactions may be coordinated by the small GTPase RAB22.[226] Consistent with a role for BLOC-1 in regulating the actin cytoskeleton, comparative proteomic analyses of brains from wild-type or BLOC-1-deficient mice suggest that loss of BLOC-1 function results in depletion of the actin nucleation complex, Arp2/3, and that this interaction is

important for actin dynamics in HEK293 cells and neuronal plasticity at *D. melanogaster* synapses.[227] Similarly, BLOC-1 interacts with the WASH complex, an Arp2/3 activator, to regulate endosomal sorting of phosphatidylinositol-4-kinase type IIα (PI4KIIα) in several cell types.[228] Together, these data suggest a role for BLOC-1 in linking cargo sorting to the actin and microtubule cytoskeletons with potential implications for neuronal function. Indeed, BLOC-1-deficient mice with an inactivating dysbindin mutation show defects in the kinetics of neurotransmitter release[229], and several studies have suggested that variations in the genes encoding dysbindin and other BLOC-1 subunits correlate with increased schizophrenia risk in humans, although others dispute this conclusion.[230-232]

BLOC-1 and SNARE interactions.—In addition to its role in regulating the cytoskeleton, BLOC-1 might also regulate SNARE-mediated membrane fusion in an as yet undefined way. The pallidin subunit interacts with the endosomal Qa t-SNARE subunit, syntaxin 13[196,199], and snapin interacts with the Qbc t-SNARE subunit, SNAP25.[197,199,233] Interestingly, syntaxin 13 labels the tubular endosomal transport carriers through which melanosomal cargoes are delivered.[218,219] Furthermore, the endolysosomal R-SNARE, VAMP7 (a.k.a. TI-VAMP – the vSNARE required for fusion of BLOC-1-dependent tubules with melanosomes[224]) – localizes to AP-3-containing vesicles in neuronal cells in a BLOC-1-dependent manner[166], suggesting a wider role for BLOC-1 in SNARE sorting. In addition to these direct effects on SNARE proteins, the dysbindin subunit of BLOC-1 can bind directly to N-ethylmaleimide-sensitive factor (NSF) to regulate neuronal activity.[213] How these different binding events are coordinated is not yet understood.

BLOC-1 vs. BORC.—Three BLOC-1 subunits, BLOS1, BLOS2, and snapin, were recently identified as members of a separate complex called BORC. BORC also contains five additional subunits: KXD1, myrlysin, lyspersin, diaskedin, and MEF2BNB[214]; the human genes encoding the five BORC-specific subunits are named *BORCS4-8*. BORC functions on lysosomes, where it facilitates lysosome motility on distinct microtubule tracks toward the cell periphery by recruiting the Ras-like GTPase, ARL8. Active ARL8, via the adaptor SKIP, then recruits the KIF5B-containing kinesin-1 or the KIF1A-containing kinesin-3 microtubule motors.[214,234] Interestingly, BORC also interacts with the Ragulator, a lysosomal complex that controls mTORC1 activation and downstream autophagy induction in response to low amino acid levels. The Ragulator-BORC interaction suppresses BORC and kinesin-mediated movement of lysosomes, causing sequestration of lysosomes at the perinuclear region in response to low nutrient levels.[235,236] BORC also regulates fusion of lysosomes with autophagosomes, and is required for autophagosome transport and clearance in distal axons.[237,238] Consistent with this, BORC regulates axonal transport of synaptic vesicle precursors in *C. elegans,* also in an Arl8-dependent manner.[239] Moreover, a mouse mutant in the gene encoding the diaskedin subunit causes axonal dystrophy, motor defects, and early death in mice, suggesting a role for BORC-dependent lysosome transport in proper motor neuron function.[240] Whether BORC controls LRO positioning, functions, or effector localization is not known, although gene targeting of the KXD1 subunit was reported to produce mild melanosome and platelet dense granule defects.[241]

The facts that BORC and BLOC-1 share three subunits and that BORC was only recently discovered have caused some confusion in the literature regarding the function of each complex. For example, knockout of the gene encoding snapin disrupts retrograde transport of synaptic vesicles, endosomes, and late endosomes, and impairs lysosomal function in neurons of embryonic mice.[242-245] Expression of dynein-binding mutants of snapin cause synaptic vesicles to be trapped in synaptic terminals.[246] Further, depletion of BLOS1 impairs lysosomal degradation of the epidermal growth factor receptor (EGFR).[247] These functional requirements for snapin and BLOS1 were attributed in part to BLOC-1, but are more likely attributable to the role of BORC in lysosome motility and function. Of note, while functional gene knockouts of BLOC-1-specific subunits are tolerated in all animal systems analyzed, knockout of shared BLOC-1/BORC subunits BLOS1, BLOS2 or snapin or of the BORC-specific BORCS7 subunit are embryonic or perinatal lethal in mice or zebrafish[65,240,242,247,248] (but not in *C. elegans*[239], and curiously, knockout of the BORC-specific KXD1 gene is tolerated in mice[241]). Also confusing is the relationship of BORC and BLOC-1 to a yeast complex referred to as BLOC-1.[249] Yeast BLOC-1 was identified by bioinformatics analysis of *S. cerevisiae* proteins and consists of homologues of BLOS1, snapin and cappuccino, as well as three other alpha helical, coiled-coil proteins similar in size to mammalian BLOC-1 subunits, Vab2b, YGL079Wp, and YKL061Wp.[250] YKL061Wp and Vab2b have homologues only in fungi, but YGL079Wp contains a KxDL (Lys-x-Asp-Leu) domain and is a homologue of the mammalian BORC subunit, KxDL.[250] The yeast BLOC-1 localizes to endosomes, and depletion of its subunits caused redistribution of yeast Rab5, Vps21, from endosomes to the vacuole, but did not affect sorting of AP-3 cargo.[249] Therefore, it is unclear if this complex corresponds to mammalian BLOC-1, BORC, or a hybrid complex.

BLOC-2.

BLOC-2 subunits and HPS models.—BLOC-2 is comprised of three large subunits, HPS3, HPS5, and HPS6, the genes for which are mutated in corresponding HPS variants and mouse models of the disease.[251-255] HPS patients with BLOC-2 mutations tend to have a mild form of the disease with no lung or immune involvement, although bleeding tendency can be severe.[42-44,256] Genes encoding BLOC-2 subunits are conserved in vertebrates, and the *Xenopus tropicalis* HPS6 homologue is required for normal melanophore and iridophore formation.[73] Additionally, a *Drosophila* HPS5 homologue is required for normal eye pigmentation.[81,257] BLOC-2 mouse mutants have milder hypopigmentation phenotypes than BLOC-1 mutant mice, and choroidal melanosomes are aberrantly clustered.[172,252,253,255] Excessive bleeding in BLOC-2-deficient mice and HPS patients might be exacerbated by defects in the maturation and secretion of Weibel-Palade bodies in endothelial cells.[258,259] Upon endothelial cell damage, vWF is released from Weibel-Palade bodies into long strings that capture platelets in the blood circulation[260]; hence, the combined defects in endothelial vWF packaging and release and in platelet dense granule formation and release may impact bleeding susceptibility more in BLOC-2 mutants than in other HPS variants.

BLOC-2 function in tubular cargo transport carrier targeting.—The molecular function of BLOC-2 during LRO biogenesis is incompletely known, but is best understood in the context of melanosome maturation. Like BLOC-1, BLOC-2 in melanocytic cells

localizes to tubular endosomes, and a cohort of BLOC-1 and BLOC-2 physically interact[165], suggesting that BLOC-1 and BLOC-2 function in the same pathway. Consistently, BLOC-2 influences the melanosomal delivery of BLOC-1-dependent cargoes, including TYRP1, OCA2, ATP7A, and a cohort of TYR, from early endosomes in mouse melanocytes[165,219] (Figure 3, step 2), and labeling patterns for TYRP1 and TYR are altered in melanocytes from patients with HPS3, 5 or 6.[44,261-263] The cargoes are not uniformly trapped in early endosomes, however, and rather are widely distributed among endosomal compartments, melanosomes, the Golgi and the plasma membrane.[215,219] Dynamic analyses of endosomal transport in BLOC-2-deficient mouse melanocytes support a role for BLOC-2 in directing the BLOC-1-dependent endosomal tubules specifically to maturing melanosomes (Figure 3). Live cell imaging analyses show that BLOC-2 is required for melanosome-destined tubular carriers to make stable contacts with maturing melanosomes; in the absence of BLOC-2 these tubules form at the same rate, but they are shorter-lived, make fewer contacts with melanosomes, and the contacts they make are of shorter duration.[219] As a consequence, BLOC-1-dependent cargoes enter the recycling endosome-like tubules, but are delivered to classical targets of such endosomes – the Golgi and the plasma membrane – resulting in increased cycling through these organelles.[219] Whether BLOC-2 functions in a similar capacity in other cell types is not yet known.

How BLOC-2 promotes the contact of recycling endosomal tubules with melanosomes is unknown, but might reflect either a classical membrane tethering function[264] or a stabilizing function for the membrane tubules along microtubules or with the KIF13A kinesin-3 motor. Consistently, pull-down experiments suggest that the stalk domain of KIF13A might interact with BLOC-2, perhaps in association with RAB22.[226] When overexpressed in HEK293 cells, the HPS6 subunit was found to coprecipitate with the dynactin p150glued subunit[265], but it is not clear if this reflects a physiological function of intact BLOC-2. Moreover, depletion of HPS6 in HeLa cells or fibroblasts associated with lysosomal dispersal[265], contrary to the effects on the remaining pigment granules in BLOC-2-deficient melanocytes.[219] Clearly, more work needs to be done to resolve the molecular mechanism underlying BLOC-2 function.

BLOC-3, RAB32 and RAB38.

BLOC-3 subunits, activity, and HPS models.—BLOC-3 is a two-subunit complex consisting of the products of the HPS1 and HPS4 genes[41,266,267]. HPS1 and HPS4 have limited homology to the MON1 and CCZ1 subunits of the guanine nucleotide exchange factor (GEF) for the small GTPase, RAB7.[268,269] Accordingly, Gerendopoulos *et al.* found that BLOC-3 has GEF activity for two highly related small GTPases, RAB32 and RAB38[270], that had been previously implicated in the biogenesis of melanosomes[271-273], platelet dense granules[274,275], AT2 lamellar bodies[59,276], *D. melanogaster* eye pigment granules[82,277] and *C. elegans* gut granules.[91,94] Indeed, *Rab38* mutations underlie the pigmentation and vision defects in *chocolate* mice[55,56,273] and an HPS-like disorder in Fawn-hooded and Tester Moriyama rats.[58,278] Depletion of HPS1 or HPS4 in melanocytic cells resulted in mislocalization[270] or cytoplasmic displacement[224] of RAB32 and/or RAB38-GFP, and *Hps1* gene knockout in an AT2 cell line resulted in RAB38 mislocalization[62], suggesting that BLOC-3 is the major GEF for RAB32/RAB38 in these

cell types. Interestingly, in *C. elegans* the RAB7 and RAB32 homologues are activated by different GEFs that share the same CCZ1 subunit but distinct MON1 orthologues and that function respectively in lysosome and gut granule (LRO) biogenesis.[94,279]

BLOC-3 and RAB38/32 function in melanosome biogenesis.—A cellular function for BLOC-3 and its target Rabs has been best characterized in melanocytes. Depletion of both RAB32 and RAB38 from melanocytes led to mislocalization of melanosome cargoes such as TYRP1 and TYR[271], and the data suggested that RAB32 and RAB38 function largely redundantly in this system. Consistent with a role in forward trafficking to melanosomes, immunofluorescence and immunoelectron microscopy analyses of endogenous or epitope-tagged RAB32 and RAB38 isoforms suggested that these Rab proteins localize largely to melanosomes, as well as to tubulovesicular structures in proximity to melanosomes and the Golgi.[224,270-272] Such a function in cargo trafficking to melanosomes would explain how HPS1 and HPS4 patients suffer from oculocutaneous albinism, and how depletion of HPS1, HPS4 or RAB32 from a human melanoma cell line resulted in a loss of pigmentation.[270] However, unlike AP-3, BLOC-1 and BLOC-2, BLOC-3 is not absolutely required for pigmentation in mice. For example, *pale ear* and *light ear* mice that bear inactivating mutations in *Hps1* and *Hps4*, respectively, have – as the name suggests – pigment dilution in the skin and eyes but not in the hair.[280] Indeed, melanosomes in melanocytes from the hair bulb or choroid of these mice are normally pigmented and enlarged[281-283], as are those in immortalized melanocytes from these lines[224], whereas melanosomes in the retinal pigment epithelia and interfollicular melanocytes of the skin are small, poorly melanized, and largely depleted.[282-284] The intact pigmentation and enlargement of melanosomes in some pigment cell types lacking BLOC-3 are inconsistent with a primary requisite function in anterograde cargo transport to melanosomes.

Rather, BLOC-3 and its target Rabs seem to play a primary role in retrograde transport from melanosomes[224] (Figure 3, step 4). Melanosomes from “wild-type” black mice emit short, motile tubules that are enriched in VAMP7, a vesicular SNARE fusion protein required for BLOC-1-dependent anterograde cargo traffic.[224,285] These tubules are also enriched in RAB38 and its effector, VARP[224], a scaffolding protein that engages VAMP7 and plays a role in melanosome biogenesis[286] (Figure 3, step 4). RAB38 and VARP recruitment to melanosomes - and consequent formation of the VAMP7-containing tubules - is drastically reduced in BLOC-3-deficient *pale ear* or *light ear* melanocytes, despite only a minor reduction in melanosome components.[224] These data suggest that RAB38 and BLOC-3 function directly in recycling from melanosomes and perhaps not in anterograde traffic via the BLOC-1- or AP-3-dependent pathways. The large melanosome phenotype might result from the accumulation of uninhibited VAMP7 on melanosomes, driving dysregulated fusion with other melanosomes and perhaps with autophagosomes and/or lysosomes.[287-290] By contrast, hypopigmentation in other BLOC-3-deficient melanocytes might reflect the loss of VAMP7 recycling. We speculate that the ultimate destinations for the retrograde VAMP7-containing tubules are early endosomes; if this is true, then the failure to recycle VAMP7 in some cells might deplete VAMP7 from early endosomes, the source of anterograde cargoes, and thus secondarily impair anterograde transport. A differential requirement for this recycling pathway to supply endosomal VAMP7 might therefore explain the differing

phenotypes in distinct pigment cell types in *pale ear* and *light ear* mice and in HPS1 and 4 patients.

RAB32 and RAB38 might have additional functions in melanocytes. Both Rab proteins have been shown to associate physically with AP-3, AP-1 and BLOC-2 in melanocyte extracts[272], suggesting potential roles in anterograde trafficking. Another effector of both Rabs is Myosin Vc, knockdown of which also impacts anterograde trafficking of melanosome cargoes in a human melanoma line.[291] Moreover, depletion of RAB32 alone or of Myosin Vc results in destabilization of DCT[272,291], a cargo of a distinct RAB6-dependent trafficking pathway from the TGN/Golgi to melanosomes[222], suggesting that RAB32 might specifically tether RAB6-dependent cargo carriers to melanosomes in an anterograde pathway. It is possible that RAB32 and/or RAB38 coordinate traffic into and out of melanosomes, such that retrograde tubules emanate only at sites of input from one or more of the anterograde routes. This would provide a homeostatic mechanism to maintain a constant amount of melanosome limiting membrane, accounting for the maintenance of melanosome size during maturation. Interestingly, another myosin, Myosin VI, functions in collaboration with the branched actin regulators WASH and Arp2/3 in severing retrograde tubules from melanosomes. As a consequence, melanocytes depleted of Myosin VI are impaired in pigment transfer to keratinocytes, perhaps due to a lack of maturation.[292] Whether Myosin VI is recruited to melanosomes by RAB32 or RAB38 is not yet known; if so, it might suggest that BLOC-3 and its target Rabs facilitate melanosome maturation to a secretory organelle in epidermal melanocytes.

BLOC-3 and RAB32/38 function in the lung.—Precise pathway functions for BLOC-3 or RAB32/38 in other cell types are less clear. BLOC-3 and RAB38 play critical functions in the maturation of lamellar bodies in AT2 cells, but how is not known. RAB38 localizes to lamellar bodies in AT2 cells[276], and AT2 cells lacking either RAB38 or BLOC-3 subunits have greatly enlarged lamellar bodies with altered surfactant contents.[32,59,276] A long-term consequence of this effect on AT2 cells in HPS1 and HPS4 patients is a progressive lung fibrosis that is typically lethal in the 5th decade of life.[29] Modeling of the disease in double *Hps1*/*AP3b1*-deficient mice[31,176] – and more recently in single *Hps1*- or *Ap3b1*-deficient mice treated with bleomycin[30,174] – indicates that the affected lung epithelium hypersecretes nitric oxide synthase and the chemokine MCP-1.[31,34] Both of these factors activate alveolar macrophages to hypersecrete additional chemokines, inflammatory cytokines and TGFβ, all of which contribute to AT2 apoptosis and fibrotic macrophage infiltration.[33,34,174] Increased circulating levels of galectin-3 and of chitinase 3-like-1 protein, a cytokine that stimulates fibroproliferative repair in the lung, also contribute to enhanced fibrosis and AT2 apoptosis.[293,294] The molecular mechanisms by which BLOC-3 or its target Rabs might enhance chemokine secretion by AT2 cells are not clear, but recent development of an HPS1 model in an AT2 cell line that recapitulates phenotypes of primary AT2 cells, including increased MCP-1 production[62], will likely accelerate discovery in this area.

BLOC-3 and RAB32/38 function in inflammation.—Although the primary effect of BLOC-3 and RAB32 in lung fibrosis (at least in mouse models) is mediated by AT2 cells[174],

their depletion impacts macrophages and monocytes directly in their ability to restrict bacterial infections. RAB32 is highly expressed in macrophages and monocytes[295], and both RAB32 and RAB38 accumulate on phagosomes or vacuoles harboring several pathogenic bacteria following phagocytosis.[296-298] Intriguingly, RAB32 and RAB38 are targets of a bacterial effector protease, GtgE, secreted into the cytosol of infected macrophages by the type III secretion system of *Salmonella* Typhimurium, a pathogen of both mice and humans. *S. typhi*, a related pathogen, lacks GtgE and is thus unable to establish a productive infection in wild-type mice but effectively infects *Hps4*-deficient mice.[297] *S.* Typhimurium also secretes a RAB32 GAP, and loss of both the protease and the GAP impairs virulence in wild-type but not *Hps4*-deficient mice.[299] The mechanism by which this restriction occurs is not clear, but overexpression of a dominant negative form of RAB32 in a macrophage cell line impaired the recruitment of cathepsin D to latex bead phagosomes[296], suggesting a possible role for RAB32 in facilitating phagosome/lysosome fusion in this cell type.

In addition to oculocutaneous albinism, bleeding diathesis and lung fibrosis, a subset of HPS1 and HPS4 patients (~20-30%) suffer from a debilitating form of inflammatory bowel disease, referred to as granulomatous colitis.[29] The incidence of this symptom does not appear to be related to genotype and likely reflects heightened sensitivity of HPS1 and 4 patients to an environmental trigger. The cellular and molecular basis for this susceptibility is not yet known, but might reflect a unique role for BLOC-3 and RAB32/38 in epithelial cells or secretory cells of the gut. Alternatively or additionally, since heritable forms of inflammatory bowel syndrome are often associated with innate immune defects[300,301], the impact of BLOC-3 and RAB32 in macrophages and monocytes might underlie the susceptibility. Consistent with the latter, conditional knockout of *Rab32* in $CD11c^+$ cells (dendritic cells, monocytes and other innate immune cells) causes increased susceptibility to dextran sodium sulfate-induced colitis and enhanced production of proinflammatory cytokines and chemokines.[302] It will be important to validate this finding in the human system and to determine if the inflammatory response underlies the susceptibility to colitis in HPS1 and 4 patients.

HOPS and CORVET.

HOPS and CORVET subunits and model systems.

The HOPS and CORVET complexes play critical roles in membrane tethering and fusion within the early endosomal and endolysosomal pathways, respectively.[303-307] Both complexes contain the class c core complex (VPS-C) comprised of VPS11, VPS16, VPS18 and VPS33A.[303-305,308,309] Complex specificity is dictated by the CORVET-specific subunits VPS3 and VPS8[305] and the HOPS-specific subunits VPS39 and VPS41.[308,309] The genes encoding all HOPS and CORVET subunits are highly conserved across species[310,311] with a few exceptions. Of the two complexes, HOPS has been better studied in both yeast and higher eukaryotic model systems. HOPS functions to bind and tether apposing membranes through interactions between its HOPS-specific subunits and either ras-like GTPases or adaptor proteins.[312-314]

The HOPS subunits were initially discovered in screens to identify genetic mutants that interfered with protein sorting to the vacuole (vacuole protein sorting or vps mutants) in the

yeast, *Saccharomyces cerevisiae*.[315,316] Null mutations in the genes encoding any of the four VPS-C subunits, Vps11p, Vps16p, Vps18p, or Vps33p, were sufficient to cause major defects resulting in loss of recognizable vacuoles, an accumulation of small vesicular structures, and decreased processing of vacuolar proteins.[315-317] Unsurprisingly, most studies of HOPS and CORVET that have been done in yeast as null mutations are lethal in higher eukaryotes.[85,86,306,318] However, many interesting questions about the functions of HOPS and CORVET have been raised by studying hypomorphic alleles of subunit genes. In particular, several HOPS or CORVET subunit mutations cause LRO defects in *Drosophila*, *C. elegans*, *Tetrahymena* or vertebrate models[52,84-87,91,94,120,306,319,320], suggesting a possible specific role for VPS-C in LRO biogenesis.

HOPS and CORVET function as endosomal tethers and SNARE regulators.

The architecture of the HOPS complex has been most clearly defined using single particle negative stain electron microscopy analysis of HOPS purified from yeast. These studies reveal a seahorse shape with a large head region, a smaller tail region[321], and the HOPS-specific subunits Vps39p and Vps41p at either end, thereby providing a model of how HOPS facilitates tethering of apposing membranes.[321,322] In yeast models, Vps39p and Vps41p both tether membranes through direct interactions with the RAB7 homologue.[308,309,322,323] By contrast, mammalian VPS39 and VPS41 have not been shown to directly engage RAB7, but rather bind to late endosomes, lysosomes, and autophagosomes through the adaptor proteins RILP[313] and PLEKHM1[312] and the small GTPase ARL8b.[312] Accordingly, knockdown of VPS-C subunits in mammalian cells results in endosome-lysosome and autophagosome-lysosome fusion defects[307,324,325], and a point mutation in *VPS11* appears to cause an autosomal recessive form of leukoencephalopathy associated with dysfunctional autophagosome: lysosome fusion.[326]

Whereas the major role of the VPS-C proteins VPS11, VPS16A, and VPS18 seems to be in organizing the complex for tethering function[321,323,327], core protein VPS33A is a member of the Sec1/Munc18 (SM) family of proteins[308,327-331]; hence, it binds syntaxin family SNAREs[328,332], facilitates SNARE complex assembly in order to overcome the energy barrier for membrane fusion[329,330,333], and protects SNARE complexes from premature disassembly.[334] Upon VPS41- and VPS39-dependent membrane tethering, VPS33A binds lysosomal and autophagosomal SNARES[307] to catalyze SNARE complex formation and fusion; it is as yet unclear whether VPS33A can bind a single syntaxin t-SNARE or prefers 3- and/or 4-helical SNARE bundles.[321,328,335,336] Structural models suggest how VPS33A binds t- and v-SNAREs.[330,331] Overlapping data on the structure of *C. thermophilum* Vps33 with the syntaxin/Qa-SNARE orthologue Vam3 bound to domain 1 or with the v-SNARE Nyv1 bound to domain 3a suggest that both SNAREs can bind simultaneously, aligning the two SNAREs such that they are in register to form a partially zippered SNARE pair.[330] *Vps33* mutations that are predicted to impact SNARE binding disrupt proper fusion and maturation in the yeast endolysosomal pathway[330], demonstrating that SNARE binding is critical for Vps33p function. Specifically, *Vps33* mutations along the predicted v-SNARE binding region reduced v-SNARE binding and induced accumulation of small vacuoles, whereas introduction of a *Vps33* deletion predicted to disrupt both v-SNARE and t-SNARE

binding phenocopied complete loss of Vps33p expression.[330] Thus, binding to both vSNARE and tSNARE appears to be critical for VPS33 function.

HOPS and CORVET functions in LRO biogenesis.

A number of HOPS subunit mutations in animal models cause HPS-like phenotypes, implicating HOPS in LRO biogenesis. In *C. elegans*, knockdown or mutation of HOPS subunits results in a loss of gut granules.[91,94] Null mutations in *vps18* and *vps11* in zebrafish[319] and medaka[320], respectively, cause hypopigmentation due to fewer melanosomes in epidermal and retinal pigment epithelia, suggesting a role for VPS-C in the biogenesis of melanosomes. In *D. melanogaster*, HOPS subunit genes – including those encoding homologs of VPS18[85], VPS41[87], VPS16A[83,84] and VPS33A[85,306,337] – are among the granule group of genes that function in the formation of eye pigment granules.[83,85,87] Deletion or loss of function alleles of the VPS18[85,86], VPS41[87], or VPS33A[306] homologs are lethal as these genes are required for normal trafficking to lysosomes; however, hypomorphic alleles and clonal knockouts of these genes or the VPS16A homolog in the eye cause changes in eye color due to defective protein trafficking to pigment granules.[83,84,306,338] Flies with eye-specific knockdowns of HOPS subunits have strong retinal degeneration characterized by defective trafficking to lysosomes, aberrant autophagosome accumulation, and loss of Type I and Type II pigment granules.[84,306,338] Interestingly, null mutations of *Syntaxin 17*, encoding the autophagosomal SNARE conserved in flies and mammals, result in an accumulation of autophagosomes[339] but no change in eye color[338], suggesting that the LRO defect in HOPS mutants is not a consequence of defective autophagosome-lysosome fusion and must involve a distinct tSNARE.

VPS33A mutations and HPS.

The mouse model *buff* (*bf*) most closely links a HOPS subunit mutation to HPS.[52] *Buff* mice harbor a point mutation in *Vps33a*, and have an autosomal recessive phenotype that is similar to other mouse HPS models characterized by coat hypopigmentation[52,340], decreased melanosome number and size in the RPE[52], and prolonged bleeding times associated with decreased ATP secretion and dense granule count in platelets.[52,172] The causative mutation, a missense mutation of a conserved residue of VPS33A (D251E)[52,340], lies in a region predicted to interact with the v-SNARE – most likely VAMP7.[327] Therefore, the HPS phenotypes observed may be due to altered v-SNARE binding to VPS33A, impairing the ability of CORVET and HOPS to properly couple tethering and SM activity in the biogenesis of melanosomes and platelet dense granules. However, whether the coat color defect reflects a defect in melanosome biogenesis per sé is not completely clear. Two reports suggest that cultured or *in situ buff* melanocytes are hypopigmented and harbor more immature melanosomes[52,341], whereas another report suggests that cultured *buff* melanocytes are normally pigmented.[342] Hypopigmentation in the eye is also only partial[52,340,343], perhaps reflecting the hypomorphic nature of the *buff* mutation. Interestingly, fusiform vesicles (FVs) - a secretory granule-like putative LRO found in urothelium - accumulate as multivesicular bodies in *buff* mice[344], suggesting a possible role for VPS33A in their trafficking or maturation as well.

Several groups have attempted to uncover the effect of the *buff* mutation on VPS33A function.[328,345] Unlike *vps33* null mutations, introduction of an orthologous *bf* mutation in yeast Vps33p (D300E) has no effect on growth rate, vacuole morphology, or protein trafficking to vacuoles.[328] However, a more dramatic change at this residue, D300G, causes Vps33p mislocalization, zinc-dependent growth defects at non-permissive temperatures, and partial defects in protein trafficking to the vacuole.[328] These data support an important function for this conserved residue and suggest that its mutagenesis might impact function under specific conditions. Zhen and Wei proposed that the *buff* mutation increases the affinity of VPS33A for v-SNAREs, hypothesizing that this decreases the rate of v-SNARE release and disrupts fusion by limiting the concentrations of available VPS33A and v-SNARE.[345] However, additional work is needed to validate these conclusions and to understand the full effect of the *buff* mutation on VPS33A function and its role in LRO biogenesis.

Several human disease variants of VPS33A have been reported but not carefully studied. Suzuki et al report one HPS patient with no mutations in *HPS1*, *HPS2*, *HPS3*, and *HPS4* but a mutation in VPS33A resulting in a I256L replacement[52], which falls within domain 3a adjacent to D251; in fact, the *buff* mutation is predicted to disrupt the normal interaction between D251 and I256.[327] However, it is unclear if the conservative I256L replacement is causative for the disease, and verification of this or other VPS33A mutations in HPS patients has not been reported. Another homozygous VPS33A mutation – R498W, predicted within the VPS16-interacting region of VPS33A – was identified in patients with systemic effects that appear to stem from lysosomal dysfunction[346,347], but these patients showed no obvious signs of HPS. The mechanisms underlying the different functional effects of distinct VPS33A mutations warrant further experimental attention.

Additional disorders of LRO biogenesis, secretion and motility

Chediak-Higashi syndrome.

Like HPS, CHS is characterized by a variable, often mild oculocutaneous albinism and excessive bleeding and bruising. However, the major symptom is immune system dysregulation that often leads to a lethal hemophagocytic lymphohistiocytosis (HLH) in an "accelerated phase" due to impaired cytotoxic T cell and NK cell activity and consequent lymphoproliferation and hyperinflammation.[348] Surviving patients suffer from a late-onset neurological impairment.[349] The symptoms reflect defects in lysosome and phagosome maturation[350], concomitant with the formation of giant enlarged lysosomes and LROs that cannot be secreted.[351,352] The defective gene, LYST or CHS1, encodes a ~4000 amino acid protein with several identifiable protein domains including BEACH, pleckstrin homology, WD40 repeats, perilipin-like, lectin-like, and HEAT/Armadillo-like repeats.[353-358] LYST is thought to either promote fission of endolysosomal organelles or prevent their fusion[115,359,360], as the giant organelles in cytotoxic T cells, NK cells and other cell types from CHS patients or its *beige* mouse model contain markers of both late endosomes/lysosomes and early endosomes.[361,362] However, the mechanism by which LYST does so is not yet clear. In a *Dictyostelium* model, the LYST orthologue LvsB appears to function by antagonizing homotypic lysosomal fusion mediated by RAB14.[115] Accordingly, knock

down of RAB14 in a human LYST-deficient NK cell line restored normal lytic granule number, size and agonist-stimulated secretion.[363] The latter study also suggested that the large size of the granules in LYST-deficient NK cells impeded their secretion through the cortical actin network at the immunological synapse, and that granule secretion in these cells was normalized by actin depolymerization.[363] LYST also plays a role in phagolysosomal maturation, resulting in defective TRIF/TRAM-dependent signaling by toll-like receptors 3 and 4 in LYST-deficient macrophages and dendritic cells and consequent impaired innate immune responses to bacterial pathogens.[350] Similarly, the *D. melanogaster* LYST orthologue prevents fusion of incompletely matured phagosomes.[364] LYST's enormous size has impeded mechanistic analysis of its mode of action, but analyses of cells from an increasing cohort of identified patients with missense mutations might provide key insights into the function of specific domains.[362]

Arthrogryposis, renal dysfunction, and cholestasis syndrome (ARC).

Arthrogryposis, renal dysfunction, and cholestasis (ARC) syndrome is a heritable autosomal recessive multisystem disorder characterized by arthrogryposis (congenital joint contracture), kidney tubule acidosis, cholestasis (failure of the liver to secrete bile), bleeding diathesis, and failure to thrive, among other characteristics.[365-368] Most patients do not survive past their first year due to metabolic decompensation, recurrent infections, and/or uncontrolled bleeding.[367,369] ARC is caused by loss-of-function mutations in the genes encoding either VPS33B or VIPAR (a.k.a. VPS16B or SPE-39).[367,368,370-376] Like VPS33A, VPS33B is a homolog of yeast Vps33p and is an SM protein.[310,377] However, VPS33A and B are functionally distinct and cannot compensate for each other.[306,378] Moreover, neither VPS33B nor VIPAR is incorporated into the CORVET or HOPS complexes.[84,324,327,379] Instead, VPS33B and VIPAR together form the class c homologs in endosome-vesicle interaction (CHEVI) complex.[84,324,327,374,379,380] Data from *C. elegans*[381,382], *D. melanogaster*[376,383], and zebrafish[372,374] with null alleles, mice with loss-of-function mutations[369,383-385], and ARC patient samples[370,373,374,386] indicate that the CHEVI complex functions in specific, context-dependent trafficking pathways that differ among specialized cell types. For example, the cholestasis observed in ARC patients likely reflects a role for the CHEVI complex in apical recycling in polarized epithelial cells.[370,374,384] Resident membrane proteins in hepatocytes that are continuously recycled to apical membranes via apical recycling endosomes (e.g. bile salt export pump and claudin-1) are mislocalized throughout the plasma membrane in CHEVI-deficient cells, but other resident apical membrane proteins that do not undergo recycling (e.g. multiple drug resistance-associated protein 2) are not.[370,374,384] In other cell types, the CHEVI complex functions in the biogenesis and/or trafficking of LROs such as platelet α-granules[369,371,386] and skin lamellar bodies[373,385], explaining the excessive bleeding and ichthyosis, respectively, in ARC patients. In Drosophila hemocytes and mammalian macrophages, the CHEVI complex is necessary for the fusion of phagosomes with lysosomes during phagosome maturation and for clearance of internalized toll-like receptors from endosomes[376,383]; the latter underlies hyperstimulation of inflammatory signaling in VPS33B-deficient cells.[383] Lastly, in *C. elegans*, the CHEVI subunit orthologues are required for formation of an LRO in spermatocytes called the membranous organelle.[381,382] How CHEVI regulates these events is not entirely clear, but a recent report on the VPS33B

protein interactome provides some potential clues.[379] Specifically, VPS33B interacts with CCDC22, a member of the CCC complex that functions together with the WASH complex to effect endosomal recycling[387], and with VPS53, a subunit of the Golgi-associated retrograde protein (GARP) complex and endosome-associated recycling complex (EARP)[380], both of which function as tethers during endosomal recycling. Overall, these studies suggest that the CHEVI complex functions in context-dependent, tissue-specific endosomal trafficking pathways, perhaps by regulating endosomal recycling.

Gray platelet syndrome.

GPS is a heritable disorder in which platelets from hematoxylin stained blood smears appear gray because they lack contents in their alpha granules.[388] This is accompanied by macrothrombocytopenia and typically mild but occasionally severe excessive bleeding and bruising. Most GPS patients[389] bear loss-of-function mutations in the gene encoding NBEAL2, a ~2800 amino acid protein with many of the same structural features as LYST, the causative agent of CHS.[390-392] Mice lacking a functional NBEAL2 gene phenocopy the human disease.[393-395] Like for LYST, a molecular understanding of NBEAL2 function is lacking. A recent study identified several potential binding partners for the NBEAL2 BEACH domain including the putative ER exit site regulator SEC16A, the scaffolding protein VAC14 for the phosphatidylinositol-3-phosphate 5-kinase and phosphatase, and the RAC1/CDC42 GTPase exchange factor DOCK7[396], suggesting potential roles in late endosomal maturation required for alpha granule biogenesis[397] and/or for actin-dependent signaling processes. Intriguingly, RAC1 has been implicated in platelet spreading and secretion of factors stored in alpha granules[398-401], although many of these studies rely on inhibitors with potential off-target effects.[402]

Griscelli syndrome.

GS types 1-3 and the corresponding mouse mutants reflect defects in the three components of a complex required for melanosome positioning within skin melanocytes: the unconventional myosin Va (MYOVA), the Rab GTPase RAB27A, and a linker between them, melanophilin (MLPH).[403] RAB27A associates directly with mature melanosomes and, via the linker MLPH, engages a melanocyte-specific spliced isoform of MYOVA to allow for peripheral melanosome capture and motility on actin filaments.[404-411] Consequently, melanocytes deficient in any of these components accumulate melanosomes near the microtubule organizing center and fail to efficiently transfer melanosomes to keratinocytes. This results in hypopigmentation of the skin and hair in GS1, 2 and 3 patients and corresponding mouse models.[412-414] Interestingly, MLPH that has not been phosphorylated by protein kinase A can bind to microtubules in vitro and relocate the associated MYOVA and RAB27A from actin filaments to microtubules; this might provide a mechanism for protein kinase A-dependent regulation of melanosome localization in vivo.[415] MLPH function in RAB27A-dependent organelle motility appears to be limited to skin melanocytes, and hence GS3 patients display pigment dilution in the skin and hair, but not in the eye.[413] RAB27A-dependent melanosome motility in retinal pigment epithelium employs a distinct adaptor, MYRIP, and a different myosin, MYOVIIA.[416,417]

By contrast to MLPH, MYOVA and RAB27A function in other physiologically critical venues, and hence most GS1 and GS2 patients suffer more severe consequences. MYOVA plays a number of important roles in development, secretion, plasticity, and signaling in the neuronal system.[418] Therefore, GS1 patients suffer from neurological impairment of varying severity (depending on the site of the mutation - for example, patients with mutations in the exon encoding the melanocyte-specific tail region of MYOVA resemble GS3 patients[413]). Among many other functions, RAB27A plays a critical role in the final steps of cytolytic granule secretion in cytotoxic T cells and NK cells[14,419,420], and thus GS2 patients suffer from both immunodeficiency and accelerated phase HLH due to lymphoproliferation and an ensuing cytokine storm. In these cell types, RAB27A engages a distinct group of effector proteins including Munc13-4 (see section on FHL3 below)[14,421,422], the synaptotagmin-like proteins Slp1 and Slp2a[423,424] for tethering of lytic granules to the plasma membrane, and Slp3 at an earlier stage for kinesin-1-dependent motility of lytic granules to the plasma membrane.[425] RAB27A and the homologous RAB27B function in regulated secretion in many other cell types, but their physiological importance is not clear. For example, although RAB27A appears to function in docking insulin granules to the pancreatic β cell plasma membrane[426] and the RAB27A/MLPH/MYOVA complex plays an inhibitory role for mast cell granule secretion[427], reports of any clinical consequence in GS patients are lacking.

Familial hemophagocytic lymphohistiocytosis types 3-5.

FHL, like HLH in GS2 and CHS, is characterized by defective cytolytic granule exocytosis, leading to defects in T cell and NK cell cytolytic activity and consequent lymphoproliferation, hyperinflammation, and a life-threatening cytokine storm. In addition, patients have a bleeding and bruising tendency due to defective platelet granule secretion. Whereas the gene underlying FHL1 has not been identified, and mutations in the gene encoding the cytolytic effector perforin underlie FHL2[428], FHL3-5 are due to mutations in genes encoding the machinery required for secretion of lytic granules, platelet alpha and dense granules, and other regulated secretory organelles – specifically UNC13D (encoding munc13-4, mutated in FHL3)[429], STX11 (encoding syntaxin-11, mutated in FHL4[430,431]) and STXBP2 (encoding munc18-2, mutated in FHL5[432,433]). STX11 is a Qa SNARE that is part of the tSNARE complex at the plasma membrane required for cytolytic granule and platelet granule secretion.[434-437] Munc18-2 is a SM family member that specifically stabilizes STX11 in platelets and cytotoxic T cells and is required for efficient STX11 expression at the plasma membrane[438] and for granule fusion.[433,434,439] It is particularly critical to stabilize full fusion intermediates mediated by the lipid-anchored STX11.[437] Consistent with its function, a number of FHL5 mutations disrupt the binding sites on munc18-2 for STX11 or αSNAP[440] or impede release of the N-terminal STX11 peptide and thus block subsequent munc18-2 function in facilitating SNARE complex assembly.[434] Munc13 family members are thought to function in tethering and/or regulating tSNARE conformational changes required for SNARE complex assembly.[441] Accordingly, the RAB27A effector, munc13-4, functions during granule tethering to the plasma membrane in CTLs and platelets.[421,422,442] This step appears to require RAB27A, as GS2 patients with RAB27A mutations that impair its interaction with munc13-4 suffer from HLH but not pigment dilution.[443] In CTLs, munc13-4 also appears to function independently of RAB27A at an earlier step required for cytolytic granule maturation.[14] Intriguingly, HLH is not a

spontaneous feature of the mouse FHL3 model but is induced by infection[444], suggesting that FHL in humans might similarly be triggered by infectious agents.

Perspectives

Research over the last two decades has enormously expanded our understanding of LROs and the heritable diseases in which their function is impaired. Our progress to date has opened up new areas of investigation into the basic biology of LROs and has illuminated molecular mechanisms by which the endosomal system is adapted to the needs of specialized cells. At the same time, new LROs are being discovered at a steady pace, suggesting that such adaptations may be more prevalent among cell types than previously thought. Importantly, our progress has also provided a new understanding into the mechanisms of heritable diseases that impact LROs and related organelle systems. Future work will likely build on these studies by discovering novel LRO-related disorders and by developing therapies for them.

Our progress to date in understanding LROs has largely been driven by the intensive study of specific model systems, particularly mammalian melanosomes, cytolytic granules, and Weibel-Palade bodies and several of the invertebrate model LROs (Figures 1, 2 and Table 1). These studies, driven by the identification of specific cargo transmembrane proteins and the availability of reagents to follow their fate under various genetic manipulations, have particularly illuminated the commonalities and diversity of LRO assembly pathways (Figure 2). We now need to build on these studies to gain specific insights into other medically relevant LROs. For example, we have only scratched the surface in understanding the contents and delivery pathways for lung lamellar bodies or platelet dense and alpha granules, defects in which underlie the lung fibrosis and excessive bleeding in HPS and GPS. Studies of these systems are likely to yield interesting surprises. For example, recent evidence suggests that dense granules do not mature until the final stages of platelet formation from megakaryocytes.[445] Understanding the temporal regulation of this step will likely lead to new ideas regarding signaling pathways that can regulate LRO biogenesis in specific cell types. Similarly, understanding the complex network of protein: protein interactions among NBEAL2, the CHEVI complex, and other effectors that are essential for alpha granule formation may allow us to better understand how these enigmatic organelles segregate from the late endosomal system.[446] An important contribution to our understanding will be the identification of relevant cargoes for each LRO system; availability of such cargoes and reagents to easily detect them will allow a rapid test of whether the paradigms generated in better studied systems to date apply more generally to other LROs.

Non-mammalian model systems will likely play increasingly important roles in dissecting the physiological functions of LRO biogenetic and secretion effectors. The ability in many of these systems to combine mutations and to identify gene modifiers will extend known gene interaction networks. Combining data from analyses from such tractable genetic systems with the increasingly available complex interactomes from proteomics data in mammalian systems will provide important tests of the functionality of interaction partners and their importance in the physiology of new LROs. We thus should expect more robust

molecular detail in our models of LRO biogenesis, motility and secretion in the coming years.

While diseases such as HPS, CHS and GS have opened new avenues of basic science research over the last two decades, we can expect more insights to come from new diseases in the future as whole genome sequencing of patients will expand the number of candidate genes underlying LRO biogenesis and function. This has already come to light in several ways. For example, a recent publication reported screening of nearly 1000 albino patients for known albinism genes.[203] Many harbored novel mutations in known genes, and nearly 28% of the patients lacked mutations in known albinism genes; sequencing of these patients is likely to identify novel genes that contribute either specifically to melanosome biology or generally to LRO biogenesis or function. On the other side of the spectrum, sequencing of individual patients with novel syndromic disorders can identify novel genes and mechanisms in LRO biology. For example, screening of a pediatric patient with a FLH-like disease led to the identification of a novel mutation in STXBP1 with a dominant negative phenotype[434]. Thus, we can expect many new insights from analyses of patient samples in the coming years.

In turn, future studies will allow us to build on our knowledge of LROs to devise new therapies for the diseases that have taught us so much about LRO biogenesis and secretion. New modes of gene therapy, in some cases combined with bone marrow transplant for hematologic disorders, may provide relief for some symptoms of syndromic disorders. The major challenges to be overcome in this respect are symptoms arising from non-hematopoietic cell types, such as the lung AT2 cells that are the drivers of lung fibrosis in the most common HPS patients; difficulties in specifically targeting these cells for gene therapy are exacerbated by the likely short half-life of the affected AT2 cells. In cases such as this, understanding how inflammatory sequelae contribute to disease progression might uncover other treatment options.

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Synopsis

Lysosome-related organelles are cell type-specific subcellular structures that derive from both the secretory and endolysosomal pathways and that play key roles in numerous physiological systems, in most cases following stimulus-dependent secretion of their contents. The biogenesis and/or secretion of lysosome-related organelle subsets are disrupted in hereditary syndromic disorders such as the Hermansky-Pudlak syndromes and Familial Hemophagocytic Lymphohistiocytosis. We comprehensively review lysosome-related organelles in humans and model organisms and the mechanisms by which products of disease genes regulate their formation, motility and ultimate secretion.

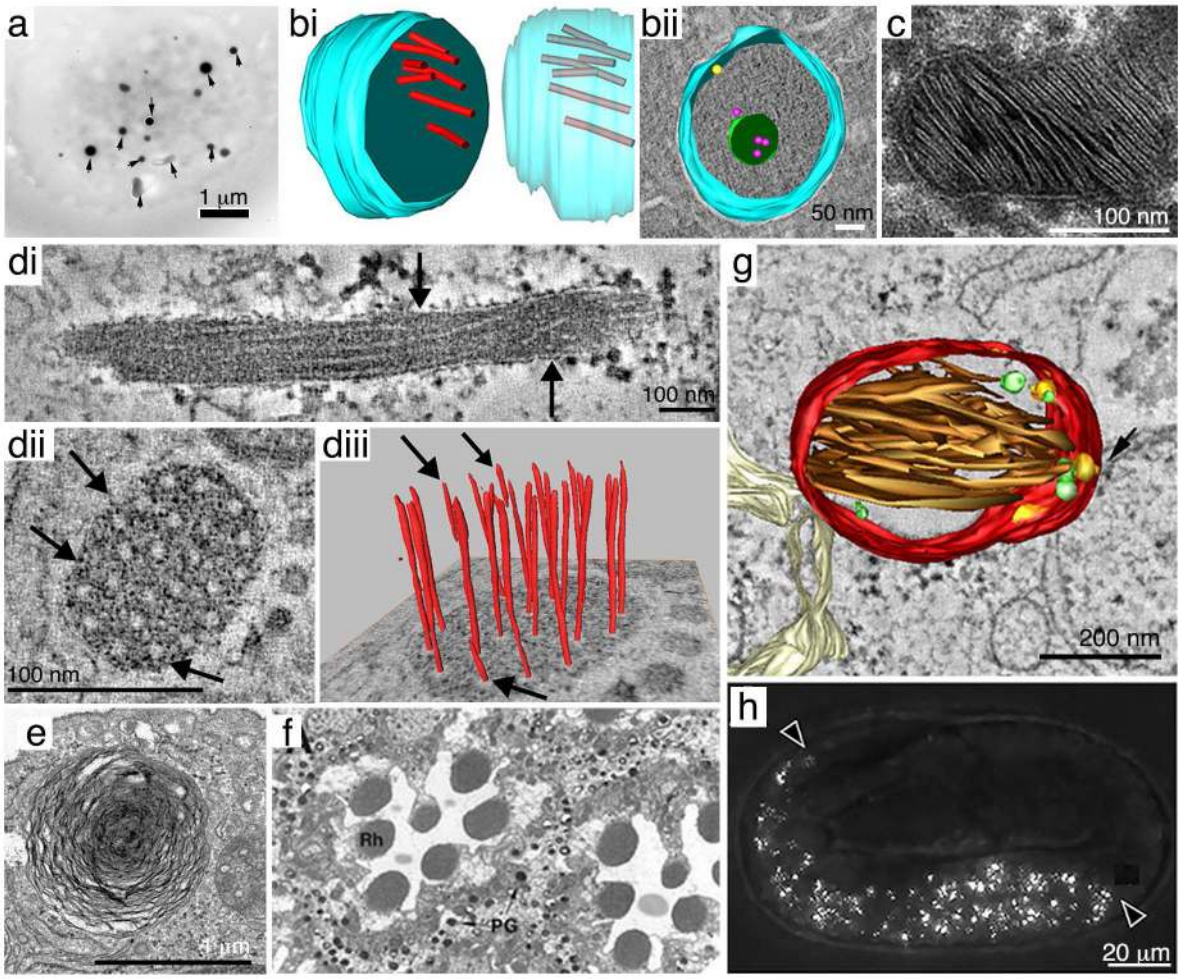

Figure 1: Examples of lysosome-related organelles.

(a) Dense granules (arrows) in a human platelet observed by whole mount electron microscopy from ref. 447. Scale bar, 1 μm. (bi – bii) 3D reconstructions of α-granules in chemically fixed human platelets analyzed by electron tomography from ref. 448. The limiting membrane is in blue. Scale bar, 50 nm. (bi) Transverse view (left) and side view with transparent membrane (right) emphasizing the arrangement of VWF tubules (red on left, red-gray on right) within the organelle. (bii) Transverse view of an alpha granule that is immunogold labeled for P-selectin (yellow) and CD63 (magenta), emphasizing an intraluminal vesicle (green). (c) A lamellar body from ex vivo human skin analyzed by thin section electron microscopy (from ref. 449). Scale bar, 100 nm. (di – diii) Electron tomography of WPBs in human umbilical vein endothelial cells from ref. 450. (di) A longitudinal tomographic slice of a WPB emphasizing vWF tubules (arrows) along the length. (dii) A transverse tomographic section of a WPB emphasizing the diameter of vWF tubules. (diii) 3D reconstruction of (dii) showing the extension of individual VWF tubules. Arrows point to VWF tubules that end halfway through the WPB. Scale bars, 100 nm. (e) A lung lamellar body from a rat type II alveolar cell analyzed by thin section electron microscopy (from ref. 451). Scale bar, 1 μm. (f) Transverse section of a wild-type *D. melanogaster* eye analyzed by thin section electron microscopy from ref. 77. Note the

pigment granules (PG) of secondary pigment cells surrounding photoreceptor cell rhabdomeres (Rh). (g) 3D reconstruction of a stage II melanosome from electron tomography analysis of a human MNT-1 melanoma cell (from ref. 452). Red, melanosome membrane; brown, intraluminal fibrils; intralumenal vesicles are in yellow (membrane-associated) or green (free). Scale bar, 200 nm. (h) Birefringent material in gut granules (arrowheads) in a *C. elegans* embryo observed by polarization microscopy (from ref. 279). Scale bar, 20 μm. All panels reprinted by permission of: (a) Taylor and Francis from *Platelets*, ref. 447, copyright 2018; (b) American Society of Hematology from *Blood*, ref. 448, copyright 2010; (c) Elsevier from the *Journal of Dermatological Science*, ref. 449, copyright 2018; (d) Elsevier from the *Journal of Structural Biology*, ref. 450, copyright 2008; (e) Springer Nature from *Pediatric Research*, ref. 451, copyright 2012; (f) John Wiley and Sons from *EMBO Journal*, ref. [77,451], copyright 1997; (g) National Academy of Sciences, U.S.A from *Proceedings of the National Academy of Sciences U.S.A.*, ref. 452, copyright 2008; and (h) *PLoS Genetics*, ref. 279.

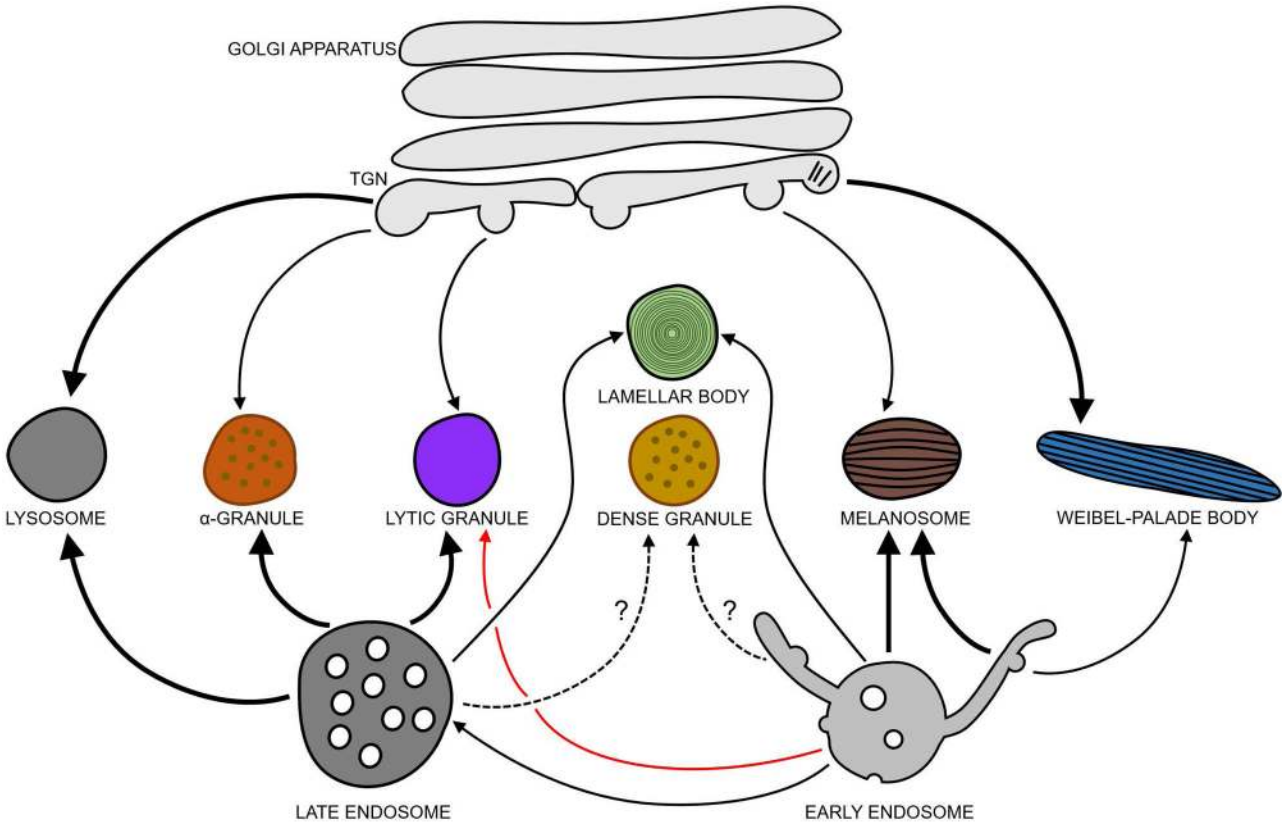

Figure 2. Biogenesis models for mammalian LROs.

Lytic granules in CTLs and natural killer cells may derive from late endosomes that fuse with secretory vesicles from the TGN, and also function as the cells' lysosomes under basal conditions. Lytic granule maturation (by fusion with early endosomal membranes; red arrow) and secretion are triggered by immune stimulation. The other indicated mammalian LROs co-exist with endolysosomes but derive from late endosomes, early endosomes, and/or the TGN as indicated. Question marks denote LRO biogenesis pathways that are not well-characterized, and thick solid lines denote pathways, where known, by which the majority of material is targeted to maturing LROs. Alpha granules obtain material from multivesicular late endosomes in platelets and likely derive from these compartments, but also receive vWF from the TGN. Platelet dense granules and lung AT2 lamellar bodies may derive components from both late endosomes and early endosomes during maturation. In pigment cell melanocytes, immature melanosomes emerge from maturing endosomes and receive transmembrane cargo via early endosomal tubule carriers, endosome-derived vesicles, and the Golgi as they mature. In endothelial cells, immature Weibel-Palade bodies harboring vWF tubules that form in the Golgi bud from the TGN and mature by addition of cargoes derived from endosomes.

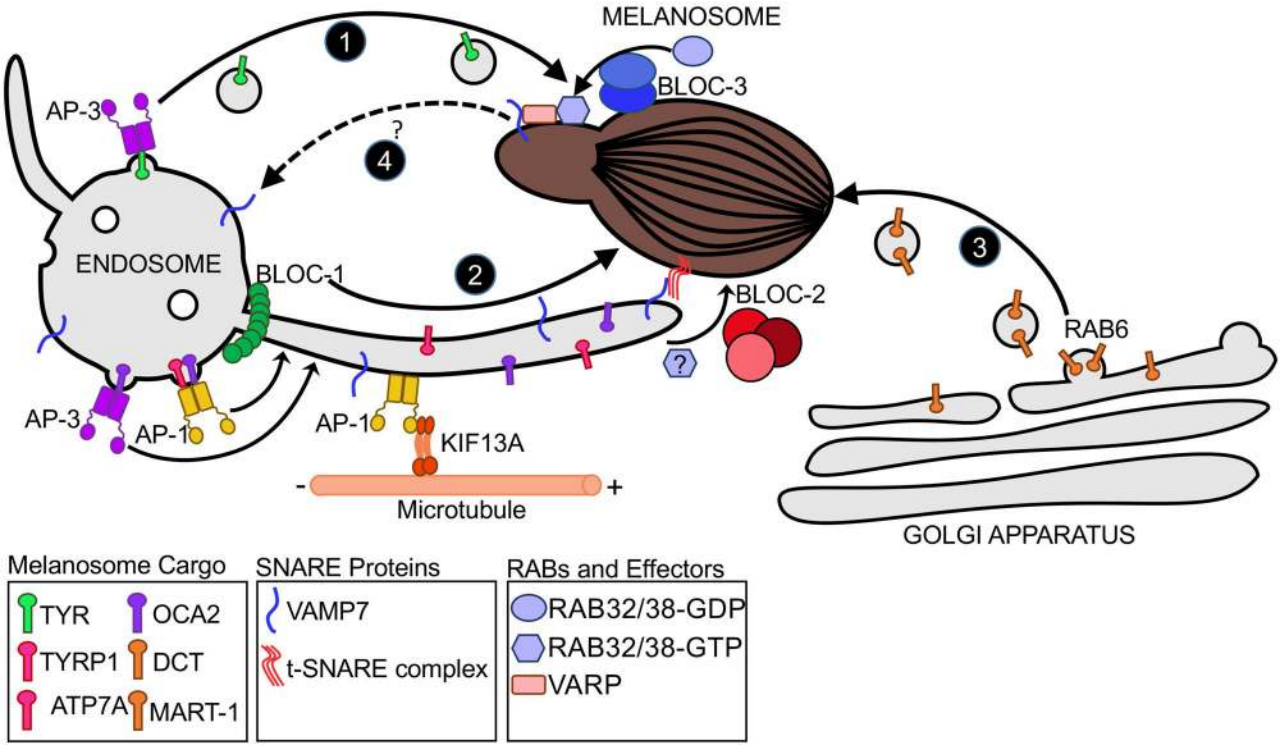

Figure 3. HPS complexes and mechanisms of cargo delivery to melanosomes.

Melanosome-destined transmembrane protein cargoes are concentrated on early endosomes by AP-3 and AP-1. The majority of TYR (green) transits a vesicular pathway that requires AP-3 (Pathway 1). Other proteins such as TYRP1, OCA2, and ATP7A, transit endosome-derived membrane tubules en route to melanosomes (Pathway 2). BLOC-1 and the KIF13A kinesin motor are required to generate the tubules along microtubules, and KIF13A is recruited to endosomes by AP-1. Cargo sorting on this pathway is mediated by AP-1 and/or AP-3; TYRP1 and ATP7A engage only AP-1, while both AP-1 and AP-3 facilitate OCA2 transport on this pathway. BLOC-2 is required to direct the tubular transport carriers to melanosome membranes, and RAB32 and/or RAB38 might also play a role in this step. Cargo delivery requires transient fusion of the tubular transport carriers with melanosome membranes mediated by the v-SNARE, VAMP7, and an unidentified t-SNARE complex. DCT and MART1 are transported to melanosomes from the Golgi Apparatus in a separate vesicular pathway that requires RAB6 (Pathway 3). VAMP7 and perhaps other cargoes are recycled from melanosomes via tubules that derive from melanosome membranes in a BLOC-3- and RAB38/RAB32-dependent manner (Pathway 4). The scaffolding protein VARP is present on these tubules and likely supports the incorporation of VAMP7 into them. The destination of these tubules is not yet known, but VAMP7 is likely ultimately returned to early endosomes.

Table 1.

LROs and their associated disease models

Lysosome-Related Organelles	Cell Types	Description	LRO disease model
LROs-Vertebrate			
Melanosomes	Melanocytes or melanophores in skin, retinal pigment epithelia and other eye pigment cells	Site of melanin synthesis and storage for photoprotection and visual acuity	HPS, CHS, GS
Lamellar bodies (mammals) or swimbladder surfactant storage organelles (teleosts)	Alveolar type II (AT2) cells	Organelles for synthesis, storage and secretion of pulmonary surfactant	HPS
Lamellar bodies / Lamellar granules	Keratinocytes	Enriched in lipids that are secreted by keratinocytes into extracellular spaces of the epidermis to form a permeability barrier	ARC
Cytolytic granules	T cells, Natural killer cells	Store granzymes, perforin and other cytotoxic proteins that induce target cell death upon secretion	FHL, GS type 2, CHS, HPS (AP-3)
Weibel-Palade bodies	Endothelial cells	Cigar-shaped secretory granules containing von Willebrand Factor and other proteins that mediate hemostasis and inflammation upon secretion	HPS (BLOC-2 and AP-3), FHL3
Alpha granules	Platelets, Megakaryocytes	Store a variety of protein factors that upon secretion mediate blood clotting, platelet adhesion, hemostasis, inflammation and vascularization	GPS, ARC
Dense granules	Platelets, Megakaryocytes (?)	Contain small molecules (e.g. serotonin, calcium, ADP and others) and polyphosphate that upon secretion enhance platelet adhesion and activation	HPS, FHL
MHC class II compartments	Activated dendritic cells, B lymphocytes, macrophages, Langerhans cells	Non-terminal late endosomes and lysosomes that are enriched in MHC class II molecules assembling with peptides	CHS
Basophilic granules	Mast cells, likely basophils	Store granzymes, heparin, histamine, serotonin, prostaglandin, and leukotrienes for secretion at sites of damage or infection to increase vasodilation	CHS, FHL
Azurophilic (primary) granules	Neutrophils, Eosinophils	Store lysosomal enzymes and anti-microbial peptides for release directly into phagosomes	HPS (AP-3), CHS
Phagosomes	Macrophages, neutrophils, dendritic cells	Surround phagocytosed microorganisms, apoptotic cells or other large particles; kill and digest the contents and initiate signal transduction cascades	HPS (AP-3), CHS, ARC in insects
$NOX2^{+}$ inhibitory lysosomes	Conventional dendritic cells	Contain the NADPH oxidase NOX2, which negatively regulates proteolysis upon fusion with phagosomes to facilitate cross-presentation	GS2
IRF7 signaling lysosomes	Plasmacytoid dendritic cells	The site of an IRF7 signaling cascade from nucleic acid sensing toll like receptors to initiate production of type I interferon	HPS
Acrosomes	Sperm cells	Organelles storing hydrolytic and glycolytic proteins that are secreted by sperm to reach the egg prior to fertilization	GS2
Notochord vacuoles	Notochord inner cells	Organelles required for body axis elongation and spine morphogenesis	HPS
LROs-invertebrate			

Lysosome-Related Organelles	Cell Types	Description	LRO disease model
Pigment granules	*Drosophila melanogaster* retinal cells	Contain red and brown pigments that are necessary for light insulation in order to prevent the loss or spread of light throughout the eye	HPS
Gut granules	*Caenorhabditis elegans* intestinal cells	Storage compartment putatively containing zinc, anthranilic acid, and lipofuscin	HPS, CHS
Zinc storage granules	*Drosophila melanogaster* Malpighian tubule epithelial cells	Storage compartment that collectively contains the total body pool of chelatable zinc	HPS
Post-lysosomes	*Dictyostelium discoideum*	Deacidified secretory compartments that mature from lysosomes and constitutively secrete undigested material into the extracellular space	CHS
Mucocysts	*Tetrahymena thermophila*	Secretory granules containing peptides that, upon stimulated exocytosis, surround the cell in a thick mucus layer as a method of cellular defense	HPS
Riboflavin granules	*Bombyx mori* Malpighian tubules	Needle-shaped yellow granules that store riboflavin	HPS
Integument urate granules	*Bombyx mori* epidermal cells	Crystal form of the uric acid-containing fat body that make the larval skin opaque for protection from ultraviolet radiation	HPS
Putative LROs-vertebrate			
Large dense-core vesicles	Specialized secretory cells (e.g. adrenal chromaffin cells)	Secretion of hormones and neuropeptides	HPS
Specific (secondary) granules	Neutrophils	Secretory granules containing cytotoxic proteins involved in the initiation of the inflammatory response	
Gelatinase (tertiary) granules	Neutrophils	Secretory granules containing gelatinase, receptors, adhesion molecules and other proteins to mediate cell adhesion to the endothelium	
Presynaptic vesicles	Neuron synaptic cleft	Secretory vesicles containing neurotransmitters that are released at the synapse upon stimulation	HPS (AP-3 and BLOC-1)
Osteoclast secretory lysosome	Osteoclasts	Secretory lysosomes involved in bone resorption and remodeling	GS2
Fusiform vesicles	Urothelium	Compartment mediating the storage and transport of urothelial plaques for bladder expansion	
Putative LROs-invertebrate			
Glue granules	*Drosophila melanogaster* larval salivary gland epithelial cells	Secretory granules containing highly glycosylated glue proteins required for pupal case adhesion to a solid substrate during metamorphosis	

TABLE 2

Disease-associated genes in humans and their model systems.

zHuman gene	Alternative human gene names	Affected protein complex/subunit	Human disease	Rodent model	Drosophila model	Other models
BLOC1S1	*BLOS1, BORCS1, RT14, GCN5L1*	BLOC-1 and BORC subunit BLOS1		*Blos1*$^{Ell\text{-}Cre/loxp}$; *Blos1*$^{nestin\text{-}Cre/loxp}$	*blos1*	*bloc1s1*^{ihb815} (z) *blos-1*(-) (c)
BLOC1S2	*BLOS2, BORCS2, CEAP, CEAP11*	BLOC-1 and BORC subunit BLOS2		*Bloc1s2*$^{-/-}$		*bloc1s2*^{ihb818}(z) p-Translucent *(op)* (d)
BLOC1S3	*Reduced Pigmentation (RP), BLOS3, HPS8*	BLOC-1 subunit BLOS3	HPS8	*reduced pigmentation*		
BLOC1S4	*CNO, BLOS4, BCAS4L*	BLOC-1 subunit Cappuccino		*cappuccino*		
BLOC1S5	*MUTED, BLOS5, MU*	BLOC-1 subunit Muted		*muted*		Tanaka's mottled translucent *(otm)* (b)
BLOC1S6	*PLDN, PALLID, BLOS6, HPS9*	BLOC-1 subunit Pallidin	HPS9	*pallid*		*glo-2(-)* (c)
SNAPIN	*BLOC1S7, BLOS7, BORCS3, SNAPAP*	BLOC-1 and BORC subunit Snapin		*snapin*$^{-/-}$		*snpn-1* (c)
DTNBP1	*BLOC1S8, DBND, SNDY, HPS7*	BLOC-1 subunit Dysbindin	HPS7	*sandy*		Mottled translucent of var *(ov)* (d)
HPS3	*BLOC2S1, SUTAL*	BLOC-2 subunit	HPS3	*cocoa*		
HPS5	*BLOC2S2, AIBP63*	BLOC-2 subunit	HPS5	*ruby-eye 2*	*pink*	*snow white* (z) Aojuku translucent *(oa)* (d)
HPS6	*BLOC2S3*	BLOC-2 subunit	HPS6	*ruby-eye*		*no privacy* (x)
HPS1	*BLOC3S1, HPS*	BLOC-3 subunit	HPS1	*pale ear*		
HPS4	*BLOC3S2, LE*	BLOC-3 subunit	HPS4	*light ear*		
AP3B1	*ADTB3A, HPS2, PE*	AP-3 β3A subunit	HPS2	*pearl; Ap3b1*^{LN}	*ruby*	*apt-6(-)* (c)
AP3D1	*ADTD, HPS10*	AP-3 δ subunit	HPS10	*mocha*	*garnet*	*apt-5(-)* (c)
AP3M1		AP-3 μ3A subunit			*carmine*	*apt-7(-) (c)*
AP3M2	P47B, AP47B, CLA20	AP-3 μ2 subunit				
AP3S1	*CLAPS3*	AP-3 σ3A subunit			*orange*	
AP3S2	*AP3S3*	AP-3 σ2 subunit				
VPS33A	*MPSPS*	HOPS/CORVET subunit VPS33A		*buff*	*carnation*	*vps-33.1(-)* (c)
VPS11	*END1, PEP5, RNF108, HLD12*	HOPS/CORVET subunit VPS11				*vps-11(-)* (c) *platinum* (z)

zHuman gene	Alternative human gene names	Affected protein complex/subunit	Human disease	Rodent model	Drosophila model	Other models
VPS16		HOPS/CORVET subunit VPS16A			*maroon*	*vps-16(-)* (c)
VPS18	*PEP3*	HOPS/CORVET subunit VPS18			*deep orange*	*vps-18(-)* (c) *vps18(hi2499A)* (z)
VPS41		HOPS subunit VPS41			*light*	*vps-41(-)* (c)
VPS39	*VAM6, TLP*	HOPS subunit VPS39				*vps-39(-)* (c) *lbk/vam6 (z)*
RAB38	*NY-MEL1*	RAB38		*Chocolate* mouse; *Ruby* rat	*lightoid*	*glo-1(-)* (c)
RAB32		RAB32			*lightoid*	*glo-1(-)* (c)
RABGGTA	*PTAR3, RGGTA*	Rab geranylgeranyltransferase II subunit α		*gunmetal*		
SLC7A11	*XCT, CCBR1*	SLC7A11		*subtle gray*		
LYST	*CHS1*	LYST	CHS	*beige*	*mauve*	*lvsA, lvsB (d)* *lyst-1*(-) (c)
VPS33B		CHEVI complex subunit VPS33B	ARC	*Vps33b*$^{fl/fl}$		*vps33.2(-)* (c) *vps33b* MO (z)
VIPAS39	*VIPAR, VPS16B, SPE-39, C14orf133*	CHEVI complex subunit VPS16B	ARC	*Vipas39*$^{fl/fl}$	*full of bacteria*	*spe39(-)* (c) *vipar* MO (z)
NBEAL2	*GPS, BDPLT4*	NBEAL2	GPS	*nbeal2*$^{-/-}$		
MYOVA	*MYH12, MYR12, MYOV*	Myosin Va	GS1	*dilute*		
RAB27A	*RAM*	Rab GTPase RAB27A	GS2	*ashen*		
MLPH	*SLC2-A*	Melanophilin	GS3	*leaden*		
UNC13D	Munc13-4	Munc13-4	FHL3	*Jinx*		
STX11		Syntaxin-11	FHL4	*Stx11*$^{-/-}$		
STXBP2	Munc18-2, UNC18-2, UNC18B	Munc18-2 (Munc18b)	FHL5	*Munc18b*$^{+/-}$		

Key:

(z): zebrafish; (c): *C. elegans*; (x): *Xenopus laevis*; (d): *D. discoideum;* (b): *Bombyx mori.*

Colored highlights indicate subunits of the same multisubunit protein complex.

Targeted gene knockouts in mice are indicated as $^{-/-}$; mice with conditional knockouts in specific cell types through Cre/loxp technology are indicated as $^{fl/fl}$.