

CORVET, CHEVI and HOPS – multisubunit tethers of the endo-lysosomal system in health and disease

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ABSTRACT

Multisubunit tethering complexes (MTCs) are multitasking hubs that form a link between membrane fusion, organelle motility and signaling. CORVET, CHEVI and HOPS are MTCs of the endo-lysosomal system. They regulate the major membrane flows required for endocytosis, lysosome biogenesis, autophagy and phagocytosis. In addition, individual subunits control complex-independent transport of specific cargoes and exert functions beyond tethering, such as attachment to microtubules and SNARE activation. Mutations in CHEVI subunits lead to arthrogyriposis, renal dysfunction and cholestasis (ARC) syndrome, while defects in CORVET and, particularly, HOPS are associated with neurodegeneration, pigmentation disorders, liver malfunction and various forms of cancer. Diseases and phenotypes, however, vary per affected subunit and a concise overview of MTC protein function and associated human pathologies is currently lacking. Here, we provide an integrated overview on the cellular functions and pathological defects associated with CORVET, CHEVI or HOPS proteins, both with regard to their complexes and as individual subunits. The combination of these data provides novel insights into how mutations in endo-lysosomal proteins lead to human pathologies.

KEY WORDS: Disease, Endosome, HOPS, Lysosome, Membrane trafficking, Tethering, CHEVI, CORVET

Introduction

The endo-lysosomal system consists of a collection of dynamic and interactive compartments that together control cellular homeostasis (for schematic overview see Fig. 1). Essential functions of the system include recycling of plasma membrane components, processing and degradation of biomaterials, sensing and controlling of the nutrient status of cells, and exocytosis (Settembre et al., 2013). To exercise these diverse tasks, endo-lysosomal compartments frequently interact with each other and other compartments, resulting in numerous membrane fusion and fission events (Fig. 1). Fusion is strictly regulated by the concerted action of three families of machinery proteins: Rab GTPases, tethers, and soluble N-ethylmaleimide-sensitive fusion protein (NSF) attachment protein receptors (SNAREs) (Spang, 2016; Wurmser et al., 2000). Rab GTPases initiate the fusion process through a GDP-to-GTP switch that leads to recruitment of a variety of effector proteins, including tethers (Pols et al., 2013b; Seals et al., 2000). Tether proteins establish the first

contact between two opposing membranes and pull them close together to allow interactions between SNARE proteins (Murray et al., 2016). SNARE assembly then provides additional fusion specificity and drives the actual fusion process (Ohya et al., 2009; Stroupe et al., 2009). In this Review, we focus on the role of tethering proteins in endo-lysosomal fusion events.

Tethering proteins can be divided into two main groups: long coiled-coil proteins (Gillingham and Munro, 2003) and multisubunit tethering complexes (MTCs). MTCs form a heterogenic group of protein complexes that consist of up to ten subunits resulting in a general length of ~50 nm (Brocker et al., 2012; Chou et al., 2016; Hsu et al., 1998; Lürick et al., 2018; Ren et al., 2009). Interestingly, the multiple subunits in MTCs allow regulatory roles in vesicular trafficking that go beyond tethering. For example, MTCs assist in SNARE complex assembly (Baker et al., 2015; Ren et al., 2009) and contribute to SNARE fusogenic activity (D'Agostino et al., 2017; Schwartz et al., 2017; Spang, 2017). MTCs are also involved in movement along microtubules (Jordens et al., 2001; van der Kant et al., 2013), endosome maturation (Huotari and Helenius, 2011), coat protein interactions (Zolov and Lupashin, 2005) and membrane bending (Hui et al., 2009; Martens et al., 2007). Moreover, different MTCs can share similar subunits (Guo et al., 2013; Lőrincz et al., 2016; Spang, 2016) and complex-independent roles for individual MTC subunits have been described (Jonker et al., 2018; Pols et al., 2013a). These data indicate MTCs are versatile multitasking complexes that form a link between membrane fusion, organelle motility and signaling. In accordance, it has become increasingly apparent that mutations in MTC subunits underlie a variety of diseases.

In this Review, we discuss the role of three related MTCs involved in endo-lysosomal transport steps: class C core vacuole/endosome tethering (CORVET), class C homologs in endosome-vesicle interaction (CHEVI; Spang, 2016) and homotypic fusion and vacuole protein sorting (HOPS) (see Box 1 for structural information). Generally, CORVET and CHEVI act in the early endosomal pathway, whereas HOPS is involved in the fusion events of late endosomes and lysosomes (Box 2 and Fig. 1). For more information on other types of MTCs, we refer to some excellent reviews (Bonifacino and Hierro, 2011; Lürick et al., 2018; Rabouille and Linstedt, 2016; Schindler et al., 2015; Spang, 2016; Witkos and Lowe, 2017). Here, we summarize our current knowledge on the role of CORVET, CHEVI and HOPS in intracellular trafficking and provide the first integrated overview of the cellular and pathological defects associated with their dysfunction. Finally, we describe how defects in different subunits can lead to highly specific phenotypes.

Organizing endo-lysosomal trafficking

The CORVET, CHEVI and HOPS complexes enable various transport steps along the endo-lysosomal trafficking system (see Box 2 and Fig. 1). Moreover, independently of these complexes, single subunits can facilitate transport of selective cargoes.

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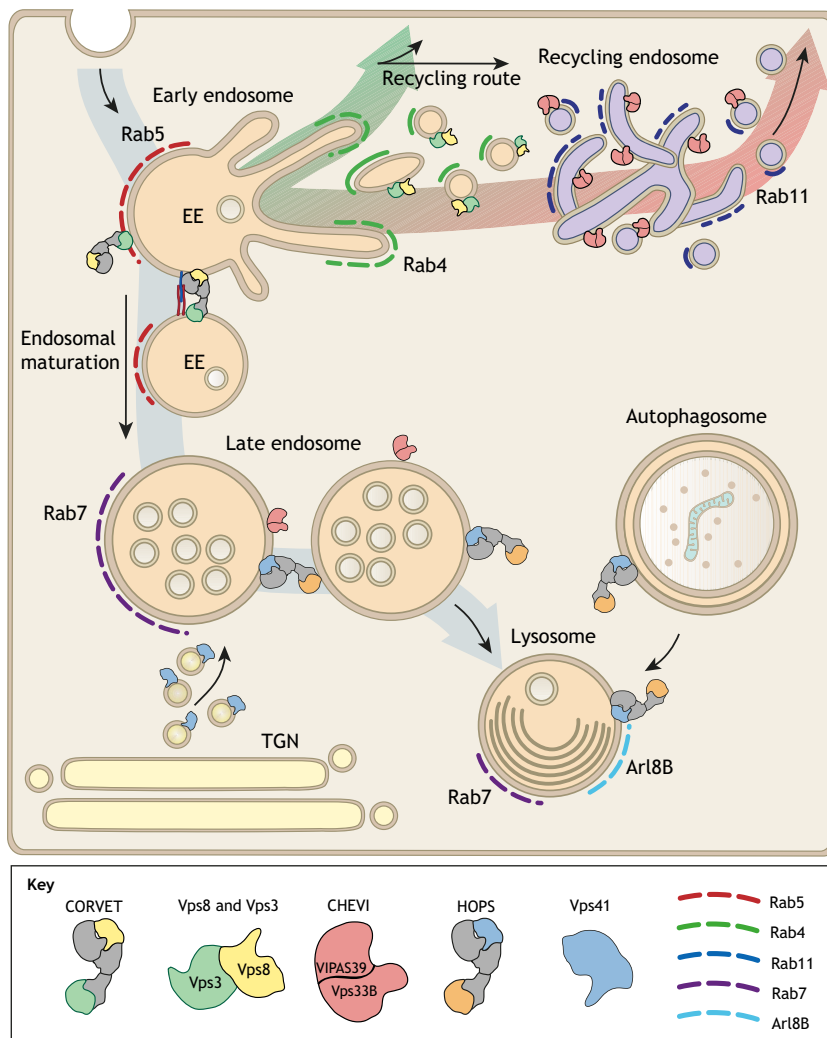


Fig. 1. Overview of endo-lysosomal pathways requiring CORVET, HOPS or CHEVI. Endocytosis begins with the formation of endocytic vesicles from the plasma membrane, which travel into the cell to fuse with Rab5-positive early endosomes (herein referring to Rab5a). Early endosomes fuse with each other and undergo changes in morphology, cargo, lipid composition, subcellular position and intraluminal acidity, which leads to their maturation into Rab7-positive late endosomes (also known as multivesicular bodies; MVBs). The process of endosomal maturation is accompanied by the generation of Rab4-positive recycling tubules, which travel directly to the plasma membrane (fast recycling), or indirectly, via specialized Rab11-positive recycling endosomes (slow recycling). Late endosomes fuse with each other and with Arl8b-positive lysosomes. Late endosomes and lysosomes also fuse with autophagosomes, membranes enclosing cytoplasmic cargo destined for degradation, resulting in amphisomes (not indicated) or autolysosomes, respectively. CORVET is required for homotypic fusion of early endosomes. CHEVI is involved in recycling through Rab11-positive recycling endosomes, whereas HOPS mediates homotypic and heterotypic fusion events between late endosomes and lysosomes. In addition, HOPS and CHEVI are required for phagocytosis (not indicated). Outside the complexes, Vps41 mediates transport of lysosomal membrane proteins from the TGN to endosomes, and Vps3 and Vps8 are involved in a specialized recycling pathway needed to transport integrins from early to recycling endosomes.

CORVET, Vps3 and Vps8 – early endosome fusion and recycling

Depletion of the CORVET-specific subunits Vps3 (also known as TGFBRAP1 in mammals) or Vps8 inhibits homotypic fusion of early endosomes and impairs conversion of early endosome into late endosomes (Balderhaar et al., 2013; Kuhlee et al., 2015; Perini et al., 2014) (Fig. 1). Strikingly, in mammalian cells, this fusion defect is limited to early endosomes that do not contain the coiled-coil tether early endosome antigen 1 (EEA1) (Perini et al., 2014), and this perhaps explains why Vps3 or Vps8 depletion does not dramatically affect lysosomal biogenesis or the overall endocytic capacity of cells (Jonker et al., 2018; Perini et al., 2014). In addition, transferrin receptor recycling is not markedly affected after Vps3 or Vps8 depletion (Jonker et al., 2018; Perini et al., 2014). Recent studies, however, unexpectedly indicated a role for mammalian Vps3 and Vps8 in a specialized recycling pathway. Through immunoelectron microscopy, Vps3 and Vps8 were found on early endosomes as well as on Rab4-positive (herein referring to Rab4a) recycling vesicles that contain $\alpha 5$ - and $\beta 1$ -integrin (Fig. 1) (Jonker et al., 2018). Integrins are the primary receptors for extracellular matrix (ECM) proteins, and are important for cell–ECM interactions and neuronal migration (De Franceschi et al., 2015; Paul et al., 2015; Rout, 2013). Their cell surface level is regulated by the balance between endocytosis, endosomal recycling and lysosomal degradation (Jonker et al., 2018; Paul et al., 2015). We showed that Vps3 or Vps8 depletion inhibited transport of endocytosed integrins

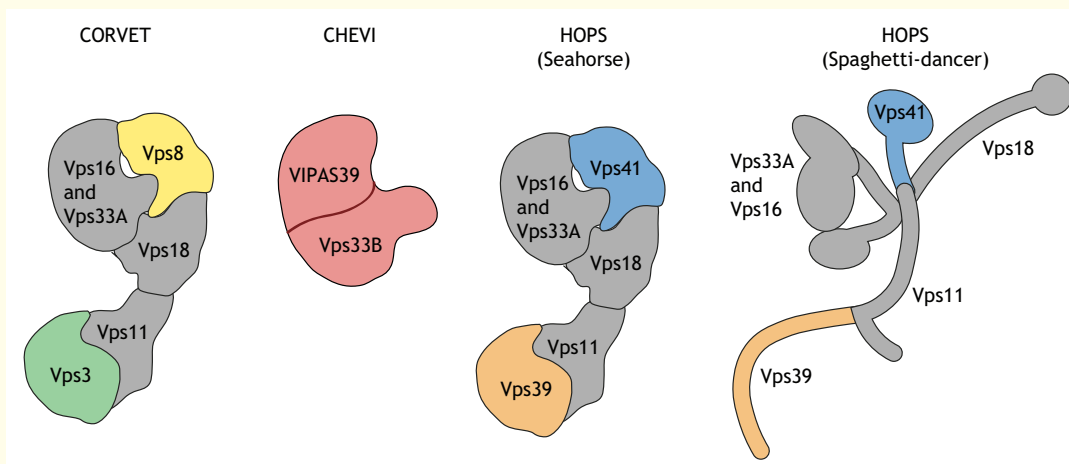
from early endosomes to Rab11–CHEVI-positive recycling endosomes and consequently affected integrin-dependent cell adhesion, migration and focal adhesion formation (Jonker et al., 2018). These data indicate that Vps3 and Vps8 regulate a specialized trafficking pathway from early to recycling endosomes. There are no indications for the requirement of core subunits (Vps11, Vps16, Vps18 and Vps33A; see Box 1) in this transport step, indicating that the role of Vps3 and Vps8 in recycling is independent of CORVET (Fig. 1). Entry into the Vps3–Vps8-mediated recycling pathway may depend on the recently discovered Retriever complex, which, at early endosomes sorts endocytosed cargo bearing a NPxY/NxxY motif into a SNX17–COMMD–CCDC22–CCDC93 (CCC) and Wiskott–Aldrich syndrome protein and SCAR homolog (WASH) complex-dependent recycling pathway (McNally et al., 2017). The NxxY motif is present in integrins as well as in other proteins whose function depend on a strict regulation of their plasma membrane levels (Reszka et al., 1992). Further studies are required to address whether Vps3 and Vps8 are also required for the recycling of other NPxY/NxxY motif-bearing cargoes.

In conclusion, Vps3 and Vps8, as part of CORVET, are required for homotypic fusion of a subset of early endosomes, and independent of the core subunits in a specialized recycling pathway that controls the plasma membrane levels of integrins and possibly other substrates. Depletion of CORVET in mammalian

Box 1. Structural biology

CORVET and HOPS were initially identified and characterized in yeast and are generally highly conserved from yeast to mammals (Li and Blissard, 2015; Seals et al., 2000; Van Der Kant et al., 2015; Wurmser et al., 2000). In contrast, the CHEVI complex is lacking in yeast and only present in metazoan species. CORVET and HOPS are hexameric complexes (see figure), which share a core of four subunits called Vps class C subunits (Vps11, Vps16, Vps18 and Vps33A). In CORVET this core is supplemented with Vps8 and Vps3 (see Table S1 for alternative names) (Lachmann et al., 2014; Perini et al., 2014; Van Der Kant et al., 2015) and in HOPS with Vps41 and Vps39. Mammalian Vps3 does not have a great deal of similarity to yeast Vps3, but is more closely related to Vps39 (Lachmann et al., 2014). *Drosophila melanogaster* entirely lacks a Vps3 homolog, and a complex consisting of Vps16, Vps18, Vps33A and Vps8 is formed called miniCORVET (Lőrincz et al., 2016). The metazoan-specific CHEVI complex consists of two subunits, Vps33B and VIPAS39. Presently, there is no indication for the requirement of additional subunits. Vps33B is a homolog of Vps33A, whereas VIPAS39 shares significant similarity to the C-terminal region of Vps16 (Gissen et al., 2005; Graham et al., 2013). Despite these homologies neither VIPAS39 nor Vps33B are incorporated into HOPS or CORVET (Cullinane et al., 2010; Hunter et al., 2018; Rogerson and Gissen, 2016; Van Der Kant et al., 2015). Recruitment of Vps33A to the human HOPS complex requires the Vps16 residues 642–736 (Graham et al., 2013). The high degree of similarity between the Vps16–Vps33A and VIPAS39–Vps33B binding interfaces suggests a structurally similar basis for interaction between the two CHEVI subunits (Cullinane et al., 2010; Graham et al., 2013).

Initial structural studies based on negative stain electron microscopy of the yeast HOPS complex revealed an elongated ‘seahorse’ shape with Vps39 and Vps41 positioned on opposing sites (Brocker et al., 2012) (see figure). This model allows Vps39 and Vps41 to bind interacting partners present on two opposing membranes, which is compatible with the tethering function of HOPS (Balderhaar and Ungermann, 2013; Brocker et al., 2012; Solinger and Spang, 2013) (Fig. 1). A more recent study (Chou et al., 2016) suggested an open ‘spaghetti-dancer’ structure for HOPS (figure). The disparity in the two structures could represent HOPS in an ‘open’ and ‘closed’ conformation (Lürick et al., 2018). Based on the similarity HOPS and CORVET, the CORVET-specific subunits Vps3 and Vps8 are tentatively positioned at the same sites as Vps39 and Vps41, respectively (Balderhaar and Ungermann, 2013).



cells only has a mild effect on endocytosis and lysosome biogenesis, but does affect cell adhesion and migration.

HOPS and Vps41: late endosome–lysosome fusion and the ALP–LAMP carrier pathway

Early studies in yeast disclosed that Vps39 and Vps41, as part of the HOPS complex, are required for fusion of endosomes and autophagosomes with the yeast lysosome (see Box 3) (Nakamura et al., 1997; Radisky et al., 1997). This function is well conserved in mammals (Caplan et al., 2001; Jiang et al., 2014; Kuhlee et al., 2015; Pols et al., 2013b; Takáts et al., 2014). In cells depleted of Vps39 or Vps41, the overall endocytic capacity of cells is not notably affected, but the transfer of endocytosed material from late endosomes to lysosomes is delayed and there is an accumulation of late endosomes (Caplan et al., 2001; Pols et al., 2013b). In addition, the Vps41-dependent alkaline phosphatase (ALP) pathway for lysosomal membrane proteins (see Box 3) is conserved in metazoan cells. Through immunoelectron microscopy, Vps41 was localized to small transport vesicles originating from the *trans*-Golgi network (TGN), which carry the integral lysosomal membrane proteins LAMP-1 and LAMP-2, but not mannose 6-phosphate receptor, the major transport receptor of lysosomal enzymes (Pols et al., 2013a). Knockdown of Vps41 results in the accumulation of LAMP carriers, indicating a defect in their fusion with late endosomes or lysosomes (Pols et al., 2013a). In *Drosophila melanogaster*, Vps41

knockdown additionally impairs the transport of the lysosomal membrane proteins v-ATPase and NPC1 (Swetha et al., 2011). Neither in yeast nor in metazoan cells does the ALP–LAMP carrier pathway require Vps39 or core subunits.

Taken together, these data demonstrate that HOPS is essential for fusion of lysosomes with late endosomes and autophagosomes. Independently of HOPS, Vps41 is required for direct trafficking of lysosomal membrane proteins from TGN to lysosomes by the ALP–LAMP carrier pathway. Both pathways are conserved from yeast to mammals (Darsow et al., 2001; Nakamura et al., 1997; Pols et al., 2013a,b).

The core subunits: late endosome–lysosome fusion

There are numerous studies on the effect of depletion of the core subunits of CORVET and HOPS (Vps11, Vps16, Vps18 and Vps33A), either as principal objects of study or as control in studies on related proteins (Carette et al., 2011; Jiang et al., 2014; Pols et al., 2013a; Sriram et al., 2003; Wartosch et al., 2015) (Fig. 2). Between these studies different assays are used, which is why a general phenotype of core subunit depletion is not easily deduced. Moreover, since core subunits can also function outside CORVET or HOPS (see below), the ultimate depletion phenotype may result from multiple cellular defects. Nevertheless, a picture that emerges is that loss of core subunits mostly affects late steps in endocytosis and autophagy. The core subunits are required for fusion of late endosome and

Box 2. Spatial distribution of CORVET, CHEVI and HOPS

The Rab GTPases Rab5, Rab7 and Rab11 are important for the spatial distribution of CORVET, CHEVI and HOPS over different endolysosomal compartments. Early endosome-associated Rab5 (Fig. 1) binds to both Vps3 and Vps8 and recruits CORVET to early endosomes (Lachmann et al., 2014; Peplowska et al., 2007; Perini et al., 2014; Van Der Kant et al., 2015). Rab7 present on late endosomes and lysosomes, together with its effector RILP recruits Vps39, Vps41 and possibly core components to these organelles (Lin et al., 2014; van der Kant et al., 2013; Van Der Kant et al., 2015). The maturation of Rab5-positive early endosomes into Rab7-positive late endosomes, a process mediated by the Rab7 GEF Mon1–Ccz1 complex, thus coincides with the switch from CORVET to HOPS (Nordmann et al., 2010; Poteryaev et al., 2010) (see Box 1). In breast cancer cells expressing enhanced levels of Rab2a, Vps39 also binds to Rab2a-GTP present on endosomal compartments that release matrix metalloproteinases from invadopodia (Kajiho et al., 2016). The precise identity of this compartment is still subject of investigation (Castro-Castro et al., 2016; Kajiho et al., 2018).

Rab11 associates with recycling endosomes (Fig. 1) and regulates membrane recruitment of CHEVI. Rab11 interacts with both Vps33B and VIPAS39, but only recruits them to membranes when they are assembled in the CHEVI complex (Cullinane et al., 2010). Overexpression of RILP induces recruitment of Vps33B to late endosomes and lysosomes (Galmes et al., 2015; van der Kant et al., 2013). Since dedicated Rab11-positive recycling endosomes are found in only a subset of cell types (Klumperman and Raposo, 2014), this implies that the localization of Vps33B differs in different cell types. Moreover, preliminary data suggest that the expression and localization of Vps33B depend on the metabolic status of the cell (Anja Zeigerer, personal communication), opening the possibility that Vps33B function and localization is susceptible to nutrient status.

In addition to Rabs, additional factors can control membrane association of CORVET, CHEVI and HOPS. Arl8b, a small GTPase present on lysosomes, recruits HOPS to lysosomes by binding to Vps41 (Garg et al., 2011). At autophagosomes, the Rab7 effector and LC3-binding protein pleckstrin homology domain-containing family M member 1 (PLEKHM-1) recruits HOPS present on lysosomes by interacting with Vps11, Vps39 and Vps41 (McEwan et al., 2015). Once lysosomes are in close proximity to autophagosomes, the HOPS subunit Vps33A interacts with the autophagosome-specific SNARE syntaxin 17 to achieve autophagosome–lysosome fusion (Jiang et al., 2014; Takáts et al., 2014).

These data show that CORVET and CHEVI are predominantly associated with early endosomes and recycling endosomes, respectively, and HOPS with late endosomes and lysosomes. However, these distributions may undergo changes dependent on cell type, environmental conditions and expression of interacting partners.

lysosomes with autophagosomes (Jiang et al., 2014; McEwan et al., 2015; Takáts et al., 2014; Xiao et al., 2009) and their depletion invariably results in a defect in late endosome–lysosome fusion (Galmes et al., 2015; Sriram et al., 2003; Wartosch et al., 2015). For example, absence of Vps11 delays the transfer of internalized epidermal growth factor (EGF) to Rab7-positive endosomes (herein referring to Rab7a) (Chirivino et al., 2011) and all core subunits are required for Ebola virus infection, which requires passage of the virus to late endosomal and lysosomal compartments (Carette et al., 2011). Thus far, the only CORVET-related defect attributed to a core subunit is decreased homotypic early endosome fusion after Vps18 depletion (Richardson et al., 2004). In conclusion, depletion of core subunits primarily affects HOPS-dependent fusion steps of late endosomes and lysosomes.

CHEVI: recycling, bacterial clearance and biogenesis of lysosome-related organelles

In polarized cells, CHEVI localizes to Rab11-positive (herein referring to Rab11a) recycling endosomes and depletion of either

Box 3. Insights from yeast

Functional insight on the importance of the HOPS complex in membrane tethering and fusion was mainly provided by yeast studies. Fusion events of the vacuole (the yeast lysosome) require the presence of the yeast Rab7 homolog Ypt7p, SNARE proteins, lipids, the SNARE disassembly chaperones Sec17p and Sec18p, and the HOPS complex (Collins and Wickner, 2007; Orr et al., 2015; Zick and Wickner, 2016). Through purification of the HOPS complex, it was shown to be required for vacuole tethering (Stroupe et al., 2006, 2009). Additional studies showed that HOPS is an essential part of the fusion machinery by regulating formation of the *trans*-SNARE complex through the S/M protein and core subunit Vps33 (Baker et al., 2013, 2015; Starai et al., 2008) and coupling Ypt7p activation to SNARE complex assembly (Krämer et al., 2011; Orr et al., 2017; Stroupe et al., 2006). Studies on HOPS and CORVET performed in mammalian cells are generally consistent with the mechanistic insight provided by the work in yeast (Balderhaar and Ungermann, 2013; Caplan et al., 2001; Pols et al., 2013b).

Yeast Vps41 was originally identified as a protein required for high-affinity iron transport (Radisky et al., 1997). Yeast strains lacking Vps41 show abnormalities in vacuolar morphology, poor growth in low-iron medium and impaired Fet3p activity, a multicopper oxidase catalyzing the oxidation of ferrous to ferric iron. It was hypothesized that Fet3p inactivity is caused by defective sorting of Fet3p to prevacuolar compartments, indicating a function of Vps41 in post-Golgi trafficking (Lu et al., 2007; Radisky et al., 1997). Indeed, in yeast cells lacking Vps41, the transport of the lysosomal membrane protein alkaline phosphatase (ALP) to the vacuole is impaired. However, delivery of soluble hydrolases such as carboxypeptidase Y is unaffected. This finding triggered the proposition of the so-called ‘ALP pathway’, in which Vps41 at the *trans*-Golgi regulates the formation of ALP-containing vesicles that traffic directly to the vacuole (Cowles et al., 1997a). Over the past few years, additional cargoes for the ALP pathway have been identified, which are all vacuolar membrane proteins (Llinares et al., 2015; Anand et al., 2009).

The ALP pathway requires interaction of Vps41 with the heterotetrameric adaptor protein complex 3 (AP-3). In humans, mutations in AP-3 subunit genes cause the pigmentation-bleeding disorder HPS, which, interestingly, is based on a defect in trafficking of lysosomal membrane proteins (Bultema et al., 2012; Dell’Angelica et al., 1999; Liu et al., 2006; Peden et al., 2004). It has been hypothesized that yeast Vps41 could act as a coat on AP-3-vesicles budding from the Golgi (Rehling et al., 1999). Others have proposed that Vps41, as part of HOPS, could bind AP-3 on ALP carriers when arriving at the vacuole (Angers and Merz, 2009; Cabrera et al., 2010; Cowles et al., 1997b; Darsow et al., 2001; Dudek et al., 2010). These scenarios are not mutually exclusive. Mammalian Vps41 also interacts with AP-3 (Asensio et al., 2013).

Vps33B or VIPAS39 impairs the correct localization of apical proteins, resulting in abnormal cell polarization (Cullinane et al., 2010; Hanley et al., 2017). It remains unclear in which recycling step CHEVI is involved, that is, whether it is from early to recycling endosomes, or from recycling endosomes to the plasma membrane, or both. As discussed in the context of the Vps3–Vps8 recycling pathway, the CCC and Retriever complexes are involved in the sorting of cargoes bearing an NPxY/NxxY motif, including integrins, into a specialized endosomal recycling pathway (McNally et al., 2017). Recent studies have shown that Vps33B interacts with CCDC22 of the CCC complex (Hunter et al., 2018), binds integrin β subunits (Xiang et al., 2015) and is required for integrin recycling (Rogerson and Gissen, 2018). This functionally links Vps33B to the CCC and Retriever complexes and raises the question of whether Vps33B can recruit the CCC complex to Rab11-positive recycling endosomes for the formation of recycling tubules. A possible link between Vps33B- and Vps3–Vps8-

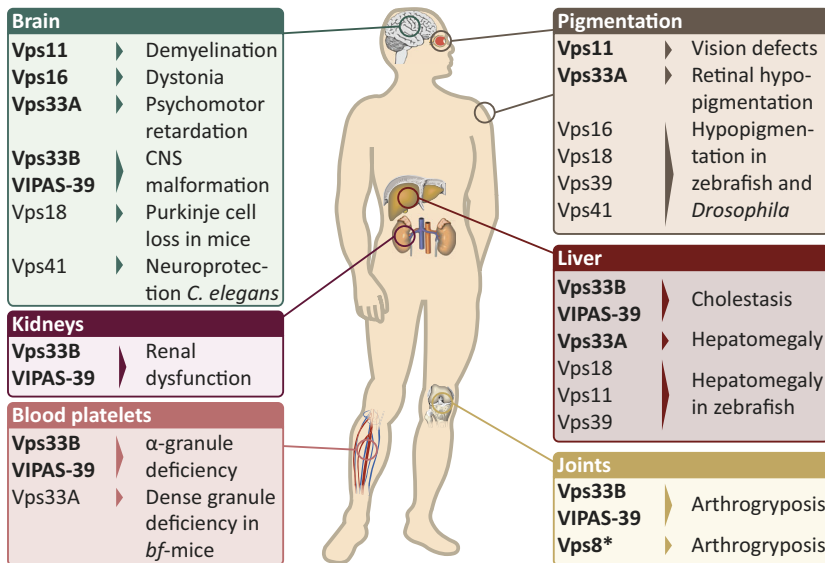


Fig. 2. Organs affected in disorders associated with mutations in core, CORVET, CHEVI or HOPS subunits. Syndromes or pathologies linked to specific subunits are indicated. Text in bold indicates this was found in human patients; standard text indicates this has been shown in animal models. See Table S2 for an overview of phenotypes in cells and animal model systems and references. CNS, central nervous system; *, symptoms could be due to additional mutations.

dependent integrin recycling pathways has not yet been investigated (Hunter et al., 2018; Jonker et al., 2018; Van Der Kant et al., 2015). There are no indications for molecular interactions between Vps3 or Vps8 and CHEVI (Hunter et al., 2018).

In addition CHEVI is required for the biogenesis of some types of lysosome-related organelles (LROs) (Rogerson and Gissen, 2016). Megakaryocytes – the progenitor cells of platelets – contain two types of LROs, dense granules and α -granules. Mutations in Vps33B or VIPAS39 that cause arthrogryposis, renal dysfunction and cholestasis syndrome (ARC, further discussed below) impair α -granule formation, likely because transport of cargo proteins from the Golgi to α -granule progenitor organelles is disrupted. The resulting phenotype is similar to gray platelet syndrome (GPS), the classic inherited platelet disorder caused by absence of α -granules (Bem et al., 2015; Dai et al., 2016; Urban et al., 2012). In the collecting duct cells of the kidney, CHEVI is required for trafficking of the collagen-modifying enzyme lysyl hydroxylase 3 (LH3, also known as PLOD3) to specialized compartments that also contain collagen IV. These compartments show features of LROs, although their mode of biogenesis is not yet clear (Banushi et al., 2016). CHEVI mediates two LH3 trafficking steps; Rab10-dependent exit from the TGN and an additional Rab25-dependent sorting step, potentially from endosomes to the collagen IV compartments (Banushi et al., 2016). Perturbation of the CHEVI complex in these cells results in disruption of ECM deposition and aberrant cell polarization (Banushi et al., 2016).

In addition to these predominant roles in recycling and LRO formation, CHEVI is involved in late endosome–lysosome fusion. Electron microscopy studies showed that depletion of Vps33B increases late endosome numbers and impairs traffic from late endosomes to lysosomes (Galmes et al., 2015), although this effect is mild and not detectable by light microscopy (Wartosch et al., 2015). Likewise, depletion of VIPAS39 leads to an increase in LAMP-1-positive compartments, that is late endosomes and lysosomes (Cullinane et al., 2010). Since neither Vps33B nor VIPAS39 are incorporated into HOPS, this role is complementary to the HOPS-dependent late endosome–lysosome fusion (Graham et al., 2013; Hunter et al., 2018; Van Der Kant et al., 2015). In addition, CHEVI has been implicated in phagosome maturation. *Mycobacterium tuberculosis* (Mtb) evades degradation in human macrophages by secreting a phosphatase that dephosphorylates

Vps33B and thereby blocks fusion of Mtb-containing phagosomes with lysosomes (Bach et al., 2008). Likewise, in a *D. melanogaster* mutant for VIPAS39 (also known as Vps16B), the immune cells are unable to degrade phagocytosed bacteria, hence the original name of VIPAS39 in *D. melanogaster* is Full-of-bacteria (Akbar et al., 2011). Intriguingly, recent studies have indicated that Vps33B is specifically required for maturation of phagosomes and endosomes containing microbial cargo, but not for regular endosomes (Akbar et al., 2016).

These data show that CHEVI has a major role in recycling of specific cargoes, the biogenesis of specialized LROs and the maturation of bacteria-containing phagosomes. It remains to be established whether these different steps are all controlled directly or indirectly, through recycling of specific cargo molecules. The diversity of functions raises the question of whether CHEVI adapts to different functions between specialized cell types.

Multitasking CORVET and HOPS subunits

CORVET and HOPS: assisting SNARE proteins in membrane fusion

Vps33A and Vps33B are both members of the Sec1/Munc18 (S/M) protein family (Baker et al., 2013, 2015; Gissen et al., 2005; Subramanian et al., 2004; Wartosch et al., 2015). These proteins promote SNARE complex formation and zippering through direct interactions with their specific SNARE partners. Vps33A interacts with the endocytic SNARE complex formed of STX7, STX8, Vti1b and VAMP7 (Collins and Wickner, 2007), as well as with the autophagic SNARE complex comprising STX17, VAMP8 and SNAP29 (Hunter et al., 2018; Jiang et al., 2014; Takáts et al., 2014). Vps33B is a known interactor of the SNARE protein Sec22B (Dai et al., 2016). It was demonstrated in yeast (see also Box 3) that the CORVET or HOPS complexes, when bound to the zippered SNARE complex via Vps33A, promote membrane fusion by forcing a curvature on the opposing membranes, thereby decreasing the required energy for fusion pore formation (D'Agostino et al., 2017; Schwartz et al., 2017; Spang, 2017). Thus, the bulky form of CORVET and HOPS facilitates the fusion process. After fusion pore formation, HOPS and CORVET also assist in pore expansion (D'Agostino et al., 2018). Since these processes rely on the physical size of the CORVET and HOPS, it is not known whether this function can be extrapolated to the small-sized CHEVI complex.

HOPS: organelle positioning

As discussed in Box 2, HOPS components Vps41 and Vps39 interact with the small GTPases Rab7 and Arl8b, as well as with the adaptor protein RILP (Lin et al., 2014; van der Kant et al., 2013). RILP also binds to Rab7 and recruits dynein, thereby linking HOPS and Rab7 to retrograde microtubule transport (Jordens et al., 2001). Moreover, both Rab7 and Arl8b recruit the anterograde transport adaptors FYCO-1 (Pankiv et al., 2010) and SKIP (Guardia et al., 2016; Rosa-Ferreira and Munro, 2011), respectively. Hence, via its interaction partners, HOPS links membrane fusion events to organelle positioning (van der Kant et al., 2013).

Vps3–Smad4: TGF β signaling

Mammalian Vps3 is also named TGFBRAP1 (Wurthner et al., 2001; see Table S1) because of its role in the transforming growth factor- β (TGF β) signaling pathway (Feng and Derynck, 2005). Activated TGF β receptors present in early endosomes phosphorylate a complex of Smad2 and Smad3 (Di Guglielmo et al., 2003; Hayes et al., 2002; Rajagopal et al., 2007), which subsequently is targeted to the nucleus to modulate target gene expression. The transfer from endosomes to nucleus requires the recruitment of Smad4 to early endosomes, which is mediated by Vps3. Overexpression of wild-type Vps3 or a dominant-negative mutant enhances and represses TGF- β signaling, respectively (Wurthner et al., 2001 and our unpublished observations). If and how this signaling function of Vps3 relates to its role in CORVET and/or Vps3–Vps8-dependent recycling has yet to be resolved.

Vps41–AP-3: vesicle formation and neuroprotection

Mammalian Vps41 interacts with the adaptor protein complex AP-3 (Asensio et al., 2013), and purified mammalian Vps41 self-assembles into large oligomeric complexes (Asensio et al., 2013). In regulated secretory cells, Vps41 and AP-3 are both required for the formation of secretory granules (Asensio et al., 2010, 2013). This has raised the question of whether Vps41 could act as a coat protein on AP-3 vesicles, as was suggested in yeast (see Box 3). However, in mammalian cells, there is a spatial paradox, since the steady-state distributions of AP-3 and Vps41 do not overlap and, as determined by immunoelectron microscopy, they are present on distinct types of vesicles (Peden et al., 2004; Pols et al., 2013a,b). This leaves the question of where and why Vps41 and AP-3 interact in mammalian cells unanswered.

Intriguingly, the Vps41–AP-3 interaction has been linked to Parkinson's disease (PD), a neurodegenerative disorder hallmarked by the accumulation of cytoplasmic α -synuclein in dopaminergic neurons. Post-mortem studies of PD patients showed that Vps41 levels in the brain are decreased (Grünblatt et al., 2007), and in a *Caenorhabditis elegans* model for PD, α -synuclein-induced death of dopaminergic neurons is prevented by overexpression of Vps41 (Hamamichi et al., 2008; Harrington et al., 2012; Ruan et al., 2010). The neuroprotective function of Vps41 depends on its interaction with AP-3 (Asensio et al., 2013; Harrington et al., 2012; Rehling et al., 1999). Neuroprotection also involves the clathrin heavy chain repeat (CHCR) domain of Vps41 (Harrington et al., 2012), which is needed for Vps41 homo-oligomerization (Asensio et al., 2013). Why especially Vps41 would be important to protect against PD is a highly captivating question, when no such function is found for Vps39 or core components. These data suggest a HOPS-independent role of Vps41 in secretory granule formation at the TGN as a tentative explanation, with a possible role for Vps41 homo-oligomerization. Further studies are required to understand the relevance of Vps41 oligomerization, its potential role in vesicle formation at the TGN and the function of the Vps41–AP-3 interaction.

Vps11, Vps8, Vps41 and Vps18: potential E3 ubiquitin ligases

Vps11, Vps8, Vps41 and Vps18 all have 'really interesting new gene' (RING) finger domains (Horazdovsky et al., 1996; Radisky et al., 1997; Rieder and Emr, 1997). Vps18 and Vps41 interact with each other via these RING domains, and this is required for formation of the HOPS complex (Hunter et al., 2017). RING domains typically confer E3 ubiquitin ligase activity to a protein, allowing them to recruit ubiquitin-conjugating enzymes and transfer ubiquitin to a specific substrate (Deshaies and Joazeiro, 2009). Ubiquitylation can target proteins for degradation by the proteasome or via 'endosomal sorting complexes required for transport' (ESCRT)-dependent sorting into late endosomes (Darsow et al., 2001; Shields and Piper, 2011). Additionally, ubiquitylation can reduce or increase protein activity and either promote or prevent interaction with other proteins (Mukhopadhyay and Riezman, 2007). Vps18 is the only subunit for which the potential ubiquitin ligase activity has been experimentally confirmed, with the substrates GGA3 and PLK2 (Yogosawa et al., 2005, 2006). GGA3 is an adaptor protein involved in the exit of lysosomal proteins from the TGN and recycling endosomes (Doray et al., 2002; Ghosh and Kornfeld, 2004; Puertollano and Bonifacino, 2004). PLK2 is a serine/threonine-protein kinase involved in cell division (Zitouni et al., 2014). Further studies are required to better understand the role of the ubiquitin ligase activity of Vps18 in intracellular trafficking. An interesting idea is that the RING domains could provide a possible mechanism to determine whether CORVET or HOPS subunits act as a complex or separately.

Vps18: transport of lysosomal enzymes?

In *D. melanogaster*, Vps18 (Dor) mutant cells show a failure in the trafficking of the lysosomal enzyme cathepsin L (Sriram et al., 2003), and conditional knockout mice of Vps18 show drastically lower amounts of active cathepsin D (Peng et al., 2012b). There is no significant effect on the transport of lysosomal membrane proteins. This phenotype is reversed in *D. melanogaster* Vps41 (Light) mutants in which intracellular transport of lysosomal membrane, but not of soluble lysosomal proteins, is affected (Swetha et al., 2011). It is not known which transport step in lysosomal enzyme delivery is affected by Vps18 depletion, but its proposed ubiquitin-ligase activity towards GGA3 suggests a possible role in the exit of lysosomal enzymes from TGN or early endosomes. Neuron-specific knockout of Vps18 in mice results in migration defects and severe neurodegeneration (Peng et al., 2012b) accompanied by accumulation of β 1-integrin at the plasma membrane. Interestingly, in mice with cathepsin D deficiency, a model for Batten's disease, integrin trafficking is also affected (Koch et al., 2013). Speculatively, these combined data suggest that a reduction in cathepsin levels and, consequently, lysosomal performance caused by Vps18 deficiency could enhance integrin recycling to the plasma membrane. Clearly, more experimental data are needed to sustain this hypothesis.

Vps39: lysosome–mitochondria contact sites

In yeast, Vps39 is a molecular component of lysosome–mitochondria contact sites (Elbaz-Alon et al., 2014; Hönscher et al., 2014). Independently of other HOPS components, yeast Vps39 binds to the yeast Rab7 homolog Ypt7, as well as to Tom40 on mitochondria. The resulting membrane contact sites are important for survival during starvation or under stress (González Montoro et al., 2018). Since the proteins constituting lysosome–mitochondria contact sites are generally well conserved, this could point to a similar, but as yet undescribed, role for mammalian Vps39 (Wong et al., 2018).

Disease phenotypes

A full knockout of a CORVET or HOPS subunit is mostly embryonic or early postnatal lethal (Aoyama et al., 2012; Messler et al., 2011; Peng et al., 2012b). This has been shown for Vps3, Vps18, Vps33A and Vps41, and is likely the case for additional subunits. Point mutations and conditional knockouts, however, exhibit less-severe phenotypes, and allow researchers to study defects in animal models (Table S2) (Cai et al., 2016; Peng et al., 2012b; Suzuki et al., 2003; Zhen and Li, 2015). In addition, an increasingly growing range of phenotypes in patients is attributed to mutations in CORVET, CHEVI or HOPS components (Fig. 2; Table 1). Patients with pathogenic mutations in Vps11, Vps16, Vps33A, Vps8, Vps33B and VIPAS39 have currently been reported (Table 1). In Fig. 2, Table 1 and Table S2, we present a compilation of all pathologies and phenotypes described in clinical studies, animal and cellular models. Although this classification is necessarily incomplete, since not all phenotypes have been studied for all subunits, it provides the first integrated overview of current *in vitro* and *in vivo* data on CORVET, CHEVI or HOPS dysfunction. The main overlapping phenotypes are neurodegeneration, pigmentation defects and liver malfunction. Moreover, mutations in CHEVI specifically lead to ARC syndrome, and an increasing number of studies describe a link between mutations in CORVET, CHEVI and HOPS to cancer.

ARC syndrome

Mutations in VIPAS39 and Vps33B, the two components of the CHEVI complex, are associated with a specific disease called human ARC syndrome (Cullinane et al., 2010; Gissen et al., 2004; Tornieri et al., 2013). Over 60 ARC-causing mutations in Vps33B and 27 in VIPAS39 are listed (Ackermann et al., 2014; Aflatounian et al., 2016; Arhan et al., 2009; Bull et al., 2006; Cullinane et al., 2009; Elmeery et al., 2013; Giraud et al., 2017; Gissen et al., 2006; Huang et al., 2017; Ilhan et al., 2016; Jang et al., 2009; Moon et al., 2017; Seo

et al., 2015; Weyand et al., 2016; Zhou and Zhang, 2014). The main symptoms are arthrogryposis multiplex congenita (congenital joint contraction), renal tubular dysfunction and cholestasis (inability of bile to flow from the liver to the duodenum). Additional features include platelet anomalies, central nervous system malformation and ichthyosis (a skin disorder) (Abu-Sa'Da et al., 2005; Alter et al., 2018; Hershkovitz et al., 2008). The symptoms of ARC patients can be largely explained by the major roles of CHEVI in protein recycling and LRO biogenesis (Cullinane et al., 2010; Rogerson and Gissen, 2016). The disruption of polarized transport in highly polarized liver and kidney cells probably causes the renal dysfunction and cholestasis symptoms (Hanley et al., 2017). Platelet abnormality is explained by defects in α -granule biogenesis (Dai et al., 2016), while impaired LH3 trafficking will induce aberrant collagen processing and connective tissue failures (Banushi et al., 2016). Recently, a patient with arthrogryposis was found to carry a homozygous missense mutation (Vps8^{Val1044Ile}) in Vps8 (Bayram et al., 2016). This is interesting since Vps8, like the CHEVI complex, is involved in endosomal recycling (Jonker et al., 2018). However, because this patient has additional mutations in other genes it cannot be unambiguously concluded that the arthrogryposis defect is indeed caused by mutations in Vps8.

Neurological defects

Defects in lysosomes are common denominators of neuronal diseases and found in, for example, Alzheimer's (Zare-Shahabadi et al., 2015), Parkinson's (Karabiyik et al., 2017) and Huntington's disease (Zhao et al., 2016). Lysosome-associated neurodegeneration is induced by a combination of mechanisms, most importantly, the accumulation of undegraded material (Jiang et al., 2014) and dysregulated signaling (Peng et al., 2012a). These events cause cellular stress and ultimately lead to apoptosis, which is especially damaging in neuronal tissues since these post-mitotic cells have little

Table 1. CORVET, CHEVI and HOPS mutations reported in human patients

Gene	Disease	Mutations	Cases	Symptoms	References
Vps11	Leukoencephalopathy	Deletion Leu387–Gly395 Missense Cys846Gly	10 patients across five families	Hypomyelination, truncal hypotonia, acquired microcephaly, variable seizure disorder, visual impairment	Edvardson et al., 2015; Hörtnagel et al., 2016; Zhang et al., 2016
Vps16	Dystonia	Missense Asn52Lys	Five patients in one family	Adolescent-onset dystonia	Cai et al., 2016
Vps33A	Mucopolysaccharidosis, lysosomal storage disease	Missense Arg498Trp	15 patients across 12 families	Coarse facial features, Psychomotor retardation, Hepatosplenomegaly, Joint contraction, Skeletal dysplasia, Respiratory difficulty	Dursun et al., 2017; Kondo et al., 2017
Vps8	Arthrogryposis	Missense Val1044Ile	One patient	Arthrogryposis*, Myotonia*, Microcephaly*, Delayed motor development*	Bayram et al., 2016
Vps33B	ARC syndrome	>60 different mutations	Likely >100 patients	Arthrogryposis, Renal tubular dysfunction, Cholestasis, Platelet anomalies, Malformation of CNS, Ichthyosis, Failure to thrive	Abu-Sa'Da et al., 2005; Ackermann et al., 2014; Aflatounian et al., 2016; Arhan et al., 2009; Bull et al., 2006; Cullinane et al., 2009; Cullinane et al., 2010; Elmeery et al., 2013; Giraud et al., 2017; Gissen et al., 2004; Gissen et al., 2006; Hershkovitz et al., 2008; Huang et al., 2017; Ilhan et al., 2016; Jang et al., 2009; Kim et al., 2011; Li et al., 2014; Moon et al., 2017; Saadah et al., 2013; Sanseverino et al., 2006; Seo et al., 2015; Taha et al., 2007; Tornieri et al., 2013; Wang et al., 2014; Weyand et al., 2016; Zhou and Zhang, 2014
VIPAS39	ARC syndrome	>27 different mutations	Likely >35 patients	Arthrogryposis, Renal tubular dysfunction, Cholestasis, Platelet anomalies, Malformation of CNS, Ichthyosis, Failure to thrive	

CNS, central nervous system; *, symptoms could be due to additional mutations.

regenerative capacity. Mutations in CHEVI or HOPS components commonly cause neurological defects in the *C. elegans*, *D. melanogaster*, zebrafish and mice animal models (Fernandes et al., 2014; Harrington et al., 2012; Kim et al., 2004; Peng et al., 2012b; Suzuki et al., 2003; Zhang et al., 2016). Patients carrying mutations in the core components Vps11, Vps16 or Vps33A (Cai et al., 2016; Edvardson et al., 2015; Hörtnagel et al., 2016; Kondo et al., 2017; Zhang et al., 2016) or ARC-causing mutations in the CHEVI subunits also show neurological symptoms (Eastham et al., 2001). Intriguingly, mutations in Vps3 or Vps8 seemingly do not impact neuronal function (Lőrincz et al., 2016).

Pigmentation defects

LROs are cell-type-specific organelles that share general features with generic lysosomes, such as the presence of LAMP proteins and a low pH, but they also carry out specialized functions. Examples of LROs are pigment-bearing melanosomes, cytotoxic granules, class II compartments and platelet α -granules involved in blood clotting. Although all LROs are interconnected with endo-lysosomal compartments, the biogenesis of distinct types of LROs can require different molecular machineries and vesicular trafficking pathways. For a more comprehensive understanding of LRO biogenesis and function, we refer the reader to topical review papers (Huizing et al., 2008; Marks et al., 2013).

Melanosomes are pigment-containing LROs present in eye and skin cells (Futter, 2006; Ishida et al., 2015; Seabra and Coudrier, 2004; Van Den Bossche et al., 2006). Melanosomes derive from a subset of early endosomes (Berson et al., 2001; Raposo et al., 2001; Theos et al., 2006) (Fig. 1), which receive key components for their differentiation from endosomes and the TGN (Marks and Seabra, 2001). Defects in melanosome biogenesis are easily identified by a reduction in the color of the skin or eyes. Mutations in core and HOPS subunits have been associated with pigmentation defects in various model systems. In *D. melanogaster*, the homologs of Vps11, Vps16, Vps18, Vps33A and Vps41 are named CG32350, Vps16A, Deep orange (Dor), Carnation (Car) and Light (Lt), respectively (Lloyd et al., 1998; Pulipparacharuvil et al., 2005; Sevrioukov et al., 1999; Warner et al., 1998; Shestopal et al., 1997) (Table S1), highlighting their importance for *D. melanogaster* eye pigmentation. Deletion of each of the genes encoding these proteins induces a block in melanosome biogenesis (Pulipparacharuvil et al., 2005; Sevrioukov et al., 1999; Sriram et al., 2003; Takáts et al., 2014). Interestingly, mutants of *D. melanogaster* Vps8 do not cause a pigmentation defect. (Lőrincz et al., 2016). In addition, in zebrafish, mutations in core and HOPS-specific subunits result in pigmentation defects (Clancey et al., 2013; Maldonado et al., 2006; Pulipparacharuvil et al., 2005; Thomas et al., 2011) (Fig. 2). Spontaneous mutations of Vps11, Vps18 and Vps39 were recognized because of such defects in pigmentation. All zebrafish mutants exhibit decreased pigmentation in eyes and skin and degeneration of the retinal pigmented epithelium. These data show that mutations in core and HOPS subunits generally lead to pigmentation defects.

Liver defects

Hepatomegaly, or enlarged liver, compromises liver function and poses a great health risk. Hepatomegaly is regularly found in 'classical' lysosomal storage disorders (Machado et al., 2015) and also in CHEVI- or HOPS-related disorders and in model systems. Zebrafish mutants of Vps11, Vps39 and, especially, Vps18 display hepatomegaly (Clancey et al., 2013; Maldonado et al., 2006; Pulipparacharuvil et al., 2005; Thomas et al., 2011). Electron microscopy of the livers of the Vps39 and Vps18 mutants revealed

that hepatocytes are filled with large, electron-lucent vesicles, which likely are swollen endosomes (Sadler et al., 2005; Schonhaler et al., 2008). Furthermore, morpholino-induced knockdown of the CHEVI subunits Vps33B or VIPAS39 (Vps16B in zebrafish) causes liver malfunction (Cullinane et al., 2010; Matthews, 2005), probably because of aberrant cell polarization (Vang et al., 2013). In humans, hepatomegaly has been found in patients with mutations in Vps33A (Kondo et al., 2017) and with ARC syndrome-causing mutations in Vps33B or VIPAS39 (Cullinane et al., 2010; Matthews, 2005). To the best of our knowledge, liver defects related to CORVET mutants have not been reported. Thus, defects in CHEVI, core or HOPS proteins generally lead to diseases of the liver.

Cancer

Lysosomes are increasingly being implicated in carcinogenesis and metastasis (Hämälistö and Jäättelä, 2016; Kallunki et al., 2013). Increased lysosomal activity and enhanced secretion of lysosomal hydrolases are a hallmark of invasive cells (Hämälistö and Jäättelä, 2016; Kallunki et al., 2013; Machado et al., 2015). Several studies have linked CORVET, CHEVI and HOPS subunits to cancer progression. High levels of Vps3 correlate with poor prognosis of human squamous carcinoma lung cancer (Bao et al., 2016). Single nucleotide polymorphisms in Vps41 strongly associate with hereditary melanoma (Ibarrola-Villava et al., 2015), and a recent study reported Vps33B as an important tumor suppressor in hepatocarcinogenesis (Wang et al., 2018). In *D. melanogaster*, mutations in Vps8 and Vps18 lead to the development of melanotic tumors, that is strongly pigmented tumors originating from immune cells (Lőrincz et al., 2016). Furthermore, deletion of Vps33A, Vps18 or Vps16 induces increased tumor growth and invasion in a *D. melanogaster* model for metastasis (Chi et al., 2010). These studies point to CORVET, CHEVI and HOPS subunits as potentially interesting targets for cancer research.

Lysosomal hydrolases that are secreted into the ECM act in concert with matrix metalloproteinases (MMPs) to degrade and remodel the connective tissue and allow cancer cells to migrate. Rab2a-GTP, an interactor of Vps39 (Gillingham et al., 2014), is upregulated in many invasive breast cancer cells (Kajiho et al., 2016). Functional studies have shown that Rab2a in concert with Vps39 is required for release of MMPs by lysosomal exocytosis; depletion of Vps39, but not Vps41, strongly impeded the capability of cells to degrade ECM (Kajiho et al., 2016). By which mechanism and through which interactors Vps39 aids in the exocytosis of MMPs is still elusive.

Subunit-specific phenotypes

Mutations in different subunits can also result in specific phenotypes (see Fig. 2). Below we summarize the most-striking subunit-specific phenotypes.

Mutations in Vps33A cause Hermansky–Pudlak syndrome and mucopolysaccharidosis

A specific mutation in the core component Vps33A, Vps33A^{Asp251Glu}, gives rise to *buff* (*bf*) mice, which are a model for human Hermansky–Pudlak syndrome (HPS) (Suzuki et al., 2003). HPS is a multigenetic disorder characterized by defects in the biogenesis of two types of LROs: melanosomes and platelet-dense granules (El-Chemaly and Young, 2016). Other causative genes for HPS encode AP-3 subunits, which we discussed above in the context of Vps41 function. The *bf* mouse mutation is particularly interesting because it leads to defects in LRO biogenesis and autophagy, while transport to lysosomes and lysosomal activity remains intact (Zhen and Li, 2015).

Patients with HPS suffer from blood-clotting problems and have reduced pigmentation in the eyes, skin and hair (El-Chemaly and Young, 2016). This is reflected in the *bf* mice, which exhibit hypopigmentation and a mild platelet-storage pool deficiency. The defect in platelet-dense granules in *bf* mice leads to a bleeding phenotype that resembles ARC. However, while mutations in CHEVI subunits lead to aberrant α -granule formation, the Vps33A^{Asp251Glu} mutation impairs dense-granule formation. Both α - and dense granules are secretory LROs important for platelet activation, but they differ in their set of secretory proteins (Heijnen and van der Sluijs, 2015; Meng et al., 2012; Pulipparacharuvil et al., 2005). The collective data indicate that the biogenesis of either type of granule requires distinct regulatory mechanisms, with Vps33A being required for dense-granule and CHEVI for α -granule biogenesis.

Vps33A^{Asp251Glu} also causes a defect in autophagy because the Vps33A^{Asp251Glu} mutation enhances its interaction with the autophagic SNARE STX17. This prevents release of the SNARE complex, resulting in the specific impairment of autophagosome–lysosome fusion (Zhen and Li, 2015). Thus, the Vps33A^{Asp251Glu} mutation impairs autophagy and the formation of LROs, but does not affect HOPS-dependent endosome–lysosome fusion. The Vps33A^{Asp251Glu} mutation therefore provides an interesting tool to study defects in autophagic flux without compromising lysosome function. In addition, further studies on Vps33A^{Asp251Glu} could help to advance our understanding of the different pathways underlying lysosome and LRO biogenesis.

Since the *bf* mutation is not embryonic lethal, these mice can be studied into adulthood. Adult *bf* mice show a reduced cerebellum size (Chintala et al., 2009), a reduction in Purkinje neurons (Chintala et al., 2009; Suzuki et al., 2003) and display progressive motor defects (Chintala et al., 2009). Because the autophagic pathway is compromised in *bf* mice, whereas lysosomal biogenesis is unaffected, these studies also illustrate the importance of autophagy for neuronal viability (Zhen and Li, 2015).

Despite the fact that HOPS-related pigmentation defects are widely observed in animal models, they are rarely observed in humans (Kondo et al., 2017) (Table 1). A screen for Vps33A mutations in 26 patients with HPS yielded only one individual with a heterozygous missense mutation in Vps33A (Suzuki et al., 2003). More recently, two other studies identified 15 patients from 12 families bearing a Vps33A^{Arg498Trp} missense mutation (Dursun et al., 2017; Kondo et al., 2017). This mutation does not impair the interaction of Vps33A with CORVET, HOPS or the autophagic SNARE STX17 and, accordingly, the endo-lysosomal and autophagic pathways appear unaffected in cells from these patients (Kondo et al., 2017). However, the patients do exhibit hypopigmentation of the retina, which is indicative for a defect in melanosome biogenesis. The most prominent aberrations in these patients are, however, coarse facial features, skeletal abnormalities, hepatosplenomegaly, respiratory problems, mental retardation and excess secretion of urinary glycosaminoglycans (GAGs) (Dursun et al., 2017; Kondo et al., 2017). These symptoms resemble that of mucopolysaccharidoses (MPS), multigenic lysosomal storage disorders caused by mutations in lysosomal enzymes that catabolize GAGs. Based on clinical and experimental data, it was concluded that Vps33A^{Arg498Trp} leads to a new type of MPS (Dursun et al., 2017; Kondo et al., 2017).

Mutations in Vps11 cause demyelination

Genetic leukoencephalopathies are a group of heterogeneous disorders with white matter abnormalities affecting the central nervous system. Through whole-exome sequencing, a missense

variant of Vps11, Vps11^{Cys846Gly}, was identified as one of the genetic causes of leukoencephalopathy syndrome (Zhang et al., 2016). In HeLa cells, the mutation causes accelerated breakdown of Vps11 and, consequently, there is no proper core complex formed. In zebrafish and human patients, the mutation causes a loss of neuron myelination (Zhang et al., 2016) (Fig. 2, Table 1). A similar reduction in myelination was found in patients bearing a Vps11^{Leu387-Gly395} deletion (Table 1). In total, 10 patients from five unrelated families are now known that bear a mutation in Vps11 that causes demyelination (Edvardson et al., 2015; Hörtnagel et al., 2016; Zhang et al., 2016). Likewise, in Rottweiler dogs, Vps11^{His835Arg} leads to axonal deterioration (Lucot et al., 2018). Since lysosomes are critical for maintaining cholesterol homeostasis (Miller and Bose, 2011), and myelination heavily relies on the availability of cholesterol (Saher and Stumpf, 2015), the reduced myelination phenotype can be explained by a metabolic defect in lysosomes. A similar demyelination defect has been reported in Niemann Pick C (NPC) patients, which is caused by a mutation in the cholesterol transporter protein NPC-1 (Goodrum and Pentchev, 1997). The Vps11 phenotype therefore implies that defects in CORVET and HOPS function can cause pathological defects that depend on the specific roles of lysosomes in maintaining protein and lipid homeostasis. The Vps11 patients in addition exhibit truncal hypotonia (decreased muscle tone), seizures, progressive microcephaly and cortical visual impairment (Edvardson et al., 2015; Hörtnagel et al., 2016). The vision defects are also found in zebrafish with mutations in Vps11 (Thomas et al., 2011; Zhang et al., 2016).

Mutations in Vps16 cause late onset dystonia

A missense mutation in Vps16^{Asn52Lys} has been identified to cause adolescent-onset dystonia in a Chinese family (Cai et al., 2016) (Table 1). The effects of this mutation were studied in detail in mice after CRISPR-Cas gene editing. At birth, Vps16^{Asn52Lys} mice were indistinguishable from wild-type pups and started to exhibit impaired motor function only at 6 months old, which matches the adolescent-onset dystonia observed in human patients. In the mice, the Vps16^{Asn52Lys} mutation leads to a reduction in Vps16 expression and protein levels, but mechanistic insights to explain the observed pathology are not yet available.

Conclusion and perspectives

CORVET, CHEVI and HOPS complexes can be regarded as hubs that combine multiple functions required for intracellular trafficking, such as membrane tethering, ubiquitin ligase activity, coat formation, SNARE activation and cytoskeleton association. This diversity in functions is enabled by the distinct actions of their individual components, which makes these multisubunit tethers great platforms for multitasking. Pathologies observed in patients can thus be due to loss of the unique function of a subunit, or of the entire complex, or both. This explains why mutations in different subunits vary in phenotype and severity. Furthermore, the severity of an effect of a mutation strongly depends on how the mutation affects protein function across different cell types. Although our understanding of the fundamental roles of CORVET, CHEVI and HOPS subunits in intracellular trafficking is increasing, fully understanding how mutations lead to disease remains a huge challenge. The availability of novel, specific gene-editing approaches in mice and other model systems could help to connect a mutation to pathology and explain symptoms observed in various cell types and at different scales of organization. Furthermore, molecular and cellular studies are required to increase our understanding of the various functions of MTCs and their subunits and further explore an emerging theme:

multitasking by protein complexes to coordinate and link various aspects of cellular trafficking.

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Competing interests

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Supplementary information

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