Chapter 1
The Endosomal Network: Mediators and Regulators of Endosome Maturation

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Contents

Abstract Endocytosis is a means for the cell to sample its environment for nutrients and regulate plasma membrane (PM) composition and area. Whereas the majority of internalized cargo is recycled back to the cell surface, select material is sent to the

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lysosome for degradation. Endosomes further play major roles in central cell activities as diverse as establishment of cell polarity and signaling, lysosomal storage and immunity. The complexity of endosomal functions is reflected by the extensive changes to endosome properties as they mature. The identity of individual endosomes is influenced by the presence of specific Rab GTPases and phosphoinositides (PIPs), which coordinate membrane traffic and facilitate endosomal functions. Motors and tethers direct the endosomes to the required locations and moderate fusion with other organelles. The maintenance of the elaborate endosomal network is supported by the ER and the *trans*-Golgi network (TGN), which promote the exchange of membrane components, provide enzymes, and assist with signaling. Additionally, V-ATPase is emerging as an underappreciated coordinator of endosome maturation and cell signaling. The inputs of the various mediators of endosome maturation are tightly regulated and coordinated to ensure appropriate maintenance and functioning of endosomes at each stage of the maturation process. Perturbations in endosome maturation are implicated in devastating diseases, such as neurodegeneration and cancer, and the endosome maturation processes are manipulated and exploited by intracellular pathogens to meet their own needs. A greater understanding of coordination and fine-tuning of endosome maturation will help us address various pathologies more effectively.

Abbreviations

EE	Early endosome
CI-M6PR	Cation-independent mannose-6-phosphate receptor
ILV	Intra luminal vesicle
LE	Late endosome
MVB	Multivesicular body
PIP	Phosphoinositide phosphate
PM	Plasma membrane
TfR	Transferrin receptor
TGN	*Trans*-Golgi network

1.1 Endosome Maturation Overview

Plasma membrane (PM) turnover and ingestion of extracellular material relies on a variety of endocytic pathways. The best studied pathway is clathrin-dependent endocytosis, which entails recognition of cargo via specific receptors, development of clathrin-coated pit, and formation of subsequent clathrin-coated vesicle (Doherty and McMahon 2009). Indiscriminate fluid sampling is concerted by macropinocytosis (Buckley and King 2017). A number of alternative endocytic pathways have been described and may be categorized by their PM-associated mediators, such as

caveolin, IL2R, Arf6, flotillin, or CLIC/GEEC (Mayor and Pagano 2007; Doherty and McMahon 2009). These distinct pathways may be selective for specific cargoes and play unique roles in endocytosis directing the fate of cargoes (Doherty and McMahon 2009). Larger particles, such as debris and bacteria, are taken up via receptor-mediated phagocytosis, a process mainly reserved for professional phagocytes, such as amoebae and macrophages (McDermott and Kim 2015; Doherty and McMahon 2009). It is conceivable that the spatial organization required at the PM for the different endocytic pathways to proceed also initiates the early sorting steps, further dealt with in the early endosomes (EE).

The newly formed endocytic vesicles of all origins move away from the cell surface and fuse with EEs (Fig. 1.1). The heterogeneous endocytic vesicles do not fuse with each other and show different maturation kinetics; however, all converge at the EE (Danson et al. 2013; Mayor and Pagano 2007). At some point, the EE stops accepting endocytic vesicles and becomes a sorting endosome. The trigger for this transition is poorly characterized (Spang 2016). The sorting endosome consists of tubular and vacuolar regions. The large surface area of the tubules allows the majority of membrane to be recycled back to the cell surface. Recycling proceeds directly to the PM or indirectly via recycling endosomes or *trans*-Golgi network (TGN) retrograde pathways (Lakadamyali et al. 2006; Clague and Hammond 2006). Luminal cargo is concentrated in the vacuolar regions and is targeted for degradation. Any membrane cargo destined for degradation is ubiquitinated and internalized into intraluminal vesicles (ILVs), giving the endosomes their characteristic multivesicular body (MVB) morphology.

To enable cargo degradation, the EE first has to acquire late endosome (LE) properties to prepare itself for fusion with the highly acidic lysosomes. These maturation events include the Rab5–Rab7 conversion, which in turn governs specificity of fusion with other compartments, and are accompanied by acidification, PIP conversion, and gain of lysosomal hydrolases and the protective highly glycosylated proteins, such as LAMP1. LEs are trafficked toward the perinuclear space, where the lysosomes are situated. Coordination of these events is poorly understood.

The TGN is not considered as a part of the endosomal network, but participates in sorting, recycling, and delivery of lysosomal hydrolases. The TGN sorts not only the cargoes coming from endosomes, but also cargoes destined to endosomes and to the PM. Retrograde transport is important for retrieval of receptors for future reuse, whereas anterograde pathway is important for delivery of lysosomal hydrolases, e.g., via cation-independent mannose-6-phosphate receptors (CI-M6PR) (McDermott and Kim 2015), and also for cargo destined to the PM (Spang 2015). Interestingly, in plants, the TGN functions as an EE able to receive incoming cargo directly from the PM, highlighting the partially overlapping functions of the two organelles (Scheuring et al. 2011).

Once all sorting receptors are recycled and all ubiquitinated cargoes are internalized into ILVs, LE content is transferred to lysosomes. The LE may directly be able to fuse with the lysosome to form an endolysosome, or deliver the luminal content via a "kiss-and-run" mechanism. The hydrolytic environment of the lysosome breaks down the cargo, which is then transferred out of the lysosome via specific transporters

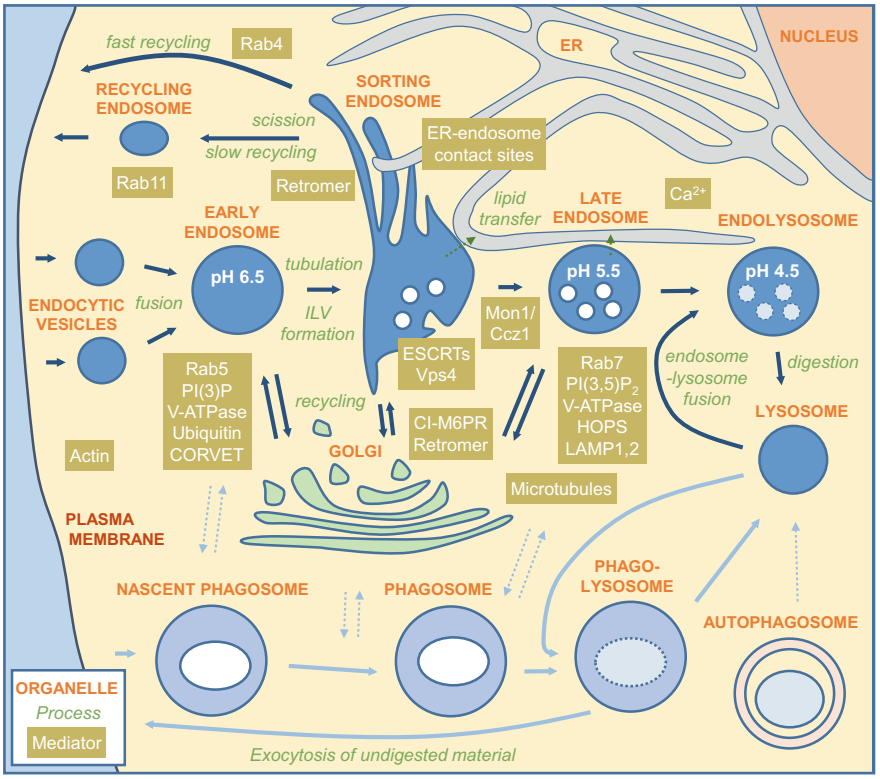

Fig. 1.1 Endosome maturation scheme. Endocytic vesicles containing endocytosed material fuse with early endosomes, which sort cargo for recycling and degradation. The cargo destined for recycling is sorted into tubular domains and sent directly to the plasma membrane or to recycling endosomes via fast and slow recycling pathways, respectively. Ubiquitinated membrane cargo destined for degradation is packaged into intraluminal vesicles (ILVs), which gives the late endosomes their characteristic multivesicular body appearance. The lipids are transferred to the ER via the ER–endosome contact sites. The continuous exchange of material with the TGN ensures supply of the required enzymes and membrane components to the maturing endosomes. Once the sorting steps are complete, the endosome fuses with the lysosome to form an endolysosome, where the cargo is digested and transported to the cytosol, to allow the lysosome to be regenerated and reused. Larger particles, such as bacteria, can be taken up by phagocytosis. As phagosomes mature, they interact with the endosomal pathway and the Golgi and, like endosomes, eventually fuse with lysosomes to facilitate cargo degradation. Undigested material is exocytosed. Lysosomes also receive material for degradation from the autophagy pathway. Endosome maturation is regulated by various Rabs and phosphoinositol phosphate (PIP) species, such as Rab5 and PI(3)P in early endosomes, Rab7 and $PI(3,5)P_2$ in late endosomes, and Rab4 and Rab11 in the recycling pathways. These regulators help recruit further essential mediators of endosome maturation, which include specific tethers (e.g., CORVET, HOPS), structural proteins (e.g., ESCRTs, SNX–BAR–retromer complexes), and cytoskeletal components (e.g., actin, dynein, kinesin), necessary for fusion, fission, and endosomal positioning, respectively. Gradual acidification accompanies endosome maturation, mediated by the proton pump V-ATPase, which is critical for endosomal function and maturation

and channels, allowing the lysosome to be regenerated and reused (Guerra and Bucci 2016). The lysosome also acts as a hub for integration of endocytic and autophagic pathways, thus being able to receive and digest cargo from both pathways. In yeast, lysosomes form one or more vacuoles.

Phagosomes display a lot of similarities with the endocytic pathway, their maturation consisting of early, late, and lysosome-interacting stages (Guerra and Bucci 2016). Unlike endosomes, the sorting stage is usually very short-lived and the majority of the phagosomal content gets targeted for degradation. The kinetics of phagosome maturation are strongly dependent on the phagocytic receptor, with the Fcγ receptor the one most extensively studied (Dill et al. 2015). Like endosomes, the phagosomes need PIP conversion to drive maturation and acquire LAMP1 and hydrolytic enzymes to form a phagolysosome (Kim et al. 2014). Indigestible material in phagosomes is exocytosed.

1.2 Endosome Functions

One of the primary functions of the endosomal network is nutrient acquisition and protein and lipid degradation. Sorting is an essential part of this process, allowing for extensive exchange of internalized cargo between compartments and ensuring only appropriate cargo reaches the lysosome (Villasenor et al. 2016; Stasyk and Huber 2016). Integrity of the endosomal system is required for lysosome biogenesis and its hydrolytic capacity to fulfill its functions to digest both extracellular material from the endocytic pathways and intracellular material from the autophagy pathways (Jacomin et al. 2016). Lysosomal degradation is also a central feature in immunity, allowing for inactivation of phagocytosed pathogens and partial digestion for antigen presentation via the MHC class II pathway (Boes et al. 2004).

Acidification is an important aspect of endosome maturation and function. Each stage of endosome maturation is characterized by a specific luminal pH, with EEs having pH of around 6.0–6.5, which drops to pH 5.0–5.5 in LEs and down to pH of below 4.5 in lysosomes, although the final pH in lysosomes may be highly heterogeneous (Wang et al. 2015; Johnson et al. 2016). Acidic pH is required for proper localization of many vacuolar proteins in yeast, including vacuolar hydrolases, proton pump subunits, enzymes for membrane biogenesis, and various transporters (Matsumoto et al. 2013). Acidification plays a role in uncoupling of internalized ligand–receptor complexes following receptor-mediated endocytosis, efficient sorting, inactivation of internalized pathogens, MVB formation, and activation of degradative enzymes (Matsuo et al. 2004; Fairn and Grinstein 2012; Kane 2006; De Luca and Bucci 2014; Kharitidi et al. 2015). Interestingly, pharmacological disruption of pH did not affect phagosome–lysosome fusion in mouse macrophages (Kissing et al. 2015). Low pH promotes acid sphingomyelinase (ASM)-mediated sphingomyelin conversion to ceramide, which regulates NPC2 participation in cholesterol transport and MVB maturation (Sandhoff 2016).

Additionally, endocytosis itself is a means to regulate PM composition, consequently contributing to fundamental cell properties such as cell polarity (Gao and

Kaestner 2010), cell adhesion (e.g., via integrin endocytosis) (Sandri et al. 2012), and cell motility (e.g., via endocytosis, recycling, and degradation of N-cadherin) (Tang 2016). Intercellular communication is mediated through exocytosis of MVBs containing DNA and RNA materials, which can function as messengers or participate in miRNA-mediated gene silencing (Soria et al. 2017; Gibbings et al. 2009). Endocrine and paracrine signaling, as well as cytotoxic immune functions, may also be mediated by exosomes generated in MVBs (Soria et al. 2017).

The endosomal system is a major regulator of cell signaling. Endocytosis modulates numbers of transmembrane proteins involved in signaling at PM, including growth factor receptors, such as EGFR. Internalization of activated signaling receptors is a mechanism to silence signaling. Once endocytosed, the signaling receptors may remain active, until inactivated through ubiquitination or ILV packaging. In neurons, the silencing of the Hedgehog receptor Patched by its targeting into ILVs was implicated in axon pruning (Issman-Zecharya and Schuldiner 2014). Surprisingly, accumulation of Notch and receptor tyrosine kinase (RTK) receptors at the enlarged EEs in Dmon1 mutant *Drosophila melanogaster* cells did not result in the expected overactive signaling, suggesting additional silencing mechanisms (Yousefian et al. 2013). Activity of signaling receptors at endosomes may also be spatiotemporally controlled, depending on access to their effectors. For example, hepatocyte growth factor receptor Met mediates cytoskeleton remodeling to control cell migration via two distinct pathways, which depends on endosome positioning (Stasyk and Huber 2016; Menard et al. 2014). Endosomal sensing and sorting are an important part of signaling regulation. Thus, the EGFR is recycled at low EGF concentration, but sent for lysosomal degradation when EGF levels are high (Sigismund et al. 2008). Additional Akt-dependent signaling functions have been demonstrated for a non-canonical subset of sorting endosomes marked with adaptor proteins APPL1 and APPL2 in zebrafish and mammalian cells (Urbanska et al. 2011; Kalaidzidis et al. 2015).

The lysosome acts as a major signaling hub to convey the nutrient status to the cell, which in turn influences the dynamics of endosome maturation, induction of autophagy, and cell growth and division, via the mTORC1 complex positioned at the lysosome. Lysosomes are able to store Ca^{2+} and participate in Ca^{2+}-dependent signaling. The transcription factor TFEB regulation is controlled through phosphorylation by mTORC1, which is sensitive to lysosomal amino acid levels, and dephosphorylation by the Ca^{2+}-dependent phosphatase calcineurin (Medina et al. 2015).

The endosome network also contributes to storage of nutrients, such as the reservoir of amino acids and carbohydrates in the yeast vacuole, or yolk granules in *Caenorhabditis elegans* and *D. melanogaster* oocytes (Teixeira et al. 2016; Armstrong 2010; Poteryaev et al. 2010). The integrity of the endosomal system also affects the dynamics of lipid droplets, an organelle used for lipid storage but also for signaling and hydrophobic protein metabolism (Bouchez et al. 2015). In case of PM damage, lysosomes are involved in injury-induced exocytosis and contribute to wound repair (Andrews et al. 2015). Harmful content, such as misfolded proteins, may be channeled through the endosomal system to be secreted in exosomes generated in MVBs (Soria et al. 2017). Secretory lysosomes are used by cells with

antimicrobial, clotting, and other specialized functions to secrete proteins such as histamine, perforin, and von Willebrand factor (Griffiths 2016). Secretory lysosomes are also used during intercellular cell fusion to establish continuous tubular networks such as the *D. melanogaster* tracheal system (Caviglia et al. 2016).

1.3 Mediators of Endosome Maturation

1.3.1 Phosphoinositides

The endosomal network is maintained through continuous fusion and fission events, membrane exchange, and recruitment of various regulators to coordinate endosome maturation. PIPs play a central role in compartmental identity, including that of endosomes, serving as binding platforms for proteins, assisting with the properties and functions of each endosome stage and sustaining directionality of the maturation process (Santiago-Tirado and Bretscher 2011; Fili et al. 2006). The seven species of PIPs (PI(3)P, PI(4)P, PI(5)P, PI(3,4)P_2, PI(3,5)P_2, PI(4,5)P_2, PI(3,4,5)P_3) are tightly controlled spatially and temporally by specific phosphatases (myotubularins) and kinases. Disruption of these enzymes leads to aberrant endosome trafficking.

The role of PIPs in endosome formation and maturation starts at the PM. PI(4,5)P_2 is present at the PM and is required for maturation of late-stage clathrin-coated pits prior to fission (Antonescu et al. 2011). PIP4K, which contributes to the generation of PI(4,5)P_2, regulates EE dynamics during clathrin-mediated endocytosis (Kamalesh et al. 2017). PI(3,4)P_2 has also recently emerged as a major mediator in clathrin-mediated endocytosis (Posor et al. 2013). Subsequently, the early endocytic pathway is dominated by PI(3)P. It is unclear how this conversion to PI(3)P is mediated, but the steps are likely to involve the Sac2 PI(4)P phosphatase and class III PI3K (PI3KC3 or Vps34 in yeast) (Hsu et al. 2015). PI(3)P is recognized by proteins with FYVE or PX domains, such as the EE tether EEA1 and the mediator of ILV formation Hrs (Schink et al. 2013; Candiello et al. 2016; Katzmann et al. 2003). During recycling, hydrolysis of PI(3)P and generation of PI(4)P on secretory/recycling endosomes are required for exocyst recruitment to enable fusion with PM, as visualized by transferrin receptor (TfR) recycling in HeLa and COS-1 cells (Ketel et al. 2016). A further regulatory step is accomplished by PI(5)P, the enrichment of which can delay endosome maturation to ensure completion of EE events prior to LE transition (Boal et al. 2015).

During EE to LE transition, PIKfyve catalyzes phosphorylation of PI(3)P to PI(3,5)P_2 and leads to conversion of PI(3)P at EEs to PI(3,5)P_2 at LEs and lysosomes. PI(3,5)P_2 was found to be enriched in the vesicular domain of endosomes in HeLa cells and was required for delivery of endocytic cargo into MVB, potentially via its interaction with the ESCRT-III component Vps24 (Shaw et al. 2003; Takatori et al. 2016; Jin et al. 2016). One of the principal functions of PI(3,5)P_2 is to regulate the fission in LEs and lysosomes (Dove et al. 2009). PI(3,5)P_2 was proposed to be important for membrane retrieval from matured lysosomes in *C. elegans* (Nicot et al.

2006). Its role in retrograde trafficking is essential in yeast, plants, and mammalian cells (Jin et al. 2016). In plants, PI(3,5)P_2 has been shown to mediate maturation of LEs by promoting their organization along the cortical microtubules (Hirano et al. 2015). PIKfyve activity is likewise important for regulation of the reformation of terminal storage lysosomes from endolysosomes (Bissig et al. 2017). An additional PIP species PI(3,4)P_2 assists in fission events by localizing at tubular domains and aiding scission (Posor et al. 2013; Tan et al. 2015). In phagosomes, PIPs act as markers of phagosome maturity and are required for fusion of phagosomes with endosomes and lysosomes (Jeschke et al. 2015). Phagocytic receptors determine PIP dynamics and dictate phagosome fate (Sarantis and Grinstein 2012; Bohdanowicz and Grinstein 2013; Levin et al. 2015; Posor et al. 2015).

1.3.2 Rab GTPases

In parallel with PIPs, Rab GTPases have central roles in membrane organization and trafficking and likewise serve as platforms at membranes for effector protein recruitment (Jean and Kiger 2012). Inactive Rabs are recruited to membranes and are activated by specific Rab GEFs (GDP/GTP exchange factors). Active Rabs control specificity of endosome fusion by interacting with PIPs and tethering complexes, thereby determining functional identity of the endosome at which they are positioned (Balderhaar and Ungermann 2013). Rabs can be inactivated by inherent GTP hydrolysis, which is further enhanced by specific Rab GAPs (GTPase-activating proteins). Over 70 different Rabs have been identified in humans. Besides Rabs, other types of GTPases have been reported to mediate lysosomal interactions with LEs and phagosomes. Arf and Arf-like GTPases are recruited to endosomes and lysosomes and play a role in directing traffic to lysosomes and recycling endosomes (Garg et al. 2011; Marwaha et al. 2017). Septins, filamentous heteromeric GTPases, are also implicated in endocytic membrane traffic without affecting Rab5 and Rab7, by promoting LE–lysosome fusion (Dolat and Spiliotis 2016).

The main Rab in EEs, Rab5, is recruited to EEs and facilitates fusion with endocytic and Golgi-derived vesicles. Rab5 plays an essential role in the biogenesis of the endolysosomal system (Zeigerer et al. 2012). Rab5 has three isoforms in mammalian cells, with Rab5a being the major Rab5 species to facilitate EE progression to LEs (Chen et al. 2009). As endosomes mature, Rab5 is replaced by Rab7, which mediates fusion with LEs and lysosomes (Rink et al. 2005). Rab7 is directly or indirectly involved in every step between EEs and lysosomes, including EE transition to LEs, LE transport to lysosomes, lysosome biogenesis, and LE–lysosome fusion. Additional Rabs, such as Rab11, Rab4, and Rab22, are involved in recycling pathways at EEs and are displaced following, or concomitant with, Rab5–Rab7 conversion, reflecting restriction of sorting and recycling pathways to early stages of endosome maturation (Grant and Donaldson 2009; McDermott and Kim 2015; D'Souza et al. 2014; Szatmari et al. 2014). Other Rabs, such as Rab7b, Rab6, and Rab9, contribute to the transport between endosomes and Golgi (Progida and Bakke 2016; Gutierrez

2013; Progida et al. 2010). Phagosomes contain at least 20 different Rab species, but their contribution to phagosome maturation remains to be investigated (Fairn and Grinstein 2012). Rab dynamics in phagosomes differ from those in endosomes. For example, in phagosomes Rab10 might be acting upstream of Rab5 to facilitate recycling of GPI anchor (Cardoso et al. 2010), and phagosome–lysosome fusion might be enhanced by Rab34 independently of Rab7 (Kasmapour et al. 2012). In macropinosomes in Cos-7 cells, Rab7 started to accumulate around the timing of cup closure and continued to increase even after fusion with lysosomes (characterized by the decrease of CI-M6PR), with its activity highest in lysosomes (Yasuda et al. 2016).

1.3.3 Tethers

Rabs execute their functions in part through interaction with tethering complexes, such as CORVET and HOPS, which activate and proofread SNARE assembly to drive membrane fusion. CORVET, a Rab5 effector, is involved in homotypic fusion of EEs and is required for MVB formation, possibly by facilitating fusion to supply membrane for ILV generation (Balderhaar and Ungermann 2013). HOPS is a Rab7 effector and is involved in the trafficking and docking of LEs to lysosomes. CORVET–HOPS conversion may facilitate Rab conversion, as the Rab conversion mediator Mon1 also interacts with HOPS (Solinger and Spang 2013; Poteryaev et al. 2010). Replacement of CORVET with HOPS ensures fusion with LEs, autophagosomes, and lysosomes, but no longer with EEs. Accordingly, disruptions of CORVET and HOPS lead to premature and delayed endosome maturation, respectively (Solinger and Spang 2014). An additional role has been proposed for the Vps39 subunit of HOPS in assisting with the formation of contact sites between vacuoles and mitochondria to promote exchange of nutrients, lipids, and ions between the two organelles, although it is not clear whether this additional function is independent of its function in the tethering complex (Honscher et al. 2014; Elbaz-Alon et al. 2014). In yeast, CORVET and HOPS share four core subunits (Vps11, Vps16, Vps18, and Vps33) and differ in a further two subunits (Vps8/3 for CORVET and Vps41/39 for HOPS), which bind the corresponding Rabs and bring the vesicles together for fusion. The SNARE-interacting core subunit Vps33 facilitates the SNARE-mediated fusion between the two vesicles and provides an additional layer of specificity, with different SNAREs present on EEs and LEs (Spang 2016). Lower abundance hybrid tethering complexes also exist, but their role in tethering and endosome maturation remains to be explored. In metazoans, there are at least two isoforms of the core subunits Vps33 and Vps16, which provide additional diversity and roles to tethering complexes. For example, Vps33b and Vps16b (Spe39 or VIPAR) form a complex, either a dimer or part of a larger complex, CHEVI, which has been proposed to accept cargo from the TGN (Spang 2016). Vps16b also forms a complex with a Vps33 homolog, Vps45, and a Rab5 effector Rabenosyn-5, and may form part of a larger complex, FERARI, which is believed to be involved in recycling and retrograde traffic (Spang 2016; Tornieri

et al. 2013; van der Kant et al. 2015). A further unrelated multi-subunit tethering complex called endosome-associated recycling protein (EARP) has been shown to play a role in recycling of endocytic receptors to the cell surface (Schindler et al. 2015). Additional prominent tethers, such as the EEA1 homodimeric protein at EEs, contribute to membrane exchange and endosome maturation in concert with specific Rabs and PIPs (Balderhaar and Ungermann 2013; McDermott and Kim 2015; Kummel and Ungermann 2014). EEA1 ubiquitination status governs its functionality, with perturbations leading to severe disruptions to endosome morphology and trafficking (Ramanathan et al. 2013).

1.3.4 ESCRTs

Membrane cargo destined for degradation is ubiquitinated and sorted into ILVs. Ubiquitinated cargo is recognized by the ESCRT-0 component Hrs (Vps27 in yeast), resulting in the recruitment of further ESCRT I–III complexes to assist with budding and fission during ILV formation. Cargo deubiquitination takes place prior to the ILV fission and internalization into the MVB (Huotari and Helenius 2011; Hubner and Peter 2012; Gschweitl et al. 2016; McDermott and Kim 2015; Katzmann et al. 2003; Santiago-Tirado and Bretscher 2011). The AAA-ATPase Vps4 cooperates with ESCRT-III to induce membrane scission and disassembles the ESCRT components from ILVs to recycle them back into the cytoplasm (Schmidt and Teis 2012; Adell et al. 2014).

1.3.5 V-ATPase

Critical to endosome maturation is the acidic pH of endosomal network. The pH drop and the maintenance of acidified compartments are achieved by the vacuolar proton pump V-ATPase. V-ATPases are multi-subunit complexes that consist of the cytosolic ATPase sector V_1 and a transmembrane proton-translocating sector V_0. The two sectors are assembled separately, V_1 in the cytosol and V_0 in the ER, and are brought together into a functional proton pump at the required organelles (Cotter et al. 2015). Nascent phagosomes may acquire V-ATPase directly from lysosomes (Sun-Wada et al. 2009). Blocking V-ATPase function with specific pharmacological inhibitors or by siRNA leads to accumulation of cargo in EEs and subsequent inhibition of endocytosis (Pena-Llopis et al. 2011; Smith et al. 2016). In AtT20-secreting cells, V-ATPase deficiency led to the formation of large hybrid organelles containing markers of immature granules, lysosomes, and autophagy, affecting both degradation and secretory pathways (Sobota et al. 2009) and reflecting broader functions of the V-ATPase besides the endosomal pathway. Although secretory functions and correct targeting of PM proteins in yeast depend on V-ATPase-mediated acidification (Huang and Chang 2011), the functionally

overlapping recycling pathways appear not to require V-ATPase (Baravalle et al. 2005). Initially shown to be important for the delivery of ILVs to lysosomes (van Deurs et al. 1996), V-ATPase activity does not appear to be essential for lysosome ability to fuse with endosomes and phagosomes (Kissing et al. 2015; Mauvezin et al. 2015) or indeed may even negatively regulate vacuole fusion (Desfougeres et al. 2016). During exocytosis of indigestible material in the phagolysosome, V-ATPase is retrieved just prior to exocytosis allowing the phagosome lumen to neutralize. Any V-ATPase that ends up at PM gets rapidly endocytosed (Clarke et al. 2010).

Besides vacuolar acidification, V-ATPase is involved in extracellular acidification in specialized cells, such as renal intercalated cells and osteoclasts, to assist with pH homeostasis and bone resorption, respectively (Cotter et al. 2015). Apart from proton-pumping function, the V-ATPase appears to act as a sensor for the luminal pH and also helps to regulate cytosolic pH and proteasome behavior in the cytosol (Peters et al. 2013; Hurtado-Lorenzo et al. 2006). V-ATPase has been shown to modulate vesicular trafficking through recruitment of small GTPases such as Arf6 (Hurtado-Lorenzo et al. 2006). The V-ATPase can also sense lysosomal amino acid levels and control mTORC1 activity at lysosomes, although the mechanisms underlying this sensory function remain unclear (Maxson and Grinstein 2014; Zoncu et al. 2011). Additionally, the V_0 sector by itself is able to facilitate membrane fusion and plays a role in sorting and secretion independently of its acidification functions (Jefferies et al. 2008; Merz 2015; Sobota et al. 2009; Liegeois et al. 2006; Sreelatha et al. 2015). V-ATPase membrane fusion function appears to be important for the retrieval and recycling of the Rab7 effector HOPS from the lysosome, indirectly modulating downstream Rab7 functions. The V_1 sector subunit H might be involved in the phosphorylation of the HOPS subunit Vps33b to promote endosome maturation and endosome–lysosome fusion (Wong et al. 2011). It is feasible that other subunits may have further roles in endosome maturation and elsewhere in the cell. For example, the V_1 sector subunit B interaction with actin nucleation-promoting factor WASH was important in recycling functions and lysosome neutralization prior to exocytosis of undigested material in *D. melanogaster* cells, implicating V-ATPase in coordination with multiple aspects of endosome maturation (Nagel et al. 2017). Such an array of functions makes it challenging to dissect the contributions of V-ATPase-mediated acidification and alternative V-ATPase functions during endosome maturation.

1.3.6 Additional Mediators of Vacuolar pH

Proton pump activity is complemented and potentially regulated by proton channels, such as the Na^+/H^+ and Cl^-/H^+ exchangers (Xinhan et al. 2011; Satoh et al. 2016; Prasad and Rao 2015). These channels act as a proton leak, important for counterbalancing V-ATPase activity and fine-tuning pH at specific organelles. The chloride channel CLC-5 has been implicated in creating a proton flux necessary for V-ATPase activation, whereas the sodium channel NHE6 locates to EEs and affects TfR uptake and recycling. In yeast, Nhx1p sodium channel plays a role in luminal pH regulation,

critical for recycling, retromer, and endocytic pathways (Kojima et al. 2012). Nhx1 activity was found to promote MVB fusogenicity, consistent with observations that MVB fusion with lysosomes is highly sensitive to manipulations of both luminal and cytosolic pH (Cao et al. 2015; Karim and Brett 2017). Besides V-ATPase, acidification in plants is mediated by an additional pump, the vacuolar pyrophosphatase (V-PPase), with a unique and essential role in endocytic and secretory trafficking. V-PPase is a homodimer of a single polypeptide, which uses energy from the biosynthetic by-product pyrophosphate (PPi) to drive proton transport. Combined activity of V-ATPase and V-PPase is required for vacuolar acidification (Kriegel et al. 2015; Zhou et al. 2016). Their functional coordination remains to be established.

1.3.7 Cytoskeleton

Actin organization plays an essential role in endocytosis and endosome maturation. Actin polymerization through WASH, a nucleation-promoting factor and an activator of Arp2/3 complex, powers assembly of endocytic vesicles and their movement toward EEs (Nannapaneni et al. 2010). Myosin VI interacts with the endocytic marker and Rab5 effector APPL1 through its adaptor GIPC and helps transport the nascent vesicles away from the actin-rich periphery of the cell toward the EEs (Granger et al. 2014; Nielsen et al. 1999). Moesin supports F-actin network formation on endosomes through its interaction with Rab7 and is required for recycling and endosome maturation, possibly through membrane remodeling and segregation of tubular and multivesicular structures (Duleh and Welch 2010; Muriel et al. 2016; Chirivino et al. 2011). Actin also interacts with HOPS, suggesting that actin cytoskeleton plays an important role in later maturation stages too, perhaps by helping lysosomes maintain their position within the cell (Solinger and Spang 2013), or for the delivery of protease- and lipase-containing vesicles to endosomes (King et al. 2013; Kirkbride et al. 2012). Actin cytoskeleton remodeling is likewise essential for phagocytosis and for phagosome maturation (Freeman and Grinstein 2014). While actin polymerization drives membrane expansion around the particle during its internalization, larger particles also require F-actin disassembly prior to phagosome cup closure, potentially to avoid substrate exhaustion for further polymerization to complete internalization (Schlam et al. 2015). Actin assembly at phagosomes promotes their fusion with LEs and lysosomes, thereby affecting phagosome pH, membrane recycling and delivery of hydrolytic enzymes, essential events during phagosome maturation (Marion et al. 2011; Dieckmann et al. 2012; Gopaldass et al. 2012).

Endosome spatial organization and exchange of internalized material between compartments are facilitated by endosome movement along the microtubule cytoskeleton. The molecular mechanisms underlying the transition from actin cytoskeleton at the cell periphery to the microtubule cytoskeleton during endosome maturation remain to be elucidated (McDermott and Kim 2015). Kinesins and dyneins move cargo, including endosomes, toward the peripherally anchored plus ends and centrally located minus ends of the microtubule cytoskeleton, respec-

tively. Dyneins use adaptor molecules such as dynactin and the Rab7 effectors RILP or Hook1 to transport endosomes toward lysosomes, whereas kinesins may interact with Rab4 and Rab11 to recycle cargo back toward the cell periphery (Granger et al. 2014; Solinger and Spang 2013; McDermott and Kim 2015). Rab5 might regulate EE motility on microtubules (Nielsen et al. 1999), since Rab5 co-immunoprecipitates with dynein (Zajac et al. 2013); however, it is unclear how dynein binds EEs. Dynein activity was shown to be necessary for efficient endocytic uptake and endosome maturation in *D. melanogaster* oocytes (Liu et al. 2015) and likewise has been implicated in sorting TfR away from EGF-containing EEs in HeLa cells (Driskell et al. 2007). It is possible that dynein mediates sorting by facilitating elongation and scission at the sorting endosome and by maintaining its position while kinesins transport recycling endosomes to PM. Near the PM, actin takes over to assist with the final stages of exocytosis. In LEs, Rab7 can direct movement both ways, via RILP and dynein—dynactin interactions toward perinuclear location, or via the FYVE and coiled-coil (CC) domain-containing protein FYCO1 and kinesin toward the periphery (Guerra and Bucci 2016; Pankiv et al. 2010). In phagosomes, Rab7 interaction with RILP and dynein–dynactin promotes the formation of tubular extensions toward LEs and subsequent fusion (Harrison et al. 2003). Furthermore, in HeLa cells, Rab7 directly interacts with and phosphorylates vimentin, a type III protein of the intermediate filament cytoskeletal network, further reinforcing the role of Rab7 in endosome positioning within the cell (Cogli et al. 2013).

1.4 Coordination of Endosome Maturation

As endosomes mature, from early to sorting to late endosomes and ultimately to endolysosomes, their identities change to reflect their functions. For example, the peripheral location and the slightly acidic milieu of the EEs allow them to accept cargo from PM and sort it to the recycling pathways. In contrast, LEs translocate toward the perinuclear space, assemble a different set of tethers, and acquire components necessary for the lysosomal environment where the cargo is to be degraded. Rab5 and PI(3)P at early stages and Rab7 and $PI(3,5)P_2$ at later stages of endosome maturation seem to be major determinants of endosomal functions and are therefore tightly regulated. While Rab conversion and PIP conversion are recognized as major contributors to endosome maturation, V-ATPase activity is also participating in this transition. No single master coordinator of this transition has yet been identified. Rather, the coordination of these regulatory changes seems to exist at the level of significant cross talk between the key players in endosome maturation.

1.4.1 Sorting Compartments

During sorting, membrane domains destined for recycling organize into tubular domains, which then undergo fission to form recycling vesicles. Meanwhile, membrane domains destined for degradation bud in the opposite direction to form ILVs. During tubular-based membrane sorting, the tubular network formation requires various cargo adaptor sorting nexin (SNX) proteins, which step in at specific maturation stages to aid recycling to the PM and retrieval to Golgi (van Weering et al. 2012). Retrieval to the Golgi is mediated by the retromer complex, which interacts with PI(3)P, Rab5, and Rab7 for its recruitment to endosomes in mammalian cells (Seaman et al. 2009; Takatori et al. 2016; Bean et al. 2017). In yeast, retromer plays a dual role in retrograde cargo export and in control of LE–vacuole fusion dynamics (Liu et al. 2012). SNX–BAR recruitment to Rab7-positive membranes displaces Rab7 from the cargo-bound cargo selection complex (CSC), thus separating the retromer-positive tubule from the Rab7-positive vesicular domain (Purushothaman et al. 2017). In mammalian cells, the retromer has recently been shown to play a role in controlling Rab7 localization and activity via Rab7 GAP TBC1D15, with further research underway to dissect this unanticipated retromer function (Jimenez-Orgaz et al. 2017). As well as functioning as a structural component of the retromer-mediated tubule formation, SNX–BAR heterodimers independently can sense proteins for recycling or retrieving, for example, through association with the hydrophobic tripeptide WLM motif, as in the case of CI-M6PR (Kvainickas et al. 2017; Simonetti et al. 2017). In many instances, cargo retrieval proceeds independently of retromer and instead relies on the newly identified and functionally distinct retriever complex, such as in the case of $\alpha_5\beta_1$ integrin (McNally et al. 2017). Sorting of membrane cargo is facilitated by ubiquitination and deubiquitination steps. Ubiquitination at PM triggers internalization of the cargo and tags it for packaging into ILVs, whereas deubiquitinated cargo is targeted back to the cell surface via recycling pathways (MacDonald and Piper 2016). Catabolism of lipids and membrane-bound cargo in ILVs requires the help of lipid binding and transfer proteins that can distort membrane structures and bind membrane proteins and present them to the water-soluble lysosomal hydrolases. ILV maturation involves cholesterol removal by the glycoprotein NPC2, which transfers it to other vesicles or to NPC1 for efflux. This makes membrane cargo, such as sphingolipids, more accessible to lysosomal degradation (Sandhoff 2016). Rab7 effector and microtubule adaptor RILP interacts with ESCRT-II, thereby coordinating ILV formation with endosome motility (Solinger and Spang 2013). Interestingly, endosomes in *Aspergillus nidulans* were able to form MVBs in absence of Rab7 and were degradation competent but had a compromised vacuole in the form of multiple minivacuoles with EE features (Abenza et al. 2012).

1.4.2 Rab Conversion

Regulation of Rab5 and Rab7 on EEs and LEs, respectively, helps the two compartments maintain their identity and functions. The Rab5–Rab7 conversion is the hallmark of EE–LE transition, and its perturbations delay endosome–lysosome fusion, prolong homotypic fusion, and result in enlarged endosomes, such as Dmon1 mutation in *D. melanogaster* (Yousefian et al. 2013) or *SAND-1* mutation in *C. elegans* (both homologs of the mammalian Mon1) (Poteryaev et al. 2010). During Rab5–Rab7 conversion, Rab5 is displaced by Rab7, a process that is driven by a combination of repression of Rab5 activation, withdrawal of Rab5 recruitment factors, Rab7 recruitment and activation, and physical displacement of Rab5 by Rab7. The Mon1–Ccz-1 complex mediates all of these processes. In *C. elegans* coelomocytes, Mon1 homolog SAND-1 has been shown to be required for Rab5 repression and for Rab7 recruitment. SAND-1 interacts with the Rab5 GEF RABX-5, displacing it from the endosomes into the cytosol, hence leading to the repression of Rab5 recruitment and activation (Poteryaev et al. 2010). In absence of SAND-1, RABX-5 was trapped on EEs, leading to enlarged endosomes. Similarly, Mon1 siRNA in HeLa cells also led to enlarged EEs, suggesting a defect in endosome maturation progression. In parallel with Rab5 repression, the Mon1–Ccz1 complex acts as a Rab7 GEF and activates Rab7, which arrives to the endosomes concomitantly with the Mon1, leading to the displacement of Rab5 by the Rab7 (Nordmann et al. 2010). Mon1–Ccz1 also interacts with the HOPS complex, also thought to act as a Rab7 GEF alongside its tethering functions (Balderhaar and Ungermann 2013; Poteryaev et al. 2010). Additionally, Rab5 inactivation is coordinated with Rab7 activation in a cross talk involving Rab5 effector BLOC-1, which ensures that Rab5 is inactivated only when Rab7 and HOPS are present (John Peter et al. 2013; Rana et al. 2015). Such displacement of Rab5 by Rab7 has been described as a cutout switch, which ensures the mutually exclusive domains of the two Rabs and a unidirectional progression of endosome maturation. This model accommodates for the observations that Rab5 levels gradually increase and then drop suddenly concomitant with the Rab7 increase (Del Conte-Zerial et al. 2008). The onset and coordination of Rab5–Rab7 conversion are still poorly understood, but are likely influenced by endosome size and PI(3)P levels (Poteryaev et al. 2010). Indeed, PI(3)P levels, alongside Rabex-5, are important for Mon1 recruitment to EEs to initiate Rab5–Rab7 conversion (Vieira et al. 2003; Poteryaev et al. 2010; Lawrence et al. 2014). Interestingly, Mon1–Ccz1 is recruited to autophagosomes by PI(3)P independently of Rab5, where it functions to recruit Rab7 to enable autophagosome fusion with lysosomes. Rab5 is still required by those organelles for the acquisition of hydrolases (Hegedus et al. 2016).

1.4.3 Rab5 Regulation

Rab5 is recruited to EEs via endocytic vesicles from PM or via direct activation by the Rabaptin5–Rabex5 complex. The Rab5 GEF Rabex5 might already be present on endocytic vesicles prior to fusion with EEs (Balderhaar and Ungermann 2013) or be recruited to EEs by Rab22, Rab4, and ubiquitinated cargo (Kalin et al. 2015; Zhu et al. 2009). Stabilization and amplification of endosomal Rab5-GTP levels are achieved via the two positive feedback loops generated by the Rab5 interactions with its GEF Rabex5 as well as with the PI(3)P kinase Vps34, which is present at the EE (Zerial and McBride 2001). The PI(3)P allows for recruitment of the FYVE-domain-containing Rabenosyn-5, which recruits further Rabex5. The PM-located PI(4,5)P_2 was required for endocytosis and Rab5 recruitment in *Drosophila* oocytes and was subsequently released from endosomes in a Rab5-dependent manner, a step necessary for further endosome maturation (Compagnon et al. 2009). In interferon-γ-activated RAW264.7 macrophages, Rab20 prolonged Rab5 association with phagosomes, explaining the delay in phagosome maturation associated with macrophage activation (Pei et al. 2014). The Rab5–Rab7 conversion involves Rab5 inactivation, which is mediated by the displacement of Rabex5 by the Mon1–Ccz1 complex (Poteryaev et al. 2010). Inactivation of Rab5 can also be mediated by RabGAP5, which is in part coordinated by the GTP-binding protein DRG2 (Mani et al. 2016). Additionally, the decrease of ubiquitinated cargo following its internalization into ILVs, and inactivation of Rab4, may contribute to the loss of Rab5 activation (Kalin et al. 2015). Monoubiquitination of Rab5 itself has been proposed to prevent its interaction with downstream effectors such as EEA1 (Shin et al. 2017). The rising levels of Vps34 and its product PI(3)P in the maturing endosome lead to the recruitment of the Rab5 GAP TBC-2, facilitating the rapid drop of Rab5 levels at the endosome, as demonstrated in *C. elegans* and mammalian cells (Shin et al. 2005; Law et al. 2017). V-ATPase activity also contributes to Rab5 displacement, as clamping endosomal pH at 6.2, i.e., the typical pH of EEs, delayed Rab5 release, prolonged the EE state, and inhibited the EE–LE transition in HeLa cells (Wang et al. 2015). Thus, multiple parallel processes contribute to Rab5 regulation and turnover.

1.4.4 Rab7 Regulation

Rab7 recruitment is regulated by the Rab7 GEF, Mon1–Ccz1, and modulated by phosphorylation by the tumor suppressor PTEN, which promotes ILV formation and growth receptor inactivation (Shinde and Maddika 2016; Nordmann et al. 2010). Interestingly, the Mon1–Ccz1 complex promotes Rab7 activity on late endosomes only. In Cos-7 and HeLa cells, Mon1–Ccz1 has been shown to dissociate from lysosomes and not be required for Rab7 activity on those organelles. This may ensure unidirectionality in LE–lysosome transition (Yasuda et al. 2016). The protective lysosomal glycoprotein LAMP-2, which is recruited to LEs independently of Rab

conversion or acidification, is required for the recruitment of Rab7 and fusion of LEs with lysosomes (Huynh et al. 2007; Endo et al. 2015). PI3KC3 was shown not to be necessary for Rab7 recruitment; however, it participates in subsequent Rab7 regulation through recruitment of Rab7 GAP, Armus (Vieira et al. 2003; Jaber et al. 2016). Furthermore, the PI3KC3 complex component and activator of PI(3)P production, UVRAG, interacts with HOPS and acts as a Rab7 GEF. Rab24 has been proposed to be in a complex with Rab7 and promote endosome maturation and degradation (Amaya et al. 2016). Various posttranslational modifications of Rab7, such as palmitoylation, phosphorylation, and ubiquitination, have been proposed to play a role in modifying and fine-tuning specific interactions with Rab7 effectors, facilitating coordination of different pathways at the LE (Modica and Lefrancois 2017; Modica et al. 2017; Lin et al. 2017).

1.4.5 PIP Conversion

Phosphorylation of PI(3)P to PI(3,5)P_2 during endosome maturation is catalyzed by the PIKfyve kinase (Fab1p in yeast), thought to be important for regulation of vacuole size (Dove et al. 2009). PI(3,5)P_2 promotes membrane fission during endosome maturation, whereas HOPS and the V-ATPase promote fusion. HOPS binding to PI(3,5)P_2 promotes coordination between the two opposing events (Solinger and Spang 2013). As expected, PIKfyve deficiency in mammalian cells depleted PI(3,5)P_2 levels and led to the formation of multiple enlarged endosomes, unable to fuse with lysosomes, which was rescued by addition of PI(3,5)P_2 (Compton et al. 2016). The PI(3,5)P_2 deficiency phenotype could also be countered by inhibition of Rab5, via suppression of homotypic fusion and hence prevention of vacuole enlargement (Compton et al. 2016).

1.4.6 PIP Regulation

PI(3)P, whose presence is necessary for the EE identity, is generated by Vps34 (PI3KC3), which is recruited to the membranes by Rab5-GTP (Shin et al. 2005; Law et al. 2017; Christoforidis et al. 1999). PI3KC3 localization, stability, and activity can be regulated through phosphorylation, ubiquitination, and SUMOylation (Schink et al. 2013). PI3KC3 activity is stimulated by Rabex-5, when it forms a complex with ArfGAP1, mediated by AP-1 clathrin-coated vesicle adaptor protein complexes (Candiello et al. 2016). The PI3KC3 activity levels are positively regulated by UVRAG, which also interacts with the C-VPS/HOPS complex, a Rab7 GEF. UVRAG in turn is regulated positively by Rab7, which competes with UVRAG for the binding partner Rubicon, another component of the endosomal PI3KC3 complex. The Rab7-sequestered Rubicon liberates UVRAG to bind HOPS in a feed-forward loop (Sun et al. 2010). mTORC1 provides an additional layer of regulation to endo-

some maturation by phosphorylating UVRAG and preventing its interaction with HOPS, leading to an inhibition of endosome maturation (Kim et al. 2015). In line with these observations, PI3KC3 deficiency did not compromise TfR recycling, but resulted in elevated levels of Rab5-GTP and Rab7-GTP at endosomes, enlarged LEs, and reduced EGFR degradation. Elevated Rab7-GTP led to a failure of ILV formation and lysosome maturation in mammalian cells (Jaber et al. 2016). PI(3)P serves as the main source for $PI(3,5)P_2$ production by phosphorylation by PIKfyve. $PI(3,5)P_2$ levels can be reversed by dephosphorylation by Fig4 (Sac3) phosphatase to yield PI(3)P or by myotubularin 3 to yield PI(5)P. Interestingly, Fig4 also acts as a PIKfyve activator (Currinn and Wassmer 2016). Coordination of $PI(3,5)P_2$ production in relation to endosome maturation remains to be explored. A recent study identified a WD40-repeat protein WDR91 as a Rab7 effector that inhibits PI3KC3 activity, potentially coupling Rab conversion to PIP conversion in EE to LE transition (Liu et al. 2017). In phagosomes, association of PI3KC3 with the phagosomal membrane and the production of PI(3)P by PI3KC3 are pH-sensitive and stop when the phagosome is acidified, highlighting the role of acidification in coordinating phagosome maturation (Naufer et al. 2017).

1.4.7 V-ATPase Regulation

The V-ATPase complex consists of over a dozen different subunits, many of which have multiple isoforms and splice variants at least in higher eukaryotes, and is associated with several accessory proteins, which may regulate V-ATPase assembly and activity (Cotter et al. 2015; Maxson and Grinstein 2014). This degree of complexity allows control of V-ATPase activity and pH at multiple levels. The association–dissociation kinetics of the V_0 and V_1 sectors are determined by various stimuli, such as glucose availability and cytosolic pH, and provide immediate and direct control over V-ATPase activity. An intact microtubular network is required for dissociation, whereas the V-ATPase regulator protein RAVE is required for reassociation through interaction with the V_1C subunit (Jefferies et al. 2008; Xu and Forgac 2001). The expression of genes encoding V-ATPase subunits is at least partly regulated by the transcription factor TFEB. In response to nutrient deprivation or lysosomal dysfunction, inhibition of mTORC1 activity at lysosomes induces TFEB-mediated transcription of V-ATPase components (Ben-Sahra and Manning 2017). This regulation highlights the role of acidification in nutrient acquisition and ensures matching demand and supply. Phosphatidic acid phosphatase, whose main role is in lipid biosynthesis, is another recently discovered negative regulator of V-ATPase gene expression as shown for Pah1p in yeast (Sherr et al. 2017), reinforcing the connection between nutrient homeostasis and endosome acidification.

The different isoforms may be responsible for varying coupling efficiencies of the proton pump and are targeted to different compartments in the cell (Kane 2006; Sun-Wada et al. 2009). The spatial and functional separation of the different isoforms is evident with the V_0a subunit isoforms, such as in PC-3 cells, in which the V_0a1

subunit is responsible for TfR recycling, whereas V_0a3 is associated with the LEs and lysosomes (Smith et al. 2016). Isoform-specific assembly factors are involved in regulating V-ATPase in specific organelles. For example, RAVE assembly factor interacts only with the endosome-specific Vph1p but not with the Golgi-specific Stv1p isoform of the yeast V_0a subunit of the V-ATPase, hence allowing for regulation of V-ATPase activity specifically in endosomes (Smardon et al. 2014). Additionally, CORVET and HOPS are required for V-ATPase assembly at the lysosome, and Rab7 effector RILP controls the V_1G subunit stability and localization, potentially assisting with regulation of V-ATPase activity and lysosomal acidification (De Luca and Bucci 2014; De Luca et al. 2014; Bucci et al. 2000). When not bound to Rab7, free RILP is responsible for V_1G ubiquitination and proteasomal degradation. Thereby, functional Rab7 is required to sequester RILP and promote acidification (Yasuda et al. 2016).

PI3KC3 regulates V-ATPase assembly and trafficking in coordination with other V-ATPase regulators, such as mTORC1 and glucose (Stransky and Forgac 2015; Sautin et al. 2005). PI3KC3 has been shown to interact with the V_1B subunit in plants (Liu et al. 2016) and to regulate interaction between V-ATPase and F-actin; however, no known PIP binding sites exist in any of the V-ATPase subunits, so the mechanisms of V-ATPase regulation by PI3KC3 remain to be established (Chen et al. 2004). The downstream product of PI3KC3 and PIKfyve, PI(3,5)P_2, is required for the acidification activity of V-ATPase, at least in yeast, *D. melanogaster* and *C. elegans* (Dove et al. 2009). The mechanisms of this function are unclear, as PI(3,5)P_2 status of the cell does not appear to affect V-ATPase localization. However, it is likely to be involved in direct or indirect activation of the V-ATPase. Interestingly, phagosomes in mouse macrophages with defects in PIKfyve appeared to acidify normally but recruitment of lysosomal proteins LAMP1 and Cathepsin D was reduced and phagosome–lysosome fusion was compromised (Kim et al. 2014). This is supported by previous observations that fully functional PIKfyve does not appear to be essential for acidification in mice, probably because only small amount of PI(3,5)P_2 is required to support lysosomal acidification (Dove et al. 2009).

The downstream product of PI3KC3 and PIKfyve, PI(3,5)P_2, which is involved in endosome fission, does so in part by counteracting the membrane fusion function of the V-ATPase in LEs (Compton et al. 2016). Enlarged endosomes due to deficient PI(3,5)P_2 activity could be rescued by depletion of V-ATPase by RNAi, implicating V-ATPase in the cross talk with PIPs to regulate endosome size. Pharmacological alteration of endosomal pH did not rescue the PI(3,5)P_2 deficiency phenotype of aberrant vacuolation, suggesting that V-ATPase activity that is independent of its acidification function is responsible for PIP-mediated coordination of endosome maturation.

1.5 Contributions of Other Organelles to Endosome Maturation

1.5.1 ER

Besides the cytoskeleton, endosome positioning may also be affected by endosome interaction with the ER. The capture of endosomes by the ER might be mediated by various endosomal adaptors and scaffold proteins, which contain ubiquitin-binding domains and are ubiquitinated by the ER-located E3 ubiquitin ligase RNF26. This ensures that the endosomes are retained in the perinuclear region, where their functions can be efficiently supported by the proximal ER, TGN, and lysosomes (Jongsma et al. 2016). Such ubiquitination and the opposing deubiquitination regulate endosome motility and their position in the cell. These mechanisms allow for orchestration of endosomal maturation and cargo trafficking. Additionally, endosomes form contact sites with the ER, which increase in number as endosomes mature, with 50% EEs and 99% LEs associated with the ER, highlighting the importance of their interaction at later maturation stages (Friedman et al. 2013). The ER contact sites might mediate endosome association with the microtubule motors dynein and kinesin, thus influencing endosome traffic and maturation (Raiborg et al. 2015). Both endosome-localized PI(3)P and Rab7 are recognized by the ER protein protrudin at the ER–LE contact sites, which leads to the transfer of kinesin-1 from protrudin to FYCO1 on LEs, to regulate endosome traffic in mammalian cells (Raiborg et al. 2015). As endosomes traffic, their interaction with the ER causes a dramatic deformation in the ER tubules and formation of new ER tubules, which follow the endosome movement (Zajac et al. 2013). Such observations suggest that the ER–endosome interactions are long-lived and strong enough for mobile endosomes to restructure the ER. Both the endosomes and the ER connect to microtubules at or near ER–endosome contact sites, implying that at least some endosomes traffic while coupled to the ER rather than in isolation (Friedman et al. 2013).

The ER plays a major supportive and regulatory role in endosome maturation, with the endosome–ER contact sites permitting cholesterol transfer, inter-organellar communication through Ca^{2+} signaling, ILV biogenesis, and inactivation of receptors by ER-resident phosphatases, such as EGFR inactivation by PTP1B (van der Kant and Neefjes 2014). The ER also forms contact sites with other compartments, such as mitochondria, Golgi, lipid droplets, and PM, and allows lateral transfer of lipids from endosomes to other organelles. The ER contact sites have been proposed to play a role in endosome fission, with almost every fission event preceded by an ER contact site formation at the budding endosome (Friedman et al. 2013; Rowland et al. 2014; Zajac et al. 2013). ER contact sites might allow recruitment of necessary fission factors, such as the SNX–BAR complexes, or supply lipids to modify membrane curvature to promote fission, or increase local Ca^{2+} concentration to promote Ca^{2+}-dependent endosome fission. Whether all fission events are orchestrated by the ER or only a certain subset, such as recycling, remains to be investigated.

Ca^{2+} signaling provides an important layer of regulation to endosome maturation and is required for SNARE-mediated membrane docking and fusion (Hay 2007). Endosomal compartments are able to maintain Ca^{2+} at levels much higher than those in the cytosol, and its release activates secondary messengers such as calmodulin and mediators of endosome maturation such as the tethering factor Munc13-4 (He et al. 2016; Luzio et al. 2010). Pharmacological buffering of Ca^{2+} induces phenotypes associated with lysosomal storage disorders, highlighting the significance of endosomal Ca^{2+} in endosome function (Lloyd-Evans and Platt 2011). Endosomal and lysosomal Ca^{2+} channels include the two-pore channels TPCs and the mucolipins TRPML1, TRPML2, and TRPML3. Importantly, ER–LE contact sites might contribute to the maintenance of endosomal Ca^{2+} levels by providing Ca^{2+} from the ER storage. This is supported by observations of a secondary spike in Ca^{2+} from the ER following initial Ca^{2+} release from lysosomes (Garrity et al. 2016; van der Kant and Neefjes 2014; Kilpatrick et al. 2013). Given their role in membrane fission, it is tempting to speculate that PIKfyve and its product $PI(3,5)P_2$ might be involved in regulation of Ca^{2+} signaling. Indeed, Ca^{2+} channels including TPCs, TRPML1, and TRPML2 appear to be gated by $PI(3,5)P_2$, and their silencing prevents phagosome–lysosome fusion, which can be rescued by pharmacological Ca^{2+} release (Dong et al. 2010; van der Kant and Neefjes 2014; Dayam et al. 2015). PIKfyve might also directly regulate Ca^{2+} channels (Luzio et al. 2007). Thus, it seems that integration of Ca^{2+} signaling and PIPs is one of the key aspects of membrane traffic control (Marchant and Patel 2015). Ca^{2+} signaling seems to respond not only to inputs from PIKfyve activity but also to V-ATPase activity, as the endosomal calcium channel TRPML3 is inhibited by acidic pH (Kim et al. 2008). In contrast, Ca^{2+} refilling into Ca^{2+}-depleted lysosomes seems to proceed independently of V-ATPase activity (Garrity et al. 2016). In turn, luminal Ca^{2+} homeostasis is important for proper acidification and membrane fusion, with elevated Ca^{2+} levels inhibiting acidification and increasing membrane fusion (Lelouvier and Puertollano 2011).

1.5.2 Lipid Droplets

Lipid droplets may also form transient contact sites with endosomes, believed to supply membrane components required for endosome function and maturation (Liu et al. 2007). Lipid droplets recruit Rab5 and are able to interact with the Rab5 effector EEA1, and therefore with EEs, implicating this organelle in endosomal membrane traffic (Liu et al. 2007). Lipid droplets have also been reported to form close associations with endosomes in macrophages taking up high levels of high-density lipoprotein (Schmitz et al. 1985), supporting their role in lipid storage and metabolism. Lipid droplets are emerging as major regulatory and signaling hubs and may yet have unidentified roles in endosome maturation.

1.5.3 Cross talk with the Autophagy Pathway

While extracellular substrates are delivered to lysosomes by the endosomal network, intracellular substrates reach the lysosomes via the autophagic pathways. Although viewed as a separate degradation pathway, autophagy by no means acts independently, and there is a significant overlap and cross talk between the two pathways. As such, Rab5, Rab7, and Rab11 have been shown to act in both pathways (Ao et al. 2014). For example, Rab11 was observed to translocate from recycling endosomes to autophagosomes following autophagy induction in *D. melanogaster* cells (Szatmari et al. 2014). Likewise, PI(3)P endosomal distribution and levels may be maintained by the autophagy protein Beclin-1, as observed in mouse fibroblasts (McKnight et al. 2014). Furthermore, endosomes can take on autophagy functions, as damaged mitochondria, ubiquitinated by Parkin, can be taken up by Rab5-positive endosomes to form MVBs in ESCRT-dependent manner to be subsequently delivered to lysosomes (Hammerling et al. 2017).

1.6 Perturbations of Endosome Maturation in Disease

The endosomal system is emerging as a central player in a wide range of neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's Disease (PD), Lewy body dementia, amyotrophic lateral sclerosis (ALS), and hereditary spastic paraplegia (HSP) (Luzio et al. 2010; Schreij et al. 2016). Neurodegeneration may be a result of impaired lysosomal degradation, such as the case of alpha-synuclein in PD (Miura et al. 2014), or a defect in broader endosomal functions, which may lead to protein mislocalization or aberrant secretion. Frequently, PIPs, Rabs and their effectors, proteins involved in V-ATPase assembly and function, and retromer components are involved in endosomal dysfunction-mediated neurodegeneration. There are many excellent reviews summarizing the effects of various aspects of the endosomal system on the vast number of neurodegenerative disorders (Schreij et al. 2016; Hu et al. 2015; Williamson and Hiesinger 2010; Borland and Vilhardt 2017; Progida and Bakke 2016; Colacurcio and Nixon 2016; Waugh 2015). Inherited neuropathies and myopathies also tend to be associated with mutations specific to the endosomal pathways, such as Rab7 in Charcot–Marie–Tooth disease, the PI(3)P and PI(3,5)P_2 3-phosphatase myotubularin in X-linked centronuclear myopathy, and PIKfyve in Francois–Neetens fleck corneal dystrophy (Nicot and Laporte 2008). The progressive neurological disorder Niemann–Pick type C (NPC) is caused by mutations to lysosomal cholesterol transporters NPC1 and NPC2 and indeed, like many other lysosomal storage disorders, is exacerbated by the resulting impairment to ER–endosome contact sites and lysosomal Ca^{2+} homeostasis (van der Kant and Neefjes 2014; Garrity et al. 2016; Jiang and Mizushima 2014; McDermott and Kim 2015).

Intracellular pathogens have long been known to subvert host defense pathways using a wide variety of mechanisms, the majority of which target the endosomal

network that is designed to kill the pathogen. These include the *Mycobacterium* virulence factor PtpA, which targets the tethering factor subunit Vps33b for dephosphorylation, *Legionella* SidK, which inhibits the V-ATPase-mediated acidification, and *Salmonella* SopD, which interacts with Rab7, blocking its binding to RILP and FYCO1, hence blocking fusion with lysosomes (Wong et al. 2011; Bach et al. 2008; Akbar et al. 2016; Xu et al. 2010; D'Costa et al. 2015). Many intracellular pathogens also target PIPs to slow down phagosome maturation, either by directly phosphorylating or dephosphorylating specific PIP species, or by deregulating the host enzymes involved in PIP conversions (Pizarro-Cerda et al. 2015). *Mycobacterium* ManLAM and MptpB, *Legionella* SidP, and *Salmonella* SopB are the notable examples of pathogen virulence factors required for pathogen survival that act by disrupting PIP pathways. Another aspect of endosome maturation, actin cytoskeleton remodeling, is essential for phagocytosis and for phagosome maturation and may be used by pathogens, such as the protozoan parasite *Leishmania*, to stall maturation (Freeman and Grinstein 2014; Lodge and Descoteaux 2005). Viruses also exploit the endosome system at various stages of viral lifecycle, from gaining entry into cells and capsid uncoating to envelopment and transmission (Vale-Costa and Amorim 2016). For example, inhibition of endosome-related processes, such as actin polymerization or TRPML2 activity, led to a decrease in viral infectivity for rabies and Ebola viruses, respectively (Piccinotti et al. 2013; de Armas-Rillo et al. 2016; Grimm et al. 2017). ESCRT–Vps4 complexes are necessary for capsid uncoating during early infection by human papillomavirus (HPV) and are likewise hijacked by herpes simplex virus-1 (HSV-1) at later stages to orchestrate its envelopment and hence assembly of the infectious virion (Kharkwal et al. 2016; Broniarczyk et al. 2017).

Many immune functions, such as antigen presentation, are strongly dependent on a fully functional endosomal system. Silencing of Arl8b, which regulates LE–lysosome interaction via HOPS, results in impaired formation of CD1 antigen-presenting complex in lysosomes, its delivery to PM, and phagosome–lysosome fusion (Garg et al. 2011). The normal functioning of platelets, i.e., the activation-dependent release of effectors from storage granules, relies on normal PIKfyve function in endosome maturation (Min et al. 2014). The CHEVI tethering complex subunits Vps33b and VIPAS39 are implicated in the arthrogryposis–renal dysfunction–cholestasis (ARC) syndrome, which is a fatal recessive disorder characterized by trafficking defects in multiple organs, persistent infections, and sepsis. Specifically, the clearance of endosomes with internalized pathogen recognition receptors (PRRs) is affected, and hence, PRR inactivation and modulation of inflammatory responses are compromised (Akbar et al. 2016).

Cancer development is frequently assisted by endosomal upregulation of oncogenic signaling, through defective trafficking of growth factor receptors, increased recycling, or decreased degradation (Stasyk and Huber 2016). The components and regulators of the endosomal–lysosomal network, such as dynamin, Beclin-1, and mTORC1, which act as oncogenes and tumor suppressors, feature extensively in many cancers, whether stalling EE maturation to enhance growth factor receptor signaling or promoting further endosome maturation to boost recycling functions, efficient nutrient degradation, and subsequent cell growth and migration.

1.7 Conclusions

The endosomal system is a complex network of membrane-bound compartments that communicate and exchange components with each other. Its diverse functions span not only nutrient acquisition, but also regulation of membrane composition and signaling at many different levels, affecting fundamental cell functions such as growth and polarity. Endosome maturation is essential for its integrity and function and is regulated by a wide array of inputs, ranging from small GTPases and regulatory lipids to pH and Ca^{2+} signaling, from scaffolding proteins and tethers to the cytoskeletal and ER networks. Coordination of endosome maturation is mediated by the cross talk between Rab GTPases, PIPs, and V-ATPase, which ensure the identity of endosomes as well as unidirectionality and appropriate timing at each step of endosome maturation. A properly functioning endosomal network is essential to life, and even the slightest perturbations in the endocytic pathways lead to severe consequences in cellular functions, many of them associated with neurological diseases, infections, immune regulation, and cancers. Continuing discoveries in basic cell biology are acutely needed for the development of therapies to treat the neglected genetic disorders as well as the highly prevalent neurodegenerative diseases and cancer.

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