Chapter 2
Integration of the Endocytic System into the Network of Cellular Functions

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Abstract Maintenance of physiologic cellular functions and homeostasis requires highly coordinated interactions between different cellular compartments. In this regard, the endocytic system, which plays a key role in cargo internalization and trafficking within the cell, participates in upkeep of intracellular dynamics, while communicating with multiple organelles. This chapter will discuss the function of endosomes from a standpoint of cellular integration. We will present examples of different types of interactions between endosomes and other cellular compartments, such as the endoplasmic reticulum (ER), mitochondria, the plasma membrane (PM), and the nuclear envelope. In addition, we will describe the incorporation of endocytic components, such as endosomal sorting complexes required for transport (ESCRT) proteins and Rab small GTPases, into cellular processes that operate outside of the

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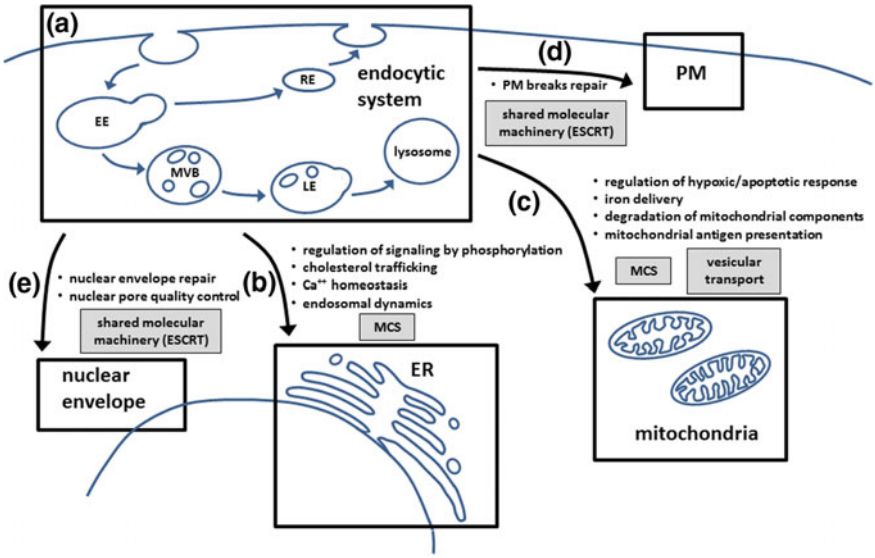

Fig. 2.1 Functional implications (bulleted lists) and the mechanisms involved (gray-filled boxes) of endosomal interactions with other cellular compartments. Selected examples for communication between organelles of the endocytic pathway (**a**) and the ER (**b**), mitochondria (**c**), PM (**d**), or the nuclear envelope (**e**)

endolysosomal pathway. The significance of endosomal interactions for processes such as signaling regulation, intracellular trafficking, organelle dynamics, metabolic control, and homeostatic responses will be reviewed. Accumulating data indicate that beyond its involvement in cargo transport, the endocytic pathway is comprehensively integrated into other systems of the cell and plays multiple roles in the complex net of cellular functions.

2.1 Introduction

The endolysosomal system is the cellular machinery specialized in uptake of (macro) molecules and sorting of the engulfed cargo either for degradation or for recycling back to the plasma membrane (PM). Hence, the two destinations of cargo internalized by membrane-bound vesicles within the endocytic compartments are well defined. Cargo designated for degradation travels within early endosomes (EE) during their maturation into late endosomes (LE) that fuse with lysosomes. Recycling back to the plasma membrane occurs by transport of cargo either directly from EE or via recycling endosomes (RE) (Fig. 2.1a).

However, when looking globally at cellular functions, accumulated data indicate that the endocytic system plays a broader role than simply serving as a trafficking

and sorting platform. Endosomes are dynamic organelles, as they continuously move from budding sites at the PM toward the cell center, and constantly change their lipid and protein composition due to sorting, fusion, and fission events. Along this pathway, in the compact intracellular milieu, endosomes interact with different cellular systems and organelles at multiple levels and mediate various processes (Fig. 2.1b–e). In general, membrane contact sites (MCS) between the endomembrane system and other compartments serve as hubs for inter-organellar communication. Fission and fusion of endosomes occur in contact with other organelles. Moreover, endosomal proteins can also act in different cellular compartments and participate in processes that take place outside of the endocytic system, a phenomenon known as "moonlighting" (Huberts and van der Klei 2010; Jeffery 1999).

The cooperation between endosomes and other cellular compartments governs balanced membrane flow and endosome dynamics, metabolic control, cell signaling, transcription regulation, and other homeostasis-related functions. In this chapter, we will discuss primarily two topics demonstrating the function of endosomes as an integral part of the organellar system of a cell: (1) cross talk between the endosomal system and other organelles, and (2) the role of endosomes in regulation of metabolic pathways. While we are unable to comprehensively cover these topics within the scope of this chapter, we will provide a selection of examples highlighting the involvement of endosomes in homeostatic and adaptive functions of a cell.

2.2 Cross Talk Between the Endosomal System and Other Organelles

Various cellular processes are compartmentalized in different subcellular organelles, which ensure their efficient proceeding but at the same time poses the need for their proper coordination with each other. One mechanism of such inter-organellar communication involves MCS, which are microdomains of close apposition between two organelles. In these sites, close proximity of membranes facilitates communication by signaling and exchange of molecules between the two compartments (Prinz 2014).

By interactions with various cellular compartments, endosomes contribute to maintenance of inter-organellar cross talk, coordinated signaling and metabolic reactions, membrane dynamics and organelle identity [discussed in (Henne 2016)]. Indeed, the sites of interaction between endosomal membranes and other cellular membranes serve as "hot spots" for signal transduction and membrane remodeling events that affect structure and function of the involved organelles. To demonstrate how endosomes are integrated within the organellar system of a cell to mediate homeostatic and adaptive responses, we will discuss interactions of the endocytic system with the endoplasmic reticulum (ER) and with mitochondria and describe the role of endosomal sorting complexes required for transport (ESCRT) proteins in preserving membrane integrity.

2.2.1 Endosomal-ER Contact Sites Regulate Multiple Cellular Processes

The ER is a network of branched cisternae and tubules that extensively interact with other membranous organelles in the cell by various mechanisms. Communication of the endolysosomal system with the ER is facilitated by several types of MCS that differ in their molecular composition and functionality [reviewed in (Eden 2016; Raiborg et al. 2015b)]. Although the roles of endosome-ER MCS are not fully understood, they clearly influence a number of cellular processes to be mentioned below (Fig. 2.1b).

Regulation of receptor signaling. Interactions of endosomes with the ER are suggested to negatively regulate signaling from receptors internalized by the endosomal system. This was shown to be mediated by an ER-associated protein tyrosine phosphatase 1B (PTP1B) (Prinz 2014) that dephosphorylates two receptors located on endosomes: the cytokine receptor granulocyte colony-stimulating factor receptor (G-CSFR) on EE (Palande et al. 2011) and epidermal growth factor receptor (EGFR) on LE (Eden et al. 2010), a member of the receptor tyrosine kinases (RTK) family. The interaction of PTP1B with the RTK on the ER was found to be endocytosis-dependent (Haj et al. 2002) and seems to occur at the endosome-ER MCS, where the close apposition of two organelles allows such interaction. Since various RTK and cytokine receptors can still signal from endosomes after their internalization (Cendrowski et al. 2016; Platta and Stenmark 2011), this direct deactivation of receptors on endosomes may be important for controlling the magnitude and length of signaling transduced after the pathway stimulation. Furthermore, PTP1B decreased phosphorylation of G-CSFR even in the absence of its ligand (Palande et al. 2011), implying that interaction with the ER plays a role also in balancing basal signaling from non-activated receptors on endosomes.

In contrast, ER-associated PTP1B may also augment signaling of endosomal receptors in a non-receptor specific manner, by inhibiting activity of the ESCRT machinery. ESCRT components are recruited to the endosomal membrane for targeting internalized receptors toward lysosomal degradation. Two ESCRT components, hepatocyte growth factor-regulated tyrosine kinase substrate (HRS) and signal-transducing adaptor molecule 2 (STAM2), were identified as substrates of PTP1B (Eden et al. 2010; Stuible et al. 2010). Hence, decreased activity of the ESCRT machinery after dephosphorylation of its components can attenuate degradation and increase the signaling propagated from internalized receptors on endosomes.

Cholesterol transport. Another role of the endosome-ER communication is to coordinate transfer of metabolites, ions, and proteins between these compartments, which is of major importance for regulation of signaling and metabolic status at the whole-cell level. In this regard, the regulation of endosome-ER transfer of cholesterol will be discussed under the topic of "metabolic pathways regulation" below.

Ca^{2+} homeostasis. Cooperation between the endolysosomal system and the ER is important also for inter-organellar mobilization of Ca^{2+} ions and regulation of Ca^{2+} release to the cytoplasm. Ca^{2+} is a universal second messenger in many fun-

damental signaling cascades, and hence, its levels have to be tightly controlled in a spatiotemporal manner. Both the ER and lysosomes serve as cellular storage compartments of Ca^{2+}, and data from different reports imply that Ca^{2+} release from both these organelles is coordinated [discussed in (Eden 2016; Lam and Galione 2013)]. Experimental data support the "trigger hypothesis," arguing that a relatively small wave of Ca^{2+} that is released from lysosomes is required for activation of prominent Ca^{2+} efflux from the ER (Kilpatrick et al. 2013).

Interestingly, during Ca^{2+} signaling, Ca^{2+} is transferred also from the ER to lysosomes and this Ca^{2+} shuttling is assumed to be mediated via endosome-ER MCS (Morgan et al. 2013). Recently, it has even been proposed that the ER, rather than the pH gradient, is actually the primary source of Ca^{2+} for the lysosome (Garrity et al. 2016). This idea is supported by the fact that inhibition of Ca^{2+} uptake by the lysosome induced Ca^{2+} release from the ER (Lopez-Sanjurjo et al. 2013). The Ca^{2+} ions accumulated in lysosomes are rapidly returned to the ER (Lopez-Sanjurjo et al. 2014), indicating efficient bidirectional coordination between the compartments. Hence, cross talk between the ER and lysosomes seems to participate in maintenance of Ca^{2+} homeostasis of the cell.

Regulation of endosomal dynamics. In addition, the spatial relationship between endosomes and the ER modulates the dynamics of the endocytic system itself. Motile EE and LE keep close contacts with the ER during their movement (Friedman et al. 2013), and lysosomes move along ER tubules (Lopez-Sanjurjo et al. 2013). The contact of endosomes with the ER increases with their transition from EE into LE (Friedman et al. 2013), implying that maturation process of endosomes is regulated by the ER. Direct interaction of lysosomes and the ER in both juxtanuclear and peripheral cell regions was also recently demonstrated by systematic interactome analysis using multispectral fluorescence imaging (Valm et al. 2017).

Interestingly, several studies indicate that the ER is involved in defining the intracellular distribution of endosomes by modulating their motility. A key player in this modulation is the ER protein VAP [VAMP (vesicle-associated membrane protein)-associated ER protein] that interacts with several endosomal proteins. The binding of VAP to two LE-proteins, STARD3 [StAR (steroidogenic acute regulatory protein)-related lipid transfer (START) domain-3] and STARD3 N-terminal like (STARD3NL), was shown to alter endosomal dynamics (Alpy et al. 2013). In addition, a direct interaction of VAP with the endocytic protein ORPlL induced peripheral positioning of the endosomes (Rocha et al. 2009). This effect was a consequence of decreased association between endosomes and the minus-end-directed microtubule motor dynein. Conversely, interaction with the plus-end-directed microtubule motor kinesin 1 was increased by another type of MCS formed by binding of the ER protein protrudin to the small GTPase Rab7 and phosphatidylinositol 3-phosphate (PI3P) that reside in the endosomal membrane (Raiborg et al. 2015a). These two mechanisms of endosome-ER tethering are suggested to regulate the motility of endosomes from the perinuclear region toward the plasma membrane in a coordinated "gear shift" mechanism (Raiborg et al. 2016).

Finally, interaction with the ER also regulates constriction and fission of both EE and LE, which occur at the endosome-ER MCS (Rowland et al. 2014). Endosomal

fission is an important mean for sorting of cargo and resident membrane proteins, and therefore, the involvement of the ER in this process represents another level of ER-mediated regulation over functionality of the endocytic pathway. Together, the changes in endosome motility, distribution, and fission indicate that interaction with the ER dramatically affects the intracellular architecture of the endosomal network. However, it is yet to be elucidated whether and how these effects influence the function of endosomes and other organelles.

2.2.2 Endolysosomal–Mitochondrial Interactions Are Mediated by Various Mechanisms

Mitochondria play an important homeostatic role by their crucial participation in various cellular processes, including energy metabolism, oxidative stress-related pathways, and Ca^{2+} signaling. Being integrative signaling hubs, mitochondria communicate with other organelles at physical and functional levels. The interaction of the endocytic system with mitochondria was shown to participate in different cellular processes. Most recent data indicate that the endosomal system is also directly involved in degradation of damaged mitochondria, after sequestrating them in EE by a Rab5 and ESCRT-dependent mechanism (Hammerling et al. 2017). Interestingly, communication of the endocytic system with mitochondria was found to be facilitated by both vesicular and non-vesicular mechanisms (Fig. 2.1c).

Endosomal–mitochondrial MCS. Although much less studied than the endosome-ER MCS, membranes of LE and lysosomes also form contacts with mitochondria. Multispectral imaging analysis indicates that lysosome-mitochondria contacts are stable over time and less abundant in the peripheral areas of the cell (Valm et al. 2017). In yeast, an MCS complex connecting mitochondria and vacuole (the yeast lysosomal compartment) was identified and named vacuole and mitochondria patch (vCLAMP) (Elbaz-Alon et al. 2014; Honscher et al. 2014). The exact role of these physical contacts remains to be clarified, but they are suggested to participate in lipid exchange and metabolic regulation in the cell (Daniele and Schiaffino 2016). Interestingly, vCLAMP was found to be reciprocally co-regulated and (at least partially) functionally redundant with the mitochondrial-ER MCS complex ERMES (Elbaz-Alon et al. 2014; Honscher et al. 2014).

In mammalian cells, until now no equivalent endosomal–mitochondrial MCS have been described to exist under physiological conditions, although similar MCS may occur between mitochondria and melanosomes, which are endosome-related organelles found in specific cell types [discussed in (Daniele and Schiaffino 2016)]. Nevertheless, in a hypoxic environment, local contacts and microfusion between mitochondria and LE/lysosome membranes have been reported (Brahimi-Horn et al. 2015). This fusional contact is suggested to mediate cleavage of the mitochondrial outer membrane protein voltage-dependent anion channel 1 (VDAC1) by endosomal asparaginyl endopeptidase (AEP). Another example of a close association between

mitochondria and endosomes was detected in the course of apoptotic response to *Helicobacter pylori* infection (Calore et al. 2010). This MCS is induced in infected cells by vacuolating cytotoxin (VacA), a bacterial virulence factor, and is required for recruitment of the apoptotic mediator BAX to mitochondria.

Endosomal-derived vesicles. Recent studies indicate that inter-organellar communication between endosomes and mitochondria can also occur via direct vesicle trafficking between these compartments. Endosomal-derived vesicles targeted to mitochondria were described in both erythrocytes and non-erythroid cells as involved in intracellular delivery of transferrin-bound iron (Das et al. 2016; Hamdi et al. 2016). These studies revealed a direct transient interaction between transferrin-loaded endosomes and mitochondria, supporting the existence of a "kiss and run" mechanism for efficient delivery of iron to mitochondria, rather than uptake of iron by mitochondria from the cytosol after its release from endosomes. This is consistent with previous findings indicating that endocytosed iron can bypass the cytosol on its way to mitochondria and that this delivery requires vesicular motility (Sheftel et al. 2007; Zhang et al. 2005). Interestingly, the dissociation of endosomes from mitochondria was found to depend on release of iron from the endosomes, implying that intra-endosomal iron levels regulate this vesicular contact (Das et al. 2016; Hamdi et al. 2016).

Mitochondrial-derived vesicles (MDV). Intriguingly, vesicular transport in the opposite direction (from the mitochondrial reticulum to the endosomal system) was described recently, indicating that the endosomal–mitochondrial trafficking route is actually bidirectional. Reports available so far suggest the existence of a few different types of MDV. One kind of MDV can be stress-induced by parkin/PINK1-dependent machinery (McLelland et al. 2014) to selectively deliver oxidized or damaged components of the mitochondrial matrix and inner membrane to LE/lysosomes (Soubannier et al. 2012). In this route, fusion of MDV with endo-lysosomes is mediated by the homotypic fusion and vacuole protein sorting (HOPS) tethering complex and by the soluble NSF attachment protein receptor (SNARE) pairing machinery (McLelland et al. 2016). Another type of MDV targeted to the endolysosomal system delivers the large GTPase DLP1 (that controls mitochondrial fission) to lysosomal degradation, a process regulated by the retromer component, vacuolar protein sorting 35 (VPS35) (Wang et al. 2016). Together, these data indicate a role of the endolysosomal–mitochondrial interaction in mitochondrial quality control and regulation of mitochondrial division. In turn, biogenesis of another type of endolysosomal-directed MDV, that is induced by heat stress or bacterial lipopolysaccharide (LPS) and inhibited by parkin/PINK1, was reported to mediate mitochondrial antigen presentation, implying an important role for endolysosomal–mitochondrial interaction in immune response (Matheoud et al. 2016).

2.2.3 Endosomal ESCRT Machinery Maintains Integrity of the PM and Nuclear Envelope

Accumulating evidence documents that some endocytic proteins play additional roles, not related to the endolysosomal pathway. A prominent example for this type of "moonlighting" is various functions of the ESCRT protein machinery. Apart from their role in sorting of endocytosed cargo into intraluminal vesicles (ILV) in endosomes, ESCRT proteins act at the mitotic spindle during cellular abscission, at the PM during viral budding, and in the cell nucleus where they regulate transcription (Alonso et al. 2016; Christ et al. 2016; Pyrzynska et al. 2009).

Moreover, as it might be expected, the abilities of ESCRT proteins to remodel membranes are used for repair of membranes at additional cellular sites, apart from the endocytic system (Fig. 2.1d, e). Hence, ESCRT is unambiguously established as a general machinery for maintaining intactness of diverse membranes within the cell.

Repair of PM breaks. Breaks in the PM appear during various export and import functions, but also due to mechanical stress or exposure to toxins. Because of its dynamic nature and ability to exchange and modify membranes, the endocytic system is of major importance in PM damage repair. The PM breaks can be filled by fusion with endo-membranes or removed via internalization or extracellular budding. In addition, it was found that components of the endocytic ESCRT machinery are directly active in resealing PM breaks (Jimenez et al. 2014). ESCRT proteins are recruited to the site of PM wound to participate in its efficient repair by pinching out the broken membrane piece. Preserving intactness of the PM is essential for maintenance of cell integrity and survival, indicating an important homeostatic role played by the ESCRT machinery.

Nuclear envelope repair and quality control. Moreover, ESCRT proteins were demonstrated to participate in sealing of the nuclear membrane. The nuclear envelope has to be broken during cell division to allow the formation of two nuclei in daughter cells. ESCRT components were found to act at the post-mitotic stage, sealing the nuclear membranes (Olmos et al. 2015; Vietri et al. 2015). This indicates the essential involvement of endocytic proteins in ensuring proper re-establishment of nucleocytoplasmic compartmentalization during mitosis.

In the same fashion, ESCRT proteins act in resealing discontinuities that are formed in the nuclear envelope during cell migration (Denais et al. 2016; Raab et al. 2016). Interestingly, an inhibition of DNA-repair machinery in migrating cells had no effect on cell viability, whereas it led to cell death when combined with depletion of ESCRT components (Raab et al. 2016). This observation implies a possible cooperation between these two machineries and brings up a speculation that sensing DNA damage is the trigger for recruitment of ESCRT to the site of rupture (Ventimiglia and Martin-Serrano 2016).

In addition to closing membrane breaks, ESCRT components were found to participate in quality control during the assembly of nuclear pores in yeast (Webster et al. 2014). This study revealed another level of ESCRT-mediated regulation of nuclear

membrane function. In this respect, ESCRT components take part in the cellular surveillance over formation of nuclear pores: When a defective pore is assembled, ESCRT proteins are recruited and exert its removal. In general, by preserving integrity and functionality of the nuclear envelope, the ESCRT machinery contributes to maintaining genomic stability and cell viability.

2.3 The Role of Endosomes in Regulation of Metabolic Pathways

The endocytic system regulates cellular metabolism by controlling uptake and trafficking of nutrient carriers, transporters, and signaling receptors (Antonescu et al. 2014). Since the metabolic regulation is highly dynamic, a well-coordinated interpretation of external cues is critical for inducing the proper cellular response, and endosomes serve as efficient mediators in this process. The best recognized endosomal organelles in metabolic regulation are the lysosomes, with much data emerging in recent years acknowledging their role as hubs for integration of metabolic sensing and signaling activation. The topic of lysosomes is covered by another chapter of this book; hence, it will not be discussed herein. We will describe the involvement of several other endocytic organelles and components in spatial and temporal regulation of metabolic pathways.

Endosomal machineries in metabolic signaling. The endosomal system regulates appropriate distribution of metabolite transporters between the PM and intracellular compartments. Intriguingly, the same extracellular cue can mobilize partly different endocytic machineries acting on individual transporters that lead to diverse metabolic consequences. This type of regulation was demonstrated for two different transporters, facilitating uptake of glucose and long-chain fatty acid (LCFA), in isolated cardiomyocytes (Steinbusch et al. 2010). Both transporters are recruited to the PM in response to insulin/oligomycin stimulation, yet distinct vesicular trafficking machineries are involved in their translocation. Specifically, actin filaments and endosomal acidification are required for the stimulated uptake of glucose, but not of LCFA. By this mechanism, the endocytic system is involved in selective regulation of nutrient uptake to directly control the metabolite status.

Cross talk between endosomal trafficking and metabolic signaling is also demonstrated by the widespread involvement of Rab proteins in both processes. Rab GTPases play a crucial role as molecular switches that direct intracellular vesicular transport, also through the endocytic system. Moreover, different Rab proteins were found to participate in signal transduction of multiple metabolic-related pathways [reviewed in (Chua and Tang 2015)]. A recent study identified a role for endosomal Rab5 in regulation of hepatic gluconeogenesis (Zeigerer et al. 2015). In this study, depletion of Rab5 resulted in loss of endosomes in liver cells and induction of severe metabolic abnormalities in vivo in mice. The findings indicated the existence of an endosomally controlled regulation of transcription factors responsible for expression

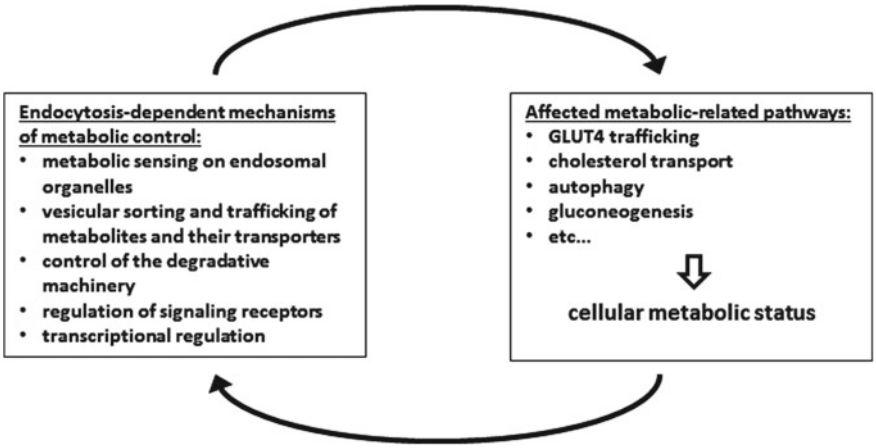

Fig. 2.2 Overview of a bidirectional interplay between endocytosis and cellular metabolism

of gluconeogenic genes. This implies that functional coordination between endocytosis and metabolism goes beyond a traditional concept of simple regulation exerted by the endocytic system controlling the abundance of receptors and transporters at the PM.

Trafficking regulation by the metabolic status. In a reciprocal manner, the metabolic state of a cell directly affects endolysosomal trafficking [discussed in (Antonescu et al. 2014)]. This was demonstrated by systematic quantitative assessment of changes observed in endocytic trafficking in a genome-wide siRNA screen (Collinet et al. 2010). Depletion of metabolism-related proteins induced endocytic phenotypes, most prominently upregulated endocytosis, as measured by internalization of transferrin receptor (a prototype marker for the endosomal recycling pathway). The authors suggested that this may reflect a cellular adaptive response, aiming to increase uptake of nutrients under conditions of metabolic deficiency. This view is supported by another study, demonstrating a metabolic adaptive response mediated by the endocytic system that is observed during glucose starvation in yeast (Lang et al. 2014). In this setting, modulation of the endocytic pathway is essential for cellular survival, facilitated by inhibition of endosomal recycling to the PM to allow vacuolar hydrolysis of cell components for energy production. Together, the data imply that the endolysosomal system and metabolic pathways are interdependent on one another. In the following subchapters, we will present how they intersect at various compartments and multiple functional levels and can bidirectionally affect cellular signaling and vesicular transport (summarized in Fig. 2.2). Specifically, we will discuss the cross talk between the endocytic system and three pathways of cellular metabolism: (i) trafficking of glucose transporter type 4 (GLUT4), (ii) intracellular cholesterol transfer, and (iii) autophagy, all of paramount importance for maintenance of metabolic homeostasis.

2.3.1 Involvement of the Endocytic System in Vesicular Trafficking of GLUT4

Glucose is taken up from an extracellular environment by a family of transmembrane transporters, named GLUT, which are expressed in different cell types. By controlling the trafficking of these transporters, the endocytic system determines their distribution on endo-membranes versus the PM and hence regulates the cellular dynamics of glucose uptake. A well-studied member of this family is GLUT4, which is primarily expressed in adipose and striated muscle tissues and plays a key role in the development of type 2 diabetes. Translocation of GLUT4 to the PM is induced by insulin to facilitate glucose uptake and control postprandial blood glucose levels. Trafficking of GLUT4 is a very dynamic process, and when blood insulin levels decrease it is directed back from the PM to unique endo-vesicles, named GLUT4 storage vesicles (GSV) (Bogan 2012).

Several different internalization routes of GLUT4 and mechanisms regulating its translocation have been described in various cell types under basal and insulin-stimulated conditions (Antonescu et al. 2014). Two mechanisms, termed "dynamic exchange" and "static retention," control the intracellular trafficking of GLUT4 and both require endosome-mediated transport (Muretta et al. 2008). Regulation of GLUT4 trafficking is of main importance for upkeep of normal glucose metabolism in the cell; therefore, this process remains a subject of intense research.

Intracellular routes of GLUT4. It is believed that after internalization into EE, GLUT4 is directed to an intermediate compartment, which could be RE and/or the trans-Golgi network (TGN), from where it is transported into GSV (Kandror and Pilch 2011). Some findings indicate that the TGN is the main site of GSV biogenesis [discussed in (Kandror and Pilch 2011)]. This view is in agreement with a unique role suggested for clathrin heavy chain 22 (CHC22) and syntaxin 10 (STX10) in retrograde sorting of internalized GLUT4 from EE to the TGN, a delivery step found to be crucial for intracellular GLUT4 storage (Esk et al. 2010). However, a partial role of RE in GSV assembly cannot be excluded and is even supported by the dual-mode working model of insulin action (Xu et al. 2011). According to this model, GLUT4 is delivered to the PM by two circuits: The first is activated after short exposure to insulin and represents TGN-originated GSV, and the second appears after prolonged insulin stimulation, involving exocytosis of larger vesicles which probably bud from RE. Hence, the endosomal recycling compartment plays a specialized role in insulin-regulated GLUT4 trafficking, coordinating GLUT4 translocation to the PM.

Involvement of Rab proteins. Several Rab proteins were found to regulate various steps of the GLUT4 trafficking itinerary. Translocation of GSV to the PM is facilitated by Rab10, which can be used as a marker to distinguish GSV from GLUT4-containing endosomes in adipocytes (Chen et al. 2012). This specificity of Rab10 is additionally confirmed by the fact that Rab10 is not essential for exocytosis of GLUT4 in fibroblasts which have no GSV and therefore deliver GLUT4 to the PM only via the constitutive endosomal recycling pathway (Brewer et al. 2016b). Using Rab10 as a GSV marker allowed demonstrating that GSV which fuse with the PM

upon insulin stimulation do not merge with endosomes, but rather constitute the main source that directly conveys GLUT4 to the cell surface (Chen et al. 2012). Yet, fusion of GLUT4-containing endosomes with the PM was found to independently contribute another portion of GLUT4 redistributed to the PM in response to insulin, in a Rab14-dependent manner (Chen et al. 2012). More recent studies indicated that Rab14 actually functions in preceding GLUT4 trafficking steps, from EE to later compartments (RE and/or Golgi), rather than in fusion of GLUT4-endosomal vesicles with the PM (Brewer et al. 2016a; Reed et al. 2013). A similar role, in sorting of GLUT4 from RE to GSV, was suggested also for Rab11 (Zhang et al. 2005), a general regulator of endocytic recycling. In agreement with the involvement of Rab proteins in GLUT4 trafficking, the insulin-sensitive Rab GTPase-activating protein AS160 (Akt substrate of 160 kDa) was introduced as the main switch of GLUT4 redistribution, regulating both sorting of GLUT4 from EE into GSV (through Rab14) and GLUT4 exocytosis from GSV (through Rab10) (Brewer et al. 2016a).

In muscle cells, Rab10 appears to be less critical for GLUT4 exocytosis after insulin stimulation, while Rab8A, Rab13, and Rab14 are required for the translocation of GLUT4 to the PM (Ishikura and Klip 2008; Sun et al. 2010). Here, Rab8A functions to mobilize GLUT4 vesicles through association with myosin motors (Ishikura and Klip 2008; Sun et al. 2014), and Rab13 assembles the molecular complex necessary for GLUT4 exocytosis (Sun et al. 2016). AS160 is suggested to act upstream of Rab proteins to mediate GLUT4 translocation also in muscle cells, since over-expression or silencing of Rab8A reverses the effects observed after AS160 activation or depletion, respectively (Ishikura and Klip 2008; Sun et al. 2010).

The reason for some redundancy of Rab proteins and discrepancies in their action between cell types is unknown, but it seems that GLUT4 trafficking is regulated by different endocytic components in different tissues. The involvement of multiple Rab proteins in various steps of the GLUT4 routing emphasizes that, in addition to their general roles in the endosomal pathway, these GTPases have specific functions in trafficking of GLUT4. However, while aberrant function of Rab proteins was suggested to contribute to diabetes (Bogan 2012), the global alterations of the endolysosomal system under pathological conditions still remain to be studied.

2.3.2 The Endolysosomal Pathway Mediates Intracellular Cholesterol Transfer

Exogenous cholesterol is internalized into the cell via endocytosis of circulating low-density lipoproteins (LDL) which bind to the LDL receptor (LDLR). Subsequently, LDLR is recycled back to the PM and LDL-bound cholesterol is delivered to late endosomal compartments for hydrolysis of lipoprotein particles, after which free cholesterol is redistributed from LE to several other cellular locations [reviewed in (Ikonen 2008)]. Indeed, LE contains many different cholesterol-binding proteins, such as NPC1 and NPC2 (Niemann–Pick type C1 and C2), indicating the existence

of various pathways for cholesterol handling in this organelle. Although it is of main importance for metabolic homeostasis, the regulatory mechanisms of intra-endosomal cholesterol sensing are poorly understood. Interestingly, apoptosis-linked gene 2-interacting protein X (Alix), a regulator of endocytic trafficking, was found to control endosomal cholesterol levels by an interaction with an unconventional phospholipid lysobisphosphatidic acid (LBPA) (Chevallier et al. 2008). According to the suggested model, the amount of cholesterol stored in LE is determined by the buffering capacity of the LBPA-rich internal membranes of the multi-vesicular endosomes (MVE).

In addition, only partly known are the mechanisms of cholesterol redistribution from endosomes to other cellular destinations which includes the ER, the PM, and mitochondria (Luo et al. 2017; Pfisterer et al. 2016). The ER is the main site for cholesterol sensing and de novo synthesis, and for regulation of cellular sterol homeostasis. Cholesterol from the ER can be delivered to the PM to fulfill several essential functions, including determination of membrane rigidity, assembly of subdomains, and regulation of signal transduction. The PM can also function as an intermediate location for cholesterol redistribution to other organelles. In the mitochondria, cholesterol ensures maintenance of mitochondrial membranes and is in some cases needed for production of steroids and oxysterols.

Cholesterol transfer between endosomes and the ER. Cholesterol transfer between the endocytic system and the ER is an emerging subject of research, since some of the MCS between these compartments are mediated by cholesterol-binding proteins. These include the endocytic proteins STARD3 and ORPlL, which both bind to the ER protein VAP (Alpy et al. 2013; Rocha et al. 2009). Moreover, the ORPlL–VAP interaction was shown to be induced by low levels of cholesterol in endosomes. This effect is mediated by a conformational change of ORPlL which induces enhancement of the LE-ER tethering (Rocha et al. 2009). Since STARD3-VAP associations were found to be assembled and to function independently of the lipid transfer ability of STARD3 (Alpy et al. 2013), it was proposed that their primary role is sensing cholesterol levels. A more recent study, however, indicates that STARD3-VAP complexes actually transport cholesterol from the ER to endosomes (Wilhelm et al. 2017). Cholesterol transfer from the ER to endosomes was also shown to be mediated by another subpopulation of MCS formed between ER and EGFR-positive endosomes (Eden et al. 2016). These MCS are tethered by annexin A1 and its ligand S100A11, while sterol trafficking via these sites depends upon ORP1L–VAP interaction. The findings indicate that ER-to-endosome cholesterol delivery occurs when endosomal cholesterol levels are low, to support the formation of EGF-stimulated MVE. Yet, it is unknown whether any of these interactions are bidirectional and also mediate cholesterol transfer in the opposite direction, from LE to the ER.

Interestingly, formation of endosomal-ER MCS also affects the spatial distribution of LE, directing them toward the cell periphery (Rocha et al. 2009). Since these MCS are induced when cholesterol levels in LE are low, possible roles of this positioning are to facilitate uptake of exogenous cholesterol and/or egress of cholesterol from endosomes to the PM.

Endosome-to-PM cholesterol delivery. Regardless of the role played by STARD3 in the formation of endosomal-ER MCS (Alpy et al. 2013), this endosomal protein was proposed to mediate cholesterol transfer between LE and the PM (van der Kant et al. 2013). It was suggested that STARD3-containing endosomes differ from ORP1L-containing endosomes, representing a distinct "earlier" subpopulation of LE (van der Kant et al. 2013). Accordingly, internalized cholesterol is transferred from EE to the STARD3 "early" LE, from where it can be delivered to the PM or transported to the ORP1L "late" LE for further distribution to the ER. This possible existence of specialized LE subpopulations, used for differential sorting of cholesterol into various destinations, highlights the importance of endosomes in ensuring cellular homeostasis of cholesterol trafficking.

Furthermore, the results of siRNA-based screening imply that appropriate supply of cholesterol from endosomes to the PM is essential also for maintenance of functional clathrin-mediated endocytosis (Kozik et al. 2013). In addition, inhibition of the endosomal V-ATPase in HeLa cells was found to increase biogenesis of cholesterol-rich extracellular vesicles (exosomes) which are intraluminal vesicles generated inside endosomes and released from cells by fusion of MVE with the PM (Edgar et al. 2016). This finding indicates that by influencing endosome-PM fusion, the endocytic system also regulates cholesterol export from the cells. It was further discovered that exosomes induced by manipulating the endolysosomal function are attached to the PM by a protein named tetherin (Edgar et al. 2016). The authors suggested that the tetherin content in the exosome membrane is increased in cholesterol-enriched vesicles, representing a mechanism for selective release of certain vesicles while tethering others to the PM. This implies that the endosomal system controls exosome release via a mechanism regulated by cholesterol.

Cholesterol transfer via peroxisomes and via TGN. Interestingly, indirect routes, passing via other organelles, are also suggested to facilitate cholesterol delivery from the endolysosomal system to the ER and the PM. A recent study revealed direct transfer of cholesterol from lysosomes to peroxisomes via transient MCS formed by binding of a lysosomal protein synaptotagmin VII to PI(4,5)P_2 on the peroxisomal membrane (Chu et al. 2015). The role of this trafficking route is still ill-defined, but it is suggested to participate in distribution of cholesterol to the ER and the PM. Additionally, cholesterol can be transported from NPC1-positive endosomes to the TGN through SNARE-mediated vesicular trafficking (Urano et al. 2008).

Endosomal–mitochondrial cholesterol transfer. Finally, the endocytic system participates also in cholesterol transport to mitochondria. Interestingly, delivery of cholesterol from LE/lysosomes to mitochondria can be mediated by the cholesterol-binding protein STARD3, which, as described above, was suggested to be involved in cholesterol transfer between endosomes, the ER and the PM (Charman et al. 2010; Zhang et al. 2002).

To summarize, the endocytic system facilitates different aspects of the complex network of cellular cholesterol transport, storage, and distribution. Hence, endocytosis has multiple direct and indirect effects on cellular cholesterol homeostasis.

2.3.3 Interplay Between the Endocytic System and Autophagy

Macroautophagy (henceforth referred to as autophagy) is the main cellular pathway mediating lysosomal degradation of cell components, to eliminate damaged organelles and invading pathogens. In addition, as an important pathway for cellular housekeeping of nutrient supply, autophagy is activated by metabolic stress and starvation. During autophagy, the contents designated to be degraded are surrounded by a small portion of cup-shaped isolation membrane, termed phagophore, which later elongates to form a double-membrane vacuole known as autophagosome. Autophagosomes then fuse with lysosomes, creating autolysosomes, where lysosomal enzymes catalyze degradation [described in (Glick et al. 2010)]. Hence, autophagy directly depends on a stable cohort of lysosomes.

The endocytic and autophagic systems serve as cellular degradative pathways and share the same endpoint. As it may be expected, both routes are interconnected by several overlapping molecular mechanisms and functional interactions. Discussing all aspects of this multifaceted interplay is beyond the scope of the current chapter [for review, see (Barth and Kohler 2014; Tooze et al. 2014)]. Herein we will present some key findings indicating the complex communication between the endolysosomal and autophagy systems.

Diverging routes of autophagy. The autophagy pathway in yeast was described as a sequential maturation process of a phagophore, converging with the endolysosomal pathway at the point of autophagosome fusion with lysosome. However, the existence of another bypass route was discovered in mammalian cells, where autophagosomes do not fuse directly with lysosomes, but rather with LE, generating intermediate organelles named amphisomes (Fader and Colombo 2009). Amphisomes were detected also in flies and nematode (Djeddi et al. 2012; Rusten et al. 2007) and identified as prelysosomal compartments, containing both endocytic and autophagic cargo, which continue to fuse with lysosomes to form autolysosomes. Interestingly, amphisomes were found to contain not only LE markers, but also proteins typically located on EE (Berg et al. 1998), raising the possibility that fusion of autophagosome with EE may also occur. Hence, several intertwined routes may connect different endosomal organelles with the autophagy pathway. Understanding the regulation and importance of these endocytic-related routes in the multistep process of autophagy is still a challenge.

Autophagosome formation. The cellular sources of membrane material for formation of autophagosome as well as their assembly mechanisms are being intensely studied. Among contributors, such as the ER, mitochondria, the Golgi apparatus, and the PM, endosomes are also suggested to take part in incorporation of membrane fragments during formation and elongation of the isolation membrane [discussed in (Chan and Tang 2013)]. A recent report, using ultrastructural investigation, identified MCS formed between the phagophore membrane and other organelles, including endosomes, implying that these contacts may participate in cross talk or lipid transport, contributing to autophagosome formation (Biazik et al. 2015).

Indeed, fusion of vesicular and multi-vesicular endocytic organelles with nascent autophagosomes has already been shown earlier (Liou et al. 1997). In agreement, RE marked with Rab11 were found to participate in formation of autophagosomes by delivery of membrane to the expanding phagophore (Longatti et al. 2012). It was suggested that vesicular transfer from RE is activated by amino acid deficiency and repressed by the Rab11 effector TBC1D14, which shuttles between RE and the Golgi apparatus depending on the nutrient availability (RE under fed conditions, the Golgi during starvation) (Longatti et al. 2012).

Interestingly, a recent study revealed a role for vesicular transport from the endosomal system in facilitating the delivery of autophagy-related 9A (Atg9A), an integral membrane protein which is required for the formation of autophagosome (Imai et al. 2016). The sorting of Atg9A from RE and the Golgi is regulated via interaction with the adaptor protein AP-2. Interrupting this interaction resulted in accumulation of Atg9A in RE and dysregulated autophagy. These findings indicate that proper trafficking of Atg9A in the endolysosomal pathway is essential for functional activation of autophagy. This assumption is in agreement with an earlier study implying that Atg9A transport mediated by the endosomal retromer–WASH complex is required for autophagy (Zavodszky et al. 2014).

Endolysosomal regulation of autophagy. The central regulator of autophagy is mammalian target of rapamycin (mTOR), a component of the mTOR complex 1 (mTORC1) activated according to nutrient availability at the LE/lysosomal surface (Lim and Zoncu 2016). Hence, the endolysosomal system is directly interconnected to the autophagy pathway not only via endocytic organelles facilitating degradation, but also at a regulatory level controlling autophagy induction.

Actually, dynamics of the endolysosomal pathway was shown to directly influence mTOR signaling and therefore activation of autophagy (Korolchuk et al. 2011). In this study, the intracellular positioning of endosomes was found to modulate mTOR activation and hence the autophagic flux. Moreover, it was suggested by the authors that nutrient levels dictate lysosomal distribution and that peripheral localization of lysosomes favors mTOR activation due to a closer proximity to upstream activators near the PM. This demonstrates a spatial mechanism of metabolic regulation coordinated by the endocytic system.

Another level of autophagy regulation by the endocytic system was revealed by a recent work using proteomics analysis to study how endolysosomal proteolysis is coordinated with activation of autophagy-mediated degradation in response to starvation in yeast (Muller et al. 2015). The findings confirmed that autophagy was induced immediately upon introduction of starvation. However, during the first hours of nutrient depletion the destruction of membrane proteins by the endocytic system was the main source for amino acid supply to maintain cellular functions and activate an adaptive response. This adaptation included the de novo synthesis of vacuolar hydrolases that allowed potentiation of autophagy, which was suggested to be essential for restoration of amino acid levels during extended periods of starvation. Interestingly, this also demonstrates that selective (ubiquitin-dependent) degradation of membrane proteins via the endocytic system activates a catabolic cascade during starvation, by induction of the non-selective autophagic pathway. This timely regulated response

was found to be required for cell survival. These findings uncover another homeostatic role played by the endocytic system, which requires intimate cooperation with the autophagic pathway and evokes a survival response at the whole-cell level.

Shared molecular machineries. Similarly to the endosomal pathway, autophagy requires membrane remodeling events such as elongation, closure of gaps, and fusion. Indeed, many molecular mechanisms are shared between the endocytic and autophagic pathways, adding another complexity level to the interactions between these two systems [discussed in (Fader and Colombo 2009)]. As one may expect, an example of effector molecules common for endocytosis and autophagy are the components of ESCRT.

Several alternative scenarios have been proposed to explain the involvement of ESCRT proteins in autophagy [presented in (Rusten and Stenmark 2009)]. The possible mechanisms include the involvement of ESCRT in phagophore closure, lysosome biogenesis, lysosomal fusion or in preventing proautophagic signaling by maintaining proper endosomal flux. None of these options can be ruled out, and it is possible that the mechanisms differ between distinct biological systems and/or that several mechanisms coexist.

Indeed, depletion of ESCRT components was found to inhibit autolysosome formation and impair autophagy (Filimonenko et al. 2007). The authors of this study proposed that autophagy was diminished due to dysfunction of endosomal transport caused by loss of ESCRT, indicating the dependence of autophagic degradation on a functional endocytic pathway. These findings are in agreement with accumulation of autophagosomes observed upon ESCRT-III disruption in cultured cells and in flies in vivo (Lee et al. 2007; Oshima et al. 2016; Rusten et al. 2007), all supportive of a role for ESCRT in fusion of lysosomes with both endosomal and autophagic organelles. The ESCRT-I subunit TSG101 was also implicated in vesicular fusion of lysosomes with LE and with amphisomes (Majumder and Chakrabarti 2015).

Similarly, autophagosome accumulation was observed also in ESCRT-depleted nematode (Djeddi et al. 2012). However, in this model autophagosomes were claimed to accumulate due to increased autophagic flux, rather than inhibition of lysosome fusion. In this setting, increased levels of aberrant ESCRT-depleted endosomes induced autophagy that played a protective, pro-survival role. These findings support the existence of cross talk between the endosomal and autophagy pathways, responsible for preserving cellular and organismal homeostasis.

Of note is that although the ESCRT machinery is highly conserved from yeast to humans, it was not found to be involved in the autophagic function in yeast, with no accumulation of autophagosomes observed in ESCRT mutants (Muller et al. 2015).

In addition to ESCRT, many other molecular players were suggested to be shared between the endosomal and autophagy systems and possibly to mediate the interplay between these pathways, which include ESCRT-associated protein Alix (Murrow et al. 2015), Rab machinery (Chen et al. 2014; Ganley et al. 2011; Longatti et al. 2012; Popovic et al. 2012; Szatmari et al. 2014), HOPS tethering complex (Jiang et al. 2014; Liang et al. 2008; Lindmo et al. 2006; Wartosch et al. 2015), and others [also discussed in (Fader and Colombo 2009)].

2.4 Conclusions

The cumulative evidence discussed above indicates that the endolysosomal pathway acts in coordination with other cellular systems, to support essential life processes and cell homeostasis. Hence, the endocytic system should not be referred to as a stand-alone machinery for uptake and degradation of vesicle-engulfed cargo, but rather as an integrated part of the cellular network of organelles and processes that are interconnected.

As demonstrated by several examples throughout this chapter, while playing their established roles in vesicle trafficking, endosomes keep close relations with other organelles and are dynamically involved in functions that have global cellular implications such as membrane flow, signaling control, and metabolic regulation. Yet, in many of these processes, the molecular mechanisms underlying the functional involvement of the endocytic system are not fully understood and remain an important challenge for future research.

Moreover, some functions of endosomes are universal, while others are specialized and vary between different cell types. Thus, it is highly possible that the interaction mechanisms of endosomes with other organelles and pathways are in part tissue-specific, which adds another level of complexity to their mutual co-regulation. Finally, the roles played by endosomal trafficking in various cellular processes are affected in pathological conditions involving dysregulated nutrient metabolism, improper immunological responses, developmental disorders or tumorigenesis. Therefore, understanding the participation of the endocytic system in the cellular network of organelles and pathways has important implications for human health and disease.

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