Moving and Positioning the Endolysosomal System

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Abstract

The endolysosomal system is extremely dynamic, yet highly organized. The spatiotemporal distribution of endolysosomal organelles depends on transport driven by microtubule motors such as kinesins and dynein, and by actin-based myosin motors. It has recently become appreciated that interactions with motors are controlled by contacts with other organelles, particularly the endoplasmic reticulum (ER). The ER also controls the concentration of endolysosomal organelles in the perinuclear area, as well as their fission and fusion, through a complex system of tethering proteins. Dynamic interactions go both ways, as contacts with endosomes can influence the movement of the ER and peroxisomes. The dynamics of endolysosomal organelles should thus no longer be studied in isolation, but in the context of the whole endomembrane system.

Introduction

The steady-state distribution of organelles within the cell is the result of highly regulated, dynamic processes. Indeed, organelles move throughout the cytoplasm along cytoskeletal structures such as microtubules and actin filaments. In general, microtubule motors such as kinesins and dynein drive long-range transport, whereas actin-based myosin motors drive short-range transport. An assortment of adaptor proteins mediate coupling of organelles to the motor proteins. Various regulatory mechanisms ensure that organelle-motor interactions occur at the right place and time. One of these mechanisms involves contacts with other organelles. The endoplasmic reticulum (ER), in particular, is omnipresent throughout the cytoplasm and plays a major role in controlling the movement and overall positioning of other organelles. A prime example of an organelle ensemble that is subject to this dynamic control is the endolysosomal system. This system comprises various membrane-bound organelles, including early endosomes (EEs), recycling endosomes (REs), late endosomes (LEs), lysosomes, lysosome-related organelles (LROs), and other specialized organelles (Table 1). In this minireview, we discuss recent findings on the distribution and dynamics of

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endolysosomal organelles mediated by interactions with motor proteins and with the ER. These findings reveal that movement of endolysosomal organelles is highly interdependent with that of other organelles, and subject to cross-compartmental control mechanisms.

Microtubule-dependent transport

Endolysosomal organelles move bidirectionally between the center and the periphery of the cell along microtubule tracks (Fig. 1). In non-polarized cells, microtubules are radially distributed, with their minus-ends at a juxtanuclear microtubule-organizing center (MTOC), and their plus-ends pointing towards the periphery. Most kinesin motors drive organelle transport from the minus-end to the plus-end (anterograde or centrifugal transport), while the cytoplasmic dynein motor drives organelle transport in the opposite direction (retrograde or centripetal transport). Polarized cells such as epithelial cells and neurons have more complex microtubule organizations, with some microtubules pointing their plus-ends towards the nucleus. Thus, whether transport is centrifugal or centripetal in these cells depends on the specific microtubules to which the organelles are attached.

Anterograde transport

Mammalian genomes encode approximately 45 different kinesin heavy chains (KIFs), several of which drive movement of endolysosomal organelles [1] (Table 1) (Fig. 1). In general, there is not a simple correspondence of one organelle to one kinesin. In some cases, distinct organelles depend on the same kinesin for movement. For example, anterograde transport of EEs [2], SARA signaling endosomes [3] and transcytotic endosomes [4] depends on the kinesin-3 KIF16B. Similarly, anterograde transport of LEs and lysosomes [5], melanosomes [6] and proto-lysosomes in the process of autophagic lysosome reformation [7], involves the kinesin-1 KIF5B. In other cases, the same organelle can use multiple kinesins for motion, as exemplified by LEs and lysosomes, which use not only KIF5B [5], but also the kinesin-2 KIF3A [8], kinesin-3 KIF1A and KIF1Bβ [9], and kinesin-13 KIF2A [10] for anterograde transport.

The coupling of endolysosomal organelles to kinesins is often mediated by small GTPases and their effectors, as well as membrane phospholipids, all of which function as organelle ("cargo") adaptors (Table 1) (Fig. 1). KIF16B, for example, is recruited to EEs through interaction of its PX domain with membrane phosphatidylinositol 3-phosphate (PtdIns3P), which is generated by the class III phosphatidylinositol 3-kinase VPS34, an effector of the small GTPase Rab5 [2]. The recruitment of KIF5B and KIF1A/KIF1Bβ to LEs/lysosomes, on the other hand, depends on the multisubunit complex BORC and the small GTPase Arl8 [11,12]. Arl8 engages these two kinesin types by different mechanisms. Whereas interactions with the Arl8-effector SKIP and the kinesin light chain (KLC) mediate coupling to KIF5B [12], Arl8 interacts directly with the CC3 domain of KIF1A/KIF1Bβ [13]. A recent study showed that KIF5B and KIF1A/KIF1Bβ preferentially couple LEs/lysosomes to distinct microtubule tracks localized to the perinuclear and peripheral regions of the cytoplasm, respectively [14]. In this case, the association of the same organelle with distinct kinesins enables movement in different regions of the cell.

Retrograde transport

In contrast to the many different kinesins, there is only one cytoplasmic dynein heavy chain [15]. Structural and functional diversification of dynein is achieved by the association of the heavy chain with various intermediate, light intermediate and light chains, as well as many cargo adaptors. Another multisubunit complex named dynactin associates with dynein to activate its transport towards microtubule minus-ends. Virtually all endolysosomal organelles can recruit dynein-dynactin following a template similar to that of the kinesins: a Rab GTPase that binds to the target organelle, and a Rab effector that directly or indirectly interacts with the motor (Table 1) (Fig. 1). Centripetal transport of EEs, for example, is mediated by Rab5 and the Rab5-effector FHF complex, composed of FHIP, Hook and FTS subunits [16,17,18,19,20]. FHIP is the subunit that directly interacts with Rab5 [20], whereas Hook simultaneously binds to dynein and dynactin, stabilizing this complex and enhancing the processivity of transport [21,22].

Centripetal transport of LEs/lysosomes depends on Rab7 and its effector RILP [23], which interacts with the dynactin subunit p150[Glued] [24] and the dynein light intermediate chain [25] (Figs. 1 and 2). The Rab7-RILP-dynein-dynactin complex associates with a cholesterol sensor named ORP1L, which adopts different conformations depending on cellular cholesterol levels. At low cholesterol levels, an FFAT motif in ORP1L interacts with the ER protein VAP-A at membrane contact sites (MCS) between LEs/lysosomes and the ER [68]. Interaction with VAP-A dissociates dynein-dynactin from the Rab7-RILP complex, resulting in peripheral localization of LEs. At high cholesterol levels, the FFAT motif is occluded, allowing long-term engagement of RILP with dynein-dynactin and thus promoting transport of LEs/lysosomes towards the MTOC [68]. This mechanism explains not only how LE/lysosome transport is controlled by cholesterol and the ER, but also the LE/lysosome clustering phenotype caused by endolysosomal cholesterol accumulation in cells from Niemann-Pick type C patients [68].

Role of the actin cytoskeleton

The actin cytoskeleton and associated myosin motors also modulate the transport of endolysosomal organelles by a variety of mechanisms. One of these mechanisms involves the dynamic capture of organelles within actin-rich regions of the cell such as the acto-myosin cortex that underlies the plasma membrane. This mechanism also fits a small GTPase-adaptor-motor model similar to that observed for organelle interactions with microtubule motors. This process has been extensively investigated for LROs such as melanosomes and cytotoxic T-cell lytic granules, which rely on a complex of Rab27a, a corresponding adaptor protein (melanophilin, munc13-4) and myosin Va for peripheral retention and/or exocytosis of the organelle content [26,27,28]. Late endosomal MHC class II compartments (MIIC) are also LROs that fuse with the plasma membrane upon maturation of dendritic cells (DC). In immature DC, MIIC are maintained intracellularly by the action of the small GTPase Arl14, the effector ARF7EP, and Myo1e, a single-leg myosin that is unable to move but can attach cargos to actin [29]. Inactivating this system yields immature DC with an MIIC distribution similar to that of mature DC. Another mechanism of actin-based motility involves the formation of actin comet tails on endosomes and

lysosomes that propel them through the cytoplasm [30], and aid in the budding and fission of endosomal tubules [31,32]. The WASH complex plays a critical role in actin nucleation for this type of organelle motility [30,32]. The versatility of the actin cytoskeleton suggests that this system might contribute to endolysosomal motility and positioning in additional ways, functioning either in cooperation [33,31] or opposition to microtubules [34].

Regulation by organelle contacts

The overall distribution of endolysosomal organelles within the cytoplasm is not only determined by interaction with cytoskeletal motors but also by contacts with other organelles, particularly the ER (Table 2) (Fig. 2). In 1964, Alex Novikoff and colleagues coined the term "GERL" to describe the close apposition of ER, Golgi and lysosomes observed in electron micrographs of spinal ganglia neurons [35]. Beyond the fact that these organelles are connected by the biosynthetic/secretory pathway, the significance of their close apposition was not grasped until recently, with the recognition that organelles cross-control each other through membrane contact sites (MCS) [36,68]. The ER, in particular, plays a crucial role in this control because of its presence throughout the cytoplasmic space. Three basic endolysosomal processes are under control of the ER: motility, overall positioning, and fusion/fission.

Regulation of LE/lysosome transport by the ER

Besides its role in regulating the cholesterol-dependent coupling of LEs/lysosomes to dynein-dynactin, as described above, the ER is also involved in controlling the kinesin-dependent transport of LEs. This latter mechanism involves an ER-anchored protein named protrudin that also has a VAP-A-interacting FFAT motif, and a FYVE domain that binds PtdIns3P on LEs (Fig. 2). These interactions allow protrudin to bridge the ER and endosomal membranes. In addition, protrudin delivers kinesin-1 ($KIF5B_2$-KLC_2) to a complex of Rab7 and its effector FYCO1 on LEs, thus promoting their plus-end-directed transport [37,38] (Fig. 2). The VAP-A-dependent control of dynein-dependent transport (see above) and kinesin-dependent transport of LEs could be functionally coupled, but the molecular details of such coupling are not known. The biology of intercompartmental control of endolysosomal transport is likely more complex, as recently illustrated by findings that the LE protein folliculin supports the binding of RILP to the Golgi-associated Rab34, also contributing to the perinuclear accumulation of LEs [39,40] (Fig. 2).

The ER organizes the positioning of the entire endolysosomal system

Although endolysosomal organelles can move bidirectionally between the center and the periphery of the cell, at steady state the majority is concentrated in a region around the MTOC (i.e., the "perinuclear cloud"). Recent studies have shown that this pericentrosomal concentration of endolysosomal organelles is controlled by the ubiquitin ligase RNF26, which localizes to the perinuclear ER [41]. RNF26 associates with and then ubiquitinates the adaptor protein p62/SQSTM1. Ubiquitinated p62/SQSTM1 in turn interacts with various endolysosomal adaptor proteins, including TOLLIP (LEs and phagosomes), EPS15 (EEs) and TAX1BP1 (TGN) (Fig. 2). These adaptor proteins are characterized by specific

ubiquitin- and membrane-binding domains that allow tethering of their respective compartments to the perinuclear ER where RNF26 resides. These interactions are countered by a de-ubiquitinating enzyme named USP15, which releases the organelles from the ER, enabling their movement by kinesin and dynein motors [41] (Fig. 2). How endosomal vesicles are deemed ready for release to the cell periphery by USP15 is unclear, but may be related to their correct maturation state.

Regulation of endosomal fission and fusion by the ER

Another important aspect of endolysosomal dynamics is the ability of the organelles to undergo fission and fusion. Remarkably, a recent study showed that fission of EEs and LEs occurs at sites of contact with the ER [42]. Free diffusion of cargo is restricted at these sites, suggesting that this mechanism also plays a role in cargo sorting. Although the molecular mechanism of this particular process remains to be elucidated, another study showed how the ER contributes to the budding of retromer-containing tubules from endosomes [32]. This mechanism involves the same ER proteins that participate in the control of dynein and kinesin binding to LEs, VAP-A and its paralog VAP-B. These proteins establish a network of interactions with the PtdIns4P transporter OSBP (an ORP1L homolog) and the retromer-associated SNX2 protein. These interactions lead to PtdIns4P- and WASH-dependent actin nucleation and consequent budding of retromer-containing tubules. Like ORP1L and OSBP, two other lipid-transfer proteins on LEs, STARD3 and STARD3NL interact with VAP proteins via FFAT motifs, as well as with endosomes, providing yet another means for the ER to contact endosomes [43].

Fusion of LE/lysosomes with other organelles such as autophagosomes is also subject to regulation by interaction of ORP1L with VAP-A at the ER [44,45]. Release of ORP1L from VAP-A is required for a Rab7-RILP-PLEKHM1 complex to recruit the tethering complex HOPS to LEs/lysosomes so that they can fuse with other LEs/lysosomes and with autophagosomes [45]. These examples illustrate how endolysosomal transport is integrated with fission and fusion, and highlight the role of the ER in regulating these processes.

Hitchhiking on early endosomes

The dynamic interaction of the ER with endosomes goes both ways. In filamentous fungi, various organelles and particles such as the ER, lipid droplets, peroxisomes, polysomes and ribonucleoprotein particles exhibit some form of microtubule-dependent motility that results from tethering to moving EEs rather than direct coupling to motor proteins [46,47,48,49,50]. This process, termed "hitchhiking", is also mediated by proteins that bridge an organelle or particle with the EE membrane. For example, the large coiled-coil protein PxdA links peroxisomes to EEs, partly through a predicted F-BAR domain that binds to the EE membrane [49]. Similarly, the RNA-binding protein Rrm4 links ribonucleoprotein particles to another protein named Upa1/rififylin, which in turn has a FYVE domain that binds to PtdIns3P on EEs [48]. It remains to be determined if hitchhiking also occurs in higher eukaryotes and what the corresponding tethers might be. In the case of ER hitchhiking, it would be interesting to test whether ER movements depend on the same proteins previously identified as components of ER-endosome MCS.

Concluding remarks

Our current view is that the movement and positioning of endolysosomal organelles involves not only interactions with cytoskeletal motors but also contacts with other cytoplasmic organelles. The endosomal system can thus no longer be considered in isolation, but as part of an integrated system with other organelles, particularly the ER. A picture is emerging of the cell as a social network, with a mother compartment (the ER) instructing the behavior of its offspring (the endolysosomal organelles). Interactions go both ways, though, and we can expect other organelles to influence ER behavior in return. Despite progress in the elucidation of these processes, the organelle interaction field is still in its infancy. Particularly lacking is information concerning the regulation of these processes by nutrients, signaling pathways, cellular stresses, developmental programs, cell proliferation, and other physiological and pathological conditions. These processes will be even more complex in polarized cell types such as epithelial cells and neurons, with cell-type specific components and pathways that do not exist in the non-polarized cells that have been most intensively studied to date. Finally, we anticipate greater interest in the importance of endolysosomal organelle movement and positioning for various cellular functions. There are already numerous examples of how the motor-driven translocation of endosomes and lysosomes contributes to processes such as autophagy, metabolic signaling, and cell adhesion and migration, to name a few [11,51]. Likewise, contacts of endolysosomal organelles with the ER in the perinuclear cloud are critical for the transfer of fluid phase materials from endosomes to lysosomes, and for attenuation of EGF receptor signaling [41]. Future work will likely expand the range of cellular functions that are dependent on the spatial and temporal dynamics of endolysosomal organelles.

Acknowledgments

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Highlights

- Endolysosomal organelles are dynamically distributed throughout the cytoplasm

- Movement of endolysosomal organelles depends on coupling to microtubule motors and actin

- Contacts with the endoplasmic reticulum regulate organelle movement and positioning

- Other organelles move by hitchhiking on endolysosomal organelles

- Cellular functions depend on movement and positioning of endolysosomal organelles
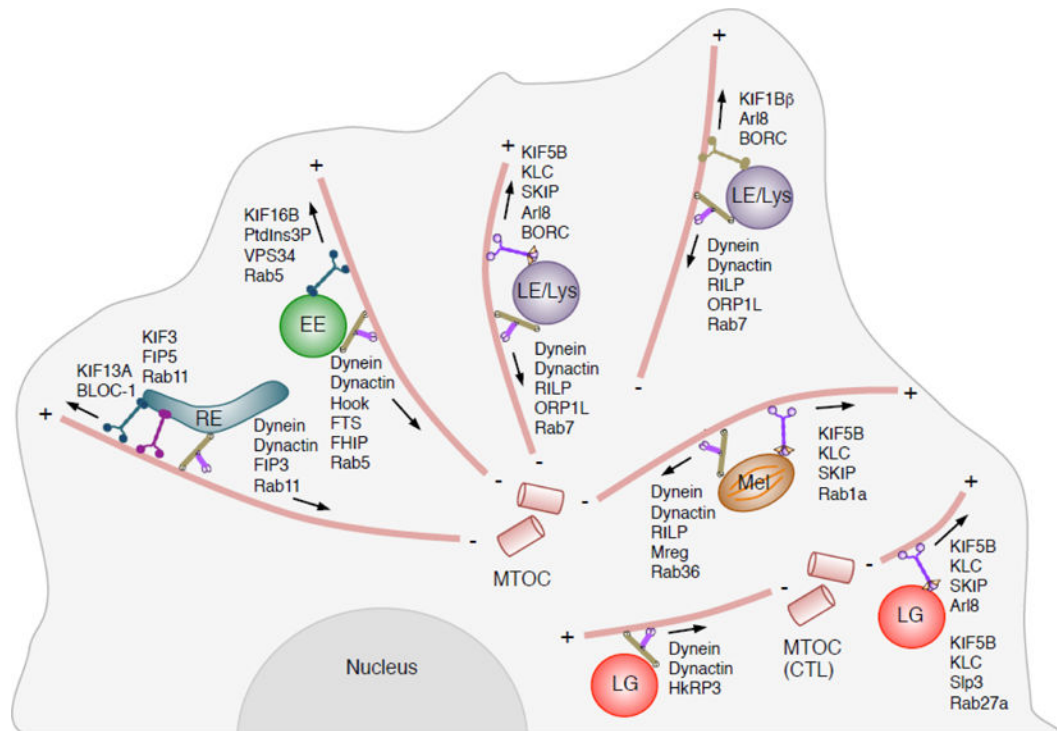
Figure 1.
Microtubule-dependent transport of endolysosomal organelles. This cartoon depicts different endolysosomal organelles and the microtubule motors and adaptors that drive their movement. EE, early endosome; RE, recycling endosome; LE, late endosome; Lys, lysosome; Mel, melanosome; LG, lytic granule; MTOC, microtubule-organizing center. The minus (−) and plus (+) ends of microtubules are indicated. Arrows indicate the direction of movement driven by the corresponding motor-adaptor combinations. Notice that whereas in most cells the MTOC is located near the cell center, in activated cytotoxic T lymphocytes (CTL) it is relocated to an area under the immunological synapse. See Table 1 for references.
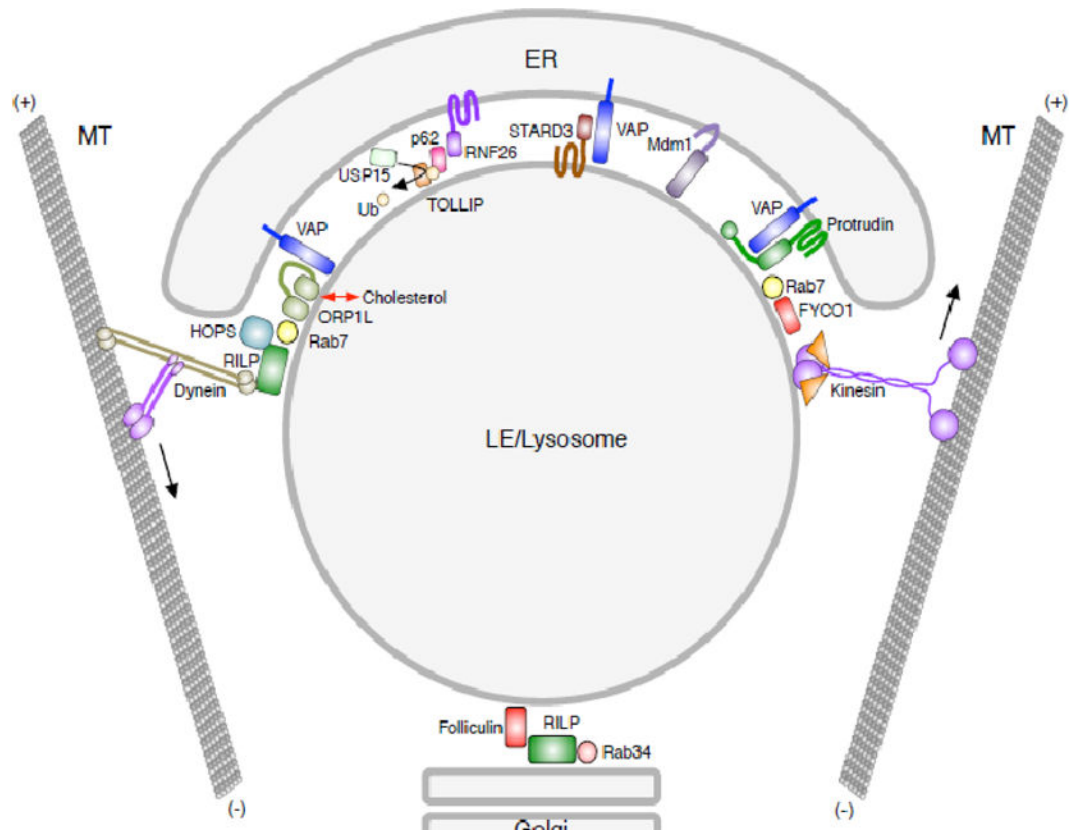
Figure 2.
Contacts of LEs/lysosomes with the ER and Golgi complex. Schematic representation of interactions between LEs/lysosomes and other organelles. The multiple interactions with the ER often involve the ER protein VAP (A and B isoforms). These interactions control the overall positioning of the LEs/lysosomes, their association with kinesin and dynein motors, and their fission and fusion with other organelles. Also depicted are interactions of LEs/lysosomes with the Golgi complex. See Table 2 for references.

Table 1

Examples of microtubule motors and adaptors/regulators involved in the movement of endolysosomal organelles

Organelles	Motors	Cargo adaptors and regulators	References
EEs	KIF5B	KLC, Gadkin, AP-1	52
	KIF16B	Rab5, PtdIns3P, VPS34	2,53
	Dynein-Dynactin	Rab5, FHF (FTS, Hook, FHIP)	17,19,20
REs	KIF13A	BLOC-1, Rab11	31,54
	KIF13B		55
	Dynein	Rab11, FIP3	56,57
LEs/lysosomes	KIF1A	BORC, Arl8	14,55
	KIF1Bβ	BORC, Arl8	9,14,55
	KIF2A		10
	KIF3A	KAP3	8
	KIF5B	KLC, BORC, Arl8b, SKIP Rab7, FYCO1	11,12,38,58
	Dynein-Dynactin	Rab7, RILP, ORP1L, JIP3, HPS6	23,24,59,60
Proto-lysosomes (ALR)	KIF5B	PtdIns(4,5)P2, clathrin	7
Apical REs	KIF3A KIF3B	Rab11, FIP5	61
Transcytotic endosomes	KIF16B	Rab11	4
Sara signaling endosomes	Dmel Klp98 (KIF16B)		3
Cytokinetic recycling endosomes	KIF5B	Arf6, JIP4	62
	Dynein-Dynactin	Arf6, JIP4	62
Melanosomes	KIF5B	Rab1A, SKIP	6
	Dynein-Dynactin	Rab36, RILP Melanoregulin	63, 64
Lytic granules	KIF5B	Rab27a, Slp3, KLC1 Arl8, SKIP	65,66
	Dynein-Dynactin	HkRP3 Rab7, RILP	67,68

Table 2

Examples of organelle contacts involving endolysosomal organelles

Organelle contacts	Contact molecules and regulators	References
ER-LEs/lysosomes	VAP, ORP1L	69
	VAP, STARD3/MLN64, STARD3NL/MENTHO	43
	Protrudin, Rab7, PtdIns3P	37,38
ER-retromer tubules	VAP, SNX2, PI4P, OSBP	32
ER-endolysosomal organelles	RNF26, p62/SQSTM1, EPS15, T6BP/TAX1BP1, TOLLIP, USP15	41
ER-yeast vacuole	Mdm1, PtdIns3P	70
Golgi-LEs/lysosomes	Rab34, RILP, folliculin	39,40
Peroxisomes-lysosomes	Synaptotagmin VII, PtdIns(4,5)P2	71
Peroxisomes-endosomes	PxdA	49
RNP-endosomes	Rrm4, Upa1	48