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Protein Interactions in the Last Steps of the Endosomal Degradative Pathway

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Abstract

Endocytosis, the procedure whereby the plasma membrane invaginates to form endosomes, is essential for bringing many materials into the cell and for membrane recycling. Multiple cellular processes require endocytosis, including nutrient uptake, signal transduction, and cell-pathogen interactions. The fate of cargoes internalized in early endosomes depends on their nature. Some cargoes are recycled back to the plasma membrane, while others are delivered to late endosomes and finally degraded after fusion with lysosomes. During these processes, endosomes suffer translocation from the cell periphery to the perinuclear region, which is accompanied by fusion, invagination, tubulation, and membrane fission events. As expected, complex cellular signaling processes tightly control the endocytic pathway at different steps. Several GTPases, such as Rab7, Rab24 and Arl8b, associated with their effectors RILP, FYCO1 and PLEKHM1, are crucial for endosome trafficking. Here, we examine the current knowledge concerning endosome-lysosome fusion, emphasizing the main protein interactions related to this process.

Keywords: Late endosomes; Lysosomes; Endosomal degradation; Rab GTPases

Trafficking through Endo/Lysosomal Compartments

Endocytosis is a process by which cells take up extracellular materials *via* the inward budding of vesicles formed from the plasma membrane. Subsequently, efficient sorting of the material internalized by endocytosis is essential for key cellular functions and represents the major trafficking pathway in mammalian cells [1]. Incoming material, solutes, receptors and cargos, lipids and even microorganisms are routed to sorting stations: the early and late endosomes [2]. The early endosome collects material from the plasma membrane, as well as from the Golgi, and serves as an initial segregation for molecules that have to go back to the cell surface through recycling endosomes, to the trans-Golgi network by retrograde transport, or to the late endosome/lysosome vesicles [3]. Late endosomes are the penultimate maturation products of the endosomal pathway, and normally fuse with lysosomes for degradation of the incorporated materials [4]. They provide a central hub for incoming and outgoing traffic. Endosomal acidification, in part, determines the sorting, and Rab GTPase proteins serve to dynamically define membrane compartments along the endocytic pathway [2,5].

During endocytosis, membrane fusion is a key process that allows various membrane-enclosed compartments to exchange their contents [6]. Membrane fusion depends on a specific machinery, which includes Rab GTPases, tethering complexes and SNARE (soluble N-ethylmaleimide-sensitive factor attachment protein receptor) proteins. Rab GTPases are master regulators of membrane traffic in all eukaryotes. Similar to the activation and inactivation of other small GTPases, the activation and inactivation of Rabs are strictly coordinated by specific GEFs (guanine nucleotide exchange factors) and GAPs (GTPase-activating proteins), respectively [7]. Thus, Rabs associate with precise compartments after activation, being ideal candidates for controlling protein binding to specific membranes [8]. Actually, during endocytic trafficking, Rab GTPases recruit and activate several proteins involved in membrane fusion and vesicular transport.

Late endosomes function as a key sensing/signaling platform that informs the cell about the nutrient situation [2]. The study of the complex signaling mechanisms of all these processes has become very interesting, since they might be altered during aging and pathologies such as Alzheimer, Parkinson, Huntington, Charcot-Marie-Tooth 2B, atherosclerosis and cerebral ischemic diseases [9–12]. Defining the molecular interactions at the level of late compartments may be helpful to identify novel strategies for the treatment of late-compartments-related diseases.

Specifically referring to the late stage of endosome trafficking, the small GTPase Rab7 is an important regulator of this process, governing the early-to-late endosomal maturation, microtubule minus-end and plus-end migration, and endosome-lysosome fusion, through different protein interaction cascades. Rab7 regulates these activities, by interaction with several proteins, including Mon1-Ccz1, RILP, FYCO1, Rab24, HOPS, PLEKHM1 and Armus [13–16].

Rab7 is recruited and activated on late endosomes by its GEF, the Mon1-Ccz1 complex, facilitating endosomal maturation and fusion with the lysosome [17]. Up to the present, Mon1–Ccz1 is the only known GEF for Rab7, and its activity has been better characterized in yeast than in humans. Mon1 is recruited to endosomes and vacuoles by the phospholipid PI3P (Phosphatidylinositol 3-phosphate), and, after activating Ypt7, it is phosphorylated and released from vacuoles for recycling [18]. However, our present understanding of the molecular mechanism regulating Rab7 activation at this level is extremely limited.

After Rab7 positioning on the endosomal membrane and activation, its function may be connected to cytoskeletal elements. Indeed,

activated Rab7 recruits on late endosomes the effectors RILP (Rab interacting lysosomal protein) and FYCO1 (FYVE and coiled-coil domain containing 1), that are responsible for the movement of Rab7-labeled vesicles on microtubule tracks [19]. Many membrane vesicles, including endosomes, phagosomes and lysosomes, move along microtubules in a bidirectional mode, due to the opposite activities of a plus-end directed kinesin motor and a minus-end directed dynein-dynactin motor (Figure 1 A), [8].

The regulation of Rab7 activity has been intensely studied since it was shown to be critically involved in diseases and pathological disorders. Basically, the lack of Rab7 activity conducts to hampering fusion of endosomes with lysosomes having a critical functional impact on cellular degradation, leading to pathological processes like Parkinson's disease [20,21]. In this pathology, it was found that Rab7 is important for the aggregates' disappearance, since increasing Rab7 activity promoted the clearance of α-synuclein aggregates, reduced cell death, and rescued the phenotype in a fly model of Parkinson's disease [22]. Other disorders, such as fatal neurodegenerative prion diseases, have also been related to malfunctioning modulation of endo-lysosomal vesicle trafficking. The prion infection interferes with Rab7 membrane association, and, consequently, both lysosomal maturation and degradation are impaired [23].

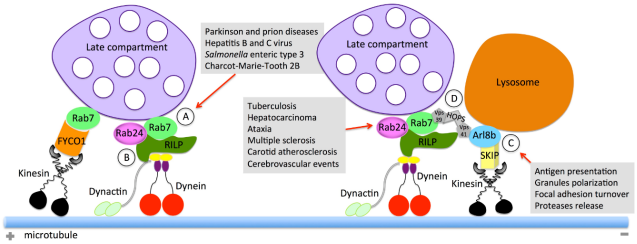

Figure 1: Model of main protein interactions during endosomal degradation and related processes. Late endosomes are the major trafficking center in the cell at the intersection between endocytosis, autophagy, and lysosomal degradation. Fusion of mature endosomes with the lysosome requires the activity of specific proteins. A) Rab7 is localized to the late endosomal compartment and plays a fundamental role in controlling late endocytic processes. B) The Rab7 effector RILP recruits the dynein-dynactin motor complex to these compartments and the motor complex drives transport of a wide variety of cargoes towards the minus end of microtubules. Rab24 is also a component of the endosome-lysosome degradative pathway interacting with Rab7 and RILP. C) On the other hand, Arl8b is localized to lysosomal membranes and controls the spatial distribution of these vesicles *via* recruitment of kinesin motors. Interaction between kinesin and Arl8b is mediated by SKIP and this complex drives the anterograde movement of lysosomes. D) Finally, the HOPS complex mediates the tethering of intracellular vesicles to lysosomes.

However, inactivation of Rab7 is a tactical mechanism by which some pathogens such as Mycobacterium leprae, Salmonella and Hepatitis B and C virus modify trafficking patterns of infected cells [24–27]. The Hepatitis B virus escapes from degradation, downregulating Rab7 expression [25]. Alternatively, the Hepatitis C virus modifies intracellular trafficking processes by cleaving the Rab7 effector RILP, which serves to redirect Rab7-containing vesicles to a prevalent kinesin-dependent trafficking mode, promoting virion secretion [24]. Interestingly, the Salmonella enteric type 3 secreted effector SopD2 binds to Rab7 and inhibits its nucleotide exchange [26]. This action limits Rab7 interaction, with the effectors RILP and FYCO1 disrupting the endocytic trafficking by microtubule motors.

On the other hand, it was recently found that decreasing the Rab7-GTP levels is needed for normal endosome maturation, and the Rab7 GAP Armus, also known as TBC1D2 (TBC1 domain family member 2), is in charge of this function. Armus can directly bind to PI3P on the endosomal membrane to inhibit Rab7, facilitating the traffic to lysosomes. It has been shown that the lack of activity of Armus elevates Rab7-GTP levels, resulting in an accumulation of enlarged late endosomes and decreased epidermal growth factor receptor degradation [16]. However, it was observed that mutations enhancing the cellular levels of activated Rab7 resulted in a pathological increase of the lysosomal activity, producing peripheral sensory neuropathies such as the Charcot-Marie-Tooth 2B disease. In this case the traffic of neurotrophic factors in peripheral sensory neurons is affected, thus being susceptible of premature degradation [28].

The significance of post-translational modifications in Rab GTPase regulation has been scantily investigated, except for prenylation. Besides the GTPase activity, the activity of Rab7 can also be associated to phosphorylation. Rab7 is a substrate for Src kinase, and this Rab protein is tyrosine-phosphorylated, the Y183 residue being the optimal phosphorylation site. This is physiologically induced by EGF (epidermal growth factor), and impairs the interaction of Rab7 with RILP, consequently inhibiting endosome lysosome fusion and cargo degradation [29]. On the contrary, Rab7 dephosphorylation is mediated by PTEN (phosphatase and tensin homolog), which is essential for its GDI membrane targeting and further activation by the GEF. Thus PTEN promotes late endosome maturation by its phosphatase activity [30].

The Rab7 downstream effector RILP fundamentally recruits the dynein/dynactin motor complex to late compartments [31]. RILP interacts with active Rab7 on late endosomes and lysosomes, and prevents further cycling of Rab7. Consequently, these compartments are transported by motors proteins toward the minus end of microtubules, effectively inhibiting their transport to the cell periphery and controlling the transport to endocytic degradative compartments [8]. Structurally, RILP binds Rab7-GTP at its C-terminal and the motor proteins by its N-terminal [31]. Expression of a truncated form of RILP deficient in the N-terminal half inhibits protein degradation (such as the epidermal growth factor and low-density lipoprotein), causes dispersion of lysosomes, and redirects Rab7-containing vesicles to a kinesin-dependent trafficking mode (Figure 1 B), [24].

It has been found that RILP also regulates the pH of endosomes and lysosomes controlling the vacuolar-ATPase subunit V1G1 stability and localization, affecting the V-ATPase assembly and function [32]. Moreover, RILP is a key protein for phagosome maturation; in this case, RILP recruits dynein-dynactin motors on Rab7-GTP-positive phagosomes. This recruitment of RILP not only moves phagosomes centripetally, but also stimulates the extension of phagosomal tubules to late endocytic compartments, being essential for the phagolysosome biogenesis [33,34]. The ultimate stage in the degradative pathway requires the fusion of late endosomes with lysosomes, and, at this point, RILP interacts with a specific tethering complex to coordinate the process [35].

Trafficking of cargo through the endosomal system depends on endosomal fusion events mediated by Rab GTPases, SNARE proteins

and multisubunit tethering complexes. Membrane tethering is a physical association of two membranes before their fusion. Many membrane tethering factors have been identified, but the specific interactions that mediate inter-membrane associations are not fully understood [36]. The HOPS (homotypic fusion and protein sorting) complex is a multi-subunit complex conserved from yeast to mammals that modulates late endosome and lysosome fusion. The HOPS tethering complex is comprised of 6 subunits, Vps11, Vps16, Vps18, Vps33, Vps39 and Vps41, and its role has been better established in yeast than in mammalian cells [37,38]. In mammals, it was shown that Vps41 and Vps39 associate with the limiting membrane of late endosomes and lysosomes controlling the homotypic fusion of late endosomes, as well as the heterotypic fusion of late endosomes and lysosomes (Figure 1 D), [39]. Recently, it was clarified that in late endosomal compartments, RILP directly interacts with the HOPS complex recruiting HOPS subunits. Structurally, the N-terminal portion of RILP interacts with the Vps41 subunit, and this interaction is independent of Rab7 [35]. Moreover, it was reported that the lack of these proteins resulted in an accumulation of late endosomes, a depletion in the number of lysosomes and a block in the degradation of endocytosed cargo [39]. Thus far, the last step of membrane fusion has been better studied in yeast. After the membrane tethering mediated by the HOPS complex, fusion is driven by the SNAREs assembly [40,41]. SNAREs proteins, in conjunction with accessory proteins, drive efficient merger of two distinct lipid bilayers into one interconnected structure [42,43]. Overall, coordination of the activities of HOPS and SNAREs are required for efficient delivery of endocytosed cargo to lysosomes.

Lysosomes are the principal site for degradation of misfolded proteins and recycling of cellular material, which are trafficked to this organelle, not only by endocytic pathways, but also by macroautophagy and chaperone-mediated autophagy. The small GTPase Arl8b, a member of Arf-like (Arl) family of proteins, is a crucial regulator of lysosome positioning and membrane trafficking toward lysosomes [44]. Arl8b localizes on the membrane of lysosomes and through interaction with its effector SKIP, mediates kinesin motors dependent motility of lysosomes on microtubule tracks toward the cell periphery [4]. In addition, Arl8b coordinates membrane tethering by association of the HOPS complex with lysosomal membranes. Specifically, Arl8b interacts with the Vps41 subunit of the HOPS complex, being essential for the function of this tethering complex in endocytic degradation (Figure 1 C), [45,46]. It has been reported that important roles for Arl8b in processes related to lysosomal trafficking and endosome tabulation occur [47]. The Rab7 effector PLEKHM1 (Pleckstrin homology domain-containing protein family member 1) simultaneously binds Rab7 and Arl8b, stimulating the clustering and fusion of late endosomes and lysosomes [48]. The N-terminal domain of PLEKHM1 is necessary and sufficient for the interaction with Arl8b and its subsequent localization to lysosomes. PLEKHM1 competes with SKIP for Arl8b binding, which dictates lysosome positioning; thus, the interaction of Arl8b with SKIP and PLEKHM1 plays opposing roles in regulating lysosome distribution. Arl8b–PLEKHM1 interaction is required for cargo delivery to lysosomes, whereas the interaction with SKIP might regulate assigned roles of lysosomes at the cell periphery including exocytosis, cell migration, and plasma membrane repair.

Arl8b has been involved in regulating immunological functions, such as antigen presentation in dendritic cells and the lytic granules polarization in natural killer lymphocytes [45,46,49]. Also, this protein has links with cancer progression, regulating the focal adhesion turnover required for cell migration [50], as well as proteases release in invasive phenotypes of cancer cells [51,52]. In a model of xenografts in mice, it was demonstrated that Arl8b modulates anterograde lysosome trafficking in response to growth factors and acidic extracellular pH. Through lysosome positioning at the cell periphery, Arl8b facilitates the release of lysosomal proteases to stimulate matrix remodeling, leading to a cellular invasive phenotype, which is critical for tumor invasion [52]. These significant roles emphasize that Arl8b is an important objective in the study of illnesses related to lysosome degradation.

Rab GTPase family includes a large group of proteins, with more than 50 gene products located in diverse subcellular compartments. Rab24 is one of the small GTPases with roles in the late steps of vesicle trafficking and autophagy [53,54]. Rab24 localizes predominantly to the endoplasmic reticulum, but it is not clear what the specific role of this Rab is in endoplasmic reticulum functions, such as tubulation, contact with other organelles or autophagosome formation [55]. Nevertheless, it has lately been demonstrated that this protein participates in the late stages of endocytosis and the autophagy process [15,56]. Rab24 is a singular GTPase with unusual characteristics that distinguish it from other Rab proteins. It is predominantly present in the GTP state when expressed in cultured cells, because it has a low GTPase activity, and it seems not to associate with GDP dissociation inhibitors (GDI) [57]; however, lately, a proteomic analysis has shown interactions with GDI1 and GDI2 [58]. Also, Rab24 suffers tyrosine phosphorylation that could guide the targeting and interactions with effector protein complexes [59]. In fact, comparisons of soluble and particulate cell fractions have demonstrated that the cytosolic pool of Rab24 was more heavily phosphorylated than the membrane pool.

Rab24 displays a perinuclear reticular localization that partially overlaps with endoplasmic reticulum markers, cis-Golgi, and the endoplasmic reticulum-Golgi intermediate compartment. When cells are starved to induce autophagy, the distribution of Rab24 changes dramatically localizing in vesicles that colocalize with the autophagy marker LC3 [53]. Lately it was shown that prenylation and guanine nucleotide binding to Rab24 are necessary for targeting, maturation and clearance of autophagic compartments under nutrient-rich conditions [56]. Besides, very recently our group demonstrated the role of Rab24 in later stages of the endosomal trafficking [54]. We have shown that Rab24 interacts with Rab7 and RILP on the membranes of late compartments (Figure 1 B). Moreover, the distribution of Rab7 in vesicles depends on a functional Rab24, and the lack of Rab24 activity interrupts endosomal degradation. Furthermore, overexpression of the HOPS subunit Vps41 hampered the colocalization of Rab24 with RILP or with Arl8b, suggesting that Vps41 would affect the Rab24/RILP association. In addition, Rab24 also seems to be necessary for membrane fusion, since it coimmunoprecipitates with the SNARE protein SNAP-29 [60], but this observation requires further analysis.

The study of Rab24 has become intriguing for the research community, since its gene expression has been found to be related to several diseases, such as tuberculosis [61], hepatocarcinoma [62], ataxia [63], multiple sclerosis [64], carotid atherosclerosis and cerebrovascular events [64]. Studies regarding the molecular mechanisms underlying hepatocarcinogenesis and metastasis have indicated that increased Rab24 expression facilitated the hepatocarcinoma growth *in vivo* and *in vitro*. Specifically, it was reported that the upregulation of Rab24 promotes the epithelial-mesenchymal transition, adhesion and vasculogenic mimicry of hepatocarcinoma cells, contributing to cell motility and metastasis

[62]. In a model of Old English Sheepdogs to study the hereditary ataxia, which is analogous to hereditary ataxia in humans, it was demonstrated that a defect in Rab24 is highly associated with and may contribute to this disease. Evaluation of the brains of affected dogs showed accumulation of autophagosomes, ubiquitin positive inclusions and a diffuse increase in cytoplasmic neuronal ubiquitin staining [63]. Modified expression of Rab24 has been described in several human disorders, but further analyses are necessary to clarify whether the changes in Rab24 expression levels are connected with alterations in endocytosis or autophagic activity.

Conclusion

The final events in the endocytic pathway have to be tightly synchronized, in order to ensure the correct degradation of material internalized, the transport of newly synthetized lysosomal enzymes and the recycling of sorting receptors from degradative compartments. Several studies have demonstrated that mutations in factors involved in these transport pathways result in various pathologies, in particular lysosome-associated diseases and diverse neurological disorders. Likewise, some microorganisms employ novel endosomal fusion-triggering mechanisms, manipulating protein interactions and membrane fusion. A strategic infection progression is seen in certain pathogens that enter cells, by fusing with endosomes and navigating the endocytic pathway until they reach vesicles that have adequate environmental conditions (pH, proteases, ions, receptors and lipid composition) to survive and replicate. Additionally, a strict regulation of the immune system is critical for effective immune responses, and its function is, in several cases, directly dependent on the organization and activity of endosomal compartments associated with cargo sorting, membrane trafficking and signaling pathways. The arrival of new microscopy techniques and protein interaction analysis to follow these important routes will definitely bring a broader knowledge of these processes and new insights in the area, to identify novel approaches for treatment and drug development.

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