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Actin-dependent endosomal receptor recycling

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Endosomes constitute major sorting compartments within the cell. There, a myriad of transmembrane proteins (cargoes) are delivered to the lysosome for degradation or retrieved from this fate and recycled through tubulo-vesicular transport carriers to different cellular destinations. Retrieval and recycling are orchestrated by multi-protein assemblies that include retromer and retriever, sorting nexins, and the Arp2/3 activating WASH complex. Fine-tuned control of actin polymerization on endosomes is fundamental for the retrieval and recycling of cargoes. Recent advances in the field have highlighted several roles that actin plays in this process including the binding to cargoes, stabilization of endosomal subdomains, generation of the remodeling forces required for the biogenesis of cargo-enriched transport carriers and short-range motility of the transport carriers.

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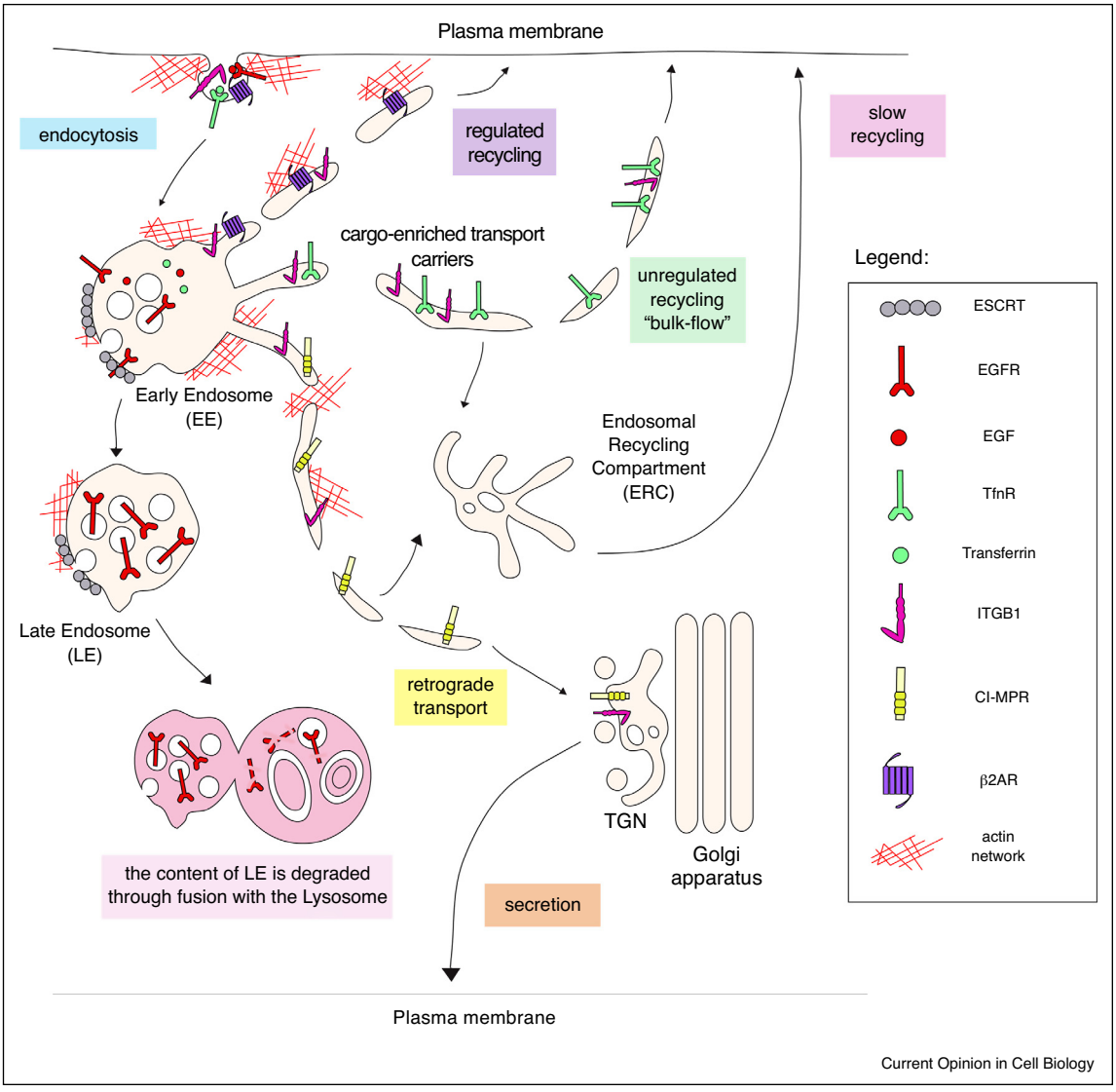
Introduction

The endosomal network is a series of intracellular membrane bound compartments that comprise a central trafficking hub for the sorting of integral transmembrane proteins such as nutrient and iron transporters, adhesion molecules and signaling receptors (together termed 'cargoes'). Cargoes chiefly enter the network from the biosynthetic pathway and following endocytosis from the cell surface, a process that is well known to be regulated by the actin cytoskeleton [1]. The endosomes that first receive cargo following endocytosis are termed early endosomes [2], which undergo transition into late endosomes through a complex alteration in endosomal characteristics that is termed 'endosomal maturation' [2]. Within early and late endosomes cargoes are sorted to one of two fates [3]: either they are sorted for degradation in the lysosome by the endosomal sorting complex required for transport (ESCRT) complex, or they are retrieved from this fate for subsequent recycling back to the cell surface [4], or to the *trans* Golgi network (TGN) [5] (Figure 1). The retrieval and recycling of cargoes can occur through a 'bulk' flow, as in the case of the transferrin receptor (TfnR) or through a regulated, sequence-dependent process [6•]. The latter is thought to be a multistep process: first, the cargo is first recognised by a retrieval complex(es) and segregated away from the degradative pathway [3,7•], and second, the retrieved cargo is then packaged into tubulo-vesicular transport carriers that pinch off from the endosome and couple to cytoskeletal motor proteins for transport to the target compartment [3,7•].

This retrieval and recycling process relies on precise sequence motifs in the cytosolic domain of cargo which are recognized by a series of evolutionarily conserved complexes, including the evolutionarily conserved retromer complex [3]. The retromer complex is a trimeric assembly consisting of the subunits VPS35, VPS29 and VPS26 that, directly or indirectly, through the association with sorting nexin proteins, interacts with the retrieval and recycling motifs of cargo proteins [3]. The retromer complex directly associates with sorting nexin 27 (SNX27) that binds the cytosolic domain of transmembrane proteins containing a carboxy-terminal class I PDZ-binding motif, such as the β2 adrenergic receptor (β2AR), via its PDZ domain [8–10]. Retromer can also directly interact with sorting nexin 3 (SNX3) [11,12] resulting in the presentation of a binding site for the recognition of a ØX(L/M/V) motif (where Ø is an aromatic residue) present in several receptors including the divalent metal transporter DMT1–II [13••] (Figure 2). Two other multiprotein complexes, the COMMD/CCDC22/CCDC93 (CCC) complex and the retriever complex, are emerging as important regulators of cargo retrieval and recycling through their association with the sorting nexin 17 (SNX17) that recognizes a NPx(Y/F)/Nxx(Y/F) motif present in cargoes such as β1 integrin (ITGB1) [7•,14••,15,16] (Figure 2). Furthermore, it was recently shown that the heterodimers of the Bin/Amphiphysin/Rvs (BAR) domain-containing sorting nexins SNX1/SNX2: SNX5/SNX6, which are responsible for the remodelling of endosomal membranes into tubular profiles, have cargo selective activity and bind a WLM motif in the cation-independent mannose-6-phosphate receptor CI-MPR [17,18] (Figure 2).

Actin has long been observed on endosomes [19,20–24]. In recent years it has become evident that actin regulates

Figure 1



Endosomal sorting of receptors. Transmembrane proteins that are fated for degradation, such as the activated epidermal growth factor receptor (EGFR), are initially subjected to ubiquitylation. Ubiquitin serves as a signal to sort the ubiquitylated cargo from the limiting membrane of the endosome into regions that invaginate and pinch off into the lumen of the endosomal vacuole to form cargo-enriched intralumenal vesicles (ILVs) [94]. The most important players in the sorting of ubiquitylated cargo into the forming ILVs are the endosomal sorting complex required for transport (ESCRT): ESCRT-0, ESCRT-I, ESCRT-II and ESCRT-III. ESCRT-0, -I and -II act to recognize the cohort of ubiquitylated cargoes while ESCRT-III is involved in the process of ILV biogenesis [94]. Through iterative rounds of cargo sorting and ILV biogenesis, the mature ILV ladened late endosome becomes competent to fuse with the lysosome, leading to the formation of a hybrid organelle termed the endo-lysosome. Here the cargo present within the ILVs are degraded [95]. Alongside cargo sorting into ILVs, cargoes destined for recycling are sorted from the endosomal limiting membrane into branched tubular profiles, from where they are packaged in tubulo-vesicular carriers for transport to the cell surface or the biosynthetic pathway [2]. Cargo proteins that undergo endosome-to-*trans* Golgi network (TGN) recycling, this is given the specific term 'retrograde transport', include TGN-resident proteins that have reached the endosomal system through anterograde traffic including the sorting receptors that deliver the lysosomal hydrolases (such as the CI-MPR) [5]. Delivery of cargo back to the cell surface can occur directly, namely fast recycling, or indirectly, namely slow recycling, by means to transit through the endosomal recycling compartment (ERC) and possibly the TGN [6•]. A subset of plasma membrane cargoes that include β1 integrin (ITGB1) can take multiple recycling routes and might also undergo recycling trough the TGN to be re-secreted in a controlled manner [96,97]. Historically, the mechanistic details of cargo recycling were considered to occur through sequence-independent 'bulk' flow, as in the case of the Transferrin receptor (TfnR) [6•]. However, more recent evidence is revealing that recycling of a multitude of cargos, including the β2 adrenergic receptor (β2AR), is a highly regulated and sequence-dependent process that requires specialized endosomal sorting complexes that bind to retrieval and recycling motifs found in the cytosolic facing regions of functionally diverse cargoes [3]. It is now clear that several of these processes of cargo retrieval and recycling are regulated by actin.