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EHDs meet the retromer
Complex regulation of retrograde transport

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Retrograde trafficking mediates the transport of endocytic membranes from endosomes to the trans-Golgi network (TGN). Dysregulation of these pathways can result in multiple ailments, including late-onset Alzheimer disease. One of the key retrograde transport regulators, the retromer complex, is tightly controlled by many factors, including the C-terminal Eps15 homology domain (EHD) proteins. This mini-review focuses on recent findings and discusses the regulation of the retromer complex by EHD proteins and the novel EHD1 interaction partner, Rabankyrin-5 (Rank-5).

Endocytic Transport

Endocytic transport is essential for various cellular functions such as the regulation of membrane homeostasis, expression of cell surface receptors and signal transduction.[1,2] It is also exploited by certain pathogens and protein toxins for their entry into the cell and subsequent cytotoxic activities.[3,4] Therefore, elucidation of the underlying mechanisms of this trafficking is crucial for identifying new therapeutic targets and for successful drug delivery.

Endocytic pathways are highly regulated by numerous proteins, including Rab GTPases,[5-8] soluble NSF attachment protein receptor (SNAREs) proteins[9,10] and the C-terminal Eps15 homology domain (EHD) proteins.[11,12] Rab proteins are key regulators of endocytic trafficking. They are reversibly associated with specific membrane organelles in a manner dependent on their GTP-bound status, and they mediate distinct endocytic steps via recruitment of coat components,[14] molecular motors,[15-17] and tethering factors.[18,19] Ultimately vesicle fusion to target membranes is facilitated by SNARE-induced activity.[20,21]

Another family of endocytic regulators, the EHD proteins, has drawn intense interest in recent years. The four mammalian EHDs, EHD1–4, regulate multiple steps in the endocytic trafficking pathways.[12] In contrast to Rabs, EHD proteins contain an ATP-binding G domain.[22] The structure of EHDs suggests a function in the scission of vesicles upon ATP hydrolysis.[23] This is supported by a recent study demonstrating that EHD1 promotes clathrin- and dynamin-dependent synaptic vesicle budding,[24] in coordination with amphiphysin.[25]

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Retrograde Transport and Retromer

Following their transport through the TGN, newly synthesized proteins are dispatched to the plasma membrane (and/or secreted) or targeted to endocytic organelles via anterograde transport. To maintain membrane homeostasis in the TGN, proteins and lipids need to be replenished by the process of retrograde transport, which returns membranes from early, late, and recycling endosomes to the TGN (**Fig. 1**).[26,27] Retrograde transport is important for many cellular functions, including lysosome biogenesis[28-30] and development.[31-36] Dysregulation of this pathway is associated with a variety of diseases including late-onset Alzheimer disease and other neuronal disorders.[37]

Protein sorting into the retrograde pathway is regulated by multiple factors, and the better known ones include clathrin and epsinR,[38] AP-1,[39] oculocerebrorenal syndrome of lowe (OCRL),[40] Golgi-associated γ-ear-containing ARF binding protein 3 (GGA3),[41] phosphofurin acidic cluster sorting protein 1 (PACS1),[41] Rab9, TIP47,[42,43] SNX3[33,44-47] and the retromer complex, a key regulator of retrograde transport.[48,49]

Retromer is an evolutionary conserved heteropentameric complex that consists of two subcomplexes: a sorting nexin (SNX) dimer comprised of SNX1/2[50,51] or SNX5/6,[52,53] and a cargo recognition heterotrimer comprised of vacuolar protein sorting (Vps) 26/29/35.[54] The retromer SNX proteins contain a phox homology (PX) domain that can bind to the phosphatidylinositol 3-monophosphate/3,5-bisphosphate,[55,56] and a Bin-Amphiphysin-Rvs (BAR) domain that detects membrane curvature and/or tubulates membranes.[57-59] Retromer-mediated tubule formation occurs with the highest frequency during the Rab5-to-Rab7 endosomal transition,[60,61] and the scission of the tubules is regulated by the WASH (Wiskott-Aldrich Syndrome protein family Homolog) complex.[62-64]

The cargo-recognition complex trimer interacts with retromer cargos via Vps35.[28,65] The other two subunits, Vps29 and Vps26, bind to the C- and N-termini of Vps35, respectively.[66] Unlike the SNX proteins, the cargo-recognition complex does not contain lipid-binding domains. Its recruitment to the endosome requires the small GTPase Rab7, and can be inhibited by TBC1D5, a member of the Rab GAP family.[67,68] Rab5 is also involved in the recruitment of Vps26/29/35, possibly via its effect on the phosphatidylinositol 3-kinase.[67] The mechanism of mammalian retromer recruitment and assembly is still not fully understood.

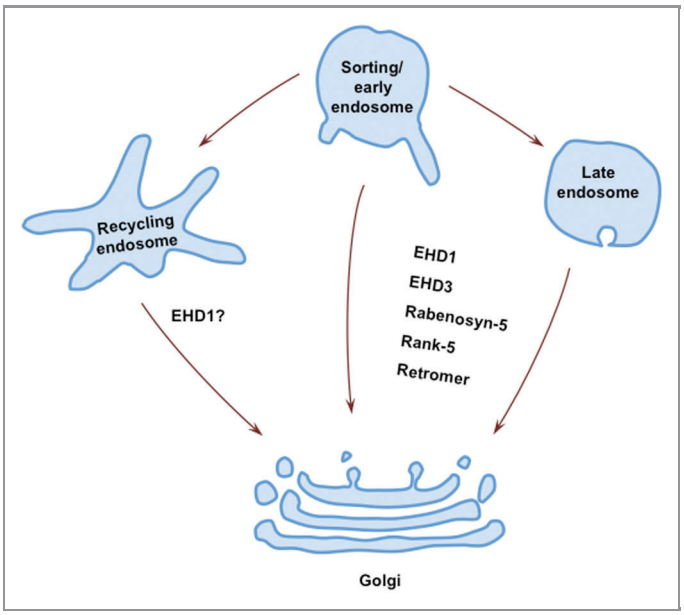

Figure 1. Retrograde transport and EHD proteins. Retrograde transport of endocytic membranes occurs from early endosomes, late endosomes and/or recycling endosomes to the TGN. EHD1 and EHD3 interact with the retromer complex and regulate retromer-mediated membrane transport. For simplicity, only EHD proteins and their interaction partners are shown.

EHD and Retromer

EHD proteins interact with and regulate retromer-mediated retrograde transport to the Golgi. EHD1 colocalizes and interacts with Vps26 and Vps35, and affects retromer-mediated retrieval of mannose-6-phosphate receptor (M6PR).[69] The C-terminal EH domain and nucleotide-binding of EHD1 is required for maintaining normal retromer localization and M6PR transport. However, no direct binding between EHD1 and retromer has been detected, suggesting the involvement of additional factors, possibly through recruitment by the EH domain.

Another EHD family member, EHD3, regulates endosome-to-Golgi trafficking and affects Golgi morphology.[29] Depletion of EHD3 or its interaction partner Rabenosyn-5, a divalent Rab4/5 effector, alters the localization of SNX1 and SNX2 to enlarged early endosomes, and disrupts the retrograde transport of Shiga Toxin B subunit.[29] As a consequence, the biosynthetic transport of cathepsin D, a lysosomal lumenal hydrolase, is impaired upon EHD3 or Rabenosyn-5 knock-down. Although EHD1 and EHD3 are both required for the retromer-mediated transport to the Golgi, EHD3 might play a more prominent role at the early endosome.[70] The underlying mechanism by which EHDs regulate the retromer complex remains to be elucidated.

Rabankyrin-5 (Rank-5) and Retromer

The wide variety of EHD-based functions is further enhanced by their interactions with multiple binding partners. These interactions generally occur between the EHD EH domain and a region of the binding partner that contains one or more asparagine-proline-phenylalanine (NPF) motif flanked by acidic residues.[71,72] An example is the recently identified new EHD1 binding partner, Rank-5, that plays a role in retromer-mediated retrograde transport.[73]

Rank-5, a Rab5 effector, is required for macropinocytosis and early endosome fusion.[74] It is comprised of an N-terminal BTB (Bric-a-brac, Tramtrack and Broad complex)/POZ (Pox virus and zinc finger) domain, followed by 21 consecutive ankyrin repeats, and a C-terminal FYVE (Fab1, YOTB, Vac1, EEA1)-finger domain. While there is a NPFED motif located within the fifth ankyrin domain, we were initially unsure if this site would be exposed for binding; however, subsequent studies confirmed a direct interaction (ref. 73 and see **Fig. 2**). It is noteworthy that Rank-5 specifically binds to EHD1, but not the other EHDs, including EHD3. The latter EHD protein is the closest paralog of EHD1, sharing 86% sequence identity, suggesting the fine-tuning of individual EHD protein functions by their selective binding partners, despite the high level of homology among family members.

Rank-5 interacts with retromer to regulate its subcellular localization, and binding to EHD1 is required for Rank-5 regulation of retromer, since mutating the NPF motif did not rescue retromer mislocalization upon Rank-5 knockdown.[73] The regulatory roles of Rank-5 at distinct steps of the membrane transport pathways are summarized in the model shown in **Figure 3**. Rank-5 promotes the formation of macropinosomes and plays a role in homotypic early-endosome fusion.[74] Through binding to EHD1, Rank-5 is recruited to the retromer and influences the latter's localization and retromer-mediated membrane transport. Depletion of Rank-5 or EHD1 compromises vesicular stomatitis virus-G (VSV-G) secretion, possibly indirectly by affecting Golgi membrane maintenance.[73]

How EHD1 and Rank-5 regulate retromer function is still largely unknown. EHD1 localizes to the same complex with the retromer cargo-recognition units, but has little or no interaction with the SNX dimer.[69,73] This led us to suggest that EHD1 might

Figure 2. Schematic diagram of Rank-5 domain architecture. Rank-5 contains a C-terminal BTB domain and an N-terminal FYVE domain, with 21 consecutive ankyrin repeats in between. The NPFED motif localizes to the fifth ankyrin repeat.

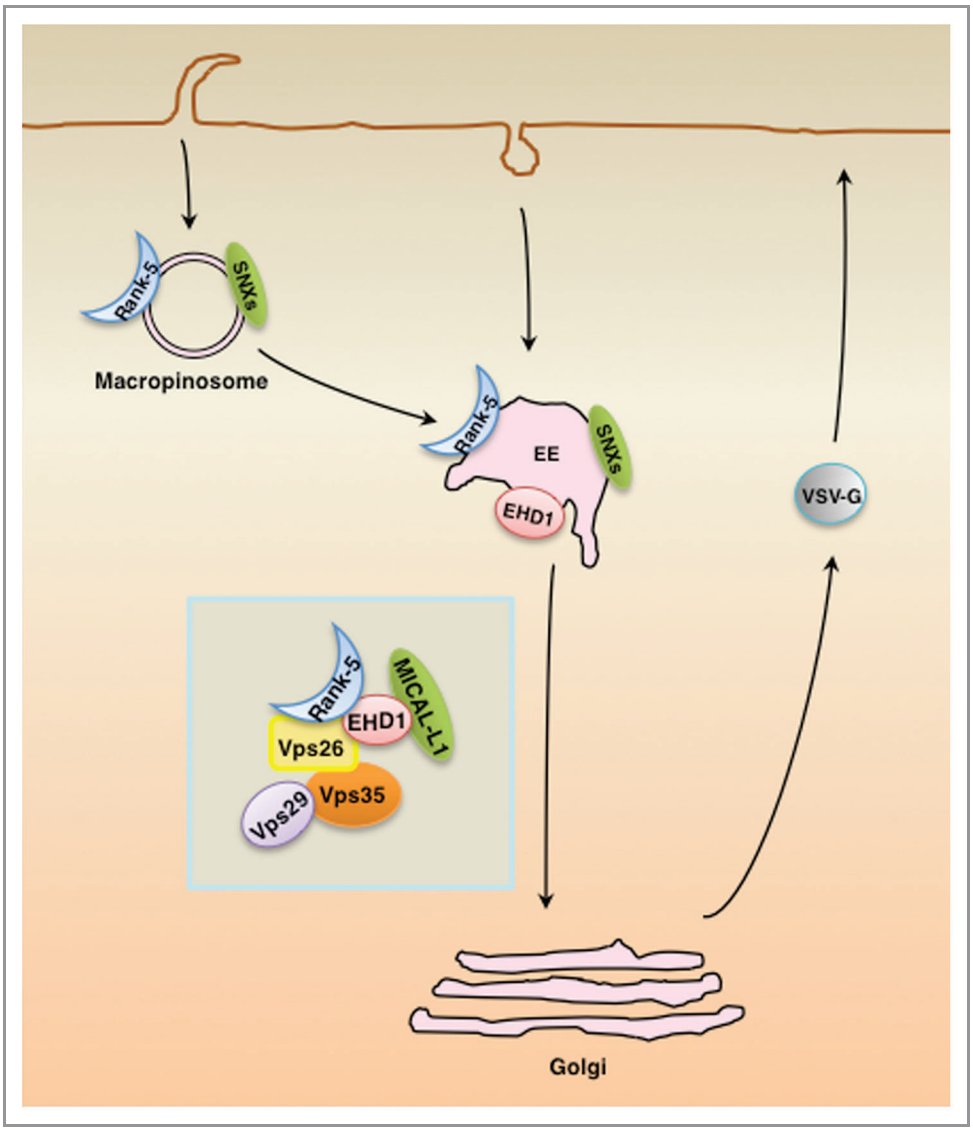

Figure 3. Proposed model for Rank-5 function. Rank-5 is required for the formation of macropinosomes and plays a role in homotypic early-endosome fusion. Through binding to EHD1 and MICAL-L1, Rank-5 is recruited to the retromer and influences retromer-mediated retrograde transport. Furthermore, depletion of either Rank-5 or EHD1 affects VSV-G secretion, possibly through its effect on the homeostasis of the TGN. EE, early endosomes.

act on the Vps subcomplex and indirectly affect SNX localization and SNX1-decorated tubules. Since no direct interaction has been identified either between EHD1 or Rank-5 and the retromer, this highlights the importance of elucidating the other proteins in the complex to further understand the mechanisms of the EHD-mediated retromer regulation.

Conclusion/Summary

Much progress has been made in understanding the regulation of the retromer complex. The recent studies demonstrating the involvement of EHD proteins in retromer-based transport raise many new questions. For example, where is the site of EHD action? Do EHD proteins act in the recruitment of retromer components or the scission of retromer-containing tubules? Do EHD paralogs play distinct roles in the regulation of retrograde transport? Are recycling endosomes involved (ref. 13 and **Fig. 1**)? Are there other binding partners that participate in this process? How do Rab5, EHDs and their common interaction partners orchestrate the regulation of retromer? Further investigation will be required to significantly enhance our understanding of the role of EHDs on retromer regulation.

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