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VIEWPOINT

Hitchhiking on vesicles: a way to harness age-related proteopathies?

Doryaneh Ahmadpour[1,2], Roja Babazadeh[1,3] and Thomas Nystrom[1]

1 Institute for Biomedicine, Sahlgrenska Academy, Centre for Ageing and Health-AgeCap, University of Gothenburg, Sweden
2 Institute of Neuroscience and Physiology, Department of Psychiatry and Neurochemistry, Sahlgrenska Academy at the University of Gothenburg, Sweden
3 Department of Biology and Biological Engineering, Chalmers University of Technology, Gothenburg, Sweden

Keywords
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Correspondence
T. Nystrom, Institute for Biomedicine, Sahlgrenska Academy, Centre for Ageing and Health-AgeCap, University of Gothenburg, Gothenburg 413 90, Sweden
Tel: +46 7069299260
E-mail: thomas.nystrom@cmb.gu.se

Doryaneh Ahmadpour and Roja Babazadeh contributed equally.

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Central to proteopathies and leading to most age-related neurodegenerative disorders is a failure in protein quality control (PQC). To harness the toxicity of misfolded and damaged disease proteins, such proteins are either refolded, degraded by temporal PQC, or sequestered by spatial PQC into specific, organelle-associated, compartments within the cell. Here, we discuss the impact of vesicle trafficking pathways in general, and syntaxin 5 in particular, as key players in spatial PQC directing misfolded proteins to the surface of vacuole and mitochondria, which facilitates their clearance and detoxification. Since boosting vesicle trafficking genetically can positively impact on spatial PQC and make cells less sensitive to misfolded disease proteins, we speculate that regulators of such trafficking might serve as therapeutic targets for age-related neurological disorders.

Preface

Neurodegenerative diseases affect millions of people worldwide. A hallmark of many such diseases is the formation of misfolded proteins accumulating in aggregates and oligomers leading to cellular toxicity and proteostatic failure [1-3]. A vast amount of evidence links vesicle trafficking to such protein aggregation and protein toxicity in different neurodegenerative diseases. For example, in amyotrophic lateral sclerosis (ALS)—a multifactorial disorder—aberrant endoplasmic reticulum (ER)–Golgi trafficking has been linked to several cellular defects, including protein misfolding and aggregation, stress within the

Abbreviations
AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; COG complex, the conserved oligomeric Golgi complex; COP, coat protein complex; CORVET, class C core vacuole/endosome tethering; DRGs, dorsal root ganglia neurons; ER, endoplasmic reticulum; EV, extracellular vehicle; HD, Huntington's disease; HOPS, homotypic fusion and vacuole protein sorting; IPOD, insoluble protein deposit; JUNQ/INQ, juxtanuclear and/or nuclear-internal quality control site; LCD, low complexity domains; LE, late endosomes; MVB, multivesicular body; PD, Parkinson's disease; PKA, protein kinase A; PNS, peripheral nervous system; PQC, protein quality control; SG, stress granules; sHSP, small heat shock protein; SNAREs, soluble *N*-ethylmaleimide-sensitive factor attachment protein receptors; TGN, trans-Golgi network; TOR, target of rapamycin.

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ER, and mitochondrial dysfunction [4]. Moreover, in ALS, as in other neurodegenerative diseases, including Parkinson's (PD), Alzheimer's (AD), Huntington's (HD), prion diseases, and spinal muscular atrophy, the continuous Golgi ribbon of a specific group of neurons is broken into fragmented and isolated elements at very early stages before clinical and other pathological symptoms become evident [5]. This defect in Golgi organization appears to be due to aberrant intracellular transport linked to alterations in the levels of proteins regulating transport between the ER and the Golgi, such as the t-SNARE protein syntaxin 5 [5,6]. Syntaxin 5 deficiency also leads to enhanced sensitivity toward the misfolded PD protein α-synuclein [7]. It is well established that deficits in ER-to-Golgi anterograde axonal transport contribute to the pathology of AD, HD, and ALS [8,9] but it is not clear whether such axonal transport defects are the cause or consequence of the formation of disease aggregates [8-11]. Thus, the impact of Golgi organization and protein trafficking between the ER and the Golgi with respect to neurodegenerative diseases and protein aggregation is far from clear and insights into this area can provide inroads to novel therapeutic targets aimed at mitigating the effects of protein misfolding.

In this perspective, recent data employing yeast as model system for studying how cells cope with protein misfolding and aggregation [7] indicate that defects in trafficking make cells particularly sensitive to mutated, aggregation-prone, disease proteins. This is suggested to be due to such trafficking pathways being an integral part of the cell's protein quality control (PQC), especially the control of sequestering misfolded proteins into specific, organelle-associated, spatial compartments within the cell. In addition, we propose that such trafficking pathways, rather than primary members, such as chaperones and proteases, of PQC might become bottlenecks during aging.

A brief overview of temporal and spatial protein quality control

Protein homeostasis (proteostasis) refers to a set of highly complex and interlinked processes that ensures the level, conformational stability, and subcellular localization of proteins in the cell [12,13]. The maintenance of protein homeostasis is absolutely vital for cellular function, growth, reproduction, and longevity. Therefore, cells across the evolutionary tree have evolved systems of temporal and spatial PQC to maintain a functional proteome [7,12-18]. The molecular chaperones of temporal PQC govern the proper folding of newly synthesized polypeptides, refolding of misfolded proteins, and degrading, with the help of proteases, the proteins that cannot be refolded [3,16,19-22]. Correct folding of the nascent peptides is vital for their function and prevents them from undesired interactions in the crowded environment of the cell [13,23]. This process depends on Hsp70 and cochaperones of the Hsp40 family targeting Hsp70 to its polypeptide substrate, promoted by nucleotide exchange factors (Sse1/Sse2, Fes1, and Snl1) [13,21,24-27]. If aggregating, the misfolded proteins can, in some organisms, first be pulled out from the aggregates by proteins of the Hsp100 family (such as Hsp104 disaggregase in yeast), which make them accessible to Hsp70/Hsp40s for refolding [21,28,29]. If the proteins are not refolded and rescued by the chaperone machinery, they can be either tagged by ubiquitin chain and recognized by 26S proteasome for degradation by ubiquitin–proteasome system (UPS) [30], packed in vesicles for exocytosis [31,32], or transported to the vacuole/lysosome by autophagy [33]. Autophagy has also been identified as the major degradation pathway for many aggregation-prone proteins that are associated with neurodegenerative disorders [34].

Another system of protein homeostasis, spatial PQC, acts in parallel to temporal PQC and deposits the misfolded proteins into specific deposition sites or compartments [16,35-41]. In yeast, misfolded proteins in the cytoplasm first accumulate at multiple sites called CytoQs, also known as Q-bodies or stress foci, which requires the small heat shock protein (sHsp) Hsp42 [41,42]. Further on, CytoQs coalesce into larger deposition sites commonly referred to as inclusions. These inclusions are localized to at least three distinct sites known as the juxtanuclear and/or nuclear-internal quality control site (JUNQ/INQ); the peripheral, vacuole-associated insoluble protein deposit (IPOD); and a site adjacent to mitochondria [3,37,41,43-48]. Different sorting mechanisms seem to play a role in the sorting of the misfolded protein to each specific site. Ubiquitination has been shown to be important in sequestering aggregates into JUNQ/INQ sites for proteasome-dependent degradation [37]. However, some substrates can be sequestered to these sites even in the absence of such modification [44]. Although the additional factors directing INQ/JUNQ to their sites are not completely elucidated, some players such as Hsp104, Hsp70/Hsp40, and Hsp42 are among the ones identified by candidate approaches [16,37,46]. The vacuole-associated IPOD [37] seems to be the deposition site for both amyloid and amorphous aggregates in yeast [37,41], and Hsp104, Hsp42, myosin motor protein Myo2, and the myosin-dependent vacuole adaptor protein Vac17 are required for deposition of the

substrates into this site [16,21,37,41,44,49]. How aggregates are recruited to the surface of mitochondria is not clear but this also depends on Myo2 in addition to proteins creating contact sites between the vacuole and mitochondria [7]. A number of evidences indicate that this association of aggregates with mitochondria is beneficial for aggregate clearance [7,45,46]. Spatial sequestration of unfolded, misfolded, and damaged proteins into discrete inclusions also facilitates the asymmetrical distribution of such proteins during cell division, allowing an old progenitor cell to produce an immaculate daughter cell harboring a rejuvenated, damage-free proteome [50-56].

Another interesting possibility for clearing itself of aggregates could be the cellular export of such aggregates by extracellular vehicles (EVs) such as exosomes or ectosomes, which formation depends on local microdomains assembled in endocytic membranes for exosomes and on the plasma membrane for ectosomes [57]. EVs have been shown to contain both protein aggregates and organelles and are recognized as cellular systems for discarding unwanted components, possibly aggregates, and, primarily, a powerful means for intercellular communication [57]. However, in AD and ALS, neurodegenerative effects were found to actually depend on the transfer of molecules, including miRNAs, gangliosides, and proteins, by EVs from healthy cells, suggesting that EVs in these diseases are a burden rather than a blessing [57]. Yeasts, including *Saccharomyces cerevisiae*, are able to form exosomes, and several studies suggest that their release to the extracellular space requires elements of the conventional post-Golgi secretory pathway. It is presently not known whether yeast can rid itself of aggregates through such export of exosomes and whether the effects of ER-to-Golgi and trans-Golgi trafficking (see below) on protein inclusion formation are, in part, dependent on exosome formation [58].

Vesicle trafficking pathways, a brief overview

Recent data from yeast suggest that spatial deposition of misfolded proteins formed in the cytosol depends, apart from different kinds of chaperones, on ER-to-Golgi vesicle trafficking, multisubunit tethering proteins, and membrane fusion proteins [7,49,59]. Therefore, we briefly describe here the trafficking pathways implicated in such deposition of misfolded proteins into organelle-associated aggregates and some key proteins involved in this process (Fig. 1).

Proteins translocated at the ER during protein synthesis [60] must be targeted to the correct organelle/location for their proper modification, function, or degradation [61]. Vesicle trafficking processes ensure that such proteins are not only delivered to their correct subcellular compartment but also that specific protein concentrations in the various subcellular compartments are properly maintained [61]. Following synthesis at ER, proteins are transported to the Golgi through a forward (anterograde) transport. Membrane trafficking between the ER and the Golgi is bidirectional (Fig. 1) in which a carrier forms on the donor organelle and then tethers to and fuses with the target organelle. This cargo transport requires budding, movement, tethering, as well as uncoating and fusion of coat protein complex II (COPII) involved in anterograde trafficking and COPI (retrograde) carriers with their respective compartments (Fig. 1) [62,63]. The COPII complex consists of the secretion-associated RAS-related 1 (Sar1) GTPase and the two subcomplexes Sec23–Sec24 and Sec13–Sec31 [64]. Sar1 is activated by guanine nucleotide exchange factor Sec12 and through interaction with Sec23 recruits Sec23–Sec24 heterodimers [65,66]. Following direct interaction of Sar1-Sec23 with Sec31, the Sec13-Sec31 heterodimers recruit to the existing complex and form the COPII coat [67].

Coat protein complex I, on the other hand, operates in retrieval from the Golgi to the ER, in intra-Golgi transport (Fig. 1) [68-71], and maintains ER- and Golgi-resident chaperones and enzymes in their proper intracellular location. Several reports have also highlighted a role for COPI in endosomal transport and function [72-79]. COPI coat proteins localize to Golgi or ER–Golgi intermediate compartment membranes through the action of Arf1, which is a small GTPase related to Sar1 and a heptamer called coatomer [79]. The coatomer consists of two subcomplexes composed of Ret1, Sec27, and Sec28 as a trimeric assembly and Sec26, Sec21, Ret2, and Ret3 as the second subcomplex [79]. Fusion of membrane and vesicles along the vesicle trafficking pathway are mediated by a family of proteins called soluble *N*-ethylmaleimide-sensitive factor attachment protein receptors (SNARE) proteins. SNARE proteins can be classified into v-SNAREs that are associated with the vesicle and t-SNAREs that are associated with the target compartments. Interaction of v-SNAREs and t-SNAREs on the two opposing membranes leads to docking of the vesicle with the target compartment. Finally, the SNARE complex is disassembled, the released v-SNARE is recycled to the donor compartment by retrograde transport, and the t-SNARE subunits are reorganized for the next docking and fusion events [80,81].

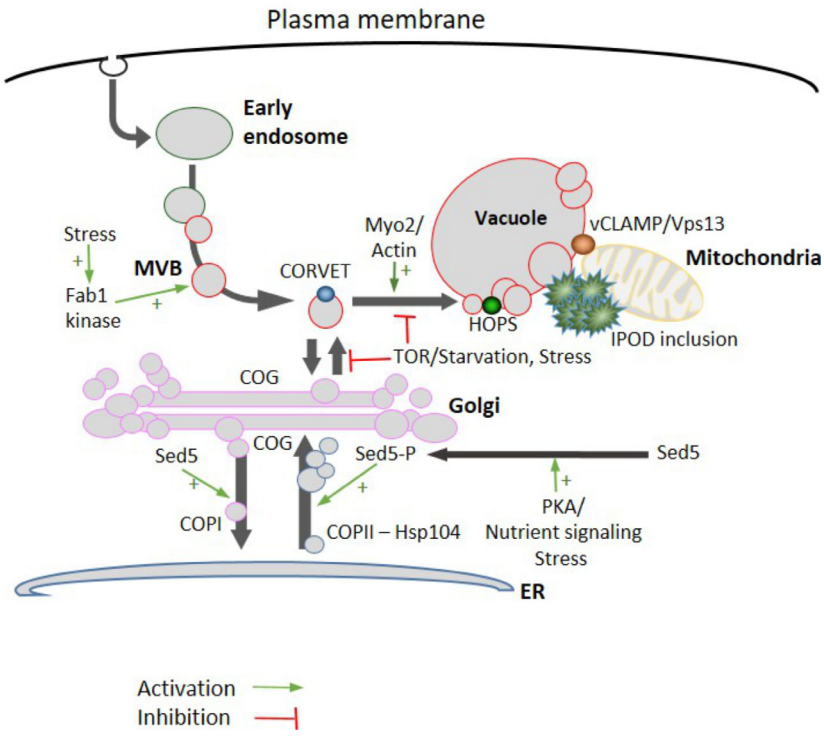

Fig. 1. Schematic representation of vesicle trafficking pathways and components involved in IPOD inclusion body formation and clearance. Thick arrows indicate the directional flow of processes, whereas thin green arrows indicate positive regulation of a process and thin red T-lines indicate negative regulation of a process. The red color surrounding MVB, endosomal vesicles, and the vacuole indicate the presence of the signaling lipid phosphatidylinositol-3,5-bisphosphate, the product of the Fab1 kinase.

The cis-Golgi t-SNARE syntaxin 5 (Sed5 in yeast) is a phosphoprotein, and the conserved membrane-proximal protein kinase A (PKA) consensus site (serine-317) in the Sed5 appears to regulate ER–Golgi transport, as well as Golgi morphology. A Sed5 phosphorylation and dephosphorylation cycle seems to be required for normal t-SNARE function, affects vesicle trafficking, and arranges Golgi ordering and dispersal [7,82]. Sed5 plays a key role in protein transport from the ER to the Golgi through a SNARE complex with Sec22, Bet1, and Bos1 [83,84] as well as intra-Golgi transport through other SNAREs such as Sft1, Ykt6, Gos1, and Vti1 to mediate intra-Golgi and endosome-to-Golgi transport [85]. In addition, the conserved oligomeric Golgi (COG) complex, a vesicle tethering complex, interacts and colocalizes with Sed5 in the SNARE complexes and enhances intra-Golgi SNARE complex stability as well as mobility [86].

Following exit from Golgi, proteins are then either sorted into secretory (SEC) vesicles and secreted or targeted to the cell surface, or through two different pathways, transported from Golgi to the vacuole. The CPY pathway takes the protein via late endosomes (LE) and multivesicular bodies (MVB) to the vacuole. The ALP pathway, on the other hand, targets the vacuolar-destined proteins to the vacuole from the late Golgi bypassing the endosomal network [87,88]. Tethering events from Golgi and plasma membrane to early endosomes is mediated by the class C core vacuole/endosome tethering (CORVET) complex (Fig. 1), consisting of Vps3, Vps11, Vps18, Vps16, Vps8, as well as the Sec1/Munc18 family protein Vps33 interacting with Rab5-positive membranes. The homotypic fusion and vacuole protein sorting (HOPS) complex, on the other hand (Fig. 1), acts downstream of CORVET, fusing LE with vacuoles. The HOPS complex consists of the core proteins Vps11, Vps16, and Vps18, the Ypt7/Rab7 interacting subunits Vps39 and Vps41, as well as the Vps33 [89].

Routing misfolded proteins of the cytosol to specific sites through vesicle trafficking

Recent data, using yeast as a model, demonstrate that misfolded proteins formed in the cytosol, similar to proteins translocated at the ER, depend on the systems described above for their deposition at aggregation sites close at the vacuole and mitochondria [7,49,59]. Specifically, Hsp104-associated aggregate fusion and inclusion body formation upon heat stress and aging require vesicle trafficking from the ER to the Golgi (COPII-dependent), vesicle exit from Golgi to endosomes, tethering of vesicles to the vacuole (HOPS/CORVET-dependent), vacuole–mitochondrial contact sites (vacuole and mitochondria patch/Vps13-

dependent), and the myosin motor protein Myo2, via its functions linked to the actin cytoskeleton [7,49].

Intriguingly, the t-SNARE syntaxin, Sed5, and the the conserved oligomeric Golgi complex (COG complex), known to stabilize the Sed5 complex [86], are key players in this deposition of misfolded proteins at the surface of vacuoles and mitochondria and Sed5 overproduction; otherwise, wild-type cells are actually boosting inclusion formation and disaggregation suggesting that Sed5 is a bottleneck component of cytosolic PQC [7].

In view of the fact that elements of protein aggregates have been shown to be RNA-binding proteins with the presence of low complexity domains that are prone to self-assemble and form aggregates commonly known as stress granules (SG) [90,91], it is possible that the Sed5-dependent aggregates described in this perspective are indeed SGs and/or share features with such granules. However, the aggregates and inclusions described herein as relying on Sed5 for their formation and localization at the vacuole and mitochondria do not appear to be similar to SG since reporters of SG (FUS) do not colocalize with these inclusions. This does not rule out that SGs and misfolded proteins colocalize early during proteostatic stress and are subsequently partitioned to different compartments in the cell. Also, it is not known whether local liquid phase separation occurs at the surface of vacuoles and mitochondria upon a temperature shift from 30 to 38°C, which could explain why misfolded proteins accumulate at such sites. If so, it would have to be hypothesized that phase separation relies on a t-SNARE protein required for ER-to-Golgi trafficking, which seems unlikely. Moreover, although Sed5 plays an important role in autophagy by regulating the formation of Atg9-containing vesicles necessary for autophagosome formation in the Golgi [92,93], the role of Sed5 in the formation and clearance of aggregates does not appear to be linked to the canonical autophagy pathway in yeast [7,92]. Nevertheless, while the clearance of aggregates in wild-type yeast cells to a large extent relied on active 26S proteasomes, Sed5-overproducing cells instead relied on the activity of serine peptidases, presumably vacuolar peptidases, including the vacuolar peptidase Pep4 [7]. These results raise the question of how vesicle trafficking routes bring misfolded proteins of the cytosol to the vicinity of these organelles, and if so, how misfolded and aggregated proteins enter the vacuole?

One possible explanation is that components of the PQC systems interact directly with vesicles. Indeed, it has been shown that Hsp104 is associated with components of the surface of COPII vesicles [49] and its movement is regulated by Sed5, and its phosphorylation [7], in a manner consistent with Hsp104 being associated with COPII vesicles and anterograde trafficking (Fig. 1). Hsp104 being a resident protein on the surface of COPII vesicles may thus recruit misfolded and aggregating proteins to such vesicles and hitchhike to the surface of vacuoles: the IPOD deposition site [37]. In support of this notion, Sed5, known to cluster in foci on COP vesicles and Golgi [94,95], is transiently colocalizing during heat stress with Hsp104-associated aggregates suggesting that at least some misfolded/aggregated proteins are associated directly with the ER–Golgi COPII-dependent trafficking system. Hsp104-associated aggregates also colocalize transiently with the *trans*-Golgi network and endosomal Vps1 prior to their deposition at the surface of the vacuole [96]. Consistently, Hsp104 interacts physically with Vps1 and Vps1 is required for the formation of IPOD inclusions [49]. How aggregates are finally translocated to the surface of mitochondria is not clear but inclusions detected at later time points during heat stress displayed extensive colocalization with both Vps39 and Vps13, proteins involved in creating contact sites between the vacuole and the mitochondria [7,97,98].

Another, mutually inclusive, explanation for how misfolded proteins are directed toward the vacuole and mitochondria is that partly unfolded proteins are recruited, in a nonspecific fashion, to vesicles by hydrophobic interactions with endomembrane lipids. In addition, it is possible that the lipid environment at specific patches on organelles and vesicles is especially prone to interact with misfolded proteins and in this way provide a site for the accumulation and aggregation of such aberrant proteins. However, since Hsp104, Hsp70s, Hsp40s, and sHsps are required for proper deposition of inclusions, including IPODs [17,99,100], lipid environments alone, without interaction with PQC components, do not appear to be sufficient for sequestration of misfolded protein at discrete quality control sites. The sorting of aggregates toward mitochondria appears physiologically relevant as aggregates associated with this organelle are cleared out faster than aggregates that are not [7]. One possible explanation might be that sites at the proximity of mitochondria are enriched in ATP [101] and disaggregating, refolding, and degrading damaged proteins are highly ATP-consuming processes. Another possible explanation for why the vacuole–mitochondria contact sites seem to play an important role as aggregate destination and clearance [7] might be that the lipid and metabolite composition of these contact sites serve as chemical chaperones, like lipid droplets [102], accelerating clearance of aggregates.

Despite advanced and detailed knowledge about the vesicle trafficking pathways, little is known about how the levels and activities of these pathways involved in protein inclusion formation are regulated genetically and by environmental cues or stress. However, it is known that the nutrient-sensing PKA pathway is involved in the regulation of some t-SNAREs, which confer exo- and endocytic transport in yeast. Considering that Sed5 is a phosphoprotein that harbors a highly conserved PKA phosphorylation site proximal to its transmembrane domain [82], it is very much possible that the PKA pathway is also important for phosphorylation of Sed5 and COPII anterograde trafficking. Therefore, it is expected that PKA, and nutrient, signaling also affects formation of aggregates and inclusions, which have been shown to be the case [103,104]. In addition, the target of rapamycin (TOR) signaling pathway is negatively regulating trafficking from cis-Golgi to the vacuole ([105], Fig. 1) suggesting that high TOR activity and low TOR activity would result in a decrease and increased inclusion formation, respectively. Indeed, genetic screens of aggregate and inclusion formation have indicated that there is such a relationship between TOR activity and inclusion formation [7,49]. Another regulator of trafficking of vesicles toward the vacuole is Fab1, a 1-phosphatidylinositol-3-phosphate 5-kinase that generates the phosphatidylinositol (3,5)P2, which resides on MVBs, LE, and vacuoles, is involved in vacuolar sorting, and required for proper localization of CORVET and HOPS ([106-108], Fig. 1). Consistently, Fab1, and other components of the Fab1 complex, is required for proper formation of IPOD inclusions [7] and their asymmetric inheritance during cytokinesis [49]. Fab1 levels are elevated during stress, for example, salt stress [109] but less is known about how this kinase is regulated under proteostatic stress. HOPS-dependent fusion of vesicles to the vacuole depends also on the F-actin and the myosin motor protein Myo2 ([110-112], Fig. 1), and a reduced activity in either of these components drastically reduces the cell's ability to form IPOD inclusions [7,49,113]. As the trafficking pathways described appear to be part of a spatial PQC system, it would be interesting to elucidate to what extent their regulation is coordinated with canonical stress responses elicited by proteostatic stress, such as the Hsf1- and Msn2/4-dependent stress responses.

Implication of vesicle trafficking in age-related proteopathies

Defects in vesicle trafficking are known to make organisms more susceptible to many misfolded disease proteins, and an early effect of carrying a disease protein implicated in age-related neurodegenerative disease is defective in intracellular trafficking [4-7,114]. We propose that this phenomenon is the result of trafficking being an integral part of spatial PQC aimed at harnessing the potential toxicity of misfolded and aggregating proteins. It has been shown that mutations in the early endocytotic pathway render yeast and mammalian cells sensitive to polyQ-expanded huntingtin aggregation [115] and soluble misfolded huntingtin interacts with proteins functioning in trafficking events [116]. Likewise, the Parkinson disease protein α-synuclein interacts with lipid rafts on endocytotic vesicles [117,118] and a genetic screen identified increased α-synuclein aggregate load in yeast mutants displaying reduced endocytic trafficking [117]. In AD, amyloid precursor protein causes defects in endocytosis-dependent processes [119] and abnormal endosomes are an early sign of AD pathology, preceding the appearance of aggregated proteins [120].

It has also been shown that endocytosis in various systems declines during 'normal' aging [121,122], and defects in vesicle trafficking have been linked to an age-related decline in neuronal activity. However, it is not clear whether such defects in trafficking are the cause of neurodegeneration or another diagnostic marker of aging. In yeast, endocytic trafficking markedly slows down during replicative aging, and mitigating such a decline genetically prolongs lifespan and counteracts the buildup of protein aggregates [49]. In the worm *Caenorhabditis elegans*, it has been shown that synaptic vesicles moving in the anterograde direction are decreased in some motor neurons upon aging and that this correlates with impaired synaptic transmission [123]. In long-lived *daf-2* and *eat-2* mutant worms, a prolonged maintenance of trafficking is associated with the lifespan extension seen in these mutant animals, implicating the insulin-like signaling pathway in the regulation of vesicle, and mitochondrial, motility during aging [123]. Studies using mouse as a model have likewise showed that axonal transport undergoes an age-dependent decline, for example, an age-dependent reduction in the transport of the Golgi-derived nicotinamide mononucleotide adenylyltransferase 2 vesicles already from 3 to 6 months of age in both the central nerve system and the peripheral nervous system [124]. Moreover, recent work has demonstrated that the biogenesis of the autophagosome decreases in cultured dorsal root ganglia neurons from aged mice [125]. It has also been shown that oxidatively damaged proteins accumulate within endosomes isolated from aged mice [126] and there is a general decline in endocytosis in

neurons of both mice and rats isolated from aged individuals [127].

Thus, there is a clear association between axonal vesicle transport, aging, and the maintenance of neuronal health, but it is not completely understood how transport mechanistically affects PQC and neuronal function in aging animals. We speculate that defects in vesicle trafficking may represent a causal event occurring early in life, which sets off a damaging cascade, including failures in spatial PQC, leading to late-onset neuronal dysfunction and, perhaps, aging itself. If true, drugs affecting endocytic activity could possibly be used in therapeutic approaches to such age-related proteopathies. In this context, it is interesting that the overproduction of one single protein, Sed5, can boost inclusion formation, disaggregation, and resistance to a neurological disease protein α-synuclein of the PD [7], indicating that this t-SNARE protein is a limiting factor, at least in yeast, in spatial PQC. Moreover, a phosphorylated mimetic mutant of Sed5, favoring anterograde COPII trafficking, is increasing resistance to α-synuclein on its own suggesting that boosting ER-to-Golgi anterograde trafficking may be an effective means of increasing resistance against neurological disease proteins [7] and that inhibiting a syntaxin 5 phosphatase may constitute a therapeutic means to do so. This appears relevant also in light of studies showing that components involved in COP-dependent transport are associated with increased AD risk [128] and protecting yeast cells against human disease proteins associated with proteopathies [59].

Conclusion

In conclusion, the t-SNARE syntaxin, Sed5, plays a role in directing misfolded proteins to the surface of vacuoles and mitochondria and is doing so by controlling ER-to-Golgi COPII-dependent anterograde trafficking. COPII components and the disaggregase Hsp104 interact physically suggesting that vesicles of the trafficking pathway may serve as platforms on which misfolded and aggregated proteins can hitchhike toward specific deposition sites, including the surface of vacuoles and mitochondria. The deposition of aggregates at the surface of mitochondria speeds up their clearance from the cell, and this deposition relies on proteins known to make contact sites between vacuoles and mitochondria. Deficiency in endocytosis, and vesicle trafficking in general, renders cells more sensitive to damaged proteins, including neurological disease proteins while boosting ER-to-Golgi trafficking mitigates the toxicity of some such disease proteins, indicating that COPII anterograde trafficking might be an interesting target for therapeutic intervention of age-related proteopathies as the activity and fidelity of such trafficking pathways are known to decline during aging.

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Conflict of interest

The authors declare no conflict of interest.

Author contributions

DA, RB, and TN conceived and wrote the manuscript and prepared the figure.

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