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ER and Golgi Trafficking in Axons, Dendrites, and Glial Processes

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Abstract

Both neurons and glia in mammalian brains are highly ramified. Neurons form complex neural networks using axons and dendrites. Axons are long with few branches and form presynaptic boutons that connect to target neurons and effector tissues. Dendrites are shorter, highly branched, and form post-synaptic boutons. Astrocyte processes contact synapses and blood vessels in order to regulate neuronal activity and blood flow, respectively. Oligodendrocyte processes extend toward axons to make myelin sheaths. Microglia processes dynamically survey their environments. Here, we describe the local secretory system (ER and Golgi) in neuronal and glial processes. We focus on Golgi outpost functions in acentrosomal microtubule nucleation, cargo trafficking, and protein glycosylation. Thus, satellite ER and Golgi are critical for local structure and function.

Keywords

Neuron; axon; dendrite; astrocyte; oligodendrocyte; microglia; ER; Golgi; Golgi outpost; microtubules; transport; glycosylation

Introduction

Brain cells, including glia and neurons, are ramified in order to perform specific functions, such as the formation of synapses for electrical signaling by neurons, the ensheathment and wrapping of myelin sheaths around axons by oligodendrocytes, and association with blood vessels by astrocytes. Due to these specialized shapes and structures, these cells require special pathways for protein secretion.

The classic secretory pathway starts in the endoplasmic reticulum (ER) and proceeds through the Golgi network. Rough ER (RER) are sections of ER with attached ribosomes while smooth ER (SER) are sections without ribosomes. Ribosomes on the ER membrane can translate mRNA from the cytoplasm into proteins in the ER lumen. Transmembrane

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proteins are similarly translated on RER, but intercalate through translocon channels before integrating into the ER membrane. Properly folded proteins leave the ER at ER exit-sites (ERES) via COPII (coat protein complex II) vesicles. COPII proteins soon fall off and these vesicles use SNAREs (Soluble NSF attachment protein receptors) to merge into vesicular tubular clusters called ER–Golgi intermediate compartments (ERGICs). At the same time, escaped ER proteins bud off in COPI vesicles that are transported back to the ER. Proteins from the ERGIC then head to the Golgi for further glycosylation and proteolysis, traversing multiple layers of the *cis*-Golgi network (CGN), the medial Golgi cisternae, and then the *trans*-Golgi network (TGN).

At the TGN, exiting proteins can diverge along several different processing pathways based on their function and localization. First, Golgi-derived vesicles containing secreted proteins or transmembrane proteins can bud off then fuse with the plasma membrane; this results in either releasing secreted proteins into the extracellular milieu or integrating transmembrane proteins into the plasma membrane. Second, secretory vesicles packed with secreted proteins can be stored near the plasma membrane or in endosomes until a stimulus arrives. Third, proteins destined for endosomes and lysosomes are modified with an oligosaccharide signal (mannose 6-phosphate), then exit the TGN in clathrin-coated vesicles. Thus, the secretory pathways that are taken through the ER and Golgi are determined by the function, destination, and fate of individual cargo proteins.

In the subsequent sections, we will describe specialized pathways in neuronal axons and dendrites for the delivery of specialized cargos. These pathways include somatodendritic sorting as well as diverse pathways involving satellite ER and Golgi organelles found outside the cell body.

Axonal versus somatodendritic targeting

Following secretion from the cell body TGN, neuronal proteins can be targeted toward one of two distinct compartments: the axonal region and the somatodendritic region (cell body and dendrites). These two regions are separated by the pre-axonal-exclusion zone (PAEZ), a region within the axon hillock where organelles or cargos destined for transport down the axon associate with distinct motor proteins specialized for long-distance transport (Figure 1) [1]. Past the PAEZ, the axon can be further divided into an immediate proximal region known as the axon initial segment (AIS). The AIS functions as a barrier for transport and somatodendritic cargos typically cannot penetrate the AIS due to their selective association with specific kinesins [2–4]. Interestingly, a new paper demonstrated that the somatodendritic cell-adhesion molecule neuroligin may transiently insert at the plasma membrane of the AIS [5], which suggests that the boundary between axonal and somatodendritic domains may be at distal end of the AIS rather than the PAEZ for certain cargos. Nevertheless, these studies indicate that the PAEZ and AIS functionally divide the neuron into axonal and somatodendritic domains.

Several distinct pathways allow cargos to be sorted either to the axon or to the somatodendritic domain. Cargos destined for the axon can either be directly delivered to the axon or undergo selective retention, which is also referred to as transcytosis. In

transcytosis, an axonally targeted protein, like VAMP2 or NgCAM, can first be sorted to the somatodendritic domain, then subsequently endocytosed so that it ultimately accumulates in axons [6–8]. For the transcytosed cargo TrkA, an NGF (nerve growth factor) receptor, somatodendritic sorting is essential for differentiating between activated phosphorylated TrkA and naive non-phosphorylated TrkA so that naive TrkA is selective transported down the axon [9]. On the other hand, cargos destined for the somatodendritic domain, like transferrin receptor, are excluded from vesicles bound for the axon via binding to the adaptor protein-1 (AP-1) complex. AP-1 is a clathrin adaptor and recognizes tyrosine-based and dileucine-based motifs in cytoplasmic domains of somatodendritic proteins. This interaction, likely at the level of the TGN, results in selective sorting of somatodendritic proteins [10]. Thus, direct sorting of axonal and somatodendritic proteins as well as transcytosis function together to maintain distinct axonal and somatodendritic domains.

Satellite ERs in axons and dendrites

Compared to a non-ramified cell, the neuron differs in its secretory pathways, because satellite organelles are distributed along axons and dendrites [11]. Specifically, satellite ER organelles are found in both axons and dendrites.

In axons, both SER and RER are present and may have important functions for protein folding and local translation. Early immunostaining studies in hippocampal neurons visualized SER present along both axons and dendrites using G6Pase and HMG-CoA reductase antibodies. Additional staining against protein disulfide isomerase (PDI), which can act as a chaperone, indicates that SER in the axon may be involved in protein folding [12]. In dorsal root ganglion (DRG) sensory neurons, axons contain RER that may be involved in local translation of transmembrane proteins. These RERs contain proteins that are part of the co-translation machinery for transmembrane proteins; these include SRP54, a component of the signal recognition particle, as well as translocon-associated protein (TRAP) and ribophorin II, which are components of the translocon. Examples of transmembrane proteins that may be locally translated in the axon include neural membrane protein 35 (NMP35), hyperpolarization-activated cyclic nucleotide-gated channel 4 (HCN4), and calcium voltage-gated channel subunit alpha1 c (CACNA1c). These proteins were found along axons by immunostaining and their RNAs were detected by qPCR of axonal fractions [13]. Thus, in the axon, SER likely plays a role in local protein folding while RER may be important for local translation of transmembrane proteins.

Dendrites contain both RER and SER. Early studies in hippocampal neurons visualized RER present in dendrites using an antibody against signal sequence receptor (SSR); these RER localized near the cell body in proximal dendrites, but were not present in all dendrites [12]. RER in dendrites contain classic proteins that participate in co-translation, including the translocon protein Sec61, ribosomal protein S3, and KDEL-containing ER lumenal proteins, which were detected by immunogold labeling EM in the hippocampus and dentate gyrus [14]. In addition, cultured hippocampal neurons contain Sec23-positive ERES, which localize to dendritic branch points and cluster next to Golgi outposts [15]. Moreover, ERGICs ~200–400 nm in size are found in dendrites and dendritic spines and have been visualized using immunogold labeling of ERGIC53/58 [16]. A recent paper identified small

ribosome-associated vesicles (RAVs) in dendrites of primary neurons that are positive for ER markers and have diameter ~200–400 nm [17], which are consistent in size with dendritic ER from earlier EM studies [14].

Dendrites also contain SER and a subclass of SER found in synapses called the spine apparatus. 3D reconstructions of serial electron micrographs (SEM) of rat hippocampus visualized SER that can extend a protrusion into dendritic spines, then form a stacked ER structure called a spine apparatus [18,19]. The stabilization of ER in the spine followed by its subsequent conversion into a spine apparatus requires the calcium sensor caldendrin. In *in vitro* motility assays, caldendrin binding to myosin V slows or stops its motility. Thus, synaptic activity likely triggers an increase in calcium, which can activate caldendrin in order to stabilize the protruding ER for enough time to convert it into a spine apparatus [20]. Thus, a diverse array of ER components are found in dendrites and spines.

The complexity of ER structure and function may be interrelated. Dendrites with more synapses and dendritic branch points contain more complex ERs (as quantified by smaller ER segments and more reticulation). The generation of zones of higher ER complexity at branch points involves the phosphorylation of the ER-protein cytoskeleton-linking membrane protein 63 (CLIMP63). CLIMP63 is a transmembrane protein that links the ER to microtubules [15]. Recent work in the U2OS epithelial cell line demonstrates that starvation leads to increased CLIMP63 expression, which redistributes or contracts ER back to the perinuclear region [21]; it is unclear if dendritic ER also shifts its localization following nutrient deprivation. Therefore, ER complexity and localization may be intricately tied to local stimuli, like synaptic inputs and nutrient availability, but the precise mechanisms underlying this regulation remain unclear.

Axons and dendrites contain many subtypes of ER that form a complex system for local translation and protein trafficking and enable compartment-specific needs. These ER components then intercalate with local Golgi organelles that modify specific cargo proteins for subsequent delivery to their final destinations.

Golgi outposts in axons and dendrites

Satellite Golgi organelles are found in both glial cells (Box 1) and neurons [22]. In neurons, a vast and heterogeneous group of local Golgi organelles are found in both axons and dendrites.

In axons, satellite Golgi organelles may play roles in ion channel trafficking, local translation, and lysosomal enzyme delivery. In the PNS, rat sciatic nerves contain myelinated axons with both satellite ER and Golgi organelles. These satellite Golgi, which are positive for both *cis*/medial Golgi and TGN markers, preferentially localize in the node of Ranvier and the adjacent paranodal region [23]. In addition, in DRG axons, TRPM8 (transient receptor potential melastatin 8) ion channels, which are involved in cold sensation, colocalize with Golgi markers as well as with Rab6, a marker for exocytic vesicles [24]. These studies suggest that ion channels can be shuttled from axonal Golgi to the axonal surface via exocytic vesicles.

In addition, axonal Golgi organelles may also play a role in local translation. Golgi compartments are found in close proximity to axonal ER [13, 23]. Some of these axonal ER contain translocons and co-translation machinery [13], which indicates that axonal Golgi may further modify locally translated transmembrane proteins and traffick them to the axonal plasma membrane. However, some evidence suggests that locally translated transmembrane proteins may bypass Golgi entirely and directly shuttle to the cell surface via lysosomal or endosomal vesicles [25]. Thus, the role of axonal ER and Golgis in local translation of transmembrane proteins needs further confirmation and clarification.

Axonal Golgi organelles also interact with lysosomes. A recent paper found that TGN-positive Golgi vesicles in the axon colocalize with the lysosomal enzyme cathepsin D. In addition, in live-cell experiments, motile organelles labeled with LAMP1, a marker for late endosomes and lysosomes, co-transport with a TGN marker. The authors suggest that TGN-positive Golgi vesicles may deliver lysosomal enzymes to LAMP1-positive organelles [26]. However, these experiments may also indicate that axons contain hybrid organelles of mixed lysosomal and Golgi identity. Thus, more mechanistic experiments on satellite Golgi organelles in the axon are needed to better understand their functions and interactions with other axonal organelles, like ER and lysosomes.

In dendrites, Golgi outposts can serve multiple local functions, including microtubule nucleation, protein secretion or trafficking, and protein modification or glycosylation. Dendritic Golgi outposts are heterogeneous in size, composition and compartmentalization, and therefore serve diverse roles depending on their components. For example, multi-compartment Golgi outposts containing the *cis*-Golgi marker GM130 are more likely than single-compartment Golgi outposts to initiate microtubule growth [27]. Though it is unclear how multi-compartment Golgi outposts arise, in mammalian neurons, Golgi outposts can fission off the cell body Golgi then are transported along dendrites [28], where they are oriented with Golgi stacks in parallel to the dendrite [29].

In *Drosophila* da sensory neurons that lack centrosomes, Golgi outposts are important for local acentrosomal microtubule nucleation. This is a gamma-tubulin dependent process and important for dendritic branching [30]. In addition, the organization and compartmentalization of Golgi outposts may also be important to maintain microtubule polarity patterns in the dendrite [31].

There are at least three ways by which secretory cargo is transported in dendrites. Firstly, in the classical secretion pathway, proteins produced in the cell body ER and modified in the cell body Golgi can be directly transported along dendrites to their final destinations along dendrites or in synapses (Figure 1, Pathway 1). These cargos can be either transmembrane proteins or secreted proteins that are released extracellularly. Transmembrane proteins may also undergo transcytosis or somatodendritic sorting, which further ensures selective retention or rejection of axonal versus somatodendritic proteins.

Secondly, proteins emerging from dendritic ER, which can be locally translated, can be trafficked from dendritic ER to dendritic Golgi (Figure 1, Pathway 2) [11]. This has been

reported for integral membrane proteins such as VSV-G and the neuronal growth factor brain-derived neurotrophic factor (BDNF) [32].

Thirdly, cargo that is translated off cell body ER can bypass cell body Golgi and be targeted directly to dendritic Golgi outposts, where they can be modified then further transported in post-Golgi vesicles (Figure 1, Pathway 3). An important example of this is the N-methyl-D-aspartate receptor (NMDAR). After exiting the cell body ER, NMDARs are trafficked via ER subcompartments to Golgi outposts, then subsequently exit Golgi outposts in a COPI-dependent manner. The absence of adaptor proteins CASK and SAP97 causes mis-sorting of NMDARs through the cell body Golgi, resulting in fewer NMDARs at synapses [33].

Both Pathways 2 and 3 can further traffic cargo proteins from dendritic Golgi outposts to synapses via post-Golgi vesicles, which bud off Golgi outposts then fuse with nearby plasma membranes. An example cargo protein is the guanine nucleotide exchange factor (GEF) kalirin, which utilizes the adaptor protein X11α for post-Golgi vesicle trafficking to the synapse [34].

Dendritic Golgi dynamics may be important for cleavage and trafficking of the transmembrane protein amyloid precursor protein (APP). APP can be cleaved by beta-secretase 1 (BACE1) and gamma-secretase into beta-amyloid peptides, which aggregate in Alzheimer's disease. ADAM10, the alpha-secretase involved in non-amyloidogenic APP cleavage, can be trafficked from dendritic Golgi outposts to the postsynaptic plasma membrane [35]. In *Drosophila* da neuron dendrites, APP colocalizes with Golgi outposts that are positive for medial Golgi (mannosidase II) or trans-Golgi (galactosyltransferase) markers. In live-cell imaging experiments, these markers were used to define multi-compartment Golgi outposts. Golgi outposts containing APP were less motile and preferentially distributed in the proximal dendrite. Results of a screen suggest that the adaptor protein Sunday driver (Syd), which is known as JIP3 in mammals, may be an adapter protein that links APP-positive Golgi outposts to motor proteins in dendrites. Loss of Syd affects dendrite morphology, leading to more branch points [36]. Interestingly, in axons, the adaptor JIP1, which can dimerize with JIP3 [37], regulates the directionality of APP-positive vesicle transport [38]. However, it is unclear if axonal APP-positive vesicles also share Golgi markers.

Finally, recent studies show that Golgi satellites are involved in local protein modification or glycosylation in dendrites. Golgi satellites are relatively immobile, range in size from ~250–1000 nm, and are smaller than Golgi outposts. They contain glycosylation enzymes but lack GM130. They are found in close proximity to ERGICs and retromer-associated endosomes, which indicates that local trafficking of cargos likely proceeds from ERGICs to Golgi satellites then to the dendritic plasma membrane [39]. Consistent with early studies demonstrating that dendrites exhibit glycosyltransferase activity [40], recent proteomic studies have identified glycosylation sites on a number of synaptic transmembrane proteins that are modified in response in neuronal excitation [41]. The functional consequence of this is that neuronal activity can result in the incorporation of sialylated glycoproteins to the dendritic plasma membrane, thereby impacting subsequent signaling and neuronal activity. Indeed, neuronal excitation leads to the formation of dispersed Golgi satellites

that contain glycosylation enzymes and are closely associated with ERESs and endosomes. These modifications have been suggested to be present on both newly synthesized locally translated proteins and pre-existing dendritic membrane proteins that can be endocytosed, modified by Golgi satellites, and then returned to the plasma membrane [42]. Thus, Golgi satellites serve an important function to link neuronal activity and glycosylation of dendritic transmembrane proteins.

Conclusion

Both satellite ER and Golgi organelles are present in neuronal axons and dendrites, where they are critical in maintaining neuronal function. Local ERs are important not only for local trafficking, but also for local translation. Local Golgis include Golgi outposts, which are important for microtubule nucleation and secretion, as well as Golgi satellites, which are important for protein glycosylation. Though less is known functionally about satellite ERs and Golgis in glial cells (Box 1), they likely also play important roles in compartment-specific and cell-specific functions.

In a quickly changing landscape of terms for these specialized organelles (Box 2), it can be difficult to segregate the properties of diverse satellite ER and Golgi organelles among different species, cell types, and cell compartments. Importantly, functional markers can be used to distinguish subclasses of organelles, for example RER versus SER and multi-stack versus single-stack Golgis using *cis*-, medial-, or *trans*-Golgi specific markers. As we learn more about these enigmatic but important organelles, future studies will need to clearly define the relationships between nomenclature, markers, and functions.

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References

* Of special interest

** Of outstanding interest

1. Farías GG, Guardia CM, Britt DJ, Guo X, Bonifacino JS: Sorting of Dendritic and Axonal Vesicles at the Pre-axonal Exclusion Zone. Cell Rep 2015, 13:1221–1232. [PubMed: 26527003]
2. Leterrier C: The Axon Initial Segment: An Updated Viewpoint. J Neurosci 2018, 38:2135–2145. [PubMed: 29378864]
3. Song AH, Wang D, Chen G, Li Y, Luo J, Duan S, Poo MM: A selective filter for cytoplasmic transport at the axon initial segment. Cell 2009, 136:1148–60. [PubMed: 19268344]
4. Jenkins B, Decker H, Bentley M, Luisi J, Banker G: A novel split kinesin assay identifies motor proteins that interact with distinct vesicle populations. J Cell Biol 2012, 198:749–61. [PubMed: 22908316]
5. Bourke AM, Schwartz SL, Bowen AB, Kleinjan MS, Winborn CS, Kareemo DJ, Gutnick A, Schwarz TL, Kennedy MJ: zapERtrap: A light-regulated ER release system reveals unexpected neuronal trafficking pathways. J Cell Biol 2021, 220:e202103186. [PubMed: 34241635] * This study developed a live-cell imaging tool that uses a focused pulse of light to trigger the release of proteins from either the cell body or dendritic ER. Interestingly, the authors found that NL1 can be trafficked from the cell body ER to the plasma membrane of the AIS.

6. Radler MR, Suber A, Spiliotis ET: Spatial control of membrane traffic in neuronal dendrites. Mol Cell Neurosci 2020, 105:103492. [PubMed: 32294508]

7. Sampo B, Kaech S, Kunz S, Banker G: Two Distinct Mechanisms Target Membrane Proteins to the Axonal Surface. Neuron 2003, 37:611–624. [PubMed: 12597859]

8. Wisco D, Anderson ED, Chang MC, Norden C, Boiko T, Fölsch H, Winckler B: Uncovering multiple axonal targeting pathways in hippocampal neurons. J Cell Biol 2003, 162:1317–1328. [PubMed: 14517209]

9. Yamashita N, Joshi R, Zhang S, Zhang Z-Y, Kuruvilla R: Phospho-Regulation of Soma-to-Axon Transcytosis of Neurotrophin Receptors. Dev Cell 2017, 42:626–639.e5. [PubMed: 28919207]

10. Farías GG, Cuitino L, Guo X, Ren X, Jarnik M, Mattera R, Bonifacino JS: Signal-Mediated, AP-1/Clathrin-Dependent Sorting of Transmembrane Receptors to the Somatodendritic Domain of Hippocampal Neurons. Neuron 2012, 75:810–823. [PubMed: 22958822]

11. Hanus C, Ehlers MD: Specialization of biosynthetic membrane trafficking for neuronal form and function. Curr Opin Neurobiol 2016, 39:8–16. [PubMed: 27010827]

12. Krijnse-Locker J, Parton RG, Fuller SD, Griffiths G, Dotti CG: The organization of the endoplasmic reticulum and the intermediate compartment in cultured rat hippocampal neurons. Mol Biol Cell 1995, 6:1315–1332. [PubMed: 8573789]

13. Merianda TT, Lin AC, Lam JSY, Vuppalanchi D, Willis DE, Karin N, Holt CE, Twiss JL: A functional equivalent of endoplasmic reticulum and Golgi in axons for secretion of locally synthesized proteins. Mol Cell Neurosci 2009, 40:128–142. [PubMed: 19022387]

14. Pierce JP, van Leyen K, McCarthy JB: Translocation machinery for synthesis of integral membrane and secretory proteins in dendritic spines. Nat Neurosci 2000, 3:311–313. [PubMed: 10725917]

15. Cui-Wang T, Hanus C, Cui T, Helton T, Bourne J, Watson D, Harris KM, Ehlers MD: Local Zones of Endoplasmic Reticulum Complexity Confine Cargo in Neuronal Dendrites. Cell 2012, 148:309–321. [PubMed: 22265418]

16. Pierce JP, Mayer T, McCarthy JB: Evidence for a satellite secretory pathway in neuronal dendritic spines. Curr Biol 2001, 11:351–355. [PubMed: 11267872]

17. Carter SD, Hampton CM, Langlois R, Melero R, Farino ZJ, Calderon MJ, Li W, Wallace CT, Tran NH, Grassucci RA, et al. : Ribosome-associated vesicles: A dynamic subcompartment of the endoplasmic reticulum in secretory cells. Sci Adv 2020, 6:eaay9572. [PubMed: 32270040] * Multiple cell types contain small ribosome-associated vesicles (RAVs). In primary neurons, RAVs are positive for ER markers and have diameter ~200–400 nm.

18. Spacek J, Harris KM: Three-Dimensional Organization of Smooth Endoplasmic Reticulum in Hippocampal CA1 Dendrites and Dendritic Spines of the Immature and Mature Rat. J Neurosci 1997, 17:190–203. [PubMed: 8987748]

19. Cooney JR, Hurlburt JL, Selig DK, Harris KM, Fiala JC: Endosomal Compartments Serve Multiple Hippocampal Dendritic Spines from a Widespread Rather Than a Local Store of Recycling Membrane. J Neurosci 2002, 22:2215–2224. [PubMed: 11896161]

20. Konietzny A, Grendel J, Kadek A, Bucher M, Han Y, Hertrich N, Dekkers DHW, Demmers JAA, Grünewald K, Uetrecht C, et al. : Caldendrin and myosin V regulate synaptic spine apparatus localization via ER stabilization in dendritic spines. EMBO J 2022, 41:e106523. [PubMed: 34935159] ** The interaction between the myosin activator caldendrin and myosin V may be important for formation of spine apparatuses, which are stacked smooth ERs in dendritic synapses.

21. Zheng P, Obara CJ, Szczesna E, Nixon-Abell J, Mahalingan KK, Roll-Mecak A, Lippincott-Schwartz J, Blackstone C: ER proteins decipher the tubulin code to regulate organelle distribution. Nature 2022, 601:132–138. [PubMed: 34912111]

22. Valenzuela A, Meservey L, Nguyen H, Fu M: Golgi Outposts Nucleate Microtubules in Cells with Specialized Shapes. Trends Cell Biol 2020, doi:10.1016/j.tcb.2020.07.004.

23. González C, Cánovas J, Fresno J, Couve E, Court FA, Couve A: Axons provide the secretory machinery for trafficking of voltage-gated sodium channels in peripheral nerve. Proc Natl Acad Sci 2016, 113:1823–1828. [PubMed: 26839409]

24. Cornejo VH, González C, Campos M, Vargas-Saturno L, Juricic M de los Á, Miserey-Lenkei S, Pertusa M, Madrid R, Couve A: Non-conventional Axonal Organelles Control TRPM8 Ion Channel Trafficking and Peripheral Cold Sensing. Cell Rep 2020, 30:4505–4517.e5. [PubMed:

32234483] * In DRG axons, TRPM8 ion channels, which participate in sensing cold temperatures, colocalize with Golgi markers as well as with Rab6, a marker for exocytic vesicles. This suggests that TRPM8 are trafficked from local axonal Golgi to the axonal plasma membrane via Rab6-positive exocytic vesicles.

25. González C, Cornejo VH, Couve A: Golgi bypass for local delivery of axonal proteins, fact or fiction? Curr Opin Cell Biol 2018, 53:9–14. [PubMed: 29631154]
26. Lie PPY, Yang D-S, Stavrides P, Goulbourne CN, Zheng P, Mohan PS, Cataldo AM, Nixon RA: Post-Golgi carriers, not lysosomes, confer lysosomal properties to pre-degradative organelles in normal and dystrophic axons. Cell Rep 2021, 35:109034. [PubMed: 33910020] * TGN-positive Golgi vesicles in the axon colocalize with the lysosomal enzyme cathepsin D. In live-cell experiments, motile organelles labeled with LAMP1, a marker for late endosomes and lysosomes, co-transport with a TGN marker.
27. Zhou W, Chang J, Wang X, Savelieff MG, Zhao Y, Ke S, Ye B: GM130 is required for compartmental organization of dendritic Golgi outposts. Curr Biol CB 2014, 24:1227–1233. [PubMed: 24835455]
28. Quassollo G, Wojnacki J, Salas DA, Gastaldi L, Marzolo MP, Conde C, Bisbal M, Couve A, Caceres A: A RhoA Signaling Pathway Regulates Dendritic Golgi Outpost Formation. Curr Biol 2015, 25:971–82. [PubMed: 25802147]
29. Horton AC, Racz B, Monson EE, Lin AL, Weinberg RJ, Ehlers MD: Polarized secretory trafficking directs cargo for asymmetric dendrite growth and morphogenesis. Neuron 2005, 48:757–71. [PubMed: 16337914]
30. Ori-McKenney KM, Jan LY, Jan Y-N: Golgi Outposts Shape Dendrite Morphology by Functioning as Sites of Acentrosomal Microtubule Nucleation in Neurons. Neuron 2012, 76:921–930. [PubMed: 23217741]
31. Yang SZ, Wildonger J: Golgi Outposts Locally Regulate Microtubule Orientation in Neurons but Are Not Required for the Overall Polarity of the Dendritic Cytoskeleton. Genetics 2020, 215:435–447. [PubMed: 32265236] * In Drosophila da sensory neurons, organization and compartmentalization of Golgi outposts are important for maintaining microtubule polarity in dendrites.
32. Horton AC, Ehlers MD: Dual Modes of Endoplasmic Reticulum-to-Golgi Transport in Dendrites Revealed by Live-Cell Imaging. J Neurosci 2003, 23:6188–6199. [PubMed: 12867502]
33. Jeyifous O, Waites CL, Specht CG, Fujisawa S, Schubert M, Lin EI, Marshall J, Aoki C, de Silva T, Montgomery JM, et al. : SAP97 and CASK mediate sorting of NMDA receptors through a previously unknown secretory pathway. Nat Neurosci 2009, 12:1011–9. [PubMed: 19620977]
34. Jones KA, Eng AG, Raval P, Srivastava DP, Penzes P: Scaffold protein X11α interacts with kalirin-7 in dendrites and recruits it to Golgi outposts. J Biol Chem 2014, 289:35517–35529. [PubMed: 25378388]
35. Saraceno C, Marcello E, Di Marino D, Borroni B, Claeysen S, Perroy J, Padovani A, Tramontano A, Gardoni F, Di Luca M: SAP97-mediated ADAM10 trafficking from Golgi outposts depends on PKC phosphorylation. Cell Death Dis 2014, 5:e1547–e1547. [PubMed: 25429624]
36. Du Q, Chang J, Cheng G, Zhao Y, Zhou W: Sunday Driver Mediates Multi-Compartment Golgi Outposts Defects Induced by Amyloid Precursor Protein. Front Neurosci 2021, 15:673684. [PubMed: 34140878]
37. Kristensen O, Guenat S, Dar I, Allaman-Pillet N, Abderrahmani A, Ferdaoussi M, Roduit R, Maurer F, Beckmann JS, Kastrup JS, et al. : A unique set of SH3-SH3 interactions controls IB1 homodimerization. EMBO J 2006, 25:785–97. [PubMed: 16456539]
38. Fu MM, Holzbaur EL: JIP1 regulates the directionality of APP axonal transport by coordinating kinesin and dynein motors. J Cell Biol 2013, doi:10.1083/jcb.201302078.
39. Mikhaylova M, Bera S, Kobler O, Frischknecht R, Kreutz MR: A Dendritic Golgi Satellite between ERGIC and Retromer. Cell Rep 2016, 14:189–199. [PubMed: 26748700]
40. Torre ER, Steward O: Protein Synthesis within Dendrites: Glycosylation of Newly Synthesized Proteins in Dendrites of Hippocampal Neurons in Culture. J Neurosci 1996, 16:5967–5978. [PubMed: 8815879]

41. Boll I, Jensen P, Schwämmle V, Larsen MR: Depolarization-dependent Induction of Site-specific Changes in Sialylation on N-linked Glycoproteins in Rat Nerve Terminals. Mol Cell Proteomics MCP 2020, 19:1418–1435. [PubMed: 32518069] ** This study links neuronal activity with local changes in N-linked glycoprotein sialylation, which likely occurs on Golgi outposts. Nerve terminals isolated by synaptosome preparations from rat brains were subjected to membrane depolarization, then used for mass spectrometry to generate a sialylated proteome.

42. Govind AP, Jeyifous O, Russell TA, Yi Z, Weigel AV, Ramaprasad A, Newell L, Ramos W, Valbuena FM, Casler JC, et al. : Activity-dependent Golgi satellite formation in dendrites reshapes the neuronal surface glycoproteome. eLife 2021, 10:e68910. [PubMed: 34545811] ** This study proposes that dendritic Golgi satellites function as local sites for glycosylation in response to neuronal activity. In primary neurons, dispersed Golgi satellites form as a result of neuronal activity; these Golgi satellites contain glycosylation enzymes and are closely associated with ERES and endosomes.

43. Weigel M, Wang L, Fu M: Microtubule organization and dynamics in oligodendrocytes, astrocytes, and microglia. Dev Neurobiol 2020, doi:10.1002/dneu.22753.

44. Fu MM, McAlear TS, Nguyen H, Oses-Prieto JA, Valenzuela A, Shi RD, Perrino JJ, Huang TT, Burlingame AL, Bechstedt S, et al. : The Golgi Outpost Protein TPPP Nucleates Microtubules and Is Critical for Myelination. Cell 2019, 179:132–146 e14. [PubMed: 31522887]

45. Nguyen H, Meservey LM, Ishiko-Silveria N, Zhou M, Huang T-T, Fu M: Fear Deficits in Hypomyelinated Tppp Knock-Out Mice. eneuro 2020, 7:ENEURO.0170–20.2020.

46. Madry C, Kyrargyri V, Arancibia-Cárcamo IL, Jolivet R, Kohsaka S, Bryan RM, Attwell D: Microglial Ramification, Surveillance, and Interleukin-1β Release Are Regulated by the Two-Pore Domain K+ Channel THIK-1. Neuron 2018, 97:299–312.e6. [PubMed: 29290552]

47. Rosito M, Sanchini C, Gosti G, Moreno M, Panfilis SD, Giubettini M, Debellis D, Catalano F, Peruzzi G, Marotta R, et al.: Reactive microglia and cytokine release entails microtubule remodeling from acentrosomal to centrosomal arrays. 2022, doi:10.1101/2022.02.21.481355.

48. Chung WS, Welsh CA, Barres BA, Stevens B: Do glia drive synaptic and cognitive impairment in disease? Nat Neurosci 2015, 18:1539–1545. [PubMed: 26505565] ** Immunostaining of primary microglia cultures revealed a link between inflammation state and microglial shape and microtubule organization. In the ramified homeostatic state, microglia contain Golgi outposts that can nucleate microtubules, but in the amoeboid pro-inflammatory state, they do not.

49. Boulay AC, Saubamea B, Adam N, Chasseigneaux S, Mazare N, Gilbert A, Bahin M, Bastianelli L, Blugeon C, Perrin S, et al. : Translation in astrocyte distal processes sets molecular heterogeneity at the gliovascular interface. Cell Discov 2017, 3:17005. [PubMed: 28377822]

50. De Camilli P, Moretti M, Donini SD, Walter U, Lohmann SM: Heterogeneous distribution of the cAMP receptor protein RII in the nervous system: evidence for its intracellular accumulation on microtubules, microtubule-organizing centers, and in the area of the Golgi complex. J Cell Biol 1986, 103:189–203. [PubMed: 3522603]

51. Oddoux S, Zaal KJ, Tate V, Kenea A, Nandkeolyar SA, Reid E, Liu W, Ralston E: Microtubules that form the stationary lattice of muscle fibers are dynamic and nucleated at Golgi elements. J Cell Biol 2013, 203:205–13. [PubMed: 24145165]

Box 1.

Golgi outposts in glia

Golgi outposts have also been observed in glia, the non-neuronal cells of the central nervous system (Figure 2). In oligodendrocytes and microglia, Golgi outposts play a role in microtubule organization and establishment of branching morphology. In astrocytes, Golgi outposts are found in endfeet that contact blood vessels, but their specific function remains unclear.

Oligodendrocytes

Oligodendrocytes dynamically extend their processes toward axons and are capable of forming as many as 50 myelin sheaths per cell. They contain two populations of microtubules — radial microtubules that reach toward axons and lamellar microtubules that spiral around the myelin sheath from outer to inner layers [43]. Recently, Golgi outposts were demonstrated to function as acentrosomal microtubule organizing centers (MTOCs) in oligodendrocytes. The Golgi-outpost marker TPPP is a microtubule-associated protein that is sufficient in *in vitro* cell-free assays to nucleate microtubules. Additionally, *Tppp* KO oligodendrocytes displayed aberrant branching, mixed microtubule polarity (instead of uniform polarity), and shorter and thinner myelin sheaths [44]. *In vivo*, *Tppp* KO mice display aberrant learned and innate fear responses [45]. Thus, Golgi outposts are crucial for oligodendrocyte morphology and myelin formation.

Microglia

Microglia, the resident immune cells of the brain, can transition from a ramified surveillance state to an amoeboid phagocytic state [43] in response to inflammatory signals [46]. Ramified homeostatic microglia in culture contain Golgi outposts along microtubules in proximal processes, but microglia cultured in the presence of pro-inflammatory or anti-inflammatory signals are not ramified and do not contain Golgi outposts. After nocodazole treatment to depolymerize microtubules, microtubules nucleated out of gamma-tubulin-positive Golgi outposts [47]. Thus, microglial Golgi outposts likely function to nucleate microtubules in the ramified surveillance state.

Astrocytes

Astrocytes are large stellate cells critical for synaptogenesis, synapse elimination during development, and blood-brain barrier maintenance [48]. In recent TEM and immunostaining experiments, astrocytic endfeet that contact blood vessels contain both SER and RER as well as Golgi outposts. An assay using a methionine analog to label newly translated proteins in *ex vivo* blood vessels indicated that local translation occurs at distal astrocytic perivascular processes [49]. Thus, local ER and Golgi outposts likely play a role in local translation in astrocytes. Future studies should address how this affects endfeet functions, like regulating blood flow and hindering immune cell infiltration.

Box 2.

Nomenclature of satellite ER and Golgi organelles

ERGICs (ER-Golgi intermediate compartments) - small ~200–400-nm vesicles found in dendrites that share markers with the ER [16] and are frequently found near Golgi satellites [39]; also refers to ERGICs in the cell body

Golgi elements – another name for Golgi outposts that was initially used in the 1980's to describe tubular Golgi along proximal dendrites in rodent brain immunostaining experiments [50]; also refers to Golgi outposts in muscle cells [51]

Golgi outposts - large multi-compartment satellite Golgi organelles typically several μm in size that can function as acentrosomal microtubule nucleators in neuronal dendrites, oligodendrocytes, and muscle cells [22]

Golgi satellites – organelles in dendrites ~250–1000 nm (generally smaller than Golgi outposts) that function as an intermediate local secretory compartment between ERGICs and endosomes and that mediate local transmembrane protein glycosylation [39,42]

Post-Golgi vesicles - small vesicles that traffic locally from larger Golgi outposts or smaller Golgi satellites to the dendritic or synaptic plasma membrane [33,35]

RAVs (ribosome-associated vesicles) - small ER vesicles with diameter ~200–400 nm that are motile along dendrites and may be involved in local translation [17]

Spine apparatus - small, stacked smooth ER found inside dendritic spines [18–20]

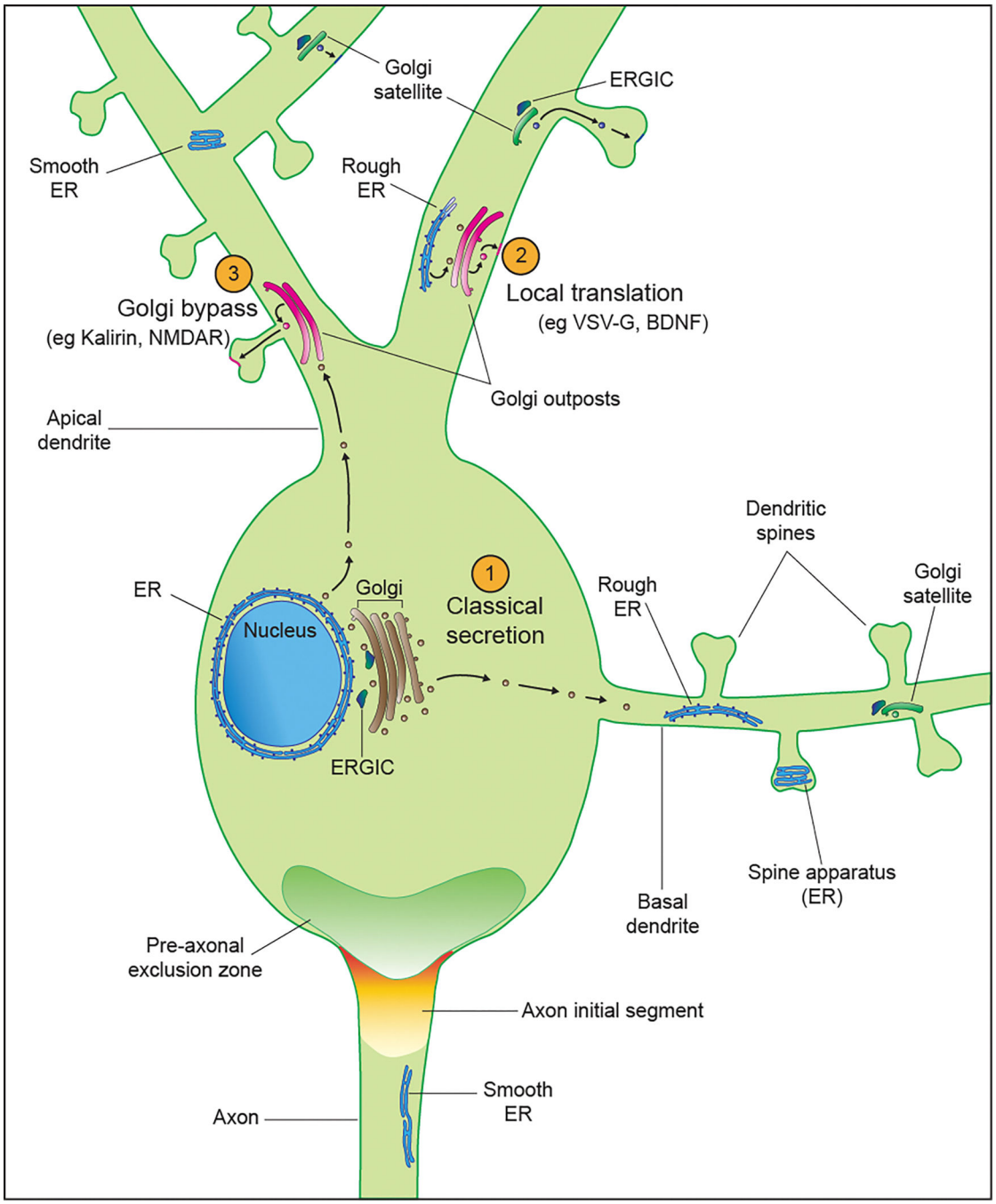

Figure 1. Secretory pathways and satellite organelles in neuronal dendrites.

Three potential pathways for dendritic cargo transport. 1) Classical secretion: Protein translation occurs in the neuronal cell body on ribosomes associated with the ER. These proteins exit the cell body ER, then merge with ER-Golgi intermediate compartments (ERGICs), are further processed through the cell body Golgi, and finally are trafficked via vesicles to dendrites or elsewhere in the neuron. 2) Local dendritic translation: Proteins may be locally translated off dendritic ER then trafficked to dendritic Golgi outposts, where they can be modified. After leaving the Golgi outpost in post-Golgi vesicles, these proteins can

be further transported along dendrites or targeted for fusion with dendritic plasma membrane or synaptic spines. 3) Golgi bypass: Cargo translated off cell body ER can bypass cell body Golgi and be directly transported to dendrites, where they may be modified by Golgi outposts and subsequently transported in post-Golgi vesicles destined for synapses or the plasma membrane.

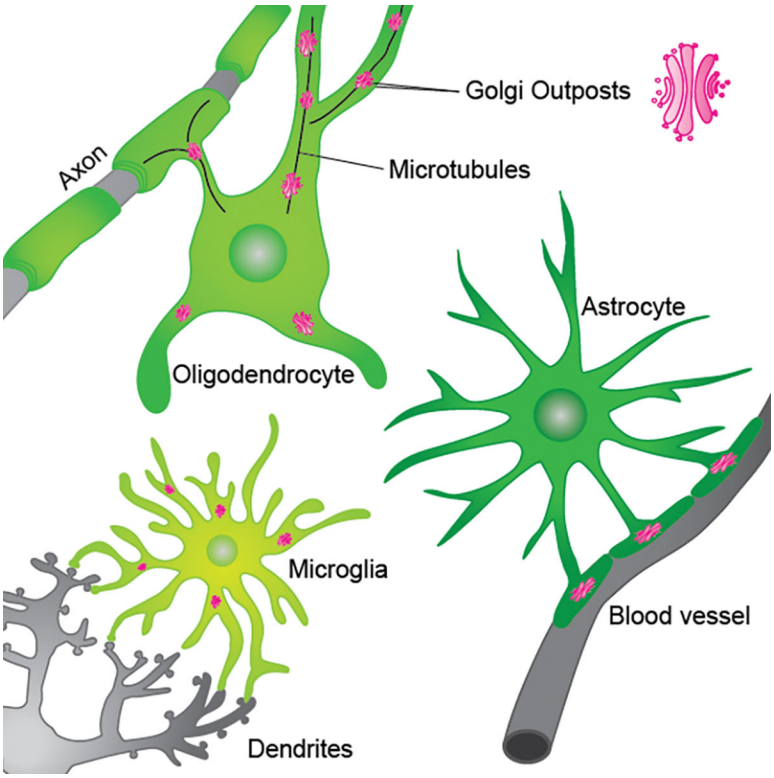

Figure 2. Glial cells have Golgi outposts.

In oligodendrocytes, Golgi outposts are present in processes and in the myelin sheath. They are found along both radial microtubules that contact axons and along lamellar microtubules that spiral around the myelin sheath. These Golgi outposts use TPPP to nucleate or form new microtubules. In microglia, Golgi outposts also function to nucleate new microtubules and to establish branched processes. In astrocytes, endfeet that contact blood vessels contain Golgi outposts by EM, but their function remains unclear.