Review

The endoplasmic reticulum and protein trafficking in dendrites and axons

Omar A. Ramírez and Andrés Couve

Program of Physiology and Biophysics, Institute of Biomedical Sciences, Faculty of Medicine and Nucleus of Neural Morphogenesis (NEMO), Universidad de Chile, Santiago, Chile

Neurons are highly polarized cells whose dendrites and axons extend long distances from the cell body to form synapses that mediate neuronal communication. The trafficking of membrane lipids and proteins throughout the neuron is essential for the establishment and maintenance of cell morphology and synaptic function. However, the dynamic shape and spatial organization of secretory organelles, and their role in defining neuronal polarity and the composition of synapses, are not well delineated. In particular, the structure and function of the continuous and intricate network of the endoplasmic reticulum (ER) in neurons remain largely unknown. Here we review our current understanding of the ER in dendrites and axons, its contribution to local trafficking of neurotransmitter receptors, and the implications for synaptic plasticity and pathology.

Introduction

Polarized protein trafficking is a crucial determinant of neuronal morphogenesis and synaptic function which in turn govern connectivity and information processing. The marked cellular asymmetry that is established during neuronal differentiation is maintained throughout the lifespan of an organism. At the level of the individual neurons, this asymmetry begins with one neurite growing at a faster rate. This neurite generates the axon, whereas the remaining neurites develop into a complex and diverse dendritic arbor [1]. The establishment and maintenance of neuronal polarity is critically dependent on the integrity and spatial organization of the secretory pathway [2]. For example, altering the orientation of the Golgi apparatus in hippocampal neurons, which is constituted by a perinuclear organelle oriented towards the apical dendrite and additional satellite structures distributed throughout the dendritic arbor (Golgi outposts), differentially limits dendritic growth [3].

Synapses are specialized and dynamic structures formed at the junction of two communicating neurons. Intracellular trafficking of synaptic proteins and neurotransmitter receptors plays a key role in synapse formation and in the regulation of synaptic strength [4]. For instance, rapid insertion or removal of AMPA-type glutamate receptors (AMPARs) modifies synaptic strength during experience-dependent plasticity, providing a molecular correlate for cognitive functions [5].

The endomembrane trafficking system in eukaryotic cells includes a forward biosynthetic route constituted by the ER, the ER–Golgi intermediate compartment (ERGIC, Glossary), the Golgi apparatus and post-Golgi vesicles, and a recycling-degradative route constituted by endosomes and lysosomes. In neurons, little is known of how the membrane trafficking mechanisms found in simpler cells have adapted spatially to accommodate the unparalleled morphological requirements of the neuron. Recent studies have begun to elucidate the function of satellite Golgi outposts and endosomes in polarized neuronal trafficking [4,6–9]. By contrast, the dynamic structure of the ER in dendrites and axons remains for the most part unexplored [10,11]. Importantly, the relevance of axo-dendritic ER trafficking and its contribution to neuronal morphogenesis and synaptic function are still major unanswered questions.

In this review we examine the structural and dynamic features of the neuronal ER and consider its function in the control of local axo-dendritic trafficking and the assembly and export of neurotransmitter receptors. We also discuss the contribution of the ER to synaptic plasticity and pathology.

The structure of the ER in dendrites and axons

The ER is a single and continuous membrane-bound organelle responsible for lipid and sterol synthesis, the synthesis and post-translational modification of most secretory and membrane proteins, and the regulation of Ca^{2+} levels and arachidonic acid release. The shape of the ER is heterogeneous, and varies between cell types and cell stages, but can be divided into three domains: the nuclear envelope, the ribosome-bound rough ER (RER) and the ribosome-free smooth ER (SER) [12]. Structurally the ER is a network that is present throughout the cytoplasm, and consists of

Glossary

COPII: coat protein complex II, required for the formation of ER-to-Golgi transport vesicles.
dERES: ER exit sites in dendrites.
ERES: ER exit sites.
ER fragmentation: loss of ER continuity in response to signaling cascades, yet to be fully characterized.
ERGIC: ER–Golgi apparatus intermediate compartment.
Golgi outposts: dendritic satellite organelles equivalent to the Golgi apparatus.
Rapid tubule extension: the formation of ER tubules along microtubules driven by molecular motors, also referred to as ER sliding.
RER: rough ER, rich in ribosomes.
SER: smooth ER, bearing few ribosomes.
Spine apparatus: ER specialization in dendritic spines.
TAC-mediated extension: extension of ER tubules driven by association to the growing plus-end of microtubules via tip-attachment complexes (TACs).

Corresponding author: Couve, A. (andres@neuro.med.uchile.cl).

0962-8924/$ – see front matter © 2010 Elsevier Ltd. All rights reserved. doi:10.1016/j.tcb.2010.12.003 Trends in Cell Biology, April 2011, Vol. 21, No. 4

cisternae, flattened sheets, and 60–100 nm diameter tubules that form irregular polygons with a common luminal space connected via three-way junctions [13]. The RER is constituted primarily by sheets or cisternae, whereas the SER is predominantly composed of tubules [14].

Several recently identified proteins are known to regulate the structure and stability of the ER and to contribute to its heterogeneous morphology (reviewed in [11,15,16]). Reticulons and DP1 are two families of ubiquitous and structurally related eukaryotic proteins associated with ER membranes, and these are responsible for maintaining the tubular shape of the ER [17]. Atlastin-1, a dynamin-like GTPase, interacts with reticulon proteins to promote fusion and the formation of the tubular network [18]. CLIMP-63 is a microtubule-binding protein that regulates the abundance of interaction sites between the ER and the microtubule cytoskeleton, effectively stabilizing the network [19]. Fusion of membrane tubules also requires NSF/α, γ-SNAP, the p97/p47/VCIP135 complex, syntaxin 18, and BNIP1/sec20 [11]. Other candidates for the maintenance of ER structure include huntingtin, the EF-hand Ca^{2+}-binding protein p22, spastin, and kinectin [20,21]. Mitochondria and microtubules are also necessary for the maintenance of its dynamic shape, but *in vitro* an ER network can be generated by the fusion of membrane vesicles without additional cytoskeletal components [22].

The neuronal ER shares many essential features with other eukaryotic cells and connects the soma with the entire dendritic arbor and axon. The ER present in the soma and proximal dendritic compartment is rich in ribosomes, corresponding to the RER, whereas the ER distributed in distal dendrites and axons corresponds mostly to SER and bears only few sparse ribosomes [23,24]. The dendritic ER consists of a continuous irregular network of thin tubules and flat widened regions of variable diameter [25] (Figure 1). The continuity of the SER is important for the propagation of Ca^{2+} signals over long distances and for the transport of lipids and proteins [9,26]. Topologically, the dendritic ER is located in the cortex of the cytoplasm with thin branches traversing the opposite side [27,28]. Similarly, yeast and non-neuronal mammalian cells contain a thin cortical ER adjacent to the plasma membrane [29]. Within the dendritic shaft the area occupied by the ER correlates with the local density and maturation stage of excitatory synapses in the respective segment [25]. The ER appears to anchor at perisynaptic sites via cytoskeletal elements or by tethering ER components to the postsynaptic density. These attachment mechanisms are exemplified by the physical interaction between inositol 1,4,5-trisphosphate receptors (IP_3Rs) in the ER membrane and the postsynaptic density proteins Homer and Shank [30]. The dendritic SER is present in the head or neck of 20% of dendritic spines, and is associated with a prominent specialization termed the spine apparatus, which is characterized by the presence of synaptopodin, an actin-binding protein [25]. It is still debated whether the spine apparatus is directly derived from the SER, constituting a *bona fide* ER, or if it represents a complex secretory organelle combining ER, Golgi and endosomal functions.

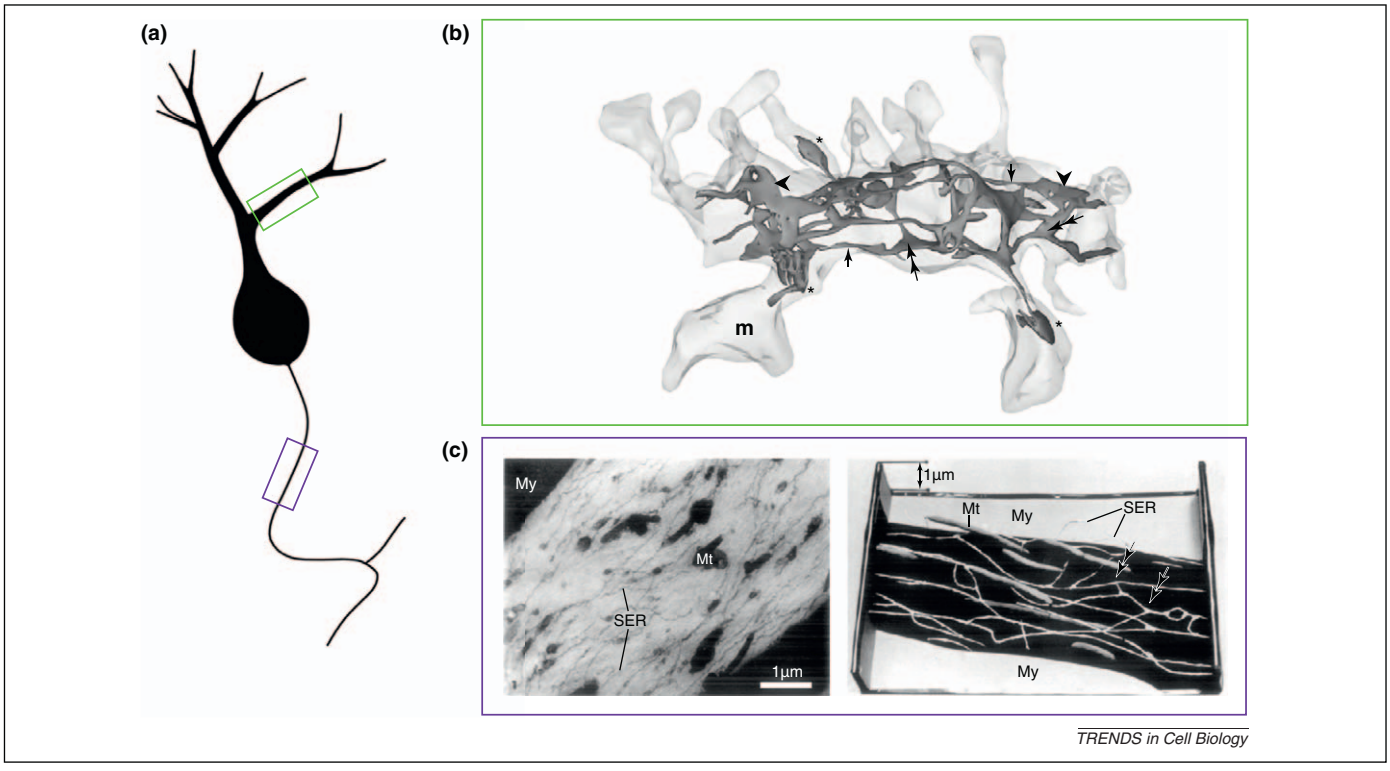

Figure 1. The structure of the ER in dendrites and axons. **(a)** A schematic neuron with multiple dendrites and one axon. Colored boxes indicate dendritic (green) and axonal (purple) regions. **(b)** Schematic magnification of the dendritic box showing a 3D reconstruction of the SER network with flat regions (arrowheads), thin tubules (arrows), three-way junctions (double arrows) and spine apparatus (stars). Figure adapted with permission from [27]. **(c)** Left panel: schematic magnification of the axonal box showing an electron micrograph of a longitudinal section through the internodal part of the axon from a sciatic nerve. SER, smooth ER; Mt, mitochondria; My, myelin. Original magnification, ×22 000. Right panel: a 3D model reconstructed from electron micrographs revealing that the overall structural organization of the ER in axons is similar to that in dendrites, for instance in relation to continuous tubules and three-way junctions (double arrows). Figure adapted with permission from [24].

As in other eukaryotic cells, the dendritic ER is not uniform but is instead an irregular network containing a variety of microdomains. Dendritic ER exit sites (dERES) concentrate correctly folded proteins and regulate ER export, a rate-limiting step in membrane trafficking [31]. dERES resemble cytoplasmic ER exit sites in non-neuronal cells and accumulate characteristic components of the coat protein complex II (COPII), such as the soluble GTPase Sar1, Sec23/24 and Sec13/31 [31]. In spite of its continuity, the ER has a heterogeneous distribution of IP_3Rs, ryanodine receptors and other major ER-resident proteins such as calsequestrin and calreticulin [32–34]. In addition, a highly mobile vesicular ER component could participate in local Ca^{2+} dynamics, but these isolated compartments were observed with fluorescent reporters that often trigger protein aggregation [32]. Thus, although local ER heterogeneities probably impact upon Ca^{2+} release and buffering, how the minute morphology of the dendritic ER affects local Ca^{2+} signaling and trafficking has not been thoroughly investigated [26].

The structure of the dendritic ER is regulated by extracellular signals. A dramatic rearrangement of the tubular ER into lamellar bodies in Purkinje cell dendrites occurs in response to activation of type I metabotropic glutamate receptors (mGluRs) [35]. Similarly, activation of NMDA-type glutamate receptors (NMDARs) reversibly disrupts the continuity of the dendritic ER in hippocampal neurons [36]. Although mGluR- and NMDA-dependent dendritic ER rearrangement awaits further validation with a broader cast of ER probes, these data suggest acute regulation of local ER morphology by synaptic signaling. The potential consequences are fascinating. For example, transient dendritic ER discontinuity could favor local protein processing and export from the ER, ensuring a local and accurate supply of synaptic proteins. In addition, discrete ER rearrangement during synaptic activity could specify local patterns of intracellular Ca^{2+} signaling. Furthermore, discontinuity of the network might protect the neuron against the propagation of excessive Ca^{2+} release under threatening conditions such as ischemia.

Although current evidence firmly establishes that COPII components and Golgi outposts are required for dendritic growth and maintenance, local secretory organelles are not equally necessary for rapid axonal outgrowth [3,8,9]. Nevertheless, secretory organelles are an integral part of the axon. Earlier studies unveiled a continuous 3D ER network of irregular tubules and cisternae in central and peripheral axons. In the sciatic or phrenic nerves the network runs parallel to the axon, is predominantly adjacent to the plasma membrane, and contains occasional free elements [24] (Figure 1). The ER at the nodes of Ranvier contains more cisternae-like structures and displays a beaded appearance [24]. SRP54 (a component of the signal recognition particle), TRAPα (a translocon-associated protein), and the lumenal ER chaperones calreticulin, grp78/BiP, ERp29, and protein disulfide isomerase, all localize to growing dorsal root ganglion (DRG) axons and can be contained in vesicular structures [37,38]. Calnexin, a resident ER protein, also localizes to axons in DRG neurons [39] and the enzymatic activity of glucose-6-phosphatase is detected within the axonal ER, demonstrating the functional resemblance of the axonal ER to its somatic and dendritic counterparts [40]. The ER in CNS axons contains tubules 20–40 nm in diameter and dilated cisternae proximal to the plasma membrane with a membrane thickness comparable to that of the somatic RER (60–100 Å) [40]. In developing hippocampal neurons, components of the protein folding and export machineries, such as calnexin, Sar1, Sec23, Sec12 and Yip1a, all localize to the axon. Similarly, exogenously expressed fluorescently tagged ER proteins are axonally targeted [41]. More importantly, COPII components are required for axon outgrowth during the early stages of development, suggesting that neurons respond to developmental biosynthetic demands by regulating ER function spatially and temporally [41].

It remains unclear how recently identified proteins that shape the ER, such as reticulons, DP1, atlastin-1 and CLIMP-63, define the structure and function of the dendritic and axonal organelle [42]. Interestingly, CLIMP63 interacts with MAP2, a dendrite-specific microtubule-associated protein, indicating that cytosolic linker proteins participate in maintaining the ER structure in dendrites, and suggesting that binding to microtubules takes place through different mechanisms in dendrites and axons [43].

Knowledge of the components that define ER structure in eukaryotic cells will aid in understanding the morphological properties of the ER in the neuronal soma, dendrites and axons. In addition, advances in parameterization and computational models to represent accurately the complex geometry of the ER will provide the tools necessary for the investigation of neuronal ER structure/function relationships under physiological and pathological conditions [44].

ER dynamics in neurons

The ER network is constantly remodeling (reviewed in [13,45]) and three major components contribute to its mobility. First, mobility is achieved by rapid ER tubule extension along microtubules, also referred to as microtubule sliding. In VERO cells, a kidney epithelial cell lineage, tubules extend toward the cell periphery driven by kinesin-1, and towards the cell center powered by cytoplasmic dynein [46]. The adaptor protein kinectin probably mediates kinesin-1 binding to ER membranes [20]. ER tubules also extend to the growing plus-end of microtubules where their association is mediated by tip-attachment complexes (TACs). In newt lung epithelial cells TACs are responsible for 31.4% of ER tubule motility, whereas rapid ER tubule extension contributes the remaining 68.6% [47]. Finally, the ER attached to microtubules moves by actomyosin-based retrograde flow [47]. This constant flux of ER membranes allows dramatic alterations of overall ER morphology. For example, elevated Ca^{2+} in oocytes during egg maturation and fertilization [48], and signaling cascades during mitosis, produce major and reversible transformations in the architecture of the ER network [49–51].

The relative contributions of these processes to the dynamics of the ER in dendrites and axons are still largely unexplored. However, in peripheral axons a dynamic component related to rapid tubule formation has been associated with fast axonal transport [52,53]. ER dynamics has also been explored in the axons of DRG neurons using

fluorescently tagged ER-resident proteins. The axonal ER in these neurons appears very dense, and two resident proteins, sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase and IP_3R, move bidirectionally at 0.1 μm/s. Their mobility is predominantly non-vesicular and microtubule-dependent [54]. In dendrites, ER motility is also microtubule- and kinesin-dependent and contributes to the transport of ER-resident proteins from the soma [32]. Although still mechanistically unclear, ER dynamics is undoubtedly coupled to protein trafficking in neurons, and most probably contributes to the modulation of morphogenesis and synaptic function.

Protein trafficking within the neuronal ER

Major issues presently under study include the role of local secretory organelles in the rapid entry and exit of neurotransmitter receptors from synaptic sites, and the contribution of ER dynamics to this process. Current evidence indicates that there are two protein-trafficking modalities in dendrites (Figure 2). In the canonical secretory route, membrane proteins are synthesized and exported from the somatic ER to a centralized Golgi compartment. Proteins are then sorted by means of long-range post-Golgi vesicles, and insert specifically at their functional sites or in their vicinity before lateral diffusion at the plasma membrane [4]. Although the actual itineraries of endogenous AMPARs and glycine receptors (GlyRs) still need to be fully delineated, their trafficking mechanisms exemplify this pathway. The transport of AMPARs is mediated by conventional kinesin and glutamate-receptor-interacting protein 1/AMPAR-binding protein. This motor complex mediates the dendritic mobility of AMPARs in post-Golgi vesicles before plasma membrane delivery [55]. Similarly, newly synthesized exogenous GlyRα1 subunits assemble in the soma, and possibly use perinuclear organelles to insert in the somatic and proximal dendritic plasma membrane before diffusing for synaptic targeting [56].

A more complex topological organization of secretory organelles has provided evidence to support an alternative trafficking route [3,6,8,9,57–60]. This modality utilizes the dendritic ER, functional dERES, and Golgi outposts for plasma membrane delivery [61] (Figure 2). In the next few paragraphs we examine the contribution of neuronal ER in protein trafficking via this non-canonical modality.

At least two distinct ER functions contribute to non-canonical trafficking. First, mRNAs for membrane and secreted proteins traffic and translate locally in the dendritic ER. Substantial evidence supports this claim (reviewed comprehensively in [62]). A second alternative involves somatic synthesis and the transport of protein cargo along the dendritic and axonal ER for local delivery.

The tubular structure and motile components of the ER define its capacity to function as an intracellular transport system. Luminal proteins diffuse throughout the continuous and aqueous lumen three- to sixfold slower than in the cytoplasm, and membrane proteins diffuse laterally along the ER membrane even under conditions of tightly packed cisternae [63,64]. Mobility of the ER network, export of cargo from the ER, and transport to the Golgi apparatus all involve dynein and kinesin-1 motors [65]. In neurons, diffusion alone might not be sufficient to drive proteins outwards along the dendritic ER, but transport could require the activity of molecular motors. Thus, one can speculate that the components which specify directional ER motility (e.g., rapid tubule extension) will also control protein trafficking in polarized structures such as dendrites and axons.

Although the relative contribution that mobility along the dendritic ER makes to distal trafficking of nascent NMDARs is still not clear, recent studies support a non-canonical modality. The KIF17/mLin-10 complex mediates the vesicular transport of NMDARs *in vitro* and of large NMDAR-containing packets in hippocampal neurons [66,67], but NR1 subunits concentrate in dERES enriched

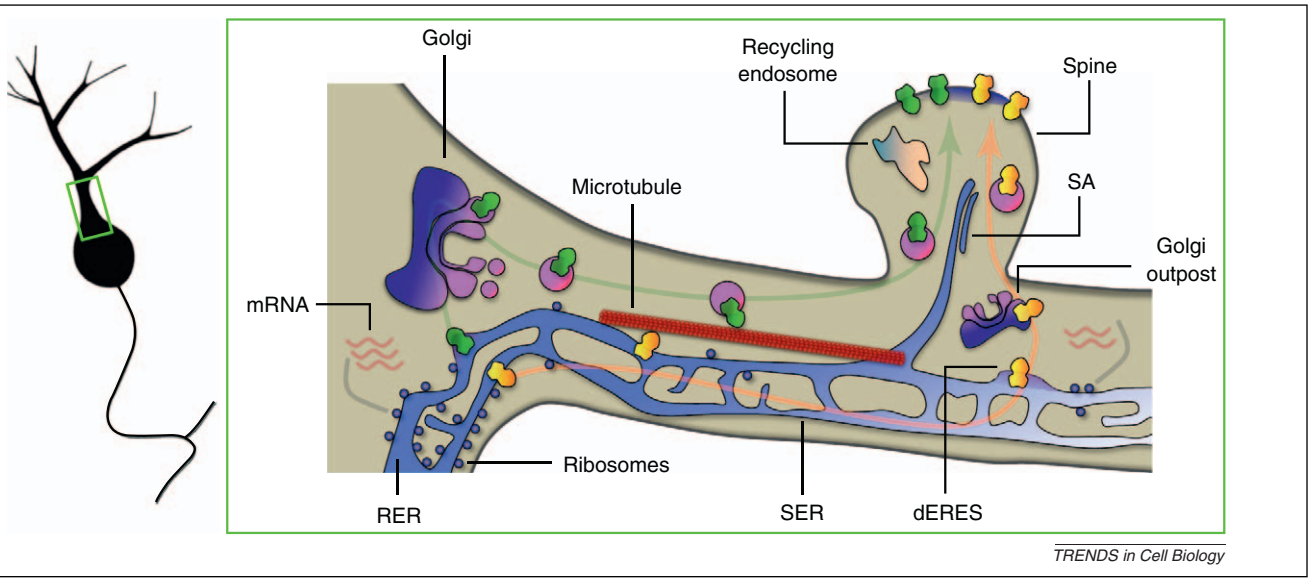

Figure 2. Two modalities for nascent protein trafficking in dendrites. Membrane proteins using a canonical pathway (green receptors and green arrow) are synthesized and exported from the somatic ER, traverse a centralized Golgi compartment, and are sorted by means of long-range post-Golgi vesicles that travel assisted by molecular motors before plasma membrane delivery. Trafficking of membrane proteins through a non-canonical route (orange receptors and orange arrow) utilizes the dendritic ER, that allows protein synthesis or long-distance transport through the network, and dERES that control ER export along dendrites. Cargo exits the ER distally and travels across Golgi outposts before inserting into the plasma membrane. dERES, dendritic ER exit site; RER, rough ER; SER, smooth ER; SA, spine apparatus.

in Sar1-positive puncta that assemble >350 μm away from the cell body [31]. In agreement with these findings, CASK and SAP97 regulate the ER-export of NMDARs which are later trafficked via unconventional Golgi outposts [68]. Given that NMDARs move along microtubules assisted by molecular motors, and probably unload in the vicinity of synapses in a Ca^{2+}-dependent manner [66], accumulated evidence indicates that dendritic ER transport and dERES contribute to the regulation of local trafficking and synaptic availability of NMDARs.

Metabotropic type B GABA receptors ($GABA_BRs$) provide an additional example of non-canonical dendritic ER trafficking. Although $GABA_BR$ heteromers are efficiently detected at the plasma membrane, abundant levels of monomeric subunits have been reported in dendritic intracellular compartments [69,70]. In addition, $GABA_BR1$ colocalizes with the ER in dendrites of hippocampal neurons [71] and a dominant negative kinesin-1 alters the dendritic localization of ER-retained $GABA_BR1$ but not of a mutant that escapes the ER [72]. Upon blockade of ER exit, assembled $GABA_BR$ heteromers accumulate in the somato-dendritic ER, suggesting that newly assembled receptors rapidly exit via dERES *en route* to the plasma membrane [70]. It remains to be determined whether $GABA_BRs$ traffic via local Golgi outposts to insert locally in the vicinity of functional sites in dendrites, or whether somato-dendritic export increases the cargo load of a centralized Golgi apparatus.

The study of serotonin receptors has revealed an intriguing connection between ER trafficking and dendritic transport. Distal dendritic localization of the serotonin 5-HT_{1A} receptor requires its short C terminus and Yif1B. Yif1B is an ERGIC-associated protein and its absence causes the redistribution of 5-HT_{1A} receptors to the somatic and proximal dentritic compartment [73]. Thus, ER-to-Golgi transport is necessary for their long distance mobility.

Other channels and receptors are also trafficked via the non-canonical route. When the potassium channel KV4.2 is associated with the auxiliary subunit KChip1, the channel is trafficked from the ER via a COPII-independent pathway and KChip1 accumulates in Golgi outposts in neurons [74]. Interestingly, KV4.2 is trafficked by KIF17, the same molecular motor that trafficks NMDARs through the ER in dendrites [68,75]. Finally, the α7 nicotinic acetylcholine receptor (nAChR) is also transported along the dendritic ER [76].

AMPARs illustrate the canonical secretory pathway, but recent evidence raises challenging questions about the effect of subunit composition on intracellular trafficking. The GluR2 subunit colocalizes extensively with the ER in dendrites of hippocampal neurons and exhibits long ER residency times that affect plasma-membrane availability [77,78]. These observations are in agreement with a non-canonical dendritic ER-trafficking mode for GluR2. Nevertheless, another AMPAR subunit, GluR1, does not colocalize with the dendritic ER and accumulates preferentially in the somatic Golgi upon transport blockade, despite evidence of dendritic synthesis [79–81], suggesting that it is trafficked via the canonical modality [68,78]. These observations suggest that defined AMPAR subunit combinations prefer specific secretory pathways, a hypothesis that needs to be investigated further.

Combined, these results suggest that the ER contributes to a non-canonical pathway of protein trafficking in dendrites and indicate that multiple mechanisms coexist to accommodate the specialized morphological demands of the neuron. Importantly, the ER could function as a storage compartment before membrane insertion because significant pools of AMPARs, $GABA_BRs$, nAChRs and mGluRs are present in the dendritic ER [70,77,82–84]. Further, rapid changes in the cell-surface abundance of AMPARs are controlled by entry and exit of recycling endosomes into the spine in a myosin Vb-dependent manner [7]. These findings indicate that protein synthesis is not a major factor regulating short-term changes in receptor availability, and suggest that regulated ER export of reserve pools could constitute a replenishment mechanism for recycling endosomes that contributes to local trafficking in polarized cells.

Formation of ERES also takes place in developing axons [41], and support for axonal ER trafficking has emerged from the study of $GABA_BRs$. Axonal localization of $GABA_BRs$ is controlled by a robust targeting signal in the Sushi domains of the $GABA_BR1a$ subunit [71]. Unexpectedly, this signal still operates in the absence of heterodimerization with $GABA_BR2$, a requisite for ER export and plasma membrane localization. Although the transport and sorting mechanisms require detailed characterization, these observations raise the unexpected possibility that $GABA_BR1a$ is targeted to the axon within the ER.

Trafficking signals for ER retention and export

ER retention and export control the assembly and plasma-membrane delivery of multi-subunit neurotransmitter receptors and ion channels. They prevent unassembled or misfolded proteins from reaching the plasma membrane, thereby avoiding deleterious effects on neuronal function and survival. It has been firmly established that sequences different from KDEL and di-lysine, the best-described ER retrieval/recycling and retention signals for ER luminal and membrane proteins, control the trafficking of many neurotransmitter receptors and ion channels [85]. Although it is still unclear how these signals operate as dendritic checkpoints and how they contribute to non-canonical trafficking, their molecular determinants are analyzed below.

The masking of arginine-based ER retention motifs, normally through heteromerization, is a requisite for ER export and plasma membrane delivery [86]. The LRSRR sequence in the C-terminal intracellular domain of $GABA_BR1$ functions as an ER-retention motif that is masked upon assembly with $GABA_BR2$, resulting in export and subsequent delivery of the functional heteromeric receptor to the plasma membrane [87,88]. The NR1-1 and NR2B subunits of NMDARs contain several signals that mediate ER retention, including a conventional RRR motif in the C-terminus of NR1-1 and other sequences in the third transmembrane segments of NR1-1 and NR2B subunits [89–91]. Similarly, the Kir6.1/2 and SUR1 subunits of the ATP-sensitive potassium channel, kainate receptors, and metabotropic glutamate receptors, all contain arginine-based retention sequences that are masked before ER exit

[92–94]. Correct subunit assembly of nAChRs promotes ER exit and delivery of functional receptors to the plasma membrane by masking a PL(Y/F)(F/Y)XXN motif [82]. Further examples of ER retention–retrieval are provided by an aspartate residue at the boundary of the M3–M4 loop and M4 domain of ionotropic $GABA_A$ receptors [95], and by ER retention signals in the first cytoplasmic loop of the 5-HT3B serotonin receptor subunit [96].

ER trafficking is not only regulated by retention but also by positive trafficking signals that improve the efficiency of ER export. For example, an ER export mechanism is present in inwardly rectifying potassium channels. Here, different subunits display distinct efficiencies of plasma membrane delivery. Sequences present in the C-termini of Kir1.1 (VLS and EXD) and Kir2.1 (FCYENE) differentially allow potassium channels to exit the ER [97]. In addition, EAAC1, an excitatory amino acid transporter that regulates extracellular glutamate concentration, is also regulated at the ER stage. EAAC1 is trapped in the ER by its binding partner GTRAP3-18, but the interaction with the reticulon family member RTN2B facilitates EAAC1 ER exit, revealing novel roles for ER structural components in the regulation of ER export [98]. RNA editing of a single amino acid (Q/R) and the gating motions of the GluR2 subunit, or changes in the ligand-binding interface, control the export kinetics of AMPARs from the ER and their expression at synapses [77,99–101]. Similar RNA-editing and ER-export mechanisms operate for kainate receptors [102]. Precisely how the dendritic distribution of membrane proteins is affected or specified by their ER dwell times remains to be investigated. However, the conservation and widespread use of ER retention/export mechanisms suggest that tight dendritic checkpoints can control the local delivery of neurotransmitter receptors.

Protein trafficking to post-ER compartments

Post-ER secretory compartments located distally support a functional role for dendritic and axonal ER trafficking. Cargo exits the ER to enter the ERGIC in dendrites [9], and specific markers for ERGIC (Rab1 and ERGIC-53) and Golgi (Giantin) have been reported in distal dendrites and dendritic spines [6,28,57]. A trihydrophobic motif (VMI 569–571) of the GABA transporter 1 (GAT1) is required for export from the ERGIC, and substitution of these residues results in accumulation of GAT1 in pre-Golgi punctate structures in the soma and neurites of hippocampal neurons [103]. In addition, three proteins in *Drosophila* that mediate ER-to-Golgi trafficking, namely Rab1, Sar1 and Sec23, specifically control dendrite growth [8]. Finally, compelling evidence supports the existence of functional Golgi outposts in dendrites [58,61]. Similarly, the presence in axons of post-ER markers, such as Giantin, GM130, TGN38, clathrin and AP1, confirms that the axonal ER is functionally competent for protein trafficking and suggests that mobilization of cargo along the ER supports axonal function, elongation or maintenance [38,41].

The role of the ER in synaptic plasticity and pathology

The close proximity of the ER to inhibitory postsynaptic sites and the presence of the spine apparatus in a subset of excitatory dendritic spines implicate the ER in the modulation of synaptic transmission [25]. Interestingly, ER export of NMDARs near synaptic sites is regulated by neuronal activity, supporting this hypothesis [31]. In addition, a subset of spines in hippocampal CA1 pyramidal cells contain ER structures that are continuous with the dendritic ER [104]. These spines have characteristic large heads and frequently associate with high-strength or potentiated synapses (Figure 3). The spine ER is not a major regulator of fast, NMDAR-mediated Ca^{2+} transients, but is implicated in mGluR- and IP_3R-dependent Ca^{2+} signaling, playing a role in mGluR-dependent depression, and contributing to compartmentalized synaptic plasticity [104]. The ER in spines can be stable or highly dynamic, and can enter or exit dendritic spines over the time course of hours; this could underlie the spine-to-spine variation in Ca^{2+} spike magnitude or localized protein synthesis and trafficking [105]. Interestingly, the ER content of a spine could depend on physical interactions between transmembrane proteins of the ER and the plasma membrane [30,106].

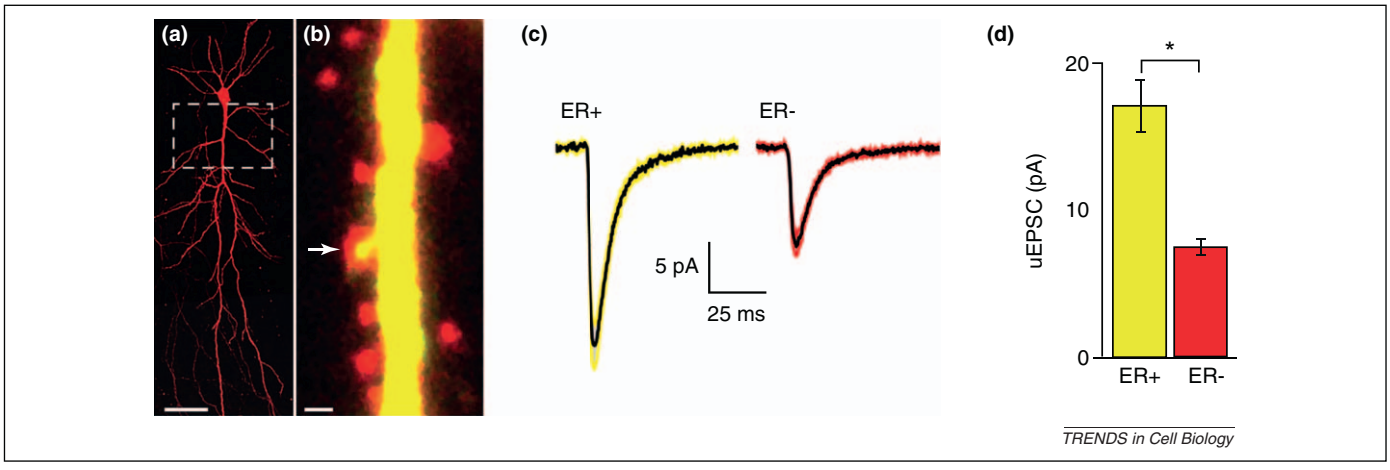

Figure 3. Plasticity and the ER in spines. Dendritic spines that contain ER have larger amplitude Ca^{2+}-release events. **(a)** Two-photon image of a CA1 pyramidal neuron transfected with cytoplasmic red fluorescent protein (RFP, red) and ER-targeted enhanced green fluorescent protein (EGFP, green). The white box indicates the region of analyzed dendrites (scale bar, 50 μm). Overlay of red and green uorescence generates yellow coloration. **(b)** Dendrite with one large ER-containing spine (arrow); scale bar, 1 μm. **(c)** Mean excitatory postsynaptic current (EPSC) magnitudes for ER-containing versus other spines; the colored regions represent the standard error of the mean (SEM). **(d)** Peak EPSC amplitudes were significantly larger in ER-positive spines compared to ER-negative spines. Values in (d) represent means ± SEM. Figure adapted with permission from [104].

EB3, a growing plus-end microtubule-binding protein, enters spines and modulates spine morphology, and thus provides a potential cytoskeletal link for rapid ER entry and exit [107]. The spine apparatus also contributes to synaptic plasticity because mice deficient in synaptopodin lack a spine apparatus and show deficits in long-term potentiation and spatial learning [27,108,109]. Intriguingly, synaptopodin is also found in a stacked ER formation in the axon initial segment, but no functional abnormalities have been detected in synaptopodin-deficient axons [110].

Not surprisingly, alterations of ER structure and function in dendrites and axons have been implicated in numerous pathological conditions [111]. ER stress could alter dendritic ER morphology and thus locally affect protein quality control [112]. Sixty percent of individuals with hereditary spastic paraplegia, a condition characterized by axonopathy of cortico-spinal motor neurons, carry mutations affecting spastin, atlastin-1, or REEP1, all of which interact with each other through their hydrophobic hairpin domains to form complexes responsible for new tubule connections and interactions with the cytoskeleton, thus indicating that loss of proper ER structure is a neuropathogenic threat [21]. Similarly, swelling and disorganization of the ER in dendrites and spines is characteristic of Purkinje cells after chronic ethanol abuse, and could contribute to the dendritic degeneration seen in injured human brain tissue [113–115]. Purkinje cell spines of the dilute–opisthotonus ataxic mutant rat, which corresponds to mutations in myosin Va, are devoid of ER [116,117]. Cerebellar-specific Atg5-null mice accumulate stacked and lamellar membranous structures that resemble ER in axons and exhibit mild and slow-onset ataxic gait, abnormal limb-clasping reflex, and motor dyscoordination [118]. Expansion of axonal varicosities and accumulation of vesicular membranes of an as yet undefined nature are observed in the APP_{Swe} transgenic mouse model of Alzheimer's disease – a phenotype that is enhanced in mice expressing reduced kinesin-1 levels and in the early stages of Alzheimer's disease in humans [119]. One interpretation is that the axonal varicosities represent altered secretory sites, suggesting that local axonal biosynthetic trafficking occurs physiologically. Despite these recent advances our understanding of the relationship between axo-dendritic ER structure and behavioral abnormalities is still incomplete.

Concluding remarks

The actively shaped ER network supports high connectivity and segregated functions, but central questions concerning the structure, dynamics and function of the ER in dendrites and axons remain open. Increased understanding of the ER in non-neuronal cells will certainly provide a basis for structural and dynamic analyses in neurons. Pioneering studies have already demonstrated that reticulon proteins RTN2B and RTN3 are localized to developing neurites, and that overexpression of RTN3 causes aggregation and neuritic dystrophy [98,120]. In addition, atlastin-1 depletion results in fragmentation of the neuronal ER in *Drosophila* [121]. The local control of the ER during neuronal activity, and the local compartmentalized responses of the ER that contribute to the modulation of neuronal function, will no doubt remain active topics of research in the future. Thus, this emerging field is generating challenging results that demand a reconsideration of the intricate relationship between axo-dendritic ER morphology, dynamics and trafficking, and the degree to which they contribute to neuronal function and dysfunction.

Acknowledgments

A.C. is funded by Fondo Nacional de Desarrollo Científico y Tecnológico (FONDECYT) grant 1100137, O.A.R. is funded by FONDECYT grant 3110157, and A.C. and O.A.R. are funded by Iniciativa Científica Milenio (ICM) grant P07-048-F.

References

1 Dotti, C.G. *et al.* (1988) The establishment of polarity by hippocampal neurons in culture. *J. Neurosci.* 8, 1454–1468
2 Ye, B. *et al.* (2006) The secretory pathway and neuron polarization. *J. Neurosci.* 26, 10631–10632
3 Horton, A.C. *et al.* (2005) Polarized secretory trafficking directs cargo for asymmetric dendrite growth and morphogenesis. *Neuron* 48, 757–771
4 Kennedy, M.J. and Ehlers, M.D. (2006) Organelles and trafficking machinery for postsynaptic plasticity. *Annu. Rev. Neurosci.* 29, 325–362
5 Clem, R.L. and Barth, A. (2006) Pathway-specific trafficking of native AMPARs by in vivo experience. *Neuron* 49, 663–670
6 Pierce, J.P. *et al.* (2001) Evidence for a satellite secretory pathway in neuronal dendritic spines. *Curr. Biol.* 11, 351–355
7 Wang, Z. *et al.* (2008) Myosin Vb mobilizes recycling endosomes and AMPA receptors for postsynaptic plasticity. *Cell* 135, 535–548
8 Ye, B. *et al.* (2007) Growing dendrites and axons differ in their reliance on the secretory pathway. *Cell* 130, 717–729
9 Horton, A.C. and Ehlers, M.D. (2003) Dual modes of endoplasmic reticulum-to-Golgi transport in dendrites revealed by live-cell imaging. *J. Neurosci.* 23, 6188–6199
10 Park, M.K. *et al.* (2008) The endoplasmic reticulum as an integrator of multiple dendritic events. *Neuroscientist* 14, 68–77
11 Vedrenne, C. and Hauri, H.P. (2006) Morphogenesis of the endoplasmic reticulum: beyond active membrane expansion. *Traffic* 7, 639–646
12 Baumann, O. and Walz, B. (2001) Endoplasmic reticulum of animal cells and its organization into structural and functional domains. *Int. Rev. Cytol.* 205, 149–214
13 Borgese, N. *et al.* (2006) Endoplasmic reticulum architecture: structures in flux. *Curr. Opin. Cell Biol.* 18, 358–364
14 Shibata, Y. *et al.* (2006) Rough sheets and smooth tubules. *Cell* 126, 435–439
15 Sparkes, I.A. *et al.* (2009) The plant endoplasmic reticulum: a cell-wide web. *Biochem. J.* 423, 145–155
16 Park, S.H. and Blackstone, C. (2010) Further assembly required: construction and dynamics of the endoplasmic reticulum network. *EMBO Rep.* 11, 515–521
17 Voeltz, G.K. *et al.* (2006) A class of membrane proteins shaping the tubular endoplasmic reticulum. *Cell* 124, 573–586
18 Hu, J. *et al.* (2009) A class of dynamin-like GTPases involved in the generation of the tubular ER network. *Cell* 138, 549–561
19 Vedrenne, C. *et al.* (2005) Phosphorylation controls CLIMP-63-mediated anchoring of the endoplasmic reticulum to microtubules. *Mol. Biol. Cell* 16, 1928–1937
20 Santama, N. *et al.* (2004) Distribution and functions of kinectin isoforms. *J. Cell Sci.* 117, 4537–4549
21 Park, S.H. *et al.* (2010) Hereditary spastic paraplegia proteins REEP1, spastin, and atlastin-1 coordinate microtubule interactions with the tubular ER network. *J. Clin. Invest.* 120, 1097–1110
22 Dreier, L. and Rapoport, T.A. (2000) In vitro formation of the endoplasmic reticulum occurs independently of microtubules by a controlled fusion reaction. *J. Cell Biol.* 148, 883–898
23 Broadwell, R.D. and Cataldo, A.M. (1983) The neuronal endoplasmic reticulum: its cytochemistry and contribution to the endomembrane system. I. Cell bodies and dendrites. *J. Histochem. Cytochem.* 31, 1077–1088
24 Tsukita, S. and Ishikawa, H. (1976) Three-dimensional distribution of smooth endoplasmic reticulum in myelinated axons. *J. Electron Microsc. (Tokyo)* 25, 141–149

25 Spacek, J. and Harris, K.M. (1997) Three-dimensional organization of smooth endoplasmic reticulum in hippocampal CA1 dendrites and dendritic spines of the immature and mature rat. *J. Neurosci.* 17, 190–203
26 Petersen, O.H. and Verkhratsky, A. (2007) Endoplasmic reticulum calcium tunnels integrate signalling in polarised cells. *Cell Calcium* 42, 373–378
27 Cooney, J.R. *et al.* (2002) Endosomal compartments serve multiple hippocampal dendritic spines from a widespread rather than a local store of recycling membrane. *J. Neurosci.* 22, 2215–2224
28 Krijnse-Locker, J. *et al.* (1995) The organization of the endoplasmic reticulum and the intermediate compartment in cultured rat hippocampal neurons. *Mol. Biol. Cell* 6, 1315–1332
29 Lavieu, G. *et al.* (2010) Induction of cortical endoplasmic reticulum by dimerization of a coatomer-binding peptide anchored to endoplasmic reticulum membranes. *Proc. Natl. Acad. Sci. U. S. A.* 107, 6876–6881
30 Xiao, B. *et al.* (2000) Homer: a link between neural activity and glutamate receptor function. *Curr. Opin. Neurobiol.* 10, 370–374
31 Aridor, M. *et al.* (2004) Endoplasmic reticulum export site formation and function in dendrites. *J. Neurosci.* 24, 3770–3776
32 Bannai, H. *et al.* (2004) Kinesin dependent, rapid, bi-directional transport of ER sub-compartment in dendrites of hippocampal neurons. *J. Cell Sci.* 117, 163–175
33 Gatti, G. *et al.* (2001) Head-to-tail oligomerization of calsequestrin: a novel mechanism for heterogeneous distribution of endoplasmic reticulum luminal proteins. *J. Cell Biol.* 154, 525–534
34 Copray, J.C. *et al.* (1996) Calreticulin expression in spinal motoneurons of the rat. *J. Chem. Neuroanat.* 11, 57–65
35 Banno, T. and Kohno, K. (1998) Conformational changes of the smooth endoplasmic reticulum are facilitated by L-glutamate and its receptors in rat Purkinje cells. *J. Comp. Neurol.* 402, 252–263
36 Kucharz, K. *et al.* (2009) NMDA receptor stimulation induces reversible fission of the neuronal endoplasmic reticulum. *PLoS One* 4, e5250
37 Willis, D. *et al.* (2005) Differential transport and local translation of cytoskeletal, injury-response, and neurodegeneration protein mRNAs in axons. *J. Neurosci.* 25, 778–791
38 Merianda, T.T. *et al.* (2009) A functional equivalent of endoplasmic reticulum and Golgi in axons for secretion of locally synthesized proteins. *Mol. Cell Neurosci.* 40, 128–142
39 Weclewicz, K. *et al.* (1998) Targeting of endoplasmic reticulum-associated proteins to axons and dendrites in rotavirus-infected neurons. *Brain Res. Bull.* 46, 353–360
40 Broadwell, R.D. and Cataldo, A.M. (1984) The neuronal endoplasmic reticulum: its cytochemistry and contribution to the endomembrane system. II. Axons and terminals. *J. Comp. Neurol.* 230, 231–248
41 Aridor, M. and Fish, K.N. (2009) Selective targeting of ER exit sites supports axon development. *Traffic* 10, 1669–1684
42 Renvoisé, B. and Blackstone, C. (2010) Emerging themes of ER organization in the development and maintenance of axons. *Curr. Opin. Neurobiol.* 20, 531–537
43 Farah, C.A. *et al.* (2005) Interaction of microtubule-associated protein-2 and p63: a new link between microtubules and rough endoplasmic reticulum membranes in neurons. *J. Biol. Chem.* 280, 9439–9449
44 Bouchekhima, A.N. *et al.* (2009) Geometric quantification of the plant endoplasmic reticulum. *J. Microsc.* 234, 158–172
45 Bola, B. and Allan, V. (2009) How and why does the endoplasmic reticulum move? *Biochem. Soc. Trans.* 37, 961–965
46 Wozniak, M.J. *et al.* (2009) Role of kinesin-1 and cytoplasmic dynein in endoplasmic reticulum movement in VERO cells. *J. Cell Sci.* 122, 1979–1989
47 Waterman-Storer, C.M. and Salmon, E.D. (1998) Endoplasmic reticulum membrane tubules are distributed by microtubules in living cells using three distinct mechanisms. *Curr. Biol.* 8, 798–806
48 Stricker, S.A. (2006) Structural reorganizations of the endoplasmic reticulum during egg maturation and fertilization. *Semin. Cell Dev. Biol.* 17, 303–313
49 McCullough, S. and Lucocq, J. (2005) Endoplasmic reticulum positioning and partitioning in mitotic HeLa cells. *J. Anat.* 206, 415–425
50 Puhka, M. *et al.* (2007) Endoplasmic reticulum remains continuous and undergoes sheet-to-tubule transformation during cell division in mammalian cells. *J. Cell Biol.* 179, 895–909
51 Lu, L. *et al.* (2009) Cisternal organization of the endoplasmic reticulum during mitosis. *Mol. Biol. Cell* 20, 3471–3480
52 Droz, B. *et al.* (1975) The smooth endoplasmic reticulum: structure and role in the renewal of axonal membrane and synaptic vesicles by fast axonal transport. *Brain Res.* 93, 1–13
53 Tsukita, S. and Ishikawa, H. (1980) The movement of membranous organelles in axons. Electron microscopic identification of anterogradely and retrogradely transported organelles. *J. Cell Biol.* 84, 513–530
54 Aihara, Y. *et al.* (2001) Movement of endoplasmic reticulum in the living axon is distinct from other membranous vesicles in its rate, form, and sensitivity to microtubule inhibitors. *J. Neurosci. Res.* 65, 236–246
55 Setou, M. *et al.* (2002) Glutamate-receptor-interacting protein GRIP1 directly steers kinesin to dendrites. *Nature* 417, 83–87
56 Rosenberg, M. *et al.* (2001) Dynamics of glycine receptor insertion in the neuronal plasma membrane. *J. Neurosci.* 21, 5036–5044
57 Gardiol, A. *et al.* (1999) Dendritic and postsynaptic protein synthetic machinery. *J. Neurosci.* 19, 168–179
58 Dotti, C.G. and Simons, K. (1990) Polarized sorting of viral glycoproteins to the axon and dendrites of hippocampal neurons in culture. *Cell* 62, 63–72
59 Torre, E.R. and Steward, O. (1996) Protein synthesis within dendrites: glycosylation of newly synthesized proteins in dendrites of hippocampal neurons in culture. *J. Neurosci.* 16, 5967–5978
60 Lowenstein, P.R. *et al.* (1994) Polarized distribution of the trans-Golgi network marker TGN38 during the *in vitro* development of neocortical neurons: effects of nocodazole and brefeldin A. *Eur. J. Neurosci.* 6, 1453–1465
61 Hanus, C. and Ehlers, M.D. (2008) Secretory outposts for the local processing of membrane cargo in neuronal dendrites. *Traffic* 9, 1437–1445
62 Bramham, C.R. and Wells, D.G. (2007) Dendritic mRNA: transport, translation and function. *Nat. Rev. Neurosci.* 8, 776–789
63 Snapp, E.L. *et al.* (2003) Formation of stacked ER cisternae by low affinity protein interactions. *J. Cell Biol.* 163, 257–269
64 Dayel, M.J. *et al.* (1999) Diffusion of green fluorescent protein in the aqueous-phase lumen of endoplasmic reticulum. *Biophys. J.* 76, 2843–2851
65 Gupta, V. *et al.* (2008) Kinesin-1 (uKHC/KIF5B) is required for bidirectional motility of ER exit sites and efficient ER-to-Golgi transport. *Traffic* 9, 1850–1866
66 Guillaud, L. *et al.* (2008) Disruption of KIF17-Mint1 interaction by CaMKII-dependent phosphorylation: a molecular model of kinesin-cargo release. *Nat. Cell Biol.* 10, 19–29
67 Setou, M. *et al.* (2000) Kinesin superfamily motor protein KIF17 and mLin-10 in NMDA receptor-containing vesicle transport. *Science* 288, 1796–1802
68 Jeyifous, O. *et al.* (2009) SAP97 and CASK mediate sorting of NMDA receptors through a previously unknown secretory pathway. *Nat. Neurosci.* 12, 1011–1019
69 Gonchar, Y. *et al.* (2001) Subcellular localization of GABA(B) receptor subunits in rat visual cortex. *J. Comp. Neurol.* 431, 182–197
70 Ramirez, O.A. *et al.* (2009) Dendritic assembly of heteromeric gamma-aminobutyric acid type B receptor subunits in hippocampal neurons. *J. Biol. Chem.* 284, 13077–13085
71 Biermann, B. *et al.* (2010) The Sushi domains of GABAB receptors function as axonal targeting signals. *J. Neurosci.* 30, 1385–1394
72 Vidal, R.L. *et al.* (2007) Marlin-1 and conventional kinesin link GABAB receptors to the cytoskeleton and regulate receptor transport. *Mol. Cell Neurosci.* 35, 501–512
73 Carrel, D. *et al.* (2008) Targeting of the 5-HT1A serotonin receptor to neuronal dendrites is mediated by Yif1B. *J. Neurosci.* 28, 8063–8073
74 Hasdemir, B. *et al.* (2005) Traffic of Kv4 K+ channels mediated by KChIP1 is via a novel post-ER vesicular pathway. *J. Cell Biol.* 171, 459–469
75 Chu, P.J. *et al.* (2006) A role for Kif17 in transport of Kv4.2. *J. Biol. Chem.* 281, 365–373
76 Alexander, J.K. *et al.* (2010) Ric-3 promotes alpha7 nicotinic receptor assembly and trafficking through the ER subcompartment of dendrites. *J. Neurosci.* 30, 10112–10126
77 Greger, I.H. *et al.* (2002) RNA editing at arg607 controls AMPA receptor exit from the endoplasmic reticulum. *Neuron* 34, 759–772

78 Rubio, M.E. and Wenthold, R.J. (1999) Calnexin and the immunoglobulin binding protein (BiP) coimmunoprecipitate with AMPA receptors. *J. Neurochem.* 73, 942–948
79 Ju, W. *et al.* (2004) Activity-dependent regulation of dendritic synthesis and trafficking of AMPA receptors. *Nat. Neurosci.* 7, 244–253
80 Kacharmina, J.E. *et al.* (2000) Stimulation of glutamate receptor protein synthesis and membrane insertion within isolated neuronal dendrites. *Proc. Natl. Acad. Sci. U. S. A.* 97, 11545–11550
81 Sutton, M.A. *et al.* (2006) Miniature neurotransmission stabilizes synaptic function via tonic suppression of local dendritic protein synthesis. *Cell* 125, 785–799
82 Drenan, R.M. *et al.* (2008) Subcellular trafficking, pentameric assembly, and subunit stoichiometry of neuronal nicotinic acetylcholine receptors containing fluorescently labeled alpha6 and beta3 subunits. *Mol. Pharmacol.* 73, 27–41
83 Hubert, G.W. *et al.* (2001) Differential subcellular localization of mGluR1a and mGluR5 in the rat and monkey Substantia nigra. *J. Neurosci.* 21, 1838–1847
84 López-Bendito, G. *et al.* (2002) Differential distribution of group I metabotropic glutamate receptors during rat cortical development. *Cereb. Cortex* 12, 625–638
85 Murshid, A. and Presley, J.F. (2004) ER-to-Golgi transport and cytoskeletal interactions in animal cells. *Cell Mol. Life Sci.* 61, 133–145
86 Michelsen, K. *et al.* (2005) Hide and run. Arginine-based endoplasmic-reticulum-sorting motifs in the assembly of heteromultimeric membrane proteins. *EMBO Rep.* 6, 717–722
87 Couve, A. *et al.* (1998) Intracellular retention of recombinant GABAB receptors. *J. Biol. Chem.* 273, 26361–26367
88 Margeta-Mitrovic, M. *et al.* (2000) A trafficking checkpoint controls GABA(B) receptor heterodimerization. *Neuron* 27, 97–106
89 Horak, M. *et al.* (2008) Masking of the endoplasmic reticulum retention signals during assembly of the NMDA receptor. *J. Neurosci.* 28, 3500–3509
90 Scott, D.B. *et al.* (2001) An NMDA receptor ER retention signal regulated by phosphorylation and alternative splicing. *J. Neurosci.* 21, 3063–3072
91 Scott, D.B. *et al.* (2003) Coordinated PKA and PKC phosphorylation suppresses RXR-mediated ER retention and regulates the surface delivery of NMDA receptors. *Neuropharmacology* 45, 755–767
92 Ren, Z. *et al.* (2003) Cell surface expression of GluR5 kainate receptors is regulated by an endoplasmic reticulum retention signal. *J. Biol. Chem.* 278, 52700–52709
93 Chan, W.Y. *et al.* (2001) Molecular determinants of metabotropic glutamate receptor 1B trafficking. *Mol. Cell Neurosci.* 17, 577–588
94 Zerangue, N. *et al.* (1999) A new ER trafficking signal regulates the subunit stoichiometry of plasma membrane K(ATP) channels. *Neuron* 22, 537–548
95 Lo, W.Y. *et al.* (2008) A conserved Cys-loop receptor aspartate residue in the M3-M4 cytoplasmic loop is required for GABAA receptor assembly. *J. Biol. Chem.* 283, 29740–29752
96 Boyd, G.W. *et al.* (2003) Cell surface expression of 5-hydroxytryptamine type 3 receptors is controlled by an endoplasmic reticulum retention signal. *J. Biol. Chem.* 278, 27681–27687
97 Ma, D. *et al.* (2001) Role of ER export signals in controlling surface potassium channel numbers. *Science* 291, 316–319
98 Liu, Y. *et al.* (2008) Reticulon RTN2B regulates trafficking and function of neuronal glutamate transporter EAAC1. *J. Biol. Chem.* 283, 6561–6571
99 Penn, A.C. *et al.* (2008) Gating motions underlie AMPA receptor secretion from the endoplasmic reticulum. *Embo J.* 27, 3056–3068
100 Greger, I.H. *et al.* (2006) Developmentally regulated, combinatorial RNA processing modulates AMPA receptor biogenesis. *Neuron* 51, 85–97
101 Mu, Y. *et al.* (2003) Activity-dependent mRNA splicing controls ER export and synaptic delivery of NMDA receptors. *Neuron* 40, 581–594
102 Ball, S.M. *et al.* (2010) Assembly and intracellular distribution of kainate receptors is determined by RNA editing and subunit composition. *J. Neurochem.* 114, 1805–1818
103 Farhan, H. *et al.* (2008) Signal-dependent export of GABA transporter 1 from the ER-Golgi intermediate compartment is specified by a C-terminal motif. *J. Cell Sci.* 121, 753–761
104 Holbro, N. *et al.* (2009) Differential distribution of endoplasmic reticulum controls metabotropic signaling and plasticity at hippocampal synapses. *Proc. Natl. Acad. Sci. U. S. A.* 106, 15055–15060
105 Toresson, H. and Grant, S.G. (2005) Dynamic distribution of endoplasmic reticulum in hippocampal neuron dendritic spines. *Eur. J. Neurosci.* 22, 1793–1798
106 Ng, A.N. and Toresson, H. (2008) Gamma-secretase and metalloproteinase activity regulate the distribution of endoplasmic reticulum to hippocampal neuron dendritic spines. *Faseb J.* 22, 2832–2842
107 Jaworski, J. *et al.* (2009) Dynamic microtubules regulate dendritic spine morphology and synaptic plasticity. *Neuron* 61, 85–100
108 Vlachos, A. *et al.* (2009) Synaptopodin regulates plasticity of dendritic spines in hippocampal neurons. *J. Neurosci.* 29, 1017–1033
109 Jedlicka, P. *et al.* (2008) A role for the spine apparatus in LTP and spatial learning. *Behav. Brain Res.* 192, 12–19
110 Bas Orth, C. *et al.* (2007) Loss of the cisternal organelle in the axon initial segment of cortical neurons in synaptopodin-deficient mice. *J. Comp. Neurol.* 504, 441–449
111 Fiala, J.C. *et al.* (2002) Dendritic spine pathology: cause or consequence of neurological disorders? *Brain Res. Brain Res. Rev.* 39, 29–54
112 Murakami, T. *et al.* (2007) Endoplasmic reticulum stress response in dendrites of cultured primary neurons. *Neuroscience* 146, 1–8
113 Dlugos, C.A. (2006) Smooth endoplasmic reticulum dilation and degeneration in Purkinje neuron dendrites of aging ethanol-fed female rats. *Cerebellum* 5, 155–162
114 Castejon, O.J. *et al.* (1995) Synaptic degenerative changes in human traumatic brain edema. An electron microscopic study of cerebral cortical biopsies. *J. Neurosurg. Sci.* 39, 47–65
115 Spacek, J. (1987) Ultrastructural pathology of dendritic spines in epitumorous human cerebral cortex. *Acta Neuropathol.* 73, 77–85
116 Dekker-Ohno, K. *et al.* (1996) Endoplasmic reticulum is missing in dendritic spines of Purkinje cells of the ataxic mutant rat. *Brain Res.* 714, 226–230
117 Futaki, S. *et al.* (2000) Identification of a novel myosin-Va mutation in an ataxic mutant rat, dilute-opisthotonus. *Mamm. Genome* 11, 649–655
118 Nishiyama, J. *et al.* (2007) Aberrant membranes and double-membrane structures accumulate in the axons of Atg5-null Purkinje cells before neuronal death. *Autophagy* 3, 591–596
119 Stokin, G.B. *et al.* (2005) Axonopathy and transport deficits early in the pathogenesis of Alzheimer's disease. *Science* 307, 1282–1288
120 Hu, X. *et al.* (2007) Transgenic mice overexpressing reticulon 3 develop neuritic abnormalities. *Embo J.* 26, 2755–2767
121 Orso, G. *et al.* (2009) Homotypic fusion of ER membranes requires the dynamin-like GTPase atlastin. *Nature* 460, 978–983