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Review

Emerging aspects of membrane traffic in neuronal dendrite growth

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Abstract

Polarized growth of the neuron would logically require some form of membrane traffic to the tip of the growth cone, regulated in conjunction with other trafficking processes that are common to both neuronal and non-neuronal cells. Unlike axons, dendrites are endowed with membranous organelles of the exocytic pathway extending from the cell soma, including both rough and smooth endoplasmic reticulum (ER) and the ER–Golgi intermediate compartment (ERGIC). Dendrites also have satellite Golgi-like cisternal stacks known as Golgi outposts that have no membranous connections with the somatic Golgi. Golgi outposts presumably serve both general and specific local trafficking needs, and could mediate membrane traffic required for polarized dendritic growth during neuronal differentiation. Recent findings suggest that dendritic growth, but apparently not axonal growth, relies very much on classical exocytic traffic, and is affected by defects in components of both the early and late secretory pathways. Within dendrites, localized processes of recycling endosome-based exocytosis regulate the growth of dendritic spines and postsynaptic compartments. Emerging membrane traffic processes and components that contribute specifically to dendritic growth are discussed.

Keywords: Dendrite; Golgi apparatus; Golgi outpost; Neuron; Sar 1; Syntaxin 16

1. Introduction

Neurons are highly specialized cells with elaborate junction connections with one another and with target organs. Polarized membrane traffic in neurons is necessary for both the establishment and the maintenance of the axonal and somato-dendritic plasma membrane domains [1–3]. Neuronal polarity is established during early development, as neural progenitor cells differentiate and generate processes that would become axons and dendrites. Axons typically function in neurotransmitter release in response to an action potential generated by an integration of dendritic input. Dendrites house, at their synaptic termini, receptors that serve to transduce chemical signals from several other neurons. It is clear that these plasma membrane domains must have a distinct set of proteins, and the composition of these proteins needs to be continuously maintained as such, as postmitotic neurons serve out the life span of the organism.

In general, polarized targeting to different neuronal surface domains can be achieved in several ways. Although neurons lack an equivalent of tight junctions, cytoskeletal-membrane protein complexes constituting the initial segment fence found at the axon hillock [4] could prevent free movement of membrane proteins to axonal domains. Selective, directed targeting of membrane cargoes in specific domain bound carriers has been observed for dendritic proteins [5,6]. On the other hand, some membrane cargo-ferrying carriers are not specifically targeted, and could find their way into the associated cytoplasmic region of both axons and dendrites. This is particularly the case for those utilizing plus-end-directed microtubule motors, which are present in both axon and dendrite [7]. For these, selective membrane docking/fusion is presumably required for eventual domain specific incorporation of cargo [8].

Polarized surface transport of membrane materials is required in the maintenance of adult neuron function, and is also acutely needed in polarized neurite growth during development and differentiation. How are these processes connected to, and regulated in conjunction with, the regular vesicular membrane traffic in neurons? Biosynthetic transport of membrane proteins and lipids along the exocytic pathway provides a continuous supply of membrane materials to the surface of all eukaryotic cells. Membrane proteins and secretory

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cargoes are first targeted to the endoplasmic reticulum, and then routed to the cell surface through multiple rounds of vesicle budding and fusion processes [9,10]. These processes are mediated by an evolutionarily conserved set of coat proteins that regulated vesicle budding [11] as well as Rab family GTPases, tethering complexes (such as the exocyst complex) and soluble *N*-ethylmaleimide sensitive factor (NSF) attachment protein receptors (SNARE) for vesicle docking and fusion [12]. Other than exocytosis, another way whereby membrane proteins could be added to the cell surface is through the recycling of internalized proteins via recycling endosomes [13,14]. Polarized membrane traffic in neurons could therefore be mediated by the same cellular machineries functioning along the paths and routes of exocytotic trafficking and/or endosomal recycling, but specifically regulated in some temporal and spatially unique manner [15]. There are some evidence for Rab8 [16,17], and the exocyst complex [18] being involved in exocytosis-mediated neurite extension. However, evidence for an absolute requirement for exocytic traffic in general and specific key components of the exocytic machinery, such as coat proteins and SNAREs (except TI-VAMP, which is more associated with lysosomal traffic in non-neuronal cells), are scarce. On the other hand, the requirement of for Rab11 [19] and syntaxin 13 [20]-mediated processes have implicated recycling endosome function in neurite outgrowth.

Neuronal dendrites are in most cases fairly elaborate structures with multiple branches. It is therefore conceivable that supply of nascent membrane proteins for its growth and maintenance from the cell body could be problematic. The problem may be partially alleviated by having mRNAs targeted [21] to local protein translational machinery of dendrites [22,23]. The Golgi apparatus is the penultimate membranous organelle within the cell soma where proteins destined for the secretory pathway traverse before reaching the plasma membrane. It is interesting to note that polarization in many eukaryotic cells is often associated with some morphological rearrangement of Golgi positioning, so as to facilitate directional targeting of membrane traffic to specialized plasma membrane domains [3]. However, is axonal and dendritic growth truly dependent on secretory traffic, and if so, how is membrane traffic from the cell body directed towards the growing neurites? Recent findings have revealed that growth of neuronal dendrites, unlike axons, is in fact very much dependent on the classical secretory pathway and its associated membranous compartments for its growth and function.

2. The dendrite is endowed with a localized exocytic apparatus

It has become clear over the past years that the neuronal dendrite is endowed with satellite endomembrane systems that modulate more localized membrane traffic. It was known earlier that local protein synthesis occurs in dendrites [24]. Interestingly, dendrites seemed to also possess the enzymes for N-linked glycosylation reactions that are usually associated with the Golgi apparatus [25]. Early immunocytochemical studies also suggest that membrane structures and markers of the rough and smooth endoplasmic reticulum (ER), ER–Golgi intermediate compartment (ERGIC) [26] and the Golgi apparatus could extend at least into the proximal part of major dendritic branches [27]. A large number of dendritic spines are known to contain a specialized smooth ER membrane extension known as the spine apparatus [28,29].

Ultrastructural studies by McCarthy et al. with immunogold labeling demonstrated that the ER translocon component Sec61α, ribosomes and lumenal ER proteins with the KDEL retention signal were all found associated with dendrites and dendritic spines [30]. There are also morphological evidence for the presence of ERGIC and Golgi/*trans*-Golgi network (TGN) markers within dendritic spines and distal dendrites [31]. Aridor et al. showed that ER export sites, marked by the small GTPase Sar1 and components of coat complex II (COPII), are assembled regularly throughout the dendritic tree [32]. *N*-methyl D-aspartate (NMDA) receptors were shown to be recruited to these ER export sites upon activation of metabotropic glutamate receptors, indicating that the formation of these sites could be regulated by neuronal activity [32].

With advances in live-imaging techniques, trafficking of fluorescent protein-labeled mobile transporters to both axons and dendrites could be visualized [8,33]. Horton and Ehlers [34] examined mobile carriers containing the antegrograde membrane cargo green fluorescent protein-labeled vesicular stomatitis virus G (GFP-VSVG) protein. Upon ER exit, these moves bidirectionally, and fused with both the somatic Golgi as well as some relatively static and long-live punctuated structures in the dendrite (but not the axon). The latter structures have Golgi-like membrane identities, as they are positively labeled for both the *cis*-Golgi marker GM130 [35] and the *trans*-Golgi marker galactosyltransferase [36]. Ehlers et al. further showed that these Golgi outposts are most prominently found in the longer and thicker apical dendrites. Golgi outposts appear to play a role in dendritic growth during morphological differentiation of hippocampal pyramidal neurons [37]. During dendritic growth, the Golgi apparatus becomes physically oriented towards the longest dendrite. This morphological change in Golgi polarity precedes the asymmetric dendrite elongation. Disruption of the Golgi apparatus by over-expressing GRASP65, a protein which facilitates Golgi cisternae stacking [38], abolished this asymmetry in Golgi orientation observed during dendritic growth, resulting in a marked reduction in dendritic polarity. Furthermore, a kinase-dead mutant of the TGN-localized protein kinase D (PKD-KD) [39], which blocks anterograde TGN-plasma membrane transport, had a specific and quick suppressive effect on dendritic over axonal outgrowth.

These important findings revealed that membrane traffic in growing dendrites are facilitated by discrete, satellite secretory apparatus distinct from that at the cell body. The existence of Golgi outposts poses several interesting questions, perhaps the most important of which pertains to their origin and function. Although the mode and mechanism of Golgi outpost biogenesis has remained largely unknown, several possibilities have been postulated [40]. The presence of ERGICs in dendrites [32,34] suggests that Golgi elements could be generated *de novo* by ER exocytosis at these sites remote from the cell body.