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Polarized trafficking: the palmitoylation cycle distributes cytoplasmic proteins to distinct neuronal compartments

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In neurons, polarized cargo distribution occurs mainly between the soma and axonal and dendritic compartments, and requires coordinated regulation of cytoskeletal remodeling and membrane trafficking. The Golgi complex plays a critical role during neuronal polarization and secretory trafficking has been shown to differentially transport proteins to both axons and dendrites. Besides the Golgi protein sorting, recent data revealed that palmitoylation cycles are an efficient mechanism to localize cytoplasmic, non-transmembrane proteins to particular neuronal compartments, such as the newly formed axon. Palmitoylation allows substrate proteins to bind to and ride with Golgi-derived secretory vesicles to all neuronal compartments. By allowing cytoplasmic proteins to 'hitchhike' on transport carriers in a non-polarized fashion, compartmentalized depalmitoylation may act as a selective retention mechanism.

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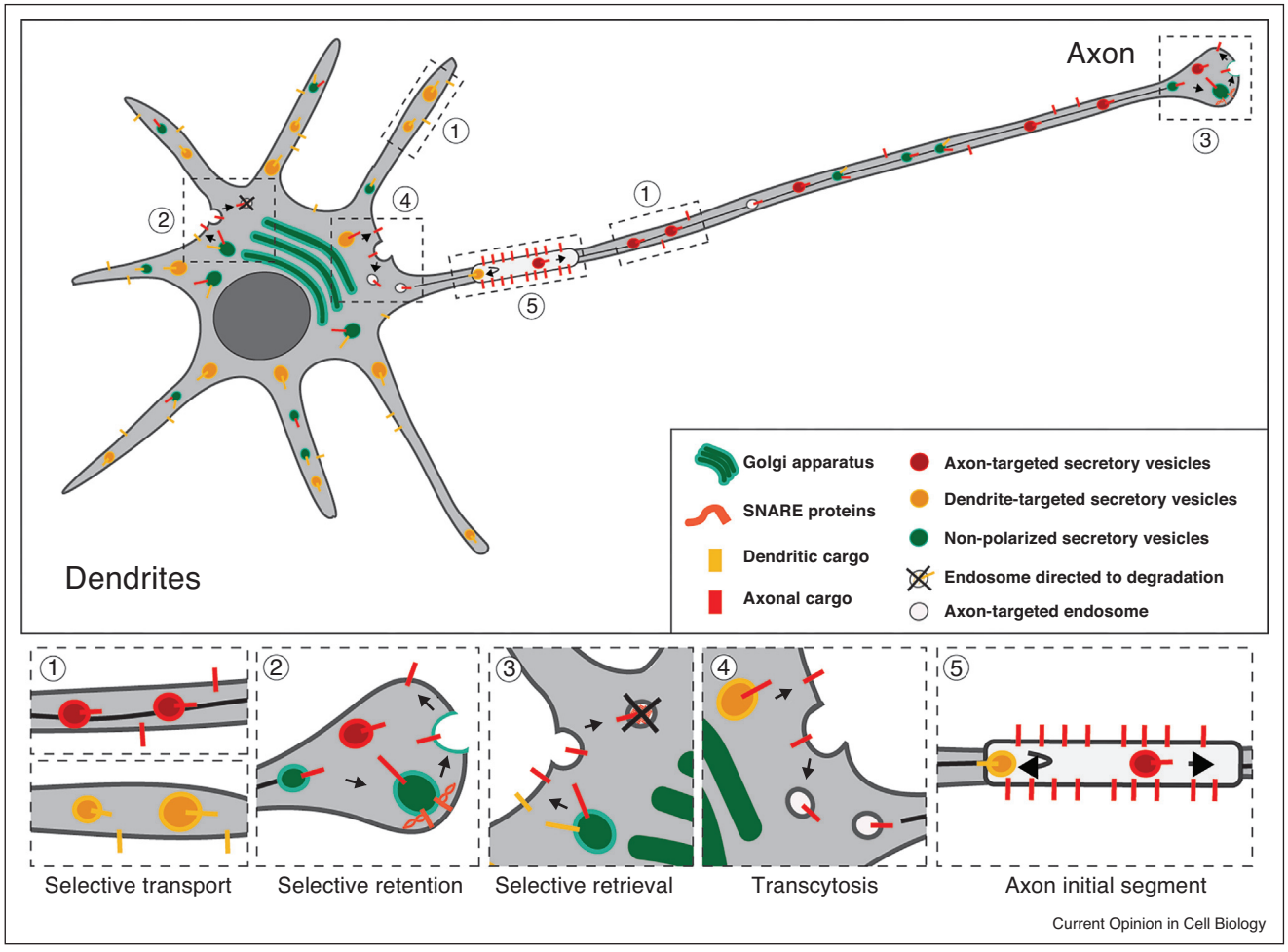
Introduction

Neurons are highly polarized cells with three main compartments: a cell body, an axon and several branched dendrites. In addition to these compartments, neurons also present specific subdomains essential for neuronal function such as pre- and post-synaptic terminals, growth cones and the axon initial segment (AIS). Like any other cell type, neurons contain a classical secretory pathway comprising the rough endoplasmic reticulum (RER), the ER-to-Golgi intermediate compartment (ERGIC), the Golgi complex and secretory vesicles, also called dense core or post-Golgi vesicles [1,2]. The secretory pathway is responsible for the synthesis and delivery of soluble factors, such as neurotrophins and neuropeptides that are secreted into the extracellular space. In addition, transmembrane proteins, such as ion-channels, adhesion molecules and neurotransmitter receptors use the secretory pathway to undergo posttranslational processing and to reach their final destination. While local protein translation and local secretory processing in axons and dendrites have been described, the majority of cytosolic and membrane proteins are synthesized in the cell body and distributed to either the axonal or dendritic compartments [3,4]. How axonal and dendritic proteins, produced in a common compartment, become differentially distributed to distinct destinations within neurons is an important question in neuronal cell biology. In this review, we provide an overview of the current models for polarized trafficking of membrane proteins and review recently discovered mechanisms by which cytoplasmic proteins are targeted to distinct neuronal compartments.

Polarized trafficking of membrane proteins through the Golgi apparatus

The Golgi complex plays a critical role during neuronal polarization [5,6]. Using primary neuronal cultures derived from rodents as a main model to study protein sorting, distinct mechanisms have been proposed to explain the axon and dendrite-specific distribution of transmembrane proteins (Figure 1). First, cargos such as cell adhesion molecule L1/neuronglia cell adhesion molecule (L1/NgCAM) or transferrin receptor (TfR) are delivered in a polarized manner from the cell body to either axons or dendrites, respectively [7–10]. Here, axonal and dendritic membrane proteins are sorted into distinct vesicles at the Golgi complex and selectively transported to their proper targets. Second, membrane proteins are delivered in a non-polarized fashion but fuse only with the correct target membrane. Here, compartment-specific soluble N-ethylmaleimide attachment protein receptor (SNARE) proteins coordinate the selective recognition between transport vesicles and target membrane. This mechanism has been shown to be involved in the polarized distribution of L1/NgCAM and neurexin (NRXN) [11]. Third, membrane proteins are delivered in a non-polarized fashion, followed by selective retrieval by endocytosis from one of the compartments [3]. For example, axonal membrane proteins like VAMP2 are delivered to both axonal and dendritic plasma membrane but are selectively endocytosed in dendrites [12]. Fourth, transcytosis has been described as another mechanism for axonal and dendritic localization. Here, membrane proteins are selectively trafficked to the axonal or dendritic surface, internalized by endocytosis and selectively

Figure 1



Mechanisms controlling axon and dendrite-specific distribution of transmembrane proteins. Polarized distribution of transmembrane proteins is mainly achieved by five different mechanisms: (1) selective transport from the Golgi apparatus to either axons or dendrites, (2) selective retention in or (3) selective retrieval from a specific compartment, (4) transcytosis and (5) the AIS. In the first case, dendritic and axonal proteins are sorted into different vesicles that are selectively transport into either axons or dendrites, where they fuse with the plasma membrane. In the second and third pathway, transmembrane proteins are transported in a non-polarized way to both, axons and dendrites. Missorted proteins are removed by endocytosis, whereas properly targeted ones remain in the right compartment. Here, selective recognition between vesicles and target membrane is mediated by compartment-specific SNARE proteins. In the fourth mechanism, axonal proteins are sorted into the somatodendritic compartment, inserted in the plasma membrane and subsequently endocytosed and transported into axons, where they fuse with the axonal membrane. Finally, the AIS acts as a diffusion barrier for plasma membrane proteins between the axon and the dendritic compartments.

targeted to the other compartment [13]. Transcytosis seems to be the preferred pathway for many axonal proteins such as L1/NgCAM, cannabinoid type 1 receptor (CB1R), the neurotrophin receptor tropomyosin receptor kinase A (TrkA), and the amyloid precursor protein (APP) [14–17]. Fifth, scaffolding molecules may also contribute to compartment-specific localization of transmembrane proteins. For instance, cytoskeleton and scaffolding proteins at the AIS restrict lateral movement of transmembrane proteins such as L1/NgCAM, the GPI-linked protein Thy-1 and concanavalin A (ConA), thereby maintaining protein compartmentalization [18,19]. Several parallel mechanisms are important to differentially distribute the same transmembrane protein and the relative importance of the different pathways described above remains unclear.

Mechanisms for selective sorting of membrane proteins at the Golgi complex

Before membrane proteins are transported to the axonal or dendritic compartment, they are packaged into distinct transport carriers at the trans-Golgi network (TGN). There, sorting adaptors recognize sorting signals within the cytoplasmic region of transmembrane proteins and concentrate them in the appropriate vesicles. Various ‘canonical’ sorting motifs, such as tyrosine-based motifs