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Specialization of biosynthetic membrane trafficking for neuronal form and function

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Neuronal growth and synaptic transmission require the continuous production of adhesion molecules, neurotransmitter receptors, ion-channels, and secreted trophic factors, and thus critically relies on the secretory pathway — the series of intracellular organelles including the endoplasmic reticulum (ER) and the Golgi apparatus (GA), where membrane lipids and proteins are synthesized. Commensurate with the gigantic size of the neuronal membrane and its compartmentalization by thousands of synapses with distinct compositions and activities, the neuronal secretory pathway has evolved to both traffic synaptic components over very long distances, and locally control the composition of specified segments of dendrites. Here we review new insights into the distribution and dynamics of dendritic secretory organelles and their impact on postsynaptic compartments.

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Distribution of dendritic secretory organelles

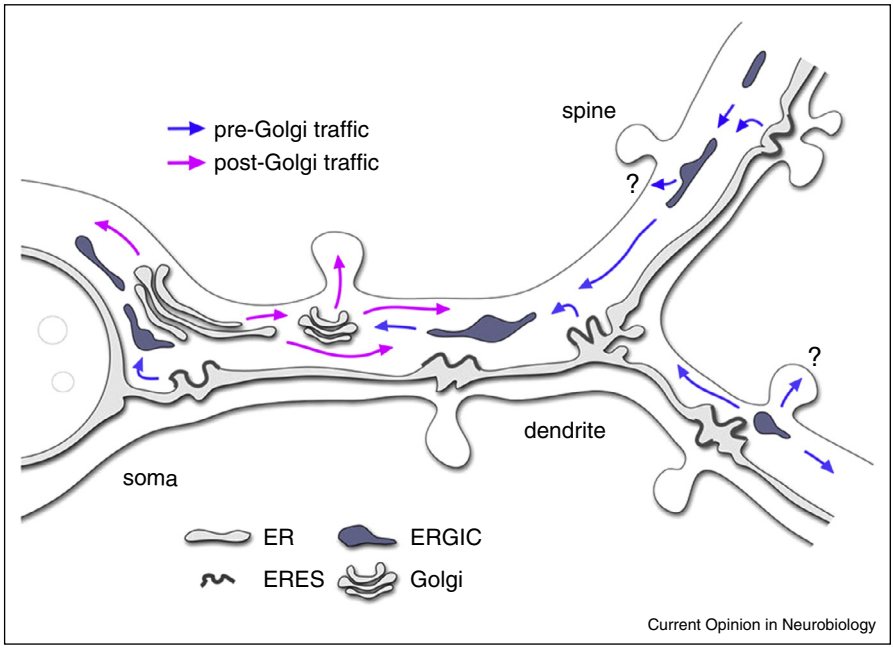
The organization of the neuronal secretory pathway and its involvement in neuronal development has been reviewed elsewhere [1,2]. Here we focus on our emerging understanding of the regulation and function of secretory trafficking in mature dendrites.

General organization of the dendritic secretory pathway

The general principles that govern the distribution of secretory compartments and the sequential processing of secretory cargo through these organelles are broadly similar between neurons and other eukaryotic cells (Figure 1). Most membrane and secreted proteins are synthesized and post-translationally modified [3,4] in the endoplasmic reticulum (ER), a continuous membrane system distributed throughout the entire cell (including the axon and some dendritic spines) [5–9]. The ER is also an important site for the synthesis and metabolism of lipids, serves as an intracellular compartment for Ca^{2+} signaling [10], and maintains direct physical contacts with other organelles, including the Golgi apparatus (GA), endosomes, mitochondria, and the plasma membrane [11]. Although the smooth ER (SER) predominates, components of the translocon and ER-bound ribosomes that identify the rough ER (RER) are found throughout dendrites [12–14], and are particularly frequent at branch points and close to synapses [15]. After quality control mechanisms that ensure proper folding, assembly, and initial post-translational modification, cargo exits the ER at discrete specialized ER-exit sites (ERES) distributed along the somatodendritic ER [15,16]. There cargo is incorporated into coat protein II (COPII) coated vesicles that bud off the ER and merge with the ER-Golgi intermediate compartment (ERGIC), a dynamic tubulo-vesicular system [17] distributed throughout the somatodendritic compartment [7,13,18,19••]. Cargo is shuttled along microtubules in labile and highly mobile ERGIC elements [19••] (see next section) and is concentrated at more defined locations. These include stable ERGIC clusters distributed in the somatodendritic compartment [19••], and polarized arrays of stacked membranes that mark the GA [5].

In the GA, cargo undergoes further maturation while progressing through the cis, medial, and trans cisternae. Cargo then reaches the trans-Golgi network (TGN) where it is sorted into multiple carrier systems defined by their coat proteins [20], and dispatched by microtubule-based transport to its destination, for example the endosomal system or the plasma membrane. The GA is also a microtubule organizing center and, in fibroblasts, extends microtubules towards the cell periphery [21]. As mature (hippocampal) neurons lack an active centrosome [22], the microtubule organizing function of Golgi membranes is likely critical for the vectorial targeting of membrane components to specific subcellular locations. Consistently, during neuronal development, the differential growth and remodeling of protrusions that are set to become the axon and the dendrites occurs in synergy with a spatial reorganization of secretory organelles [23], reflecting a need for a directed delivery of membrane components to growing neurites. The GA and resulting post-Golgi trafficking are directed first towards the newly specified axon to sustain its rapid growth [24,25]; and is

Figure 1



ER-Golgi trafficking in mature dendrites. Dendrites contain core machinery for early secretory trafficking including endoplasmic reticulum (ER), ER-exit sites (ERESs), ER-Golgi intermediate compartments (ERGICs) and occasionally Golgi outposts (GOs). Whereas ER, ERESs, and ERGICs are distributed throughout the somatodendritic compartment and in all dendrites, GOs, when present, localize to the most proximal segment of a subset of dendrites. As a consequence, post-ER carriers originating in dendrites lacking Golgi membranes must either be transported long distances back to the somatic Golgi or bypass the Golgi by utilizing ERGICs for subsequent processing and sorting.

then reoriented towards dendrites. This later process is particularly salient in pyramidal neurons where the preferential growth of the apical dendrite requires its direct spatial registration with the somatic GA [26].

In addition to these generic compartments, dendrites also occasionally contain neuron-specific organelles: the spine apparatus (SA) and Golgi outposts (GOs).

The spine apparatus

The dendritic ER often extends in dendritic spines where it occasionally adopts a specific conformation of stacked cisternae called the spine apparatus (SA) [5,27], whose formation and maintenance requires F-actin binding proteins including myosin Va [28] and synaptopodin [29]. The SA has features of both the ER and the GA. While stacked cisternae and markers such as giantin, mannosidase II, and Rab6 suggest an affiliation to Golgi membranes, its continuity with the dendritic ER and markers such as Rab1 and ERGIC53/p58 indicate an ER origin [30]. Similarly, ER-like cisternae positive for ER (Bip/Grp78) and Golgi markers (CTR433) have also been described close to inhibitory synapses [7]. The SA contains AMPA and NMDA receptors [31,32] and regulates specific forms of synaptic plasticity [29,33]. The SA occasionally displays coated membranes [34], which suggests that it locally engages in membrane trafficking. Yet, its involvement in the processing of nascent synaptic proteins is still elusive.

Dendritic Golgi outposts

In addition to the 'central' GA that is found around the nucleus in the cell body, dendrites occasionally contain mini-Golgi stacks [7,13,26,35–38] called Golgi outposts (GOs), which act as satellite Golgi membranes for the local processing of nascent secretory cargo[1]. GOs play important functions during dendritogenesis, a process that has been particularly well described in neurons of the body wall of *Drosophila* larvae. In this system, GOs are found throughout dendrites [38], including their terminal segments, and shape dendritic geometry by locally directing membrane trafficking [38] and microtubule elongation [39,40••], to sustain the growth and remodeling of emerging dendritic branches.

In mammalian cortical and hippocampal neurons, the frequency of GOs increases during the period of intense dendritic growth [35], seemingly through the fission of long tubules that emerge from the somatic Golgi. This process occurs through a RhoA-Rock mechanism that involves proteins such as LIMK1, cofilin, and PKD [41•], and brain-specific RhoA interacting proteins such