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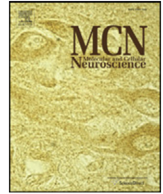

Review

Neuronal protein trafficking: Emerging consequences of endoplasmic reticulum dynamics

José Ignacio Valenzuela [a,b], Matías Jaureguiberry-Bravo [a,b,c], Andrés Couve [a,b,*]

[a] Programa de Fisiología y Biofísica, Instituto de Ciencias Biomédicas, Facultad de Medicina, Universidad de Chile, Santiago, Chile
[b] Biomedical Neuroscience Institute (BNI), Universidad de Chile, Santiago, Chile
[c] Escuela de Bioquímica, Facultad de Ciencias Biológicas, Universidad Andrés Bello, Santiago, Chile

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ABSTRACT

The highly polarized morphology and complex geometry of neurons is determined to a great extent by the structural and functional organization of the secretory pathway. It is intuitive to propose that the spatial arrangement of secretory organelles and their dynamic behavior impinge on protein trafficking and neuronal function, but these phenomena and their consequences are not well delineated. Here we analyze the architecture and motility of the archetypal endoplasmic reticulum (ER), and their relationship to the microtubule cytoskeleton and post-translational modifications of tubulin. We also review the dynamics of the ER in axons, dendrites and spines, and discuss the role of ER dynamics on protein mobility and trafficking in neurons.

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Introduction

Neural function is regulated by the delivery and removal of synaptic proteins to and from pre, post or extrasynaptic sites. Neuronal protein trafficking may thus be considered a fundamental cellular substrate for complex brain functions. Two major modalities mediate protein trafficking in neurons. In a canonical route newly synthesized proteins exit the somatic ER, mature in the somatic Golgi apparatus and reach the plasma membrane riding on post-Golgi carriers. In the more recently described non-canonical modality proteins are either synthesized locally from dendritic mRNAs and trafficked through satellite Golgi outposts to their insertion sites, or synthesized in the somatic ER, mobilized distally through the ER

* Corresponding author at: Programa de Fisiología y Biofísica, ICBM, Facultad de Medicina, Universidad de Chile, Independencia 1027, Santiago, Chile. Fax: +56 2 777 6916.
E-mail address: andres@neuro.med.uchile.cl (A. Couve).

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network and exported through specialized exit sites (ERES) in dendrites for local Golgi outpost trafficking and plasma membrane delivery (Horton and Ehlers, 2003).

In the latter modality the local ER network in dendrites, dendritic spines and axons is a critical component. In this context, two crucial functions of the ER may be envisioned. First, the ER in dendrites, and presumably spines, allows the local translation of mRNAs encoding signal peptide-containing proteins, thus bypassing the somatic ER (Bramham and Wells, 2007). Although this is still somewhat controversial all the major biosynthetic organelles have been described in spines (Pierce et al., 2001). Second, the ER network constitutes a continuous, non-vesicular transport system for proteins synthesized throughout the neuron (for a recent review see Ramirez and Couve, 2011).

The mechanisms underlying the morphology and dynamics of the ER have received considerable attention, but how the constantly changing architecture of the organelle controls the point-to-point movement of proteins through the ER, and how this mobility contributes to protein trafficking in long cellular specializations like dendrites and axons are still largely unanswered questions. These issues constitute the focus of this review.

ER morphology: conserved sheets and tubules

The ER is responsible for Ca^{2+} and lipid metabolism, and for the synthesis and post-translational modification of most secreted and membrane proteins. It is a continuous and heterogeneous organelle with functionally and spatially defined sub-compartments: the nuclear envelope, the rough ER, and the smooth ER. A central question is how this irregular, but highly connected organelle generates and maintains these distinct subcompartments. Recently a variety of proteins that shape and modulate the structure of the ER, composed by sheets and tubules, have been described. ER sheets are enriched in proteins of the translocon family (Dad1, TRAPα and Sec61β) (Shibata et al., 2010). Additionally, proteins containing a single transmembrane segment with a coiled-coil domain essential for membrane shaping (Climp-63, p180 and Kinectin) are also preferentially distributed to ER sheets (Shibata et al., 2010). Climp-63 probably acts as a membrane spacer by forming intramolecular bridges that maintain a constant distance between ER sheets (approximately 50 nm in mammalians cells) (Shibata et al., 2010). High-curvature ER tubules, on the other hand, are enriched in different classes of proteins, namely reticulons and DP1/Yop1p (Voeltz et al., 2006). These act as stabilizers by providing a large hairpin segment that spans the lipid bilayer forming a hydrophobic wedge that curves the ER tubule and maintains its diameter (approximately 60–100 nm in mammalian cells) (for review see Park and Blackstone, 2010). Not surprisingly, curvature-generating proteins also localize to the highly bent membranes at the edge of ER sheets. Regulating the abundance of reticulons in sheet edges and tubules may constitute a unifying mechanism to dynamically define the ratio between structurally different ER subcompartments (Shibata et al., 2010).

The ER morphology is highly conserved in the majority of eukaryote cells, but the distribution and proportion of the different subcompartments can vary in specific cell types. In neurons the ER present in the soma and the proximal somatodendritic compartment is principally rough ER (Krijnse-Locker et al., 1995), whereas a smooth ER with fewer polyribosomes predominates in more distal dendrites and forms a continuous tubular network that localizes near the cortex of the cytoplasm (Broadwell and Cataldo, 1983; Cooney et al., 2002; Martone et al., 1993; Spacek and Harris, 1997). In axons the ER is also a tubular structure, containing constituents of the protein folding machinery and components of the COPII complex that support axonal outgrowth (Aridor and Fish, 2009; Broadwell and Cataldo, 1984; Droz et al., 1975; Tsukita and Ishikawa, 1976).

Motility of the tubular ER network

The tubular ER network is a highly dynamic structure that is constantly remodeled by three distinct mechanisms (Bola and Allan, 2009). First, rapid tubule elongation or ER sliding occurs along existing, preferentially acetylated, microtubules (Friedman et al., 2010). ER sliding depends on kinesin-1 and dynein that extend tubules to the cell periphery or retract them towards the cell center

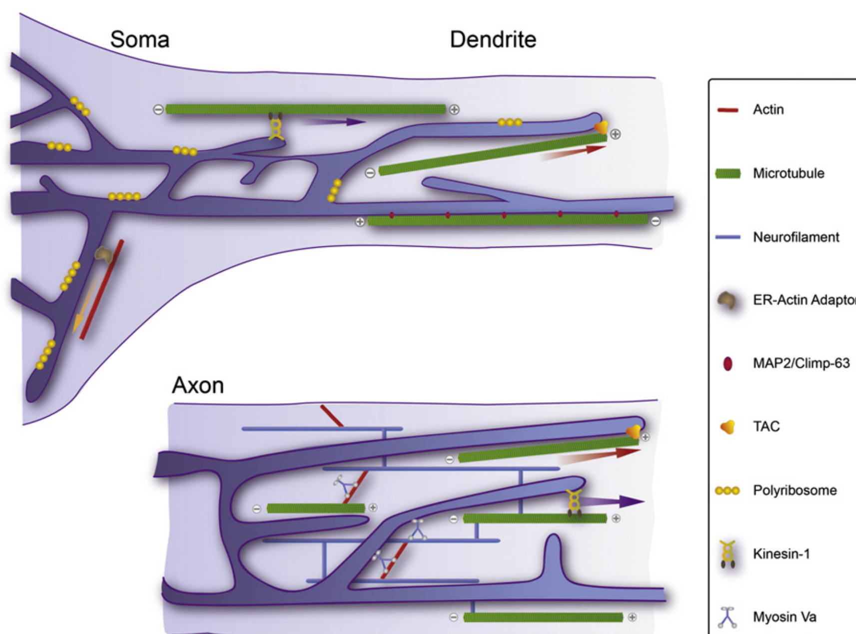

Fig. 1. Structure and dynamics of the ER in dendrites and axons. The ER in dendrites is a continuous tubular network associated to the cytoskeleton. MAP2 attaches the ER to the microtubule cytoskeleton via Climp-63. As in non-neuronal cells ER motility may occur through kinesin-1 dependent rapid tubule extension (purple arrow), TAC mediated extension (red arrow) or actomyosin-based retrograde flow (orange arrow). The linker to the actin cytoskeleton has not been identified. Similar mechanisms could operate in axons, in the context of a unipolar arrangement of microtubules. Additionally, neurofilament and myosin Va-mediated anchoring contribute to maintain the integrity and distribution of the ER. For simplicity dynein is not shown.

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