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Review

The axonal endoplasmic reticulum and protein trafficking: Cellular bootlegging south of the soma

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ABSTRACT

Neurons are responsible for the generation and propagation of electrical impulses, which constitute the central mechanism of information transfer between the nervous system and internal or external environments. Neurons are large and polarized cells with dendrites and axons constituting their major functional domains. Axons are thin and extremely long specializations that mediate the conduction of these electrical impulses. Regulation of the axonal proteome is fundamental to generate and maintain neural function. Although classical mechanisms of protein transport have been around for decades, a variety newly identified mechanisms to control the abundance of axonal proteins have appeared in recent years. Here we briefly describe the classical models of axonal transport and compare them to the emerging concepts of axonal biosynthesis centered on the endoplasmic reticulum. We review the structure of the axonal endoplasmic reticulum, and its role in diffusion and trafficking of axonal proteins. We also analyze the contribution of other secretory organelles to axonal trafficking and evaluate the potential consequences of axonal endoplasmic reticulum malfunction in neuropathology.

Contents

1. Introduction: spatio-temporal control in the nervous system

The nervous system allows multicellular animals to establish and adapt their interactions with the environment by transmitting information in the form of electrical impulses. Long distance and direction are two fundamental aspects of the system's functionality, and to improve performance neurons have evolved into large cells. Additionally, morphology has become significantly more complex than in other cell types, with polarized axons and dendrites mediating communication among local or with distant neural circuits (Fig. 1a). It is undeniable that the length of axons in large animals, such as living or extinct mammals, and reptiles including dinosaurs is an awesome evolutionary achievement of the cellular machinery (Fig. 1b). To illustrate this point the longest neurons in whales may exceed 30 m, while the recurrent laryngeal nerve in long-necked

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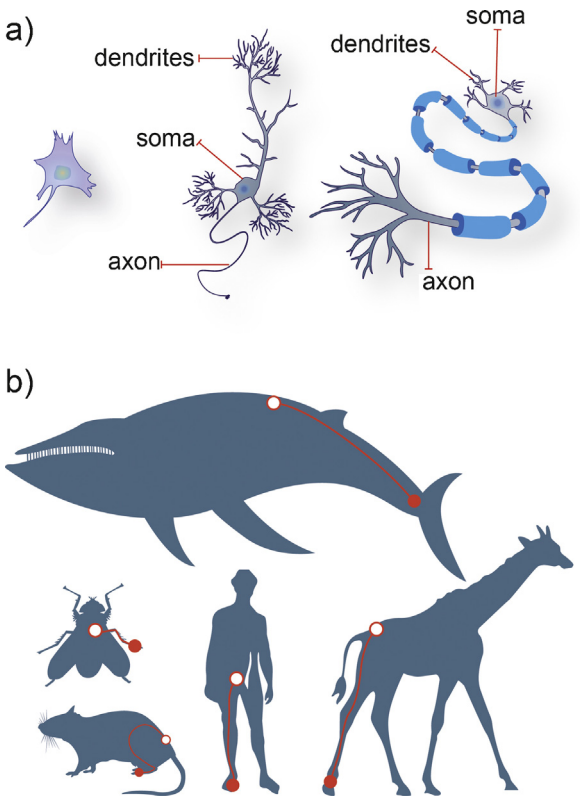

Fig. 1. Architecture and size are defining properties of neurons. (a) Comparative morphology and size of a non-polarized cell and neurons. Compared to most eukaryotic cells neurons from the central and peripheral nervous system are highly polarized with dendrites and axons extending long distances from the cell body. They have also evolved surface areas that may be up to 10,000 times greater than other cell types. Axons of the central and peripheral nervous system may be unmyelinated (center) or myelinated (right). Myelination (blue) increases the conduction velocity of electrical impulses. The drawings represent a non-polarized cell (left), a typical unmyelinated pyramidal neuron of the mammalian central nervous system (center) and a myelinated neuron such as those found in sensory and motor fibers of mammalian peripheral nerves (right). (b) Axonal length in different animals. Axonal length is highly variable within the nervous system of an organism. In addition, axons in different animals range from a few microns to meters in large mammals. Lengthy nerves in mammals include the sciatic nerve that run from the lower spinal cord to the lower extremity and is responsible for motor and sensory conduction (red). These can measure in the order of cms in small mammals like the rat, close to a meter in humans and several meters in large mammals like the giraffe and large cetaceans. Another extreme example is the left recurrent laryngeal nerve of the giraffe, which can measure up to 5 m.

mammals such as giraffes approaches 5 m and may have reached 38 m in long-necked sauropods [1].

Considering neuronal size and architecture, it is reasonable to postulate that crucial functions such as intercellular communication, intracellular signaling, energy production and consumption, and transport across the cell membrane will be regulated in a domain and temporal-specific manner. Regulating the abundance of protein, RNA, lipids and other macromolecules locally certainly impinges on these compartmentalized cellular functions during development, maintenance, plasticity and repair of neural tissue.

Axons are constituted by distinct morphological and functional domains that include the axon initial segment, the axonal shaft, Nodes of Ranvier (and the multiple specializations that encompass the nodal and internodal regions in myelinated axons), and the axon terminal or presynaptic specialization [2]. In this review we will concentrate on the control of the axonal proteome as a fundamental cellular process. Although in strict sense the proteome constitutes the entire repertoire of proteins present at a given moment within a specific domain, we will refer mostly to that part of the proteome that includes secreted and membrane proteins. Importantly, endocytosis and recycling of axonal components such as receptors, signaling molecules and synaptic vesicles [3–5] also play fundamental roles in regulating the proteome and are still topics of intense research, but is mostly anterograde protein trafficking that has continued to challenge the classical views of domain-specific regulation. Thus, we will focus on the mechanisms that allow the control of the proteome *via* direct transport and the contribution of the axonal endoplasmic reticulum (ER) to axonal biosynthesis and trafficking. Since these may operate independently of somatic or dendritic mechanisms we will refer to them as local regulation. We will also analyze the implications for pathology. We are aware that glial cells such as oligodendrocytes and Schwann cells play crucial roles in the control of local neuronal function in the central and peripheral nervous systems, but these topics have been carefully analyzed elsewhere and will not be directly considered here (reviewed in [6,7]).

2. Regulation of the axonal proteome

2.1. Axonal transport: classical transport models

A tight regulation of the axonal proteome is necessary for diverse processes such as the establishment and maintenance of neuronal polarity [8,9], axon growth and guidance [10], synapse formation and plasticity [11] and nerve regeneration [12–14]. One plausible mechanism to exert control over the abundance of axonal proteins is by transport of ready-made components.

Axonal transport is the intracellular movement of material away or toward the cell body that starts during development and continues throughout the life of the neuron. The study of axonal transport began more than 50 years ago fueled by the need to understand the intracellular dynamics that support growth, maintenance and repair of nerve fibers [13–15]. It was widely accepted initially that subcellular organelles and membrane components in axons and dendrites originated exclusively in the cell body. Classical studies of anterograde transport revealed the rate of transport of *de novo* synthesized proteins that reached the optic tectum from the retina by injecting radioactive leucine into the eyes of goldfish [16]. This knowledge gave rise to the influential concepts of fast and slow axonal transport that regulate the availability of axonal components *via* anterograde and retrograde mobility.

Fast axonal transport corresponds to the anterograde, retrograde and bidirectional movement of membrane bound cargoes propelled by the action of molecular motors along microtubules. The average velocities of fast axonal transport range between 50–400 mm/day (approximately 0.6–5 μm/s) [17]. Fast axonal transport is supported by microtubules arranged longitudinally with their plus ends pointing away from the neuronal soma [18]. This organization favors the directional mobility of molecular motors such as kinesins and the dynein complex [19], which transport and deliver cargoes to microtubule plus or minus ends in an ATP-dependent manner. A compelling body of evidence indicates that kinesins are involved in the anterograde transport of organelles, such as mitochondria, protein complexes and ribonuclear particles, whereas dynein promotes the retrograde transport of organelles such as endosomes, mitochondria, the Golgi apparatus, lysosomes and autophagosomes [19,20] (Fig. 2a).

Slow axonal transport corresponds to the movement of cytoskeletal polymers, cytosolic protein complexes and ribosomes at averages velocities of 0.2–8 mm/day (approximately 0.002–0.09 μm/s) [17]. Examination by live-cell imaging of cytosolic proteins enriched at the presynaptic terminal, such as synapsin and CamKIIa, has recently clarified the molecular

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