Multiple layers of spatial regulation coordinate axonal cargo transport
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Abstract
Nerve axons are shaped similar to long electric wires to quickly transmit information from one end of the body to the other. To remain healthy and functional, axons depend on a wide range of cellular cargos to be transported from the neuronal cell body to its distal processes. Because of the extended distance, a sophisticated and well-organized trafficking network is required to move cargos up and down the axon. Besides motor proteins driving cargo transport, recent data revealed that subcellular membrane specializations, including the axon initial segment at the beginning of the axon and the membrane-associated periodic skeleton, which extends throughout the axonal length, are important spatial regulators of cargo traffic. In addition, tubulin modifications and microtubule-associated proteins present along the axonal cytoskeleton have been proposed to bias cargo movements. Here, we discuss the recent advances in understanding these multiple layers of regulatory mechanisms controlling axonal transport.

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Introduction
Depending on the type of neuron, axons range from just a millimeter to more than a meter long, with motor neuron axons being the longest in the human body, stretching from the base of the spinal cord all the way to the toes. The axon is exquisitely built as a thin, elongated cylinder to allow electric signals to quickly travel down and transmit information to neurons, muscles, and glands at great distance from the soma. The structure of axons in various neuronal subtypes is generally the same: a single extended process that protrudes from the cell body and branches out to form synaptic connection with target cells either along the length of the axon stem or at their tips. The axon joins the cell body at a specialized junction called the axon initial segment (AIS). Because of the long distance between the soma and the axonal processes, many basic cellular processes required for proper axonal function are pushed to their physical limits. Therefore, an efficient and well-orchestrated axonal trafficking system has evolved that precisely coordinates interaction between cargos, motor proteins, and cytoskeleton to spatial and temporal regulation cargo movements. The general interest in axonal cargo mobility started by reports from Robert Allen and Scott Brady in 1982 where video microscopy was used to monitor transport of organelles in giant squid axons [1]. Since these initial publications, many cell-biology laboratories have focused on unraveling the molecular, bio-physical, and cellular mechanisms underlying axonal transport. In addition, mutations in various human genes encoding components of the axonal transport machinery have been implicated in a variety of neurological disorders, suggesting that perturbations in axonal transport are integral to the pathogenesis of neurological diseases [2]. In this review, we will focus on the most recent advances in elucidating the spatial mechanisms that regulate axonal cargo movement. We will discuss how modifications and structural components of the microtubule (MT) cytoskeleton (“tubulin” and “MAP” codes) and membrane-associated specializations (AIS and membrane-associated periodic skeleton [MPS]) at specific locations along the axon act together to precisely regulate the movement of cargos up and down the axon.

MT-associated proteins and tubulin modifications control axonal transport
The MT cytoskeleton comprises the tracks along which molecular motors drive long-distance transport in the axon. The uniform organization of axonal MTs with their plus-ends toward the distal processes allows plus-end-directed kinesin motors and minus-end-directed dynein
to driving cargo transport in the opposite direction along the axon. The various tubulin posttranslational modifications (PTMs) and tubulin nucleotide binding states (i.e., guanosine triphosphate [GTP] or guanosine diphosphate [GDP]) as well as MT decoration by MT-associated proteins (MAPs) have been proposed as additional layers of regulation on axonal transport (Figure 1). For example, tubulin polyglutamylation has attracted recent attention as a potential regulator of neuronal trafficking. Polyglutamylation generates branch chains of glutamate residues on both α- and β-tubulin subunits in neurons via the tubulin tyrosine ligase-like family of enzymes. Two studies have recently shed light on the role of tubulin polyglutamylation in regulating motor activity. In vitro motility assay revealed that KIF1A, the predominant kinesin-3 motor in axons, is paused by c-terminal polyglutamylated tubulin via a specific interaction of its K-loop (also known as the elongated loop 12 [L12]) in the conserved kinesin motor core [3]. Support for this mechanism comes from a study in cultured neurons, where tubulin hyper-glutamylation induced by blocking deglutamylases led to disruption of multiple cargo trafficking pathways [4]. This study showed that increased tubulin polyglutamylation reduced the KIF1A-dependent axon transport of secretory vesicles, confirming the role of polyglutamylation in reducing KIF1A motility. However, as that study demonstrated that hyperglutamylation also disrupts kinesin-3-independent trafficking as well as retrograde transport, it should be further examined whether different motor protein families have different sensitivity to tubulin glutamylation and what is the more general role PTMs play in controlling neuronal trafficking, for instance, by recruiting specific MAPs to axonal MTs. In addition to PTMs, the tubulin nucleotide binding states (i.e., GTP or GDP) has also been proposed to control axonal trafficking. In neurons, it is well established that the MTs are formed in an acen-trosomal fashion [5]. Recently, axonal presynaptic sites have been shown to serve as hotspots for de novo, noncentrosomal MT nucleation generating dynamic MTs rich in GTP tubulin [6,7]. By combining in vitro and live cell imaging in neurons, Guedes-Dias et al. could show that KIF1A preferably binds and walks on GDP tubulin and not GTP tubulin and that GTP tubulin at dynamic ends of MT at presynaptic boutons is the preferred site for KIF1A unloading from the MT track to locally release cargos. The interaction between motors and nonenzymatic MAPs is another emerging regulatory mechanism of cargo transport. Systematic analysis of the effects of six MAPs, such as MAP7 and MAP9, on three classes of transport motors revealed distinct influences of specific MAPs on kinesin-1, kinesin-3, and dynein motor movements [8]. In accordance with previous reports [9–11], Monroy et al. confirmed the role of MAP7 in recruiting kinesin-1 to

Figure 1

Microtubule post translational modification and microtubule-associated proteins locally controls axonal transport processes. The cartoon highlights various examples of how microtubules (MT), microtubule-associated proteins (MAPs), and posttranslational modifications (PTM) exert control over different trafficking processes at specific sites along the axon. At the axon initial segment (AIS), TRIM46 links microtubules into parallel bundles and MAP6 binds the interior of the lattice and stabilizes MTs as bent fibers. Nudel interacts with Ankyrin-G and activates dynein-based retrograde transport. MAP7 family proteins, including MAP7D2 at the AIS, recruits and stimulates kinesin-1 microtubule binding and cargo transport, whereas blocking Kinesin-3 in TRIM46-dependent manner. Actin-based Myosin V motors halt kinesin-1 cargo transport through the AIS by binding to immobile actin patches. Polyglutamylation along the MT lattice blocks Kinesin-3 binding to MT. MAP9 recruits kinesin-3 and blocks kinesin-1 binding and motility. At the presynapse, GTP-rich dynamic MT promote the dissociation of Kinesin-3 motors to facilitates local release of synaptic vesicles.
MT and shows it has an inhibitory effect on kinesin-3 binding. The authors also describe a novel function for MAP9, which in contrast to MAP7, selectively allows kinesin-3 motor KIF1A MT binding but not kinesin-1 motility. MAP9 enhancement of KIF1A motility depends on the K-loop region in the motor domain, which is the same region that recognizes and enables polyglutamylated tubulin to pause KIF1A [3], suggesting that the K-loop of KIF1A is a region for specific and opposite regulation by MAPs and MT modifications. Interestingly, human KIF1A mutations in the K-loop have been recently identified as a possible underlying cause of a spectrum of hereditary neurological disorders, including spastic paraplegia, sensory neuropathy; and Rett syndrome [12], thus highlighting the importance of proper kinesin regulation by specific MT subsets for neuronal health.

The specialized AIS cytoskeleton organization controls axonal transport

The AIS is a subcellular membrane specialization at the interface between the neuronal cell body and the axon shaft. Beyond its well-known role in generating action potentials, accumulating evidence shows that the AIS also functions as a selective filter for cargo transport in and out of the axon. The importance of the AIS structure is highlighted in a review by Stevens and Rasband in this issue, which focuses on the neuropathological function of the Ankyrin family of proteins, whose AnkG and AnkB members are key scaffold proteins that link the membrane and cytoskeletal components of the AIS [13]. Unraveling the elaborate molecular structure of the AIS is indeed key to our understanding of its functions—the Rasband lab recently used proximity biotinylation and mass spectrometry to identify the AIS proteome and found a variety of AIS components that regulate axonal architecture and cargo trafficking [14]. For example, they identify Ndel1, which was previously described as a regulator of dynein-mediated cargo trafficking at the AIS [15,16], the AIS-associated MT cross-linking factor TRIM46 [17] and MT-stabilizing protein MAP6 [18] (Figure 1). Interestingly, MAP6 has recently been shown to localize in the lumen of MTs and induce stable MTs to coil into a left-handed helix [19]. Further work will be needed to tease out the specific functions of these unique AIS-enriched MAP6-induced MTs. Previous studies have shown that AIS “actin patches” in the proximal axon selectively prevent certain cargos to pass through the AIS and entering the axon while allowing the passage of others [20]. Elegant chemically induced recruitment assays showed that kinesin-driven cargos entering the axon are arrested upon myosin V activation and accumulated in distinct actin-rich patches [21] and that the combined activity of kinesin and myosin motors at the AIS determines the destination and selectivity of neuronal cargo transport. Instead of halting cargos at the AIS, a recent study described an opposing mechanism that promotes kinesin-mediated cargo trafficking into the axon [22]. Pan et al. found that the MT-associated protein MAP7 family member MAP7D2 specifically localizes to AIS and promotes the processive transport of the kinesin-1 motor and its cargos toward the distal axon. As noted previously, the role of MAP7 family proteins in increasing MT binding and processivity of kinesin-1 through transient association with the motor was reported by multiple independent studies [8–11] and suggest that MAP7 members redundantly regulate kinesin-1-dependent transport by acting as MT-tethered recruitment factors and activators. These data may indicate that the AIS enrichment of MAP7D2 at the proximal axon is a specific adaptation to enhance kinesin-1-mediated axonal transport at the AIS. Interestingly, MAP7D2 localization at the AIS is independent of the scaffolding protein Ankyrin-G, yet depends on TRIM46 [22]. TRIM46 has an essential role in organizing parallel MT fascicles at the proximal axon [23] and forming the AIS during the early stages of neuronal development [24]. TRIM46 promotes further AIS maturation by facilitating retrograde transport of endocytosed AIS-specific adhesion molecules, such as Neurofascin-186, from the distal to the proximal axon [24]. However, a precise mechanism by which TRIM46 at the AIS modulates spatiotemporal control of bidirectional axonal cargo transport remains to be further elucidated. Nevertheless, it is likely that the coordination of myosin, kinesin, and dynein motor activities on a particular cargo by the unique actin and MT cytoskeleton architecture at the AIS determines the selectivity and destination of axonal cargo transport at this gateway. In addition, as anterograde axonal cargo transport relies on multiple different types of kinesins present on particular cargos, it will be important to determine what the individual contributions of kinesin motors are during axonal trafficking and whether they can act simultaneously on the same cargo.

Actin–spectrin rings control radial contractility and axonal transport

The role of the actin cytoskeleton in axonal cargo transport has mostly been described as local control over cargo mobility at confined domains such as the actin patches at the AIS and at presynaptic boutons via myosin motors for short-range cargo trafficking and delivery. The discovery of 190 nm-spaced, periodic actin–spectrin ring structure starting at the AIS and extending throughout the length of the axon, also termed MPS, brought many new biological questions regarding the functional relevance of this specialized structure [25] (Figure 2). As we will focus here on the MPS interplay with axonal organelle and signal transport, readers may refer to the review by Christophe Leterrier for an in-depth summary of the MPS molecular organization and its emerging cellular functions in this issue [26]. Initial studies showed that MPS contributes to both the
structure and function of the axon by acting as a scaffold to maintain the axonal MT organization and as a barrier to limit the lateral diffusion of membrane proteins to the 190 nm spectrin-rich spacing between actin rings [27,28]. A recent study has proposed that the MPS act as local signaling platforms where various signaling molecules are recruited in response to extracellular stimuli [29]. For example, MPS acts as scaffold for the transactivation of neuronal receptor tyrosine kinase TrkB by the cannabinoid type 1 CB1 G protein-coupled receptor. Interestingly, the study revealed a negative feedback loop between the downstream Extracellular-Regulated Kinase (ERK) signaling activated by TrkB, which subsequently disrupts the MPS structure and thus inhibits its transactivation. Another study from the same group describes a role of the MPS in sensing and transmitting retrograde axon-degenerative signaling from the distal axon to the soma under neurotrophic factors deprivation [30]. The disassembly of the MPS in the axon occurs before and independently of the secondary apoptotic signaling arriving from the soma, which involves Dual Leucine zipper Kinase (DLK) signaling, c-Jun phosphorylation, and Caspase-3 activation. Consistently, prolonged nonmuscle myosin II inactivation or loss-of-function mutants disrupting the MPS structure leads to the formation of focal axon swelling, a hallmark of axonal degeneration [31]. These studies highlight the cross-talk between the MPS structure and neurotrophic and degenerative signaling that use axonal transport for their propagation [32]. Intriguingly, the actomyosin network of the MPS along the axon shaft has recently been found to control the axonal diameter and local radial contractility and thus local transport dynamics [33]. Using live imaging of cultured neurons with superresolution microscopy, Wang et al. were able to visualize the dilation and contraction of actin rings and its spatiotemporal correlation with retrograde passage of large endosomal and lysosomal cargo. This study shows that the MPS actomyosin contractility facilitates the transport of large-sized cargos along the axon and suggests this newly identified structure may carry additional roles in the regulation of axonal trafficking.

Future perspective

Our understanding of the molecular mechanisms underlying axonal cargo transport has grown considerably in the decades since the publication of Allen and Brady’s seminal study of intracellular transport in squid axoplasm. The plus-end-out MT organization in axons and plus-end-directed kinesin movement have been shown as the fundamental basis for axon-selective cargo transport [34], yet many additional layers of regulation have been since uncovered. For example, the AIS is thought to function as specialized cargo filter that selectively prevents nonaxonal cargos from entering the axon while allowing the passage of other organelles. In addition, the newly discovered functions of the MPS in axonal signaling and cargo transport are only beginning to be unraveled. There is now accumulating evidence that both PTMs and MAPs have the capacity to strongly
bias directed cargo movement and that different motor proteins show different sensitivity to different combinations of MAPs and tubulin modifications. Recent reports refer to the observed effects as the “tubulin codes” and “MAP codes,” suggesting different regulatory levels. However, previous data have demonstrated that MT PTMs could lead to differential binding of various MAPs along the MT arrays, modulating axonal MT architecture and subsequently interfering with the processivity of specific motor proteins. It will be important to precisely dissect the different levels of transport regulation to determine the most relevant and effective spatiotemporal control mechanisms. Yet, to correctly deliver specific cargo into and out of the axon, local trafficking processes and sorting signals need to be integrated into the transport machinery. It will be critical to dissect the complex sorting rules of the neuronal endosomal and secretory pathways. For example, Riberio et al. followed the newly synthesized presynaptic adhesion molecule Neurexin and revealed that the receptor is initially rerouted toward the axon via recycling endosomes [35]. Moreover, it is important to understand to what extent various axonal proteins are transported in separate transport vesicles. A recent study found that the trafficking of various Ranvier node membrane proteins in sensory neurons is sorted and transported into separate axonal secretory vesicles, although they all share the same carrier for retrograde transport [36]. The complexity of neuronal transport should be met with recently developed molecular toolboxes, such as endogenous cargo labeling [37], inducible trafficking assays [38], and tunable optogenetic motor-cargo coupling [39,40], which will bring exciting discoveries to unravel the mechanisms axonal locomotion.

Conflict of interest statement
C.C.H. is an employee of Genentech Inc., a member of the Roche Group.

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