Symposium

Integrating Cytoskeletal Systems in Neurons and Glia: Dynamic Orchestration of Structure and Function

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Neurons and glia form the circuitry of our nervous system, allowing nerve cells to communicate with each other and other cell types throughout the body in a highly specific manner to integrate sensory, motor, and cognitive functions. The ability of these cells to do this is profoundly dependent on an elaborate and dynamic cytoskeleton which allows these cells to adopt complex shapes and specialized structures such as myelin sheaths, the blood–brain barrier, axonal growth cones, dendritic spines, nodes of Ranvier, synapses, and elaborate sensory organs. The cytoskeleton is also critical for morphogenetic movements, the migration of neuronal precursors, and axon growth, which together establish the organization and wiring pattern of the central and peripheral nervous system during development. This review provides a primer on our current understanding of the cytoskeleton of neurons and glia, with an emphasis on how the protein polymers of the cytoskeleton—microtubules, actin filaments, intermediate filaments, and septins—work together to orchestrate the remarkable shapes and functions of these cells. We also highlight key questions and challenges for the field and technological advances that may help address them.

Key words: **actin; glia; intermediate filament; microtubule; neuron; septin**

What Is the Cytoskeleton?

The architecture and function of nervous systems is dependent on the ability of neurons and glia to form highly complex morphologies (Ascoli et al., 2007, Ascoli 2023). For example, neurons extend long branched processes called axons and dendrites which form the wiring pattern of the nervous system, allowing these cells to communicate with each other and with other cells over long distances. These processes can form elaborate cellular specializations such as growth cones, synapses, dendritic spines, nodes of Ranvier, and axon initial segments (Fig. 1) which are critical for neuronal development and function. Similarly, glial cells adopt complex branched shapes that mediate diverse functions such as myelination, the blood–brain barrier, and tripartite synapses (Fig. 1).

The ability of neurons and glia to form and maintain such complex morphologies and structures is made possible by an elaborate and dynamic three-dimensional (3D) network of cytoplasmic protein polymers and accessory proteins called the cytoskeleton, composed of microtubules, microfilaments (actin filaments), intermediate filaments, and septins (Brady and Kirkpatrick, 2011). These polymer systems do not function in isolation and are tightly integrated to establish neuronal and glial morphology as well as to orchestrate the intracellular traffic which maintains their polarized shapes. In addition, all of the cytoskeletal components are subject to complex regulation by phosphorylation, ubiquitination, and other posttranslational modifications, which orchestrate their coordinated cross talk and can impact assembly, disassembly, transport, and scaffolding of binding partners. Newer insights reveal that many of them also modulate and spatially organize signaling cascades downstream of guidance cues or neurotransmission, adding an additional layer of coordination.

The Cytoskeleton of Axons

Axons are highly polarized cellular extensions whose structure and function depend on coordinated cytoskeletal organization (Leterrier et al., 2017). The axonal cytoskeleton faces the unusual challenge of maintaining long-term structural stability across extraordinary cellular distances while simultaneously supporting localized remodeling required for development, intracellular transport, and plasticity.

In mature axons, microtubules form parallel bundles with predominantly plus-end-out polarity that provide structural integrity and support long-range movement of intracellular

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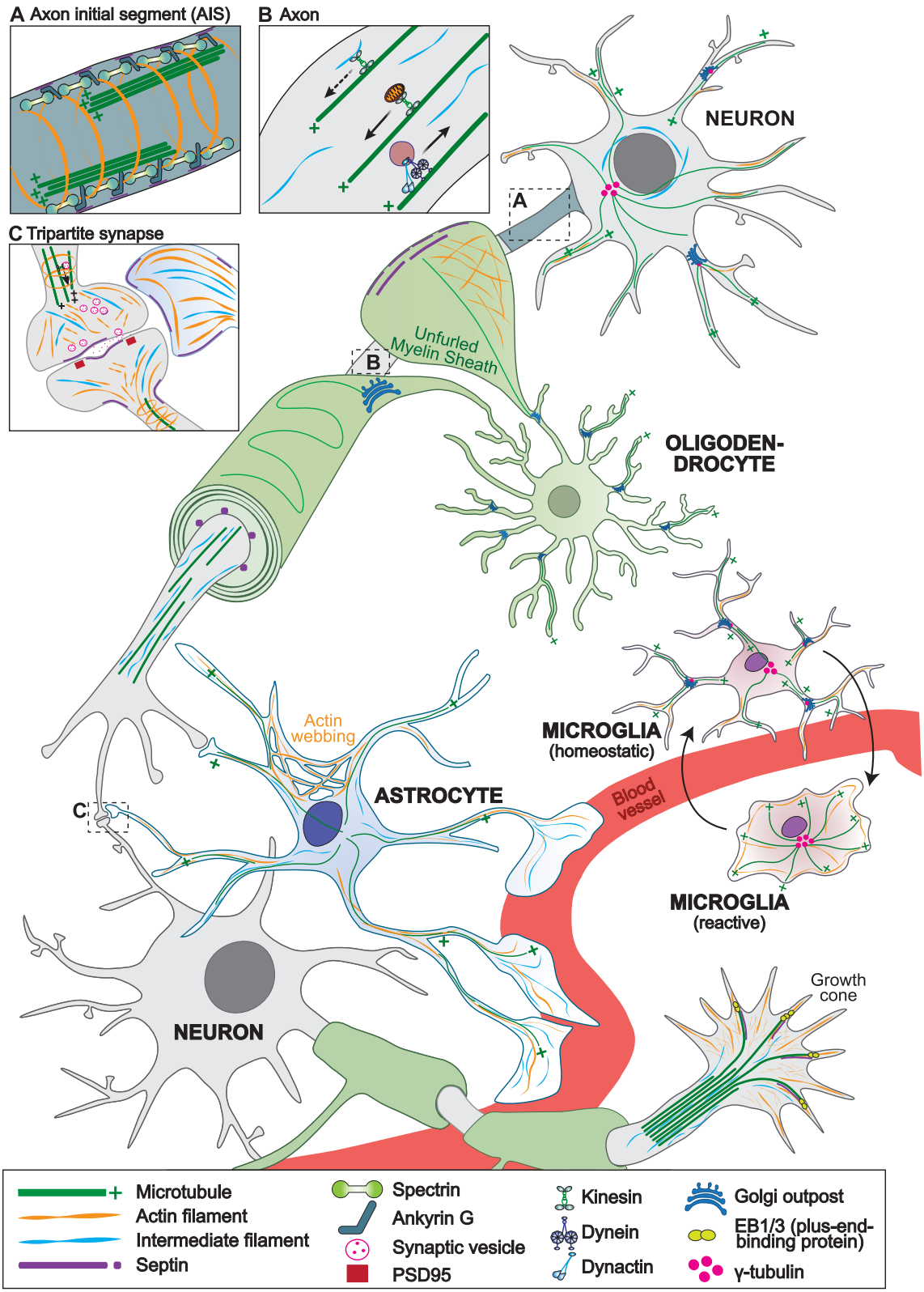


Figure 1. A roadmap to the cytoskeleton of neurons and glia. A schematic depicting the interplay of the cytoskeletal components (microtubules, actin, intermediate filaments, and septins) in maintaining cellular architecture and transport within neurons and glial cells (oligodendrocytes, astrocytes, microglia). Microtubules have uniform polarity (plus-ends out) in axons, and oligodendrocytes, but have mixed polarity in dendrites, astrocytes and homeostatic microglia. Plus ends of microtubules are indicated with plus signs (+). Though EB1/3 plus-end-binding proteins are found on all plus ends of polymerizing microtubules, we only depict them in the growth cone (bottom right). ***A***, Axon initial segment (AIS) of a neuron depicting the periodic organization of spectrins, ankyrin G, and F-actin rings to form the membrane-associated periodic skeleton (MPS). This arrangement is maintained by the interaction of actin filament rings with spectrin-ankyrin G complexes which are bound to the axon membrane via septins. ***B***, Axonal segment depicting cargoes (intermediate filaments, vesicles and organelles) being transported along the microtubules via the motors kinesin (anterograde toward the microtubule plus ends) and dynein (retrograde toward the microtubule minus ends). The membranous cargoes move rapidly and continuously (fast transport, solid arrows) whereas cytoskeletal and cytosolic cargos move intermittently (slow transport, dashed arrow). ***C***, A tripartite synapse composed of presynaptic and postsynaptic

cargoes (see Intracellular Transport in Neurons and Glia; Heidemann et al., 1981; Baas et al., 1988; Tas et al., 2017). Recent studies have highlighted that the persistence of parallel axonal microtubules is maintained through noncentrosomal nucleation sites (Weiner et al., 2021), trafficking or sliding of polymerized microtubules (Ahmad et al., 1998; Burute et al., 2022; Schelski and Bradke, 2022), and in-lattice renewal of tubulin dimers (Butler-Hallissey et al., 2026, preprint), producing a persistent but constantly remodeled network. Furthermore, distinct microtubule populations or spatially specialized domains along single microtubules coexist within individual axons, differing in stability, posttranslational modifications, and/or associated proteins (Baas et al., 2016; Janke and Magiera, 2020). The heterogeneity of microtubule subpopulations influences both the mechanical properties of axons and the selective recruitment of molecular motors and cargoes (Burute and Kapitein, 2019; Kelliher et al., 2019), but how neurons control the relative abundance and intracellular organization of microtubules is still an area of active investigation.

Neurofilaments, which are the intermediate filaments of neurons, are both structural polymers and cargos of axonal transport which are transported into and along axons along microtubule tracks (see Intracellular Transport in Neurons and Glia). While traditionally thought of as stable assemblies, axonal neurofilaments undergo a dynamic cycle of severing and annealing which regulates their length and transport (Uchida et al., 2013, 2023). These polymers accumulate in large numbers in myelinated axons, where they function as space-filling structures to increase axonal caliber (Hoffman et al., 1987; Nowier et al., 2023). They are also presumed to contribute to the structural integrity of these processes. The space-filling properties of neurofilaments are maximized by long intrinsically disordered tail domains of the neurofilament subunit proteins which project radially from the filament backbone to space these polymers apart from their neighbors (Ding and Kumar, 2024). In this way, neurofilaments influence the axial resistance of axons to the flow of current, which is a basic cable property of axons that is critical for nerve conduction. Intriguingly, loss of neurofilaments from axons, or deletion of neurofilament side arms, results in an increase in microtubule number (Zhu et al., 1997; Rao et al., 2003). This may be mediated by interaction with stathmin-2, which is a tubulin subunit binding protein (Yadav et al., 2016). Loss of stathmin-2 results in a profound compaction of axonal neurofilaments and a corresponding decrease in axon caliber and conduction velocity (Lopez-Erauskin et al., 2024). These data suggest yet-to-be-understood cross talk mechanisms between these polymer systems.

Beneath the plasma membrane, periodically arranged actin rings connected by spectrin tetramers form a highly ordered cortical scaffold called the membrane-associated periodic skeleton (MPS, also known as the axonal periodic scaffold) which contributes to axonal elasticity and membrane organization (Xu et al., 2013; Goy and Pielage, 2026). Recent work further suggests that the MPS can undergo signaling-induced rearrangement and constrains membrane trafficking by generating discrete "clearings" for localized endocytosis and exocytosis, thereby coupling nanoscale cytoskeletal organization to membrane turnover and cargo delivery (Wernert et al., 2024; Wiesner et al., 2025). Within the axon proper, live imaging has revealed dynamic actin assemblies along both developing and mature axons including actin waves, trails, and hotspots that propagate along neurites and contribute to local remodeling, cargo delivery, and synaptic organization and potentially deliver actin and actin-binding proteins to distal sites (Ganguly et al., 2015; Chakrabarty et al., 2019). These examples highlight an evolving perspective that the stable organization of the axon is dependent on local cytoskeletal remodeling and organization.

Axon initial segments and nodes of Ranvier

In addition, the axon contains specialized subcompartments harboring unique cytoskeletal structures. At the boundary between the soma and axon, the axon initial segment (AIS) represents a highly ordered cytoskeletal architecture enriched in actin, spectrin, ankyrin, and specialized arrays of microtubule fascicles (Fig. 1*A*) that together establish a selective diffusion and trafficking barrier between axonal and somatodendritic domains (Leterrier, 2018). This organization is required for polarized protein distribution and clustering of voltage-gated ion channels necessary for action potential initiation. Several key AIS components, including βIV-spectrin, ankyrin G, and voltage-gated sodium channels, are also enriched at nodes of Ranvier, highlighting shared cytoskeletal mechanisms underlying the assembly of these excitable membrane domains (Prokop, 2020).

Growth cones

In contrast to the relatively stable architecture of the mature axon shaft (Papandreou and Leterrier, 2018), nascent neurites and growth cones exhibit highly dynamic cytoskeletal organization resembling that of migratory cells (Lowery and Van Vactor, 2009). Growth cones contain dense actin networks within peripheral filopodial and lamellipodial domains coupled to dynamic microtubules that selectively invade actin-rich protrusions (Fig. 1, bottom right), where their stabilization promotes protrusion persistence and neurite extension (Tanaka and Kirschner, 1995; Dent and Kalil, 2001; Schaefer et al., 2008). Recent evidence highlights the oscillatory interplay between actin polymerization, actomyosin contractility, and microtubule dynamics in the soma during axon initiation (Lin et al., 2026). Coordinated interactions between these filament systems determine whether neurites extend, retract, or branch, which is critical for building the wiring of the central and peripheral nervous systems. Growth cone steering in response to guidance cues in development thereby emerges from tightly regulated cytoskeletal cross talk in which signaling and mechanical processes are integrated across filament systems rather than operating independently (Buck and Zheng, 2002; Dent et al., 2011; Alfadil and Bradke, 2023). In this framework, interactions between actin-associated proteins such as drebrin, EB3-decorated microtubule plus ends, and the broader network of plus-end tracking proteins create a dynamic molecular interface that coordinates protrusion selection, microtubule invasion, and directional growth (Geraldo et al., 2008; Bearce et al., 2015; Alfadil and Bradke, 2023). In addition to actin filaments and microtubules, septin filaments regulate growth cone dynamics (see Septins:

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neuronal synapses and a perisynaptic astrocytic process (PAP). Actin filaments, intermediate filaments, and periodic actin rings are present at the synapse providing structural support. Motor proteins traffic synaptic vesicles, which are eventually released at the cleft for synaptic transmission. Septins line the base of pre- and postsynaptic terminals and are necessary for vesicle and receptor docking. PAPs are enriched in dynamic F-actin, intermediate filaments, and septins.

The Overlooked Fourth Element), and immature types of intermediate filaments modulate growth cone responses to guidance cues (Bott and Winckler, 2020).

The Cytoskeleton of Glia

Glial cells (oligodendrocytes, astrocytes, and microglia) constitute >50% of the brain and are essential for neural circuit maintenance and function (Azevedo et al., 2009; von Bartheld et al., 2016; Bahney and Von Bartheld, 2018). Within the peripheral nervous system, the glia such as Schwann and satellite cells play equally critical roles. While neuronal cytoskeletal organization has been studied extensively, the equivalent machinery in glia remains understudied. The dynamic regulation of microtubules, actin, intermediate filaments, and septins underlies the capacity of glial cells to adopt specialized morphologies and execute diverse functions.

Oligodendrocytes

In the vertebrate CNS, oligodendrocytes produce myelin sheaths that wrap around neuronal axons to facilitate rapid saltatory conduction. Mature myelin sheaths, which contain specialized lipids (Poitelon et al., 2020) and myelin proteins (Siems et al., 2020), are compacted membranous structures devoid of cytoplasm. Each oligodendrocyte is ramified or branched and can form as many as 15–40 myelin sheaths per cell (Chong et al., 2012; Thornton et al., 2024).

Oligodendrocytes contain two populations of microtubules, radial microtubules along branched processes that reach toward the axon, and lamellar microtubules contained inside the myelin sheath, traversing from the outer to inner layers (Weigel et al., 2021). Oligodendrocyte microtubules are oriented plus-ends out and rely on acentrosomal nucleation performed by Golgi outposts, small 1–2 µm satellite organelles (Valenzuela et al., 2020), found along both radial and lamellar microtubules (Fig. 1). Golgi outposts in oligodendrocytes nucleate microtubules using the liquid condensate protein tubulin polymerization promoting protein (TPPP; Fu et al., 2019; Kemal et al., 2023) and do not associate with γ-tubulin. Absence of TPPP results in decreased myelin sheath length and thickness as well as behavioral defects (Fu et al., 2019; Nguyen et al., 2020), indicating that lamellar microtubule nucleation is important for myelin sheath structure. FIB-SEM studies of oligodendrocytes revealed lamellar microtubules inside cytoplasmic channels, tunnel-like structures within the myelin sheath (Snaidero et al., 2014). Cytoplasmic channels in oligodendrocytes resemble Schmidt–Lanterman incisures in Schwann cells, which also contain microtubules (Hall and Williams, 1970). Recent live-cell imaging studies on oligodendrocytes confirmed that cytoplasmic channels mediate microtubule-dependent organelle transport, which is important for maintaining axon health (Chapple et al., 2024, preprint). Thus, microtubules perform both developmental and maintenance functions in oligodendrocytes.

Actin and septins are also important for the formation of the myelin sheath. During the initial ensheathment of the axon, Arp2/3-dependent actin assembly is important; during the subsequent stage of myelin wrapping, which proceeds from outer to inner layers, actin depolymerization mediated by ADF/cofilin is important (Nawaz et al., 2015; Zuchero et al., 2015). At the inner tongue, the myelin layer adjacent to the axon, septin filaments associated with anillin are oriented longitudinally along the length of the myelin sheath. Because anillin is a scaffolding protein capable of binding to both actin and membranes, these filaments likely act in a zipper-like fashion to facilitate the tight juxtaposition of the inner tongue to the axon (Fig. 1). Septin loss results in myelin outfoldings, which are aberrant large floppy loops of myelin that do not conform to the stereotyped tight wrapping of myelin layers (Patzig et al., 2016). Together, these findings reveal a tightly coordinated cytoskeletal program across successive stages of myelination.

Astrocytes

Astrocytes are highly ramified glial cells whose processes interface with neurons, vasculature, and other glial cells. The elaborate branching complexity observed in astrocytes relies on many cellular interactors, including neuroligins that mediate direct contact with neurons (Stogsdill et al., 2017) and hepaCAM that mediates contact between neighboring astrocytes (Baldwin et al., 2021). In addition, astrocyte-intrinsic processes contribute to the branched morphology. For instance, loss of DRP1 (dynamin related protein 1), which mediates mitochondrial fission in distal branches, results in reduced astrocyte morphological complexity (Rodriguez Salazar et al., 2025). Astrocytes generate distinct processes to perform their diverse functions, such as ion and neurotransmitter homeostasis, modulation of synaptic signaling, and formation of the blood–brain barrier. Some processes terminate in perisynaptic astrocytic processes (PAPs) while others terminate in perivascular astrocytic processes (PVAPs), also known as end feet. The contact site formed by a presynaptic axon terminal, a postsynaptic bouton, and an astrocyte PAP is known as a tripartite synapse (Fig. 1*C*). Recent two-photon imaging in vivo demonstrated that each astrocyte is capable of forming many PAPs and ∼2–5 PVAPs (Hösli et al., 2022). Thus, each astrocyte interfaces with multiple cell types simultaneously via morphologically and functionally heterogeneous processes.

Astrocyte processes contain three major classes of cytoskeleton: microtubules, actin filaments, and intermediate filaments, including glial fibrillary acidic protein (GFAP), which is commonly used as a histology marker for astrocytes. Confocal microscopy and cryo-ET (Fig. 2) of cultured astrocytes reveal three distinct cytoskeletal zones. First, proximal primary processes are enriched in acetylated and detyrosinated microtubules. Second, distal primary processes contain microtubules and GFAP intermediate filaments, which are enriched at the distal tips. Third, an actin-rich reticular webbing is found proximal to the cell body, often connecting primary branches (Fig. 1, Wynne et al., 2025, preprint). The coordinated regulation of these cytoskeletal components sustains the complex morphology of astrocyte processes.

Microglia

Microglia, the brain's resident immune cells, perform immune surveillance, synapse pruning, and clearance of cellular debris in both development and disease. During phagocytosis, the distal processes of these cells form a characteristic C-shaped phagocytic cup around the target. The local actin reorganization that forms this phagocytic cup likely involves local translation of actin regulatory proteins (Vasek et al., 2023).

Under homeostatic conditions, cultured microglia adopt a ramified morphology with major processes containing microtubules of mixed polarity and numerous filopodia containing actin filaments. Notably, microtubule nucleation in this state occurs acentrosomally in a γ-tubulin dependent manner at Golgi outposts found throughout microglial branches (Rosito et al., 2023). Strikingly, this morphology shifts to an amoeboid shape when the cells are exposed to different inflammatory

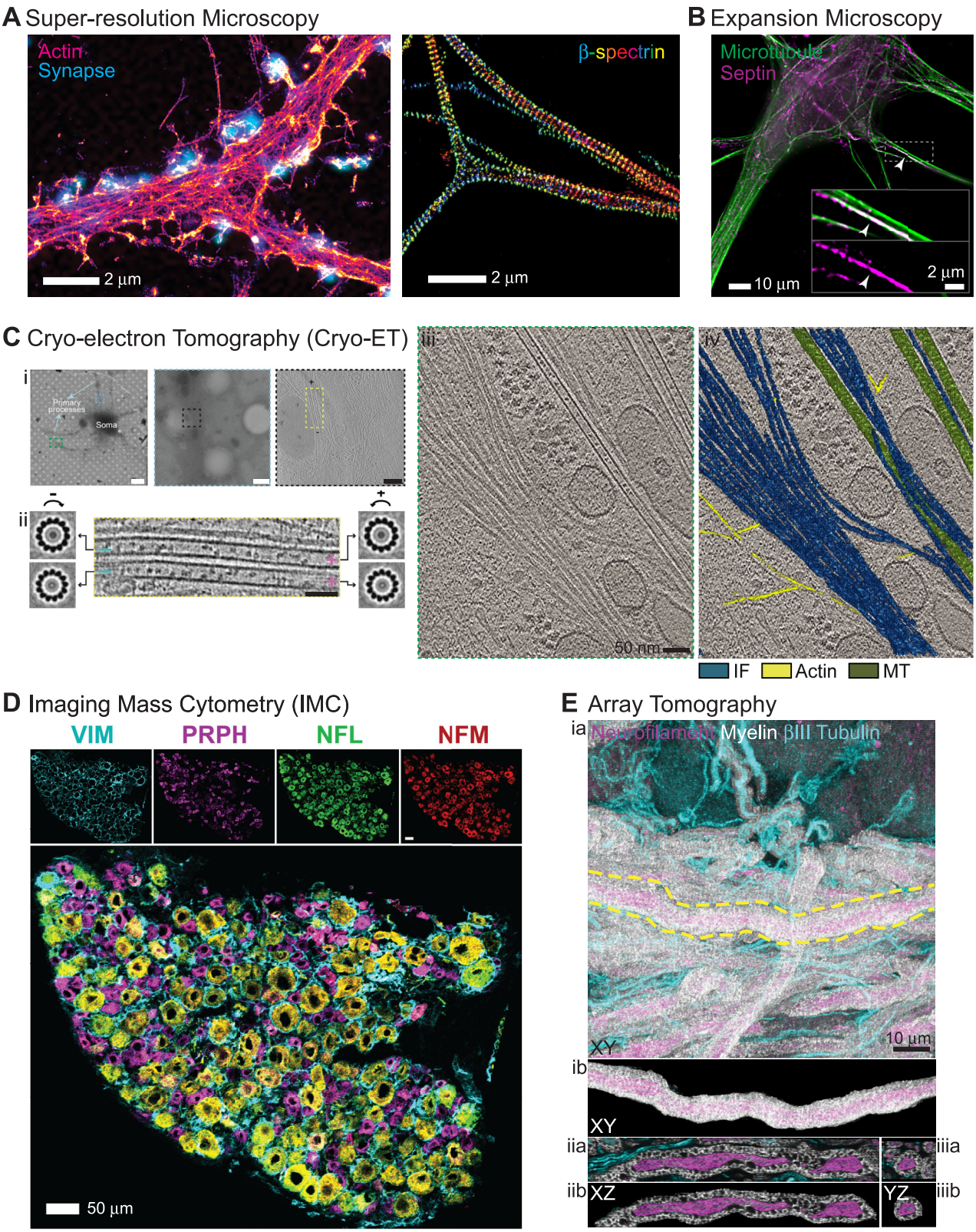


Figure 2. Imaging the cytoskeleton of neurons and glia. ***A***, STORM (Stochastic Optical Reconstruction Microscopy) of cultured hippocampal neurons. Left, Image of actin (fire) and synapses (blue, bassoon, and synapsin together). Right, ßII-spectrin labeling of axons with clear periodicity of the MPS (membrane-associated periodic skeleton). Color code indicates depth (3D-STORM). Images adapted with permission from Christophe Leterrier lab. ***B***, Expansion microscopy of a cultured hippocampal neuron immunostained for acetylated tubulin (microtubules, green) and septin 9 (magenta), following ∼4-fold expansion and imaging by 3D deconvolution wide-field microscopy. The image is an average intensity projection of optical sections spanning the apical-medial depth of the neuron. The arrowhead, shown in the outlined region and corresponding higher magnification inset, points to a septin 9-decorated microtubule bundle. Images with permission from Elias Spiliotis lab. ***C***, Cryo-electron tomography of an astrocyte. ***i***, Left, An astrocyte grown on a cryo-EM grid. The blue and green dashed boxes highlight regions of primary processes used for acquiring a tomographic tilt series shown in the middle panel and subfigures ***iii***/***iv***, respectively. Scale bar, 5 μm. Middle, Zoomed-in image of the blue dashed box in the left panel. Scale bar, 500 nm. Right, 2D slice of a reconstructed tomogram (black dashed box, middle panel) highlighting the microtubules in the yellow dashed box used for determining polarity and protofilament

environments (Fig. 1). This transition is accompanied by extensive cytoskeletal remodeling, most notably the redistribution of actin filaments to the cell membrane border. Concurrently, γ-tubulin-mediated microtubule nucleation shifts to the perinuclear centrosome, which promotes radial microtubule growth with a uniform plus-ends-out orientation (Adrian et al., 2023; Rosito et al., 2023). Thus, cytoskeletal reorganization dramatically reshapes microglia morphology in response to inflammation, which is an important mechanism in neurological diseases.

Intracellular Transport in Neurons and Glia

The complex and elaborate morphologies of neurons and glia depend on intracellular transport for their development, maintenance, and plasticity. While this movement is fundamental to all eukaryotic cells, what sets neurons and glia apart are the distances traveled. In large animals, central projection neurons and peripheral motor and sensory neurons can project axons over a meter in length and a single Schwann cell extends the length of an entire internode, which can be a millimeter or more for large axons. Yet, all transcription and most protein synthesis and organelle biogenesis is confined to the cell body. This extreme cellular polarization presents a major logistical challenge, requiring efficient intracellular transport systems capable of delivering proteins, organelles, lipids, RNAs, and signaling molecules across vast intracellular distances. Consequently, neuronal and glial development, maintenance, and synaptic plasticity are critically dependent on the continual movement and delivery of intracellular cargo.

The machinery of intracellular transport

Intracellular transport is mediated by three families of motor proteins which hydrolyze ATP to generate force and directional movement. These motors "walk" along the cytoskeleton of the cell such as actin filaments and microtubules redistributing their cargos. The myosin protein family travel along actin filaments and are responsible for short range movement of cargos. In contrast, long-range intracellular cargo transport in cells is primarily mediated by two families of microtubule-based motor proteins: kinesins and cytoplasmic dynein. In general, kinesins move toward the plus ends of the microtubules, which in axons are directed away from the cell body toward axon terminals, whereas dynein drives retrograde transport back toward the soma traveling toward the minus ends of the microtubules. The kinesin superfamily is highly diverse, consisting of >40 distinct kinesin proteins in mammals, each with specialized cargo-binding and trafficking functions (Hirokawa et al., 2009). In contrast, there is a single cytoplasmic dynein protein that interacts with numerous adaptor and regulatory proteins to achieve cargo specificity and regulatory diversity (Reck-Peterson et al., 2018; Cason and Holzbaur, 2022). Motor proteins are regulated through several complementary mechanisms. First, motors are highly sensitive to the biochemical properties of the tracks upon which they travel. For example, microtubules undergo extensive posttranslational modifications, including acetylation, detyrosination, and polyglutamylation, which can alter microtubule motor affinity, velocity, and cargo selectivity (Sirajuddin et al., 2014; Gadadhar et al., 2017; Janke and Magiera, 2020; McKenna et al., 2023). Second, a wide array of adaptor and scaffolding proteins link specific cargos to particular motors, thereby conferring transport specificity and allowing precise spatial regulation of trafficking (Maday et al., 2014; Cross and Dodding, 2019; Cason and Holzbaur, 2022). Finally, motor activity itself can be directly regulated through phosphorylation, autoinhibition, and competitive recruitment mechanisms that control whether motors bind microtubules, engage cargo, or remain inactive (Verhey and Hammond, 2009). Together, these regulatory mechanisms ensure that intracellular transport remains dynamic, adaptable, and tightly coordinated with cellular activity and physiological state.

The diversity of intracellular cargoes

Like all cells, neurons and glia employ two strategies to localize proteins, either transporting the protein or transporting the mRNA transcript and synthesizing the protein locally. In neurons, hundreds of proteins and transcripts move anterogradely along axons in association with distinct cargo structures (Fig. 1*B*). These cargos show great diversity and include Golgi-derived vesicles, mitochondria, lysosomes, peroxisomes, cytoskeletal and cytosolic protein complexes, and ribonucleoprotein (RNP) complexes; all are essential for supporting cell physiology. Additionally, anterograde transport of mRNAs and ribosomal components supports local protein synthesis within axons and dendrites, enabling rapid and spatially restricted responses to extracellular stimuli (Holt et al., 2019).

Equally important is retrograde transport, which enables neurons and glia to recycle damaged organelles and communicate signals from the distal processes back to the nucleus. In neurons, dynein-dependent retrograde trafficking conveys autophagosomes, lysosomes, and signaling endosomes containing activated neurotrophin receptor complexes such as NGF-bound TrkA receptors. These endosomes are critical for relaying signals from distal axons to the soma, ultimately influencing gene expression, stress responses, and neuronal fate decisions (Winckler et al., 2018).

In axons, we distinguish distinct rates of intracellular transport termed fast and slow, differentiated by the duty ratio, or the proportion of time a cargo spends actually moving (Brown, 2003). While the membranous cargoes, which undergo fast axonal transport, are largely known, cytoskeletal and cytosolic cargo proteins, which undergo slow transport, are less well understood. Neurofilaments, which are unique among axonal cargoes in that they are assembled polymers, move bidirectionally along

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number. Scale bar, 100 nm. ***ii***, Two adjacent microtubules (center) and end-on views of their corresponding subtomogram averages showing 13-protofilament architecture and plus-ends-out polarity, based on protofilament skew. Plus and minus ends are indicated. ***iii***, 2D slice of a reconstructed and 3D CTF-corrected tomogram showing cytoskeletal filaments present in the primary process of an astrocyte. ***iv***, Trained neural network-based segmentation (on Dragonfly) of cytoskeletal filaments, with microtubules in green, intermediate filaments (IFs) in blue, and actin filaments in yellow. Images adapted with permission from Dharshini Gopal, Eva Nogales lab. ***D***, Mass cytometry of multiple intermediate filament subunit proteins expressed in the DRG (dorsal root ganglion) of a P50 (postnatal day 50) mouse. VIM (vimentin, cyan), PRPH (peripherin, magenta), NFL (neurofilament light, green), NFM (neurofilament medium, red). Images with permission from Isaiah Swann, Bettina Winckler lab. ***E***, Immunofluorescence array tomography of DRG. ***i***, 3D rendering of adult mouse DRG. ***a***, Full volume (10.8 μm thick), yellow dashed lines indicate isolated myelinated axon. ***b***, X-Y view of myelinated axon isolated from 3D volume. ***ii***, X-Z orthogonal view through the axon of interest (***a***) full volume and (***b***) isolated axon. ***iii***, Y-Z orthogonal view through the axon of interest (***a***) full volume and (***b***) isolated axon. Images with permission from Hannah Bailey, Anthony Brown lab.

microtubule tracks (Fenn et al., 2018; Boyer et al., 2022; Fenn et al., 2023). In contrast, the transport of actin and tubulin is unresolved. Chakrabarty et al. (2019) proposed an intriguing mechanism of actin transport based on biased actin polymerization that is independent of motors and tracks. There is also evidence that cytosolic protein complexes may be transported by a variety of mechanisms. For example, the synaptic protein synapsin can move by transient "dynamic recruitment" to moving vesicles (Tang et al., 2013), the retrograde motor dynein can move by transient direct interaction with kinesin (Twelvetrees et al., 2016), and clathrin moves intermittently in the form of stable macromolecular transport "packets" which resemble clathrin-coated vesicles or clathrin cages and may function as carriers for other cytosolic proteins (Ganguly et al., 2017, 2021). In addition, mRNA can hitchhike on vesicular cargoes (Cioni et al., 2019; Liao et al., 2019; De Pace et al., 2024) and mitochondria (Cohen et al., 2022; Harbauer et al., 2022). The emerging picture, therefore, is of a diversity of transport mechanisms that reflects the diversity of macromolecular interactions in cytoplasm (Roy, 2020).

There is also extensive transport of materials in dendrites which entails large distances. Like the processes of glia (see above), dendrites contain Golgi outposts (Fig. 1), which contribute to dendritic membrane traffic and are important for dendritic branching and microtubule nucleation (Ori-McKenney et al., 2012; Valenzuela et al., 2020), though the latter role has been challenged (Nguyen et al., 2014; Weiner et al., 2021). Dendritic transport is conceptually more complex than axonal transport since the microtubule arrays are of mixed polarity, thus dynein and kinesins can in principle support transport toward and away from the soma. The mechanisms underlying directional dendritic transport are thus still being actively investigated (Kapitein and Hoogenraad, 2015; Delandre et al., 2016; Yap et al., 2022).

The vulnerability of transport and trafficking in disease

The importance of intracellular transport in neuronal function is underscored by the fact that disruptions in axonal trafficking are implicated in numerous neurodevelopmental and neurodegenerative disorders, including Alzheimer's disease, amyotrophic lateral sclerosis, and Huntington's disease (Stokin et al., 2005; Caviston et al., 2007; Turner and Twelvetrees, 2026). Many of the genes that are mutated in genetic neurological diseases are associated with the cytoskeleton and trafficking such as mutations in the kinesin motor, KIF1A (Nair et al., 2023; Lin et al., 2025). Defects in motor proteins, microtubule stability, mitochondrial trafficking, or cargo adaptor complexes can impair neuronal (Cason and Holzbaur, 2022; McKenna et al., 2023; Basak and Holzbaur, 2025; Turner and Twelvetrees, 2026) or glial homeostasis (Weigel et al., 2021; Nowacki et al., 2022) and promote axonal dysfunction or demyelination. As neurons are highly dependent on long-distance trafficking for survival, precise regulation of motor activity is essential for neuronal viability.

Intracellular transport in glia

Studies on intracellular trafficking in glia have largely focused on microtubule-based transport. Oligodendrocytes transport diverse organelles, including mitochondria (Nakamura and Kennedy, 2021) and peroxisomes, which are important for lipid production and are transported in a KIF21B-dependent manner (Chapple et al., 2024). Oligodendrocytes also transport many locally translated mRNAs (Meservey et al., 2021), including *Mbp* (myelin basic protein), which is the most abundant mRNA in these cells (Topkar et al., 2025, preprint; Nowacki et al., 2025, preprint). *Mbp* mRNA is distributed throughout the cell via bidirectional transport, which relies on both kinesin (KIF1B; Lyons et al., 2009) and dynein/dynactin activity (Herbert et al., 2017). Astrocytes also transport organelles, including lysosomes (Smith et al., 2025, preprint), autophagosomes (Kulkarni et al., 2020), mitochondria (Riley et al., 2026, preprint), and vesicles containing astrocyte-specific cargo, such as glutamate transporters and gap junction proteins (Creighton et al., 2019). Astrocytes also rely heavily on local translation (Sakers et al., 2017) and transport of mRNA granules (Meservey et al., 2021). Though less is known about cargo transport in microglia, they rely on cathepsin-positive late endosomes and lysosomes for function (Liu et al., 2020). Thus, glial cells transport some of the same classes of organelles that are transported in neurons as well as many specialized cell-specific cargos.

The Cytoskeleton of Synapses

The formation and maintenance of synapses present a formidable logistical challenge for neurons. A single neuron must distribute proteins, membranes, organelles, and signaling complexes across thousands of synaptic sites while maintaining the capacity for continual remodeling throughout life. Increasing evidence suggests that this challenge is solved through coordinated interactions among microtubule and actin cytoskeletons, molecular motors, and membrane trafficking pathways, which together regulate cargo delivery, local organization, and synaptic plasticity. Synapse assembly therefore requires the integration of long-range intracellular transport with localized mechanisms for cargo capture and retention that collectively establish, maintain, and remodel synaptic connections.

Presynaptic cytoskeleton

Presynapses are not assembled molecule-by-molecule at their final destination. Rather, many presynaptic components are transported through the axon in preassembled cargo complexes, including synaptic vesicle precursors (Hall and Hedgecock, 1991; Okada et al., 1995), active zone transport vesicles (Ahmari et al., 2000; Zhai et al., 2001; Shapira et al., 2003; Dresbach et al., 2006), mitochondria (Li et al., 2004; Vagnoni and Bullock, 2018), endolysosomal organelles (Farías et al., 2017; Niwa et al., 2017), and local translation machinery (Kanai et al., 2004; Cioni et al., 2019). The challenge facing developing neurons is therefore not simply delivering cargo throughout the axon but determining where and when these transported components should be retained and assembled into functional presynaptic compartments.

Microtubules play a central role in this process by supporting long-range transport powered by kinesin and dynein motors. However, emerging evidence suggests that microtubules are far more than passive tracks for cargo movement. For example, local microtubule organization can actively influence where synaptic cargo accumulates and presynaptic structures emerge (Guedes-Dias et al., 2019; Aiken and Holzbaur, 2024). In developing human neurons, spastin-dependent microtubule dynamics establish periodic presynaptic accumulation zones along the axon that function as landing sites for KIF1A-transported synaptic vesicle precursors (Aiken and Holzbaur, 2024). These findings suggest that local cytoskeletal remodeling contributes directly to presynaptic positioning by regulating where transported cargo pauses and accumulates. Similarly, activity-dependent recruitment of γ-tubulin and local microtubule nucleation at mature

boutons suggest that presynaptic sites can actively remodel their own microtubule architecture (Qu et al., 2019). Dynamic microtubules have also been implicated in interbouton vesicle exchange and neurotransmitter release (Qu et al., 2019; Velasco et al., 2023), indicating that microtubule organization remains functionally important long after synapses are established.

Local actin filament networks provide an additional layer of presynaptic organization. Distinct actin architectures contribute to synaptic vesicle clustering (Pieribone et al., 1995; Bloom et al., 2003), vesicle mobilization and interbouton exchange (Sankaranarayanan et al., 2003; Gramlich and Klyachko, 2017; Chenouard et al., 2020), SV endocytosis (Shupliakov et al., 2002; Bourne et al., 2006), active zone stability (Pielage et al., 2005), and bouton morphology (Pawson et al., 2008). Recent work suggests that actin organization within presynaptic boutons is itself spatially heterogeneous, raising the possibility that distinct actin subdomains may support specialized aspects of presynaptic function (Bingham et al., 2023; Tumminia et al., 2023). Importantly, microtubule and actin networks appear to play complementary rather than independent roles in presynaptic assembly. Microtubules facilitate long-range delivery of synaptic building materials, whereas local actin networks capture, organize, and retain these cargos within developing synaptic compartments (Bharat et al., 2017). How these two cytoskeletal systems are coordinated to specify presynaptic position, identity, and plasticity remains an important unresolved question.

Postsynaptic cytoskeleton

The postsynaptic compartment has historically been viewed through an actin-centric lens. Dendritic spines are highly enriched in filamentous actin (Matus et al., 1982), and actin remodeling drives both spine morphogenesis (Fischer et al., 1998) and activity-dependent structural plasticity (Matsuzaki et al., 2004; Okamoto et al., 2004). During development, dendritic filopodia dynamically explore the local environment and establish contacts with presynaptic partners (Dailey and Smith, 1996; Ziv and Smith, 1996). A subset of these transient structures subsequently mature into stable dendritic spines through progressive actin-dependent remodeling and scaffold assembly (Yuste and Bonhoeffer, 2004). Superresolution light microscopy of distinct populations of actin filaments in spines forming a membrane periodic skeleton surrounding longitudinally oriented filaments within the neck and a branched network within the head (Bar et al., 2016). Once established, actin networks continue to regulate receptor trafficking, postsynaptic density organization, and spine morphology, providing the structural basis for experience-dependent synaptic plasticity (Allison et al., 1998; Kim and Lisman 1999; Zhou et al., 2001).

More recently, microtubules have emerged as important contributors to postsynaptic organization. Dynamic microtubules transiently invade dendritic spines, particularly following synaptic stimulation, providing a mechanism through which long-range transport systems can directly influence local synaptic architecture (Hu et al., 2008; Jaworski et al., 2009; Merriam et al., 2011). Microtubule invasion has been linked to cargo delivery, receptor trafficking, spine enlargement, and activity-dependent structural remodeling, suggesting that microtubules contribute to both synapse formation and plasticity. Similar to the presynapse, postsynaptic organization therefore emerges from the coordinated interplay between microtubule-dependent delivery and actin-dependent local organization. Intermediate filaments (Yuan and Nixon, 2016) and septins (Yadav et al., 2017) also play roles at postsynaptic sites but are generally less well understood, highlighting the many opportunities in this field for better understanding the cross talk between the well-established players (such as actin filaments and microtubules) and less well-studied cytoskeletal components (such as intermediate filaments and septins).

Together, these studies support a view of synapses as specialized cytoskeletal compartments whose formation and plasticity emerge from coordinated interactions between intracellular transport systems and local cytoskeletal architectures. Advances in live-cell superresolution imaging, lattice light-sheet microscopy, expansion microscopy, cryo-electron tomography, and multiplexed imaging approaches (Fig. 2) are beginning to reveal these interactions with unprecedented spatial and temporal resolution (Carvalhais et al., 2020; Aleksejenko and Heller, 2021). Simultaneous visualization of cargo transport, cytoskeletal organization, and synaptic remodeling promises to provide a more integrated understanding of how neuronal connectivity is established and maintained.

Human genetics increasingly implicates microtubules (Poirier et al., 2007; Dols-Icardo et al., 2016), molecular motors (Nicolas et al., 2018; Kaur et al., 2020), actin regulators (Pathania et al., 2014), and membrane trafficking machinery (Abdollahpour et al., 2015) in neurodevelopmental and neurodegenerative disease which are often accompanied by synaptic dysfunction. The convergence of these diverse genetic variants on synaptic dysfunction suggests that disruption of the cellular mechanisms coordinating intracellular transport and cytoskeletal organization may represent a common cause of neuronal connectivity defects. Defining how cytoskeletal organization and intracellular transport cooperate across synaptic development and plasticity may therefore provide a unifying framework for understanding both the formation and failure of neuronal circuits.

Septins: The Overlooked Fourth Element

Septins are increasingly recognized as a fourth cytoskeletal component alongside actin filaments, microtubules, and intermediate filaments (Ageta-Ishihara and Kinoshita, 2021; Radler and Spiliotis, 2022). Despite essential functions in neuronal morphogenesis and physiology, septins remain vastly understudied relative to these classical elements, even though they are linked to a growing number of neuropathies, neurodegenerative, intellectual, and mental health disorders (Alkhanjari et al., 2025).

In mammals, 13 septin genes are classified into four groups (SEPT2, SEPT3, SEPT6, SEPT7) with ubiquitous and tissue-specific expression patterns, SEPT3 being notably neuron-specific (Kinoshita, 2003; Xue et al., 2004; Cavini et al., 2021). Driven by GTP-binding and hydrolysis, septins assemble combinatorially into nonpolar dimers of trimers (hexamers) or tetramers (octamers) arranged in a tail-to-tail orientation, which serve as the protomeric units of septin filaments (Cavini et al., 2021). Paralogs within the same group can substitute for one another, generating complexes with distinct localizations and functions (Kinoshita, 2003; Cavini et al., 2021). Septins associate with hourglass-shaped membrane curvature domains, and subsets of actin filaments and microtubules, functioning predominantly as scaffolds and diffusion barriers that selectively recruit and restrict, respectively, membrane and cytoskeletal proteins (Spiliotis and Nakos, 2021; Curtis and Gladfelter, 2024; Holt and Spiliotis, 2026). New studies suggest that septins also provide mechanical support akin to intermediate filaments (Mayca-Pozo et al., 2026, preprint; Utgaard et al., 2026, preprint).

Septins in neuronal development

Septins are functionally modular, playing critical roles in neuronal development and homeostasis (Falk et al., 2019). During neurogenesis, septins contribute to the spatial control of asymmetric division in neural stem and progenitor cells (NPCs), a process that determines the balance between proliferation and differentiation underlying brain development (Xing et al., 2021). Septins orient the mitotic spindle and specify the cleavage site of actomyosin contraction through their affinity for specific cortical sites and membrane domains. In *Drosophila* neuroblasts, septins localize asymmetrically to maintain the axis of successive divisions (Loyer and Januschke, 2018). In murine NPCs, SEPT7 interacts with KIF20A at the intercellular bridge to maintain proliferative identity (Qiu et al., 2020). In chick neural crest cells, SEPT7 demarcates cortical sites of postmitotic neurite re-emergence, enabling daughter DRG cells to inherit the bipolar polarity of their progenitor (Boubakar et al., 2017).

Roles in neuronal polarity, axon growth, and myelination

As neurons take their specialized shapes, septins are essential for neurite formation and differentiation into axons and dendrites (Radler and Spiliotis, 2022). In embryos, SEPT4/SEPT14 are critical for neuronal migration during corticogenesis, promoting the extension of leading processes in neurons that transition from a multipolar-to-bipolar morphology (Shinoda et al., 2010). In neuronal cell bodies, a SEPT7-containing wreath-like network coordinates branched actin polymerization and contractility to consolidate protrusions into neurites, suppressing lamellipodial protrusions in favor of filopodia (Radler et al., 2023). Axon formation involves microtubule bundling by SEPT9, which drives asymmetric outgrowth of the presumptive axon (Bai et al., 2013; Alam et al., 2026, preprint), while SEPT7 promotes elongation of both axons and dendrites, possibly by maintaining microtubule turnover due to α-tubulin deacetylation by HDAC6 (Ageta-Ishihara et al., 2013). In DRGs, axon collateral branching involves a two-step mechanism with SEPT6 mediating filopodial formation from actin patches and SEPT7 enabling microtubule entry to consolidate the branch formation (Hu et al., 2012).

The AIS, myelin sheath, and growth cone are also septin dependent. SEPT5 and SEPT6 interact with ankyrin G to stabilize the AIS (Hamdan et al., 2020; Weiss et al., 2026), while septins act synergistically with anillin at PI(4,5)P_2-rich membrane domains to link the neuronal membrane to adaxonal myelin of oligodendrocytes (see The Cytoskeleton of Glia). SEPT7, enriched at the transition zone between the microtubule-rich central and actin-rich peripheral domains of the growth cone, regulates the cytoskeletal cross talk underlying its morphology and dynamics (Nakos et al., 2022). Thus, septins have remarkably diverse roles in axonal function.

Septins in dendrites

Dendrite differentiation depends on polarized membrane traffic. On proximal dendritic microtubules, SEPT9 sorts membrane traffic by hindering the motility of kinesin-1 (KIF5)-driven axonal vesicles while promoting the anterograde transport of kinesin-3 (KIF1A)-driven dendritic cargo (Karasmanis et al., 2018). Septins promote the formation of dendritic spines, where they are enriched at the base-neck spine curvature and act as diffusion barriers to membrane proteins including AMPA receptors (Tada et al., 2007; Xie et al., 2007; Ewers et al., 2014). Spine maturation is regulated through TAOK2, an autism- and schizophrenia-risk kinase, which phosphorylates SEPT7, triggering translocation to the spine head where it immobilizes PSD95 and promotes AMPA receptor retention (Yadav et al., 2017). In the dentate gyrus, phosphorylation of SEPT3 during L-LTP shifts it to the endoplasmic reticulum (ER), where it engages myosin 5A to drive ER entry into spines and locally enhance Ca^{2+} responses, which is a mechanism required for long-term spatial memory and task-specific responses (Ageta-Ishihara et al., 2025a,b,c).

Septins at presynaptic terminals

At presynaptic terminals, septins modulate vesicle exocytosis in a paralog-specific manner, which might be due to distinct patterns of localization or expression. SEPT5 is inhibitory, forming a physical barrier around vesicles and competing with α-SNAP at the trans-SNARE complex, potentially hindering SNARE recycling (Beites et al., 2005; Taniguchi et al., 2007). SEPT4, in contrast, promotes synaptic vesicle exocytosis in dopaminergic neurons by scaffolding presynaptic complexes that comprise syntaxin-1A, SNAP25, Munc-18, and a-synuclein, while also shielding α-synuclein from toxic aggregation through direct binding (Ihara et al., 2007). SEPT8 also promotes VAMP2-syntaxin-1 assembly by displacing synaptophysin (Ito et al., 2009), and SEPT2 supports glutamate transporter GLAST localization at the astrocyte plasma membrane (Kinoshita et al., 2004).

In summary, septins are a modular cytoskeletal system that spatially regulates diverse mechanisms at the interface of membranes, actin, and microtubules, exerting spatiotemporal control over fundamental processes of neuronal development and physiology. Though understudied relative to other cytoskeletal polymers, septins continue to yield novel insights into long-standing questions in neuronal cell biology.

Conclusion

Given its structural nature, it is perhaps no surprise that our understanding of the cytoskeleton is limited by the methods that we can use to visualize it. Since the earliest electron microscope images in the 1960s, when the adoption of glutaraldehyde fixatives first revealed the existence of a cytoskeleton, technological advances in microscopy have driven the field forward. The introduction of techniques such as immunofluorescence microscopy in the 1970s, video microscopy in the 1980s, and live imaging with genetically encoded fluorescent tags in the 1990s have led to successive revolutions in our understanding of the organization, dynamics, and interactions of cytoskeletal polymers in the nervous system, but many questions remain. Today, advances in superresolution and volumetric imaging (Fig. 2) continue to move the field forward leading to new and unanticipated insights into the dynamics and interactions of the different filament systems. Examples include visualizing the 3D organization of the cytoskeleton with unprecedented resolution, elucidating the many roles of additional players (such as septins), discovering new tricks by old dogs (such as signaling modulation by many of the cytoskeletal filaments), and revealing the organization, dynamics, and function of the cytoskeleton in glia. Looking to the future, there is a pressing need to image cytoskeletal dynamics with superresolution in vivo and to map the macromolecular composition and interactions of the cytoskeleton in volumetric data sets. While the next technological advances may be hard to predict, it is certain that they will continue to drive this field forward and lead us a step closer to understanding how the cytoskeleton enables the unique and dynamic morphology of neurons and glia which is so critical for neuronal function.

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