

**MINIREVIEW**

Emerging roles of the centrosome in neuronal development

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Abstract

The role of the centrosome—a microtubule-organizing center—in neuronal development has been under scrutiny and is controversial. The function and position of the centrosome have been shown to play an important role in selecting the position of axon outgrowth in cultured neurons and in situ. However, other studies have shown that axonal growth is independent of centrosomal functions. Recent discoveries define the centrosome as an F-actin organizing organelle in various cell types; thus, giving a whole new perspective to the role of the centrosome in lymphocyte polarity, cell division, and neuronal development. These discoveries compel the need to revisit centrosomal functions by investigating the fundamental mechanisms that regulate centrosomal F-actin remodeling during neuronal differentiation and polarization. In this review, we summarize the up-to-date knowledge regarding the function of the centrosome in neuronal differentiation. We put special emphasis on recent findings describing the centrosome as an F-actin organizing center. Additionally, with the available data regarding centrosome, microtubules and F-actin organization, we provide a model on how centrosomal F-actin could be modulating neuronal differentiation and polarity.

KEYWORDS

centrosome, F-actin, neuronal differentiation

1 | INTRODUCTION

Neurons are complex cells with distinct functional domains for information processing: Dendrites receive synaptic input and relay signals to the soma, where the integrated information is transmitted via the axon over short or long distances. Differentiating neurons follow an intricate process during which one of the neurites is specified as an axon and the remaining into dendrites. Axon specification is the defining step for neuronal polarization, this event defines the connectivity of a neuron for the rest of its lifetime. We, however, do not completely understand the mechanisms behind the process of axon specification. There is contradicting research suggesting either cell-intrinsic or -extrinsic regulating factors of neuronal polarization.

Although several studies suggest the centrosome—also known as the microtubule-organizing center (MTOC)—as a key organelle regulating neuronal differentiation/polarity establishment via cell-intrinsic mechanisms, this issue is still under debate.

The centrosome is a membrane-less cell organelle present in most eukaryotic cells. Functionally, centrosomes are involved in many different cell processes, such as cell division, intracellular signaling, trafficking, cilia formation, cell polarity and motility, protein homeostasis, and immune response (Azimzadeh & Bornens, 2007; Bettencourt-Dias & Glover, 2007; Bornens, 2012; Conduit, Wainman, & Raff, 2015; Cowan & Hyman, 2004; De La Roche, Asano, & Griffiths, 2016; Joukov & De Nicolo, 2019; Nigg & Raff, 2009; Vora & Phillips, 2016; Wileman, 2007). It is composed of a pair of centrioles and

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pericentriolar material (PCM). The centrioles are cylindrical structures each made of nine triplets of microtubules situated perpendicular to each other. High-resolution microscopy showed that the structure of the centrioles is rather dynamic and remodels during the cell cycle with dramatic structural reorganization before mitosis (Bowler et al., 2019). The PCM is a dense proteinaceous scaffold containing a large number of proteins including γ -tubulin, centrin, pericentrin, and ninein. Some of these proteins present at the PCM act as microtubule nucleators— γ -tubulin and γ -TuRCs (gamma-tubulin ring complex) (Kollman, Polka, Zelter, Davis, & Agard, 2010; Oakley, 1992; Zheng, Wong, Alberts, & Mitchison, 1995), where proteins like ninein play a role in the anchoring of microtubules (Delgehyr, Sillibourne, & Bornens, 2005; Mogensen, Malik, Piel, Boukxon-Castaing, & Bornens, 2000). A nonclassical centrosomal protein, PCM-1 (Pericentriolar Matrix protein-1), that is present in the electron-dense protein granules in the cytoplasm was shown to recruit centrin, pericentrin, and ninein to build the PCM. Loss of PCM-1 disrupts the radial organization of microtubules without affecting microtubule nucleation, due to impaired recruitment of microtubule anchoring proteins to the centrosome (Dammermann & Merdes, 2002). High-resolution microscopic imaging methods revealed that the PCM is organized into two major structural domains—an inner layer juxtaposed to the centriole wall, and the outer layer with proteins extending further away from the centriole organized in a matrix—that provide separate functionality (Mennella et al., 2012). For instance, the key centrosomal proteins, such as pericentrin-like protein, pericentrin etc., form radially elongated fibrils from the centriole wall that extend outwards to support the 3D organization of the PCM by recruiting outer PCM proteins like Cnn and γ -tubulin (Mennella et al., 2012).

In most of the proliferating and migrating animal cells, the centrosome nucleates and anchors microtubules radially with their minus-ends oriented towards the centrosome and growing plus-ends towards the cell periphery (reviewed in Bartolini & Gundersen, 2006). Although cells of some lower organisms do not contain centrosomes, they possess equivalent structures: in higher fungi—*Saccharomyces cerevisiae*, and Amoebozoa—*Dictyostelium discoideum*, centrosome equivalents are known as spindle pole bodies and nuclear-associated body, respectively (Azimzadeh, 2014), which can still organize microtubules in a radial fashion (reviewed in Bartolini & Gundersen, 2006). However, in the case of most fungal, somatic plant cells, and differentiated animal cells, such as muscle, epithelial, and neuronal cells, microtubules are arranged in a centrosome-independent nonradial array (reviewed in Bartolini & Gundersen, 2006). Interestingly, cells with noncentrosomal microtubule organization are typically polarized and nonmigratory. This makes developing neurons an interesting case, for which several in vitro and in situ studies suggest a key role of centrosome-dependent radial microtubule organization in migrating and differentiating neurons (Higginbotham & Gleeson, 2007; Kuijpers & Hoogenraad, 2011; Rivas & Hatten, 1995; Schaar & McConnell, 2005; Tsai & Gleeson, 2005). It is suggested that the centrosome gradually loses its ability to radially organize microtubules after axons specification in cultured primary neurons (Stiess et al., 2010). Additionally, recent studies show that the centrosome can

organize the actin cytoskeleton (Farina et al., 2016) during lymphocyte polarity (Obino et al., 2016), cell division (Plessner, Knerr, & Grosse, 2019), and neuronal development (Meka et al., 2019).

This review is intended to summarize the data regarding the role of the centrosome during axon specification and neuronal migration with special focus on recent discoveries, which suggest the centrosome as an F-actin cytoskeleton regulator during neuronal differentiation. Due to the scope of the review, we will not deeply discuss the work related to molecular pathways regulating the microtubule and actin cytoskeleton described during axon extension.

1.1 | Neuronal differentiation in vitro

The initial attempts to study neuronal differentiation were made in dissociated hippocampal pyramidal neurons (Dotti, Sullivan, & Banker, 1988) and cerebellar granular neurons (Powell, Rivas, Rodriguez-Boulán, & Hatten, 1997). Dotti et al. (1988) observed a stereotypical pattern of hippocampal pyramidal neuronal differentiation in vitro—which they divided into five stages. Neurons appear round in the first few hours after plating (Stage 1) followed by lamellipodia and filopodia formation. In Stage 2, several hours after plating, neurons develop 4–6 short neurites with dynamic growth cones. After extensions and retractions, one of the neurites outgrows the others (18–24 hr in vitro) to become the axon (Stage 3)—this marks the first step of polarity (Figure 1). In the following days the remaining neurites mature into dendrites (Stage 4, after 4 days in culture) with dendritic spines (Stage 5, >2 weeks in culture) to establish synapses.

Developing in vitro cerebellar granular neurons initially form a single neurite (unipolar morphology) followed by a second neurite growing on the opposite pole of the cell body (bipolar morphology). The future axon continues to develop into a T-shaped branched process, whereas the second neurite becomes one of multiple emerging dendritic processes around the cell body (Powell et al., 1997). These in vitro studies demonstrate that axon and dendrite formations can occur without the need for a complex environment, implicating cell-intrinsic mechanisms to guide neuronal polarization.

1.2 | Axon elongation

One important question to understand the process of neuronal differentiation/polarization is by which means one neurite initiates elongation as an axon. On this line, it has been shown that local actin instability in the growth cones or microtubule stability in the neurite shafts of Stage 2 neurons sustains axon elongation (Bradke & Dotti, 1999; Witte, Neukirchen, & Bradke, 2008). The neurite with more dynamic F-actin in the growth cone and more microtubules that are eventually more stable, develops as an axon, whereas the remaining neurites become dendrites (Bradke & Dotti, 1999; Geraldo, Khanzada, Parsons, Chilton, & Gordon-Weeks, 2008; Neukirchen & Bradke, 2011; Witte et al., 2008; Yu & Baas, 1994; Zhao et al., 2017). In cultured rat hippocampal neurons, the future axon was suggested to

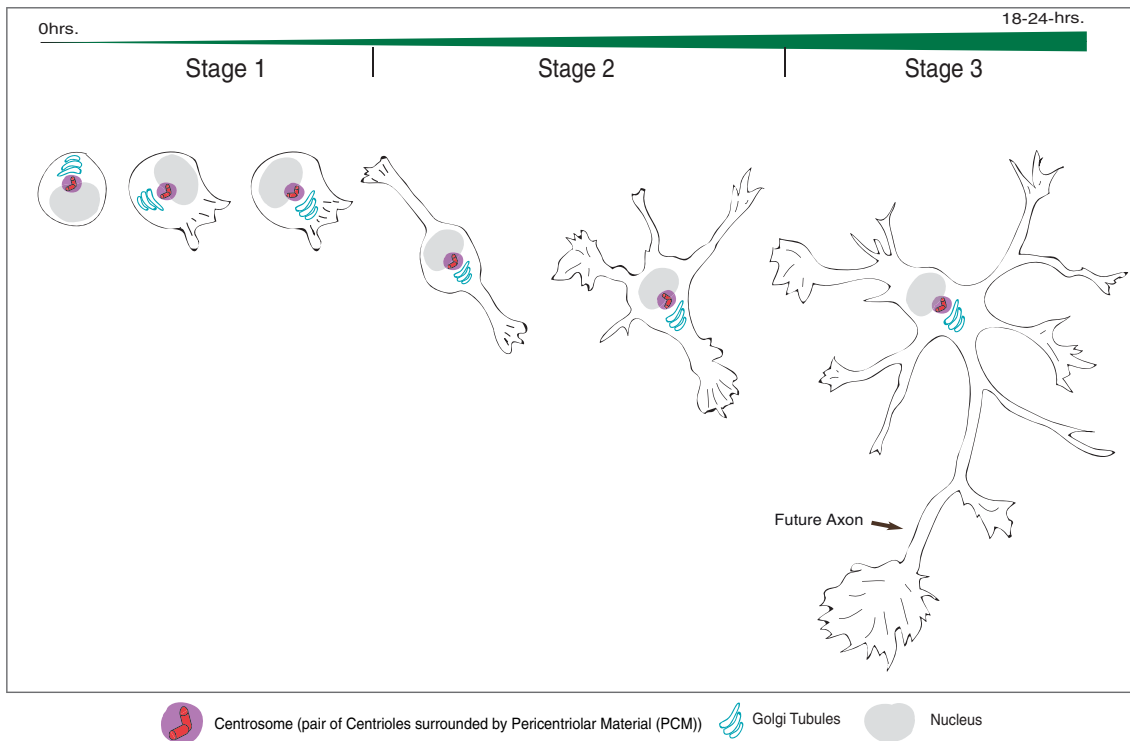


FIGURE 1 Early stages of neuronal development in culture, with the positioning of the centrosome and Golgi apparatus, indicated during symmetry breakage. The drawings show different stages of neuronal development, in culture, from the time of plating (0 hr) until axon specification (18–24 hr), marking the position of the centrosome and the Golgi at each developmental stage. The illustration is adapted from (Calderon de Anda, Gartner, Tsai, & Dotti, 2008) [Color figure can be viewed at wileyonlinelibrary.com]

have more stable microtubules in its shaft, due to the enrichment of acetylated microtubules (Witte et al., 2008). Accordingly, global application of the MT-stabilizing drug Taxol, induced the formation of multiple axons (Witte et al., 2008). Moreover, microtubules stabilization increased F-actin dynamics in growth cones (Zhao et al., 2017). Altogether, these observations support the hypothesis that the interplay between microtubule stabilization in the axonal shaft and actin filament dynamics in the axonal growth cone set up the conditions to break the Stage 2 symmetry.

1.3 | Post-translational modifications (PTMs) of microtubules and stable microtubules in centrosomal components and axons

Several tubulin PTMs that occur on microtubules like acetylation/deacetylation, tyrosination/detyrosination, glycylation/deglycylation, glutamylation/deglutamylation, and polymodifications (such as polyglycylation, polyglutamylation, and polyamination) provide a potential mechanism for the functional specialization of tubulin (reviewed in Janke, 2014; Magiera & Janke, 2014; Magiera, Singh, & Janke, 2018; Song & Brady, 2015; Wloga & Gaertig, 2010; Wloga, Joachimiak, & Fabczak, 2017). Enzymes that catalyze these PTMs revealed key roles of PTMs on microtubules in the regulation of motor protein movement, microtubule-stability, polymerization, and dynamics (reviewed in

Magiera & Janke, 2014; Magiera et al., 2018; Song & Brady, 2015; Wloga, Joachimiak, Louka, & Gaertig, 2017; Wloga et al., 2017). Tubulin PTMs, and specifically acetylation, detyrosination, and polymodifications have crucial roles in the assembly, maintenance, and function of complex and stable microtubule-based organelles that form the core components of the centrosome such as the centrioles, basal bodies (the protein structure at the base of a cilium or flagellum) and axonemes (the central strand of a cilium or flagellum) (reviewed in Wloga, Joachimiak, Louka, & Gaertig, 2017).

On the other hand, various studies point out the presence of stable microtubules in axons—determined either by measuring acetylated (Witte et al., 2008) or detyrosinated microtubules (Arregui, Busciglio, Caceres, & Barra, 1991). Yet, it is not completely clear which of the post translational modifications (PTMs) stabilize microtubules. Selective translocation of the Kinesin-1 motor domain into the nascent axon was described as one of the earliest events during the axon elongation (Jacobson, Schnapp, & Banker, 2006). Tubulin acetylation and detyrosination were shown to be required for Kinesin-1 motor domain translocation into the axons (Konishi & Setou, 2009; Reed et al., 2006). A later study, however, showed that acetylation of microtubules itself is not enough for sorting of Kinesin-1 into axons (Hammond et al., 2010). Moreover, taxol-induced translocation of Kinesin-1 into supernumerary axons correlated with the enhancement of three different microtubule PTMs (acetylation, detyrosination, and glutamylation; Hammond et al., 2010).

It was well described that polyamination, catalyzed by transglutaminase, another form of PTM, confers stability to the microtubules (Song et al., 2013). Whereas acetylation and detyrosination accumulate on long-lived microtubules (Garnham & Roll-Mecak, 2012; Song & Brady, 2015). The polyaminated microtubules are the most stable pool that are presumably acetylated and detyrosinated as well. While acetylated and detyrosinated microtubules are stable, they are still dynamic but not as dynamic as the unstable or labile pool of microtubules (reviewed in Baas, Rao, Matamoros, & Leo, 2016). Overall, it seems that axons contain a higher percentage of stable microtubules compared to their dendritic counterparts (reviewed in Baas et al., 2016). However, more research is needed to unveil the exact mechanisms of how differential microtubule stability is achieved in axons versus other minor neurites (future dendrites).

1.4 | Centrosomal and noncentrosomal factors contributing to axon specification

The position of axon outgrowth cannot be merely explained by the microtubule-actin cytoskeleton interactions in the growing neurite. In order to gain insight into the understanding of axon selection, it is crucial to consider whether or not it is intrinsically mediated or sustained through external cues. Early studies show that inhibition of microtubule nucleation at the centrosome hinders microtubule reassembly and compromises axonal growth (Ahmad, Joshi, Centonze, & Baas, 1994) attributing an important role for the centrosome and its microtubule-assembling ability in axon formation. In support of this idea, the first neurite in an early neuron (round, Stage 1) correlates with the position of the centrosome and the Golgi apparatus. Eventually the first emerged neurite becomes the axon (Figure 1; de Anda et al., 2005; Zmuda & Rivas, 1998). Interestingly, the second neurite usually forms at the opposite pole of the first one, suggesting an inherent bipolar program within the cells. Axotomy experiments support the cell-intrinsic bipolarity organization: when the existing axon is cut, the neurite on the opposite pole tends to become the axon (Calderon de Anda et al., 2008).

In addition to the centrosome, the Golgi apparatus can nucleate microtubules, too (Chabin-brion, Perez, Drechou, & Pou, 2001; Efimov et al., 2007). Golgi protein GM130 recruits AKAP450 (a γ -TuRC-interacting protein) to the cis-side of Golgi membranes to promote microtubule nucleation. Thus, GM130 allows centrosome-associated nucleating activity to extend to the Golgi, to ensure specific functions within the Golgi or for sorting specific cargos to the cell periphery (Rivero, Cardenas, Bornens, & Rios, 2009). Given that Golgi and centrosome colocalize during initial axon formation/specification (de Anda et al., 2005; Zmuda & Rivas, 1998), it is plausible to envision one of them acting as a compensatory factor while the function of the other is disrupted. Clear mechanistic data is still lacking to dissect specific functions of the centrosome and the Golgi to better understand their independent contributions to axon specification. Although, these results suggest a cell-intrinsic mechanism behind axon selection, the possibility of external cues playing a role cannot be discarded.

In this regard, N-cadherin, a membrane-bound adhesion molecule, clusters at the site of first neurite formation, which then triggers the accumulation of F-actin, centrosome, and Golgi. Extracellular N-cadherin is capable of determining the site where the first neurite emerges. The centrosome and Golgi apparatus are then guided towards this site (Gärtner et al., 2012; Gärtner, Fornasiero, Valtorta, & Dotti, 2014). Similarly, laminin—a cell-associated extra cellular matrix protein—attracts the centrosome to the site of axon formation in cultured retinal ganglion cells from zebrafish (Randlett, Poggi, Zolessi, & Harris, 2011). Therefore, the site of axon formation can be predicted by the positioning of centrosome and Golgi apparatus and extracellular substrates could attract them to the site of axon specification. Altogether, these studies suggest an interplay between external cues and intracellular organization of the cell during initial polarization.

In contrast, several studies suggest a stochastic axon selection process, in which one of the minor neurites of a Stage 2 cell elongates and becomes an axon under the stimulus of extrinsic factors (Andersen & Bi, 2000; Bradke & Dotti, 2000). The axon specification is positively regulated by extracellular substrates such as laminin and neuron–glia cell adhesion molecules (Esch, Lemmon, & Banker, 1999). Similarly, Netrin-1, a chemoattractant, induces axon outgrowth by modulating F-actin in the growth cone via Pak1-mediated Shootin1 phosphorylation (Toriyama, Kozawa, Sakumura, & Inagaki, 2013). However, these studies did not clarify, whether or not the extracellular substrates relocate the centrosome and/or Golgi to the site of axon specification. Therefore, it is possible that the organelle (centrosome/Golgi) positioning is vital to sustain the trafficking of material required to promote initial axon specification/growth, but not during extension or regeneration.

Once the axon is growing, the organization of microtubule arrays shifts from centrosome-dependent to centrosome-independent in hippocampal neurons in culture. Centrosome ablation during axon elongation does not affect axon extension or regeneration (Stiess et al., 2010). The same study reported decentralization of centrosomal proteins, such as γ -tubulin, which in turn can organize acentrosomal microtubules in older neurons (Stiess et al., 2010). Along these lines, Augmin and γ -TuRC are shown to be crucial for uniform plus-end out microtubule polarity in axons of matured neurons (Sánchez-Huertas et al., 2016). CAMSAP2, a microtubule minus-end protein can establish and maintain noncentrosomal microtubule networks and is suggested to be crucial for axon specification and polarity of neurons in vivo and in vitro (Yau et al., 2014). However, recently it has been described that CAMSAP3, but not CAMSAP2, affects axon formation (Pongrakhananon et al., 2018). CAMSAP3 regulates microtubules stability and its absence promotes microtubules acetylation leading to the formation of multiple axons. In contrast, the lack of CAMSAP2 did not affect neuronal polarity (Pongrakhananon et al., 2018) as suggested earlier (Yau et al., 2014).

1.5 | Centrosome and neuronal development in situ: From genesis to differentiation

Multiple studies describe how the centrosome's position needs to be precisely regulated during neurogenesis, migration, and differentiation.

Newborn neurons detach from the neuroepithelium for correct neuronal architecture and functional circuitry—a process known as neuronal delamination (Duband, 2006; Theveneau & Mayor, 2012). Delamination abnormalities can lead to various disorders, such as epilepsy, dyslexia, and intellectual disability (Sarnat & Flores-Sarnat, 2014; Scambler, 2000). Apical microtubule and actin dynamic-dependent centrosome retention is important for proper neuronal delamination (Kasioulis, Das, & Storey, 2017). AKNA, a centrosomal protein, regulates the delamination process during the formation of the subventricular zone through its ability to organize centrosomal microtubules and to promote their nucleation and growth (Camargo Ortega et al., 2019). The centrosome along with microtubule-associated proteins has been shown to be important for maintaining the progenitor pool during neuronal development (Bond et al., 2002, 2005; Bond & Woods, 2006; Feng & Walsh, 2004; Hung, Tang, & Tang, 2000; Kouprina et al., 2005; Zhong, Liu, Zhao, Pfeifer, & Xu, 2005). Along these lines, silencing Cep120 (a centrosomal protein) impaired both interkinetic nuclear migration—a characteristic pattern of nuclear movement in neural progenitors, and neural progenitor self-renewal (Xie et al., 2007). Furthermore, Hook3 via its interaction with PCM-1, which regulates PCM at the centrosome (Ge, Frank, Calderon de Anda, & Tsai, 2010), Cdk5rap2 via its interaction with a centrosomal protein pericentrin (Buchman et al., 2010), and Cenpj, a centrosomal protein crucial for centrosome biogenesis (Ding, Wu, Sun, Pan, & Wang, 2019; Garcez et al., 2015), were shown to be critical to maintain the neural progenitor pool in the developing neocortex.

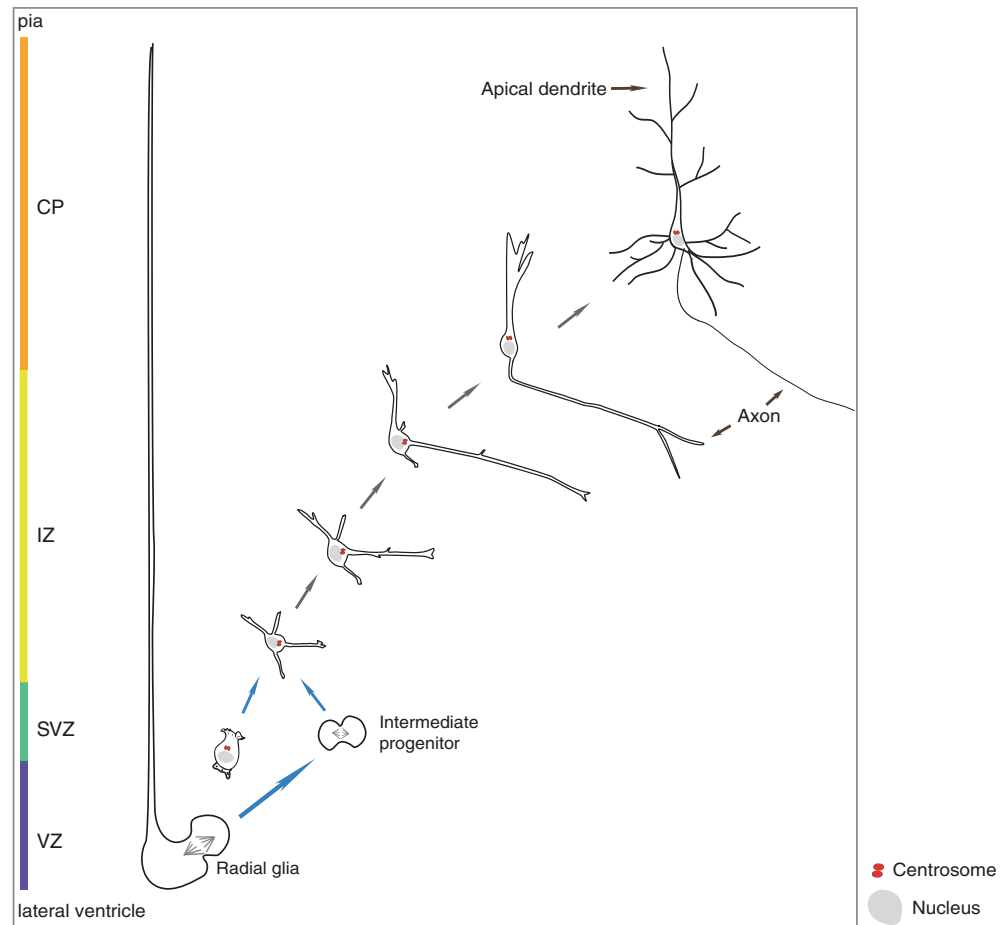
Neurons either migrate radially (e.g., cortical pyramidal neurons) or tangentially (e.g., cortical interneurons) to find their final position in the brain (Kriegstein & Noctor, 2004). Centrosome positioning along with microtubule and actin cytoskeleton dynamics plays an important role during neuronal migration (Higginbotham & Gleeson, 2007; Kuijpers & Hoogenraad, 2011; Schaar & McConnell, 2005; Tsai & Gleeson, 2005). Neurons follow a two-stroke saltatory movement during migration. This movement is characterized by a repetitive pattern of rapid extension and retraction of the leading process, which stabilizes 10 of microns ahead of the soma, followed by forward displacement of the centrosome into the leading process. Subsequently, the nucleus and soma translocate forward with concurrent retraction of the trailing process. During this process, the microtubules emanate from the centrosome, anteriorly into the leading process and posteriorly to envelope the nucleus to form a perinuclear tubulin cage (Rivas & Hatten, 1995). Live in situ imaging of organotypic mouse cortical and cerebellar slices showed that the centrosome first translocates to the leading process and displaces the nucleus forward along the microtubule network (Solecki, Model, Gaetz, Kapoor, & Hatten, 2004; Tsai, Bremner, & Vallee, 2007; Vallee, Seale, & Tsai, 2009). Along these lines, mParó overexpression disrupts the perinuclear tubulin cage and inhibits centrosomal motion as well as neuronal migration in mouse cerebellar granule neurons (Solecki et al., 2004; Solecki, Govek, & Hatten, 2006). These data establish the centrosome as a functional link between the microtubule-based pulling forces generated in the leading process and the perinuclear microtubule network. Moreover, proper positioning of the centrosome in facial

bronchio motor neurons of zebrafish seem to be important for their tangential migration (Grant & Moens, 2010).

However, studies from mouse cerebellar granule cells (Umeshima, Hirano, & Kengaku, 2007) and zebrafish neurons from tegmental hindbrain nuclei (Distel, Hocking, Volkmann, & Köster, 2010) differ with the centrosome-dependent pulling mechanisms of the perinuclear-cage during migration, suggesting a centrosome-independent nuclear movement. Another study from cortical neurons in situ shows that Myosin II motors-dependent F-actin drives the coordinated movement of centrosome and soma during neuronal migration (Solecki et al., 2009). Although the presence of the actin cytoskeleton underlying the membrane in the leading and trailing process is already known in migrating neurons (Tsai & Gleeson, 2005), the data from Solecki et al. (2009) attributes an important function of the actin cytoskeleton in centrosome dynamics during neuronal migration.

In the developing cortex, neuronal migration and axon specification are intertwined, meaning that the axon specification happens while neurons migrate (Noctor, Martinez-Cerdeño, Ivic, & Kriegstein, 2004). Neurons originate in the ventricular zone/intermediate zone, where they generally have a multipolar shape. Eventually, they change to a bipolar morphology and migrate towards the cortical plate to stop migration (Figure 2) and form different layers in the cortex. Early electron microscopic studies on mouse cortex, in situ, revealed that the centrosome is generally located at the origin of the extending axon in the multipolar neurons of the intermediate zone, which projects tangentially or towards the ventricular zone (Shoukimas & Hinds, 1978). However, in more mature neurons already located in the cortical plate, the centrosome can be found in proximity to the apical/leading process or future apical dendrite, which is oriented towards the cortex surface (Shoukimas & Hinds, 1978). This initial observation suggests that the centrosome is dynamic during neuronal differentiation in the developing cortex. Indeed, live-imaging of multipolar cells in the intermediate zone demonstrated that the centrosome translocates transiently to the site of axon formation before or at the time of initial axon outgrowth (de Anda, Meletis, Ge, Rei, & Tsai, 2010). These observations were confirmed by another study (Sakakibara et al., 2014), that described centrosome dynamics during migration and axon specification (Figure 2). Multipolar neurons in the intermediate zone have the centrosome positioned at the base of the actively growing process. Then, the centrosome moves towards the newly formed process. When a multipolar neuron initiates an axon by tangential extension of a dominant process, the centrosome localizes to the base of a growing axon. After formation of a pia-directed leading process, reorientation of the centrosome towards the leading process occurs (Figure 2) (de Anda et al., 2010). In turn, centrosomal disruption or silencing of PCM-1 affects axon formation in situ (Froylan Calderon de Anda et al., 2010). In zebrafish Rohon-Beard sensory neurons, Andersen and Halloran discovered a spatiotemporal relationship between centrosome position and the formation of peripheral axons. They showed that laser-induced centrosome ablation (before axon formation) inhibits axon outgrowth in these neurons (Andersen & Halloran, 2012). In the same study, centrosome position and motility

FIGURE 2 Centrosome positioning in a migrating cortical pyramidal neuron in situ in the developing cortex. The drawings show different developmental stages of a migrating cortical pyramidal neuron, in situ—from genesis to axon specification and dendritogenesis. The position of the centrosome is marked while the newly born neuron originated from the Radial Glia progenitors in the ventricular zone (VZ) or the intermediate progenitors in the intermediate zone (IZ) migrate to the cortical plate while forming neurites that eventually become axon or dendrites [Color figure can be viewed at wileyonlinelibrary.com]



are shown to be regulated by LIM homeodomain transcription factor activity, which is specifically required for the development of peripheral axons in the Rohon-Beard sensory neurons. Furthermore, centrosome mis-localization is correlated with ectopic axon formation in laminin alpha-1 mutants (Andersen & Halloran, 2012).

In some bipolar neurons located in the cortical plate of the developing cortex, however, axon formation occurs at the opposite pole to the centrosome position. The centrosome of those bipolar cells is already at the base of a pia-directed leading process or future apical dendrite (Sakakibara et al., 2014), as described in zebra fish (Distel et al., 2010; Zolessi, Poggi, Wilkinson, Chien, & Harris, 2006). Altogether, the research from various biological systems confirms the following things: (a) The dynamic nature of the centrosome during neuronal migration and axon specification. (b) The positioning of the centrosome either at the site of axon specification or on the opposite pole during axon specification.

In contrast, *Drosophila* devoid of centrioles (mutants of Sas-4 and Sas-6) develop normally with typical axon trajectories (Basto et al., 2006; Peel, Stevens, Basto, & Raff, 2007). Interestingly, other studies show a PCM structure that is still present in those flies without centrioles, which is enough to form a polarized microtubule array (Baumbach, Novak, Raff, & Wainman, 2015; Pollarolo, Schulz, Munck, & Dotti, 2011). Moreover, acute ablation of centrioles does not affect the pericentriolar material (Cabral, Laos, Dumont, & Dammermann, 2019). Altogether the data from various in situ studies

suggest an indispensable role of the centrosome, or at least a functional PCM, for axon specification.

1.6 | Centrosome as an F-Actin organization center during early neuronal differentiation

Somatic microtubules organized by the centrosome ensure neurite outgrowth and axon formation during initial stages of neuronal migration and polarization (Ahmad et al., 1994; Ahmad & Baas, 1995; Baas, 1996, 1999; Bamberg, Bray, & Chapman, 1986; Yu & Baas, 1994). Whereas, initial attempts to show F-actin delivery to distant growth cones or neurite terminals was not successful (Bernstein & Bamberg, 1992; Sanders & Wang, 1991). It was shown, however, that F-actin is organized locally in the growth cone (Paul Forscher, Lin, & Thompson, 1992; Okabe & Hirokawa, 1991). Moreover, altering F-actin dynamics at the growth cone affect neurite growth (Flynn et al., 2012; Gallo, Yee, & Letourneau, 2002; Lowery & Van Vactor, 2009). In parallel, growth cone-like anterograde actin-waves moving along the neurite shaft could help sustain neurite growth in cultured neurons (Flynn, Pak, Shaw, Bradke, & Bamberg, 2009; Ruthel & Banker, 1998, 1999; Winans, Collins, & Meyer, 2016). More recently, an anterograde F-actin flow was described during neuronal migration (He, Zhang, Guan, Xia, & Yuan, 2010; Solecki et al., 2009) and at the base of the growth cones (Burnette et al., 2008). Importantly, using high-resolution microscopy techniques, it was demonstrated that

mature axonal shafts contain actin “hotspots” and “trails,” which contribute to axon anterograde actin transport (Chakrabarty et al., 2019; Ganguly et al., 2015). Altogether, these studies suggest a strong centrifugal component to the neuronal F-actin organization, in addition to the existing local assembly of filaments of F-actin in the growth cones.

Recent studies identified the centrosome as an F-actin organization center in vitro (Farina et al., 2016), with implications in lymphocyte polarity (Farina et al., 2016; Obino et al., 2016) and cell division (Plessner et al., 2019). The centrosome nucleates actin filaments in vitro in an Arp2/3 complex, WASH nucleation promoting factor, and PCM-1 mediated-manner (Farina et al., 2016). On this regard, a following study showed that in resting lymphocytes, the centrosomal Arp2/3-dependent F-actin nucleation is required for centrosome tethering to the nucleus (Obino et al., 2016). In activated lymphocytes, however, the centrosomal F-actin nucleation is downregulated to facilitate the centrosome polarization to the immune synapse (Obino et al., 2016). More recently, centrosomal actin assembly was shown to be crucial for proper mitotic spindle formation and chromosome

congression, which is required for maintenance of genomic integrity during mitosis (Plessner et al., 2019). These recent studies raise the necessity to investigate the function of centrosomal F-actin organization in neurons.

Accordingly, our recent work uncovered a somatic F-actin organization concentrated around the centrosome in developing cultured neurons and in situ (Meka et al., 2019). The F-actin in the soma of neurons appeared as dynamic aster-like structures, closely associated with PCM-1 satellites (Figure 3). Furthermore, with Live-STED (stimulated emission depletion) microscopy, we discovered constant extensions of F-actin fibers from these dynamic F-actin asters (Meka et al., 2019). Interestingly, the F-actin asters in the soma of developing neurons (Meka et al., 2019) and the so-called actin hotspots in axon shafts of more matured neurons (Chakrabarty et al., 2019; Ganguly et al., 2015) are Formin but not Arp2/3-dependent. Using a photoactivatable F-actin probe, PaGFP-UtrCH, (Burkel, Bement, & Labs, 2015), we were able to show an anterograde F-actin movement from the soma to the growth cones/neurite tips. Photoactivation of

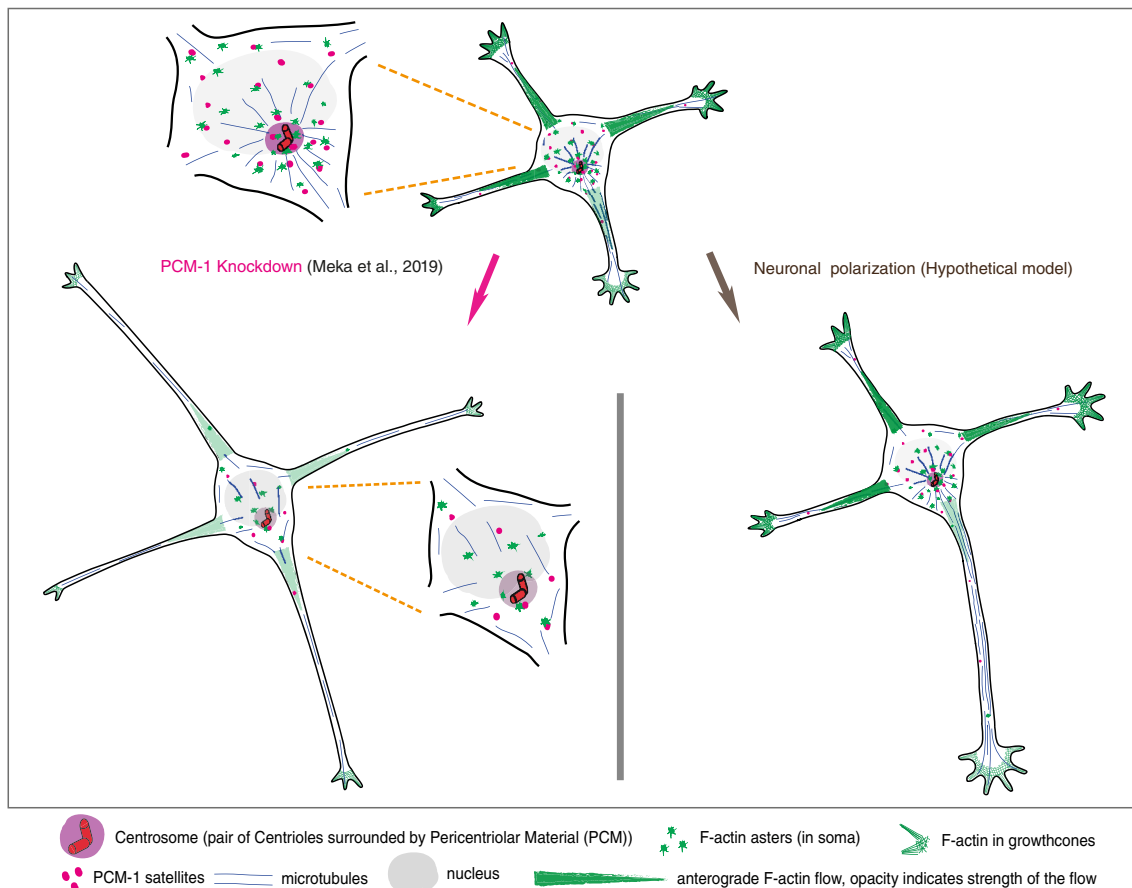


FIGURE 3 Illustration of the radial somatic F-actin organization in a developing neuron and how it is affected upon on PCM-1 knockdown and its implications in neuronal polarization (a hypothetical idea). F-actin organized around the centrosome is a source of peripheral F-actin, which helps to modulate growth cone dynamics (Meka et al., 2019). PCM-1 knockdown (that affects PCM protein recruitment and disturbs radial MTOC organization—discussed in the introduction section) results in the reduction of somatic F-actin asters and promotes neurite elongation due to decreased F-actin delivery to the periphery (left side). We hypothesize that the neurite elongating more during symmetry breakage is receiving less F-actin compared with the neurites that are not growing (Right side). Insets show zooms of soma of a developing Stage 2 neuron (top) and a PCM-1 downregulated neuron (left) [Color figure can be viewed at wileyonlinelibrary.com]

PaGFP-UtrCH in soma (in region with a diameter of $\sim 5 \mu\text{m}$) and quantification of signal intensity in the neurite tips revealed enrichment of F-actin (photoactivated-UtrCH) in the neurite tips with a simultaneous decrease of the signal in the photoactivated region of the soma (Meka et al., 2019).

Alternatively, with molecular manipulation experiments by over-expressing actin stabilizing phospho-mimetic mutants of Drebrin and Cofilin, DrebrinS142D and CofilinS3E, (Garvalov et al., 2007; Worth, Daly, Geraldo, Oozer, & Gordon-Weeks, 2013) along with an F-actin probe (Lifeact), we were able to show F-actin release from the somatic asters in cultured primary neurons. The F-actin released from a somatic F-actin aster moves in a comet-like fashion into the cell periphery. Additionally, proper centrosomal constitution and functions are important for the F-actin organization in the neuronal growth cones: centrosomal disruption (by chromophore-assisted light inactivation) or shRNA-mediated knock down of PCM-1—a protein that was shown to build the PCM (Dammermann & Merdes, 2002) and polymerizes F-actin (Farina et al., 2016)—affected the somatic F-actin content, resulting in a decrease of peripheral F-actin content and treadmill rate in the growth cone/neurite tips of cultured primary neurons (Meka et al., 2019). Altogether, these results suggest a robust flow of actin from the cell body to the periphery (neurite growth cones).

1.7 | Radial F-actin translocation as a potential inhibitory loop to promote polarization

One important question in the field is how early developing neurons cope to sustain the elongation of only one neurite during axon formation? In other words, why do dendrites and axon not grow simultaneously? Previous studies suggest that positive and negative feedback signals play a crucial role in axon and dendrite specification. Local increase of cAMP in one neurite decreases cAMP in all other neurites of the same neuron. The alterations in the cAMP and cGMP levels in the neurites are mutually opposing. Thus, local and long-range reciprocal regulation of cAMP and cGMP together ensure a coordinated development of one axon and multiple dendrites (Shelly et al., 2010). Whereas, Semaphorin 3A acts as an inhibitory signal that suppresses axonal growth (and thus promotes dendritogenesis) in cultured hippocampal neurons (Shelly et al., 2011). Long-range inhibitory signaling mediated by Ca^{2+} waves suppresses outgrowth of minor processes by activating RhoA, and thereby ensuring neuronal polarization (Takano et al., 2017). These data suggest that positive feedback signals are continuously activated in one of the minor neurites resulting in axon specification and elongation. In turn, negative feedback signals are propagated from a nascent axon terminal to all minor neurites to inhibit the outgrowth of all neurites at the same time, thereby leading to an asymmetric growth. All the downstream signaling mechanisms suggested for the positive and negative feedback signals seem to converge at two fundamental aspects related to cytoskeleton dynamics. (a) Increased microtubule stabilization and (b) enhanced F-actin dynamics (actin instability) (Andersen & Bi, 2000; Bradke & Dotti, 2000; Takano, Funahashi, & Kaibuchi, 2019).

Our recent experiments offer a novel point of view for this conundrum, given that our photoactivation experiments with PaGFP-UtrCH show that the intensity of the photoactivated somatic F-actin signal reaching the periphery is inversely proportional to the length of the neurites (Meka et al., 2019). Therefore, F-actin in growth cones could act as a growth-inhibiting factor. Along these lines, removal of F-actin from growth cones/neurite tips by pharmacological means promotes neurite outgrowth (Bradke & Dotti, 1999; Forscher, 1988). Moreover, photoactivation of PaGFP-UtrCH in PCM-1 downregulated cells show that the intensity of the photoactivated F-actin signal moving from soma to the periphery is significantly reduced, compared to the control counterparts (Meka et al., 2019). These findings could explain the F-actin content depletion observed in growth cone/neurite tips of the PCM-1 downregulated neurons described above. Altogether, it is possible to envision that impaired somatic F-actin delivery in PCM-1 knockdown cells could be the reason for the excessive neurite extension observed in these neurons (Figure 3; Meka et al., 2019). Based on these observations, we hypothesize that the somatic organization of F-actin around the centrosome preferentially provides F-actin to peripheral places, where the outgrowth should be limited (eventually the shorter neurites, Figure 3). Thus, acting as an inhibitory or a pulling force, which suppresses neurite growth. On the other hand, places receiving less F-actin, but more microtubules (Baas, 1999; Yu & Baas, 1994), should be primed for growth, leading for asymmetrical outgrowth/axon formation.

2 | CONCLUSION

An important question in neurobiology is how neurons achieve distinct functional domains, one axon and several dendrites, which allow them to connect properly? Axon specification is the key event determining polarity. Although there is data suggesting either extracellular cues or cell-intrinsic factors—such as centrosome positioning—playing a role in axon specification, it is not clear if one of these factors influences the other or if they function in tandem. Research on extracellular cues-guided polarity signals suggests microtubule and actin cytoskeleton as their key targets to promote neurite extensions and axon specification. Similarly, centrosomal activities have been shown to directly modulate the microtubule cytoskeleton dynamics in early developing neurons, both in culture and in situ migration neurons. Not until recently we could envision a completely unexpected role of the centrosome as an F-actin organizer in early developing neurons. The centrosome-dependent radial F-actin delivery preferentially to growth cones of the shorter neurites (future dendrites), along with the established role of centrosomal microtubules in the nascent axon provides a mechanistic explanation for asymmetric neurite extension during cell polarization. The centrosome-dependent cell-intrinsic activities and the signaling mechanisms induced by extracellular cues seem to commonly target the microtubule and actin cytoskeleton to guide axon specification and neurite extensions. In spite of the fact that the recent data is just a first step in establishing the function of the centrosome as an F-actin organizer in early developing neurons,

these findings prompt us to redefine (and revisit) the functions of the centrosome during neuronal polarity and in general. The molecular dissection of this novel centrosome-dependent F-actin organization and identification of the exact anterograde F-actin delivery mechanisms are now the challenges ahead. Moreover, it will be interesting to know the underlying mechanism by which the centrosome plays an antagonizing role in delivering more microtubules and less F-actin to a growing neurite. The emerging microscopic technologies with high spatial and temporal resolution could unravel these unknown aspects of centrosome- cytoskeleton organization/dynamics for a better understanding of their role in neuronal polarization and development.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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REFERENCES

- Ahmad, F. J., & Baas, P. W. (1995). Microtubules released from the neuronal centrosome are transported into the axon. *Journal of Cell Science*, 108(8), 2761–2769. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/7593317>
- Ahmad, F. J., Joshi, H. C., Centonze, V. E., & Baas, P. W. (1994). Inhibition of microtubule nucleation at the neuronal centrosome compromises axon growth. *Neuron*, 12(2), 271–280. [https://doi.org/10.1016/0896-6273\(94\)90270-4](https://doi.org/10.1016/0896-6273(94)90270-4)
- Andersen, E. F., & Halloran, M. C. (2012). Centrosome movements in vivo correlate with specific neurite formation downstream of LIM homeodomain transcription factor activity. *Journal of Cell Science*, 125(19), e1. <https://doi.org/10.1242/jcs.122424>
- Andersen, S. S. L., & Bi, G. Q. (2000). Axon formation: A molecular model for the generation of neuronal polarity. *BioEssays*, 22(2), 172–179. [https://doi.org/10.1002/\(SICI\)1521-1878\(200002\)22:2<172::AID-BIES8>3.0.CO;2-Q](https://doi.org/10.1002/(SICI)1521-1878(200002)22:2<172::AID-BIES8>3.0.CO;2-Q)
- Arregui, C., Busciglio, J., Caceres, A., & Barra, H. S. (1991). Tyrosinated and detyrosinated microtubules in axonal processes of cerebellar macroneurons grown in culture. *Journal of Neuroscience Research*, 28(2), 171–181. <https://doi.org/10.1002/jnr.490280204>
- Azimzadeh, J. (2014). Exploring the evolutionary history of centrosomes. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 369, 20130453. <http://dx.doi.org/10.1098/rstb.2013.0453>
- Azimzadeh, J., & Bornens, M. (2007). Structure and duplication of the centrosome. *Journal of Cell Science*, 120(13), 2139–2142. <https://doi.org/10.1242/jcs.005231>
- Baas, P. W. (1996). 6 the neuronal centrosome as a generator of microtubules for the axon. *Current Topics in Developmental Biology*, 33, 281–298. [https://doi.org/10.1016/S0070-2153\(08\)60341-5](https://doi.org/10.1016/S0070-2153(08)60341-5)
- Baas, P. W. (1999). Microtubules and neuronal polarity: Lessons from mitosis. *Neuron*, 22(1), 23–31. [https://doi.org/10.1016/S0896-6273\(00\)80675-3](https://doi.org/10.1016/S0896-6273(00)80675-3)
- Baas, P. W., Rao, A. N., Matamoros, A. J., & Leo, L. (2016). Cytoskeleton (Hoboken), 73(9), 442–460. <https://doi.org/10.1002/cm.21286>
- Bamburg, J. R., Bray, D., & Chapman, K. (1986). Assembly of microtubules at the tip of growing axons. *Nature*, 321(6072), 788–790. <https://doi.org/10.1038/321788a0>
- Bartolini, F., & Gundersen, G. G. (2006). Generation of noncentrosomal microtubule arrays. *Journal of Cell Science*, 119(20), 4155–4163. <https://doi.org/10.1242/jcs.03227>
- Basto, R., Lau, J., Vinogradova, T., Gardiol, A., Woods, C. G., Khodjakov, A., & Raff, J. W. (2006). Flies without centrioles. *Cell*, 125(7), 1375–1386. <https://doi.org/10.1016/j.cell.2006.05.025>
- Baumbach, J., Novak, Z. A., Raff, J. W., & Wainman, A. (2015). Dissecting the function and assembly of acentriolar microtubule organizing centers in Drosophila cells in vivo. *PLoS Genetics*, 11(5), 1–22. <https://doi.org/10.1371/journal.pgen.1005261>
- Bernstein, B. W., & Bamburg, J. R. (1992). Actin in emerging neurites is recruited from a monomer pool. *Molecular Neurobiology*, 6(2–3), 95–106. <https://doi.org/10.1007/BF02780546>
- Bettencourt-Dias, M., & Glover, D. M. (2007). Centrosome biogenesis and function: Centrosomes brings new understanding. *Nature Reviews Molecular Cell Biology*, 8(6), 451–463. <https://doi.org/10.1038/nrm2180>
- Bond, J., Roberts, E., Mochida, G. H., Hampshire, D. J., Scott, S., Askham, J. M., ... Geoffrey Woods, C. (2002). ASPM is a major determinant of cerebral cortical size. *Nature Genetics*, 32(2), 316–320. <https://doi.org/10.1038/ng995>
- Bond, J., Roberts, E., Springell, K., Lizarraga, S., Scott, S., Higgins, J., ... Woods, C. G. (2005). A centrosomal mechanism involving CDK5RAP2 and CENPJ controls brain size. *Nature Genetics*, 37(4), 353–355. <https://doi.org/10.1038/ng1539>
- Bond, J., & Woods, C. G. (2006). Cytoskeletal genes regulating brain size. *Current Opinion in Cell Biology*, 18(1), 95–101. <https://doi.org/10.1016/j.ceb.2005.11.004>
- Bornens, M. (2012). The centrosome in cells and organisms. *Science*, 335(6067), 422–426. <https://doi.org/10.1126/science.1209037>
- Bowler, M., Kong, D., Sun, S., Nanjundappa, R., Evans, L., Farmer, V., ... Loncarek, J. (2019). High-resolution characterization of centriole distal appendage morphology and dynamics by correlative STORM and electron microscopy. *Nature Communications*, 10(1), 993. <https://doi.org/10.1038/s41467-018-08216-4>
- Bradke, F., & Dotti, C. C. (1999). The role of local Actin instability in axon formation. *Science*, 283(5409), 1931–1934. <https://doi.org/10.1126/science.283.5409.1931>
- Bradke, F., & Dotti, C. G. (2000). Differentiated neurons retain the capacity to generate axons from dendrites. *Current Biology*, 10(22), 1467–1470. [https://doi.org/10.1016/S0960-9822\(00\)00807-1](https://doi.org/10.1016/S0960-9822(00)00807-1)
- Buchman, J. J., Tseng, H.-C., Zhou, Y., Frank, C. L., Xie, Z., & Tsai, L.-H. (2010). Cdk5rap2 interacts with pericentrin to maintain the neural progenitor pool in the developing neocortex. *Neuron*, 66(3), 386–402. <https://doi.org/10.1016/j.neuron.2010.03.036>
- Burkel, B. M., Bement, W. M., & Labs, F. H. (2015). Versatile fluorescent probes for Actin filaments based on the Actin-binding domain of utrophin. *Cell Motility and the Cytoskeleton*, 64(11), 822–832. <https://doi.org/10.1002/cm.20226>
- Burnette, D. T., Ji, L., Schaefer, A. W., Medeiros, N. A., Danuser, G., & Forscher, P. (2008). Myosin II activity facilitates microtubule bundling in the neuronal growth cone neck. *Developmental Cell*, 15(1), 163–169. <https://doi.org/10.1016/j.devcel.2008.05.016>
- Cabral, G., Laos, T., Dumont, J., & Dammermann, A. (2019). Differential requirements for centrioles in mitotic centrosome growth and

- maintenance. *Developmental Cell*, 50(3), 355–366.e6. <https://doi.org/10.1016/j.devcel.2019.06.004>
- Calderon de Anda, F., Gartner, A., Tsai, L.-H., & Dotti, C. G. (2008). Pyramidal neuron polarity axis is defined at the bipolar stage. *Journal of Cell Science*, 121(2), 178–185. <https://doi.org/10.1242/jcs.023143>
- Camargo Ortega, G., Falk, S., Johansson, P. A., Peyre, E., Broix, L., Sahu, S. K., ... Götz, M. (2019). The centrosome protein AKNA regulates neurogenesis via microtubule organization. *Nature*, 567(7746), 113–117. <https://doi.org/10.1038/s41586-019-0962-4>
- Chabin-brion, K., Perez, F., Drechou, A., & Pou, C. (2001). The Golgi complex is a microtubule-organizing organelle. *Journal of Cell Biology*, 154(1), 2047–2060.
- Chakrabarty, N., Dubey, P., Tang, Y., Ganguly, A., Ladit, K., Letierrier, C., ... Roy, S. (2019). Processive flow by biased polymerization mediates the slow axonal transport of Actin. *Journal of Cell Biology*, 218(1), 112–124. <https://doi.org/10.1083/jcb.201711022>
- Conduit, P. T., Wainman, A., & Raff, J. W. (2015). Centrosome function and assembly in animal cells. *Nature Reviews Molecular Cell Biology*, 16(10), 611–624. <https://doi.org/10.1038/nrm4062>
- Cowan, C. R., & Hyman, A. A. (2004). Centrosomes direct cell polarity independently of microtubule assembly in *C. elegans* embryos. *Nature*, 431(7004), 92–96. <https://doi.org/10.1038/nature02825>
- Dammermann, A., & Merdes, A. (2002). Assembly of centrosomal proteins and microtubule organization depends on PCM-1. *Journal of Cell Biology*, 159(2), 255–266. <https://doi.org/10.1083/jcb.200204023>
- de Anda, F. C., Meletis, K., Ge, X., Rei, D., & Tsai, L.-H. (2010). Centrosome motility is essential for initial axon formation in the neocortex. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 30(31), 10391–10406. <https://doi.org/10.1523/JNEUROSCI.0381-10.2010>
- de Anda, F. C., Pollarolo, G., da Silva, J. S., Camoletto, P. G., Feiguin, F., & Dotti, C. G. (2005). Centrosome localization determines neuronal polarity. *Nature*, 436(7051), 704–708. <https://doi.org/10.1038/nature03811>
- De La Roche, M., Asano, Y., & Griffiths, G. M. (2016). Origins of the cytoskeletal synapse. *Nature Reviews Immunology*, 16(7), 421–432. <https://doi.org/10.1038/nri.2016.54>
- Delgehr, N., Sillibourne, J., & Bornens, M. (2005). Microtubule nucleation and anchoring at the centrosome are independent processes linked by ninein function. *Journal of Cell Science*, 118(8), 1565–1575. <https://doi.org/10.1242/jcs.02302>
- Ding, W., Wu, Q., Sun, L., Pan, N. C., & Wang, X. (2019). Cenpj regulates cilia disassembly and neurogenesis in the developing mouse cortex. *Journal of Neuroscience*, 39(11), 1994–2010. <https://doi.org/10.1523/JNEUROSCI.1849-18.2018>
- Distel, M., Hocking, J. C., Volkmann, K., & Köster, R. W. (2010). The centrosome neither persistently leads migration nor determines the site of axonogenesis in migrating neurons in vivo. *Journal of Cell Biology*, 191(4), 875–890. <https://doi.org/10.1083/jcb.201004154>
- Dotti, C. G., Sullivan, C. A., & Banker, G. A. (1988). The establishment of polarity by hippocampal neurons in culture. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 8(4), 1454–1468. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/3282038>
- Duband, J.-L. (2006). Neural crest delamination and migration. In *Neural Crest Induction and Differentiation* (pp. 45–77). Boston, MA: Springer. https://doi.org/10.1007/978-0-387-46954-6_4
- Efimov, A., Kharitonov, A., Efimova, N., Loncarek, J., Miller, P. M., Andreyeva, N., ... Kaverina, I. (2007). Article asymmetric CLASP-dependent nucleation of noncentrosomal microtubules at the Trans-Golgi network. *Developmental Cell*, 12(6), 917–930. <https://doi.org/10.1016/j.devcel.2007.04.002>
- Esch, T., Lemmon, V., & Banker, G. (1999). Local presentation of substrate molecules directs axon specification by cultured hippocampal neurons. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 19(15), 6417–6426.
- Farina, F., Gaillard, J., Guérin, C., Couté, Y., Sillibourne, J., Blanchoin, L., & Théry, M. (2016). The centrosome is an Actin-organizing Centre. *Nature Cell Biology*, 18(1), 65–75. <https://doi.org/10.1038/ncb3285>
- Feng, Y., & Walsh, C. A. (2004). Mitotic spindle regulation by Nde1 controls cerebral cortical size. *Neuron*, 44(2), 279–293. <https://doi.org/10.1016/j.neuron.2004.09.023>
- Flynn, K. C., Hellal, F., Neukirchen, D., Jacob, S., Tahirovic, S., Dupraz, S., ... Bradke, F. (2012). ADF/Cofilin-mediated Actin retrograde flow directs neurite formation in the developing brain. *Neuron*, 76(6), 1091–1107. <https://doi.org/10.1016/j.neuron.2012.09.038>
- Flynn, K. C., Pak, C. W., Shaw, A. E., Bradke, F., & Bamberg, J. R. (2009). Growth cone-like waves transport Actin and promote axonogenesis and neurite branching. *Developmental Neurobiology*, 69(12), 761–779. <https://doi.org/10.1002/dneu.20734>
- Forscher, P. (1988). Actions of cytochalasins on the organization of actin filaments and microtubules in a neuronal growth cone. *The Journal of Cell Biology*, 107(4), 1505–1516. <https://doi.org/10.1083/jcb.107.4.1505>
- Forscher, P., Lin, C. H., & Thompson, C. (1992). Novel form of growth cone motility involving site-directed actin filament assembly. *Nature*, 357(6378), 515–518. <https://doi.org/10.1038/357515a0>
- Gallo, G., Yee, H. F., & Letourneau, P. C. (2002). Actin turnover is required to prevent axon retraction driven by endogenous actomyosin contractility. *Journal of Cell Biology*, 158(7), 1219–1228. <https://doi.org/10.1083/jcb.200204140>
- Ganguly, A., Tang, Y., Wang, L., Ladit, K., Loi, J., Dargent, B., ... Roy, S. (2015). A dynamic formin-dependent deep F-actin network in axons. *Journal of Cell Biology*, 210(3), 401–417. <https://doi.org/10.1083/jcb.201506110>
- Garcez, P. P., Diaz-Alonso, J., Crespo-Enriquez, I., Castro, D., Bell, D., & Guillemot, F. (2015). Cenpj/CPAP regulates progenitor divisions and neuronal migration in the cerebral cortex downstream of Ascl1. *Nature Communications*, 6(1), 6474. <https://doi.org/10.1038/ncomms7474>
- Garnham, C. P., & Roll-Mecak, A. (2012). The chemical complexity of cellular microtubules: Tubulin post-translational modification enzymes and their roles in tuning microtubule functions. *Cytoskeleton*, 69(7), 442–463. <https://doi.org/10.1002/cm.21027>
- Gärtner, A., Fornasiero, E. F., Munck, S., Vennekens, K., Seuntjens, E., Huttner, W. B., ... Dotti, C. G. (2012). N-cadherin specifies first asymmetry in developing neurons. *The EMBO Journal*, 31(8), 1893–1903. <https://doi.org/10.1038/emboj.2012.41>
- Gärtner, A., Fornasiero, E. F., Valtorta, F., & Dotti, C. G. (2014). Distinct temporal hierarchies in membrane and cytoskeleton dynamics precede the morphological polarization of developing neurons. *Journal of Cell Science*, 127(20), 4409–4419. <https://doi.org/10.1242/jcs.149815>
- Garvalov, B. K., Flynn, K. C., Neukirchen, D., Meyn, L., Teusch, N., Wu, X., ... Bradke, F. (2007). Cdc42 regulates cofilin during the establishment of neuronal polarity. *Journal of Neuroscience*, 27(48), 13117–13129. <https://doi.org/10.1523/JNEUROSCI.3322-07.2007>
- Ge, X., Frank, C. L., Calderon de Anda, F., & Tsai, L.-H. (2010). Hook3 interacts with PCM1 to regulate pericentriolar material assembly and the timing of neurogenesis. *Neuron*, 65(2), 191–203. <https://doi.org/10.1016/j.neuron.2010.01.011>
- Geraldo, S., Khanzada, U. K., Parsons, M., Chilton, J. K., & Gordon-Weeks, P. R. (2008). Targeting of the F-Actin-binding protein drebrin by the microtubule plus-tip protein EB3 is required for neuriteogenesis. *Nature Cell Biology*, 10(10), 1181–1189. <https://doi.org/10.1038/ncb1778>
- Grant, P. K., & Moens, C. B. (2010). The neuroepithelial basement membrane serves as a boundary and a substrate for neuron migration in the zebrafish hindbrain. *Neural Development*, 5(1), 1–17. <https://doi.org/10.1186/1749-8104-5-9>
- Hammond, J. W., Huang, C., Kaech, S., Jacobson, C., Banker, G., & Verhey, K. J. (2010). Posttranslational modifications of tubulin and the polarized transport of Kinesin-1 in neurons. *Journal of Cell Biology*, 189(1), 572–583. <https://doi.org/10.1091/mbc.E09-01-0044>

- He, M., Zhang, Z. -h., Guan, C. -b., Xia, D., & Yuan, X. -b. (2010). Leading tip drives soma translocation via forward F-actin flow during neuronal migration. *Journal of Neuroscience*, 30(32), 10885–10898. <https://doi.org/10.1523/jneurosci.0240-10.2010>
- Higginbotham, H. R., & Gleeson, J. G. (2007). The centrosome in neuronal development. *Trends in Neurosciences*, 30(6), 276–283. <https://doi.org/10.1016/j.tins.2007.04.001>
- Hung, L.-Y., Tang, C.-J. C., & Tang, T. K. (2000). Protein 4.1 R-135 interacts with a novel centrosomal protein (CPAP) which is associated with the gamma-tubulin complex. *Molecular and Cellular Biology*, 20(20), 7813–7825. <https://doi.org/10.1128/mcb.20.20.7813-7825.2000>
- Jacobson, C., Schnapp, B., & Banker, G. A. (2006). A change in the selective translocation of the kinesin-1 motor domain marks the initial specification of the axon. *Neuron*, 49(6), 797–804. <https://doi.org/10.1016/j.neuron.2006.02.005>
- Janke, C. (2014). The tubulin code: Molecular components, readout mechanisms, and functions. *The Journal of Cell Biology*, 206(4), 461–472. <https://doi.org/10.1083/jcb.201406055>
- Joukov, V., & De Nicolo, A. (2019). The centrosome and the primary cilium: The Yin and Yang of a hybrid organelle. *Cell*, 8(7), 701. <https://doi.org/10.3390/cells8070701>
- Kasioulis, I., Das, R. M., & Storey, K. G. (2017). Inter-dependent apical microtubule and actin dynamics orchestrate centrosome retention and neuronal delamination. *eLife*, 6, 1–31. <https://doi.org/10.7554/eLife.26215>
- Kollman, J. M., Polka, J. K., Zelter, A., Davis, T. N., & Agard, D. A. (2010). Microtubule nucleating γ -TuSC assembles structures with 13-fold microtubule-like symmetry. *Nature*, 466(7308), 879–882. <https://doi.org/10.1038/nature09207>
- Konishi, Y., & Setou, M. (2009). Tubulin tyrosination navigates the kinesin-1 motor domain to axons. *Nature Neuroscience*, 12(5), 559–567. <https://doi.org/10.1038/nn.2314>
- Kouprina, N., Pavlicek, A., Collins, N. K., Nakano, M., Noskov, V. N., Ohzeki, J. I., ... Larionov, V. (2005). The microcephaly ASPM gene is expressed in proliferating tissues and encodes for a mitotic spindle protein. *Human Molecular Genetics*, 14(15), 2155–2165. <https://doi.org/10.1093/hmg/ddi220>
- Kriegstein, A. R., & Noctor, S. C. (2004). Patterns of neuronal migration in the embryonic cortex. *Trends in Neurosciences*, 27(7), 392–399. <https://doi.org/10.1016/j.tins.2004.05.001>
- Kuijpers, M., & Hoogenraad, C. C. (2011). Centrosomes, microtubules and neuronal development. *Molecular and Cellular Neuroscience*, 48(4), 349–358. <https://doi.org/10.1016/j.mcn.2011.05.004>
- Lowery, L. A., & Van Vactor, D. (2009). The trip of the tip: Understanding the growth cone machinery. *Nature Reviews. Molecular Cell Biology*, 10(5), 332–343. <https://doi.org/10.1038/nrm2679>
- Magiera, M. M., & Janke, C. (2014). Post-translational modifications of tubulin. *Current Biology*, 24(9), R351–R354. <https://doi.org/10.1016/j.cub.2014.03.032>
- Magiera, M. M., Singh, P., & Janke, C. (2018). SnapShot: Functions of tubulin posttranslational modifications. *Cell*, 173(6), 1552–1552.e1. <https://doi.org/10.1016/j.cell.2018.05.032>
- Meka, D. P., Scharrenberg, R., Zhao, B., Kobler, O., König, T., Schaefer, I., ... Calderon de Anda, F. (2019). Radial somatic F-actin organization affects growth cone dynamics during early neuronal development. *EMBO Reports*, 20, e47743. <https://doi.org/10.15252/embr.201947743>
- Mennella, V., Keszthelyi, B., McDonald, K. L., Chhun, B., Kan, F., Rogers, G. C., ... Agard, D. A. (2012). Subdiffraction-resolution fluorescence microscopy reveals a domain of the centrosome critical for pericentriolar material organization. *Nature Cell Biology*, 14(11), 1159–1168. <https://doi.org/10.1038/ncb2597>
- Mogensen, M. M., Malik, A., Piel, M., Boukson-Castaing, V., & Bornens, M. (2000). Microtubule minus-end anchorage at centrosomal and non-centrosomal sites: The role of ninein. *Journal of Cell Science*, 113(17), 3013–3023.
- Neukirchen, D., & Bradke, F. (2011). Through microtubule and growth cone. *Dynamics (Pembroke, Ont.)*, 31(4), 1528–1538. <https://doi.org/10.1523/JNEUROSCI.3983-10.2011>
- Nigg, E. A., & Raff, J. W. (2009). Centrioles, centrosomes, and cilia in health and disease. *Cell*, 139(4), 663–678. <https://doi.org/10.1016/j.cell.2009.10.036>
- Noctor, S. C., Martinez-Cerdeño, V., Ivic, L., & Kriegstein, A. R. (2004). Cortical neurons arise in symmetric and asymmetric division zones and migrate through specific phases. *Nature Neuroscience*, 7(2), 136–144. <https://doi.org/10.1038/nn1172>
- Oakley, B. R. (1992). γ -Tubulin: The microtubule organizer? *Trends in Cell Biology*, 2(1), 1–5. [https://doi.org/10.1016/0962-8924\(92\)90125-7](https://doi.org/10.1016/0962-8924(92)90125-7)
- Obino, D., Farina, F., Malbec, O., Sáez, P. J., Maurin, M., Gaillard, J., ... Lennon-Duménil, A. M. (2016). Actin nucleation at the centrosome controls lymphocyte polarity. *Nature Communications*, 7, 10969. <https://doi.org/10.1038/ncomms10969>
- Okabe, S., & Hirokawa, N. (1991). Actin dynamics in growth cones. *The Journal of Neuroscience*, 11(7), 1918–1929. <https://doi.org/10.1523/JNEUROSCI.11-07-01918.1991>
- Peel, N., Stevens, N. R., Basto, R., & Raff, J. W. (2007). Overexpressing centriole-replication proteins in vivo induces centriole overduplication and de novo formation. *Current Biology*, 17(10), 834–843. <https://doi.org/10.1016/j.cub.2007.04.036>
- Plessner, M., Knerr, J., & Grosse, R. (2019). Centrosomal actin assembly is required for proper mitotic spindle formation and chromosome congression. *Food Science and Human Wellness*, 15, 274–281. <https://doi.org/10.1016/j.isci.2019.04.022>
- Pollarolo, G., Schulz, J. G., Munck, S., & Dotti, C. G. (2011). Cytokinesis remnants define first neuronal asymmetry in vivo. *Nature Neuroscience*, 14(12), 1525–1533. <https://doi.org/10.1038/nn.2976>
- Pongrakhananon, V., Saito, H., Hiver, S., Abe, T., Shioi, G., Meng, W., & Takeichi, M. (2018). CAMSAP3 maintains neuronal polarity through regulation of microtubule stability. *Proceedings of the National Academy of Sciences*, 115(39), 9750–9755. <https://doi.org/10.1073/pnas.1803875115>
- Powell, S. K., Rivas, R. J., Rodriguez-Boulán, E., & Hatten, M. E. (1997). Development of polarity in cerebellar granule neurons. *Journal of Neurobiology*, 32(2), 223–236. [https://doi.org/10.1002/\(SICI\)1097-4695\(199702\)32:2<223::AID-NEU7>3.0.CO;2-A](https://doi.org/10.1002/(SICI)1097-4695(199702)32:2<223::AID-NEU7>3.0.CO;2-A)
- Randlett, O., Poggi, L., Zolessi, F. R., & Harris, W. A. (2011). The oriented emergence of axons from retinal ganglion cells is directed by laminin contact in vivo. *Neuron*, 70(2), 266–280. <https://doi.org/10.1016/j.neuron.2011.03.013>
- Reed, N. A., Cai, D., Blasius, T. L., Jih, G. T., Meyhofer, E., Gaertig, J., & Verhey, K. J. (2006). Microtubule acetylation promotes kinesin-1 binding and transport. *Current Biology*, 16(21), 2166–2172. <https://doi.org/10.1016/j.cub.2006.09.014>
- Rivas, R., & Hatten, M. (1995). Motility and cytoskeletal organization of migrating cerebellar granule neurons. *The Journal of Neuroscience*, 15(2), 981–989. <https://doi.org/10.1523/JNEUROSCI.15-02-00981.1995>
- Rivero, S., Cardenas, J., Bornens, M., & Rios, R. M. (2009). Microtubule nucleation at the cis-side of the Golgi apparatus requires AKAP450 and GM130. *EMBO Reports*, 10(1), 1–13. <https://doi.org/10.1038/emboj.2009.47>
- Ruthel, G., & Banker, G. (1998). Actin-dependent anterograde movement of growth-cone-like structures along growing hippocampal axons: A novel form of axonal transport? *Cell Motility and the Cytoskeleton*, 40(2), 160–173. [https://doi.org/10.1002/\(SICI\)1097-0169\(1998\)40:2<160::AID-CM5>3.0.CO;2-J](https://doi.org/10.1002/(SICI)1097-0169(1998)40:2<160::AID-CM5>3.0.CO;2-J)
- Ruthel, G., & Banker, G. (1999). Role of moving growth cone-like “wave” structures in the outgrowth of cultured hippocampal axons and dendrites. *Journal of Neurobiology*, 39(1), 97–106. [https://doi.org/10.1002/\(SICI\)1097-4695\(199904\)39:1<97::AID-NEU8>3.0.CO;2-Z](https://doi.org/10.1002/(SICI)1097-4695(199904)39:1<97::AID-NEU8>3.0.CO;2-Z)
- Sakakibara, A., Sato, T., Ando, R., Noguchi, N., Masaoka, M., & Miyata, T. (2014). Dynamics of centrosome translocation and microtubule

- organization in neocortical neurons during distinct modes of polarization. *Cerebral Cortex*, 24(5), 1301–1310. <https://doi.org/10.1093/cercor/bhs411>
- Sánchez-Huertas, C., Freixo, F., Viais, R., Lacasa, C., Soriano, E., & Lüders, J. (2016). Non-centrosomal nucleation mediated by augmin organizes microtubules in post-mitotic neurons and controls axonal microtubule polarity. *Nature Communications*, 7(1), 12187. <https://doi.org/10.1038/ncomms12187>
- Sanders, M. C., & Wang, Y. (1991). Assembly of actin-containing cortex occurs at distal regions of growing neurites in PC12 cells. *Journal of Cell Science*, 100(4), 771–780.
- Sarnat, H. B., & Flores-Sarnat, L. (2014). Morphogenesis timing of genetically programmed brain malformations in relation to epilepsy. In *Progress in Brain Research* (Vol. 213, 1st ed., pp. 181–198). Elsevier. Radarweg 29, PO Box 211, 1000 AE Amsterdam, The Netherlands. The Boulevard, Langford Lane, Kidlington, Oxford, OX5 1GB, UK. <https://doi.org/10.1016/B978-0-444-63326-2.00010-7>
- Scambler, P. J. (2000). The 22q11 deletion syndromes. *Human Molecular Genetics*, 9(16), 2421–2426. <https://doi.org/10.1093/hmg/9.16.2421>
- Schaar, B. T., & McConnell, S. K. (2005). Cytoskeletal coordination during neuronal migration. *Proceedings of the National Academy of Sciences*, 102(38), 13652–13657. <https://doi.org/10.1073/pnas.0506008102>
- Shelly, M., Cancedda, L., Lim, B. K., Popescu, A. T., Cheng, P. I., Gao, H., & Poo, M. m. (2011). Semaphorin3A regulates neuronal polarization by suppressing axon formation and promoting dendrite growth. *Neuron*, 71(3), 433–446. <https://doi.org/10.1016/j.neuron.2011.06.041>
- Shelly, M., Lim, B. K., Cancedda, L., Heilshorn, S. C., Gao, H., & Poo, M. -m. (2010). Local and long-range reciprocal regulation of cAMP and cGMP in axon/dendrite formation. *Science*, 327(5965), 547–552. <https://doi.org/10.1126/science.1179735>
- Shoukimas, G. M., & Hinds, J. W. (1978). The development of the cerebral cortex in the embryonic mouse: An electron microscopic serial section analysis. *Journal of Comparative Neurology*, 179(4), 795–830. <https://doi.org/10.1002/cne.901790407>
- Solecki, D. J., Govek, E.-E., & Hatten, M. E. (2006). mPar6 controls neuronal migration. *Journal of Neuroscience*, 26(42), 10624–10625. <https://doi.org/10.1523/jneurosci.4060-06.2006>
- Solecki, D. J., Model, L., Gaetz, J., Kapoor, T. M., & Hatten, M. E. (2004). Par6 α signaling controls glial-guided neuronal migration. *Nature Neuroscience*, 7(11), 1195–1203. <https://doi.org/10.1038/nn1332>
- Solecki, D. J., Trivedi, N., Govek, E.-E., Kerekes, R. A., Gleason, S. S., & Hatten, M. E. (2009). Myosin II motors and F-actin dynamics drive the coordinated movement of the centrosome and Soma during CNS glial-guided neuronal migration. *Neuron*, 63(1), 63–80. <https://doi.org/10.1016/j.neuron.2009.05.028>
- Song, Y., & Brady, S. T. (2015). Post-translational modifications of tubulin: Pathways to functional diversity of microtubules. *Trends in Cell Biology*, 25(3), 125–136. <https://doi.org/10.1016/j.tcb.2014.10.004>
- Song, Y., Kirkpatrick, L. L., Schilling, A. B., Helseth, D. L., Chabot, N., Keillor, J. W., ... Brady, S. T. (2013). Transglutaminase and polyamination of tubulin: Posttranslational modification for stabilizing axonal microtubules. *Neuron*, 78(1), 109–123. <https://doi.org/10.1016/j.neuron.2013.01.036>
- Stiess, M., Maghelli, N., Kapitein, L. C., Gomis-Ruth, S., Wilsch-Brauninger, M., Hoogenraad, C. C., ... Bradke, F. (2010). Axon extension occurs independently of centrosomal microtubule nucleation. *Science*, 327(5966), 704–707. <https://doi.org/10.1126/science.1182179>
- Takano, T., Funahashi, Y., & Kaibuchi, K. (2019). Neuronal polarity: Positive and negative feedback signals. *Frontiers in Cell and Developmental Biology*, 7(April), 1–10. <https://doi.org/10.3389/fcell.2019.00069>
- Takano, T., Wu, M., Nakamura, S., Naoki, H., Ishizawa, N., Namba, T., ... Kaibuchi, K. (2017). Discovery of long-range inhibitory signaling to ensure single axon formation. *Nature Communications*, 8(1), 1–17. <https://doi.org/10.1038/s41467-017-00044-2>
- Theveneau, E., & Mayor, R. (2012). Neural crest delamination and migration: From epithelium-to-mesenchyme transition to collective cell migration. *Developmental Biology*, 366(1), 34–54. <https://doi.org/10.1016/j.ydbio.2011.12.041>
- Toriyama, M., Kozawa, S., Sakumura, Y., & Inagaki, N. (2013). Conversion of a signal into forces for axon outgrowth through pak1-mediated shootin1 phosphorylation. *Current Biology*, 23(6), 529–534. <https://doi.org/10.1016/j.cub.2013.02.017>
- Tsai, J.-W., Bremner, K. H., & Vallee, R. B. (2007). Dual subcellular roles for LIS1 and dynein in radial neuronal migration in live brain tissue. *Nature Neuroscience*, 10(8), 970–979. <https://doi.org/10.1038/nn1934>
- Tsai, L. H., & Gleeson, J. G. (2005). Nucleokinesis in neuronal migration. *Neuron*, 46(3), 383–388. <https://doi.org/10.1016/j.neuron.2005.04.013>
- Umeshima, H., Hirano, T., & Kengaku, M. (2007). Microtubule-based nuclear movement occurs independently of centrosome positioning in migrating neurons. *Proceedings of the National Academy of Sciences*, 104(41), 16182–16187. <https://doi.org/10.1073/pnas.0708047104>
- Vallee, R. B., Seale, G. E., & Tsai, J. W. (2009). Emerging roles for myosin II and cytoplasmic dynein in migrating neurons and growth cones. *Trends in Cell Biology*, 19(7), 347–355. <https://doi.org/10.1016/j.tcb.2009.03.009>
- Vora, S. M., & Phillips, B. T. (2016). The benefits of local depletion: The centrosome as a scaffold for ubiquitin-proteasome-mediated degradation. *Cell Cycle*, 15(16), 2124–2134. <https://doi.org/10.1080/15384101.2016.1196306>
- Wileman, T. (2007). Aggresomes and pericentriolar sites of virus assembly: Cellular defense or viral design? *Annual Review of Microbiology*, 61(1), 149–167. <https://doi.org/10.1146/annurev.micro.57.030502.090836>
- Winans, A. M., Collins, S. R., & Meyer, T. (2016). Waves of Actin and microtubule polymerization drive microtubule-based transport and neurite growth before single axon formation. *eLife*, 5(February), e12387. <https://doi.org/10.7554/eLife.12387>
- Witte, H., Neukirchen, D., & Bradke, F. (2008). Microtubule stabilization specifies initial neuronal polarization. *The Journal of Cell Biology*, 180(3), 619–632. <https://doi.org/10.1083/jcb.200707042>
- Wloga, D., & Gaertig, J. (2010). Post-translational modifications of microtubules. *Journal of Cell Science*, 123(20), 3447–3455. <https://doi.org/10.1242/jcs.063727>
- Wloga, D., Joachimiak, E., & Fabczak, H. (2017). Tubulin post-translational modifications and microtubule dynamics. *International Journal of Molecular Sciences*, 18(10), 2207. <https://doi.org/10.3390/ijms18102207>
- Wloga, D., Joachimiak, E., Louka, P., & Gaertig, J. (2017). Posttranslational modifications of tubulin and cilia. *Cold Spring Harbor Perspectives in Biology*, 9(6), a028159. <https://doi.org/10.1101/cshperspect.a028159>
- Worth, D. C., Daly, C. N., Geraldo, S., Oozer, F., & Gordon-Weeks, P. R. (2013). Drebrin contains a cryptic F-Actin-bundling activity regulated by Cdk5 phosphorylation. *The Journal of Cell Biology*, 202(5), 793–806. <https://doi.org/10.1083/jcb.201303005>
- Xie, Z., Moy, L. Y., Sanada, K., Zhou, Y., Buchman, J. J., & Tsai, L. H. (2007). Cep120 and TACCs control interkinetic nuclear migration and the neural progenitor pool. *Neuron*, 56(1), 79–93. <https://doi.org/10.1016/j.neuron.2007.08.026>
- Yau, K. W., van Beuningen, S. F. B., Cunha-Ferreira, I., Cloin, B. M. C., van Battum, E. Y., Will, L., ... Hoogenraad, C. C. (2014). Microtubule minus-end binding protein CAMSAP2 controls axon specification and dendrite development. *Neuron*, 82(5), 1058–1073. <https://doi.org/10.1016/j.neuron.2014.04.019>
- Yu, W., & Baas, P. W. (1994). Changes in microtubule number and length during axon differentiation. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 14, 2818–2829.
- Zhao, B., Meka, D. P., Scharrenberg, R., König, T., Schwanke, B., Kobler, O., ... Calderon De Anda, F. (2017). Microtubules modulate F-actin dynamics during neuronal polarization. *Scientific Reports*, 7(1), 9583. <https://doi.org/10.1038/s41598-017-09832-8>

- Zheng, Y., Wong, M. L., Alberts, B., & Mitchison, T. (1995). Nucleation of microtubule assembly by a γ -tubulin-containing ring complex. *Nature*, 378(6557), 578–583. <https://doi.org/10.1038/378578a0>
- Zhong, X., Liu, L., Zhao, A., Pfeifer, G. P., & Xu, X. (2005). The abnormal spindle-like, microcephaly-associated (ASPM) gene encodes a centrosomal protein. *Cell Cycle*, 4(9), 1227–1229. <https://doi.org/10.4161/cc.4.9.2029>
- Zmuda, J. F., & Rivas, R. J. (1998). The Golgi apparatus and the centrosome are localized to the sites of newly emerging axons in cerebellar granule neurons in vitro. *Cell Motility and the Cytoskeleton*, 41(1), 18–38 [https://doi.org/10.1002/\(SICI\)1097-0169\(1998\)41:1<18::AID-CM2>3.0.CO;2-B](https://doi.org/10.1002/(SICI)1097-0169(1998)41:1<18::AID-CM2>3.0.CO;2-B)
- Zolessi, F. R., Poggi, L., Wilkinson, C. J., Chien, C. B., & Harris, W. A. (2006). Polarization and orientation of retinal ganglion cells in vivo. *Neural Development*, 1(2), 2. <https://doi.org/10.1186/1749-8104-1-2>

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