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Radial glial cells organize the central nervous system via microtubule dependant processes

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ABSTRACT

The correct cytokinesis and polarization of radial glial cells are essential for populating and patterning the central nervous system. The microtubule (MT) cytoskeleton is central to regulating glial and neuronal functions during development and in the adult, providing the dynamic ability to extend processes, migrate, establish synaptic connections and transmit information. MT biogenesis disorders result in a spectrum of neurological deficits resulting from abnormal neuronal proliferation, migration and aberrant white matter formation. In the present review, we place a spotlight on the roles MTs play in orchestrating radial glial cell activities during interkinetic nuclear migration and neuronal translocation to cortical destinations along pia-directed processes. We also outline the consequences of MT dysfunction in the polarization and establishment of the radial glial cell scaffold.

1. Introduction

1.1. *Discovery and functions of microtubules in the central nervous system*

In 1953, De Roberts and Franchi first described microtubules (MTs) by adapting the electronic microscopic imaging procedures of the day to visualize bundles of tightly packed parallel fibrils in sciatic axons of the toad and rat (De Robertis and Franchi, 1953). By the early 1970s, the amino-acid nature of MTs was established and the existence of α- and β-tubulin and their heterodimers was discovered (Mohri, 1968; Stephens, 1970). In the superseding years, MTs were described in a host of cell types in mammalian and plant species. They are present in all cell types in the central nervous system (CNS) and function in maintaining cell structure, vesicle transport, mitosis, migration, and process extension by supporting the intracellular transport of motor proteins, including kinesin and dynein (Dent and Baas, 2014; Hirokawa et al., 2010), a process that in upper motor neurons may occur from the soma to the nerve terminal along a distance of a one meter axon.

1.2. *Formation of microtubules*

In mammalian glial cells and neurons, MT arrays are typically nucleated by discrete MT organizing centers (MTOCs), the most significant of which is the centrosome (Stiess and Bradke, 2011). The minus ends of MTs are usually anchored to the centrosome, while the plus ends are oriented distal to it, resulting in directed MT and cell polarity. Centrosomes also regulate the density and length of MTs within each cell,

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which vary depending on its developmental stage and intracellular requirements (Evans et al., 1985). The cytoplasmic volume of each subcellular compartment is maintained by MT arrays and considerable effort has been given to elaborating the mechanisms underlying how MTs maintain each cell's morphology throughout its lifetime. MTs are typically arranged into 13 protofilament configurations (Tilney et al., 1973); however, the number of protofilaments in each MT may change depending on the physiological context and cell type. In vitro experiments have shown that isolated MTs can vary from eight to 17 protofilaments (Chretien and Wade, 1991; Chretien et al., 1992) suggesting that intrinsic factors play roles in maintaining MT structure. For instance, during CNS development doublecortin (Dcx) a MT associated protein (MAP) in neurons has been shown to associate with and configure the 13 protofilament arrangement, a state required for normal neuronal migration (Bechstedt and Brouhard, 2012; Francis et al., 1999). Post-translational modifications including acetylation, tyrosination, detyrosination, polyglutamylation, polyglycylation, palmitolyation and phosphorylation (Janke and Bulinski, 2011; Westermann and Weber, 2003) subsequently allow both neurons and glia to adjust tubulin dynamics and stability in response to extracellular cues, thereby rearranging cellular structure and function throughout CNS expansion, during the migration process and after synaptic connections have been established.

1.3. *Radial glial cell functions in the developing CNS*

Radial glial cells derive from the neuroepithelium of the brain and spinal cord prior to the onset of neurogenesis and gliogenesis (Barry and McDermott, 2005; Morest and Silver, 2003). Their unique morphology creates the architectural framework for the laminar patterning of migrating neurons (Rakic, 1972) and allows radial glia to interact with axons along a number of axes, providing boundaries, conduits and axon sorting structures in the brain and spinal cord, while generating most of the neurons and glia that reside there (Barry et al., 2013; Norris and Kalil, 1991; Silver et al., 1982, 1993; Silver and Ogawa, 1983; Steindler, 1993).

Although several organelles permit radial glial cells to perform these complex processes, including intermediate filaments and membrane components, their dynamic morphology and stem-like properties indicate that a prominent role is played by MTs. In this communication, we highlight the key roles MTs play in facilitating the actions of radial glial cells during the initial expansion and subsequent patterning of the CNS and outline the neurological deficits which result from their dysfunction.

2. Roles of microtubules in CNS expansion via radial glial cell interkinetic nuclear migration

The generation of all CNS cell types depends on neuroepithelial cells, radial glial cells and basal progenitor cells dividing and differentiating at ventricular and subventricular zones. Our understanding of the contributions radial glial cells offer to this process has expanded greatly in recent decades as radial glia are now understood to give rise to progressive waves of layer specific cortical neurons (up to 80%), with lower layers generated earlier and layer VI generated last (Anthony et al., 2004; Franco et al., 2012). The remaining radial glia ultimately become astrocytes and oligodendrocytes (Barry and McDermott, 2005; Hirano and Goldman, 1988; Levitt and Rakic, 1980; Voigt, 1989; Xu et al., 2014), but some persist as a small population of multipotent cells in neurogenic niches of the adult CNS (Bonfanti and Peretto, 2007; Merkle et al., 2004). Interkinetic nuclear migration (INM) is a hallmark process of radial glial cell division, conveyed by apical–basal–apical cycling of the nucleus throughout the cell cycle (Kulikova et al., 2011). INM spans the full apical–basal axis of neuroepithelial cells and is restricted to the ventricular zone and subventricular zones of dividing radial glial cells (Gotz and Huttner, 2005). During INM, the nucleus moves to the basal surface during the G1 phase of the cell cycle where it remains for the length of the S phase, before relocating back to the apical surface for the G2 phase and mitosis (Fig. 1A). Pharmacological studies, involving the treatment of neuroepithelial cells with cytochalasin B and colchicine first implicated MTs as key components of this process (Malawista and Bensch, 1967; Webster and Langman, 1978). More recent research has shown that the basal to apical movements of neuroepithelial cells/radial glial cells are generally understood to be under the control of dynein MT motors (Del Bene et al., 2008; Gotz and Huttner, 2005; Kosodo et al., 2011; Tsai et al., 2005), while the actomyosin network or kinesin MT motors drive apical to basal movements (Fig. 1A) (Schenk et al., 2009; Tsai et al., 2010), thereby influencing symmetrical versus asymmetrical cell divisions. Likewise, MTs are vital for cytokinesis of outer radial glial cells in the human cortex, but not the preceding basal movements of the soma which seems to rely on non-muscle myosin II (Ostrem et al., 2014). Furthermore, while neuronal cell bodies tracked centrosomes during migration, the centrosome remained at the ventricular zone attachment in radial glia during interphase, only departing to participate in the formation of the mitotic spindle (Tsai et al., 2007; Wang et al., 2009). RNA interference (RNAi) of *Lis1* (a regulator of dynein) blocked apical movements of the radial glial cell body, while shRNA and RNAi experiments targeting *Kif1a* (a regulator of kinesin) showed defects in the basal movements of radial glia during INM, while preserving mitosis and nuclear migration (Tsai et al., 2007, 2010). These studies demonstrated that MTs are necessary for basal-to-apical nuclear migration and apical-to-basal migration towards a stationary centrosome respectively, utilizing both minus end (dynein) and plus end motors (kinesins) for correct positioning of the radial glial cell body. Therefore, the centrosome is a key component of INM as it determines the positioning of the radial glial cell body, and possibly the identity of the progeny pool. The MT-nucleating/bundling MAP Tpx2 has been shown to mediate basal to apical movements via MT repositioning of the nucleus into the apical radial glia process during the G2 phase of the cell cycle, acting independently of the centrosome (Kosodo et al., 2011). A variety of factors have been identified as mediating centrosomal movements. For example, DOCK7, a RAC activator, Cep120 and Pax6 have been shown to mediate basal to apical INM via signaling to the centrosome (to the transforming acidic coiled-coil (TAAC) centrosomal proteins in the case