Mini-Review

mPar6α Controls Neuronal Migration

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We review studies on the polarity of developing cerebellar granule, showing that the centrosome localizes to the pole of the neuron that extrudes the nascent axon, and the Rho GTPase Cdc42 (cell division cycle 42) activates the mPar6α/Par3 (Par for partitioning defective) complex to coordinate actin dynamics in the growth cone. Subsequently, mPar6α signaling controls the migration of immature granule neurons down the Bergmann glial fibers into the internal granule cell layer in which they establish synaptic connections.

Key words: **neuronal polarity; cerebellum; granule cell; neurite extension; neuronal migration; mPar6α; Rho GTPases**

The development of the architectonics of the vertebrate brain involves neurogenesis in specialized germinal zones, followed by the migration of immature neurons from the sites in which they are generated to specific positions in which axon–target interactions establish the synaptic circuitry. Although several types of neuronal migration occur during the formation of the principal brain regions, two modes of cell motility provide experimental models for defining the mechanisms of cell and axon locomotion (Hatten, 2002). The predominant form of cell motility, common to all metazoan cells (Abercrombie, 1961), involves the polarization of the cytoskeleton in the direction of an external cue and the extension of a specialized motile structure at the front of the cell, known as the "leading edge." This mode of motility provides the core mechanism for growth cone motility and for tangential cell migrations during CNS development.

A number of laboratories have recently provided evidence that the small GTPase cell division cycle 42 (Cdc42) and homologs of the *Caenorhabditis elegans* Par6 (partitioning defective) polarity signaling complex partitioning defective homolog mPar6a orient the nucleus and centrosome/Golgi apparatus in both non-neuronal and neuronal growth cone motility (Etienne-Manneville and Hall, 2001, 2003; Shi et al., 2003). The spatial localization of protrusive activity in the extending growth cone occurs by a mechanism that involves Cdc42 signaling that localizes Rac activity to the leading edge and recruits βPIX (PAK-interacting exchange factor), a Rac guanine nucleotide exchange factor, to the front of the cell. Thus, Cdc42 signaling orchestrates the polarization of actin and microtubule dynamics in migrating cells through separate signaling pathways (Cau and Hall, 2005). Although these conserved signaling pathways orchestrate growth cone motility in response to spatially defined external cues during CNS development, the mechanism of locomotion of immature neurons along radial migrations of neurons in cortical regions of the developing brain is unique. Rather than localizing actin assembly and regulatory elements to the front of the cell, neurons migrating on glial fibers assemble a specialized motility apparatus in the cell soma and proximal region of the leading process. This apparatus includes a perinuclear tubulin cage that holds the nucleus in the rear of the cell, a specialized adherens junction beneath the cell soma (rather than focal adhesions at the front of the cell), thick bundles of cortical actin that rim the soma (rather than a system of stress fibers that project to the leading edge), and microtubules that project to the tip of a highly motile leading process that extends in the direction of migration. The tip of the leading process is not a leading edge, and the motility of this process does not correlate with the forward locomotion of the cell on the glial guide (Edmondson and Hatten, 1987; Gregory et al., 1988). Recent studies show mPar6α in the centrosome (Solecki et al., 2004) and demonstrate that Par6α-mediated signaling controls the movement of the centrosome (Fig. 1). Thus, whereas the motors for most metazoan cells, including many types of motile neurons and growth cones in the CNS, are in a leading edge, the mechanisms that control directed migrations along glial fibers in cortical regions of developing brain are localized to the cell soma and proximal region of the motile leading process. Glial-guided neuronal migration is thus a highly specialized form of neuronal polarity.

Although the hippocampus has provided the central experimental system for defining mechanisms that distinguish polarity pathways required for axonal versus dendritic outgrowth, the cerebellar granule neuron also provides an excellent experimental model system for neurite formation. The cerebellar cortex, or "little cortex," has long been an important model system for CNS development because of the remarkable regular array of two principal classes of neurons, the granule cell and the Purkinje neuron. The Purkinje neuron, like the pyramidal cells of hippocampus, is the output neuron of the cerebellum. Development of the cerebellar circuitry (Ito, 2006) depends on the formation of synaptic connections of granule neurons with mossy fibers from a number of sources and on connections of Purkinje cells with climbing fibers from the olivary nucleus, as well as local circuit synapses with a variety of cerebellar interneurons. Recent studies demonstrate that the cerebellum provides adaptive control for motor learning, balance, sensory discrimination, and complex cognitive tasks (Fiez, 1996; Gao et al., 1996; Boyden et al., 2004; Ito, 2006).

Received Sept. 17, 2006; accepted Sept. 17, 2006.

This work was supported by National Institutes of Health Grants R01-NS 15429 and R01-NS051778 (M.E.H.).

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DOI:10.1523/JNEUROSCI.4060-06.2006

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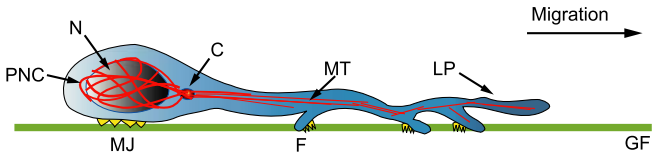

Figure 1. During glial-guided neuronal migration in developing brain, the centrosome controls the polarity and direction of cell movement. The neuron is polarized in the direction of migration (arrow) with the nucleus (N), enwrapped in a perinuclear tubulin cage (PNC), in the posterior aspect of the cell. The nucleus, Golgi apparatus (not shown), and centrosome (C, red) are forward of the nucleus, and a system of microtubules (MT, red) extends into the leading process from the microtubule organizing center. An interstitial junction forms beneath the cell soma (MJ, yellow), and punctae adherentia (yellow) form beneath the short (1–5 μm) filopodia (F), extending from the leading process (LP) as it enwraps the glial fiber (GF, green). In contrast to growth cones, there is no leading edge at the tip of the leading process, and, although the leading process is highly motile, the movement of the cell corresponds to the movement of the cell soma, not the movement of the tip of the leading process [modified from Solecki et al. (2006), their Fig. 3].

The vast number of granule cells and unique morphology of granule neuron axons (extending two parallel axons) make the granule cell an opportune model system for molecular analyses of neurogenesis, migration, and synaptogenesis (Tomoda et al., 1999). Recent studies point to an important role for the centrosome in granule cells and hippocampal neurons (Zmuda and Rivas, 1998; de Anda et al., 2005). The development of granule cell polarity can be examined *in vitro* as purified progenitor cells exit the cell cycle and develop the classic morphology of granule neurons *in vivo* (Powell et al., 1997). As demonstrated by Rivas and colleagues, as purified granule cell precursors exit the cell cycle, the centrosome moves to the pole of the cell from which a lamellipodium protrudes and develops into an axon. The Golgi and late/recycling endosomes also localize at the pole that generates the first neurite (Zmuda and Rivas, 1998). Subsequently, the centrosome moves to the other side of the cell and a second axon emerges, generating the classic bipolar morphology of the cerebellar granule neuron (for review, see Solecki et al., 2006).

To examine the role of polarity proteins in neuronal migration, Solecki et al. (2004) imaged the conserved polarity complex mPar6α in migrating and stationary cerebellar granule neurons As the neuron migrates, Par6α/PKCζ localizes to the centrosome and signals forward movement of the centrosome before the translocation of the cell soma. Thus, migration occurs by a "two-stroke" mechanism controlled by mPar6α signaling (Solecki et al., 2004) (Fig. 1). mPar6α overexpression disrupts the stoichiometry of polarity complexes and inhibits glial-guided migration. The perinuclear tubulin cage seen in migrating neurons is absent, and a number of "signature" centrosome proteins, including γ-tubulin, Pericentrin, centrin2, PKCζ, and mPar6α, fail to target to the centrosome. Deciphering the signaling pathways that regulate the activity of the mPar6α polarity complex, as well as the downstream control of cytoskeletal dynamics, contractile force generation, and vesicle trafficking will hopefully lead to insights on the defects in formation of the cortical laminas that characterize human brain malformations and many of the epilepsies (Ross and Walsh, 2001).

Conclusions

The emergence of an evolutionarily conserved mechanism that regulates cell polarity provides an exciting opportunity to define the role of polarity proteins in the generation of the diverse array of cell types and patterns of connections in the developing mammalian brain (Macara, 2004; Govek et al., 2005; Kishi et al., 2005; Knoblich, 2005; Wiggin et al., 2005). In the future, it will be important to determine how all of these signaling pathways and mechanisms are integrated to control directed cell migrations and the development and growth of the axon and dendrites, which establish the architectonics of the brain.

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