

# Neuronal migration re-purposes mechanisms of cytokinesis

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The capacity of cells to transition through the cell cycle is among the most complex and carefully orchestrated in biology, and yet also among the most fundamental. A cascade of cytoskeletal events occurs that involves the coordination of microtubules and actin filaments, under the regulation of signaling pathways that include a variety of proteins. These pathways are so finely orchestrated that it would seem wasteful for them to be completely abandoned as differentiated cells permanently leave the cell cycle. Neurons, for example, no longer divide, but instead utilize their cytoskeletal machinery to migrate to their ultimate destinations, to extend and maintain complex axonal and dendritic arbors, form synapses, and orchestrate organelle transport. A compelling possibility is that differentiated cells such as neurons, in fact, do not entirely abandon cell cycle pathways, but instead re-purpose them to meet new challenges faced in their post-mitotic lives.

We have found that kinesins classically considered mitosis-specific continue to be expressed in terminally post-mitotic neurons, where they play important roles in organizing microtubules in axons and dendrites, regulating the transport of short microtubules in these processes, and also imposing a balance of forces on longer microtubules critical for determining whether axons grow or retract and for their navigation toward appropriate targets.<sup>1,2</sup> However, until our recently published article,<sup>3</sup> little evidence existed that neurons re-purpose signaling cascades involving these motor proteins.

Shortly after their final mitotic division, newborn neurons have a multi-polar morphology. In order to migrate through

the layers of the brain, the neuron becomes bipolar, with a single designated leading process extended in the direction of migration, and a trailing process co-linear with it, on the other side of the soma. While the specifics vary in different kinds of migrating neurons, a general theme has emerged in which most but not all microtubules are attached to the centrosome, with some extending into the leading process and others reaching back toward the trailing process, with many of these engulfing the nucleus.<sup>4</sup> Forces generated by cytoplasmic dynein contribute to a 2-step forward movement of the centrosome and nucleus as the neuron migrates. Actin-based forces are also important for nuclear movement and centrosomal movement, as well as for the contraction of the trailing process toward the soma. F-actin is highly concentrated in the proximal region of the leading process, suggesting that this region is critical for the generation of forces relevant to the advance of structures in the soma.<sup>5</sup> The proximal F-actin enrichment occurs only in the leading process, not in the trailing process, suggesting that the capacity to concentrate F-actin in one specific process is crucial to the neuron's ability to distinguish one process as the leader.

Cytokinesis represents one of biology's best examples of F-actin distribution being constrained to a particular locale of the cell, in response to a defined signaling cascade. During cytokinesis, F-actin is directed into the region of the cortex in the vicinity of the mid-zone of the mitotic spindle, to form the cleavage furrow necessary for pinching off the 2 daughter cells. Assembly of the cleavage furrow is accomplished via a signaling cascade involving kinesin-6. Two molecules of kinesin-6

join together with 2 molecules of a Rho family GTPase-activating protein called MgcRacGAP, to form a complex called centralspindlin, which localizes to the microtubules in the spindle mid-zone and signals to the actin cytoskeleton through RhoA.<sup>6</sup>

We previously reported that kinesin-6 plays a crucial role in establishing microtubule polarity orientation in dendrites,<sup>2</sup> but we also found kinesin-6 to be strongly expressed in migratory neurons, long before dendrites develop.<sup>7</sup> In our recent paper, we found that depletion of kinesin-6 from migratory neurons results in a loss of bipolar morphology.<sup>3</sup> Such neurons were either stationary or continuously altered their direction of migration, with the F-actin enrichment no longer restricted to a single process. Similar results were found when MgcRacGAP activity was suppressed. Based on these and other data, we proposed that in migrating neurons, kinesin-6 functions to restrict F-actin enrichment to a single process, via a cytokinesis-like mechanism involving MgcRacGAP, thereby designating that process as the leader (Fig. 1). The "centralspindlin" complex would presumably signal through RhoA to actin filaments to elicit this response, which is supported by previous work indicating that RhoA concentrates in the leading process.<sup>8</sup>

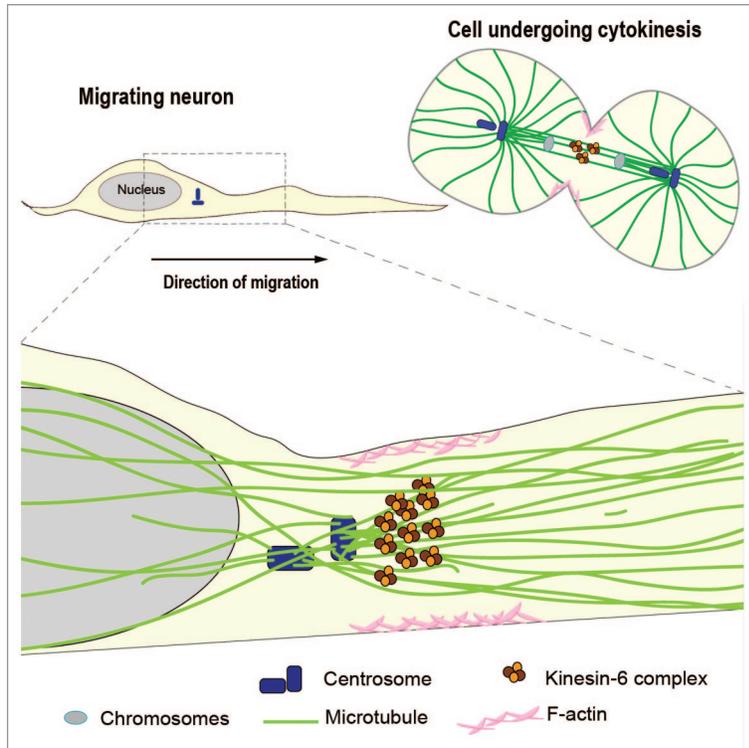
In post-migratory neurons, the main role of kinesin-6 is to establish the non-uniform polarity pattern of dendritic microtubules.<sup>2</sup> The fact that kinesin-6 has such different roles in migratory and post-migratory neurons suggests the possibility that once its migratory journey is complete, the neuron may then abandon the cytokinesis pathway. However,

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**Figure 1.** Molecular motor protein kinesin-6 functions in an analogous manner during neuronal migration and cytokinesis. During this stage of cell division, a protein complex consisting of kinesin-6 and a Rho family GTPase-activating protein, localized at the spindle midzone, regulates the formation of the actin-rich cleavage furrow in this region, via a downstream signaling cascade. During migration, kinesin-6 restricts F-actin enrichment to a single process, defining that process as the leader.

another possibility is that the pathway is re-purposed in yet another way, perhaps utilizing other players in the pathway such as PRC1, which belongs to the MAP65/ Ase1 family of proteins that bundles microtubules preferentially of opposite orientation.<sup>6</sup> We find it compelling that nature is both conservative and creative in its re-purposing of fundamental cell cycle pathways to serve the needs of terminally differentiated cells.

#### References

1. Liu M, et al. *J Neurosci* 2010; 30:14896-906; PMID:21048148; <http://dx.doi.org/10.1523/JNEUROSCI.3739-10.2010>
2. Lin S, et al. *J Neurosci* 2012; 32:14033-49; PMID:23035110; <http://dx.doi.org/10.1523/JNEUROSCI.3070-12.2012>
3. Falnikar A, et al. *Curr Biol* 2013; 23:1215-20; PMID:23791725; <http://dx.doi.org/10.1016/j.cub.2013.05.027>
4. Kuijpers M, et al. *Mol Cell Neurosci* 2011; 48:349-58; PMID:21722732; <http://dx.doi.org/10.1016/j.mcn.2011.05.004>
5. Solecki DJ, et al. *Neuron* 2009; 63:63-80; PMID:19607793; <http://dx.doi.org/10.1016/j.neuron.2009.05.028>
6. Barr FA, et al. *Cell* 2007; 131:847-60; PMID:18045532; <http://dx.doi.org/10.1016/j.cell.2007.11.011>
7. Ferhat L, et al. *Eur J Neurosci* 1998; 10:1383-93; PMID:9749792; <http://dx.doi.org/10.1046/j.1460-9568.1998.00159.x>
8. Guan CB, et al. *Cell* 2007; 129:385-95; PMID:17448996; <http://dx.doi.org/10.1016/j.cell.2007.01.051>