Neuronal migration is an essential step of mammalian brain development. Because neural stem cells are distributed only in the germinal zones in limited regions of the brain, newborn neurons need to migrate to their final destination in the cortex or nucleus to form correct neuronal networks. Impairment of neuronal migration thus causes brain malformation and neurological disorders. Neurons typically migrate by repeating 2 distinct steps. They first extend a long leading process tipped with a growth cone that directs the migration. Next, the nucleus in the cell soma is translocated into the process. It has been shown that these steps are independently regulated in some neurons.

The nucleus is the largest cargo in the neuron, and therefore some force is required for its transport. It has been demonstrated that the actin and microtubule cytoskeletons are involved in the regulation of nuclear translocation. Actomyosin is found to accumulate in either the proximal leading process or rear of the cell soma depending on the cell type, and local inactivation by drug treatment or laser ablation has demonstrated that the contractile tension of actomyosin is converted to a pulling or pushing force to the nucleus. Microtubules have been shown to emanate from the leading process, where the centrosome is typically positioned, with the plus ends toward the cell soma. These microtubules are thought to associate with the nucleus and work as rails on which the cytoplasmic dynein motor carries the nucleus into the leading process by its minus end-directed motor activity. The linker of nucleoskeleton and cytoskeleton (LINC) complex mediates the interaction between the nucleus and cytoskeletons because its loss or inhibition results in the failure of neuronal migration. However, it should also be noted that the force generated by the cytoskeletons does not always directly act on the nucleus; it has been reported that actomyosin regulates the position of the centrosome by interacting with microtubules in the leading process. Other reports have also demonstrated that microtubule sliding in the leading process is implicated in nuclear translocation. Differences in model systems as well as invasiveness of pharmacologic perturbation and laser ablation approaches also partly contribute to the ambiguity of general conclusions. Thus, the interplay between actin, microtubules, and the nucleus is not fully clarified, and the precise driving force for nuclear translocation remains to be elucidated.

To better understand the dynamics of the nucleus and associated cytoskeletons in intact condition, we have adopted spinning-disk confocal microscopy for live imaging of migrating cerebellar granule cells at a high spatiotemporal resolution. We have recently identified nuclear rotation, a yet uncharacterized motion of the nucleus during neuronal migration, by labeling heterochromatin spots with fluorophore-tagged HP1β instead of the nuclear localization signal, which diffuses throughout the nucleoplasm. In migrating neurons, the nucleus exhibits highly dynamic motion, including intermittent translocation, frequent rotation, and transient deformation. These phenomena are observed in cerebellar granule cells migrating...
on a flat surface in in vitro cultures as well as in organotypic brain slice cultures. The nuclei of postmigratory neurons stay still and do not show any of these motions, indicating that these nuclear dynamics are driven by forces generated in neurons in the migratory stage. The granule cell nucleus exhibits stepwise movement composed of moving and resting phases, like many other neurons.4,19,20 Nuclear rotation is often observed in the resting phases, suggesting that migrating neurons generate and transmit force to the nucleus even with no apparent nuclear translocation. In addition, we occasionally noticed a sharp deformation at the nuclear front that persisted for only a few minutes. Such peaking suggested a pulling force acting locally at small points on the nucleus. We have thus analyzed these nuclear dynamics as readouts of the properties of the forces applied to the nucleus during neuronal migration.

We envision a simple physical model comprising a large soft ball (nucleus) associated by multiple wires (cytoskeletal components) (Figure 1). When multiple forces generated by individual cytoskeletal components act on the nucleus, the resultant nuclear movement will be determined by the vector of the net force. The nucleus will undergo translocation if the net force acts on the center of mass, or else a torque will be generated and cause rotational motion. Furthermore, deformation will be induced if the nucleus is soft, and its elasticity will return the nucleus to its original shape when the force is released.

An interesting feature of the nuclear dynamics we can observe during neuronal migration is its inconsistency; the translocation occurs only intermittently, the rotation frequently changes its axis, and the nuclear shape is not always consistent. This suggests that the force acting on the nucleus changes dynamically over time. The force vector may even instantly reverse, as we have occasionally observed short-step rearward nuclear translocation and sharp nuclear peaking on the rear side.

We have demonstrated that nuclear rotation requires microtubule-dependent forces generated by dynein and kinesin-1 bound to the LINC complex. Consistently, some perinuclear microtubules labeled with green fluorescent protein–conjugated doublecortin appeared to closely associate with the nucleus and moved with the same direction and speed as the nuclear rotation. Each microtubule followed the nuclear rotation only transiently and then started to move independent of the nuclear movement. These observations support the idea that each microtubule does not continuously bind to the nucleus, but instead transiently attaches and detaches. Such dynamic interaction may underlie the inconsistency of the force applied to the nucleus.

In the classic view, microtubules are thought to stably bind to multiple points along the surface of the nucleus (Figure 2A). Assuming that the force generation among individual microtubules is not largely unbalanced, the net force applied to the nucleus would be constant and unbiased. Here, the nucleus would be transported in one direction without showing recurrent rotational motion. We instead propose a novel view of the microtubule-based regulation of nuclear movement. Each motor protein produces a point force directed toward the front or rear, depending on their directionality and the microtubule polarity. Thus, the erratic and transient binding of motor proteins to the LINC complex and microtubules results in a continuously changing vector of the net force, leading to movements of the nucleus such as translocation, rotation, and deformation (Figure 2B). It is also possible that the movement of the nucleus...
could alter the interaction among the nucleus, motor proteins, and microtubules, by changing the relative positions of these components. In such a dynamic state, nuclear translation is driven when cytoskeletal components and the nucleus stochastically adopt a suitable conformation to generate a forward force. However, these microtubule-based directional forces may not be sufficient to allow the nucleus to move into the narrow leading process, which has a diameter several folds smaller than the nucleus. Although our data negate the involvement of actomyosin in generation of the point forces driving the rotation of the nucleus or formation of the sharp nuclear peak, its strong contractile force may still contribute to nuclear movement coordinately with microtubules.

Considering neurons navigate through tissues crowded with many other cells and extracellular components, a force fixed toward a single direction may not always be desirable. Once migration is disturbed by some obstacle on the path, a force generated only to achieve smooth translocation may not be helpful for the neuron in this situation. Dynamic interactions among the nucleus and cytoskeletons and generation of an inconsistent force may appear to be an inefficient mechanism, but may be favorable in crowded environments.

**Author Contributions**

YKW and MK wrote the manuscript.

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