CellPress

Opinion

Microtubules and Growth Cones: Motors Drive the Turn

Olga I. Kahn[1] and Peter W. Baas[1,*]

Navigation of the growth cone at the tip of the developing axon is crucial for the proper wiring of the nervous system. Mechanisms of actin-dependent growth cone steering, via signaling cascades, are well documented. Microtubules are also important in growth cone guidance, because their polarized invasion into the peripheral domain on one side of the growth cone is essential for it to turn in that direction. Classically, microtubules have been considered secondary players, invading the peripheral domain only where the actin cytoskeleton permits them to go. Presented here is evidence for an underappreciated mechanism by which signaling cascades can potentially affect growth cone turning, namely through regulatable forces imposed on the microtubules by molecular motor proteins.

Trends

Polarized invasion of microtubules into one side only of the peripheral domain of the growth cone is required for the growth cone to turn.

Cytoplasmic dynein generates forces that enable some microtubules to overcome the myosin II-based retrograde flow of actin filaments in the growth cone, and thereby invade its peripheral domain.

Kinesin-5 and kinesin-12, traditionally considered mitotic motor proteins, act as polarizing motors that locally oppose cytoplasmic dynein-based forces in certain regions of the growth cone to enable microtubule invasion into other regions.

Signaling cascades can locally activate and deactivate the relevant motor proteins via mechanisms that include phosphorylation and interaction with partner proteins.

Motor-Driven Forces Provide an Underappreciated Mechanism for Microtubule Participation in Growth Cone Turning

The growth cone is a fan-shaped structure at the tip of the growing axon that is receptive to environmental cues via signaling cascades that affect the cytoskeleton [1–3]. The fan shape comprises two domains called the central domain and the peripheral domain; the former is the microtubule-rich region contiguous with the shaft of the axon, and the latter is the actin-rich lamellar region that includes filopodia [4] (Figure 1). The motility of the growth cone is achieved through the coordinated behaviors of microtubules and the actin cytoskeleton. Axon extension, retraction, and turning in response to signaling cues require changes in the distribution of microtubules within the growth cone [1,3,5,6]. For the axon to turn, microtubules from the central domain must penetrate the transition zone to invade the peripheral domain, preferentially on the side of the growth cone in the direction of the turn [7]. Microtubules must be dynamic for growth cones to turn [8,9], and there are emerging roles in axon navigation of + TIPs, proteins that associate with the plus ends of elongating microtubules [10]. Even so, most research has focused on the actin cytoskeleton as the principal target of signaling events relevant to growth cone behaviors, with microtubule reconfigurations posited to passively follow changes in actin organization.

Dynamics (i.e., assembly, disassembly, and stabilization) are not the only behaviors that microtubules undergo within cells, as dramatically illustrated by the mitotic spindle, the most-studied microtubule array. Microtubule dynamics are essential for spindle formation and function, but so too are ATP-dependent forces on the microtubules generated by molecular motor proteins [11]. Cytoplasmic dynein and a variety of specialized kinesins generate forces on the microtubules that regulate their configuration and their interplay with one another, as well as with the actin cytoskeleton. The forces generated by mitotic microtubule-based motor proteins are crucial for the separation of the duplicated centrosomes in prophase, formation of the bipolar spindle, separation of the half-spindles at metaphase, and the final phases of cytokinesis during which daughter cells are pinched off from one another. These motor proteins are subjected to regulation by modifications (such as phosphorylation) and through interaction with partner

[1]Department of Neurobiology and Anatomy, Drexel University College of Medicine, Philadelphia, PA 19129, USA

*Correspondence: pbaas@drexelmed.edu (P.W. Baas).

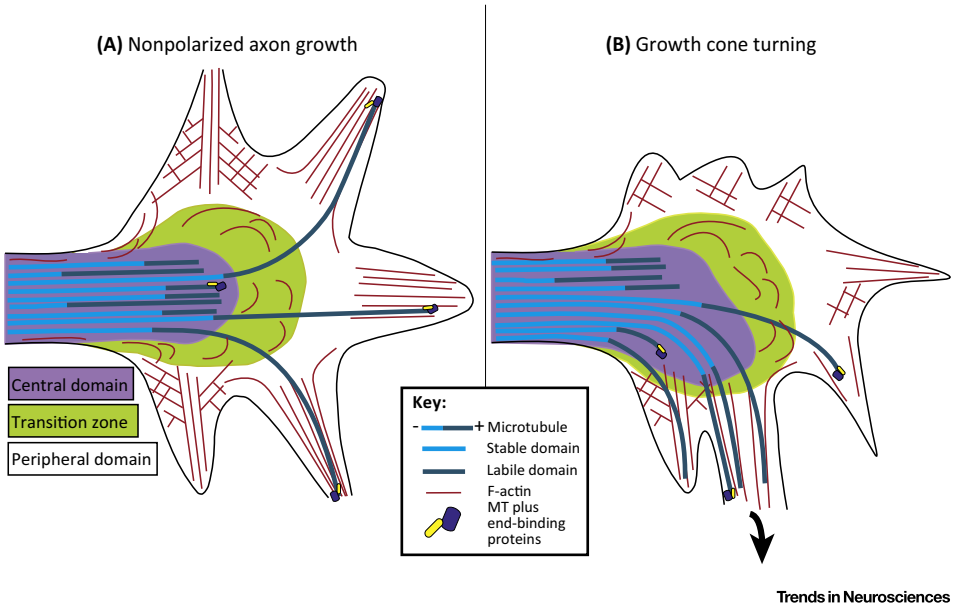

Figure 1. Growth Cone Cytoskeleton. (A) The central domain of the growth cone is the microtubule (MT)-rich region contiguous with the axon shaft. The peripheral domain is the outer-most part of the growth cone. The peripheral domain comprises a broad flat lamellar region in which actin filaments are arranged as a meshwork, as well as elongated thin filopodia in which actin filaments are arranged as aligned bundles. The transition zone is the region between these two domains. Retrograde flow of the actin cytoskeleton in the peripheral domain pushes back most microtubules, compacting them in the central domain. Individual microtubules from the central domain are able to penetrate the transition zone to enter the peripheral domain during growth cone advance. (B) During growth cone turning, microtubules extend from the central domain through the transition zone preferentially into one side of the peripheral domain.

proteins [12–19]. A decade and a half of work has revealed that terminally differentiated neurons repurpose much the same complement of motor proteins as used during cell division, as well as many of the same mechanisms that regulate them, to build the microtubule arrays of axons and dendrites [20–28]. In this Opinion, we focus on the role of motor-driven forces in reconfiguring microtubules in growth cones, which we posit to be an underappreciated but critical mechanistic aspect of axon navigation.

The Myosin II versus Dynein Competition

Myosin II is a well-studied bipolar actin-based motor protein that functions coordinately with actin dynamics to drive the retrograde flow of actin filaments within the growth cone. This retrograde actin flow provides traction for the growth cone to advance, while at the same time pushing microtubules backward from the peripheral domain into the central domain [29,30]. For microtubules to invade the peripheral domain from the central domain in a polarized fashion, the mechanism suggested has been that the actin cytoskeleton locally reconfigures or depolymerizes on the side of the growth cone in the direction of the turn, so that microtubules can then invade as a result of their dynamic properties. Indeed, local application of antiactin drugs can lead to microtubule invasion on the side of the growth cone exposed to the drug [31,32]. Without refuting the potential power of this mechanism to turn the growth cone, evidence also exists for a mechanism in which the microtubules are subjected to forces generated by microtubule-based motor proteins, with those forces in competition with the myosin II-driven retrograde flow of actin filaments. In this view, microtubules can utilize such forces to overcome the retrograde flow without the retrograde flow having to locally diminish to allow the microtubules to enter.

In the axon shaft, some of the microtubules are very short and undergo bouts of concerted and rapid transport, driven by cytoplasmic dynein [33]. Available data suggest that the cargo domain