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Review

Axonal Transport of Microtubules: the Long and Short of It

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Recent studies on cultured neurons have demonstrated that microtubules are transported down the axon in the form of short polymers. The transport of these microtubules is bidirectional, intermittent, asynchronous, and occurs at the fast rate of known motors. The majority of the microtubule mass in the axon exists in the form of longer immobile microtubules. We have proposed a model called 'cut and run', in which the longer microtubules are mobilized by enzymes that sever them into shorter mobile polymers. In this view, the molecular motors that transport microtubules are not selective for short microtubules but rather impinge upon microtubules irrespective of their length. In the case of the longer microtubules, these motor-driven forces do not transport the microtubules in a rapid and concerted fashion but presumably affect them nonetheless. Here, we discuss the mechanisms by which the short microtubules are transported and suggest possibilities for how analogous mechanisms may align and organize the longer microtubules and functionally integrate them with each other and with the actin cytoskeleton.

Key words: actin, axon, cytoplasmic dynein, katanin, kinesin, microtubule, microtubule severing, microtubule transport, molecular motor, neuron, spastin

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Microtubules form a continuous array within the axon, extending from the cell body into the growth cone at its distal tip. Each microtubule within the array is oriented with its assembly-favored 'plus' end directed away from the cell body (1,2). Although the microtubule array is continuous, the individual microtubules that comprise the array are staggered along the length of the axon and assume a variety of lengths (3). Some microtubules are over a hundred microns long, while others are only a single micron in length or even shorter. There is relatively little protein synthesis in the axon, and hence the tubulin proteins that comprise the microtubules must be actively transported from the cell body into and down the length of the axon. Early studies on the kinetics of tubulin transport suggested that tubulin moves slowly down the axon and in a relatively coherent manner compared to diffusion (4). It was posited that tubulin is transported in the form of the microtubules themselves and that this transport consists of a slow and synchronous march of the polymers. However, live-cell photobleach studies on cultured neurons in the 1990s failed to reveal evidence for such a slow march (5,6). These studies suggested that the majority of the microtubule mass in the axon is actually stationary.

After a great deal of debate and controversy on these photobleach studies, the key to interpreting them came in 2002, when Wang and Brown widened the parameters of the live-cell imaging paradigm to reveal different kinds of movements (7). They found that microtubules are, in fact, transported down the axon, but their transport is fast, intermittent, asynchronous, and bidirectional. In addition, and perhaps most interestingly, they only observed very short microtubules, a few microns in length, in transit down the axon. These results immediately explained why the previous imaging paradigms, which were biased toward the detection of slow synchronous movement of the entire microtubule array, failed to reveal any movement. In addition, they offered a highly satisfactory explanation for the slow rate of tubulin transport documented in the early kinetic studies, namely that it reflected an average rate of fast movements and non-movements. These results are exciting, because they provide the basis for understanding the fundamental mechanisms underlying microtubule transport in the axon.

It seems counterintuitive that the molecular motors that transport microtubules down the axon would somehow be specific to short microtubules and fail to engage the longer ones. Instead, we favor a model for microtubule transport that we call 'cut and run' (8). In this model, the motor proteins impinge upon all microtubules, regardless of their length, but cannot transport the longer microtubules, presumably due to drag imposed on the microtubules as a result of crosslinks with other structures. The long immobile microtubules can be mobilized by enzymes that cut them into shorter pieces. This model begs important questions such as the identity of the molecular motors that transport short microtubules and the means by which long microtubules are severed. In addition, the question arises as to exactly what effects the motor-driven forces

have on the long immobile microtubules, if not to transport them. In this article, we consider recent studies that speak to these questions.

Transport of Short Microtubules

The original live-cell imaging studies utilized a photobleach-based experimental regime. Fluorescent tubulin was introduced into the neuron and allowed to incorporate into its microtubules. After this, a narrow bleached region (just a few microns long) was introduced onto the microtubules in the axon. The axon was observed every several minutes for slow synchronous movement of the bleached zone. Instead, however, the bleached zone remained stationary and ultimately faded away due to exchange of tubulin subunits with the pool of unbleached tubulin. To their credit, the authors of some of these early papers stated that their results did not exclude the possibility that a small fraction of the microtubule mass might have been in transit but escaped detection with their experimental regime (5). Wang and Brown altered the experimental regime such that a much longer bleached zone (about 30 microns in length) was created, and the zone was imaged every several seconds rather than minutes (7). With this regime, short fluorescent microtubules originating outside of the bleached zone could be observed to move through the bleached zone. The microtubules were generally a few microns in length and moved asynchronously at the fast rates of known motors such as cytoplasmic dynein and the kinesin superfamily. At least in the growing axons of cultured neurons, the transport was observed to be bi-directional, with roughly 2/3 in the anterograde direction and 1/3 in the retrograde direction.

Since these studies were published, we have devoted a great deal of attention to studying the mechanisms by which the short microtubules are transported. We initially wished to test the merits of a popular model in which cytoplasmic dynein transports microtubules down the axon by generating forces against the actin cytoskeleton. This model was proposed on the basis of studies indicating that most of the cytoplasmic dynein is transported anterogradely down the axon at about the same rate as actin (9). It was posited that the cargo domain of cytoplasmic dynein interacts with the actin cytoskeleton, presumably via dynactin (10). The motor domain of the dynein molecules is available to move along the lattice of microtubules that intermittently come into close proximity to the actin cytoskeleton. Because the cortical actin is formed into a meshwork, it would presumably have strong resistance to backward movement and would thereby provide a rigid substrate against which the microtubules could move forward.

To test this model, we evaluated the effects of pharmacologically depleting actin filaments on the transport of the short microtubules (11). We found that after actin depletion, the frequency of anterograde microtubule movements was halved, while the frequency of retrograde movements was unaffected. This result suggests that a portion of the microtubules moving anterogradely is dependent upon actin for movement but that the retrograde movements are all actin-independent. Those movements that do not occur against actin presumably occur against longer microtubules. There is precedent for such microtubule–microtubule movements during other cellular events such as mitosis (12), and recent studies on axons of cultured neurons have reported movements along longer microtubules of tubulin-containing structures (13) that we believe to be short microtubules (11,14).

We next examined the effects of depleting cytoplasmic dynein on these axonal microtubule movements (14). Specifically, we used siRNA to deplete dynein heavy chain. Interestingly, the effects on the frequency of microtubule movements were essentially the same as observed with actin depletion. There was no diminution in the retrograde movements, while the anterograde movements were halved in their frequency. On the basis of these results, we conclude that a portion of the anterograde movements, but none of the retrograde movements, can be explained by the actin/dynein-based model.

Although we cannot dismiss the possibility that the small amount of remaining dynein heavy chain might have been enough to fuel some of the remaining movements, the most reasonable conclusion from these studies is that all of the retrograde microtubule movements and half of the anterograde movements use motors other than cytoplasmic dynein. These motors would presumably be members of the kinesin superfamily and most likely would be those that are generally considered to be 'mitotic.' These kinesins, which continue to be expressed in postmitotic neurons (15–17), are specialized to generate forces between neighboring microtubules, rather than transporting vesicles along microtubules (12). Because they move along the microtubule lattice in the same direction as cytoplasmic dynein, members of the kinesin-14a family (including CHO2 and HSET) are good motor candidates for mediating a portion of the anterograde microtubule transport. In support of this possibility, we previously showed that when CHO2 is overexpressed in certain types of non-neuronal cells, it causes the microtubules to rapidly move outward, with their plus ends leading, into axon-like cellular processes (18). In terms of a potential motor for retrograde microtubule transport, members of the kinesin-5 family (such as Eg5) may be good candidates. We have shown that pharmacologic inhibition of Eg5 causes axons to grow faster, which would be expected if the retrograde transport of microtubules were compromised (19).

Figure 1 shows a diagram depicting the potential influences on microtubule organization of molecular motor proteins as they generate forces on short and long

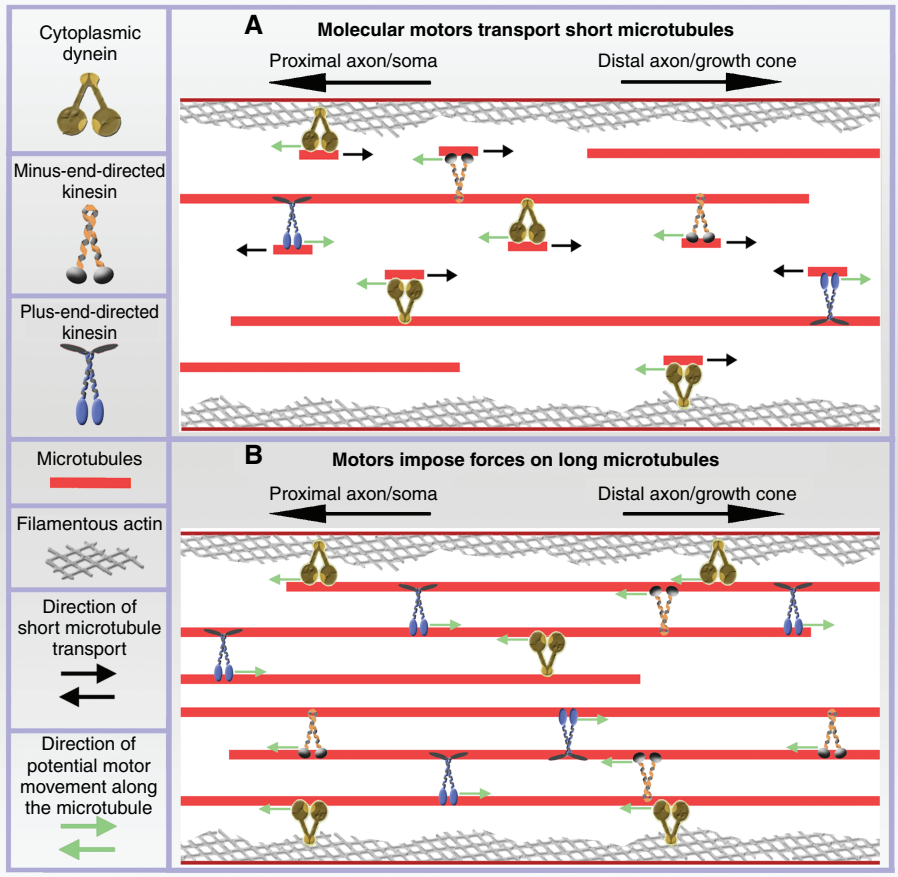

Figure 1: Schematic model depicting how forces generated by molecular motor proteins impinge upon both short and long microtubules in the axon. (A) The bidirectional transport of short microtubules is determined by their interactions with plus-end or minus-end-directed kinesin motors or with the minus-end-directed motor, cytoplasmic dynein. (B) Motor-driven forces used to transport short microtubules bidirectionally down the axon may also be generated against the longer immobile microtubules.

microtubules within the axon. Figure 1A shows the molecular motors transporting short microtubules against longer microtubules or against the cortical actin. Figure 1B shows a region of the axon in which only long microtubules are present and displays the hypothesis that the same molecular motors that transport the short microtubules also act on the long microtubules.

We should note that speculating on exactly what effects a particular motor might have is tricky. For example, we speculated earlier that kinesin-5 might be the motor for moving microtubules in the retrograde direction, but exactly how this might work remains unclear. In the mitotic spindle, kinesin-5 is thought to be a homotetramer, with four motor domains directed outward (20). If this is the case in neurons, it is not difficult to imagine how kinesin-5 might zipper together two neighboring microtubules of the same polarity orientation, as it moves toward their plus ends (21). It is also conceivable that the homotetramer could interact with neighboring microtubules of the same orientation in such a way as to crosslink them, thereby providing resistance to potential movement by other motors. If truncated versions of kinesin-5 exist in neurons, they may not tetramize and therefore could move short microtubules toward either the plus or minus end of a long microtubule, depending on the orientation of the motor relative to the long and short microtubule. These considerations accentuate the fact that much more experimental evidence is needed before any conclusions can be drawn about the role of particular kinesins in the transport and organization of microtubules in the axon.

Microtubule Severing

According to the cut and run model, longer microtubules would be unable to move (at least in a rapid and concerted manner) until they are somehow made shorter. This possibility is consistent with indirect evidence of particularly rapid and efficient transport of microtubules within the cell body (22) and during early axogenesis (23), given that microtubules in the cell body and early axon are quite short (3,24). Shorter microtubules would be easier to reconfigure than longer microtubules and hence would be advantageous for promoting morphological plasticity. This point may also be relevant to potential strategies for clinically augmenting regeneration of injured adult axons.

In order to generate short microtubules and to do so at strategic locations, it seems reasonable that neurons would have to utilize either factors that promote

disassembly of long polymers into short remnants or factors that break long microtubules into short pieces. Certainly, there are factors that destabilize and promote microtubule disassembly [such as stathmin (25)], but there are strong reasons to hypothesize that microtubule severing is critical for generating sufficient numbers of short microtubules in the right places within the neuron. One important reason is that unlike shortening of microtubules, the severing process can transform a single microtubule into many. Several years ago, we performed serial reconstructions from electron micrographs of cultured neurons and demonstrated the appearance of large numbers of short microtubules and the absence of long microtubules within the axon at sites where new branches were starting to form (26). These observations provided support for a model in which long microtubules are severed into shorter pieces during the formation of collateral branches. More recently, using live-cell imaging, we directly observed the severing of short microtubules from looped bundles of microtubules within paused growth cones and their subsequent movement into filopodia (27).

It should be noted that severing is germane not only to the transport of microtubules but also to other mechanisms that are important for how microtubules are configured and interact with other proteins and cellular structures. For example, microtubule severing generates an abundance of new microtubule ends, which can serve as sites for assembly at locations far from the centrosome (28). These free ends are also known to interact with a variety of proteins and structures such as those within the cell cortex (29).

Most of our attention on microtubule-severing proteins in recent years has been focused on katanin. Katanin is a protein originally purified from sea urchin eggs, where it was shown to sever microtubules by disrupting contacts within the polymer lattice using energy derived from ATP hydrolysis (30). The 60 and 80-kDa katanin subunits have now been identified in vertebrate cells, and it has been determined that the smaller subunit has the microtubule-severing activity (31,32). The larger subunit is thought to target katanin to the centrosome, and indeed many cells show a centrosomal enrichment of katanin (33). We have shown that katanin is present at the centrosome of cultured vertebrate neurons but is also widely distributed within the axon and throughout all neuronal compartments (34). In our first study on katanin in neurons, we also showed that microinjection into freshly plated neurons of a function-blocking antibody to P60-katanin prohibits microtubule release from the centrosome and profoundly increases microtubule length throughout the neuronal cell body (34). As a result, axonal outgrowth is severely compromised. More recently, we reported a similar result with a dominant-negative construct for P60-katanin (35). In addition, we found that the levels of P60-katanin are very high in axons that are actively growing toward their targets but then plunge precipitously when the axon reaches its target and stops growing (35). P60-katanin levels are also higher at the tips of growing neuronal processes at some developmental stages and are globally elevated at the stage corresponding to dendritogenesis (36). By contrast, P80-katanin levels are higher in the cell body than in the processes and are generally more uniform during development than P60-katanin levels. Based on our studies so far, we have posited that microtubule-severing proteins may play critical roles in various aspects of neuronal morphology such as the length, number, and branching patterns of neurites.

Other laboratories have focused on spastin, which is a protein that goes awry in some forms of the human disease known as spastic paraplegia. Recently, it was noted that spastin has homology with P60-katanin in the region of the molecule that severs microtubules (37), and indeed, spastin has been demonstrated to be a potent microtubule-severing protein (37,38). Two studies on spastin in *Drosophila* suggest complexity. One study suggests that depletion of spastin causes diminution of microtubules at the synapse (39), while the other study suggests the opposite (40). While the reasons for this discrepancy are uncertain, one possibility is that diminished severing of microtubules can certainly lead to longer microtubules and an elevation in microtubule mass, but it can also lead to impaired transport of microtubules, and hence a diminution in the delivery of microtubules to the distal axon. Thus, both results may be quite explicable by the cut and run model, but time and more experiments will tell.

Regulation of Microtubule Severing

The question arises as to how microtubule severing is regulated such that microtubules are severed when and where needed. A potential clue comes from observations on simple fibroblasts and the behavior of microtubules assembled *in vitro* from purified tubulin. In certain kinds of fibroblasts, microtubules have been observed to break upon bending, even when the bending is fairly modest (41). However, in sharp contrast, microtubules do not break when bent in purified microtubule preparations (42). A potential explanation for this discrepancy is that living cells contain katanin and spastin, which is absent from the *in vitro* preparations. When the microtubule bends, its lattice becomes more accessible to the severing proteins, thus leading to breakage. Interestingly, microtubules become highly contorted in neuronal axons that undergo retraction but show no indication of breakage (43). We know that axons are rich in katanin and spastin, so it may be that the lattice of the microtubules within the axon is somehow 'protected' from being accessed by the severing proteins, even upon bending. Indeed, we have shown that axonal microtubules are more resistant to severing by katanin than microtubules in any other neuronal compartment (36).

We have proposed a potential mechanism by which microtubule severing might be regulated. This model was inspired by the observation that katanin-induced microtubule severing becomes much more active in interphase extracts that are depleted of the frog homolog of MAP4, a fibrous microtubule-associated protein (MAP) (44). In addition, severing is more active in mitotic extracts compared to interphase extracts, and this difference is based on phosphorylation of proteins, but apparently not of katanin itself. Interestingly, phosphorylation of MAP4 causes it to lose its association with the microtubules, consistent with a model that we call the 'MAP protection model.' In this model, fibrous MAPs protect the lattice of the microtubule from being accessed by katanin (45). Phosphorylation of the MAPs results in their detachment from the microtubule, thus enabling katanin to gain access. In the axon, tau, rather than MAP4, would be the likely candidate to fulfill this role.

The MAP protection model is appealing, because it offers a potential means by which signaling cascades can regulate microtubule severing quite focally, for example at sites of impending axonal branch formation. The signaling cascades would cause tau (or other MAPs) to dissociate from the microtubules at the site where a branch is starting to form, thereby permitting katanin to break the microtubules into shorter mobile pieces, precisely where needed (see Figure 2).

The severing of microtubules by P60-katanin may also be regulated by the non-enzymatic P80 subunit. Biochemical studies suggest that P80-katanin has two different domains that have opposite influences on the severing properties of P60-katanin, although the net effect is to enhance severing (46). Interestingly, we have recently shown that the two subunits are not present at equimolar levels within cells (36). In fact, the ratio of the two subunits varies markedly in different tissues and at different stages of development. Thus far, experimental evidence suggests that P80-katanin augments the severing of microtubules by P60, but it is conceivable that different portions of the P80-katanin molecule may be masked under different circumstances, permitting the available P80-katanin to either suppress or augment microtubule severing.

At present, there is less information on how spastin might be regulated, or how its duties may be co-ordinated with those of katanin. It will be of great interest to study the patterns of expression and distribution of spastin in the nervous system and to ascertain how the consequences of its inhibition differ from that of katanin. It is unknown whether spastin has a partner similar to P80-katanin or whether its access to the microtubule might be any different from that of katanin in the presence of various MAPs.

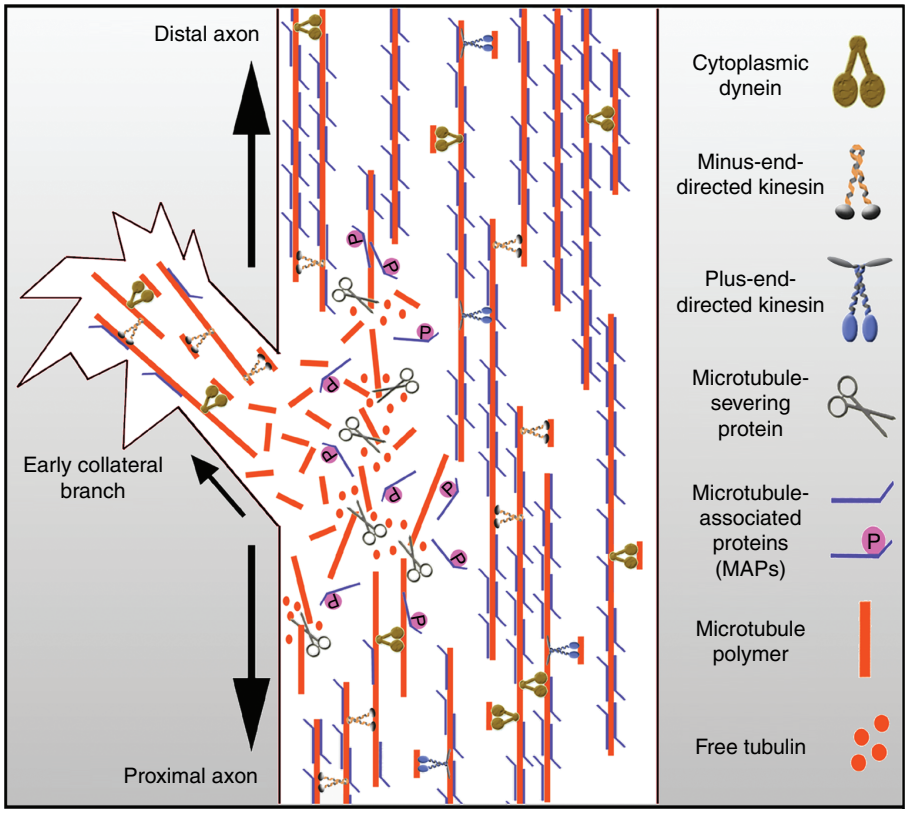

Figure 2: Model depicting how microtubule-severing proteins regulate microtubule transport and axonal branch formation. The severing of long microtubules provides short microtubules for transport into developing neuronal processes and down the axonal shaft. According to this model, MAPs (including the axonal MAP, tau) act as critical determinants of microtubule severing, by binding along the length of axonal microtubules and functioning to protect them from severing proteins including katanin. Detachment of MAPs from microtubules by phosphorylation may serve as a mechanism for controlling levels of short microtubules in specific axonal locales including regions of early collateral branch formation. These short microtubules can then be transported by motor proteins into collateral branches to promote their growth and stabilization.

What is the Fate of the Short Microtubules?

The short mobile microtubules presumably serve two main purposes. The first is to deliver tubulin and associated proteins down the axon for incorporation into the axonal cytoskeleton. The second is to act as nucleating elements for the assembly of long microtubules. Both of these would demand that the short microtubules are dynamic. In other words, the short microtubules must be able to disassemble to provide subunits for the elongation of other microtubules, and the short microtubules must also be able to elongate so that they can become long microtubules. Thus far, the live-cell movies generated of microtubule transport within the axons of cultured neurons have not revealed any detectable changes in the length of the short microtubules during transit. This may be because the movies are quite brief or might indicate that the short microtubules are relatively stable during transit. Additional imaging studies over longer periods of time will be required to better understand this issue. One possibility is that there are 'capping' proteins that keep the microtubules non-dynamic during transit, and if so, the regulation of these proteins will be of great interest for future studies.

How Do the Transport Motors Affect the Longer Immobile Microtubules?

As noted in the introduction section, it seems unlikely that the motor-driven mechanisms that transport microtubules would distinguish the short microtubules from the longer microtubules and only impinge upon the short ones. Instead, we suspect that the same forces that transport the short microtubules are generated on the longer microtubules but cannot move them due to the drag imposed on them by crosslinks with neighboring microtubules and other cytoplasmic elements. We think of this much like an isometric exercise in which no movement occurs of either of the two players, even though there is a great deal of force generated between them (47). A shift in these forces would have profound effects on the microtubules, and in turn, on the morphology of the axon.

A key example of this is observed with the phenomenon of axonal retraction, which is crucial for pruning overgrown axons during the development of the nervous system (48). It is known that the retraction of the axon requires actin filaments (49,50). We have shown that functional inhibition of myosin-II prevents axonal retraction, while functional inhibition of cytoplasmic dynein tends to promote retraction (51). Prior inhibition of myosin-II prevents retraction when dynein is inhibited. These observations suggest that the forces generated by cytoplasmic dynein offset those generated by myosin-II. We would contend that cytoplasmic dynein interacts with long micortubules and the actin cytoskeleton, imposing forces that oppose the contractility of the actin meshwork, thus offsetting the forces generated by myosin-II. According to this model, axons could retract physiologically by either enhancing the myosin-driven forces or dampening the dynein-driven forces (52) rather than depolymerizing the microtubules (43). Figure 3B shows how dynein-based forces integrate microtubules with the cortical actin cytoskeleton during axonal growth. Figure 3A shows how an attenuation of the dynein-based forces would permit the contractile forces to cause the axon to retract.

More speculative at present is a potential role for these forces in the interactions between cytoskeletal elements that occur during growth cone turning. Several studies have established that the long microtubules extending into the peripheral zone and filopodia of the growth cone are critical for it to turn in response to substrate cues (53). These studies have established that the microtubules align with bundles of actin filaments in the peripheral regions and filopodia of the growth cone and that the dynamic properties of the microtubules are essential for this to occur properly (54,55). To date, there is little evidence of any concerted transport of the polymers, at least in the anterograde direction (56), which is consistent with our cut and run model, given that these microtubules are typically quite long. Microtubules and actin filaments have been observed to co-assemble (57,58), suggesting that there may be no need for motors for them to align. It is our theory, however, that cytoplasmic dynein is important for integrating the microtubule with the actin bundle in a force-dependent fashion comparable to the manner by which microtubules interact with the cortex in other cell types (Figure 3C). Without such forces, we speculate that the two filament systems would be unable to functionally engage, such that the microtubules and actin bundle would not be able to collaborate in such a way as to cause the growth cone to turn properly.

At present, the available evidence suggests that both of these examples, axonal retraction and growth cone turning, involve microtubule–actin interactions and therefore may rely mainly on forces generated by cytoplasmic dynein rather than kinesins. The 'mitotic' kinesins presumably function by generating forces between neighboring microtubules. However, the same microtubules that interact with actin via cytoplasmic dynein may interact with other microtubules via kinesins, thus integrating all of the various components. Also, at least one of the relevant kinesins has been shown to interact with actin filaments in non-neuronal cells (17), and hence the same could be true in neurons under certain circumstances. Thus, we would not dismiss the possibility that kinesins, either directly or indirectly, may also participate in the forces relevant to axonal retraction and/or growth cone guidance.

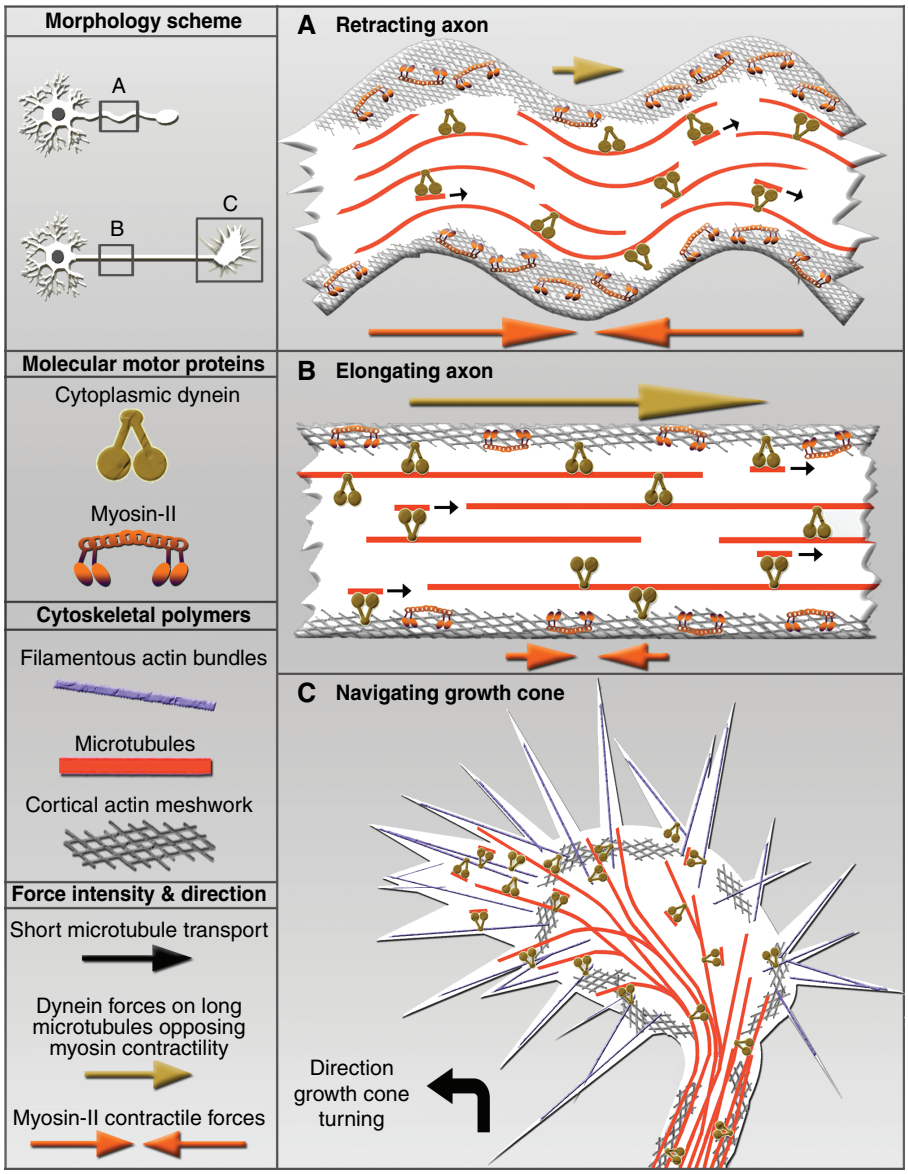

Figure 3: Schematic model for how cytoplasmic dynein opposes axonal retraction (A), promotes axonal elongation (B), and directs growth cone navigation (C). In the elongating axon, dynein-driven forces between the long microtubules and the cortical actin meshwork offset the myosin-II-driven contractility of the actin meshwork, thus preventing axonal retraction and allowing the axon to grow. Reduction of dynein-driven forces between the long microtubules and the cortical actin meshwork (or an increase in myosin-II activity, not shown) relieves attenuation of myosin-II-driven contractility, resulting in retraction of the axon. The mechanism by which dynein-driven forces might be reduced or myosin-II-driven forces might be enhanced remains speculative at present and hence is shown schematically as a 'disconnect' between the dynein motors and the cortical actin meshwork. Long microtubules invade the peripheral region of the growth cone and individual filopodia specifically in the direction of growth cone turning. The model speculates that dynein-driven forces play a role in assisting the microtubules to align with and functionally engage the actin bundles during growth cone navigation. In (A), (B), and (C), short microtubules are shown to be rapidly transported by cytoplasmic dynein, along the cortical actin meshwork, longer microtubules, or bundles of actin filaments.

Expanding the MAP-Based Hypothesis

The cut and run model suggests that molecular motors act on microtubules irrespective of their lengths, but this does not mean that all motors act equally on the microtubules at all times and in all locales. Whether an axon retracts or grows, for example, would be determined by the tipping of forces in one direction versus the other. Also, the relevant motors must be balanced in such a way so as to establish the ratio of anterograde to retrograde movements of the short microtubules. Thus, it would appear that the length of the microtubules is a key determinant of whether or not they can be rapidly transported, but additional mechanisms specify features of the transport such as the directionality and frequency of the movement. This might relate simply to the levels and/or ratio of available motors in the axon, or alternatively, to mechanisms such as phosphorylation of motors that can contribute to whether or not the motor interacts with the microtubules (59).

Another possibility that we find appealing is a potential role for the non-motor fibrous MAPs. Earlier, we discussed the idea of a 'MAP protection model' for the regulation of microtubule severing, and it seems possible that the same or perhaps other MAPs could also be important for determining motor interactions with the microtubules. The experimental evidence that prompts this hypothesis comes from the work of the Mandelkow laboratory, in which it was shown that overexpression of certain MAPs such as tau can impede the interactions of the microtubules with molecular motors. Interestingly, in these studies, there was a much stronger inhibition by MAPs of the microtubule interaction with kinesins

than with cytoplasmic dynein (45,60). If this finding holds true for motors transporting microtubules, perhaps it is the presence of MAPs such as tau in the axon that ensures that dynein-based anterograde transport of microtubules predominates over kinesin-based retrograde transport of microtubules. If so, just as alterations in MAP association with microtubules might regulate severing, it is also conceivable that MAPs might regulate the frequency and directionality of motor-based forces on the microtubules.

This hypothesis is sheer speculation at present, but we find it appealing, because it offers a consolidated model for how MAPs, severing proteins, and molecular motors function co-ordinately to regulate the transport of microtubules in the axon, as well as various other force-related aspects of axonal development such as axonal retraction and growth cone guidance. We are eager to begin testing the merits of this hypothesis in the laboratory.

Closing Remarks

It was not terribly long ago when the topic of microtubule transport was mired in controversy. Some of the prominent textbooks even claimed that it had been all but proven that microtubules are not transported down axons at all. Today, we know that microtubule transport is a broad theme utilized across cell types (61–65), and investigators have been able to visualize the movement of microtubules within the axons of living neurons. One of the most profound revelations from these imaging studies is the length of the microtubules that are in transit down the axon. The discovery that the mobile microtubules are very short has enabled us to think mechanistically about the motors that transport them, the severing proteins that produce them, and also about the effects of the motors on the microtubules that are too long to be moved. We are also beginning to think of potential models by which the severing and frequency of motor interactions with the microtubules might be regulated. Thus, a new chapter has opened for the field of axonal microtubule transport, with myriad functional issues to be explored, and an exciting palate of molecular players to be elucidated.

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