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Microtubules in health and degenerative disease of the nervous system

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Abstract

Microtubules are essential for the development and maintenance of axons and dendrites throughout the life of the neuron, and are vulnerable to degradation and disorganization in a variety of neurodegenerative diseases. Microtubules, polymers of tubulin heterodimers, are intrinsically polar structures with a plus end favored for assembly and disassembly and a minus end less favored for these dynamics. In the axon, microtubules are nearly uniformly oriented with plus ends out, whereas in dendrites, microtubules have mixed orientations. Microtubules in developing neurons typically have a stable domain toward the minus end and a labile domain toward the plus end. This domain structure becomes more complex during neuronal maturation when especially stable patches of polyaminated tubulin become more prominent within the microtubule. Microtubules are the substrates for molecular motor proteins that transport cargoes toward the plus or minus end of the microtubule, with motor-driven forces also responsible for organizing microtubules into their distinctive polarity patterns in axons and dendrites. A vast array of microtubule-regulatory proteins impart direct and indirect changes upon the microtubule arrays of the neuron, and these include microtubule-severing proteins as well as proteins responsible for the stability properties of the microtubules. During neurodegenerative diseases, microtubule mass is commonly diminished, and the potential exists for corruption of the microtubule polarity patterns and microtubule-mediated transport. These ill effects may be a primary causative factor in the disease or may be secondary effects, but regardless, therapeutics capable of correcting these microtubule abnormalities have great potential to improve the status of the degenerating nervous system.

Keywords

microtubule; neuron; axon; dendrite; katanin; spastin; fidgetin; dynein; kinesin; neurodegeneration; Alzheimer's disease; tau; tauopathy; microtubule-associated proteins; molecular motor proteins; axonal transport; CAMSAP; tubulin; tubulin code; microtubule stability; +tips

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Introduction

The microtubule arrays of axons and dendrites provide a structural backbone that allows them to acquire and maintain their specialized morphologies. In addition to acting as structural elements, microtubules are long-distance railways for proteins and organelles to be actively transported in both directions within axons and dendrites. Microtubules are crucial for early developmental stages of the neuron, such as migration of the soma and the navigation of the growth cone at the tip of the elongating axon. Microtubules are also important throughout the life of the neuron, for it to maintain its proper morphology, to enable axonal and dendritic transport, and to accommodate morphological changes such as alterations in dendritic shape that may correspond with cognitive plasticity, even in old age. Proper functioning of microtubules and their assortment of interacting and regulatory proteins as well as regulatory pathways is crucial for the health of the nervous system. Abnormalities of the microtubule systems of axons and dendrites are a major contributor to neurodegenerative diseases. The purpose of this review is to provide a brief overview of contemporary knowledge of neuronal microtubules and how they may go awry during degeneration of the diseased nervous system.

Microtubule organization in neurons

Tubulin is a heterodimer of alpha tubulin and beta tubulin, each of which is a different primary gene product believed to have diverged evolutionarily from a single gene (1). In vertebrates, there are multiple alpha tubulin genes and multiple beta tubulin genes. In the test tube, microtubules can be nucleated *de novo* if there is a sufficient concentration of free tubulin, as well as the presence of GTP and appropriate temperature and buffer conditions. In living cells, *de novo* nucleation is suppressed so that nucleation of microtubules is favored to occur from nucleating structures that are usually components of “microtubule-organizing centers” such as the centrosome. The nucleating structures are called gamma-turcs (gamma tubulin ring complexes) because they consist of gamma tubulin, together with other proteins that combine with gamma-tubulin to form a template for the nucleation of new microtubules (2, 3). Gamma tubulin is a separate gene product from alpha or beta tubulin, and binds specifically to beta tubulin to establish the polarity orientation of the microtubule that elongates away from the nucleating structure. Some microtubules may remain attached to their nucleating structures, while others may be released from their nucleating structures and then recaptured by other proteins within the microtubule-organizing center. Still other microtubules may be released and then transported away from the nucleating structure by molecular motor proteins. Which of these options predominates depends on the cell type and stage of development, for example with developing neurons displaying a great deal of transport of microtubules away from the centrosome after their release (4).

Because tubulin is a heterodimer rather than a homodimer, the microtubule is intrinsically polar with beta tubulin at the plus end and alpha-tubulin at the minus end. The plus end of the microtubule is favored for dynamic exchange of tubulin subunits, while the minus end is less favored. The structural polarity of the microtubule exists along its entire length and is recognized by molecular motor proteins, which are enzymes that move along the lattice of the microtubule. Cytoplasmic dynein moves toward the minus end of the microtubule, while

most kinesins move toward the plus end. Because different cargoes interact with different motors, the polarity orientation of microtubules in different regions of the neuron is a major determinant of where different cargoes are transported, thus allowing for subcellular localization of cytoplasmic constituents (5). Microtubules in the axon are nearly uniformly oriented, with their plus ends directed away from the soma, while microtubules in vertebrate dendrites are non-uniformly oriented, with roughly equal numbers of microtubules of each orientation (6-8). These distinct microtubule polarity patterns, shown in figure 1, are one of the most essential and earliest developmental differences to arise between axons and dendrites, and are undoubtedly of key importance for many of the compositional and morphological differences that distinguish the two types of processes (8). Other factors that contribute to the delivery of different cargoes to different compartments of the neuron include targeting information within the motor proteins themselves, post-translational modifications of the tubulin subunits that comprise the microtubules in different regions of the neuron, and the microtubule-associated proteins that adorn the microtubules (9).

As mentioned above, microtubules in developing neurons are nucleated at the centrosome and then released for transport into axons and dendrites (10-13). Molecular motor proteins transport the microtubules with either plus-end leading (into axons and dendrites) or with minus-end leading (into dendrites only). In this manner, the molecular motor proteins that transport microtubules into axons and dendrites establish the distinct polarity patterns of microtubules in each type of process (14-18). Available data suggest that cytoplasmic dynein is the chief motor protein for transporting plus-end-out (i.e., plus end directed away from the cell body) microtubules into both axons and dendrites, while kinesin-6 and kinesin-12 share the responsibility of transporting minus-end-out microtubules into dendrites but not axons. Recent studies have shown that a protein concentrated in the axon initial segment called tripartite motif-containing protein 46 (TRIM46) may function along the axon's length to preserve the uniform polarity orientation of the microtubules against corruption (19, 20). This function appears to relate to the microtubule-bundling properties of TRIM46. Other studies have shown that the centrosome may become quiescent as the neuron matures (21), such that new microtubules arise only via the severing of existing microtubules or potentially through local nucleation mechanisms.

The microtubule arrays of the neuron consist of individual microtubules that assume a variety of lengths and degrees of stability. Individual microtubules generally do not traverse the entire length of an axon or dendrite. Some microtubules are only a few micrometers in length (or even less), while other microtubules can achieve lengths that exceed a hundred micrometers (22-25). Longer microtubules act both as architectural struts that oppose the retraction of the axon or the dendrite as well as railways for organelle transport. The short microtubules are highly mobile and provide the form by which tubulin is actively transported within the axon and presumably dendrites. A short mobile microtubule may elongate into a long stationary microtubule, or it may entirely or partially depolymerize to yield subunits for other microtubules to elongate.

Microtubule dynamics and stability in neurons

Microtubule dynamics in cells are governed by a mechanism known as dynamic instability (26-29) that depends on tubulin being a GTPase. Free tubulin associates with hydrolysable GTP. Both alpha and beta tubulin associate with GTP, however the GTP bound to alpha tubulin rests in the region where alpha and beta tubulin interact. Therefore, tubulin heterodimers are only able to hydrolyze the GTP bound to beta-tubulin and this hydrolysis changes the conformation of tubulin dimer-dimer interaction (i.e., the conformation of the protofilaments that make up microtubules). GTP-bound tubulin dimers tend to orient the microtubule in a straight conformation, whereas GDP-tubulin bends the lattice and "spring loads" the microtubule with potential energy that favors catastrophe, which is an explosive bout of disassembly (30). The hydrolysis of GTP-beta-tubulin to GDP-beta-tubulin only happens after the free tubulin has assembled into the microtubule. Because GTP hydrolysis takes time and because dynamics occur principally at the plus end of the microtubule, the region of the microtubule toward the minus end is richer in GDP-tubulin than the region toward the plus end. If GTP hydrolysis catches up to the addition of new tubulin such that there is no longer a ring of GTP-tubulins at the plus end, the microtubule undergoes catastrophe. The microtubule can keep assembling as long as there is a GTP-tubulin "cap" at its plus end. Individual microtubules in a population may undergo assembly while others may at the same time undergo disassembly, depending on whether or not the GTP cap is lost from any individual microtubule.

Microtubules in the population can be stabilized either by the capture of their plus ends, for example by complexes that form at the plus-end of microtubules to promote polymerization and recruit microtubules to the cell cortex (e.g. CLIP and CLASP, respectively), or by proteins that bind to the microtubule lattice (31-33). When a microtubule or a region of a microtubule is stabilized, it may still undergo dynamics, albeit slower. A small portion of the microtubule mass in developing axons is so stable that it appears to undergo no subunit exchange whatsoever, and is resistant to factors such as cold, calcium and microtubule-depolymerizing drugs that cause microtubules to disassemble. This hyper-stable (traditionally called "cold-stable" due to its capacity to resist depolymerization in response to cold in biochemical preparations) portion of the microtubule mass is stabilized by polyamination of the tubulin, and comprises a much larger fraction of the microtubule mass in adult neurons relative to developing neurons (34, 35). Polyamination is different from other known modifications of tubulin associated with microtubule stability, namely acetylation and detyrosination, as these other modifications do not confer stability but rather accumulate on microtubules that are long-lived (36-39). In neurons, available data indicate that different microtubule stability classes exist as domains on individual microtubules, rather than as separate populations of microtubules. As shown in figure 1, a typical microtubule in a developing neuron is, on average, about half stable and half labile, with the stable domain toward the minus end of the microtubule and the labile domain toward the plus end of the microtubule (40). Polyaminated tubulin is sparse in developing neurons, but represents a substantial portion of the total tubulin in adult neurons. It has been posited that the polyaminated regions of microtubules are interspersed as patches along the microtubule (presumably within the stable domain), but this has not been sufficiently explored.

After decades of study, mystery still surrounds the factors and pathways that account for the stability properties of neuronal microtubules (9). Many different proteins have been credited with stabilizing microtubules, including traditional MAPs (microtubule-associated proteins) such as tau, MAP2 and MAP1b, as well as other proteins that bind to the microtubule lattice such as doublecortin (41-43). Most proteins that interact with microtubules can stabilize them *in vitro* or if overexpressed in cells, assuming the concentration is high enough. Tau and its related family members, MAP2 and MAP4, have repeated microtubule-binding domains that are thought to bind in a series along the microtubule lattice to hold it together and thereby prevent depolymerization (33). However, the on/off rate of these proteins with the microtubule in living cells is only milliseconds (44), which seems inconsistent with tau or its family members stabilizing microtubules in a traditional sense of strong stabilizing protein-protein interactions. Curiously, tau and MAP1b are more enriched on the labile domains of microtubules in the distal region of growing axons than on microtubules in the main shaft of the axon where stable and labile domains intermingle (45-47). This suggests that these proteins may be more important for regulating stability than conferring stability. MAP6 (also called stable tubule only peptide) is more enriched on the stable microtubule domains (48), and hence may be a better candidate for endowing stable domains with their stability properties. One possibility is that microtubule stability in neurons is the result of the combination of many different stabilizers, but another possibility is that many proteins that display microtubule-stabilizing properties *in vitro* or when overexpressed in cells may not be stabilizers of microtubules in the physiological context.

Certain proteins promote microtubule depolymerization. Examples are stathmin and its neuron-specific variant called SCG10, which shift microtubules toward disassembly by sequestering tubulin subunits and by promoting catastrophe, as well as certain “depolymerizing” kinesins (kinesin-8 and kinesin-13) that use the forces of ATP hydrolysis to remove tubulin subunits from the ends of microtubules (49, 50). Fidgetin, a novel microtubule severing protein, appears to target labile domains of microtubules, creating short microtubule fragments that quickly depolymerize into free tubulin (51). Proteins that depolymerize microtubules can promote reorganization of microtubule networks by liberating tubulin from one microtubule for incorporation into other microtubules elsewhere in the cell. Such transfer of tubulin subunits from one microtubule to another occurs via passive diffusion of free tubulin, but can be augmented by active transport mechanisms, given that tubulin can be incorporated into short polymers that are transportable by motor proteins over longer distances before yielding their subunits for the elongation of other microtubules.

Microtubule end-targeting proteins

+tips are proteins that associate with the plus end of the microtubule during bouts of assembly. Some have their own affinity for the plus end of the microtubule, by recognizing the GTP cap, while others have an affinity for other +tips and become +tips themselves for that reason. These proteins include EB1, EB3, CLIPs, CLASPs and others (52). Fluorescently conjugated +tips are useful for live-cell imaging of microtubule assembly and organization in cells. In neurons, +tips can influence the assembly dynamics of the microtubule, and integrate its behavior with a variety of proteins and structures (53). +tips

are also important players in the “search and capture” mechanism of microtubule-stabilization, wherein a microtubule undergoing bouts of dynamic instability can be selectively stabilized by plus end capture by other cellular structures. This can be important, for example, in stabilizing microtubules on the side of a cell corresponding to the direction of migration, in response to an environmental cue. In this regard, +tips have important roles in growth cone behaviors (54). Recent studies suggest interesting relationships between +tips and more classic microtubule-associated proteins, for example with overexpression of EB1 rescuing the axogenesis impairment phenotype of MAP1B knockout (55).

Recent studies have revealed a new category of proteins called calmodulin-regulated spectrin-associated proteins (CAMSAPs) (56). CAMSAPs, sometimes referred to as minus-end binding proteins, bind to free minus-ends of microtubules in various cells, and thereby block dynamics at that end of the microtubule (57). Vertebrate neurons express CAMSAP-1, CAMSAP-2, and CAMSAP-3, with CAMSAP2 being the predominant CAMSAP in these cells. Immunostained or ectopically-expressed fluorescently-tagged CAMSAPs appear as short stretches along the microtubule toward its minus end. This suggests that CAMSAPs compete with tubulin subunits for the minus end of the microtubule, until enough CAMSAP accumulates to limit any further dynamics. Depletion of CAMSAPs from neurons has detrimental effects on microtubule levels and stability and results in underdeveloped neuronal morphologies (58). Additional information on CAMSAP distribution in neurons will potentially reveal important insights into microtubule regulation in various neuronal compartments.

Microtubule-severing proteins

Microtubule-related proteins are AAA enzymes that form hexamers on the surface of the microtubule. The hexamers yank on a tubulin subunit to extract it from the microtubule lattice, causing the microtubule to break (59, 60). Such severing of microtubules can occur near their minus ends within the centrosome to release the microtubule so that it can then be transported into an axon or a dendrite. Severing can also occur at the plus end so that subunits are peeled off the more dynamic end of the microtubule. If the severing occurs in the stable domain, the result is two new microtubules, one with a stable and labile domain, and the other exclusively a stable fragment that can then assemble a new labile domain. In this manner, severing in the stable domain creates new microtubules. This is important for axonal and dendritic growth and branching to supply new microtubules for elongation and engorgement; thus reducing the dependence on new microtubules from the centrosome. Mobile microtubules observed in the axons of cultured neurons are generally about 7 micrometers in length and stable (61, 62), and hence presumably arise from the severing of longer microtubules in their stable domains. If the severing occurs in the labile domain, the result would be one microtubule with a stable domain and a shorter labile domain, as the microtubule fragment without a stable domain would presumably vanish as it would completely depolymerize (63). Thus, severing in the labile domain would not create new microtubules, but rather would pare down the labile domains, keeping them shorter than they would otherwise be. It is likely that the existence of multiple severing proteins allows for certain ones to target the stable domain and others to target the labile domain. Tight regulation of the expression levels and activities of the various severing proteins could

thereby impose control over the expansion or tamping back of the microtubule array during axon growth, non-growth or retraction. This would be reminiscent of the circumstances in *Drosophila* cells undergoing mitosis, wherein katanin, spastin, and fidgetin play unique roles in the microtubule-mediated movement of chromosomes (64).

Katanin and spastin are microtubule-severing proteins with a preference for severing in the stable domain of the microtubule, resulting from a preference for tubulins that have been post-translationally acetylated or polyglutamylated (65, 66). Suppressing katanin or spastin can be deleterious to axonal growth and branching (13, 67-69), as would be expected, given the important roles these proteins play in generating new microtubules via the severing of existing ones. Recent data suggest that fidgetin targets labile domains of microtubules through a preference for tubulins that are not post-translationally acetylated (51). Knocking down fidgetin causes axons of fetal cortical neurons to grow longer, potentially due to elongation of the labile domains of microtubules (51). Thus knocking down or inhibiting proteins that prune the labile domain, such as fidgetin, may be a useful therapeutic approach for elevating labile microtubule mass in injured or diseased axons.

The tubulin code

Why do cells so tightly regulate tubulin post-translational modifications that do not impose stability on microtubules directly, but often reflect their stability? A great deal of evidence suggests that post-translational modifications of tubulin impose a “code” on the microtubule that is read by other proteins (37, 70). The idea is that many microtubule-related proteins have preferential affinities for microtubules (or domains of a microtubule) that are enriched or deficient in certain modified tubulins. For example, kinesin-1 prefers microtubules rich in detyrosinated and acetylated tubulins, while kinesins 5 and 13 prefer microtubules rich in tyrosinated tubulin (71-73). Thus, the post-translational modifications of a microtubule may make it a more or less favored substrate for proteins such as molecular motors. Other examples of proteins sensitive to the tubulin code include microtubule-severing proteins, as discussed earlier (51, 65, 66), and certain +tips that have a preference for tyrosinated over detyrosinated tubulin (74). This is important because when experiments demonstrate a functional role for stable or labile microtubules (or domains of a microtubule), it may not be the stability properties of the microtubule, per se, that is relevant so much as the tubulin modifications that accompany the microtubule's stability properties.

The tubulin code is regulated by highly conserved and tightly regulated enzymes, and for some modifications, the enzymes orchestrate a cycle wherein the modification is imposed only after assembly of the tubulin into the microtubule and only reversed when the tubulin subunits are liberated from the microtubule during bouts of disassembly. For example, the enzymes may be differentially enriched or regulated in axons versus dendrites, enabling axonal microtubules to be richer in post-translationally modified tubulin subunits compared to dendritic microtubules. These enzymes provide a hub for regulation of the tubulin code, and may also provide an avenue for therapeutics, as they can be experimentally or clinically manipulated to change the tubulin code in a manner that might be conducive to reversing the ill effects of disease.

A recent article on nerve regeneration after injury provides a good example of the potential for therapeutics, based on manipulating the tubulin code. Transgenic mice with constitutively active GSK3 displayed decreased detyrosination of microtubules in growth cones of injured axons as well as improved sciatic nerve regeneration (75). Drugs that inhibit tubulin detyrosination resulted in similar regenerative enhancing effects, whereas microtubule stabilization negated these effects. These findings support the notion that manipulating the tubulin code has different effects than simply manipulating microtubule stability, thus providing different tools to achieve changes in the microtubule array that may assist in treating various disease or injury scenarios.

Microtubule defects in nervous system disease

The various aspects of the neuronal microtubule arrays thus far discussed can be corrupted over the life of the neuron by the aging process as well as by neurodegenerative disease mechanisms. For example, the axon must preserve a nearly uniform polarity orientation of microtubules in order for the anterograde and retrograde transport of various cargoes to be properly orchestrated. Corruption of the microtubule polarity pattern (i.e., appearance of too many mal-oriented microtubules) would send cargoes moving in the wrong direction and potentially cause traffic jams. Preserving the microtubule polarity pattern of the axon is ongoing work for the neuron, requiring cytoplasmic dynein to transport mal-oriented microtubules back to the cell body (76). This clearing mechanism could be overwhelmed by pathogenic factors that promote the formation of mal-oriented microtubules or the flipping of short microtubules. The clearing mechanism itself could also be degraded by pathology. This has not yet been explored in the context of known diseases, but mutation of the fly ortholog of an epilepsy gene causes notable microtubule polarity flaws in the axon (77).

Microtubule loss (i.e. reduction in microtubule mass) from axons and dendrites is often associated with neurodegenerative diseases (78, 79). This is best documented in diseases called tauopathies, in which tau dissociates from microtubules as a result of abnormal phosphorylation (80, 81). Pure tauopathies result from mutations that render tau prone to such effects. Tau is not mutated in Alzheimer's disease, but rather becomes hyper-phosphorylated in response to abnormal amyloid-β (82). Popularly, microtubules are said to disintegrate as they lose tau, due to the microtubules being destabilized (27). Such a mechanism would suggest that stable domains of microtubules become labile, which would then somehow lead to a degradation of the microtubule mass. Another theory posits that detachment of tau from microtubules causes them to become more sensitive to microtubule-severing proteins, mainly katanin (83, 84). There has also been evidence that tau tangles themselves can promote microtubule depolymerization (85), and the same could be true of soluble abnormal tau. For example, abnormal tau, either in the form of soluble protein or in the form of abnormal filaments, is known to produce toxicity that could theoretically contribute to microtubule loss via Tau's phosphatase-activating domain (86). When tau abnormally enters dendrites during Alzheimer's disease, recent evidence suggests that dendritic microtubules degrade because they become more polyglutamylated and hence more sensitive to spastin (87). Loss-of-function and gain-of-function mechanisms may apply to various neurodegenerative disorders in which loss of microtubule mass or a change in microtubule dynamics or stability has been observed, including Amyotrophic Lateral

Sclerosis, Hereditary Spastic Paraplegia, Parkinson's disease, and others (88-91). Figure 2 shows potential mechanisms of microtubule loss during axonal degeneration, as well as a potential contribution to axonal degeneration of microtubule polarity flaws, as discussed earlier.

Some investigators have posited that neurons afflicted with tauopathies and other neurodegenerative diseases may benefit by treatment with microtubule-stabilizing drugs. Animal models for neurodegenerative diseases and injuries have shown histological and behavioral improvements when treated with microtubule-stabilizing drugs (92-96). In human patients, there are potential problems of increasing microtubule stability throughout the neuron and throughout the entire nervous system, especially if the drugs are taken systematically (97). It has been posited that a better idea than microtubule-stabilizing drugs may be the development of drugs that inhibit microtubule-severing proteins so that deficits in the stable or labile domains can be specifically corrected (63). A shift in focus of the research community from stabilizing existing microtubules to adding labile microtubule mass (via the elongation of labile domains of microtubules) to the degenerating axon or dendrite may benefit a number of different disease and injury scenarios. Therapies that target severing proteins are certainly not the only avenue by which this could be accomplished, as inhibition of other proteins that limit microtubule assembly, such as stathmin (98), could also be helpful. +tips are another potentially powerful target for affecting microtubule dynamics; for example, overexpression of TACC3, a +tip in frog, increases axon length, presumably by enabling the elongation of labile domains of microtubules (65).

The past decade has seen a plethora of work on other mechanisms (besides microtubule loss) by which cytoskeletal mechanisms might go awry during neurodegenerative diseases. For example, in Huntington's disease, there are findings suggesting that mutant huntingtin protein abnormally folds on the microtubule lattice to cover more surface area than it normally would and thereby impedes organelle transport by physically blocking the microtubule's interaction with motor proteins (99). Relevant to Alzheimer's disease, beta amyloid has been shown to impair hippocampal long-term potentiation and promote dendritic spine loss through a pathway involving kinesin-5 (100), a motor protein that may contribute to the regulation of microtubule polarity orientation in dendrites (72). Audouard et al. (101) recently showed that disrupted axonal transport precedes progressive muscle denervation in mice expressing pathogenic human tau, while Stevenson et al. (102) used squid giant axon to show that amyloid precursor protein interacts at the organelle/microtubule interface, possibly mediating vesicular transport and Alzheimer's pathology. Gan et al. (103) proposed that the disruption of axonal transport by a mutant kinesin light chain-1 splice variant in Alzheimer's disease follows a progression of reduced axonal transport, which leads to accumulation of protein aggregates, followed by an ER stress response. These examples illustrate that the literature is growing at a rapid pace, with novel mechanistic hypotheses pushing the field toward a better understanding of etiology and potential therapeutics.

The ill effects on microtubules of any particular neurodegenerative disease may be a primary factor in axonal and/or dendritic degeneration or may contribute secondarily. Regardless, development of therapeutics capable of correcting these microtubule abnormalities will

undoubtedly improve the status of the degenerating nervous system. Future drug development will likely be directed toward inhibitors of specific proteins or pathways that affect microtubules, in order to shift the status of the diseased microtubule array back toward normal.

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Highlights

- Microtubules are essential for development and maintenance of axons and dendrites.
- Microtubules are vulnerable in a variety of neurodegenerative diseases.
- Dysfunctional microtubules are at the center of neurodegeneration and injury.
- Microtubules undergo complex modifications and protein-protein interactions.
- Microtubule-mediated mechanisms are ripe with therapeutic targets.

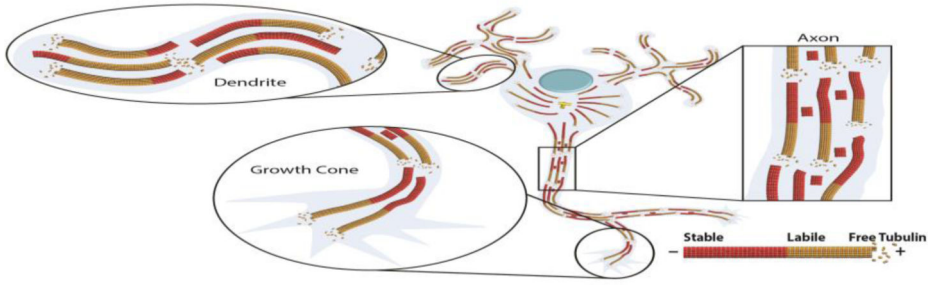

Figure 1. Microtubules are oriented differently in the axon and the dendrites

Microtubules in axons are nearly uniformly oriented with plus ends distal to the cell body while microtubules in dendrites are non-uniformly oriented. Microtubules consist of a labile domain (yellow) toward the plus end of the microtubule and a stable domain (red) toward the minus end of the microtubule.

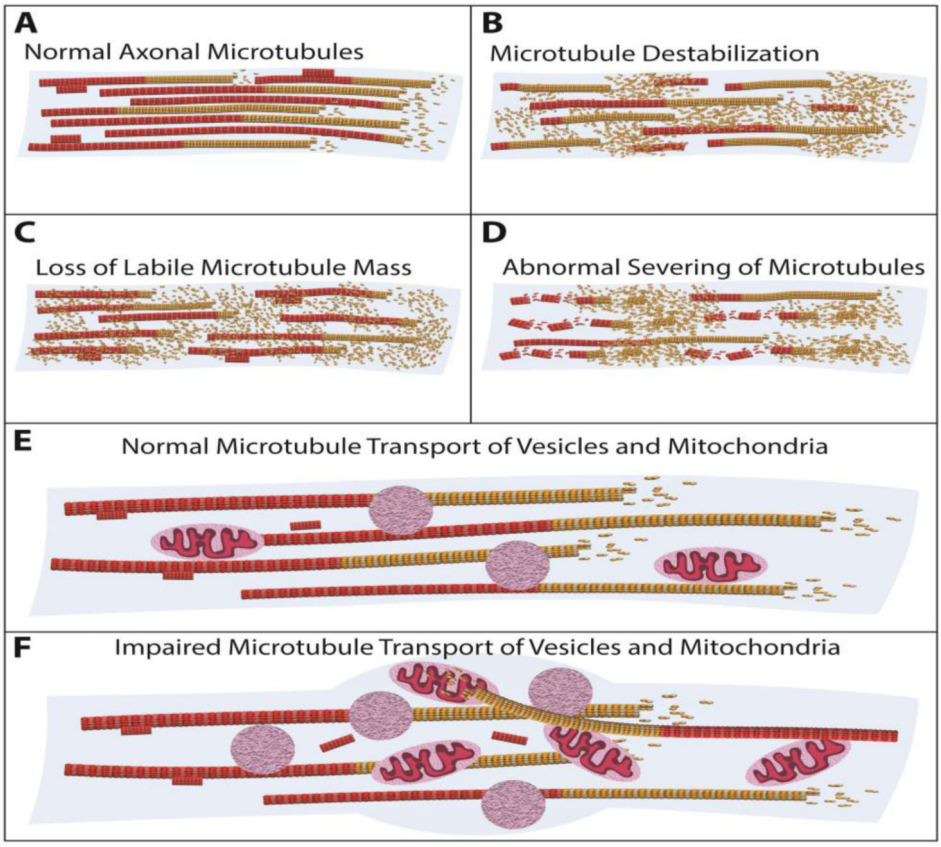

Figure 2. Corruption of the axonal microtubule array contributing to axonal degeneration during disease

Panel **A** shows the healthy adult neuron in which axonal microtubules are oriented with their plus ends (and labile domains, yellow) away from the cell body, and their minus ends (and stable domains, red) toward the cell body. Three potential mechanisms for microtubule loss during degeneration are shown in panels **B-D**). **B**) Microtubule destabilization is the conversion of a previously stable domain into a labile one. This leads to large portions of a microtubule susceptible to catastrophic events and thus results in microtubule disassembly. **C**) The labile domain of a microtubule is preferentially depolymerized, leaving behind mainly stable domains of microtubules. **D**) Microtubules become more sensitive to breakage by microtubule-severing proteins, with the breakage leading to microtubule depolymerization. Depending on the particular severing protein, this could preferentially affect either the labile or the stable domains. Panel **E** shows the healthy adult neuron with microtubules providing railways for motor-based organelle transport. Panel **F** represents traffic jams and other abnormalities in organelle transport resulting from microtubule polarity flaws in the axon (i.e., microtubules of inverse orientation). This can lead to axonal swelling and ultimately degeneration. Variations on these various pathogenic scenarios can also occur in dendrites (not shown).