Published in final edited form as:

N Engl J Med. 2011 December 15; 365(24): 2330–2332. doi:10.1056/NEJMcibr1112481.

Microtubules, Axonal Transport, and Neuropathy

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A physical dimension of a cell is seldom its Achilles' heel. Yet for the neurons that are affected in most kinds of peripheral neuropathy, it is the length of their axons that best accounts for their selective vulnerability. As shown in Figure 1, the axon is contiguous with its cell soma. The soma synthesizes the components of the axon and its terminals, which may be as far as a meter away. Axonal transport is driven by molecular motors that run on a polarized "highway" formed by microtubules. Kinesins drive transport outward, delivering new building blocks for axons (e.g., neurofilaments) and terminals and shuttling organelles such as mitochondria to areas of high energy demand. Transport from the terminals back to the cell soma is driven by cytoplasmic dynein and its activator, dynactin; they carry degradative organelles (lysosomes and autophagosomes) and endosomes that contain signaling platforms from the terminals.

Microtubules are formed from the association of dimers of α -tubulin and β -tubulin into proto-filaments, which associate laterally to form a tubule. The addition of tubulin subunits to the plus end of the filament leads to growth of the polymer, whereas subunit loss leads to shortening. In dividing cells, this dynamic remodeling is a constant process, but in neurons, microtubule-associated proteins (e.g., tau) dampen microtubule dynamics. The importance of microtubules and the motors that move along them has long been appreciated but has been underscored by recent discoveries of mutations in the genes that encode microtubules and their motor proteins. These cause neurodevelopmental and neurodegenerative diseases of diverse phenotypes, such as asymmetric polymicrogyria, the Perry syndrome, a form of motor neuropathy, a form of hereditary spastic paraplegia, and several forms of Charcot–Marie–Tooth disease, the term for hereditary neuropathy.

Dominant mutations of *HSPB1* and *HSPB8* also cause a hereditary axonal neuropathy.² These genes encode members of the family of small heat-shock proteins (sHSPs), all of which bind to unfolded proteins and prevent their aggregation.³ Despite the widespread expression of *HSPB1* and *HSPB8*, a motor-predominant axonal neuropathy is the sole phenotype of these dominant mutations. Building on their prior work, which showed that a subset of dominant *HSPB1* mutants have enhanced binding to their client proteins, Almeida-Souza et al.¹ recently reported that tubulin is a binding partner of *HSPB1*. With the use of biochemical and cellular assays, the authors showed that some *HSPB1* mutants have increased binding to tubulin, enhancing the stability of microtubules and leading to dampened dynamics. They proposed that the stabilization of microtubules is the mechanism by which dominant *HSPB1* mutant proteins cause a length-dependent neuropathy.

Their idea has an interesting parallel with regard to paclitaxel (Taxol), a chemotherapeutic drug that can cause neuropathy. Paclitaxel binds to microtubule polymer with high affinity, leading to stabilization, an effect similar to that apparently caused by some dominant

HSPB1 mutants. Because stabilized microtubules remain effective tracks for microtubule motors, it is unclear how the modest stabilization observed leads to axonal degeneration. One possibility is that this stabilization blocks remodeling of the cyto-skeleton at synaptic sites, a newly appreciated site of action.⁴ Alternatively, the binding of mutant HSPB1 along the microtubule might sterically block transport; the mobility of kinesin-1 in particular has been shown to be susceptible to this effect.⁵

Stabilized microtubules, however, are unlikely to be the complete answer to the question of how HSPB1 mutants cause neuropathy. Not all HSPB1 mutants affect chaperone activity. The sHSPs bind to many substrates, and there are other reported effects of sHSP mutants.³ For example, overexpression of the two different HSPB1 mutants (but not wild-type HSPB1) results in aggregates of HSPB1 together with other proteins, including neurofilament subunits. These aggregates could be taken as evidence that the HSPB1 mutants have decreased chaperone activity, at least toward these substrates. Another issue that makes the elucidation of the mechanism particularly challenging is that if a neuropathy takes years to develop, the mutants that cause such a neuropathy would be expected to have relatively subtle defects. (This has recently been shown to be the case with a specific mutant version of Rab7, which causes Charcot–Marie–Tooth disease.) Only with time are the cumulative effects of the mutation on cellular function likely to become fully apparent.

References

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Figure 1. Axonal Integrity and the Microtubule

Microtubules and their motor proteins maintain axons. Microtubules are formed by the polymerization of dimers of α -tubulin and β -tubulin, which dynamically assemble into a polarized structure that serves as a track for micro-tubule motor proteins (dynein–dynactin and kinesins). Genetic defects that affect tubulin, dynein, dynactin, kinesins, and cargo-associated molecules such as Rab7 and neurofilament light (NEFL) are linked to Charcot–Marie–Tooth (CMT) disease and other neuropathies. A recent report by Almeida-Souza et al.¹ suggests that HSPB1, a small heat-shock protein that is mutant in CMT disease, also affects microtubule dynamics and thus the health of axons.