In This Issue

Finding the dark side of tau

On page 1051, Stamer et al. have uncovered what may be a critical early step in the pathogenesis of Alzheimer’s disease and a previously unappreciated regulatory system for microtubule-based motors. The work focuses on the microtubule-associated protein tau, which is thought to cause the pathological changes seen in some neurodegenerative diseases. The prevailing view is that tau stabilizes microtubules, and disease results when the protein detaches from microtubules and aggregates into paired helical filaments. According to the authors, the opposite situation—having too much tau attached to microtubules—may be just as bad.

Overexpressing tau in neuroblastoma cell lines, primary hippocampal neurons, or retinal ganglion cells leaves microtubules intact. Rather than forming filaments, the overexpressed tau binds to microtubules and appears to lay the groundwork for neurodegeneration. Excess tau causes the depletion of mitochondria and peroxisomes from the cells’ processes, retarding growth and increasing the cells’ sensitivity to oxidative stress. The transport of Golgi-derived vesicles into axons is inhibited, and neurofilament proteins and vesicles carrying the amyloid precursor protein (APP) accumulate in the cell body. These changes are likely to increase the production of toxic amyloid Aβ peptides, a hallmark of Alzheimer’s disease.

Thus, whereas low levels of tau are necessary for microtubule stability, higher levels interfere with transport. Detachment of tau from microtubules and aggregation of tau into filaments might be a later consequence of the trafficking problems caused by excess tau attaching to microtubules. The results also suggest a novel regulatory system for microtubule-based motors, in which tau and other proteins on microtubules might act as roadblocks that determine the rate of vesicle trafficking.

Tubulin but not microtubule

The pathogens that cause malaria, cryptosporidiosis, and toxoplasmosis share a baffling common feature: a cone-shaped apical structure called the conoid. Previous research has suggested that the conoid is composed of microtubules and has simultaneously provided evidence that it is not. Now, on page 1039, Hu et al. resolve this longstanding dilemma by demonstrating that the conoid is made of tubulin, but not in the form of classical microtubules. In addition to describing a previously unknown form of cytoskeletal structure, the results could help in the development of new treatments for some of the world’s most devastating diseases.

Conoids consist of tubulin in an unconventional arrangement.

The conoid is part of the apical complex, the defining feature of the phylum Apicomplexa and a structure thought to be involved in host cell invasion by these parasites. Although tubulin was considered the most likely building block of the conoid, the bends in the structure appeared too tight to be accommodate by microtubules. Combining transgenic Toxoplasma gondii and an array of imaging techniques, the authors confirmed that the conoid is composed of tubulin protofilaments, supporting the microtubule hypothesis. But careful ultrastructural analysis shows that the tubulin in the conoid assembles in a manner never before observed, creating a structure with a comma-shaped cross section rather than a microtubule. Previously described tubulin structures are generally circular or semicircular in cross section.

Hu et al. also found that the conoid fibers are assembled rapidly during the early phases of cell division. The flattened cross section explains how tubulin can conform to the tight bends found in the conoid—a ribbon is easier to bend than a straw—but more work will be needed to understand how the cell directs the assembly of this novel structure, and how the increased pitch of the fibers and the translation of the entire structure contribute to the spring-like action of the conoid. The conoid’s unique architecture makes it an attractive drug target, especially since parasite and host microtubules are known to differ in their sensitivity to various compounds.
Actin (green) and ADF/cofilin (red) are disorganized in the absence of tropomyosin (bottom).

Previously, the authors found that worms with mutations in a muscle-specific ADF/cofilin isoform could not assemble normal myofibrils. ADF/cofilin appears to increase actin turnover, but myofibrils are highly stable structures, suggesting that some additional factor must inhibit ADF/cofilin in order to stabilize the myofibrils. The new study demonstrates that purified tropomyosin and ADF/cofilin compete for binding to purified F-actin, and that ADF/cofilin cannot bind to isolated myofibrils unless the attached tropomyosin is removed from the myofibrils first. RNAi suppression of tropomyosin disrupts myofibril organization in wild-type worms, but not in ADF/cofilin mutant worms. The results suggest that in vivo tropomyosin preserves myofilaments by blocking the destabilizing effects of ADF/cofilin.