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**Microtubule-Severing Proteins in the Axon: Implications for Degeneration and Regeneration.**

Neurons express high levels of enzymes called microtubule-severing proteins. These proteins break the lattice of the microtubule, which can result in individual long microtubules becoming many short ones. Alternatively, severing of microtubules can be so thorough as to cause substantial loss of microtubule mass. There are seven different microtubule-severing proteins in vertebrate neurons, with katanin and spastin being the best studied. Others include two katanin-like proteins and three related fidgetin proteins. Tight regulation of these severing proteins is important for releasing microtubules from the centrosome, for maintaining the proper balance between long and short microtubules in the axon, and for the generation of interstitial branches. In addition to working on the basic biology of these severing proteins, we are now gaining new insights into how their dysregulation contributes to axonal degeneration during disease and also how experimentally manipulating the severing proteins might augment regeneration of injured adult axons. In my presentation, I will challenge the dogma that spastin-based Hereditary Spastic Paraplegia results from too little microtubule severing, but I will propose the idea that too much microtubule severing by katanin might contribute to axonal degeneration in tauopathies. In addition, I will show preliminary data suggesting that therapeutic knockdown of the fidgetins can cause injured adult axons to regenerate with greater vigor. Finally, I will discuss the possibility that the different severing proteins may selectively interact with different classes of microtubules, thus explaining the different properties of the severing proteins and their division of labor.

**Mitotic Motors co-Regulate Microtubule Organization in Axons and Dendrites.**

In vertebrate neurons, microtubules in the axon are nearly uniformly oriented with their plus ends distal to the cell body, while in the dendrites, microtubules are non-uniformly oriented. We have proposed that these distinct microtubule polarity patterns are established and maintained by molecular motor proteins that transport microtubules into these processes with either the plus or the minus end of the microtubule leading. Our hypothesis has been that cytoplasmic dynein is the principal workhorse for transporting microtubules with their plus ends leading into both types or processes, while the remainder of the work is performed by a small number of kinesins usually considered to be mitotic kinesins, namely kinesins 5, 6, and 12. The results of our recent studies on these kinesins indicate that, in fact, they do not fuel microtubule transport in the axon, but rather they somehow suppress it. We now think of these motors as "brakes" on axonal microtubule transport. In my presentation, I will discuss the evidence for this conclusion, as well as potential mechanisms by which these motors might behave as brakes. A potentially exciting hypothesis is that these motors act, at least in part, at the level of the cell body to restrain the transport of microtubules into the axon while simultaneously promoting the transport of microtubules of the opposite orientation into dendrites. We posit that it is by this mechanism that the neuron co-regulates the polarity orientation of microtubules in the axon and dendrites. I will conclude my presentation with some discussion on how disruption of these mechanisms might contribute to neurodegeneration.

For my lecture to the students, please refer them to these two papers:

<http://neurobio.drexelmed.edu/baasweb/PDFs2011/Baas.Lin.2011.pdf>

<http://neurobio.drexelmed.edu/baasweb/PDFs2011/cytoskeleton.2012.pdf>