Pathogenic role of Tubulin Post-translational Modifications in Degenerative Disease of Central and Peripheral Nervous Systems.

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Abstract. Two different neurodegenerative diseases are considered in this project: Alzheimer disease (AD) and chemotherapy induced peripheral neuropathy (CIPN) that respectively affect the central and the peripheral nervous system. Our overall aim is to understand whether alterations in synaptic plasticity or axonal viability, both associated to neurodegenerative disease, are a result of inhibition of microtubule dynamics and/or toxic accumulation of tubulin modifications associated with microtubule longevity. More specifically, we investigate the functional role of cytoskeletal modifications in hippocampal neurons induced by neurotoxic levels of amyloid-β (Aβ), the major component of amyloid plaques in AD, and chemotherapy drugs in dorsal root ganglia (DRG) neurons at the onset of peripheral neuropathy, a debilitating condition often developed by cancer patients treated with these drugs. In our lab we have developed robust assays to measure microtubule behavior and tubulin modifications and routinely use these assays to dissect the signaling pathways that lead to microtubule changes using in vitro and in vivo models of disease.

Specifically, we investigate whether: 1) inhibition of microtubule dynamics is necessary for cognitive decline in animal models of AD and 2) modifications of microtubule behavior and tubulin modifications are activities of all CIPN inducing drugs and a primary cause of sensory neuron degeneration.

In one project we hypothesized that a primary activity of Aβ is to induce pathways that alter microtubule behavior and/or tubulin post-translational modifications, and that these changes trigger a cellular stress response that leads to tau hyperphosphorylation in an attempt to restore normal microtubule stability. Indeed, we found that Aβ acutely stabilizes neuronal microtubules by reducing microtubule dynamics. Silencing or acute inhibition of the formin mDia1, a regulator of microtubule stability, suppress this activity and correct the synaptotoxicity and deficits of axonal transport induced by Aβ. We explored the mechanism of rescue and found that microtubule stabilization promotes synaptotoxicity through induction of tau hyperphosphorylation. Together, these results uncover a novel role for mDia1 in Aβ-mediated synaptotoxicity and demonstrate that inhibition of microtubule dynamics is a driving factor for the induction of tau-mediated neuronal damage (manuscript in revision).

In the other more recent project, we are investigating the effects on tubulin post-translational modifications and microtubule behavior by acute and chronic doses of CIPN drugs.

on dorsal root ganglia (DRG) and in the sciatic nerves (SNs) isolated from control and treated We have preliminary results that all the examined drugs induced tubulin modifications associated with microtubule longevity in both DRG and sciatic nerves with differences in subtype-specific DRG sensitivity. These preliminary data are very exciting as they strongly suggest that: 1) all CIPN drugs can affect tubulin; 2) the pathogenic mechanisms of these drugs may converge on the early induction of tubulin modifications. We are currently examining the effects of these drugs on microtubule dynamics, stability and tubulin modifications using cultured adult DRG neurons, a cellular model that offers the advantage to be easily manipulated and genetically modified. Further in vitro and in vivo studies are warranted to compare levels, DRG subtype specificity, intracellular localization of tubulin post-translational modifications and microtubule integrity among acute and chronic drug treatments, and to investigate the means by which acute accumulation of modified tubulin may contribute to neuropathy through its effects on microtubule integrity and axonal viability.

Once completed, these studies will lay the foundations to further analyze the pathogenic role of tubulin post-translational modifications and changes in microtubule behavior in the onset of neurodegenerative disease.