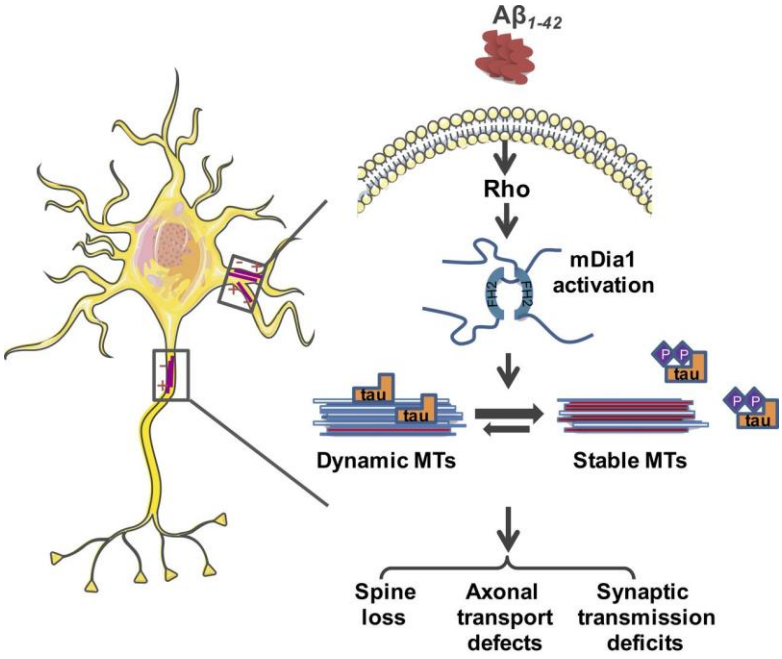
Francesca Bartolini, PhD
December 6th, 2017



Title

"Pathogenic role for Microtubule Regulating Pathways in Neurodegeneration and Chemotherapy Induced Peripheral Neuropathy (CIPN)"

Abstract

Emerging studies from several groups have indicated that dynamic microtubules, typically deprived of tubulin post-translational modifications (PTMs) associated with microtubule longevity, play key roles in neuronal function. In addition, synaptic biphasic fluctuations of microtubule instability/stability and tubulin PTMs have recently been associated with memory formation and are disrupted in aging, indicating a primary role for the regulation of microtubule dynamics and tubulin PTMs in the maintenance of synaptic plasticity. In support of this model, we recently found that stabilization of dynamic microtubules and induction of tubulin PTMs by the formin mDia1 contribute to oligomeric Aβ1-42 synaptotoxicity, and inhibition of microtubule dynamics alone is sufficient to promote tau hyperphosphorylation and tau-dependent synaptotoxicity (Qu et al., J Cell Biol, 2017). To test whether these changes occur at synapses and are directly responsible for synapse loss, we have further developed microscopy assays that measure microtubule invasions into dendritic spines and microtubule contacts with single presynaptic boutons of hippocampal and cortical neurons in culture. We are currently using these assays to investigate the temporal and spatial nature of these changes in the intact synapse upon modulation of synaptic activity and before and after treatment with oligomeric Aβ1-42. These exciting findings are in line with a parallel study in collaboration with Dr. Guido Cavaletti in which we are testing whether undesired fluctuations in microtubule stability/dynamics and tubulin PTMs are primary to axonal neurodegeneration induced by chemotherapeutic agents in sensory neurons using in vitro and in vivo models of disease. Altogether, our ongoing studies introduce a novel activity for formins in Aβ1-42 neurotoxicity through stabilization of dynamic microtubules in neurons, and demonstrate an unforeseen role for dynamic changes in microtubule behavior in regulating tau metabolism, axonal integrity and synaptic function.