How the Internal Wiring (Microtubule Cytoskeleton) Is Generated in Neurons

Eric Hwang

Institute of Molecular Medicine and Bioengineering, College of Biological Science and Technology, National Yang Ming Chiao Tung University

Microtubules (MTs) are the most abundant cytoskeleton in neurons, and control multiple facets of their development. While the function of neuronal MTs have been extensively studied, how and where these cytoskeletal filaments are generated inside the neuron remains largely unknown. Text books typically describe that MTs are originated from a membrane-less organelle called the centrosome. While the centrosome is indeed the MT-organizing center (MTOC) in mitotic cells, it loses its MT generating activity once the cell exits mitosis. Recent evidences indicate that neuronal MTs are produced from non-centrosomal sites, but the identity and composition of this non-centrosomal MTOC (ncMTOC) remain elusive. Here we provide evidence showing that a spindle assembly factor called TPX2 is an important component of the ncMTOC. In addition, we demonstrate that a small GTPase Ran is a key regulator of TPX2 and non-centrosomal MTs (ncMTs) in neurons. Ran switches between the active GTP-bound form (RanGTP) and the inactive GDP-bound form (RanGDP), and is primarily responsible for transporting cargoes into and out of the nucleus. Using an optogenetic tool that enables light-induced local production of RanGTP, we demonstrate that the active RanGTP promotes the formation of ncMTs in neurons. Finally, we discovered that the actin cytoskeleton actively targets RanGTP to the terminal of neuronal processes. This allows RanGTP to be enriched at axon and dendrite tips, and promotes the formation of ncMTs from these locations.