ABSTRACT: Microtubules (MTs) are dynamic cytoskeletal polymers. Misregulation of MT dynamics leads to catastrophic events in the cell including genomic instability and cell death. XMAP215 family members are potent microtubule (MT) polymerases, with mutants displaying reduced MT growth rates and aberrant spindle morphologies. XMAP215 proteins contain arrayed TOG domains that bind tubulin. Whether these TOG domains are functionally equivalent and how they collectively operate to drive polymerization remains unknown. Here, I present crystal structures of TOG4 from Drosophila MspS and human ch-TOG. These TOG4 structures architecturally depart from the structures of TOG domains 1 and 2, revealing a conserved domain bend that predicts a novel engagement with α-tubulin. In vitro assays show differential tubulin-binding affinities across the TOG array, as well as differential effects on MT polymerization. I used Drosophila S2 cells depleted of endogenous MspS to assess the importance of individual TOG domains. While a TOG1-4 array largely rescues MT polymerization rates, mutating tubulin-binding determinants in any single TOG domain dramatically reduces rescue activity. My work highlights the structurally diverse, yet positionally conserved TOG array that drives MT polymerization.

“The XMAP215 Family Drives Microtubule Polymerization Using a Structurally Diverse TOG Array”

March 27, 2014
12:00 p.m.
G100 Bondurant

Seminar is based upon doctoral dissertation of Jaime Campbell under the direction of Dr. Kevin Slep.