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Tubulin structural interactions with small molecule microtubule-stabilizing agents

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Tubulin, a 50 kDa protein, associates into α, β-heterodimers which polymerize into the microtubule, a major cytoskeletal component of all eukaryote cells. Microtubules consist of 13 protofilaments with α, β-dimers stacked head-to-tail. Numerous molecules, both endogenous and exogenous, bind to tubulin and affect its ability to polymerize and depolymerize. Insights into the structure of tubulin and the binding sites of different ligands were first obtained from electron crystallography of Zn- and paclitaxel-stabilized, antiparallel sheets. Paclitaxel is the first known microtubule-stabilizing agent. More recent studies have used a T2R complex consisting of a stathmin-like domain bound to two heterodimers linked in a head-to-tail fashion. Stathmin, by inducing a curved dimer structure, prevents its assembly into polymers. This T2R complex, often in combination with the enzyme tubulin tyrosine ligase has allowed detailed structural mapping by X- ray crystallography to less than 2.3 Å resolution. There are two known microtubule-destabilizing sites on β-tubulin, the colchicine site and the vinca alkaloid site, and two stabilizing sites, the taxoid site and the laulimalide/peloruside site. Recent X-ray crystallography analysis has confirmed the location of the stabilizing sites and shown that ligands that bind the two different sites can bind simultaneously. Adding both types of ligands together can lead to synergistic effects on the dynamicity of the microtubules, both in solution and inside cells; however, the mechanisms of stabilization and synergy between ligands are not fully understood. In collaboration with Eva Nogales at Berkeley, high resolution cryo-EM studies are currently underway on the structural association between peloruside and tubulin.

Biography

John H Miller has completed his PhD in Biological Sciences in 1971 from Stanford University, carried out his Post-doctoral research in Molecular Biology and Physiology at the University of California, San Diego and then accepted a Lectureship at Victoria University of Wellington in 1977. He was promoted to full Professor in 2008. He teaches courses in mammalian physiology, cell biology and development. His research interests are in the mode of action of novel natural products and their development as anticancer agents. He has published more than 113 papers in peer-reviewed journals and has written 4 book chapters.

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