Microtubule dynamic instability and its regulation: a Cryo-EM perspective

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Cell division is a complex, highly regulated process in which the microtubule (MT) cytoskeleton plays a central role, serving as energy source for dramatic chromosomal movements and acting as a scaffold that facilitates molecular encounters at the right time and place. Essential for MT function is dynamic instability, a property that can be both regulated and utilized for cellular work. The MT is built by the self-assembly of αβ-tubulin dimers and MT dynamics are due to the coupling of the assembly process to GTP hydrolysis in β-tubulin. Anticancer drugs like taxol stop cell division by interfering with MT dynamics, while many MT cellular partners modulate or utilize dynamic instability to carry out specific functions. We are using cryo-EM to visualize MTs and their ligands critical to the processes of chromosome segregation and cell division. By characterizing in atomic detail the conformational changes in MTs that accompany GTP hydrolysis, we have shed unique light into the structural basis of MT dynamic instability. We have also visualized the binding site and effect of anticancer drugs on MTs. We are now using the pipeline that we have optimized over the last three years to obtain high resolution structures of MTs bound to microtubule associated proteins (MAPs) in order to define the binding site of different MAPs, their effect of MT structure, and, if not yet known, the structure of the MAP itself in its functionally relevant state, on the MT. Among our targets is the MT nucleator/stabilizer TPX2.

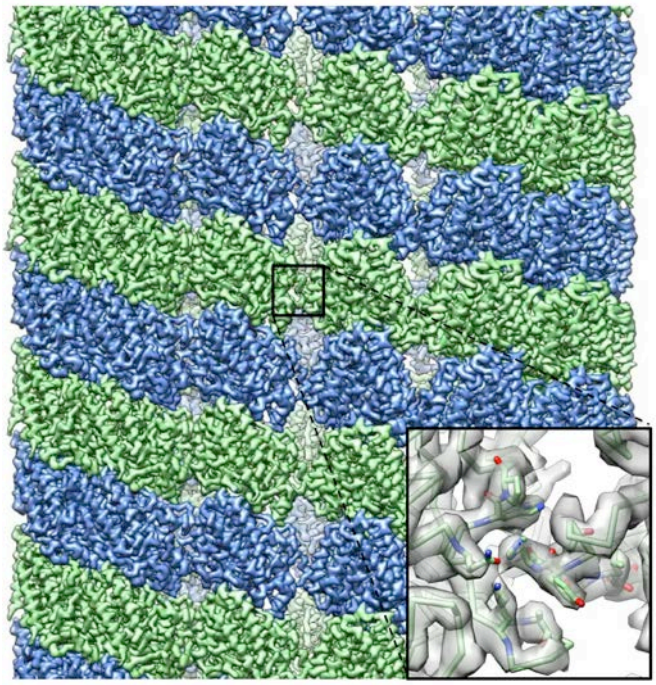

Figure 1: Cryo-EM structure of the microtubule (alpha tubulin green, beta-tubulin blue, and details of the lateral contacts between alpha subunits