ALTERATION OF MICROTUBULE MECHANICS BY TAXOL: INSIGHTS FROM MULTISCALE ANALYSIS OF TUBULIN DYNAMICS

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Introduction

The study of microtubule (MT) mechanics and the pathways involved in the transfer of vibrations between tubulins is crucial to understand how MTs are stabilized within the cell. Indeed, the hierarchical organization of MTs is the basis of their stability, mechanics, and function. Modulation of MTs mechanics can alter cell equilibrium and be exploited in therapeutic approaches in cancer [1]: the MT stabilizer Taxol is a clear example. Therefore, this work aims at shedding light on the effect of atomic structure on MT mechanics, and how changes in tubulin induced by Taxol relate to MT properties, through a computational approach connecting different scales, from atom positions to macroscopic observables.

Methods

We employed a multiscale approach to investigate the mechanics of MTs by integrating all-atom molecular dynamics (MD) simulations and Protein Structure Networks (PSN) with Normal Mode Analysis (NMA) on Elastic Network Models (ENM). All-atom structures of the dimers, in absence (MT^{Apo}) and presence (MT^{Tax}) of Taxol, were optimized in systems representative of the MT wall in a total of 600ns of MD simulations. In PSN, tubulins were modeled as a graph where amino acids are nodes connected based on their interaction strength. This approach allowed us to obtain information about the propagation of vibrations within the MT, i.e. about mechanical communication between tubulins [2]. 300nm-long MTs were built by fitting tubulin rings onto an Electron Microscopy Density (EMD) map and replicating them axially (8.15 and 8.18 nm step for MT^{Apo} and MT^{Tax}) [3,4] (Fig 1A). In ENM, residues are beads connected with springs if closer than 1.2 nm; we obtained MT vibrational frequencies and mechanical properties from NMA of ENM, assuming it as a hollow cylinder of homogeneous isotropic material [5].

Results

The analysis at the molecular level revealed remarkable differences induced by Taxol. In MT^{Apo}, β-tubulins mediate the mechanical communication between protofilaments (PFs) (Fig 1B), while the transfer of vibrations is driven mainly by α-tubulin in MT^{Tax} (Fig 1C). These results are interesting since Taxol interacts with residues in β-tubulin M-loop involved in MT^{Apo} communication path. Moreover, Taxol induces loss of structure of the β-tubulin M-loop, known to mediate the interaction between adjacent PFs. At a higher scale, the persistence length (Lp), bending (Eb), shear (G), and Young's (E) moduli of MT^{Apo} and MT^{Tax} have been computed from NMA vibrational frequencies of 3 MTs, built from MD-derived tubulins. Results highlight that MT^{Tax} has increased mechanical properties (Fig 1D), in particular the shear modulus, reflecting the atomistic result that Taxol alters the inter-PFs interaction.

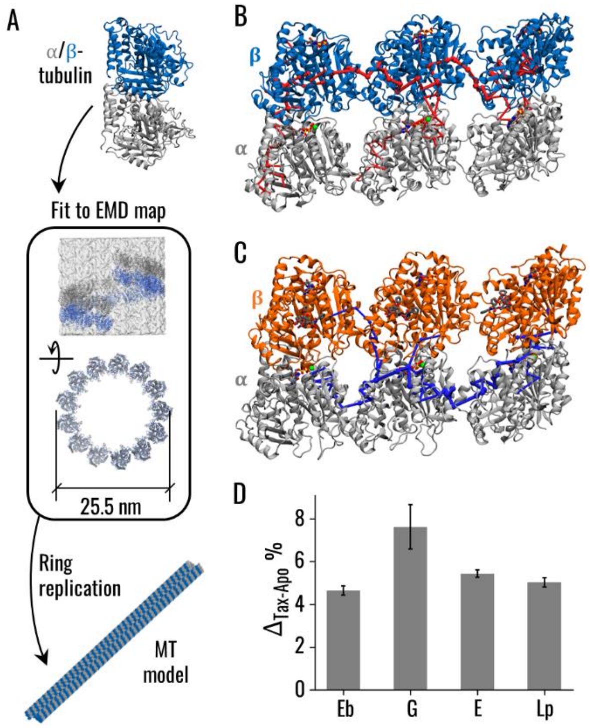

Figure 1: (A) Production of MT models from α/β-tubulins. (B, C) Pathway of communication between PFs in MT^{Apo} (B) and MT^{Tax} (C). (D) Difference in mechanical properties driven by Taxol (3 replicas).

Discussion

Our approach relates microscopic changes induced by Taxol and resulting changes in mechanics with MT stabilization. Taxol interaction with M-loop alters it structure and interferes with inter-PFs communication. This reverberates at a higher scale increasing MT mechanical properties, in particular the resistance to shear forces. Therefore, Taxol can stabilize 300nm-long MTs by strengthening inter-PFs interaction. It will be interesting to analyze the length dependance of this mechanism, providing insights for the design of drugs for cancer treatment and bioinspired nanomaterials.

References

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