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Title	In Vitro Study of Microtubule Deformation by External Stimuli and its Effect on the Interaction between Microtubule and Microtubule-Associated Motor Proteins [an abstract of dissertation and a summary of dissertation review]
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学 位 論 文 内 容 の 要 旨

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学 位 論 文 題 名

In Vitro Study of Microtubule Deformation by External Stimuli and its Effect on the Interaction between Microtubule and Microtubule-Associated Motor Proteins

(外部刺激による微小管の変形とその変形が微小管関連タンパク質との相互作用に及ぼす効果に関する研究)

Many of the biological processes in living organisms such as, embryogenesis, development and tissue homeostasis etc. are dependent on the mechanical stimuli. The cytoskeleton responds to the stimuli by changing cell shape. As the major component of cytoskeleton, microtubules, participate in cellular processes including cell shape regulation, cell division, intracellular transportation, etc. in which their structural integrity plays an important role. Moreover, microtubules help transmitting mechanical stress to activate cytoplasmic proteins and thereby rapid signal transduction occurs. However, the mechanism of mechanotransduction by the microtubules is still not clear. A probable pathway may involve the interaction between microtubules and its associated motor proteins. Moreover, any evidence showing how the mechanical stress applied on microtubules may modulate their biochemical functions has not yet been addressed.

In chapter 1, the purpose of this dissertation and background of this study is described.

In chapter 2, the response of the microtubules to the external compressive stress is addressed. Microtubules undergo buckling with increasing compressive strain which resembles an indispensable cellular event. The effect of the buckling

deformation of the microtubules on their biophysical roles was validated by monitoring the dynein-driven Quantum dot transportation along the buckled microtubules. The dynein-based transportation was accelerated by the buckling of the microtubules. An anomalous drop in the velocity of the transportation observed at a characteristic range of compressive strain indicated a clear distinction between the microtubule deformation

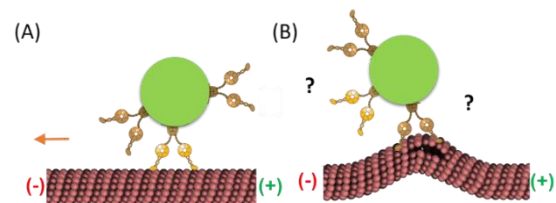


Fig. 1. The dynein driven transportation alters according to mode of the microtubule deformation.

mode at low and high compressive strains. This finding clearly reflects that the microtubules may serve as mechanotransducer. This work would benefit the current understanding of mechano-functional properties of cytoskeletal soft materials and their involvement in mechano-regulation of cellular activities.

In chapter 3, direct observation of the single kinesin transportation along the straight and the microtubule by high-speed atomic force microscopy (HS-AFM) is described. The motility of the kinesins shows dependence on the curvature of the track and enhanced binding affinities to the deformed microtubules. The alteration in microtubule-motor interaction by bending may provide understanding of how microtubules serve as mechanotransducers in cell.

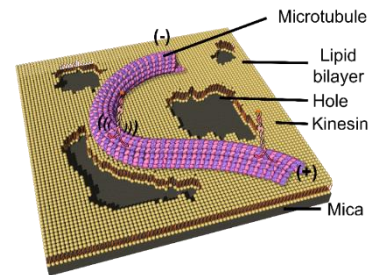


Fig. 2. The kinesins have higher affinity to bent microtubules.

In chapter 4, I focused on cevipabulin, a less explored microtubule-stabilizing agent. This synthetic microtubule stabilizing agent, strategically important in the treatment of neurodegenerative diseases, was found to affect the microtubules in ways similar to and different from paclitaxel, the most common antimetabolic drug. I found that, cevipabulin softens the microtubules and increases their gliding velocity on kinesin coated substrate. Therefore, this study shows the possibility that cevipabulin molecules with simpler molecular structure may be more advantageous in tuning the mechanical properties of the microtubules for applications in physiological purposes as well as in nanotechnology.

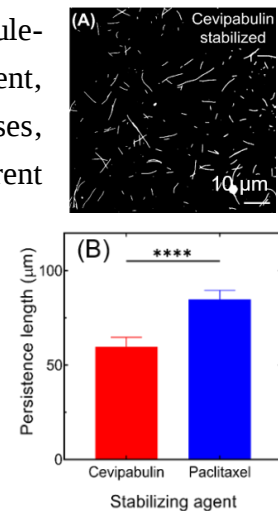


Fig. 3. Cevipabulin stabilized microtubules (A) are softer (B).

This dissertation describes how the modifications of microtubule either by mechanical stimuli or by introduction of the stabilizing agent may alter the properties of the microtubules. The compressive stress induced deformation of microtubules and modulated their interaction with dyneins as observed from the altered dynamics of dynein-driven transportation along microtubules. HS-AFM study revealed that the bent microtubules even without causing any lattice defects on the structure alter the kinesin transportation dynamics. This study is important particularly for the neurons where mechanical stress induced modulation of intracellular transportation is involved. Therefore, this study presents knowledge for developing rational design principle for nature-inspired mechanoresponsive material.