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学 位 論 文 要 約

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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. The neurodegenerative diseases caused by damaged or dead neurons are reported to arise mainly due to two reasons- i) stress-induced damage and ii) impeded cargo transportation in neurons. The stress-induced deformation of microtubule and its effect on their functionality is poorly understood. Therefore, any evidence showing how the mechanical stress applied on microtubules may modulate their biochemical functions establishes itself as an attractive issue.

In chapter 1, the purpose of this dissertation and the 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. 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 mode at low and

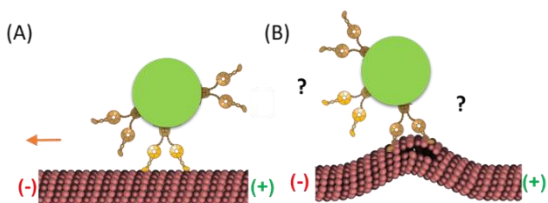


Fig. 1. The dynein driven transportation alters according to mode of the microtubule deformation.

high compressive strains. 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, high-resolution observation of the single kinesin transportation along the straight and the bent microtubule obtained by high-speed atomic force microscopy (HS-AFM) is presented. The kinesin molecules were observed to follow single microtubule protofilament. The motility of the kinesins showed dependence on the curvature of the track and enhanced binding affinities to the deformed microtubules.

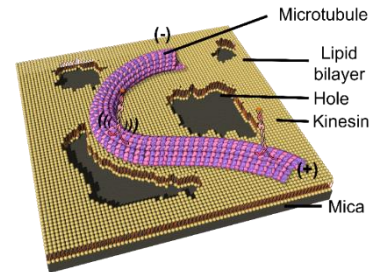


Fig. 2. The kinesin velocity along bent microtubule decreased with increasing curvature.

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.

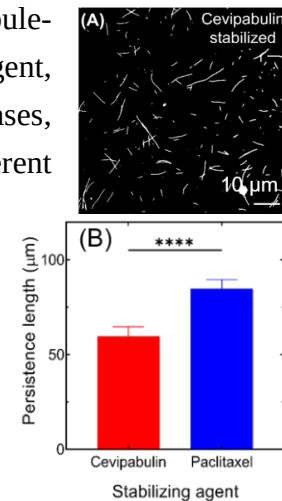


Fig. 3. Cevipabulin stabilized microtubules (A) are more flexible (B).

This dissertation describes how the modifications of microtubule either by mechanical stimuli or the 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.