reversing this detrimental effect to maintain healthy transport in cells remain unknown. Here we report the unambiguous up-regulation of multiple-kinesin travel distance along tau-decorated microtubules, via decreased single-kinesin velocity. Intriguingly, the presence of tau on microtubules also modestly reduced velocity in multiple-kinesin transport. Our stochastic simulations indicate that the tau-mediated reduction in single-kinesin travel is sufficient to recover the observed reduction in multiple-kinesin velocity. Taken together, our observations uncover a previously unexplored role of tau for inhibiting multiple-kinesin velocity via reducing single-kinesin travel distance, and suggest that single-kinesin velocity is a promising experimental handle for reversing the effect of tau on multiple-kinesin travel distance.

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The Effects of EB1 on Microtubule Mechanics and Kinesin Translocation Depend on GTP Analog and the Presence of Taxol

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Using the slowly hydrolyzable GTP analog GMPCPP and the nonhydrolyzable GTPγS, we polymerize microtubules that recapitulate the end binding behavior of EB1 along their entire length, and investigate the impact of EB1 binding on microtubule mechanics. Through equilibrium binding measurements, we find EB1 has a stronger affinity to microtubules polymerized with GTPγS than to those polymerized with GMPCPP, and that in the case of GMPCPP-microtubules the binding affinity can be modestly increased by copolymerization with taxol. Using a spectral analysis method to determine filament stiffness from the ensemble of shapes adopted by freely diffusing, fluorescently-labeled microtubules, we find that stiffness is also sensitive to polymerization conditions, and that the magnitude of the EB1-induced change in microtubule stiffness is not proportional to EB1-microtubule binding affinity. Although EB1 has a strong stiffening effect on GMPCPP-microtubules, this effect is abolished when the filaments are doubly stabilized by both GMPCPP and taxol. By observing quantum dot labeled kinesins walking on GMPCPP and GTPγS microtubules we again find that the presence of taxol is an important factor. For GMPCPP-microtubules adding 100 nM of EB1 significantly reduces kinesin speed (by ~30%) compared to the no EB1 condition, but when microtubules stabilized by both taxol and GMPCPP are used, the speed reduction is nearly abolished (~5%). Direct observation of EB1 diffusion along the microtubule lattice also shows taxol-dependent differences in EB1 mobility and may explain this effect on kinesin translocation speeds. Taken together, our data suggest a new possible mechanism for the regulation of microtubule function by EB1 in which plus end microtubule mechanics are directly modulated through structural changes of the microtubule lattice. Our results also raise important questions about the effects of taxol on microtubule-MAP interactions.

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Dynamic Force Adaptation of Lipid Droplets in Sub-Cellular Transport

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Most organelle movements in cells is due to enzymatic activity of a combination of kinesin variants and dynein molecular motors along the microtubules. In essentially all studies to date, it has been implicitly assumed that vesicular transport is unbiased throughout the cell. That is, while there can be global signaling events that change overall motion, molecular motors on ***individual*** cargos are not shown to respond to local changes in opposition to motion. The accepted models in the field predict that the groups of molecular motors function in a stochastic way. Here, we discover that this is not the case. Remarkably, our data shows that in cells, sub-cellular cargos (such as lipid droplets) can 'sense' when they are stuck, and respond by dynamically increasing efficacy of force production. This is quite surprising, and was entirely unexpected.

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Photoregulation of Molecular Motors using Photochromic Nucleotide Analogue

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Photochromic molecules can be interconverted between two quite different states with different spectroscopic properties using two different wavelength lights. Therefore, the photochromic molecules have received much attention because of their potential application to optical switches, bio-nanodevices, and molecular machines. Azobenzene is a typical photochromic molecule that undergoes rapid and reversible isomerization between the cis and trans-isomer in response to ultraviolet (UV) and visible (VIS) light irradiation, respectively. Previously, we have succeeded to control microtubule dependent ATPase activity of kinesin in which functional region was modified with azobenzene derivative photo-reversibly. Moreover, we synthesized photochromic ATP analogue PABITP composed of azobenzene to regulate ATP driven motor proteins. PABITP induced microtubule gliding for kinesin and the gliding velocity altered correlating to cis-trans photo-isomerization of azobenzene moiety. For myosin, although PABITP was hydrolyzed as a substrate for ATPase and induced conformational change of myosin motor domain, PABITP did not drive actin gliding. In this study, we designed and synthesized a novel photochromic nucleotide analogue composed of photochromic fulgimide moiety in order to regulate ATP driven molecular motors, myosin and kinesin photo-reversibly. The photochromic ATP analogue, Fulgimide-Tri-Phosphate (FITP) exhibited ring-opening and ring-closing photo-isomerization upon UV and VIS light irradiations. FITP worked as a substrate of skeletal muscle myosin and induced dissociation of acto-myosin in a different manner upon UV and VIS light irradiations. We also examined the interaction of FITP with kinesin and its effect for the polymerization of tubulin to microtubules.

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Mechanics of Kinesin-Crosslinked Microtubule Networks

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We have recently shown that the mechanical properties of chemically crosslinked microtubule networks depend sensitively on the single-molecule properties of the crosslinking molecules they contain. In particular, for networks that are rigidly crosslinked by biotin-streptavidin, a small number of crosslinkers bear stress, and their force-induced detachment from the microtubule determines the time-dependent network rearrangements. Interestingly, the network retains its elastic modulus even under conditions of significant plastic flow, suggesting that crosslinker breakage is balanced by the formation of new bonds. This leads to a remarkable resilience under repeated loading, as long as a sufficient number of the original crosslinkers are preserved per loading cycle. In this current work, we have expanded our study to include compliant crosslinkers, formed by multimeric complexes of kinesin-1. A variety of biophysical approaches are used, including electron and optical microscopy to measure network architecture under different crosslinking conditions, and magnetic tweezer-based microrheology to determine the creep response of the networks under controlled loading. We find that protein compliance and filament bundling enables load splitting among adjacent crosslinkers, thereby enhancing material strength and diminishing the importance of single crosslinker unbinding in determining the mesoscopic rheology. Our results are important to understanding how network architecture and crosslinker properties influence network mechanics, and are particularly important to understanding the role of kinesin proteins in forming stress-transmitting microtubule structures, such as the mitotic spindle.

Cell Mechanics and Motility II

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Constitutive Activation of Myosin-Dependent Contractility Sensitizes Glioma Tumor-Initiating Cells to Mechanical Inputs and Reduces Tissue Invasion

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Glioblastoma (GBM) tumors are thought to arise from a subpopulation of brain tumor-initiating cells (BTICs), which mediate therapeutic resistance and seed new tumors. Virtually nothing is known about the role of extracellular matrix (ECM) mechanical inputs in controlling BTIC invasion and tumorigenesis, despite the recognized importance of these signals in tissue dysplasia and cell motility. Here we show that human BTICs can evade the inhibition of spreading, migration, and proliferation normally imposed by compliant ECMs. Remarkably, activation of myosin II-dependent contractility restores this inhibition, strongly restricts BTIC ECM invasion