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region reduced upon widening. Unexpectedly, the reduction was also observed at one side and widened it perpendicularly to the pole-to-pole axis. We found study, we quantitatively measured the mechanical stiffness, the microtubule dynamics of this cytoskeletal architecture and provide insight into how structural and functional stability is maintained in the face of different forces, such as mechanical forces that act in diverse orientations and over a wide-range of timescales. Currently, we cannot explain how this micron-sized, dynamic cytoskeletal structure generates and responds to forces while maintaining overall stability, as we have a poor understanding of its micromechanical properties. Here we combine the use of force-calibrated needles, high-resolution microscopy, and biochemical perturbations to analyze the vertebrate metaphase spindle’s timescale- and orientation-dependent viscoelastic properties. We find that the metaphase spindle is mechanically anisotropic, and deforms either elastically or, especially under large force, plastically, depending on the timescale of applied force. We also find that spindle viscosity depends on the dynamics of microtubule crosslinking and the density of the filament. Spindle elasticity can be linked to the rigidity of kinetochore and non-kinetochore microtubules, which have different polymerization dynamics and stability, and also to spindle pole organization by kinesin-5 and dynein. These data suggest a quantitative model for the micromechanics of this cytoskeletal architecture and provide insight into how structural and functional stability is maintained in the face of different forces, such as those that control spindle size and position, and can result from deformations associated with chromosome movement.

A Single-Molecule Study to Resolve How Kinases Prevent Chromosomal Mis-Segregation

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Mitosis is an exquisitely choreographed process that relies on specialized interactions between kinetochores on chromosomes and the microtubules of the mitotic spindle. The process is orchestrated by an error-correction system that, remarkably, detects improperly aligned chromosomes by sensing a lack of tension in their kinetochore-microtubule attachments. This surveillance system ensures that each daughter cell receives exactly one copy of each chromosome; failure leads to cancer and birth defects. Two surveillance system components, the Mps1 and Ipl1 protein kinases, are of particular interest because indirect evidence suggests that they are responsible for core system functions. Direct tests of their functions have been lacking because the tension that they are thought to sense cannot be accurately measured or controlled in a cell. Very recently, our group completed the first-ever study of kinetochore-microtubule attachments reconstituted in vitro, positioning me to study the tension-sensing surveillance system in ways never before possible. I will apply precise forces to kinetochore-microtubule attachments using an optical trap, and I will make genetic changes to the kinetochores at sites where the kinases are thought to act. With these powerful single-molecule techniques, I will uncover how Mps1 and Ipl1 (1) modify kinetochores to destabilize their microtubule attachments, and (2) operate on unattached, improperly attached, and properly attached kinetochore to promote the formation of proper attachments. Ultimately, my work will guide efforts currently underway to develop new chemotherapy drugs that target the kinetochores to promote the formation of proper attachments. Ultimately, my work will guide efforts currently underway to develop new chemotherapy drugs that target the kinetochores to promote the formation of proper attachments.