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SPOTLIGHT

When push comes to shove: How chromosomes absorb spindle forces without losing grip

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Chromosomes withstand substantial forces from spindle microtubules prior to their segregation in mitosis. Using super resolution live imaging, Tran, Dumont, and colleagues (https://doi.org/10.1083/jcb.202512154) find that stiff linkages between chromosomes and microtubules coupled with pliable underlying centromeres enables force absorption while maintaining a robust grip on microtubules.

There are few more awe-inspiring moments in a cell's life than the moment it segregates its duplicated chromosomes and divides in two. This process of mitosis has captivated scientists for close to 150 years (1). Watching the chromosome dance in real time has enabled detailed dissection of the mechanisms that govern it. We now know the dance is orchestrated by dynamic spindle microtubules that can push and pull the chromosomes by virtue of a robust connection to a specialized chromosomal region known as the centromere. The connection is provided by a large protein complex, the kinetochore, named in the 1930s for its perceived role in giving chromosomes movement (2). In mammalian cells, each kinetochore is a lawn of dozens of identical multiprotein complexes (a kinetochore "unit" or "linkage") that span the centromere to the microtubule. The main business of kinetochores is to grab microtubules and hold on for dear life until segregation is completed, a big challenge. Each kinetochore of a human cell connects with up to 20 microtubules, and the pushing and pulling forces microtubules impose on kinetochores and underlying chromatin are substantial enough to disrupt the interaction of one biochemical kinetochore unit with a microtubule (3, 4). To understand how cells achieve error-free chromosome segregation, it is therefore of great interest to understand how chromosomes deal with such forces while maintaining a tight grip.

In this issue, Tran, Dumont and colleagues used live super-resolution imaging and micromanipulation to illuminate this question (5). Using rat kangaroo cells for their readily distinguishable chromosomes, the authors imaged kinetochore morphology at super resolution in metaphase cells while they were being pushed and pulled, tracking both the outer kinetochore (close to the microtubule) and the inner kinetochore (close to the centromere). They found that the size of the kinetochore lawn in the direction of the force is 4–5 times bigger than the known length of the individual biochemical units (Fig. 1). The lawn, therefore, is not a rigid array of kinetochore units. The authors convincingly show that while the units themselves can stretch a bit under force, the deformation of the lawn is due to units moving relative to each other. The underlying centromeric chromatin on which the kinetochores are built must therefore be pliable. Indeed, the distance between kinetochores of the connected sister chromatids varied more than did the length of the kinetochores themselves. The centromere, in other words, absorbed most of the force imposed by microtubules.

Super-resolution live imaging also occasionally captured kinetochores deforming asymmetrically, with a comet-like tail toward the centromere. Using genetic and chemical methods to hyper-stabilize microtubules, the authors went on to show that these asymmetric deformations represent rare faulty attachment configurations known as merotely, in which a kinetochore interacts with microtubules from opposing directions (Fig. 1). This is an important observation: persistent merotelic kinetochore–microtubule interactions cause anaphase lagging chromosomes, the most commonly observed segregation error in human cancer cells (6). The ability to visualize merotely before it manifests as a lagging chromosome, as recently also achieved by super-resolution imaging of kinetochores in fixed metaphase cells (7), will allow investigations of their origins and correction mechanisms.

To better understand how kinetochore morphology responds to force, the authors then turned to the physics concept of materials properties, the measurable traits of a substance as it reacts to external forces. Using micromanipulation, they applied acute force to a kinetochore by pulling the connected microtubule bundle sideways with a needle, causing very substantial kinetochore deformations. When they subsequently stopped pulling, the kinetochore returned to its pre-pull shape within 30 s, indicative of an elastic property of the system. Intriguingly, the sister kinetochore, which is not directly pulled on but indirectly connected to the affected kinetochore through sister–sister cohesion, showed no response whatsoever. All applied force was thus fully absorbed by the "front" centromere. Given their earlier findings, the elastic

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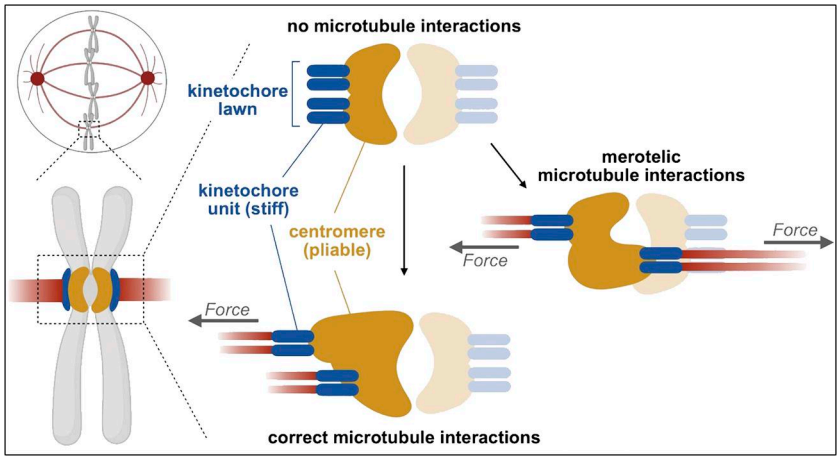

Figure 1. **To ensure correct segregation, chromosomes connect with dynamic microtubules via their kinetochore, which consists of a lawn of identical biochemical units assembled onto centromeric chromatin.** The study found that force applied by microtubules deforms kinetochores as a result of later sliding of stiff kinetochore units relative to each other, combined with pliable underlying centromeres. The stiff kinetochore units, meanwhile, maintain a robust grip on the pulling microtubules. The pliable centromere also underlies the kinetochore deformations in faulty attachment states known as merotely. The elastic nature of the system as reported in this study may enable return to the normal state when such errors are corrected.

response must come from the pliable centromeric chromatin at the base of the kinetochore lawn. This conflicts with prior studies concluding the kinetochore/centromere is plastic or viscoelastic (8, 9), possibly reflecting different experimental setups (e.g., forcing faulty attachments and then removing microtubules acutely) or cell division stages (metaphase vs anaphase). Resolving it may require controlled in vitro experiments with isolated chromosomes, which will be relevant for understanding how cells harness intrinsic properties of centromeres to establish bioriented attachments and error correction.

An obvious candidate for installing elasticity and shape in the kinetochore is the protein complex that gives mitotic chromosomes their condensed shape. These "condensins" are molecular motors that package chromosomes by organizing chromatin into complex loops and are known to also package centromeres and prevent their hyperstretching when microtubules pull on them (7, 10, 11). In agreement with this, condensin depletion caused more extensive kinetochore deformations and more faulty attachment configurations. Surprisingly, however, the elastic properties of kinetochores were not dependent on condensin activity. The molecular mechanisms that provide kinetochores with structural integrity and elastic properties are therefore not identical and can be uncoupled.

The findings by Tran, Dumont and colleagues explain how chromosomes can accommodate interactions with multiple microtubules, each with its own dynamics and end position, without losing grip. They open several interesting avenues for further exploration. What mechanism imparts material properties onto the centromere, and how does that impact microtubule capture, attachment maintenance, and error correction? And what underlies the deformation of the kinetochore under force when the individual biochemical units are stiff? One option is that kinetochore units in the lawn have flexible connections to each other. Known mechanisms of kinetochore unit clustering, however, seem inadequate to explain the large deformations observed (12). A glance at kinetochore morphology under force at high resolution offers a clue. The large kinetochore deformations resulting from the needle micromanipulations frequently reveal a splitting of the kinetochore into two or more subdomains. This is consistent with centromeres in mitosis having a bipartite organization, with the subdomains independently binding microtubule fibers and possibly harboring further substructure of their own (7). If the centromere subdomains are internally coherent structures but free to slide relative to one another, this would explain the observed deformation of the lawn under force. Live imaging kinetochore–microtubule interactions at increasing spatial and temporal resolution under various conditions, as inspired by the present study, will go a long way to solving the remaining mysteries of this vital process.

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