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Cell division: The science friction of chromosome attachment

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During mitosis, chromosomes must bind spindle microtubules via kinetochores in a stable yet dynamic manner to ensure rapid frictionless movements. A recent study identifies the first complex that specifically reduces friction in the kinetochore–microtubule interface to ensure efficient chromosome segregation.

Successful cell division relies on the equal distribution of genetic material into two daughter cells during mitosis. This is achieved by bipolarly attaching chromosomes to the microtubules of the mitotic spindle, and aligning them in the middle of the spindle on the metaphase plate, before pulling the sister chromatids apart in anaphase[1]. Microtubules are dynamic polymers that stochastically switch at their ends from growth (polymerization) to shrinkage (depolymerization), in a process termed dynamic instability[1]. Microtubules attach to chromosomes via mega-molecular protein complexes called kinetochores, which assemble onto the centromeric chromatin of each sister chromatid[2]. In mammalian cells, kinetochores bind 15–20 microtubules that form a bundle of microtubules termed 'kinetochore-fiber' (k-fiber)[3,4]. Kinetochores are elaborate protein machines that fulfill three key biomechanical functions: they tightly bind to the plus-end of spindle microtubules; they translate microtubule growth and shrinkage into a motor-independent force that drives the movement of end-on attached chromosomes; and they correct erroneous kinetochore–microtubule attachments, which often arise during the initial phases of bipolar spindle assembly[5,6]. Any disturbance of the kinetochore–microtubule interface can cause chromosome segregation defects that are associated with human pathologies such as cancer in adults or primary microcephaly during embryonic development[7,8].

During mitosis, kinetochore–microtubule attachments must be strong to tightly bind and rapidly track depolymerizing k-fibers over long time periods (e.g., during anaphase), yet at the same time be sufficiently dynamic to destabilize erroneous kinetochore–microtubule attachments or to adapt to polymerizing microtubule ends[5,6]. These requirements are particularly prominent during metaphase, as bipolarly attached chromosomes oscillate along the spindle axis to remain in the center of the cell[9]. These oscillations reflect the dynamic instability of k-fibers, forcing each sister-kinetochore to switch from a shrinking k-fiber to a growing k-fiber every 30–50 seconds (Figure 1)[9]. While past research has mostly focused on kinetochore proteins required for tight processive attachment to shrinking k-fibers, much less is known about potential actors that allow the kinetochore–microtubule interface to adapt to growing k-fibers. In a paper published recently in *Current Biology*, Rosas-Salvans and colleagues[10] demonstrate for the first time that the Astrin–SKAP (small kinetochore-associated protein) complex dampers the affinity by which kinetochores bind to kinetochore microtubules, highlighting how a 'lubricating' activity at the kinetochore–microtubule interface promotes effective chromosome segregation.

What was known so far about the kinetochore–microtubule interface? From a simplified structural point of view, kinetochores bind to microtubule ends through an elongated heterotetrametric complex named NDC80, located in the outer region of the kinetochore[11]. The NDC80 complex binds laterally to the microtubule lattice via two calponin-homology domains, and a positively charged unstructured tail domain that interacts with the negatively charged microtubule surface[11]. While a single purified NDC80 complex cannot track depolymerizing microtubules, multiple NDC80 complexes immobilized on glass beads can generate load-bearing attachments to depolymerizing microtubules[12]. Therefore, it is thought that numerous NDC80 complexes at kinetochores form sleeves or a lawn that generate a multitude of low-affinity contacts with microtubule lattices[11,13]. Once the NDC80 complex is bound to microtubules, it recruits the heterotrimeric SKA (spindle and kinetochore-associated) microtubule-binding complex, which stabilizes kinetochore–microtubule attachments and allows processive force-bearing connections to depolymerizing microtubules over long time periods[2]. The kinetochore–microtubule interface is also tightly regulated by post-translational modifications. Phosphorylation of the unstructured NDC80 tail by the mitotic Aurora kinases allows detachment of erroneous kinetochore–microtubule attachments[11]. Conversely, dephosphorylation of the same tail by the protein phosphatases PP1 and PP2A stabilizes correct kinetochore–microtubule attachments as chromosomes align on the metaphase plate[11]. Ground-breaking experiments with non-phosphorylatable NDC80 tail mutants indicate, however, that an excessive affinity of kinetochores for microtubules is detrimental[14] — cells were unable to correct erroneous kinetochore–microtubule attachments and displayed overstretched centromeres and a higher rate of chromosome segregation errors. This indicated that kinetochores must possess mechanisms to keep their interaction with microtubules dynamic and flexible.

In their study, Rosas-Salvans and colleagues[10] used live-cell imaging and laser micro-ablation to demonstrate that the Astrin–SKAP complex plays exactly this role: preventing an excessive affinity of kinetochores for microtubules. This complex had been first identified as a microtubule-binding kinetochore component that specifically accumulates on bioriented chromosomes[15,16]. Initial functional characterization suggested that Astrin–SKAP stabilizes kinetochore–microtubule interactions, promoting chromosome alignment[17]. Here, Rosas-Salvans and colleagues[10] investigated in detail how depletion of SKAP in human epithelial cells affected chromosome oscillations and interkinetochore distances. While the first read-out reflects plus-end dynamics at the microtubule–kinetochore interface, inter-kinetochore distances reflect the sum of the forces exerted on sister kinetochores[9,18]. The authors found that after SKAP depletion, chromosomes oscillated in a less coordinated manner, their inter-kinetochore distance was increased, and the order by which kinetochores switched direction was perturbed[10]. Instead of initiating directional switches from the front sister kinetochore that is bound to shrinking k-fibers as in control cells, in SKAP-depleted cells directional switches were mostly induced from the back kinetochore, as if a stronger force was holding it back[10]. This phenotype was reminiscent of the phenotype seen in cells expressing a non-phosphorylatable NDC80 tail mutant, suggesting that SKAP is required to dampen the affinity by which kinetochores bind to microtubules.

To validate this hypothesis, the authors next performed a series of very elegant laser ablation experiments, which allowed them to selectively target the front or back kinetochore, as well as the k-fibers attached to the front or back kinetochore. By measuring the velocity of single kinetochores or the deformation of the targeted kinetochore pair after the ablation, the authors could read out the forces and the dynamicity of the microtubules acting on each kinetochore. This revealed that kinetochores in SKAP-depleted cells experience indeed a higher friction and a reduced force responsiveness at both kinetochores, resulting in lower velocities when force is applied. The authors therefore conclude that the Astrin–SKAP complex reduces the grip to microtubules at both the polymerizing and depolymerizing kinetochore–microtubule interfaces[10]. Importantly, SKAP depletion changed neither the abundance nor the phosphorylation status of the NDC80 complex, implying that the Astrin–SKAP complex regulates the kinetochore–microtubule interface on its own[10].

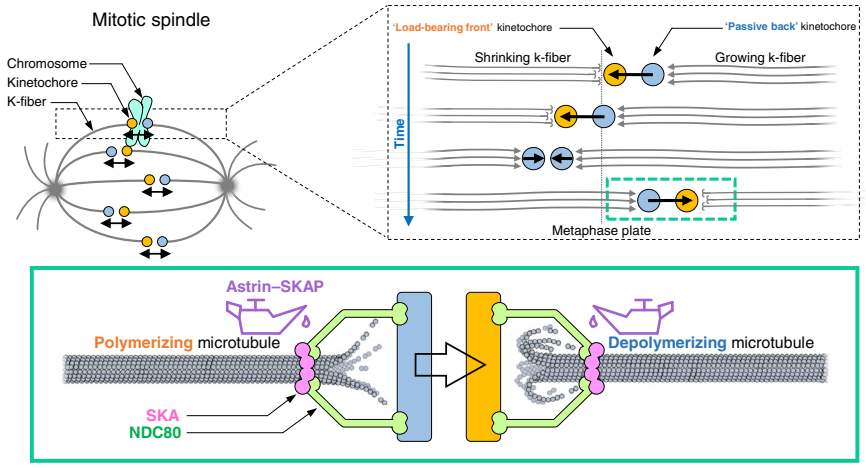

Figure 1. Model of sister kinetochore oscillations in metaphase and the function of Astrin–SKAP complex at the kinetochore–microtubule interface.
In orange are the 'load-bearing back' kinetochores bound to shrinking k-fibers with depolymerizing microtubules. In blue, the 'passive back' kinetochores bound to growing k-fibers with polymerizing microtubules. The green rectangle displays a magnification of the kinetochore–microtubule interface. For simplification, only one microtubule and NDC80–SKA complex are represented. The study of Rosas-Salvans and colleagues[10] shows how the Astrin–SKAP complex decreases friction at the kinetochore–microtubule interface, acting as a lubricant.

This study improves our biomechanical understanding of the kinetochore–microtubule interface, giving us crucial insights into how kinetochores can maintain sufficient grip to microtubules while remaining sufficiently dynamic and force-responsive. We now know that, independently of the NDC80 complex phosphorylation status, the Astrin–SKAP complex decreases friction at the kinetochore–microtubule interface to ensure a proper chromosome alignment on the metaphase plate and faithful segregation in anaphase.

Why would cells need such a lubricator protein if the kinetochore–microtubule affinity can already be controlled via phosphorylation of the NDC80 complex? The authors suggest that the presence of a dedicated lubricator complex might allow cells to maintain accurate control of the dynamic kinetochore–microtubule while avoiding losing kinetochore–microtubule attachments due to excessive NDC80 phosphorylation[10].

Precise control of the affinity/friction at the kinetochore–microtubule interface of bioriented chromosomes via a dedicated molecular lubricant is therefore a novel important concept in the field.

Looking forward, this study raises many exciting questions. At the cellular level knowing that cells have a dedicated 'lubricator' complex begs the question whether this function could be mis-regulated in pathological conditions. Indeed, SKAP is often mutated in human cancers[19,20]. Would an 'over-lubrication' due to an overexpression of the Astrin–SKAP complex affect chromosome segregation? At the mechanistic/molecular level, it will be essential to decipher how the Astrin–SKAP complex modulates the affinity/friction at the kinetochore–microtubule interface to ensure a dynamic yet stable attachment. This will most likely require in vitro reconstitution experiments, combining both the NDC80–SKA complex and purified Astrin–SKAP complexes.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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Insect navigation: Bumblebees walk the walk

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A new study shows that bumblebees can display path integration while walking in a small laboratory arena. This opens a new avenue for studying how insects' brains can encode direction and distance.

In *The Descent of Man*[1] Darwin wrote that "…*the brain of an ant is one of the most marvellous atoms of matter in the world, perhaps more so than the brain of a man*…". Nineteenth century naturalists were well aware of the remarkable cognitive capabilities of insects, and marvelled at how such intelligence could arise from matter smaller than a couscous grain. Studying something so tiny and complex was barely imaginable at the time, but we have travelled a long way since. Each step has required ever more imaginative methods, and a study reported by Patel *et al.*[2] in this issue of *Current Biology* now adds a promising new one to the list.

A great window through which to probe the insect brain is to study their navigational skills. Chase a fly off and it will come round to land exactly at the same spot. Displace a wasp by hundreds of meters and it will have no problem in returning to its nest. Follow an ant through a dense rain forest and *you* may get lost, but the ant will not. Something is clear: insects are very good at dealing with space. Navigation involves perception, memory, decision making, and motor control, which can be readily measured by displacements across space. These behaviours are thus perfect for pondering how insect brains work — at least in theory. In practice, however, movement is a terrible problem because looking closely at something so tiny usually requires the animal to keep perfectly steady.

Starting from scratch, early neuroanatomists had no choice but to observe the brain of dead insects. The development of microscopes in the nineteenth century enabled them to distinguish various regions within insects' brain, and make some inference about their function by comparing the regions' volume across species. For instance, the brain area now called the mushroom body was assumed to be the seat of insect intelligence because it was more developed in supposedly smart insects such as hymenopterans (wasps, ants,