Mitosis requires the precision of a dance number in a Hollywood musical. When sister chromatids part during anaphase, they glide in unison to opposite ends of the cell. Matos et al. reveal that microtubules’ continual movement toward the spindle poles helps produce this synchronous progress (1). The study suggests that sliding microtubules frequently loosen their grip on the chromosomes, and these slips even out the pulling force on spindle fibers to ensure that chromatids are parcelled out equitably between daughter cells.

“There’s a clear benefit for having synchronous chromosomes during mitosis,” says senior author Helder Maiato. If the movements don’t coincide, daughter cells can end up with too many or too few chromosomes, an imbalance often seen in cancer (2). By holding up anaphase until microtubules are attached to kinetochores on the waist of each chromosome, the spindle assembly checkpoint (SAC) makes sure that all of a cell’s chromosomes start to separate at about the same time (3). But some sister chromatids can lag or rush if the spindle doesn’t tug on all of them with the same force. The mechanism for keeping these forces uniform is a mystery. During metaphase, a spindle fiber is in flux, treadmilling toward the spindle pole without growing longer (4). As a result, cells continually feed in new microtubule segments at the kinetochore and remove segments at the spindle pole, replacing the entire microtubule before anaphase. Matos et al. suspected that this constant rebuilding might allow cells to balance out the tension on chromosomes.

The researchers created a mathematical model of the mitotic spindle that suggested flux was essential for equalizing force across microtubules. Stable microtubules, the model showed, couldn’t resolve divergent forces acting on chromosomes. Restoring microtubule flux allowed tension to equilibrate during the typical duration of metaphase. The team also tested the notion experimentally in cultured Drosophila cells by slashing levels of two proteins that regulate spindle length in response to the microtubule sliding forces that drive flux. CLASP adds microtubule subunits to kinetochore ends of the fibers. KLP10A, by contrast, removes subunits at the spindle pole. Knocking down both proteins with RNAi slowed the rate of microtubule flux by more than 80% and increased the degree of asynchrony during anaphase, the researchers found.

The most striking demonstration of flux’s importance came when the team made kymographs that track the position of each kinetochore throughout anaphase. In control cells, the paths of all the kinetochores produced a tight “Y” shape, signifying two groups of sister chromatids moving to opposite poles of the cell. However, when the team cut CLASP and KLP10A levels, the “Y” blurred, indicating that the separating chromatids are not traveling at the same pace.

A cell might need some time to balance the forces on its chromosomes, the team reasoned, and asynchrony might occur if mitosis was shortened. So the researchers hastened chromosome separation by knocking down Mad2, the part of the SAC that gives the “go” signal for anaphase. The cells exited metaphase early, and their chromosome movements went out of sync.

For the flux-based mechanism to work, reduced microtubule sliding should translate into unequal forces on chromosomes. To determine whether it does, the team measured the distance between sister kinetochores on either side of unseparated chromosomes. The distance—an indicator of tension on the centromere—was more variable in cells with reduced amounts of CLASP and KLP10A than in normal cells.

“Allowing the spindle to flux is a way to equalize the forces on different chromosomes,” says Maiato. Microtubules don’t detach from the kinetochores during the process, but the connection slips a bit, Maiato notes. As one chromosome’s attachment relaxes, cross-linking proteins that interconnect microtubules tighten up the fibers linked to other chromosomes. As metaphase proceeds, these adjustments even out the tension on all the chromosomes attached to the spindle, the researchers suspect. Once the cell enters anaphase, the sister chromatids are then poised to make their move in concert.

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