KIF4 helps mitotic chromosomes get in shape

A kinesin motor protein works with condensin and topoisomerase IIα to organize mitotic chromatin.

though chromosomes spend most of their time occupying amorphous territories in interphase nuclei, we typically picture them as the compact X-shaped structures that form during mitosis. Chromosomes adopt this conformation to avoid becoming entangled as they segregate into daughter cells, but how mitotic chromatin condenses into the correct shape is unclear. Samejima et al. identify an important role for the kinesin motor KIF4 in this process (1).

Condensin complexes and the DNA-remodeling enzyme topoisomerase IIα (topo IIα) help organize mitotic chromatin, but cells lacking these proteins still form recognizable mitotic chromosomes (2, 3). This suggests that an additional factor—what Bill Earnshaw from the University of Edinburgh calls a regulator of chromosome architecture (RCA)—is critical for chromosome condensation (4). A candidate for the RCA role is the DNA-binding kinesin motor KIF4, which interacts with condensin and localizes to the arms of mitotic chromosomes. Earnshaw and colleagues, led by postdoc Kumiko Samejima, therefore decided to investigate KIF4’s function in chromatin organization (1).

Samejima et al. found that KIF4 and the core condensin subunit SMC2 rely on each other for their localization on chromosome arms. At first glance, mitotic chromosomes appeared normal in KIF4-deficient cells, but treatment with a mildly hypotonic solution to resolve individual chromosomes revealed that they were fatter and shorter, and sister kinetochores were spaced farther apart than normal. Furthermore, when mitotic chromosomes were repeatedly unraveled and refolded, wild-type chromosomes “remembered” their shape and re-condensed efficiently, but chromosomes lacking KIF4 became disorganized, indicating that they had lost their structural integrity.

The mitotic chromosomes of condensin-deficient cells are also short and fat, and their structural integrity is even more compromised. “So KIF4 and condensin somehow influence how things are connected inside mitotic chromosomes,” explains Earnshaw. “If you don’t have these proteins, the chromosomes look almost normal, but things aren’t hooked up properly inside.”

Whereas KIF4 and condensin both compact mitotic chromosomes laterally, topo IIα controls an opposing pathway that shortens chromosome arms. “If you don’t have condensin or KIF4, the chromosomes are fatter and shorter,” says Samejima. “But, if you deplete topo IIα, the chromosomes become thinner and longer.”

To investigate the relationship between all three proteins, Samejima et al. depleted them in different combinations. “If you deplete KIF4 and condensin, the phenotype becomes much worse,” Samejima explains. Though recognizable mitotic chromosomes still form, hypotonic treatment causes them to become “a total mess.”

Remarkably, the structure of chromosomes lacking KIF4 and condensin was partly rescued if topo IIα was also depleted, supporting the idea that this enzyme acts in an opposing pathway. Samejima et al. think that condensin compacts chromosomes laterally by forming supercoiled loops of chromatin. KIF4 may gather these loops together or, in combination with other proteins, form supercoiled loops of its own to compact chromosomes further. Topo IIα could untangle these loops in order to keep chromosome arms from becoming too long as they compact laterally.

KIF4 requires its motor domain to organize mitotic chromosomes, because mutants lacking this domain localized to chromatin but failed to rescue the shape and integrity of chromosomes from KIF4-null cells. “We think that the motor domain interacts with other components,” Earnshaw says. “It’s probably not acting as a motor; in metazoans, microtubules aren’t inside the nucleus at this stage of chromosome condensation.”

As well as investigating how KIF4 organizes chromatin, Samejima et al. know that, because recognizable mitotic chromosomes still form in the absence of both condensin and KIF4, they have still not determined the identity of RCA. “KIF4 is part of the story, but it’s not the magic ingredient that turns a nucleus into chromosomes,” Earnshaw says. “So what is the RCA? We’re trying to find this mysterious missing factor.”

1. Samejima, K., et al. 2012. J. Cell Biol. http://dx.doi.org/10.1083/jcb.201202155.
2. Steffensen, S., et al. 2001. Curr. Biol. 11:295–307.
3. Chung, C.J., et al. 2003. J. Cell Sci. 116:4715–4726.
4. Vagnarelli, P., et al. 2006. Nat. Cell Biol. 8:1133–1142.