Kip3-ing kinetochores clustered

Comment on: Wargacki M, et al. Cell Cycle 2010; 9:2581-8.

Ryoma Ohi; Vanderbilt University Medical School; Nashville, TN, USA; Email: ryoma.ohi@vanderbilt.edu

Metaphase is the brief and highly conspicuous period during cell division where chromosomes become positioned at the spindle equator through the process of "congression". It is generally believed that congression promotes accurate chromosome segregation during anaphase, and this logic has driven research over several decades to identify the underlying mechanisms. Recent studies have demonstrated that Kinesin-8 microtubule motors are important for congression in organisms ranging from fission yeast to humans,[1-3] and that they probably act by modulating the dynamics of kinetochore-microtubule plus ends where they concentrate.[2,4-6] It has been unclear, however, if this role is conserved in the budding yeast Saccharomyces cerevisiae. Previous work by Tytell and Sorger showed that kinetochores lag during mitosis in yeast cells lacking the Kinesin-8 Kip3, and they proposed that Kip3 synchronizes poleward kinetochore movements during anaphase.[7] Gardner et al. have suggested that Kip3 is not involved in kinetochore positioning during pre-anaphase mitosis, and that the primary function of Kip3 is to govern spindle length by regulating the dynamics of interpolar microtubules.[8]

In *Cell Cycle*, Wargacki and colleagues demonstrate that Kip3 is required for chromosome congression like other Kinesin-8 motors.9 In budding yeast, metaphase sister kinetochores appear bi-lobed, forming clusters on either side of the spindle equator. Using quantitative fluorescence microscopy and live cell imaging, the authors find that kinetochores attach spindle microtubules normally in kip3Δ cells but are declustered (Fig. 1), indicating that kinetochores are scattered along the spindle axis in the mutant. This notion is confirmed through an analysis of single centromere (CEN3) positioning. Wargacki et al. show that KIP3 deletion causes CEN3 mis-positioning and, consistent with previous work,[7] that centromeric chromatin between sister kinetochores is hyperstretched, an effect probably caused by abnormally high microtubule-induced pulling forces on kinetochores. A final important observation in the Wargacki et al. study is that spindle length is normal in kip3Δ cells, suggesting that Kip3-dependent effects on kinetochore positioning are not indirect consequences of interpolar microtubule length regulation by the motor. Discrepancies between previous reports[8,10] are probably due to technical differences in how spindle lengths were measured; Wargacki et al. used spindle pole body markers instead of fluorescent tubulin to identify spindle poles.

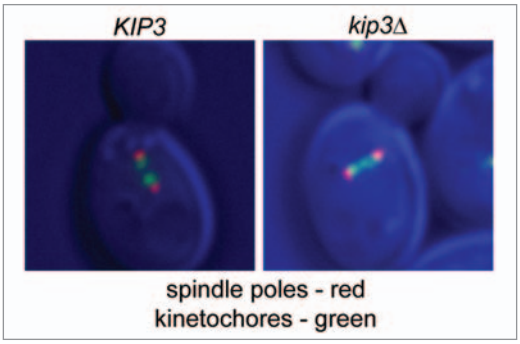

Figure 1. Kinetochores fail to congress in kip3Δ cells.

The work by Wargacki et al. is important because it establishes that Kip3, like the other Kinesin-8 motors analyzed to-date, performs a critical function during chromosome congression. It also supports the idea that proper kinetochore positioning during metaphase contributes to the accuracy of sister chromatid segregation during anaphase. As Wargacki et al. point out, sister chromatids will be scattered along the anaphase spindle if they initiate poleward movements from heterogeneous positions, reasoning which might account for the lagging chromosomes previously observed by Tytell and Sorger.[7] The next challenge is to define how Kip3 influences kinetochore positioning, and how this activity is integrated with other major chromosome positioning factors such as Kip1 and Cin8.[7,8] In vitro, Kip3 is a plus end-directed microtubule depolymerase that is capable of destabilizing filaments assembled from the GTP-mimic GMPCPP.[5,6] It is unclear, however, how loss of Kip3 would lead to increased pulling forces on kinetochores, a phenotype that suggests that Kip3 antagonizes microtubule shortening. At kinetochore-microtubule plus ends, Kip3 might act via other mechanisms to control kinetochore movements, as recently suggested for its human orthologue Kif18A.4 Future work is needed to reveal the precise mechanism(s) by which Kinesin-8 proteins govern kinetochore movements and their overall positioning during mitosis.

References

1. Savoian MS, et al. J Cell Sci 2004; 117: 3669-77.
2. Stumpff J, et al. Dev Cell 2008;14: 252-62.
3. West RR, et al. J Cell Sci 2002; 115: 931-40.
4. Du Y, et al. Curr Biol 2010; 20: 374-80.
5. Gupta ML, et al. Nat Cell Biol 2006; 8: 913-23.
6. Varga V, et al. Nat Cell Biol 2006; 8: 957-62.
7. Tytell JD, et al. J Cell Biol 2006; 172: 861-74.
8. Gardner MK, et al. Cell 2008; 135: 894-906.
9. Wargacki MM, et al. Cell Cycle 2010; 9;2581-8.
10. Straight AF, et al. J Cell Biol 1998; 143: 687-94.