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CELL CYCLE

Cyclin A corrections

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During metaphase, chromosomes align and form bi-oriented attachments to spindle microtubules, leading to faithful chromosome segregation. Errors in kinetochore–microtubule attachment occur during early mitosis (prometaphase), and failure to correct these errors, which depends on microtubule detachment from kinetochores, results in chromosome missegregation and chromosomal instability. Kabeche and Compton now show that cyclin A has a role in destabilizing kinetochore–microtubule attachments during prometaphase to allow error correction.

The authors used fluorescence dissipation after photoactivation in three cell lines to measure kinetochore–microtubule attachment stability. They found that it was low in prometaphase and sharply increased between prometaphase and metaphase, indicating a coordinated switch in attachment stability during the prometaphase–metaphase transition. Furthermore, this was proteasome-dependent, suggesting that the degradation of proteins is required for this switch.

As cyclin A is degraded in prometaphase, the authors reasoned it might be involved in the control of kinetochore–microtubule attachment stability. Indeed, expression of a degradation-resistant cyclin A mutant prevented the switch to stable attachments in metaphase but had no effect on prometaphase. Conversely, RNAi-mediated depletion of cyclin A resulted in the stabilization of kinetochore–microtubule attachments in prometaphase to a similar degree to that observed in metaphase, whereas the stability in metaphase was unchanged. Furthermore, cyclin A deficiency led to an increase in lagging chromosomes, caused by persistent merotelic kinetochore attachments (whereby a single kinetochore is attached to microtubules emanating from both spindle poles).

These results indicate that initial kinetochore–microtubule attachments in prometaphase are sufficiently robust to promote chromosome alignment, but sufficiently unstable to allow error correction, and that the switch to more stable attachments depends on the levels of cyclin A being reduced to a certain threshold. Indeed, endogenous cyclin A levels in metaphase drop to almost two-thirds of that seen in prometaphase. This study also defines prometaphase and metaphase as biochemically distinct cellular environments, the transition from one to the other being as important for cell cycle progression as other cell cycle phase transitions.

Kim Baumann

> “This study also defines prometaphase and metaphase as biochemically distinct cellular environments”

ORIGINAL RESEARCH PAPER Kabeche, L. & Compton, D. A. Cyclin A regulates kinetochore microtubules to promote faithful chromosome segregation. *Nature* http://dx.doi.org/10.1038/nature12507 (2013)

FURTHER READING Foley, E. A. & Kapoor, T. M. Microtubule attachment and spindle assembly checkpoint signalling at the kinetochore. *Nature Rev. Mol. Cell Biol.* **14**, 25–37 (2013)