CellPress

# Selfish centromeres, selfless heterochromatin

Elvira Nikalayevich[1,*] and Marie-Hélène Verlhac[1]
[1]Center for Interdisciplinary Research in Biology, Collège de France, UMR7241/U1050, PSL Research University, Paris 75005, France
*Correspondence: elvira.nikalayevich@college-de-france.fr
https://doi.org/10.1016/j.cell.2021.08.027

**Centromeres are specialized regions on chromosomes recruiting a set of proteins required for faithful chromosome segregation. Differences in centromere strength can potentially bias chromosome segregation toward one of the daughter cells during division. Kumon et al. propose a new model of evolutionary impact on the balance of centromere strength.**

Female meiosis is specialized to create a large oocyte containing much-needed materials to support embryonic development after fertilization. Meiotic divisions in oocytes are highly asymmetric, discarding the unneeded chromosome sets into small polar bodies slated for degradation. Only one set of chromosomes would remain and survive in a new organism. Such a selection process inevitably favors "survival of the fittest" chromosomes, which are more likely to persist in the genetic pool. But how can only some chromosomes influence their segregation, and how can the cell respond to restore the status quo? The work of Kumon et al. (2021) provides one answer to this fundamental question.

Each chromosome contains a specialized region called centromere, which consists of a stretch of satellite repeats packaged into the histone H3 variant CenpA-containing nucleosomes and serves as a base for kinetochore assembly. Kinetochore, a very complex multilayered protein structure, is responsible for chromosome attachment to the microtubule spindle and can tune this attachment and even break it off if it senses an error. "Selfish" centromeres capable of loading more CenpA and assembling a larger kinetochore have a higher chance of facing the "egg side" spindle pole and hence remaining in the oocyte (Iwata-Otsubo et al., 2017). It has been shown that selfish centromeres can use the kinetochores to purposely dissociate the attachment if they are facing the polar body side, sensing the proximity of the cortex. This gives the chromosome a chance to re-orient and re-attach until it faces the egg side (Figure 1A) (Akera et al., 2017; Akera et al., 2019).

The evolutionary pressure to create "bigger and badder" centromeres is known as centromere drive. This mechanism, while considered to promote speciation (Henikoff et al., 2001; Malik and Henikoff, 2001), can be harmful as constant detaching and re-attaching of kinetochores would keep the spindle assembly checkpoint (SAC) active and prolong the duration of division, increasing the possibility of chromosome mis-segregation. Selfish centromeres can delay anaphase I in oocytes, where the duration of meiotic divisions is already extremely long (Akera et al., 2017). Perhaps, evolution of selfish centromeres is one of the reasons for a "leaky" SAC in oocytes, that can tolerate a few erroneous attachments and still allow anaphase progression.

Despite the recent advances in sequencing the centromeric DNA and uncovering its variability and evolution, much less is known about how the centromere-interacting proteins evolve to respond to the centromere drive. Kumon et al. 2021 propose a parallel pathway model for centromere drive and suppression. In an impressive logical scheme, the authors predict that selfish centromeres recruitment of kinetochore proteins is suppressed by kinetochore proteins weakening their interaction with the centromeres and each other (kinetochore pathway). In addition to this, the pericentromeric heterochromatin is thought to equalize bigger and smaller centromeres, as it is able to independently recruit proteins required for segregation (heterochromatin pathway). The authors affected either the kinetochore pathway or both kinetochore and heterochromatin pathway and observed the behavior of selfish centromeres during the first meiotic division of the mouse oocyte.

In the kinetochore pathway, a divergent rat CenpC variant binds to mouse centromeres in the same quantity as mouse CenpC but is less able to recruit Sgo2, an effector protein that, among other functions, binds to mitotic centromere-associated kinesin (MCAK) (Tanno et al., 2010), which in turn promotes microtubule detachment. By contrast, African striped mouse CenpC binds to mouse centromeres better and recruits more Sgo2.

Larger centromeres, being attached to more microtubules, can be pulled more efficiently to a spindle pole (Akera et al., 2019). Overexpression of rat CenpC is able to reduce the asymmetric alignment of such bivalents, demonstrating its ability to counteract selfish centromeres.

The authors have also investigated the role of CenpB, which promotes CenpC recruitment to the centromere, but it also regulates heterochromatin formation. They found that even though CenpC levels were reduced equally on bigger and smaller centromeres (meaning that the kinetochore pathway was weakened, similar to rat CenpC overexpression), the asymmetry in their positioning was actually exacerbated, leading them to believe that another pathway requires CenpB to counteract selfish centromeres. Curiously, Y-chromosome centromeres, which are excluded from centromere drive, lack the ability to bind CenpB (Fachinetti et al., 2015).

As a parallel pathway model identifies several key components to counteract the quickly evolving selfish centromeres, it is reasonable to expect all of them to also have a higher evolution rate. In an impressive feat, Kumon et al. have

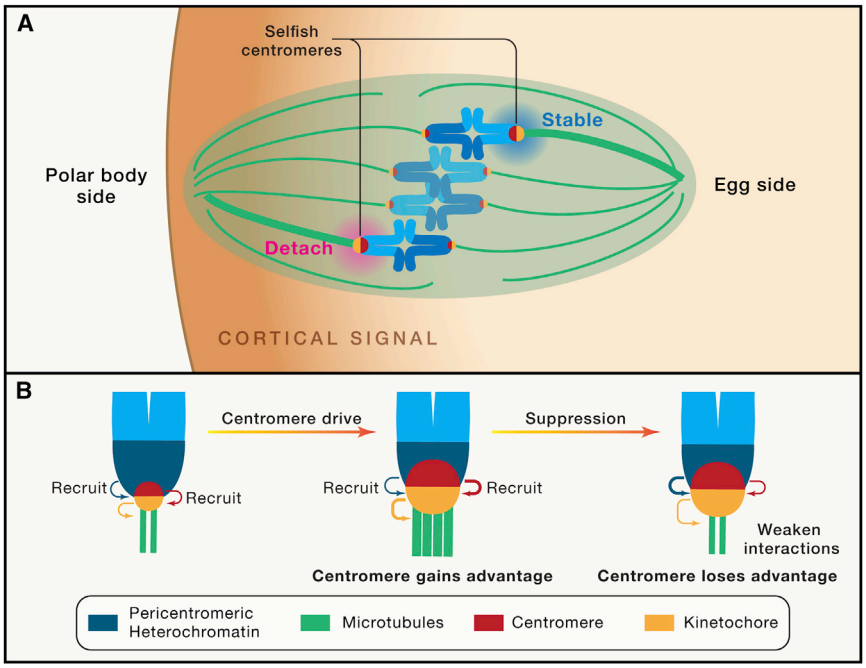


**Figure 1. Selfish centromere drive and suppression**

A. Selfish centromeres (red/yellow circles) prefer egg-side attachment to the metaphase I spindle (green). Chromosomes are in blue, oocyte cytoplasm is in brown, zone of cortical proximity in darker brown.

B. Selfish centromere drive and suppression. Centromere (red) and pericentromeric heterochromatin (dark blue) recruit kinetochore effectors (yellow) that influence microtubule (green) attachment. Centromeres evolve to increase in size and recruit more kinetochore proteins (centromere drive), whereas kinetochore proteins develop weaker interactions to suppress deleterious effects of bigger centromeres while heterochromatin acts independently of centromere size.

sequenced additional whole genomes of six Murinae species to strengthen their analysis. They discovered signs of positive selection to both kinetochore and heterochromatin pathway proteins, particularly in DNA- and protein-interacting domains.

According to the parallel pathway model proposed by Kumon et al., the centromeres evolve to attract more kinetochore proteins to attain a better ability to detach and reattach to microtubules and gain an advantage in their segregation fate. These selfish centromeres can be suppressed by two parallel pathways: either kinetochore proteins evolve to bind less well to the centromere DNA and to each other (also affecting smaller centromeres), or pericentromeric heterochromatin proteins change their binding and effector strength to act independently of centromere size, equalizing the chances of both bigger and smaller centromeres (Figure 1B).

This model provides a deeper insight into the mechanisms counteracting selfish centromeres compared to a previously suggested model of an "arms race", where only the DNA-binding domain of CenpA evolves to weaken the interaction with the centromere (Henikoff et al., 2001). Heterochromatin pathway may serve to stifle centromere expansion and to prevent kinetochores to constantly decrease efficiency. But are the two pathways truly parallel and independent? The effectors on the kinetochores and heterochromatin can influence each other, and it may prove difficult to disrupt the heterochromatin without affecting the kinetochore.

The problem of centromere drive and suppression is not dissimilar to a so-called "recombination hotpot paradox", where PRDM9 protein initiates recombination on its target sequences, resulting in their extinction and forcing PRDM9 to keep evolving to bind to new, also quickly evolving, sequences (Hochwagen and Marais, 2010).

The study by Kumon et al. is a very impressive and original work which addresses, using a combination of complementary and straightforward approaches, a major question of life sciences: how is faithful and unbiased chromosome segregation achieved while the key machinery evolves at an accelerated rate?

## REFERENCES

Akera, T., Chmátal, L., Trimm, E., Yang, K., Aonbangkhen, C., Chenoweth, D.M., Janke, C., Schultz, R.M., and Lampson, M.A. (2017). Spindle asymmetry drives non-Mendelian chromosome segregation. Science *358*, 668–672.

Akera, T., Trimm, E., and Lampson, M.A. (2019). Molecular Strategies of Meiotic Cheating by Selfish Centromeres. Cell *178*, 1132–1144.e10.

Fachinetti, D., Han, J.S., McMahon, M.A., Ly, P., Abdullah, A., Wong, A.J., and Cleveland, D.W. (2015). DNA Sequence-Specific Binding of CENP-B Enhances the Fidelity of Human Centromere Function. Dev. Cell *33*, 314–327.

Henikoff, S., Ahmad, K., and Malik, H.S. (2001). The centromere paradox: stable inheritance with rapidly evolving DNA. Science *293*, 1098–1102.

Hochwagen, A., and Marais, G.A.B. (2010). Meiosis: a PRDM9 guide to the hotspots of recombination. Curr. Biol. *20*, R271–R274.

Iwata-Otsubo, A., Dawicki-McKenna, J.M., Akera, T., Falk, S.J., Chmátal, L., Yang, K., Sullivan, B.A., Schultz, R.M., Lampson, M.A., and Black, B.E. (2017). Expanded satellite repeats amplify a discrete CENP-A nucleosome assembly site on chromosomes that drive in female meiosis. Curr. Biol. *27*, 2365–2373.e8.

Kumon, T., Ma, J., Akins, R.B., Stefanik, D., Nordgren, C.E., Kim, J., Levine, M.T., and Lampson, M.A. (2021). Parallel pathways for recruiting effector proteins determine centromere drive and suppression. Cell *184*. S0092-8674(21)00940-5. https://doi.org/10.1016/j.cell.2021.07.037.

Malik, H.S., and Henikoff, S. (2001). Adaptive evolution of Cid, a centromere-specific histone in Drosophila. Genetics *157*, 1293–1298.

Tanno, Y., Kitajima, T.S., Honda, T., Ando, Y., Ishiguro, K.-I., and Watanabe, Y. (2010). Phosphorylation of mammalian Sgo2 by Aurora B recruits PP2A and MCAK to centromeres. Genes Dev. *24*, 2169–2179.