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Meiosis: When centromeres choose compromise over conflict

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Centromeres are essential for accurate chromosome segregation, yet their DNA and proteins evolve rapidly. A new study reveals that mouse CENP-T evolved reduced centromere binding, not to counter selfish DNA, but to stabilize kinetochore dynamics and ensure successful oogenesis, reshaping ideas about centromere adaptation.

In the race to pass genetic material to the next generation, not all chromosomes play fair. During female meiosis, only one of four daughter cells becomes an egg, whereas the others become polar bodies that degenerate. This asymmetric division creates an opportunity for chromosomes to 'cheat' by preferentially segregating themselves into the future egg rather than the polar bodies — a phenomenon known as meiotic drive[1]. The centromere, a specialized chromosomal region that orchestrates chromosome segregation, is thought to be a key player in this evolutionary arms race. According to the "centromere drive" hypothesis, selfish DNA sequences can emerge at centromeres and bias their segregation into eggs by recruiting more centromeric proteins compared to their partners at homologous chromosomes[2] (Figure 1i). DNA-binding centromeric proteins are subsequently predicted to acquire changes that preferentially prevent or reduce binding to selfish DNA elements, restoring balance and suppressing centromere drive[2–4]. A new study by Dudka *et al.*[5] in this issue of *Current Biology* now challenges our understanding of how centromeric proteins can evolve to counter these selfish DNA elements.

Previous work suggests that adaptation in centromeric proteins ultimately reduces their binding specifically to selfish DNA sequences, thereby suppressing their transmission advantage (Figure 1ii), although evidence for this model is currently lacking[4,6–8]. To test this model, Dudka *et al.*[5] focused on centromere protein T (CENP-T), a kinetochore linker protein that binds directly to centromeric DNA via its histone-fold domain (HFD) and helps attach chromosomes to the cell's division machinery by recruiting the microtubule-binding outer kinetochore network[9–12]. Importantly, in rodent genomes, CENP-T HFD shows signs of rapid evolution at residues known to regulate its centromeric localization[5]. Using an elegant approach, the authors created 'evolutionary chimeras' by swapping the HFD domain of mouse (*Mus musculus*) CENP-T with orthologs from species either closely related to mouse (*Mus spretus* and *Mus caroli*) or more diverged (*Rhabdomys pumilio* and *Rattus norvegicus*). Surprisingly, they found that the mouse HFD domain showed reduced localization to all centromeres compared to HFD orthologs from other related species[5]. The rat HFD chimera (that is, the chimeric mouse CENP-T protein with rat HFD) exhibited the strongest centromere localization, and mutating four residues under positive selection in the CENP-T HFD was sufficient to reduce centromere localization[5]. These findings suggest that the positively selected residues in the mouse CENP-T HFD evolved to generally decrease CENP-T centromere binding activity.

The consequences of this evolutionary change became clear when the authors engineered mice to express a rat HFD-containing chimeric CENP-T that bound more strongly to centromeres. These mice produced fewer eggs, whereas their viability remained unaffected, thus revealing that reduced centromere binding by mouse CENP-T is important for proper female gamete formation[5]. Mechanistic insights into how reduced centromere binding by CENP-T affects female gamete formation are awaited. Further, the authors go on to show through structural predictions and cell biological experiments that mouse CENP-T achieved reduced centromere binding by evolving changes that affect its interaction with its binding partner CENP-W, rather than its direct DNA binding activity.

Does the evolution of CENP-T centromere binding activity avoid specific selfish DNA sequences as hypothesized? The authors evaluated this hypothesis using mouse CENP-T and its HFD chimeras by first measuring binding to divergent satellite centromeric DNA sequences in mouse and extended this analysis by measuring binding to more divergent centromeric satellite sequences of rat and humans[5]. Their results converged on the conclusion that the evolution of the mouse CENP-T HFD to reduce centromere binding is independent of the underlying centromeric DNA sequence. This discovery challenges the prevailing view that centromeric proteins evolve to suppress drive by specifically avoiding selfish sequences.

These findings led the authors to redefine the model for centromere drive (Figure 1iii,vi). When selfish sequences initially emerge at a single centromere, they can spread rapidly to all centromeres through mechanisms like recombination or transposition. This creates a new challenge: all centromeres now recruit too many centromeric proteins, potentially disrupting chromosome segregation[8,13]. Rather than evolving to suppress centromere drive — which is no longer possible once the selfish sequences are fixed — centromeric proteins adapt to restore proper segregation by generally reducing their binding to all

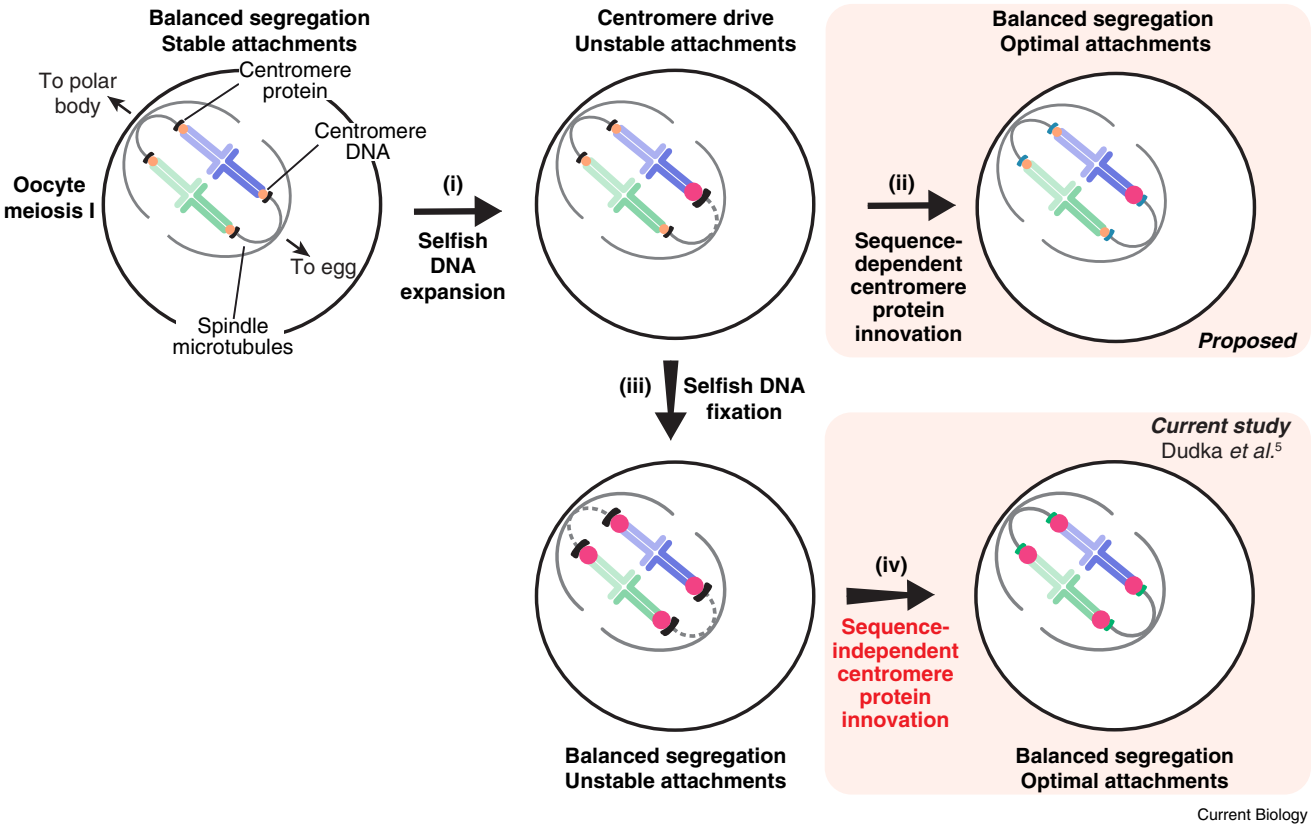

Figure 1. From conflict to adaptation at centromeres.
Chromosomes compete to be included into the future egg. (i) Expansion of selfish DNA at the centromere results in a stronger centromere with increased centromere protein binding, providing more microtubule attachment sites. Surprisingly, these stronger centromeres make less stable microtubule attachment allowing for detachment and reattachment to the winning egg side, at a cost to fitness. (ii) It was proposed that to counter the fitness cost, the evolution of centromere DNA-binding proteins would preferentially prevent binding to selfish DNA elements. (iii) Alternatively, biased segregation of selfish DNA could lead to fixation. (iv) To counter the fitness cost, the authors in the current study[5] show that centromere proteins can adapt in a DNA-sequence independent manner to reduce centromere binding and restoring parity.

centromeres. The discovery that mouse CENP-T evolved through changes in protein–protein interactions rather than DNA binding properties provides a compelling mechanism for this (centromeric DNA) sequence-independent adaptation.

This model helps resolve several paradoxes in centromere biology. It explains why centromeric DNA sequences are typically similar within species but different between species[14,15] — because selfish sequences quickly spread throughout a population before proteins can evolve to suppress them. It also accounts for why proteins that don't directly bind to DNA show signs of rapid evolution[16] — because the challenge becomes optimizing the overall protein recruitment at centromeres rather than preventing binding to specific sequences. Thus, these evolutionary innovations work to mitigate the deleterious consequences after drive rather than suppressing it.

The work raises intriguing questions about centromere evolution. How do different centromeric proteins coordinate their evolution to maintain proper chromosome segregation? Is general modulation of protein binding a common strategy in other species? And why are female gametes particularly sensitive to changes in centromere protein binding strength? The study also highlights broader principles about molecular arms races. Rather than engaging in an endless cycle of attack and defense, sometimes the most effective strategy may be to adapt to a new normal after the initial battle is lost. As we continue to uncover the intricate dynamics of cellular evolution, this work reminds us that the path of adaptation may not always be what we expect.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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