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Review

Evolution of eukaryotic centromeres by drive and suppression of selfish genetic elements

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ABSTRACT

Despite the universal requirement for faithful chromosome segregation, eukaryotic centromeres are rapidly evolving. It is hypothesized that rapid centromere evolution represents an evolutionary arms race between selfish genetic elements that drive, or propagate at the expense of organismal fitness, and mechanisms that suppress fitness costs. Selfish centromere DNA achieves preferential inheritance in female meiosis by recruiting more effector proteins that alter spindle microtubule interaction dynamics. Parallel pathways for effector recruitment are adaptively evolved to suppress functional differences between centromeres. Opportunities to drive are not limited to female meiosis, and selfish transposons, plasmids and B chromosomes also benefit by maximizing their inheritance. Rapid evolution of selfish genetic elements can diversify suppressor mechanisms in different species that may cause hybrid incompatibility.

1. Introduction

Repetitive DNA comprises the majority of eukaryotic genomes. For example, approximately half of the human genome is composed of transposons and centromeric satellites, whereas protein coding genes and gene regulatory sequences occupy less than 5% or 10% of the genome, respectively [32,56]. There is growing evidence that some repetitive DNA is selfish in that it drives, or increases the chance of inheritance at the expense of the host fitness [12,28,69]. Selfish genetic elements utilize various strategies to drive. For example, transposons drive by over-replication, and centromeric satellites drive by biased segregation in female meiosis in violation of Mendel's law of segregation (Fig. 1A). Evolutionary theory predicts that fitness costs imposed by selfish genetic elements are the evolutionary pressure that selects protein variants that suppress costs of drive. Continuous cycles of drive and suppression lead to rapid turnover of repetitive DNA and host suppressor proteins. Here, we focus on the evolutionary arms race at centromeres.

The genome of every eukaryotic cell is determined by chromosome segregation in the preceding cell division. Centromeres are the chromosomal regions that assemble kinetochores to attach to spindle microtubules for accurate segregation. Although this centromere function is required for all eukaryotes, forms of centromere DNA and proteins are diverse. Centromere DNA sequences, which are defined by the presence of functional kinetochores during cell division, are often repetitive and composed of satellites and transposons. Monomer sequences and abundance of centromeric satellites diverge between closely related species, and repeat abundance varies even within species [7,16,58,70,83]. Transposon enrichment at centromeres also varies between species [17,88,101]. However, the functional significance of centromere DNA is unclear because of the epigenetic determination of centromere identity (Fig. 1B). Most eukaryotic centromeres are defined by specialized nucleosomes containing the histone H3 variant CENP-A, with some exceptions in which centromeres are genetically defined by *cis* DNA elements as in budding yeast [11]. Indeed, the position of CENP-A chromatin assembly can change without changing the underlying DNA sequences [6,88]. Furthermore, the position and number of kinetochore assembly sites vary between species (Fig. 1C) [23,78].

In addition to centromere DNA, multiple centromere binding proteins are also rapidly evolving, including components of the constitutive centromere associated network (CCAN), the kinetochore, and the inner centromere. Centromeres are highly enriched for rapidly evolving proteins relative to other subcellular compartments in Murinae genomes [68], and signatures of adaptive evolution are detected in centromere proteins from multiple eukaryotic lineages [35,68,75,106].

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Kinetoplastids, a distant eukaryotic lineage that includes multiple animal parasites, even use a distinct set of kinetochore proteins that are not homologous to any identified in other eukaryotes [5]. In contrast to the relative simplicity of prokaryotic chromosome segregation machineries [8,9], eukaryotic centromeres are more complex (Fig. 1B) with multiple pathways to build a kinetochore, such as via CENP-ACHIKMLN, CENP-TWSX, and CENP-OPQUR [98,117,123]. In addition, centromeric CENP-A chromatin is typically flanked with pericentromeric heterochromatin [59].

The centromere drive hypothesis provides a model to explain the paradoxical rapid evolution of complex eukaryotic centromeres despite conserved function, based on the idea that centromere DNA acts as a selfish genetic element (Fig. 1A). In female meiosis, homologous chromosomes pair and segregate to the egg or the polar body. The polar body is degraded, so any selfish element that preferentially segregates into the egg will increase its chance of inheritance and its allele frequency in a population. Centromere DNA is a prime candidate to bias its segregation, as it is the chromosomal region that interacts with spindle

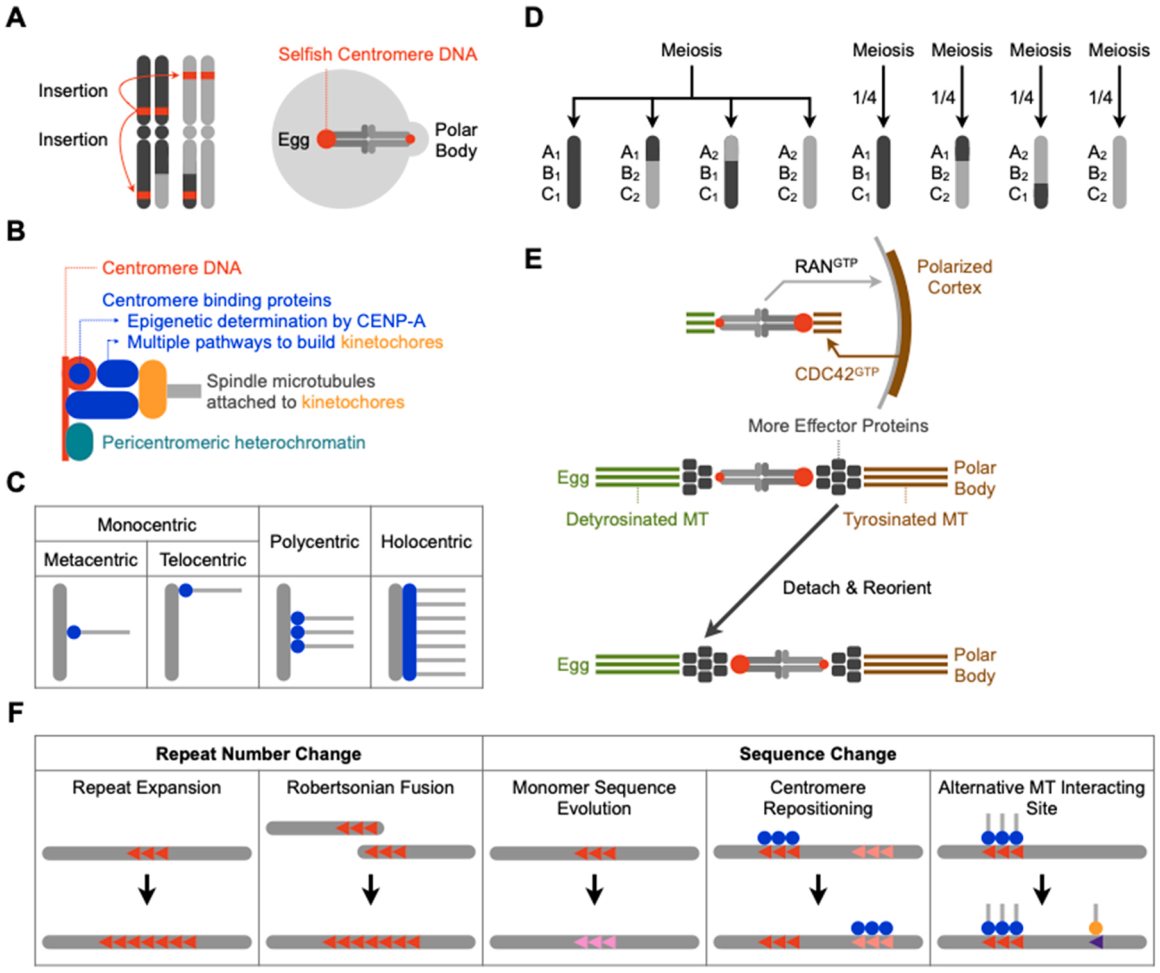

Fig. 1. Centromere drive and centromere evolution. (A) Drive strategies. Transposons drive by over-replication (left). Before insertion, 50% of gametes have the transposon. Inter-chromosomal insertion (top arrow) to the homologous chromosome (light gray) or other chromosomes (not shown) as well as intra-chromosomal insertion (bottom arrow) followed by crossover increases the number of gametes that have transposons. Centromere DNA drives by biased segregation in female meiosis (right). Selfish centromere DNA increases the chance of segregating into the egg. (B) Genetic and epigenetic components of centromeres. Centromere DNA (red) is functionally defined by the presence of kinetochores (orange). Centromere proteins (constitutive centromere associated network, CCAN proteins; blue) connect centromere DNA and kinetochores. CENP-A nucleosomes epigenetically define the kinetochore assembly position. There are multiple pathways (e.g., CENP-C and CENP-T) to build kinetochores. Pericentromeric heterochromatin (green) flanks CENP-A chromatin. (C) Diversity in centromere architecture. Blue circles represent the position of centromere binding proteins that attach to spindle microtubules. When the spindle microtubules attach near telomeres, such chromosomes are called telocentric (or acrocentric), whereas in other cases chromosomes are called metacentric. When spindle microtubules attach at a single CENP-A chromatin locus on each chromosome, as in human and yeasts, such chromosomes are called monocentric. Depending on genetic or epigenetic centromere determination, monocentric chromosomes have point or regional centromeres, respectively. When spindle microtubules attach at multiple CENP-A chromatin loci or all over the chromosome, such chromosomes are called polycentric or holocentric, respectively. (D) Fate asymmetry increases genetic diversity in gametes. In symmetric meiosis where all four haploid cells produce functional gametes (left), B and C genes, for example, are not shuffled. In asymmetric meiosis where one of four haploid cells produces the functional gamete, B and C genes can be shuffled because each meiosis creates different meiotic recombination sites. Thus, fate asymmetry diversifies combinations of genes in the limited number of eggs. (E) Coupling of three asymmetries for centromere drive in mouse oocytes. When the spindle is positioned near the oocyte cortex, the RAN^{GTP} signal from chromosomes polarizes the cortex. The polarized cortex generates the $CDC42^{GTP}$ signal, which creates the asymmetry post-translational modification in the spindle (top). Selfish centromere DNA recruits more effector proteins to drive (represented by the number of black squares). Effector proteins are microtubule destabilizers that are necessary for correcting erroneous kinetochore-microtubule attachments in all cell divisions, but selfish centromeres exploit this activity to reorient to the egg side of the spindle (bottom). (F) DNA evolution to drive in female meiosis. Red triangles represent repeat numbers. Repeat expansion can provide space for CENP-A chromatin expansion to drive. Robertsonian fusion can change the repeat number. Color change represents sequence evolution. Monomer sequence evolution can increase affinity with centromere binding proteins (blue circles). Other genomic loci can acquire centromere function, leading to centromere repositioning, or recruit another microtubule binding protein (orange circle).

microtubules. This selfish behavior is predicted to have fitness costs such as chromosome segregation errors, which select centromere binding protein variants that suppress the costs. Centromere DNA can be selfish only if centromere function has a genetic component, based on DNA sequence, whereas epigenetic centromere determination suppresses centromere drive and associated fitness costs. In this review, we first examine empirical evidence for centromere drive, how selfish DNA evolves to drive, and fitness costs imposed by selfish DNA. Then, we explain our parallel pathway model for centromere drive and suppression. Finally, we introduce other evolutionary conflicts that can explain rapid centromere evolution in species that do not undergo female meiosis.

2. Mechanisms of centromere drive

2.1. Fate asymmetry

In many eukaryotic lineages, meiosis in one sex is asymmetric in that only one cell produces a functional gamete, whereas the other haploid cells are degraded and therefore evolutionary dead-ends [47]. This meiotic fate asymmetry may be maintained because it increases genetic diversity in gametes. The number of eggs from a single female is much less than the number of sperm from a single male, and accordingly, female meiosis is less frequent than male meiosis. Because each meiosis creates different meiotic recombination sites, producing each egg from an independent meiosis maximizes genetic diversity (Fig. 1D). This fate asymmetry creates an opportunity for selfish genetic elements to cheat by increasing the chance of segregating into the egg.

Non-Mendelian segregation of selfish centromeres in female meiosis has been studied in mouse and monkeyflower. Centromeres with an expanded satellite repeat exhibit a transmission bias in monkeyflower [36,38]. In mouse oocytes, centromeres with expanded minor satellite repeats preferentially orient to the egg side of the meiotic spindle before anaphase I, implying biased segregation. The underlying mechanisms have been primarily studied in mouse due to the available genetic and cell biological tools [3,4,19,58,68]. Cell fate asymmetry is coupled to asymmetric cell division in mouse oocytes, and broadly in female meiosis in animals. The spindle is positioned close to the cortex, with chromosomes attached to the cortical side destined for the polar body. Conceptually, centromere drive therefore depends on coupling spindle asymmetry to the cell division asymmetry, and on asymmetry between centromeres of homologous chromosomes that influences their interactions with an asymmetric spindle.

2.2. Spindle asymmetry

Spindle asymmetry in female meiosis has been observed in many species [3,22,51]. In mouse oocytes, asymmetry within the spindle is intrinsically coupled to fate asymmetry. As chromosomes migrate to the cortex, RAN^{GTP} produced by the chromosomes polarizes the cell cortex. $CDC42^{GTP}$ signaling from the polarized cortex creates asymmetry in a post-translational modification of tubulin in the meiotic spindle (Fig. 1E, top) [3]. The cortical side of the spindle is enriched for tyrosinated microtubules, whereas the egg side is enriched for detyrosinated microtubules. Observations in multiple organisms [22] suggest that spindle asymmetry is a common feature of meiotic spindles. The functions of this asymmetry are unclear, and it is also possible that spindle asymmetry is an unavoidable byproduct of establishing cellular asymmetry (e.g., cortical polarization) necessary for asymmetric cell division. Given that spindle asymmetry is coupled to fate asymmetry, selfish genetic elements can exploit spindle asymmetry to drive by preferentially orienting towards the detyrosinated side of the spindle. Indeed, asymmetry in this post-translational modification of tubulin is required for biased orientation of selfish centromeres in mice [3].

2.3. Centromere asymmetry

In mouse intra-species (cross of different *Mus musculus domesticus* strains) and inter-species (cross of *Mus musculus* and *Mus spretus*) hybrids, homologous centromeres on meiotic bivalents are genetically different, and the centromere that recruits more effector proteins acts selfishly [4]. Effector proteins are microtubule destabilizers that correct erroneous microtubule attachments in every cell division, such as the kinesin-13 MCAK or the chromosome passenger complex (CPC), but selfish centromere DNA exploits this activity for its preferential orientation to the egg side of the spindle in meiosis I. Selfish centromeres that orient to the cortical side of the spindle are likely to flip to the egg side, suggesting that effector proteins preferentially destabilize interactions with the cortical side of the spindle, leading to detachment and re-orientation (Fig. 1E, bottom) [3,4]. Although the molecular details of this process are still unclear, preferential detachment from the cortical side is consistent with previous findings that MCAK preferentially destabilizes tyrosinated microtubules [97,108], as the cortical side of the spindle is more tyrosinated [3].

In other eukaryotic lineages with fate asymmetry, selfish centromeres may use different strategies to interact with spindle microtubules for preferential segregation to the egg, depending on details of how cell fate is determined. For example, in maize female meiosis where the lower cell of a linear tetrad forms an egg, selfish genetic elements called knobs (Section 3.2) recruit kinesin-14 motors to preferentially segregate to the upper and lower cells of a linear tetrad [25,109]. Selfish centromeres can recruit both microtubule binding and microtubule destabilizing activities to modulate interactions with spindle microtubules for preferential inheritance. Microtubule attachment to kinetochores is necessary for anaphase segregation, and kinetochore-microtubule attachments can be stabilized by the SKA and DAM complexes, for example. Widespread recurrent evolution of KNL1, a kinetochore protein involved in recruiting MT destabilizers, and turnover of the SKA and DAM complexes in eukaryotic species [53,114] are consistent with the idea that microtubule interaction dynamics have evolved to suppress fitness costs associated with selfish centromeres (Sections 4 and 5).

3. DNA evolution to achieve preferential inheritance in female meiosis

In the previous examples of centromere drive, genetic differences correlate with functional differences in centromeres, but it remains unclear how selfish centromere DNA creates these functional differences. Due to the epigenetic determination of centromeres, opportunities for centromere DNA variants to recruit centromere binding proteins for preferential inheritance in female meiosis are constrained. Such variants could differ in repeat number or monomer sequence of centromeric satellites (Fig. 1F). Robertsonian fusions, discussed in Section 4.4, represent a unique opportunity to change repeat number by translocation and karyotype by biased inheritance. In addition to the centromere, other genomic loci may evolve to genetically recruit centromere binding proteins (e.g., neocentromeres) or microtubule binding proteins (e.g., maize knobs) to promote their inheritance in female meiosis. Finally, possible biased segregation by transposons at centromeres is discussed in Section 5.1.

3.1. Repeat expansion and monomer sequence evolution

Satellite DNA evolves rapidly [41,83], due to either lack of constraint (drift) or adaptive evolution that increases the chance of inheritance (drive). In order to drive, satellite DNA repeats can expand to accommodate CENP-A chromatin expansion [58], or satellite monomer sequence can evolve to recruit more centromere binding proteins. The drive model proposes that new satellite variants that achieve preferential inheritance will quickly fix in a population. In sexually reproducing species that undergo meiosis, this model predicts that satellite sequences

are different between populations but similar within a population. In asexual species, satellite sequences are predicted to be as different within a population as they are between populations [26]. Satellite DNA sequence diversity observed in the sexual *Bacillus grandii* and parthenogenetic, asexual *Bacillus atticus* is consistent with this prediction [74]. Furthermore, two homologous centromeres with different abundance of satellite DNA compete in female meiosis, leading to satellite repeat expansion in sexual species. In contrast, asexual species are predicted to have less satellite DNA as having more repeats imposes a significant load to the host. Indeed, 15–20% of the sexual *Bacillus grandii* genome is composed of satellite DNA, compared to 2–5% of the asexual *Bacillus atticus* genome [79]. However, the high levels of centromere DNA haplotype diversity in human populations suggest evolutionary pressures that mitigate rapid fixation of potential driving centromere DNA haplotypes [70]. Alternatively, driving haplotypes may not be present in human populations.

3.2. Neocentromeres and ectopic microtubule binding sites

Neocentromeres are functional centromeres in ectopic chromosomal regions that are devoid of canonical centromere DNA sequences. Several cases are reported in humans, some inherited for multiple generations [49]. Such neocentromeres can either go extinct or increase their frequency by drift or drive, eventually leading to fixation as evolutionary young centromeres. Centromere repositioning is frequent in mammals [104], and centromere positions of orangutan chromosomes are polymorphic [72]. It is also possible that DNA sequences from selfish genetic elements replace endogenous centromeres. It is hypothesized that genetically defined centromeres on budding yeast chromosomes are originally from selfish plasmids [76]. The presence of lineage-specific transposons correlates with the absence of CENP-A/C in Mucoromycotina species [87], raising the possibility that transposons which recruit CENP-T take over as centromeres.

DNA sequences at other genomic loci can recruit proteins that interact with spindle microtubules to increase the chance of inheritance in female meiosis. Non-Mendelian inheritance of an abnormal “knob” at the end of maize chromosome 10 was the earliest discovery of female meiotic drive [102]. Knob-linked, Kinesin-14 derived Kindr and Trkin motors localize to repetitive DNA on heterochromatic knobs and increase knob motility to drive [25,109]. In addition to maize, multiple other plant species have acquired knobs [24]. In some cases, knobs form only in species hybrids, suggesting that knob formation is suppressed by mechanisms that are compromised in hybrids.

4. Parallel pathway model for drive and suppression

4.1. Fitness costs of drive and suppressor evolution

The centromere drive hypothesis proposes that fitness costs imposed by selfish centromeres are the selective pressure for centromere binding protein variants that suppress the costs [50] (Fig. 2A). In particular, meiosis is a likely place to have costs because divergent centromere variants are paired if heterozygous, leading to functional asymmetry within a meiotic bivalent. However, fitness costs are observed in monkeyflowers homozygous for the selfish centromere DNA variant [37,38]. The underlying mechanisms are unknown, but one possibility is that the selfish variant competes with centromeres of other chromosomes for recruitment of a limited pool of centromere proteins, leading to segregation errors. Alternatively, the selfish centromere may assemble a larger kinetochore that makes more erroneous microtubule attachments in either mitosis or meiosis [29]. Fitness costs may also arise in the zygote, where maternal and paternal centromere variants first come together in a shared cytoplasm. As extreme examples of divergent centromeres sharing the embryonic cytoplasm, some or all chromosomes from one parent are lost in some inter-species hybrids [43,113]. Overall, molecular mechanisms of fitness costs are still unclear but likely depend

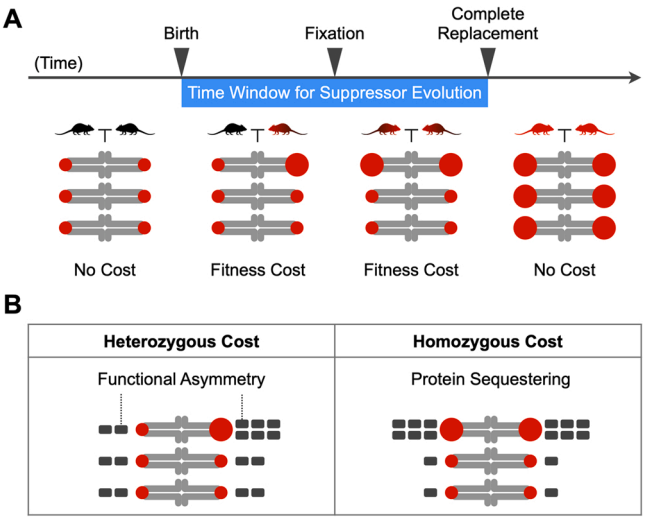

Fig. 2. Fitness costs of selfish centromere DNA variants. (A) Relative timing of selfish centromere DNA variant evolution and suppressor protein evolution. Chromosome schematics show meiotic bivalents at different evolutionary timepoints, and color changes (of mice as an example) represent spreading of the selfish variant (larger circle) in the population. Initially all individuals have the same centromere DNA, so there is no fitness cost. A selfish variant (repeat expansion or sequence change) that appears in one chromosome can drive and fix and also spread to other chromosomes. Being heterozygous or homozygous for the selfish variant is predicted to have fitness costs until the selfish variant replaces all centromeres. The time window for suppressor evolution is from birth of the selfish variant to complete replacement. (B) Possible mechanisms of fitness costs in individuals heterozygous (left) or homozygous (right) for the selfish centromere DNA variant. Black squares represent centromere binding proteins. When heterozygous, functional asymmetry between centromeres may cause fitness costs. When homozygous, selfish variants may sequester centromere binding proteins so that other centromeres recruit fewer binding proteins, leading to segregation errors. When the selfish variant replaces all centromeres, there will be no fitness cost because all centromeres are equivalent.

on functional differences between genetically different centromeres in the shared cytoplasm (Fig. 2B) and would therefore be suppressed by reducing these differences.

As selfish centromeres drive by recruiting more effectors, functional equalization could happen in two ways: weakening an effector recruitment pathway exploited by selfish centromeres and/or strengthening another effector recruitment pathway that is equal at all centromeres. The microtubule-destabilizing effector proteins identified in hybrid mouse models can be recruited through kinetochores and through heterochromatin [1,2,52,112,128]. The kinetochore pathway is amplified on selfish centromeres, while heterochromatin is insensitive to underlying DNA sequences. Thus, genetically different centromeres can be functionally equalized by weakening the kinetochore pathway or by strengthening the heterochromatin pathway (Fig. 3A). Having parallel pathways for effector recruitment allows proteins to adapt by minimizing a pathway that is exploited by a selfish element, while maintaining the essential functions via the other pathway. Similarly, multiple pathways to build a kinetochore (e.g., CENP-C and CENP-T) can modulate relative contributions to kinetochore assembly in response to a selfish element. Consistent with the parallel pathway model, signatures of adaptive evolution are found in multiple components of the kinetochore and heterochromatin pathways for effector recruitment [68].

4.2. Kinetochore pathway for recruitment of drive effectors

Selfish centromeres in mice exploit the kinetochore pathway to recruit microtubule destabilizing activity for their preferential inheritance. Different strategies to recruit more effector proteins through the this pathway converge on BUB1 kinase at kinetochores, which

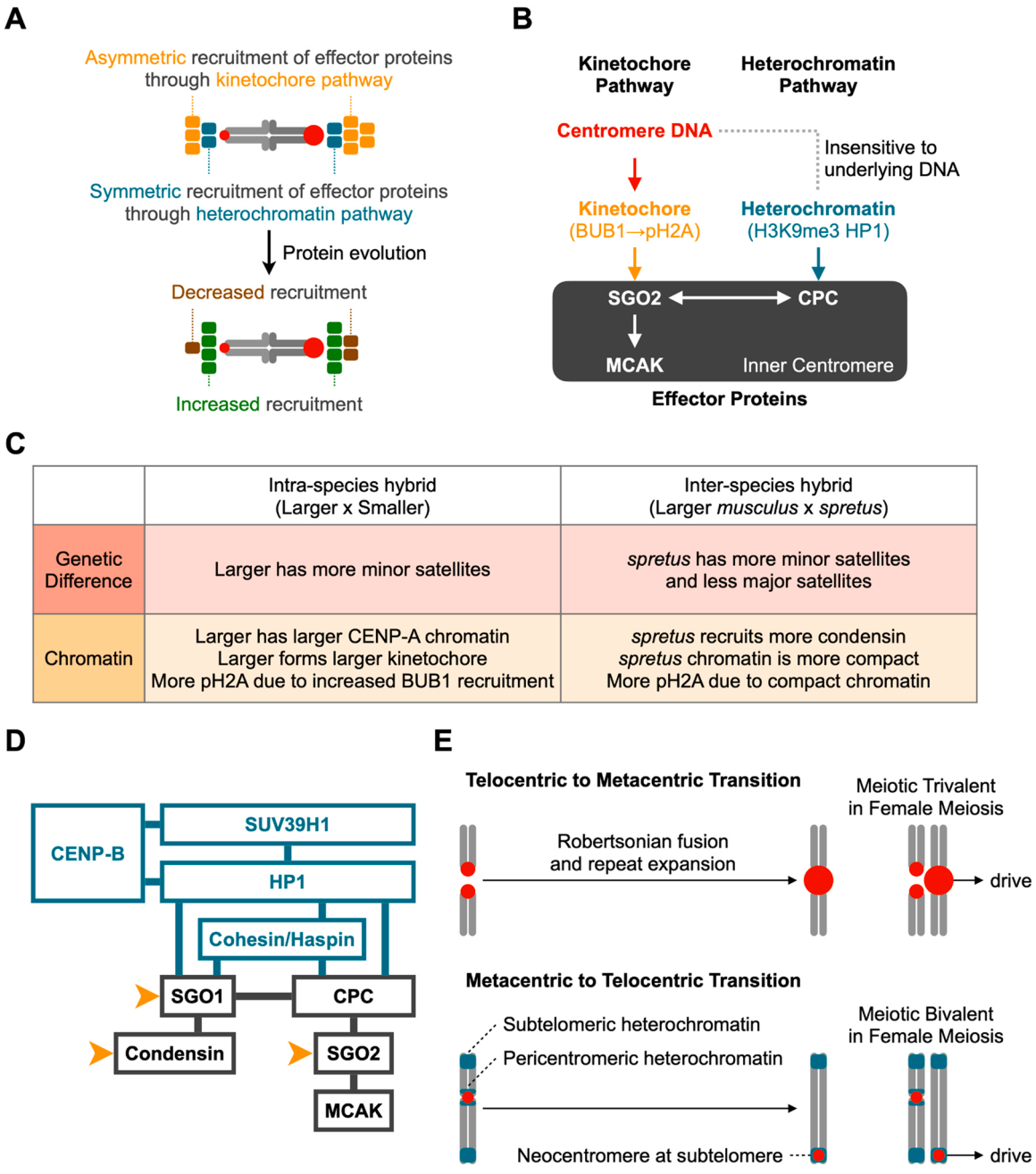

Fig. 3. Parallel pathway model for drive and suppression. (A) Parallel pathway model. Colored boxes represent effector proteins recruited by the kinetochore pathway (orange) or the heterochromatin pathway (green). Color changes represent protein evolution. Proteins in the kinetochore pathway can adapt by reducing affinity for DNA or for other proteins leading to effector recruitment. Inner centromere proteins can adapt by increasing affinity for heterochromatin or by decreasing their recruitment by the kinetochore pathway. (B) Overview of effector recruitment. Kinetochore-localized BUB1 kinase phosphorylates pericentromeric histone H2A to recruit SGO2. In parallel, pericentromeric heterochromatin also recruits SGO2 via the CPC (chromosome passenger complex) at the inner centromere. In our hybrid mouse models, selfish centromere DNA recruits more effector proteins through the kinetochore pathway. In contrast, heterochromatin appears insensitive to the underlying genetic differences. (C) Kinetochore pathway asymmetry in hybrid mouse models. In the intra-species hybrid, where minor satellite repeat abundance varies, the centromeres with more repeats (larger) assemble more CENP-A chromatin, form larger kinetochores, and recruit more effectors. In the inter-species hybrid, both minor and major satellite repeat abundance varies. Kinetochores are similar, but *spretus* centromeres recruit more condensin, leading to more compact chromatin and more histone substrates for BUB1 phosphorylation. (D) The heterochromatin pathway for effector recruitment and cross-talk with the kinetochore pathway. Heterochromatin modules are labeled green, and effector modules are labeled black. CENP-B recruits heterochromatin proteins HP1 and SUV39H1 [91,92]. Multiple chromatin marks recruit inner centromere proteins: HP1 directly recruits CPC and SGO1 [1,2,52,64,81,127], HP1 and cohesin recruit haspin to phosphorylate H3T3 and recruit CPC [128,130], and BUB1 recruits SGO1/2 by H2AT120 phosphorylation in the kinetochore pathway [115,128] (panel B). Heterochromatin and inner centromere proteins are interconnected, and effector proteins are also recruited through the kinetochore pathway (orange arrow heads). Condensin is recruited by SGO1 [94,119] and kinetochore components [110]. (E) Proposed transitions between telocentric and metacentric chromosomes. Centromeres of Robertsonian fusion chromosomes with increased satellite repeats drive in female meiosis (top). Neocentromeres formed at subtelomeres drive if subtelomeric heterochromatin recruits more effector proteins than pericentromeric heterochromatin on the homologous counterpart (bottom). In contrast, neocentromeres on chromosome arms are likely to have less heterochromatin and lose in female meiosis.

phosphorylates pericentromeric histone H2A to recruit Shugoshin-2 (SGO2) and microtubule destabilizing proteins (Fig. 3B, kinetochore pathway) [4]. In an intra-species *Mus musculus domesticus* hybrid, selfish centromeres with expanded minor satellite DNA repeats assemble more CENP-A chromatin, which forms larger kinetochores with more BUB1 kinase, leading to more effector recruitment. In inter-species hybrids of *Mus musculus* and *Mus spretus*, *musculus* and *spretus* centromeres form kinetochores of similar size, but *spretus* centromeres recruit more condensin to form more compact chromatin, leading to more histone substrates for BUB1 and more effector recruitment (Fig. 3C).

Our parallel pathway model proposes that components in the kinetochore pathway have evolved to weaken effector recruitment, thereby weakening the genetic contribution to effector recruitment by selfish centromeres. This model has two predictions. First, when the kinetochore pathway is weakened, centromeres become functionally similar. Second, the kinetochore pathway is not optimized for the maximum recruitment of effector proteins. Results from ectopic expression of divergent alleles of CENP-C are consistent with these predictions. CENP-C is a key scaffold protein in the kinetochore pathway, and signatures of adaptive evolution are found in many functional domains of CENP-C [68,106]. According to our model, CENP-C has evolved to modulate effector recruitment, so expression of a divergent allele of CENP-C in mouse cells will impact effector recruitment. We tested ectopic expression of CENP-C alleles from *Rattus norvegicus* (Rat) or *Rhabdomys pumilio* (African striped mouse) as examples of species closely related to *Mus musculus* (mouse) with divergent centromere DNA and proteins [16,42,77,111]. When rat CENP-C is expressed in mouse oocytes, effector recruitment is reduced. Furthermore, chromosome position on the meiosis I spindle provides a sensitive readout for functional differences between paired centromeres of homologous chromosomes. Bivalents are positioned at the spindle equator in the typical metaphase configuration when centromeres are functionally similar, or away from the spindle equator when centromeres are functionally different [4,19]. Based on this assay, disrupting the kinetochore pathway by rat CENP-C expression makes genetically different centromeres become functionally similar. In contrast, *pumilio* CENP-C is targeted more to mouse centromeres relative to *musculus* CENP-C, recruiting more effector proteins, consistent with the idea that proteins in the kinetochore pathway have evolved to weaken effector recruitment [68].

4.3. CENP-B paradoxes and heterochromatin pathway for recruitment of drive effectors

Although CENP-B is one of the first identified centromere proteins, functions of CENP-B remain elusive [31]. CENP-B is the only centromere protein known to bind a specific DNA sequence, the CENP-B box in mammals, but neither the protein nor the binding sequence is essential for centromere function [6,54,66,73,95]. CENP-B proteins are maintained in many mammals, however, and CENP-B boxes are present in most mammalian chromosomes with the notable exception of the Y chromosome [15,39]. This paradoxical evolution of CENP-B can be explained by the idea that CENP-B functionally equalizes genetically different centromeres by increasing heterochromatin. When CENP-B is deleted, genetically different centromeres become functionally more different based on the chromosome position assay [68]. This result implies that CENP-B contributes to a pathway that equalizes centromeres. Several lines of evidence indicate that this equalization pathway acts through heterochromatin (Fig. 3B, heterochromatin pathway): CENP-B is an established regulator of heterochromatin [68,86,91,92], the amount of heterochromatin is insensitive to underlying genetic differences in mouse intra- and inter-species hybrids [68], and heterochromatin is an established pathway to recruit effector proteins (Fig. 3D, references in the figure legend).

We propose that the centromere equalization function of CENP-B is important when homologous centromeres are genetically different, as in outbred populations but not inbred laboratory strains where CENP-B deletion does not significantly impair fertility or viability [54,66,95]. Mammalian CENP-B has an additional function of CENP-C recruitment [33], which contributes to kinetochore and CENP-A chromatin assembly. The dual functions of CENP-B for heterochromatin formation and CENP-C recruitment may allow heterochromatin to expand without invading CENP-A chromatin [90], thus preserving essential centromere function. We propose that mammalian CENP-B first acquired heterochromatin function and then evolved to recruit CENP-C as a mechanism to maintain CENP-A chromatin. Although CENP-B functionally equalizes centromeres, a centromere variant without CENP-B boxes will be at a disadvantage in female meiosis because CENP-B contributes to both the kinetochore and heterochromatin pathways for recruiting drive effectors. Thus, CENP-B boxes are maintained at most mammalian centromeres, but this selective pressure does not affect the Y chromosome, which never experiences female meiosis and does not bind CENP-B [39].

4.4. Karyotype evolution

Although centromere position on the chromosome (Fig. 1C) likely has little effect on chromosome segregation, many species have either mostly telocentric or mostly metacentric chromosomes rather than a random mixture of the two [84,93]. Furthermore, karyotypes have frequently switched between mostly telocentric and mostly metacentric [44,84,93,125]. Transitions in one direction, from telocentric to metacentric karyotypes, can be explained by centromere drive of Robertsonian (Rb) fusions [20], common chromosomal rearrangements formed by two telocentric chromosomes joining at their centromeres to create one metacentric chromosome [125]. Fusion can increase centromere satellite repeat number (Fig. 1F) and centromere chromatin, depending on the site of translocation. According to our model, increased CENP-A chromatin leads to more effector recruitment by the kinetochore pathway and preferential transmission in female meiosis, although the details of how drive effectors act in the context of a meiotic trivalent are unclear. When metacentric chromosomes are more likely to be inherited than the homologous telocentric chromosomes, metacentrics can quickly fix in a population (Fig. 3E). Indeed, in *Mus musculus domesticus* populations that have changed karyotype by accumulating Rb fusions, metacentric chromosomes have more CENP-A chromatin than telocentric chromosomes in the same cell [19].

The components of our parallel pathway model also provide a potential explanation for the transition from metacentric to telocentric karyotypes. If the endogenous centromere is silenced [80], neocentromeres at telomeres may drive if they have more subtelomeric heterochromatin compared to pericentromeric heterochromatin on the homologous counterpart (Fig. 3E). Heterochromatin alone is insufficient to recruit effector proteins, but once neocentromeres are formed at telomeres and centromeric histone marks (e.g., phosphorylation at H3T3 and H2AT120) are present, subtelomeric heterochromatin likely contributes to effector recruitment. In addition to forming heterochromatin, subtelomeric satellites may become selfish by evolving to recruit centromere proteins to exploit the kinetochore pathway. Indeed, there are several reports of subtelomeric satellite DNA used for neocentromere formation. For example, human telocentric chromosomes 14 and 15 are derived from the split of an ancestral metacentric chromosome [118]. The ancestral centromere was inactivated, and neocentromeres formed in subtelomeric regions of both chromosomes. In fission yeast, neocentromeres often form in subtelomeres after endogenous centromere inactivation [57]. More broadly, it is hypothesized that centromeric repetitive DNA sequences are derived from rapidly evolving subtelomeric repetitive sequences [120].

4.5. Other strategies to suppress costs of selfish centromeres

If selfish centromeres that cheat in female meiosis impose fitness costs in mitosis, having functionally different centromeres in mitosis vs

meiosis can suppress the mitotic costs. Mitotic holocentromeres form kinetochores on the entire chromosome, and many holocentric species have lost CENP-A [27], likely due to the relaxed requirement for epigenetic specification of kinetochore assembly sites. However, localized centromeres are required in meiosis due to the necessity of meiotic recombination and two-step loss of cohesion [55,85,96], so selfish centromere DNA can in principle achieve preferential inheritance in female meiosis. Although a kinetochore-independent mechanism segregates homologous chromosomes during female meiosis in *C. elegans*, kinetochore proteins are still required to orient chromosomes properly on the meiotic spindle [30]. Thus, there is an opportunity for selfish DNA to bias this orientation process. In another example, *Heteroptera* species form holocentromeres in mitosis, but microtubules attach to one of two ends of a chromosome in meiosis, which is usually randomly determined [55,96]. However, selfish DNA on either end might evolve to bias this process as well.

If satellite DNA imposes fitness costs, the host genome can evolve to remove such sequences in mitosis by chromatin diminution. In the parasitic nematode *Parascaris univalens*, euchromatic regions are flanked with large blocks of heterochromatic satellite DNA that comprise around 80% of the genome [45]. Microtubules attach to the heterochromatic terminal regions during meiosis. In somatic cells, heterochromatic regions are removed by chromatin diminution. During this process, microtubules bind to only euchromatin, resulting in fragmented euchromatic chromosomes [46]. Another parasitic nematode, *Ascaris suum*, undergoes chromatin diminution by loss of genomic regions with reduced CENP-A levels [65]. Fragmented chromosomes can be segregated because of mitotic holocentromeres in both species, but fragmented chromosomes likely impede meiotic recombination and two-step segregation, so longer chromosomes are maintained in meiosis.

5. Other evolutionary forces that diversify centromere DNA and proteins

In addition to centromere drive in female meiosis, other evolutionary forces may select for centromere DNA and protein variants. One possibility is that centromere binding proteins are selected for non-segregation functions. In multicellular organisms, stem cell division is a regulatory point for proliferation or differentiation. Thus, the chromosome segregation machinery may have acquired additional functions for development. Kinetochore proteins are repurposed for neural development in flies and worms [18,131], and KNL1 regulates brain size in humans [60,107]. Furthermore, the anaphase-promoting complex APC/C has additional functions in stem cell differentiation [89]. As KNL1 indirectly regulates APC/C activity through spindle assembly checkpoint signaling, it is possible that kinetochore proteins regulate cell identity. However, these functions are limited to multicellular organisms and cannot explain rapid centromere protein evolution in single-cell organisms. Furthermore, centromere DNA evolves rapidly in organisms that only undergo symmetric meiosis, from which all of the haploid cells form functional gametes [10], which is difficult to explain by selection for non-segregation functions. Another possibility is that selfish genetic elements such as transposons and extraneous genetic elements (e.g., plasmids and B chromosomes) hijack centromeres, and centromere binding proteins have evolved to suppress them, as discussed in the following sections.

5.1. Drive and suppression of transposons at centromeres

Transposons are often inserted in centromeres. CENP-A chromatin is located on islands of transposons in *Drosophila* [17], and transposons are also found in satellite-free, evolutionary young equine centromeres [88] and in a human neocentromere [21]. Transposons achieve non-Mendelian inheritance by over-replication (Fig. 1A), and in principle they can be inserted anywhere on the chromosome. However, transposons benefit themselves in centromeres by two means. First, centromeres have no genes but are transcriptionally active. Transposition requires transcription, but transposon insertion at transcriptionally active genes is often deleterious, so it is selected against. Thus, centromeres represent an ideal insertion site where transposons can be transcribed without deleterious effects on transcription of other genes. Second, transposons at centromeres can drive in female meiosis by recruiting centromere binding proteins (Fig. 1A), providing another opportunity for non-Mendelian inheritance.

Host genomes have evolved mechanisms to suppress transposon activity at centromeres. Transcriptional silencing by heterochromatin (characterized by H3K9me3 histone marks, HP1-mediated chromatin compaction, and DNA methylation) is the predominant strategy [59]. Briefly, RNA-based silencing and protein-based silencing can initiate heterochromatin formation. RNAi represses transposons and viruses, and this function is universal among eukaryotes [48]. However, RNAi alone seems insufficient to completely purge transposons from centromeres, as transcripts are required to initiate silencing. Indeed, fission yeast *S. japonicus* centromeres are mostly transposons despite the presence of RNAi machinery that targets transposons [101]. Protein-based silencing provides an additional layer of transposon silencing. After the divergence from *S. japonicus*, fission yeast species (e.g., *S. pombe*, *S. octosporus* and *S. cryophilus*) acquired CENP-B homologs, and their centromeres are largely transposon-free, despite the loss of RNAi machinery in *S. octosporus* and *S. cryophilus* [116]. Similarly, *S. pombe* RNAi machinery targets repetitive DNA instead of transposons, suggesting that RNAi has been repurposed from its ancestral function of transposon silencing to pericentromeric heterochromatin formation [101]. The absence of functional transposons at fungal centromeres correlates with the absence of RNAi [126], suggesting that once active transposons are lost by protein-based silencing, the RNAi machinery becomes dispensable.

The pogo-like transposase is one of the most widespread DNA transposons found in animals, plants, fungi and protozoans [99], and several eukaryotic lineages have domesticated pogo-like transposases that have lost transposition activity but been repurposed for other cellular processes [40,82]. CENP-B in yeasts and mammals is one such example [15,67]. CENP-B in both lineages regulates heterochromatin formation [68,86,91,92], suggesting that heterochromatin formation is the ancestral function of CENP-B. Heterochromatin formation by yeast CENP-B prevents retrotransposon insertion [13], but it is not known whether mammalian CENP-B also has this function. In summary, centromeres provide unique opportunities for transposon drive. Eukaryotic genomes have conserved RNA-based transposon silencing machinery, from which transposons often escape. Some eukaryotic lineages have evolved protein-based transposon silencing, which has successfully purged transposons from centromeres in some species. Transposons can also be domesticated to silence other types of transposons as exemplified by yeast CENP-B homologs.

5.2. Plasmids and B chromosomes

Plasmids and B chromosomes are extraneous genetic elements that are usually dispensable for the host, but they exploit the host replication and segregation machinery for their inheritance. The 2 μm plasmid is an example of a selfish plasmid found in budding yeasts [103]. This plasmid does not encode proteins beneficial to the host but has *STB* centromere-like DNA and Rep1/2 proteins that bind *STB* and microtubules for segregation. The 2 μm plasmid also encodes proteins for over-replication. B chromosomes are extraneous, dispensable chromosomes that are not homologous to any of the canonical sets of "A" chromosomes. B chromosomes drive by biased segregation toward the germline stem cell [61], or biased segregation toward the germ cells [51,61] (Fig. 1A). Although little is known about the mechanisms of B chromosome drive, repetitive DNA on B chromosomes likely biases the segregation. B chromosomes are devoid of coding genes and mostly composed of tandem repeats such as satellite DNA and ribosomal DNA

[14]. Biased segregation of ribosomal DNA in *Drosophila* male germline stem cells [122] raises the possibility that ribosomal DNA is also selfish [12].

Analogous to the centromere drive hypothesis, an evolutionary arms race between selfish extraneous genetic elements and centromere binding proteins can lead to rapid evolution of both. Under this model, plasmids and B chromosomes evolve to hijack centromere binding proteins to drive. As plasmids and B chromosomes impose significant load to the host, centromere binding protein variants that are not recruited by them are selected. In addition to centromere binding proteins, the nuclear envelope can evolve to suppress selfish genetic elements. The nuclear envelope remains intact in the closed mitosis of budding yeasts, but it breaks down in the open mitosis of mammals. It is speculated that evolutionary transitions between open and closed mitosis are driven by selfish genetic elements [105]. Plasmids and viruses first enter the cytoplasm, whereas transposons are transcribed in the nucleus. If plasmids and viruses in the cytoplasm are the immediate threat to the host genome, closed mitosis may prevent these elements from entering the nucleus, whereas if many transposons are transcribed, releasing the transcripts to the cytoplasm by open mitosis may reduce transposon insertion.

Although plasmids and transposons are also present in bacteria and archaea, only eukaryotes developed complex centromeres. The inheritance of genetic information is an essential process for all life, but it is proposed that prokaryotic chromosomes can spontaneously segregate by physical forces without sophisticated segregation machineries [62,63]. For example, the *cis*-DNA element *migS* helps promote the bipolar segregation of origins in *E. coli*, but this sequence is not essential for chromosome segregation [34,121,129]. In contrast, eukaryotes require chromosome segregation machinery for meiosis. Meiotic recombination is the predominant way to exchange genetic information in eukaryotes, and homologous chromosomes must pair and segregate each generation [71]. This requirement makes the chromosome segregation machinery indispensable for eukaryotes, providing an opportunity for selfish genetic elements to cheat. In contrast, bacteria and archaea can abandon the chromosome segregation machinery if it is exploited by selfish genetic elements.

6. Concluding remarks on speciation

Evolutionary arms races at centromeres shape the rapid evolution of selfish genetic elements and suppressor mechanisms. Selfish centromere DNA, transposons at centromeres, plasmids, and B chromosomes drive by biased segregation and over-replication. Studies of selfish centromere DNA drive in female meiosis in hybrid mouse models show that essential microtubule destabilizing proteins are exploited for preferential inheritance of selfish centromeres. Parallel pathways for recruiting these drive effector proteins are adaptively evolved to functionally equalize genetically different centromeres. Other selfish genetic elements likely have distinct mechanisms to drive and distinct suppression mechanisms. Selfish genetic elements are constantly evolving to escape suppressor mechanisms, and different species can quickly acquire species-specific suppressor variants. This rapid diversification of drive and suppression mechanisms may cause hybrid incompatibility, leading to reproductive isolation and speciation [100,124].

Conflict of interest

The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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