Cell Biology of Cheating—Transmission of Centromeres and Other Selfish Elements Through Asymmetric Meiosis

Lukáš Chmátal, Richard M. Schultz, Ben E. Black and Michael A. Lampson

Abstract Mendel's First Law of Genetics states that a pair of alleles segregates randomly during meiosis so that one copy of each is represented equally in gametes. Whereas male meiosis produces four equal sperm, in female meiosis only one cell, the egg, survives, and the others degenerate. Meiotic drive is a process in which a selfish DNA element exploits female meiotic asymmetry and segregates preferentially to the egg in violation of Mendel's First Law, thereby increasing its transmission to the offspring and frequency in a population. In principle, the selfish element can consist either of a centromere that increases its transmission via an altered kinetochore connection to the meiotic spindle or a centromere-like element that somehow bypasses the kinetochore altogether in doing so. There are now examples from eukaryotic model systems for both types of meiotic drive. Although meiotic drive has profound evolutionary consequences across many species, relatively little is known about the underlying mechanisms. We discuss examples in various systems and open questions about the underlying cell biology, and propose a mechanism to explain biased segregation in mammalian female meiosis.

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1 Introduction

Asymmetric meiotic division creates an opportunity for cheating when selfish elements increase their likelihood of transmission to the functional gamete. In cases where mechanisms of such preferential segregation are understood, they are mediated by repetitive DNA elements that ultimately interact with microtubules (MTs). The first example of such preferential transmission was observed by Marcus Rhoades in maize (Rhoades 1942), and the repetitive DNA elements were termed 'neocentromeres' because of their ability to drive segregation at cell division. It should be noted that because maize neocentromeres use a special connection to MTs (Yu et al. 1997), they are distinct from "neocentromeres" subsequently described in many other eukaryotic species that recruit a conventional kinetochore-mediated MT connection. The term "meiotic drive" was later introduced to emphasize the key role of asymmetric female meiosis (Sandler and Novitski 1957). Over time, the meaning of "meiotic drive" has been extended to include other forms of transmission ratio distortion that are not strictly a consequence of asymmetric meiosis (meiotic drive sensu lato, Fig. 1), but could be a result of post-meiotic processes (e.g., gamete competition, post-fertilization selection) (Lyttle 1991; Pardo-Manuel de Villena and Sapienza 2001a). Here, we use the term meiotic drive in its originally defined meaning, as depending on the mechanics of asymmetric female meiosis (meiotic drive sensu stricto, Fig. 1).

Meiotic drive violates Mendel's First Law, and although the mechanisms of meiotic chromosome segregation underlying Mendelian genetics have been extensively studied, the cell biology of meiotic drive is relatively unexplored. There are many open questions regarding how selfish elements exploit the meiotic chromosome segregation machinery to maximize their own propagation. We discuss examples of meiotic drive in various systems, to illustrate the breadth of the phenomenon, starting with examples (e.g., plant neocentromeres) that do not depend on typical centromeres. The mechanisms are unknown in most cases and raise intriguing questions about the underlying cell and molecular biology. We also discuss the concept of "centromere drive", for which cell biological models are more intuitive but many open questions remain, and propose a mechanism to explain biased segregation in mammalian female meiosis. Our proposed mechanism incorporates the apparent paradox that exists because centromeres in most eukaryotes are defined epigenetically (i.e., not by a particular DNA sequence; (Black and Cleveland 2011), yet centromere drive is also thought to involve changes in the underlying DNA that strengthen MT connections (Henikoff et al. 2001). In considering the applicability of our model for mammalian centromeres to other systems, one should ask the following questions: *In which cases does the drive mechanism rely on repeat expansion or other changes to the DNA sequence related to modifying a conventional, kinetochore-building centromere? And in which cases does it relate to creating something altogether different (e.g., the abnormal, specialized connections seen with maize neocentromeres, detailed immediately below)*?

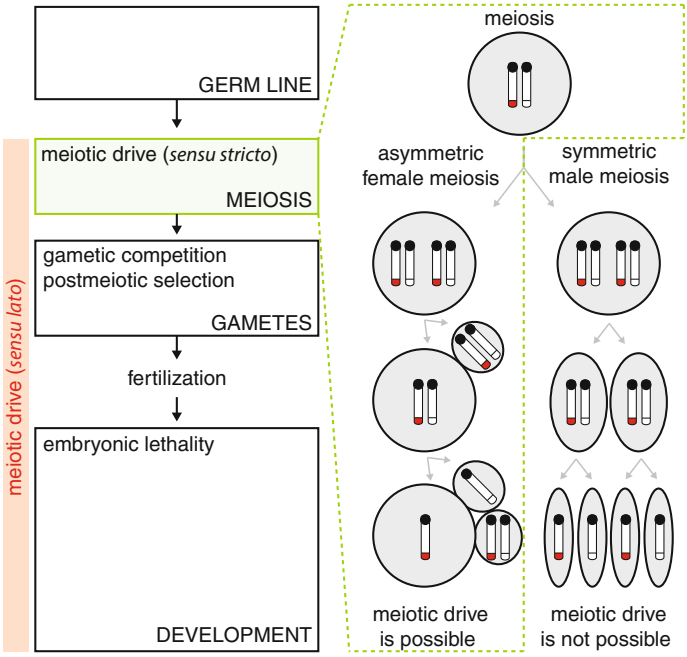

Fig. 1 Meiotic drive terminology. Meiotic drive sensu stricto refers to selfish DNA elements (*red part* of chromosome) exploiting asymmetric female meiosis by preferential transmission to the viable gamete, whereas other gametes degenerate as polar bodies. Meiotic drive sensu lato includes changes in allele frequency due to other mechanisms, such as gametic competition or embryonic lethality (Sandler et al. 1959). *Black circles* indicate centromeres. Adapted from Pardo-Manuel de Villena and Sapienza (2001a)

2 Abnormal Chromosome 10 in Maize

The first experimental evidence of meiotic drive arose from observations of abnormal chromosome 10 (Ab10) in maize (*Zea mays*). In contrast to normal chromosome 10 (N10), Ab10 contains an extra DNA segment that includes regions of euchromatin, an inverted portion of N10, and a repetitive DNA sequence (knob). By following a knob-linked genetic marker, Rhoades showed that Ab10 preferentially segregates to the surviving gamete (megaspore) during female meiosis and proposed a model to explain the phenomenon (Rhoades 1942, 1952). In this model, after recombination between the Ab10 and N10 chromosomes, Ab10 knob activity results in a shifted chromosome position toward meiotic spindle poles in anaphase I, and this position is maintained through meiosis II. Ab10 is, therefore, more likely to segregate to the basal cell that later becomes the megaspore, whereas the other cells degenerate (Fig. 2). Several lines of experimental evidence support Rhoades's model (Rhoades and Vilkomerson 1942; Dawe and Cande 1996; Yu et al. 1997). First, Ab10 knobs act as neocentromeres in that they bind MTs, although they do

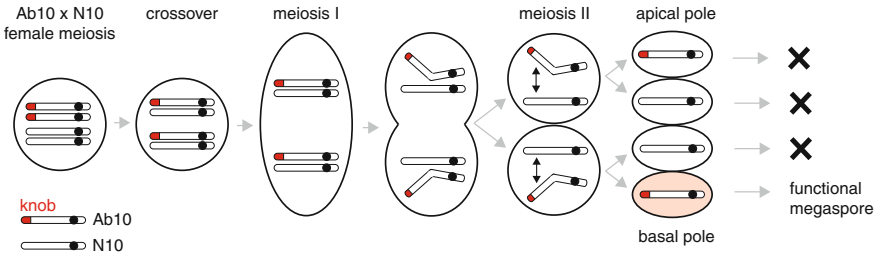

Fig. 2 Ab10 chromosome in maize. Abnormal chromosome 10 (Ab10) with an extra DNA sequence (knob, *red*) recombines with normal chromosome 10 (N10) in meiosis I. Neocentromere activity of Ab10 knobs leads to faster movement to the cell poles and preferential Ab10 position maintained through meiosis II, so that Ab10 chromosomes are transmitted into apical and basal cells. Ab10 transmits preferentially to the next generation because only the basal cell develops to a functional gamete whereas the others degenerate

not assemble typical kinetochores as shown by the absence of the major structural component CENP-C (Dawe et al. 1999). The knobs also lack nucleosomes containing the histone H3 variant, CENP-A, that specify centromere location on typical chromosomes in maize and other eukaryotes. Second, the knob drives faster movement of Ab10 to the spindle poles in anaphase, compared to N10, suggesting that the knob binds a minus-end-directed microtubule motor. Third, in telophase I the knobs are positioned peripherally, on the poleward side of the nucleus. If this localization is maintained into meiosis II, through mechanisms that are unclear, the knobs would end up in the outer megaspores. Multiple other knobs have also been identified on other maize chromosomes and drive in the presence of Ab10, likely by a similar mechanism (Longley 1945; Buckler et al. 1999).

More than seven decades after Rhoades's original model, many outstanding questions still remain. If the knob binds molecular motors, what motors are involved, and how is the interaction mediated? Why is the knob active only in meiosis and not in mitosis? How is drive suppressed by the *Smd1* (suppressor of meiotic drive 1 locus) mutation that was identified using transposon mutagenesis to isolate maize mutants with reduced meiotic drive (Dawe and Cande 1996)? Another challenge is to extend the conclusions from cytological experiments performed in male gametes to biased segregation in the female germline.

3 B Chromosomes

B chromosomes, detected in numerous plants, fungi, and animals (Jones 1995; Burt and Trivers 2006), represent dispensable DNA elements in addition to the standard (A) chromosomes. Although B chromosomes evolved from A chromosomes, they

are highly heterochromatic and mostly genetically inactive and act as independent parasitical units, increasing their frequency in the population (Östergren 1945; Jones and Rees 1982). B chromosome drive refers to preferential transmission that can occur as either a pre-meiotic, meiotic, or post-meiotic process, mediated by various mechanisms in males and females (Hewitt 1976; Jones 1991; Banaei-Moghaddam et al. 2012). In an example of meiotic B chromosome drive in grasshopper (*Myrmeleotettix maculates*), biased transmission into the egg during female meiosis is mediated by an asymmetric meiotic spindle, with the egg side of the spindle estimated as approximately three times longer than the polar body side (Hewitt 1976; Jones 1991). A simple model is that B chromosome positioning on such a meiotic spindle is random, so the chromosome more likely attaches to the larger, egg side of the spindle. The mechanistic bases are unknown for both elements of the drive model: B chromosome attachment to the spindle and meiotic spindle asymmetry.

4 Driving Loci in Mouse

Several non-centromere driving loci have been identified in mouse. One example is a homogeneously staining region (HSR) of long-range repeats of about 100 kb each, found on chromosome 1 in remote natural populations of *Mus musculus musculus* (Traut et al. 1984; Yukimenko and Korobitsyna 1988; Agulnik et al. 1990, 1993a, b, c; Sabantsev et al. 1993). An inversion (*In*) splits the HSR sequence into two distinct loci (Fig. 3a), and females heterozygous for the inverted HSR repeat (In/+) preferentially transmit *In* over the normal chromosome 1 ($\sim$85% vs. 15%). Because HSR is far from the centromere, it frequently segregates from the normal chromosome 1 in MII due to recombination, which implies that drive occurs in MII (Fig. 3b) (Ruvinsky 1995). Another example of meiotic drive at MII is the Ovum mutant locus (*Om*) mapped to mouse chromosome 11 (Pardo-Manuel de Villena et al. 2000; Wu et al. 2005). Intriguingly, MII drive in both cases depends on the genotype of the sperm, for example only if the In/+ MII egg is fertilized by sperm with the normal version of chromosome 1 lacking the HSR.

A third example of a driving locus, with as high as 94% preferential transmission in heterozygous females, is *R2d2* (Responder to drive on chromosome 2) (Didion et al. 2015), a massive copy number expansion formed by 36 units of repetitive DNA. Drive depends on *R2d2* expansion, as a strain with only one unit of this repetitive sequence does not exhibit drive. In all three cases of driving loci in mouse, the underlying mechanisms are completely unknown. Outstanding questions include whether any of the loci exhibit neocentromere activity (similar to Ab10), possible contributions of genes present in the HSR or in the *R2d2* cluster, and how the sperm contributes to drive in MII. Future studies in these drive systems may provide new insight into meiotic chromosome segregation.

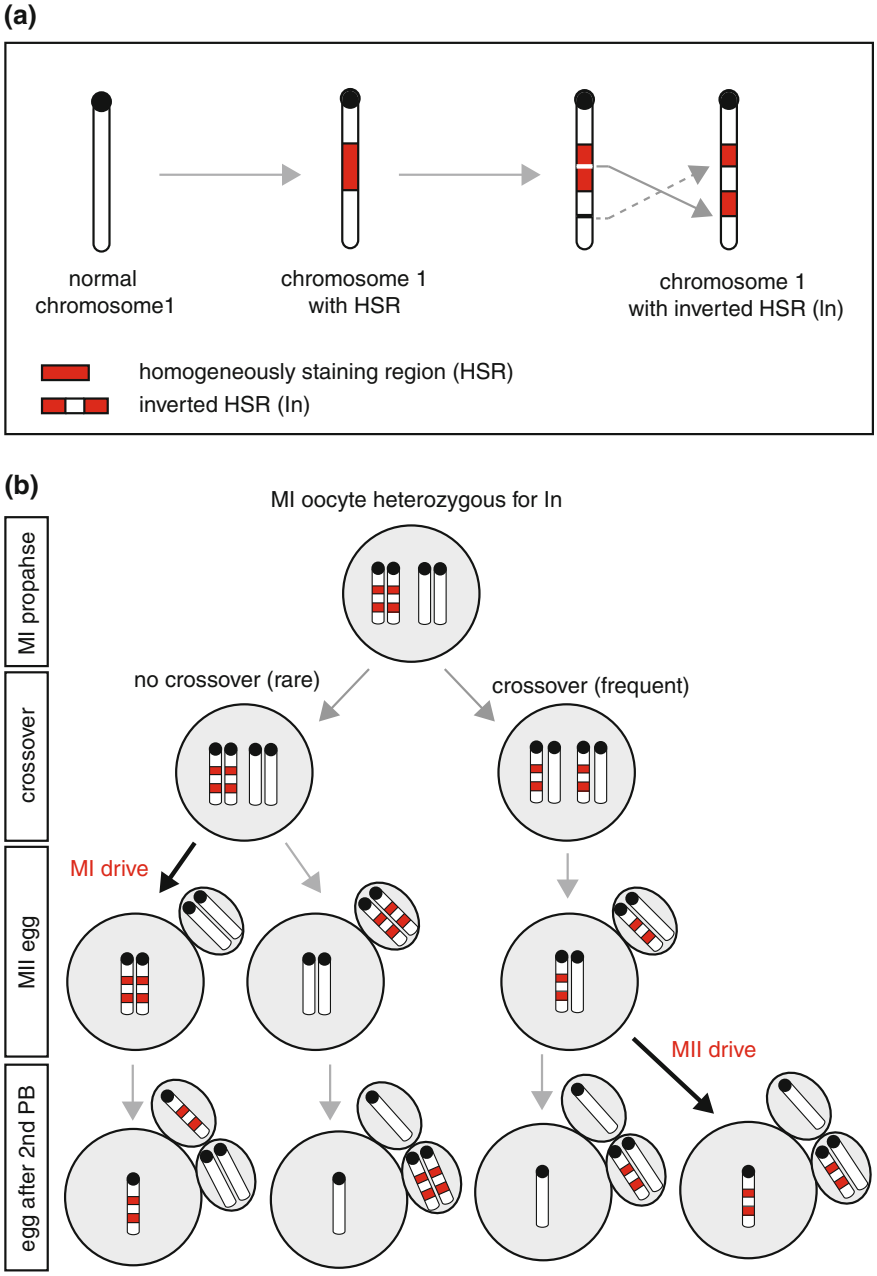

Fig. 3 Abnormal chromosome 1 in mouse. **a** Normal chromosome 1 and its abnormal forms with the homogeneously staining region (HSR) or the inverted HSR (*In*). **b** Chromosome 1 with the inverted HSR drives in MI when no crossover occurs (rare) and in MII when *In* recombines with normal chromosome 1 (frequent). Adapted from Ruvinsky (1995)

5 Univalent X Chromosome Segregation

Female mice with only one X chromosome in their karyotype (XO) are fertile (unlike human XO) and preferentially produce XX females (60%) rather than XO females (40%) when crossed to normal males (Cattanach 1962; Kaufman 1972). These findings imply that the single X chromosome is preferentially retained in female MI oocytes. Visualizing the X chromosome in MII eggs from XO females shows that 30% of the oocytes segregate the single X sister chromatids equationally in MI with no drive, and the remaining 70% of oocytes segregate the complete X univalent preferentially to the egg rather than to the polar body (2:1 bias) (Fig. 4a) (LeMaire-Adkins and Hunt 2000). How biased segregation of X univalents is achieved is unclear, but the mechanism may be similar to centromere drive as discussed below.

Caenorhabditis elegans with an additional X chromosome (XX + X) produce ~70% normal ova with a single X, and only 30% defective ova with two X chromosomes, suggesting preferential segregation of the extra X to the polar body (Hodgkin et al. 1979). Consistent with these results, X univalents are preferentially eliminated during MI in *him-8* mutants in which chiasmata fail to form between the two X chromosomes in a normal XX karyotype (Cortes et al. 2015). The biased univalent segregation during anaphase I is likely due its abnormal position on the MI spindle, closer to the cortex, and the position of the contractile ring separating the ovum and the first polar body. The contractile ring forms preferentially between the lagging univalent chromosome and the egg spindle pole, so the univalent ends up in the polar body (Fig. 4b). This mechanism is not specific for univalent X chromosomes but likely applies to all univalents (Cortes et al. 2015). How lagging univalents influence the position of the contractile ring is unclear.

6 Centromere-Associated Drive in Yellow Monkey-Flowers (*Mimulus guttatus*)

In natural populations of yellow monkey-flower (*Mimulus guttatus*), the D allele exhibits almost complete (98%) transmission advantage in interspecific crosses between *M. guttatus* and *Mylohyus nasutus* (Fishman and Willis 2005). This biased transmission strongly correlates with the presence of an extra centromere-associated DNA repeat domain (Fishman and Saunders 2008). Preferential transmission of the D allele (58%) is also detected within *M. guttatus* but is counterbalanced by male infertility, as *M. guttatus* homozygous for the D allele suffer from significantly reduced pollen viability, compared to other genotypic classes. Thus, the balance between transmission advantage of the D allele through females and pollen inviability in males leads to a D allele polymorphism in *M. guttatus* populations.

Overall the observations in monkey-flower support the centromere drive hypothesis (Henikoff et al. 2001; Malik and Henikoff 2009). In this model,

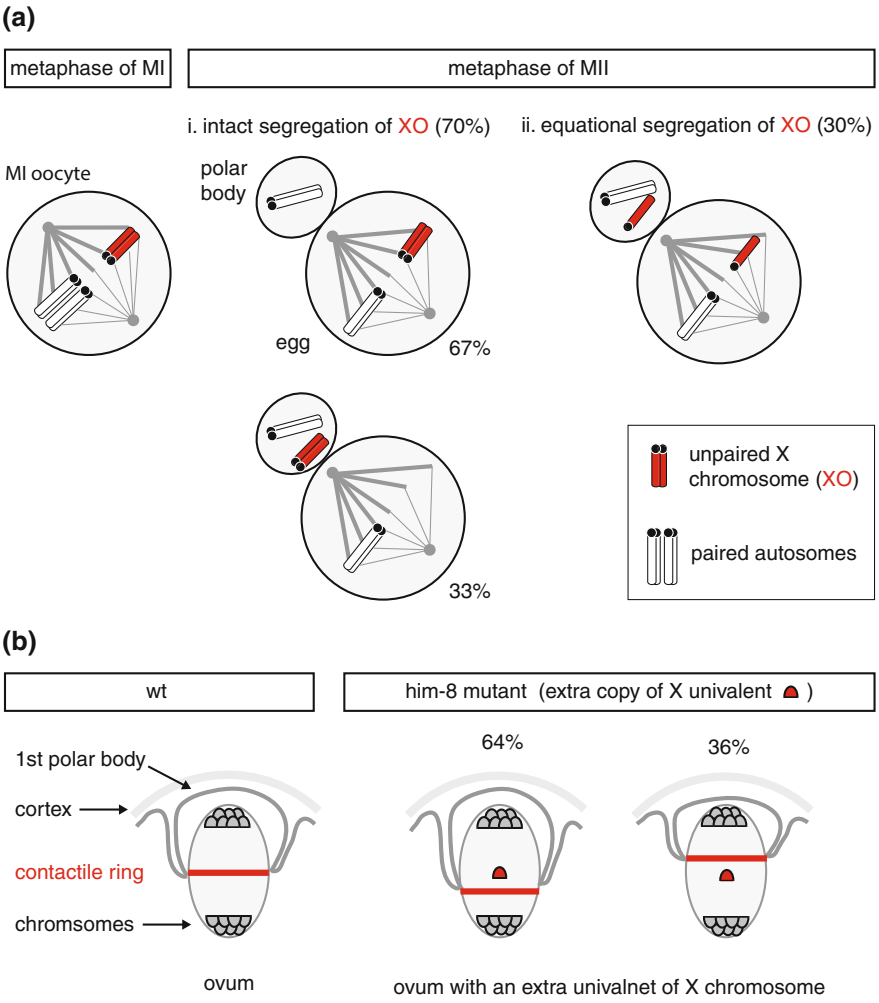

Fig. 4 XO chromosome drive in mouse and ***C. elegans***. **a** In XO mouse oocytes, an unpaired X chromosome is either preferentially retained in the egg as an intact univalent during MI (*i*) or the two sister chromatids segregate equationally in MI (*ii*). **b** A univalent X chromosome is preferentially expelled to the polar body during MI in *C. elegans* due to its lagging position at the metaphase plate and the positioning of the contractile ring. Adapted from LeMaire-Adkins and Hunt (2000) and Cortes et al. (2015)

"stronger" centromeres with expanded repetitive sequences recruit more kinetochore proteins and are more likely to remain in the egg during female meiosis, which would provide a selective advantage driving centromere expansion. However, imbalances between centromeres may also be associated with a fitness cost, such as reduced male fertility, creating selection pressure to equalize kinetochores by changing the centromere proteins binding to the expanded repeats.

Such opposite selection forces may explain the paradox of rapidly evolving centromere sequences and proteins that bind to them, despite conserved centromere function (Henikoff et al. 2001).

Although the observations in monkey-flower are largely consistent with the centromere drive hypothesis, several fundamental questions remain. *What are the consequences of the centromere expansion for kinetochore function, how do chromosomes with the D allele achieve preferential segregation, how does centromere strength relate to the typical epigenetic determinants of centromere identity, and what is the cause of reduced male fertility?* Future mechanistic studies may yield exciting insights into the cell biology of centromere drive, particularly given the magnitude of transmission bias in this system.

7 Robertsonian Fusion Chromosomes in Mouse

Robertsonian (Rb) fusions are common chromosomal rearrangements formed by two telocentric chromosomes (centromere at the end) joining at their centromeres to create one metacentric chromosome (internal centromere) (Fig. 5a) (White et al. 2010). Because they occur with high frequency in the germline compared to other rearrangements (Evans et al. 1978; Jacobs et al. 1992), their preferential accumulation through female meiosis can lead to massive karyotype change from a predominantly telocentric to a predominantly metacentric chromosome constitution. Western house mouse (*Mus musculus domesticus*) is an example of such karyotype divergence (Gropp et al. 1969; Piálek et al. 2005). The karyotype typically consists of all telocentric chromosomes ($2N = 40$), but numerous natural mouse populations have fixed multiple different Rb fusions within 10^2–10^5 years, reducing their chromosome numbers to almost a half in some cases (e.g., $2N = 22$) (Piálek et al. 2005; Garagna et al. 2014).

Fixation of Rb fusions can be explained by meiotic drive. When a new Rb fusion forms in the germline and is present in the heterozygous state, it pairs with the homologous telocentric chromosomes to form a trivalent in MI (Fig. 5a). Biased segregation of the Rb fusion can in principle drive karyotype change in a population (Fig. 5b) (Pardo-Manuel de Vill ena and Sapienza 2001b). According to this model, Rb fusions segregate preferentially to the egg in natural populations that have changed karyotype by accumulating metacentric Rb fusions, and preferentially to the polar body in other populations that have remained telocentric. Such biased transmission of Rb fusions is consistent with karyotype change in numerous other mammalian species (Buckland and Evans 1978; Pardo-Manuel de Villena and Sapienza 2001b; Aniskin et al. 2006; Mao et al. 2008; White et al. 2010) and with preferential retention of Rb fusions in the egg in humans, which tends to maintain the fusions in the female germline and increases the risk of producing aneuploid eggs (de Villena and Sapienza 2001).

Consistent with the centromere drive hypothesis (Henikoff et al. 2001), preferential transmission of Rb fusions correlates with the strength of the fusion

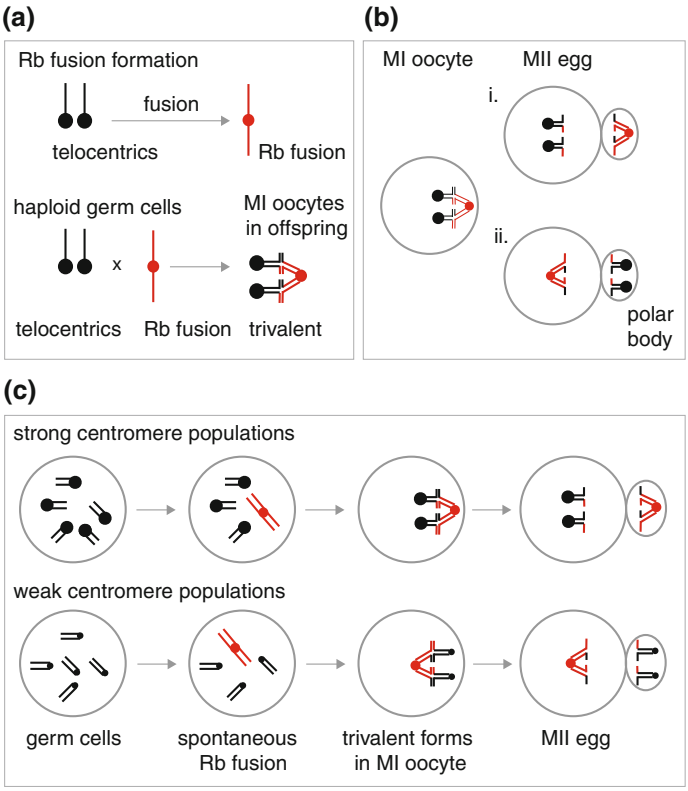

Fig. 5 Rb fusion chromosomes in mouse. **a** Rb fusion and trivalent formation. **b** Two possible outcomes of trivalent segregation in MI. **c** Model of Rb fusion drive in different directions in populations with strong or weak centromere backgrounds (see text for details). Centromere strength is indicated by the size of the circle (*red* Rb fusion, *black* telocentric). Adapted from Chmátal et al. (2014)

centromere relative to centromeres of the homologous unfused telocentrics, as determined in several ways (Chmátal et al. 2014). First, in an oocyte heterozygous for a single Rb fusion, kinetochore proteins are enriched at centromeres of the telocentric chromosomes that preferentially remain in the egg, relative to the homologous metacentric fusion that preferentially segregates to the polar body. These kinetochore proteins include CENP-A and the major MT-binding protein NDC80/HEC1. Second, in a natural metacentric population that accumulated Rb fusions (CHPO, $2n = 26$), the fusion centromeres are enriched for these same kinetochore proteins relative to the telocentric chromosomes. Biased segregation cannot be measured in CHPO because the metacentrics are present in the homozygous state, but it is likely that these fusions were subject to drive to preferentially remain in the egg as they accumulated in the population. Third, CHPO centromeres overall recruit less NDC80/HEC1 compared to a standard lab strain

such as CF-1. Because CHPO contains telocentrics as well as metacentrics, a CHPO × CF-1 cross generates asymmetric bivalents with different levels of NDC80/HEC1 on the two sides of the bivalent. These bivalents are positioned off-center on the MI spindle, indicating that the larger kinetochores bind more MTs. Together, these data establish correlations between kinetochore size as measured by the abundance of MT-binding kinetochore proteins, MT-binding capacity, and preferential retention of the chromosome in the egg; centromere strength can be considered to reflect all three characteristics.

Based on these results, we proposed a model for how Rb fusions can exhibit drive in opposite directions to either maintain a telocentric karyotype or accumulate metacentrics, based on relative centromere strength (Fig. 5c). If centromere strength varies between populations, the strength of a newly formed Rb fusion centromere relative to the homologous telocentrics may depend on the background in which the fusion occurs. In this model, fusions arising on a strong centromere background would tend to have weaker centromeres than the homologous telocentrics, so that the fusions would preferentially segregate to the polar body and disappear from the population. Conversely, fusions arising on a weak centromere background would be stronger than the telocentrics and accumulate in the population because they are preferentially retained in the egg. This model is supported by kinetochore protein (NDC80/HEC1) staining in mice from various geographical regions in Europe, which suggests that natural metacentric populations (like CHPO) generally have weaker centromeres, which would have predisposed them to accumulate metacentrics (Chmátal et al. 2014).

8 Mechanistic Models of Meiotic Drive—Weaker and Stronger Centromeres

In general, models for meiotic drive acting on homologous chromosomes include functional heterozygosity of the drive locus, which influences chromosome interactions with the meiotic spindle, and asymmetry in meiosis with respect to cell fate (Rhoades 1952; Pardo-Manuel de Villena and Sapienza 2001a; Henikoff et al. 2001). In the most intuitive case the drive locus is the centromere, and centromeres of different strengths form kinetochores that interact differently with MTs. Alternatively, the drive locus exhibits neocentromere activity, independent of the normal centromere, as shown for Ab10. Many outstanding questions remain about the cell biology of various meiotic drive systems. For example, what is the molecular basis of Ab10 neocentromere activity, and how do other non-centromere drive loci (such as *R2d2*) influence MT interactions? Furthermore, the centromere drive hypothesis suggests that centromere strength depends on centromere DNA, but it is unclear how DNA sequence can influence kinetochore function, given that centromeres are typically specified epigenetically (Black and Cleveland 2011). In particular, it is not yet clear how centromeres may drive in individuals within a

species where a centromere has moved to a location lacking centromere repeats, or within an entire species, like orangutan (Locke et al. 2011), horse (Wade et al. 2009), or chicken (Shang et al. 2010) where an 'evolutionary new centromere' has formed on one or more chromosomes. There is some evidence that human neocentromeres may be weaker by virtue of faulty mitotic error correction (Bassett et al. 2010) or through reduced recruitment of the constitutive centromere-associated network (CCAN) of proteins (Fachinetti et al. 2015).

It is clearly important to distinguish kinetochore-independent drive models, where expansion of repetitive DNA elements at a non-centromere locus generates and expands an interaction with the spindle (e.g., maize knob neocentromeres) (Fig. 6a), from those where centromere strength is increased by somehow building a larger kinetochore (e.g., mouse centromeres) (Fig. 6b). Because there is a strong epigenetic component to centromere identity that would impact the latter form of drive, proteins that define a functional centromere are likely involved in both generating a stronger centromere and as candidates to evolve to counteract the proposed detrimental consequences of imbalances between stronger and weaker centromeres (Henikoff et al. 2001).

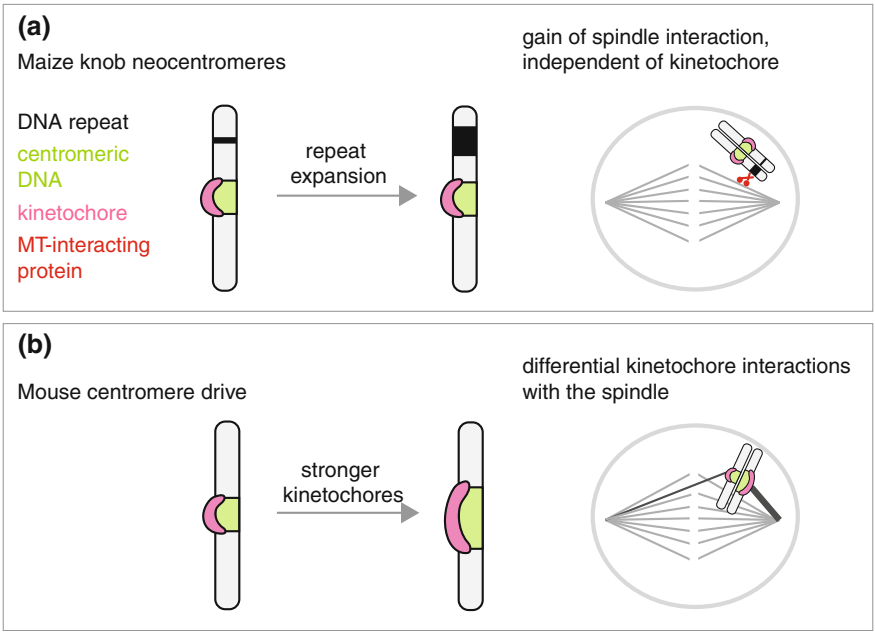

Fig. 6 Knob neocentromeres and expanded mammalian centromeres interact differently with meiotic spindle MTs. **a** Knob repeat expansion with kinetochore-independent interactions with MTs leading to a preferential position on the spindle. **b** Centromere expansion to achieve higher levels of kinetochore proteins and preferential orientation on the spindle. In each case the modified chromosome is shown on the spindle pairing with its homologous partner. Sister chromatids are not shown for simplicity

Focus has logically fallen on the CENP-A nucleosomes that mark centromere location and the proteins immediately proximal to it. A high local concentration of CENP-A nucleosomes recruit the constitutive centromere-associated network (CCAN) of 16 proteins, some of which are involved in the epigenetic recruitment of new CENP-A at each cell cycle to propagate centromere identity and/or the assembly of the mitotic kinetochore (McKinley and Cheeseman 2016). At least two CCAN components, CENP-C and CENP-N, also help maintain centromere identity by driving a nucleosome structural transition that stabilizes CENP-A at the centromere (CENP-C) (Falk et al. 2015, 2016) and fastening CENP-A to the DNA (CENP-N) (Guo et al. 2017).

The amino acid changes in CENP-A, relative to its canonical counterpart histone H3, distinguish CENP-A chromatin from bulk chromatin. Thus, it is worth considering the molecular basis for the epigenetic features that may participate in centromere drive. The CENP-A N-terminal 'tail' has been proposed to interact with CENP-B (Fachinetti et al. 2015), a protein that directly binds to a specific sequence found in typical mammalian centromere DNA repeats (Masumoto et al. 1989). The N-terminal tail also appears to have a CENP-B-independent role in centromere function (Folco et al. 2015; Logsdon et al. 2015). The histone-fold domain harbors the CENP-A targeting domain (CATD) that is sufficient for centromere targeting (Black et al. 2004) through recognition by its specific histone chaperone, HJURP (Foltz et al. 2009). The CATD also drives three structural and dynamic features particular to centromeric nucleosomes. First, the CATD contains hydrophobic stitches that stabilize the $(CENP\text{-}A/H4)_2$ heterotetramer (Black et al. 2004; Sekulic et al. 2010; Bassett et al. 2012). Second, the CATD drives an atypically shaped nucleosome (Sekulic et al. 2010; Falk et al. 2015, 2016) that only achieves its full stability after the CCAN component, CENP-C, drives a structural transition that rigidifies internal inter-histone connections (Falk et al. 2015, 2016). Third, the CATD includes residues that generate a bulged loop L1 that extends from the histone surface of the nucleosome (Sekulic et al. 2010; Tachiwana et al. 2011) and recruits the CCAN component, CENP-N (Carroll et al. 2009; Fang et al. 2015; Guo et al. 2017). In addition, the CATD and the C-terminal tail of CENP-A recruits the CCAN component CENP-C (Carroll et al. 2010; Kato et al. 2013; Logsdon et al. 2015; Tachiwana et al. 2015; Westhorpe et al. 2015). Outside of the CATD, a divergent helix (the αN helix) at the connection to the final turn of nucleosomal DNA has changes relative to H3 that lead to looser wrapping at this particular part of the nucleosome (Conde e Silva et al. 2007; Panchenko et al. 2011; Tachiwana et al. 2011; Hasson et al. 2013; Roulland et al. 2016). Ongoing research is aimed at understanding the importance of each of these distinguishing features of centromeric nucleosomes in producing the epigenetic mark that defines centromere location.

In all likely models for centromere propagation, new CENP-A deposition at the centromere involves nascent CENP-A chromatin assembly once per cell cycle at or near the site of preexisting CENP-A nucleosomes. The special stability of this chromatin (Bodor et al. 2013; Falk et al. 2015) then maintains the centromere over the demandingly long timescales required in mammalian biology (Smoak et al. 2016). It is very likely that some of the molecular features described above play prominent roles in centromere drive mechanisms in diverse eukaryotes, contributing to differences in centromere strength.

9 Mechanistic Models of Meiotic Drive-Spindle Asymmetry

In many cases, drive models also depend on functional asymmetry in the meiotic spindle that biases the segregation of bivalents or trivalents in MI or sister chromosomes in MII (Pardo-Manuel de Villena and Sapienza 2001a; Henikoff et al. 2001). Meiotic spindle asymmetry has been reported in grasshopper (Hewitt 1976), as well as examples in several other organisms (Crowder et al. 2015). We also observe asymmetry within the MI spindle in mouse oocytes, with MTs closer to the cortex more stable than those farther from the cortex (our unpublished results) (Fig. 7a). How spindle asymmetry is regulated is not known, but possible mechanisms include: (1) regulation of MT dynamics by an unknown cortical signal, or (2) asymmetric distribution of spindle pole proteins, as observed in previous studies (Carabatsos et al. 2000; Shuda et al. 2009; Meng et al. 2004; Michaut et al. 2005). The first mechanism simplifies the problem in that it would also explain how the asymmetric spindle orients relative to the cortex.

Based on our observations of spindle asymmetry in mouse oocytes and preferential retention of stronger centromeres in the egg, we speculate on models for meiotic drive in mammalian female meiosis. Two mechanisms, which are not

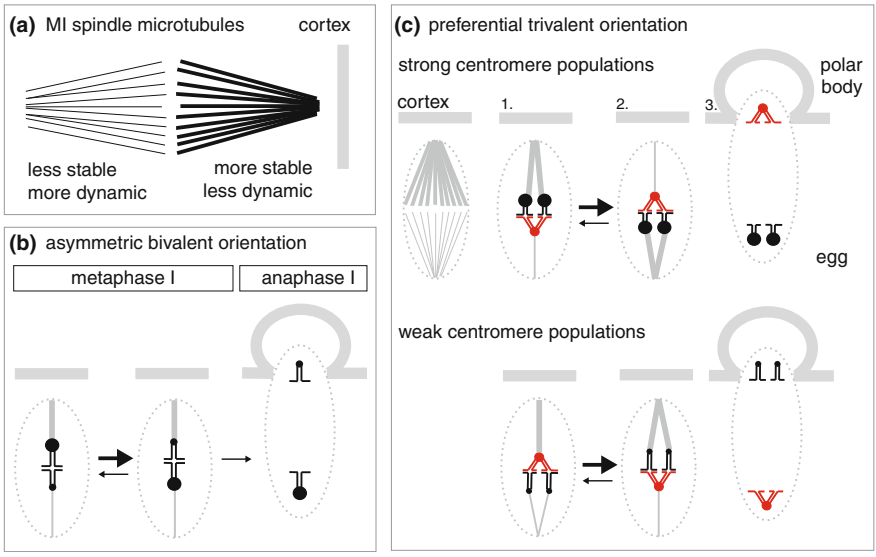

Fig. 7 Model for meiotic drive in mouse oocytes. **a** An asymmetric MI spindle with more stable MTs oriented toward the oocyte cortex. **b** Orientation of an asymmetric bivalent on the asymmetric MI spindle. The weaker centromere preferentially orients toward the more stable MTs on the cortical side of the spindle. **c** Model for preferential Rb fusion segregation in strong and weak centromere populations, based on trivalent orientation on the asymmetric MI spindle. Centromere strength is indicated by the size of the circle (*red* Rb fusion, *black* telocentric)

mutually exclusive, could explain preferential orientation of weaker centromeres toward more stable MTs at the cortical pole and stronger centromere toward less stable (more dynamic) MTs at the egg pole (Fig. 7b). First, more dynamic MTs from the egg pole may initially capture the stronger centromeres, which provide a larger target with more MT-binding proteins at their kinetochores. Weaker centromeres would subsequently bind MTs from the cortical pole to establish tension across the bivalent. Second, the bivalent may sample both orientations, and one is preferred because it is relatively more stable than the other. Under this model the interaction of the weak centromere with more dynamic MTs is labile and will tend to re-orient, and the interaction of the weak centromere with more stable MTs is preferred. This trial-and-error mechanism, in which the preferred configuration is selectively stabilized, is analogous to the long-standing model for how correct, bi-oriented attachments are stabilized by tension (Nicklas 1997), but in this case the outcome is biased orientation. Further observations from live imaging of chromosome dynamics during MI may test these models.

The same models can explain the preferential orientation and segregation of a trivalent. The stronger centromeres may attach first to the more dynamic egg pole, and/or the interaction of weak centromeres with more dynamic MTs may be unstable. As a result, the Rb fusion centromere orients preferentially to the egg pole if it is stronger relative to the homologous telocentrics, or preferentially to the cortical pole if it is relatively weaker (Fig. 7c).

10 Conclusion

Chromosomal rearrangements are frequent events involving chromosomal fusion, fission (chromosomal splitting) or translocations. Their role in speciation via meiotic drive was proposed nearly 50 years ago: *"It may be that the very few chromosomal rearrangements which play a critical role in speciation through the ability to generate powerful isolating mechanisms are precisely those which happen to possess a segregational advantage in the female meiosis"* (White 1968). Under that model karyotype of a given species is not fixed but can change over time. If karyotype changes between populations by preferential transmission of a chromosomal rearrangement (such as an Rb fusion) through female meiosis, meiotic abnormalities in the hybrids would generate a reproduction barrier, promoting speciation (Hauffe et al. 2012; Shurtliff 2013). Chromosomal reorganizations are also a major mechanism of reproductive isolation in *Saccharomyces cerevisiae* (Hou et al. 2014) and contribute to karyotype evolution in higher plants (Jones 1998). In addition, meiotic drive of Rb fusions can explain the bimodal distribution of mammalian karyotypes: most species have either predominantly telocentric or predominantly metacentric karyotypes. A similar bimodal distribution of karyotypes is found in fish (Molina et al. 2014). Transmission advantage of either chromosomal fusions (metacentrics) or fissions (telocentrics) through female meiosis predicts the biased accumulation of a given chromosomal rearrangement,

which would shape the karyotype in one direction or the other, depending on the direction of drive.

There is a deleterious effect on male carriers in several meiotic drive systems. For example, Ab10 exhibits reduced pollen fitness, probably due to late replication of the knob sequence that extends the cell cycle and leads to mitotic abnormalities in microsporogenesis (Fluminhan and Kameya 1997), and the overall frequency in natural populations is low (~14%) (Buckler et al. 1999). In monkey-flower, pollen grains from males homozygous for the D allele have reduced fitness (Fishman and Saunders 2008). Similarly, male mice with Rb fusion chromosomes in the heterozygous state, which form trivalents, tend to have decreased fitness due to higher incidence of chromosome nondisjunction during meiosis (Manieu et al. 2014; Green 1981). Such deleterious effects may be frequently linked to drive in systems that have been studied because these deleterious effects prevent complete fixation of a selfish element; otherwise, there would be no meiotic drive to measure.

The various systems exhibiting meiotic drive share one common aspect: an asymmetric meiotic division. Distinct gamete architecture is one of the strongest differences between sexes (Gorelick et al. 2016). Male gametes are typically small, abundant and autonomously moving elements, whereas female gametes are large, stockpiled, stationary cells that are limited in number. An elegant way to achieve such desired egg morphology is combining the cytoplasm from several cells while expelling the redundant DNA, by dividing asymmetrically. Alternatively, asymmetry in meiosis could be explained by selfish DNA elements competing for their transmission. In this model, the DNA elements would transform the architecture of gametogenesis to trigger the elimination of gametes that are not transmitting them (Malik and Henikoff 2009). On the other hand, evolution of asymmetric meiosis could have been driven by the opposite force, to eliminate selfish elements. Regardless of the evolutionary force driving the asymmetry in meiosis, it was evolutionarily successful as it arose independently several times (Malik and Henikoff 2009), and it seems inevitable that selfish elements will exploit the opportunity to increase their chances of survival.

We call attention to a study (Iwata-Otsubo et al. 2017) published during the production of this book. This study provides evidence that amplified satellite repeats act as selfish elements in female meiosis.

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