



Review

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Meiotic drive mechanisms: lessons from *Drosophila*

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Meiotic drivers are selfish genetic elements that bias their transmission into gametes, often to the detriment of the rest of the genome. The resulting intra-genomic conflicts triggered by meiotic drive create evolutionary arms races and shape genome evolution. The phenomenon of meiotic drive is widespread across taxa but is particularly prominent in the *Drosophila* genus. Recent studies in *Drosophila* have provided insights into the genetic origins of drivers and their molecular mechanisms. Here, we review the current literature on mechanisms of drive with an emphasis on sperm killers in *Drosophila* species. In these systems, meiotic drivers often evolve from gene duplications and targets are generally linked to heterochromatin. While dense in repetitive elements and difficult to study using traditional genetic and genomic approaches, recent work in *Drosophila* has made progress on the heterochromatic compartment of the genome. Although we still understand little about precise drive mechanisms, studies of male drive systems are converging on common themes such as heterochromatin regulation, small RNA pathways, and nuclear transport pathways. Meiotic drive systems are therefore promising models for discovering fundamental features of gametogenesis.

1. Introduction

Nearly a century has passed since Gershenson [1] discovered the first documented case of meiotic drive in *Drosophila obscura*. While conducting genetic crosses from flies he had caught near Moscow, he noticed that some males sired only female or primarily female progeny. A careful analysis then allowed Gershenson to conclude that the responsible gene (hereafter 'the driver') was located on the X chromosome and caused 'spermatozoa with the Y chromosome to participate in the fertilization process in but an insignificant number'. This phenomenon, called 'sex-ratio distortion' (hereafter SR), is widespread, particularly in *Drosophila*. In its broader definition, a meiotic driver is a selfish genetic element that biases its own transmission into the functional gametes of heterozygous individuals at the expense of the alternative allele. There are two ways to be over-represented: *gamete killing* in males (disruption of alternative sperm) and *gonotaxis* in females (preferential transmission into the ovule). Meiotic drive systems are sex-specific and most known meiotic drive systems in *Drosophila* act in males through *sperm killing*. During spermatogenesis, the driver prevents the formation of functional sperm that do not have a copy of itself. This efficient strategy is referred to as 'interference' because it is basically a game for (at least) two players: a driver and its target (reviewed in [2]).

The emergence of a gamete killer is by its very nature detrimental for the 'fair' genes that ensure their evolutionary success by being advantageous for their carriers. It sets the stage for an intragenomic conflict between, on one side, the driver and linked genomic regions and, on the other side, the rest of the genome. Drive enhancers promote transmission of the driver and drive

suppressors restore fair segregation. This arms race triggers rapid evolution towards a new genomic balance.

Since Gershenson's seminal paper, meiotic drivers have been reported in a range of animals, plants and fungi [3]. However, with few exceptions, we lack even basic information about their identity and how they operate. There are multiple reasons for this. First, genetic mapping is often difficult, because for many known systems, the drive locus (or loci) lies within a chromosomal inversion or other non-recombining regions [4–6]. Second, as a consequence of intragenomic conflict, drive systems typically involve multiple genetic elements with epistatic interactions, making it difficult to identify individual components [7–9]. Finally, drive systems involve processes and genomic regions that are still poorly understood, such as heterochromatin.

Here, we review recent advances in our understanding of meiotic drive systems, with a focus on sperm killers in *Drosophila*. We discuss the origins of meiotic drivers and the role of gene duplication. We review recent developments on drive mechanisms and note emerging themes involving small RNA pathways, heterochromatin formation and nuclear transport. Finally, we discuss possible evolutionary consequences of meiotic drive.

2. Genetic origins of drivers

(a) Where do drivers emerge?

In males, a meiotic drive system consists of at least two loci: a driver and a target. In heterozygotes, the driver skews transmission rates in its favour by destroying target-bearing gametes in trans. This requires that the two loci are genetically linked, but on opposite homologous chromosomes to avoid creating a 'suicide' chromosome where the driver causes its own destruction. Therefore, drivers are typically linked to a resistant (insensitive) allele of the target.

Since tight linkage between these loci is critical for the success of drivers, these systems tend to arise in low- or non-recombining regions of the genome (e.g. sex chromosomes and heterochromatin), or acquire modifiers of recombination (e.g. chromosomal inversions) to create or reinforce linkage. Most known meiotic drive systems are X-linked (electronic supplementary material, table S1), where the lack of recombination between X and Y chromosomes provides fertile grounds for driver systems to emerge. Autosomal drivers, however, can occur in heterochromatic regions around the centromere and telomere, where there is little recombination. For example, the autosomal *Segregation Distorter* system of *Drosophila melanogaster* (*SD*) involves at least two loci: the driver (*Segregation distorter*, or *Sd*) is in the proximal region of chromosome 2L, and its target (*Responder* or *Rsp*) corresponds to a large block of tandem satellite repeats in the pericentric heterochromatin of chromosome 2R [8].

Most known meiotic drive systems are more complicated and involve additional modifiers of drive. Suppressors counteract the driver to restore Mendelian transmission ratios, and enhancers increase the strength of the driver. While suppressors can be unlinked from the driver and the target, enhancers must be linked to the driver (figure 1b). Chromosomal inversions are often associated with meiotic drive systems [4–6], as they may either suppress recombination between the drivers and their target [8] or reinforce the linkage between the drivers and enhancers [9].

The disparity in the number of known sex-linked and autosomal drivers (electronic supplementary material, table S1) is in part due to ascertainment bias: it is easier to detect distorted sex chromosome transmission because it manifests as a deviation from the Fisherian sex ratio (1 : 1) [10]. Distorted autosomal transmission can go unnoticed in the absence of a visible or scored molecular marker linked to the distorter. For example, the autosomal *SD* system in *D. melanogaster* was discovered because of the unexpected lack of recovery of visibly marked chromosomes in a genetic screen unrelated to meiotic drive [11]. It is easier to detect drivers that are currently segregating, as the effects of a driver are only apparent in heterozygotes. Fixed drivers will be cryptic unless they are introduced into a population or species naive to the driver.

(b) Molecular origins of drivers

The molecular identities of loci that cause meiotic drive are unknown in many systems. However, we find a pattern among the known systems in *Drosophila* (six partially known systems among the 19 identified, see electronic supplementary material, table S1): most of these drivers originate in gene duplication events. Meiotic drivers correspond to duplicated genes in the *SD* system of *D. melanogaster* [8], Winters SR system of *Drosophila simulans* [12] and a similar origin is suspected in an SR system in *Drosophila neotestacea* [13]. Newly duplicated genes are often deleterious due to a dosage imbalance, while their redundancy also allows them to evolve a new beneficial function (neofunctionalization). In the case of drive systems, some duplicated genes can become selfish and survive despite having a fitness cost (figure 1a). Many known suppressors of drive also originated from gene duplications [14,15] (figure 1b). Nearly all known meiotic drive systems in *Drosophila* involve gene duplication, with one exception in *Drosophila pseudoobscura*, where a meiotic drive locus (*Overdrive*) arose from a rapidly evolving single copy gene [16]. While gene duplication is a common theme among drive systems, the genetic basis of drive is often more complex, and involves epistatic interactions among multiple loci [7,17].

3. Cytological defects during spermatogenesis

There are two categories of drivers: those that induce meiotic failure and those whose defects are observed at post-meiotic stages (electronic supplementary material, table S1). The cytological phenotype of the Paris SR system in *D. simulans* is one of the best described. In SR males, the first cytological defects occur during meiosis as aberrant segregation of the Y chromosome during anaphase II. In some cases, the two Y chromosome sister chromatids migrate together to the same meiotic spindle pole. In other cases, they appear stretched between the poles, the two daughter nuclei remain connected by a chromosome bridge and the resulting spermatids fail to elongate [18]. Meiotic defects also occur in *D. pseudoobscura* and *Drosophila athabasca* SR males, where the Y chromosome 'degenerates' during anaphase II, appearing as a chromatin mass with no centromeric activity [19]. Finally, meiotic defects are inferred when SR males give rise to XO sons (lacking a Y chromosome and usually sterile) in *Drosophila subobscura* [20] and *D. paramelanica* [4].

In other *Drosophila* drive systems, the observed cellular defects are post-meiotic and occur as spermatids differentiate into mature sperm. In the *D. simulans* Winters SR system, half

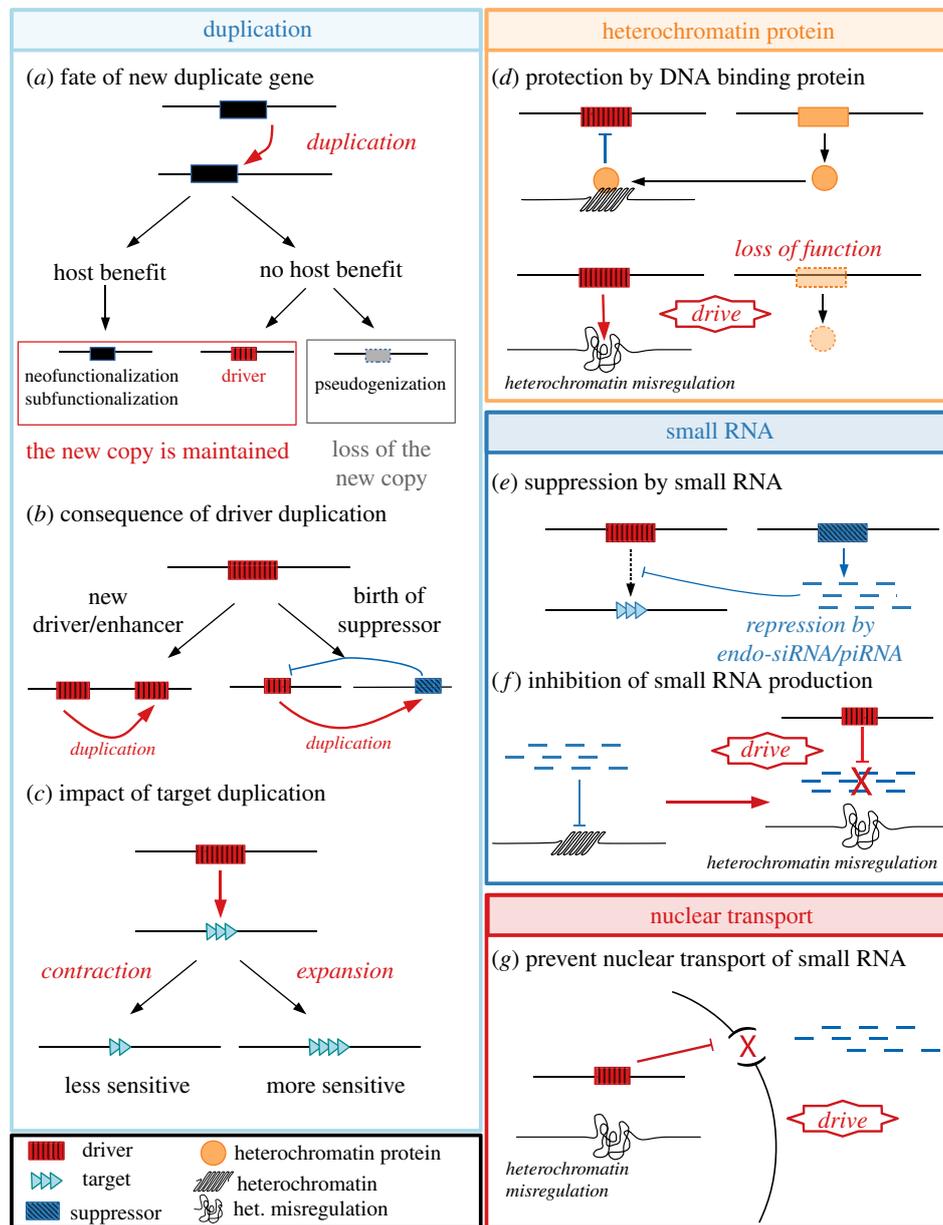


Figure 1. The schematics in the left panel show how duplication events can contribute to meiotic drive system evolution: (a) a duplicated gene can give rise to the emergence of a new driver; (b) driver duplication could give rise to a new driver/enhancer or to a suppressor element; (c) repetitive targets can expand or contract, which could affect their sensitivity to the driver. The schematics in the right panel show the different mechanisms involved in drive: (d) heterochromatin-binding proteins can protect the target from the driver. Small RNAs can be involved in drive in multiple ways: (e) they can be suppressors of drive; (f) the misregulation of small RNAs can induce drive directly; or (g) disrupted nuclear transport can prevent the proper processing or targeting of small RNAs. (Online version in colour.)

of the early spermatids (inferred to be Y-bearing sperm) display a nuclear condensation defect [12]. Defects during spermatid differentiation are also observed in *D. affinis* [21] and *D. neotestacea* [13]. In *D. melanogaster* males heterozygous for *SD*, about half of the post-elongation spermatids show defects in chromatin condensation [22] and the histone-to-protamine transition [23].

It is important to note that the stage at which cytological defects are observed can differ from when the driver acts. For example, while defects occur during meiosis II in the Paris SR system, the driver is only expressed in spermatogonia [17]. In *D. melanogaster*, although the first visible defects of *SD* occur post-meiosis, temperature sensitivity assays suggest that the driver acts early in meiosis [24]. However, the timing of *SD* may vary between *SD* chromosomes [25], and suppressors and drivers may differ in their timing [26,27]. Moreover,

cellular phenotypes are often highly variable [18,21]. Many drive systems are influenced by factors like temperature [24–26,28,29] or age [30–33].

4. Molecular mechanisms of drive

(a) Heterochromatin-binding proteins

The first implication of a heterochromatin protein in meiotic drive was in the *D. simulans* Paris SR system where the distortion results from an interaction between two X-linked drive loci. The first drive locus maps to a 37 kb tandem duplication containing six genes; however, the molecular identity of the causal element within this duplication is still unknown [7,34]. The second driver corresponds to *HP1D2* [17], a young and rapidly evolving member of the HP1 (heterochromatin protein

1) gene family that is involved in heterochromatin organization. *HP1D2* originated from a duplication of *HP1D/rhino* 15–22 Mya ago in the *Sophophora* subgenus [35]. *HP1D2* is expressed in premeiotic male germ cells and specifically binds the Y chromosome, which is entirely heterochromatic in *D. simulans*. The Paris SR system requires both the tandem duplication and a dysfunctional allele of *HP1D2* to drive. This suggests that *HP1D2* prepares the Y chromosome for meiosis (figure 1d). Heterochromatin-binding proteins, including rhino, are essential for the regulation of some piRNA clusters in *D. melanogaster* ovaries [36]. *Rhino* has strongly female-biased expression, primarily in the germline [37]. PiRNA regulation is not well understood in the male germline; however, it is possible that *HP1D2* plays a role. The other drive locus in the Paris SR system (the duplication) contains part of *Trf2*, a core transcription initiation factor that interacts with rhino to facilitate piRNA cluster expression in *D. melanogaster* [7,38]. Both the deletion of *HP1D2* and duplication of *Trf2* support the hypothesis that the piRNA pathway is involved in the Paris SR system (figure 1f).

(b) Small RNA pathways

The role of small RNAs in drive is well studied in the *D. simulans* Winters SR system, where the duplication of the X-linked driver called *Dox* gave rise to an autosomal suppressor called *Nmy* [12]. *Nmy* makes a hairpin RNA (hpRNA) that is processed into endogenous short-interfering RNAs (endo-siRNAs) that target the driver [14]. Similarly, another autosomal suppressor of the *D. simulans* Durham SR system, *Tmy*, encodes an hpRNA targeting the Winters X-linked driver [14], which suggests that these two *D. simulans* SR systems may not be independent. The *Stellate* system is suspected to be a cryptic drive system in *D. melanogaster* [39] (but see [40]). *Stellate* (*Ste*) is an X-linked multicopy gene whose product, if left unsuppressed, leads to the accumulation of crystal-like structures in testes premeiotic germ cells [41]. *Suppressor of Stellate* (*Su(Ste)*) is a multicopy Y-linked gene family paralogous to *Ste*. *Su(Ste)* loci generate small Piwi-interacting RNAs (piRNAs) that suppress *Ste* [42]. *Ste* and *Su(Ste)* independently amplified to high copy number on the X and Y chromosomes, respectively [43]. Deletions of the Y-linked *Su(Ste)* region cause low fertility or sterility in males, depending on the X-linked *Ste* copy number, and also have skewed sex ratios towards female offspring [44]. However, it is unclear whether the deletion of the *Su(Ste)* region itself or the overexpression of *Ste* causes the meiotic drive [40]. In both the Winters and *Stellate* systems, small RNAs generated from duplications of the driver suppress drive, but through different silencing pathways (piRNA and endo-siRNA, respectively, figure 1e). Interestingly, mutations in piRNA pathway genes enhance drive in the *SD* system of *D. melanogaster* [45], suggesting that piRNAs may also be involved in this drive system.

(c) Nuclear transport

One of the best-studied autosomal drive systems, *SD* in *D. melanogaster*, may involve a nuclear transport defect. The driver is a truncated duplication of *Ran GTPase Activating Protein* or *RanGAP* (the driver is referred to as *Sd-RanGAP*). *Sd-RanGAP* is missing a nuclear export signal (NES) site and a SUMO domain [46] and thus is mislocalized to the nucleus [47]. Normally, the cytoplasmic localization of *RanGAP* and the nuclear localization of its corresponding guanine

nucleotide exchange factor *RanGEF* (or *RCC1* in *Drosophila*) are critical for establishing the *Ran* gradient. The *Ran* gradient controls many important cellular processes from nuclear transport of proteins and some RNAs, to nuclear envelope assembly, and heterochromatin formation [48]. Interestingly, both the overexpression of wild-type *RanGAP* [49] and multiple copies of an unknown enhancer can cause *RanGAP* mislocalization and drive even in the absence of the *Sd-RanGAP* duplication [49,50]. The catalytic activity of *Sd-RanGAP* is required for drive, and the drive phenotype is rescued by overexpressing *RanGEF* or *Ran* [47], suggesting that drive is a result of disrupting the *Ran* gradient, perhaps due to defects in nuclear transport. Nuclear transport is also implicated in *D. neotestacea*, where an X-linked duplicated copy of *importin- α* is overexpressed in SR males and is a promising candidate for the driver [13].

As nuclear transport is important for both small RNA pathways and the histone-to-protamine transition in spermatogenesis, perturbations could lead to the chromatin condensation defects found in several drive systems (figure 4a). In the case of *SD*, the target is a pericentromeric satellite repeat, which produces small RNAs [45]; however, it is still unclear how *Sd-RanGAP* interacts with the satellite repeat. It is possible that the production of small RNAs coming from the target is disrupted (figure 1f). Alternatively, dysfunctional nuclear transport may interfere with heterochromatin regulation by preventing some critical RNAs or proteins from interacting with their target (figure 1g). These possibilities are not mutually exclusive.

5. Consequences of drive

(a) Deleterious effects of drivers

While meiotic drivers gain an evolutionary advantage by biasing their own transmission rate, they are inherently deleterious to the host genome. Because of the loss of Y-bearing sperm, driver males produce about half the functional sperm of non-driver males [51–54]. The impact on male fertility can be proportionally greater than sperm loss, especially for species with multiple mating and sperm competition [53,55–57]. Another consequence of SR drive is that abnormal segregation of the Y chromosome can lead to the production of XO males, which are sterile. This occurs in *D. simulans* [18], *D. pseudoobscura* [58], *D. paramelanica* [4], *D. testacea* [59] and *D. neotestacea* [60]. There is one known exception in *D. affinis*, where XO males are fertile and produce only sons [21,61] in the presence of SR, suggesting that the production of XO males in this species is associated with a resistance mechanism. Besides fertility costs, the fixation of SR meiotic drivers may result in extreme scarcity or complete loss of one sex and therefore the extinction of the population [10].

(b) Arms races via rapid evolution or gene duplication

In most cases, suppressors that counteract drivers should be favoured by natural selection, as they restore host fitness and/or re-balance skewed segregation [10]. However, drivers that overcome suppression will quickly spread in the population and the reduction in host fitness will subsequently lead to selection for mutations that re-establishes suppression, and so on.

Arms races are expected to occur between loci with antagonistic relationships. The clearest case is in the co-amplification

Box 1. Female drive systems.

The asymmetry in female meiosis presents an opportunity for conflicts, as only one of the four meiotic products becomes the egg. Centromeres can be selfish and gain a transmission advantage during female meiosis, biasing their segregation to the egg side of the spindle pole. There are parallels between male and female drive systems—they both seem to involve gene duplications, heterochromatin and heterochromatin-binding proteins. Female drive in plants and animals fit into two categories:

- (1) True centromere drive where centromeres compete based on ‘strength’ [85,87]: differences in satellite repeats in and near the centromeres can take advantage of a spindle asymmetry in female meiosis [88] to achieve biased segregation [86,87,89].
- (2) Driving mutations outside the native centromeres: one of the best-studied cases of female drive is of large heterochromatic ‘knobs’ consisting of tandem repeats on maize chromosomes. On abnormal chromosome 10, a non-recombining region at the distal tip of the chromosome contains a locus that converts its knobs into meiotic drivers that cheat by moving towards the spindle pole faster than their homologues [90] resulting in their biased segregation [91,92]. The causal locus is a multicopy gene called *Kinesin driver* (*Kindr*) that localizes to the knobs and facilitates their accelerated movement [93].

of a pair of antagonistic mouse genes [62,63]: the X-linked multicopy genes (*Slx* and *Slx11*) and the Y-linked multicopy gene (*Sly*). *SLX/SLXL1* are activators of sex chromosome-encoded genes while *SLY* is a repressor [64]. Interestingly, knockdown of *SLX/SLXL1* in the testes causes a male-biased sex ratio, and reciprocally, knockdown of *SLY* causes a female-biased sex ratio [64]. These genes may have co-amplified as a result of a conflict over sex chromosome transmission. Increases in *Slx/Slx11* copy number lead to increases in expression that could overcome *Sly*-induced repression, thus favouring X chromosome transmission. Increases in *Sly* copy number would either restore sex ratio or distort transmission in favour of the Y chromosome. The sex chromosomes of primates, cats and pigs also have multicopy genes [65–68], which could have resulted from similar conflicts. Similar systems exist in *Drosophila* species such as the *Ste* and *Su(Ste)* loci in *D. melanogaster* [39,69] (figure 1*b*). On the neo-sex chromosomes of *D. miranda* [70], some neo-Y genes are more highly amplified, resulting in a neo-Y chromosome nearly twice the size of their homologous neo-X chromosome. Neo-sex chromosomes are generally more gene-rich than ancient sex chromosomes, and therefore may be hot spots for drivers and their suppressors.

Recurrent positive selection on drivers and suppressors are likely consequences of arms races. In *D. melanogaster*, both longitudinal and population genetic data suggest that *SD* chromosomes turnover rapidly, with new variants displacing old ones over short time periods [71–73]. Different *SD* haplotypes in European [73] and African populations [72,73] experienced independent selective sweeps. The target satellite repeat (*Rsp*) also evolves rapidly—the organization of the repeat suggests that they originated before the divergence between *D. melanogaster* and the *D. simulans* clade species; however, the target of drive is missing in the *D. simulans* clade [74]. In the *D. simulans* Winters SR system, both the driver *Dox* and its suppressor *Nmy* show signatures of recurrent selection consistent with the model of repeated rounds of drive and suppression of drive [75].

Unlike the *SD* system, the targets of SR drive systems remain uncharacterized because a high repeat content makes the Y chromosome genetically intractable. Nevertheless, Y-linked repeats such as satellite DNA, turnover rapidly [76]. Being a target of drive may facilitate the rapid evolution of satellite DNA. *Rsp* copy number in *D. melanogaster*'s *SD* system correlates with drive sensitivity, where large copy number

alleles are more sensitive to drive [77]. In addition, resistant Y chromosomes are known in multiple SR drive systems [4,21,78,79]. These observations are consistent with a model where repeats are in a continuous struggle to escape or counteract drive (figure 1*c*).

Intragenomic conflicts can also cause the rapid evolution of some gene families. The *HP1* gene family is rapidly evolving, with recurrent gene gains and losses, mostly with testis-restricted expression [35,80]. One of the clearest cases is *HP1D2*, part of the Paris SR system [17]. We suspect that the initial function of *HP1D2* was to regulate Y-linked chromatin (figure 1*d*). Outside of the Paris SR system, conflict is implicated in the duplication of other *HP1* proteins. *Oxpecker* also arose from a duplication of *HP1D/rhino*, and is involved in transposable element (TE) silencing [80]. Another duplicated gene, *Umbrea*, is an *HP1B* paralogue [35] that became essential through neofunctionalization [81,82]. *Umbrea* localizes to the centromere and is involved in chromosome segregation, but in a species-specific manner, suggesting that there is coevolution between centromeric DNA satellites and duplicated genes [83]. These heterochromatin proteins share a common structure: a chromo domain, which mediates interactions with histones and a chromoshadow domain involved in protein–protein interactions. Heterochromatin proteins are central players in the centromere drive hypothesis proposed by Malik & Henikoff [84]. This model proposes that centromeres have the capacity to be selfish and bias their transmission through the female germline. Heterochromatin-binding proteins may evolve rapidly to mitigate this bias and restore parity in female meiosis [85,86] (see box 1).

Genetic conflicts induced by meiotic drivers can have strong impacts on genome evolution. These conflicts can drive the evolution of gene families [94], and leave signatures of selection that range from a genic to a chromosome scale. Examining these patterns as potential consequences of genetic conflict may lead to the identification of new cryptic drive systems.

(c) Hybrid incompatibility

The meiotic drive theory of hybrid incompatibility [95] posits that the observed bias of hybrid disruption towards the heterogametic sex, known as Haldane's rule, may result from the expression of divergent cryptic meiotic drivers that become unsuppressed in the hybrids. The arms race between

drivers and suppressors may fuel the divergence between species and contribute to hybrid male sterility. This idea is the subject of active debate and has long suffered from a lack of empirical data (summarized in [96]).

The first direct link between incompatibilities and drive came from *D. pseudoobscura pseudoobscura* and *D. pseudoobscura bogotana*, two subspecies that diverged 155–230 Kya [97]. Hybrid males between *D. p. pseudoobscura* males and *D. p. bogotana* females are nearly sterile and produce progeny that are almost all daughters [98]. Both phenotypes are caused by a single X-linked testis expressed gene, *Overdrive*, which encodes a polypeptide with an MADF DNA-binding domain [16]. Interestingly, another MADF domain-containing protein (HMR, for hybrid male rescue) is involved in a different hybrid incompatibility between *D. melanogaster* and sibling species [99]. In *D. p. bogotana*, *Overdrive* has autosomal suppressors not present in *D. p. pseudoobscura*, leading to de-repression of the driver in hybrids [98]. The QTL mapping of loci involved in sterility and segregation distortion revealed that both phenotypes share similar genetic basis [100]. Similarly, overlapping QTLs for hybrid incompatibility and meiotic drive were found between *D. albomicans* and *D. nasuta* [15] and *D. persimilis* and *D. pseudoobscura* [101].

In *D. subobscura*, the frequency of the SR chromosome is around 15–20% in a North African populations, but they are almost absent in a South European population [102,103]. The variation in SR frequency could be due to hybrid incompatibility [103]. This hypothesis was recently supported by Verspoor *et al.* [104] in an independent genetic background, suggesting that hybrid male incompatibility prevents the spread of SR between the North African population and the European population.

Cryptic drive systems are well studied in the *D. simulans* clade in the context of hybrid incompatibilities. Introgression of the *D. mauritiana Tmy* locus, an autosomal suppressor of the *D. simulans* Durham SR system, into a *D. simulans* background causes both meiotic drive and male sterility when homozygous [105]. Meiklejohn *et al.* [106] identified an unknown cryptic X-linked driver in *D. mauritiana* that induces SR distortion in a *D. simulans* genetic background. However, they also detected a recent introgression of *D. simulans* cryptic drivers, *Dox* and *MDox* into *D. mauritiana*, causing a local reduction in interspecific divergence, which impedes the evolution of hybrid sterility [106]. This case presents an alternative outcome of meiotic drive in the presence of gene flow for complex speciation events.

6. Conclusion: emerging themes in meiotic drive mechanisms

When we compare the key players and phenotypes involved in male meiotic drive systems across *Drosophila*, we see common themes emerge, suggesting that drivers may target similar processes in spermatogenesis. Known drive phenotypes appear to be associated with heterochromatin formation, either by targeting heterochromatic sequences directly (e.g. *SD* in *D. melanogaster*) or by involving heterochromatin-binding proteins (e.g. Paris SR of *D. simulans*). The three drive mechanisms that we reviewed here—heterochromatin regulation, small RNA pathways and nuclear transport—are inter-dependent [38,107]. These complicated interactions make it difficult to disentangle the causes and consequences

of meiotic drive. Considering how these pathways are connected may provide more insight into how meiotic drivers may have shaped the evolution of conserved germline features and pathways.

Germlines have defence mechanisms against selfish genetic elements. Most widely known are the RNA interference pathways that use small RNAs (e.g. endo-siRNAs and piRNAs) to target TEs. These small RNA pathways are well studied in the *D. melanogaster* female germline [108] but poorly understood in males, where many small RNAs are not TE-derived. Cryptic drive systems in *Drosophila* species involve suppressors that generate small RNAs, for example, the hpRNAs that generate endo-siRNAs in *D. simulans* [14,29] and the piRNAs that suppress a cryptic X-linked driver in *D. melanogaster* [108]. It is possible that one common function of small RNA pathways in the male germline is to suppress meiotic drivers.

Small RNAs need to reach their target genetic elements for silencing, and proteins that make up or interact with the nuclear pore are important for piRNA production [109–111]. Nuclear pore complexes are the gatekeepers controlling what enters and exits the nucleus [112]. Processes that mediate the transport across the nuclear pore can end up at the centre of conflicts between, for example, pathogens (reviewed in [113]), TEs (e.g. [114]) and meiotic drivers [115,116]. These conflicts may trigger the rapid evolution of nuclear pore complex proteins [116] that can cause hybrid incompatibilities between closely related species [117]. In this way, meiotic drive may have consequences for species divergence and speciation.

The evidence from across *Drosophila* drive systems connecting heterochromatin regulation, small RNAs and nuclear transport pathways suggests that selfish genetic elements may expose common vulnerabilities in spermatogenesis. While their mechanisms differ, male and female drive systems have interesting parallels. For example, gene duplication and heterochromatin-binding proteins also feature in plant female drive systems (see box 1). Studying molecular mechanisms of drive in both males and females may lend insights into some basic features of gametogenesis.

This review is focused on the *Drosophila* genus, as most known male drive systems occur in fruit flies. However, this enrichment is likely to be, at least in part, due to ascertainment bias because of the rich history of *Drosophila* genetics research in the past century. Meiotic drivers have been discovered in a wide range of organisms, suggesting that they may be pervasive, but cryptic, or go undetected without any obvious phenotypic effect. *Drosophila* are powerful models for studying drive systems and their mechanisms. Advances in long-read sequencing and genome editing technologies provide opportunities to extend these studies to new systems [94,118].

Data accessibility. This article has no additional data.

Competing interests. We declare that we have no competing interests.

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