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Epigenetics drive the evolution of sex chromosomes in animals and plants

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We review how epigenetics affect sex chromosome evolution in animals and plants. In a few species, sex is determined epigenetically through the action of Y-encoded small RNAs. Epigenetics is also responsible for changing the sex of individuals through time, even in species that carry sex chromosomes, and could favour species adaptation through breeding system plasticity. The Y chromosome accumulates repeats that become epigenetically silenced which leads to an epigenetic conflict with the expression of Y genes and could accelerate Y degeneration. Y heterochromatin can be lost through ageing, which activates transposable elements and lowers male longevity. Y chromosome degeneration has led to the evolution of meiotic sex chromosome inactivation in eutherians (placentals) and marsupials, and dosage compensation mechanisms in animals and plants. X-inactivation convergently evolved in eutherians and marsupials via two independently evolved non-coding RNAs. In *Drosophila*, male X upregulation by the male specific lethal (MSL) complex can spread to neo-X chromosomes through the transposition of transposable elements that carry an MSL-binding motif. We discuss similarities and possible differences between plants and animals and suggest future directions for this dynamic field of research.

This article is part of the theme issue 'How does epigenetics influence the course of evolution?'

1. Introduction

Sex chromosomes are a special pair of chromosomes that evolve from autosomes after acquiring sex-determining genes [1,2]. In male heterogametic systems, males are XY and females XX, while in female heterogametic systems females are ZW and males ZZ. The evolution of sex chromosomes at the genetic level has been well characterized in various groups. We know that sex chromosome differentiation initiates when recombination stops between the X and the Y in a region that surrounds the sex-determining genes. The X chromosome can then still recombine in females, but the Y chromosome acquires a non-recombining region that can increase in size through time, with adjacent regions ceasing to recombine. This Y non-recombining region is typically surrounded by recombining regions that are called pseudoautosomal regions (PAR). The lack of recombination of the Y leads to genetic interferences between linked alleles of the Y, which are transmitted as a block from one generation to the next. Beneficial and deleterious mutations on the Y are tightly linked, making it harder for selection to filter deleterious Y mutations from populations. These phenomena are called Hill–Robertson inferences [2,3]. Here, we take a step beyond genetics to review how epigenetics can take an active part in sex chromosome evolution in plants and animals.

Epigenetics encompass all chemical modifications of the DNA or chromatin that affect the accessibility of the DNA and gene expression [4]. Open chromatin,

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also called euchromatin, allows gene expression and is typically defined by active histone marks, whereas heterochromatin is formed of silenced, compacted and inaccessible DNA marked by DNA methylation and/or repressive histone marks. It has long been known that epigenetics plays an important role in sex chromosome biology, since the Y chromosome is heterochromatinized in many species and in eutherians (placentals), one of the two Xs is inactivated through heavy heterochromatinization and called the Barr body [5]. We review all typical aspects of sex chromosome evolution but focus on the role of epigenetics in sex chromosome evolutionary processes. We start by reviewing how epigenetics can determine the sex of individuals in a few species that carry sex chromosomes. We also consider the potential role of epigenetics in sex lability. We then look at how repeat accumulation causes heterochromatinization of the Y and leads to epigenetic conflict and Y toxicity. In some mammals, the sex chromosomes are epigenetically silenced during meiosis. We detail the evolutionary origin of this phenomenon and its potential underlying causes. Finally, we consider the epigenetic evolution of dosage compensation in species that have a chromosome-wide mechanism to balance gene expression between the sexes and between sex chromosomes and autosomes.

2. The epigenetics of sex determination

Separate sexes (gonochorism for zoologists) is found in about 95% of animal species [6,7]. By contrast, there are approximately 5–6% of angiosperms species (flowering plants) with male and female individuals (a situation termed dioecy by botanists) [8]. Hermaphroditism (where individuals carry bisexual flowers) is the most common sexual system in plants, but dioecious plants, despite being a minority, still represent greater than 15 000 species, which is more than the number of mammals, birds or amphibians. While dioecy has repeatedly evolved from hermaphroditic ancestors in plants, gonochorism evolved in the ancestor of all animals and hermaphroditism is a derived state [6,8,9]. In animals, the type of sex determination (environmental or genetic with or without sex chromosomes) is known for over 90% of the species. However, in plants this information is available for only approximately 3% of species [10,11]. In all plants with a known sex determination mechanism, sex is determined by sex chromosomes [12]. Because dioecy is often recent, most of these sex chromosomes have evolved recently. We will limit this review to the cases of sex determination in gonochoristic animals and dioecious plants with sex chromosomes.

(a) The epigenetics of sex lability

In most animal groups, individuals are either born male or female, and sex is often determined by sex chromosomes (such as in mammals). Some groups, however, show extraordinary sexual plasticity, changing sex naturally as part of their life cycle or reversing sex because of environmental stimuli [10]. In some fish species, for example, the sexual fate of an individual can be determined by chromosomes, the environment (temperature, population density), or through a combination of the two, and environmental stimuli often override genetic factors to redirect sexual fate [13].

Epigenetic modifications have been linked to sex determination and sex change in several fish species [13]. One of the best-studied examples of epigenetic regulation of sexual development is in the flatfish half-smooth tongue sole (*Cynoglossus semilaevis*) [14]. This species has a relatively young ZW sex-determination system (approx. 30 Myr old), but shows high rates of sex reversal. In particular, approximately 14% of genetic females (ZW) are reversed to phenotypic males (ZWm pseudomales) under normal temperature conditions, and exposure to higher temperatures during development increases the sex reversal rate to approximately 73% [14]. Differentially methylated regions between testis and ovary are enriched for genes in the sex-determining pathway, and methylation patterns in pseudomales (ZWm) resemble those of true males (ZZ). ZWm pseudomales are fertile, and their ZW offspring exhibit an extremely high reversal rate (approx. 94% ZWm pseudomales) at normal temperatures, and methylation patterns of pseudomales are accurately transmitted to their offspring [14]. These results indicate that environmental sex reversal can override sexual fate determined by genetic factors through epigenetic regulation.

In dioecious plants, an intriguing observation is the existence of naturally occurring hermaphrodite mutants at very low frequency in natural populations, even in species in which dioecy is millions of years old (a phenomenon known as 'sex leakiness' [15]). In many cases, these hermaphrodites are modified males, also called inconstant males capable of producing seeds [15]. In fewer cases, inconstant females are capable of producing pollen [16,17]. For example, in *Silene latifolia*, a dioecious plant with an 11 Myr old XY chromosome system, such a rare hermaphrodite has been studied and found to carry a Y chromosome [18]. It remained; however, unclear whether epigenetic mechanisms were implicated in this particular case, or whether this mutant was owing to a genetic mutation. In the closely related diecious species *Silene dioica*, spontaneous and heritable androhermaphroditism is more frequent (somewhat less than one in a thousand individuals) [19] than in *S. latifolia*, supporting the view that epigenetic mechanisms may be involved in the control of the stability of sexual phenotype, at least in some plants.

This situation is quite different from that in animals, where in many groups mutant hermaphrodites produce either sperm or ovule but not both (or are sterile). Sex reversal is also common in plants, and sometimes in the same plant, individual sex reversion and counter sex reversion can be observed on different branches [20]. These reversions and sex leakiness suggest that epigenetics could potentially play an important role in plant sex determination as it is typically more maleable than genetics.

Indeed, it has been known for a long time that plant sex determination can be influenced by epigenetics, even in species with documented sex chromosomes. When treated with a demethylating agent (5-azacytidine), *S. latifolia* XY males turn into andromonoecious individuals carrying both male and bisexual flowers instead of just male flowers [21]. This sex leakiness was mapped to the Y chromosome [22]. This result has recently been confirmed using zebularine, another DNA-hypomethylating drug [23]. This epigenetic state can then be passed to the next generation from father to sons only. Although the precise mechanism of this sex leakiness has not been identified, it suggests that sex determination is partly controlled by Y DNA methylation in *S. latifolia*. There are a number of other cases where the exogenous application of drugs or

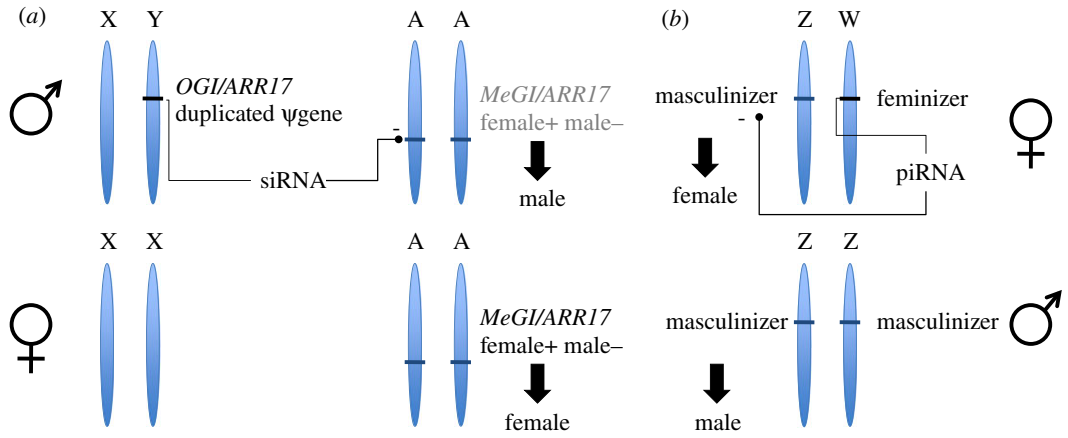

Figure 1. Epigenetic mechanisms of sex determination in animals and plants. (*a*) In persimmons and poplars. (*b*) In silkworms. In all cases, sex-specific non-coding RNAs encoded by the Y or W chromosome regulate gene expression of genes located elsewhere in the genome (either on autosomes, on the pseudoautosomal region or on the X/Z) and determine the sex of individuals (see text for details).

hormones have been shown to change plant sex, suggesting that sex determination is influenced by epigenetics [24–26].

The existence of sex leakiness and inconstant males and females may have profound effects on plant population dynamics [15,27,28]. Hermaphrodites can be efficient colonizers thanks to their capacity to self-fertilize, unlike dioecious plants which need the proximity of an individual of the opposite sex and therefore cannot reproduce in low-density populations [29,30]. However, self-fertilization has negative consequences on plant fitness owing to inbreeding depression [31]. Therefore, it could be advantageous for dioecious plants to switch their sexual systems to hermaphroditism in low-density populations at the borders of their geographical range or during range expansion [28]. Once population density gets high enough, obligatory outcrossing through separate male and female individuals could be advantageous [32]. If reversions from dioecy back to hermaphroditism are frequent in angiosperms, they might explain why dioecy is so rare [28]. Epigenetics is likely to play a crucial role in this lability of plant sexual systems.

(b) The epigenetic mechanism of sex determination in selected animals and plants

For a long time, no sex-determining genes were known in dioecious plants. The situation has dramatically changed since 2014 thanks to the development of specific methods to sequence and assemble sex chromosomes [33,34]. The first dioecious plant sex-determining gene was identified in persimmons [35–37]. *OGI* (the Japanese for 'male tree') promotes maleness and inhibits femaleness at the same time. Interestingly, *OGI* is a non-functional duplicated version of the autosomal gene *MeGI* (the Japanese for 'female tree'). *OGI* produces small interfering RNAs (siRNA) that target *MeGI* and inactivate it (figure 1*a*), providing evidence for a direct role of epigenetics in determining sex in persimmons.

In willows and poplars, a single gene *Arabidopsis response regulator 17* (*ARR17*) that promotes femaleness and inhibits maleness has also been identified [38,39]. Some species have ZW chromosomes, and in this case, *ARR17* is only present on the W—the female-determining chromosome. In other species that have XY chromosomes, a mechanism similar to the *OGI-MeGI* system has evolved: Y-linked non-coding duplicates of *ARR17* lead to the inhibition of the autosomal or pseudoautosomal copy of *ARR17* through siRNA (figure 1*a*). The formation of *ARR17* partial duplicates was probably facilitated by repeated translocations of a Helitron-like transposon [40].

Interestingly, a very similar mechanism also convergently evolved in the silkworm *Bombyx mori*. This species' W chromosome harbours a strong feminizing factor called *Feminizer* (*Fem*) [41]. Cloning of this factor revealed that it is a precursor of a female-specific W-derived PIWI-interacting RNA (piRNA). The *Fem*-derived piRNA triggers cleavage of mRNA of the Z-linked *Masculinizer* (*Masc*) gene, which encodes a protein required for both masculinization and dosage compensation (figure 1*b*).

In plants, dioecy is thought to originate from hermaphroditism through two main pathways: the gynodioecy pathway, in which there is a gynodioecious intermediate (species with both females and hermaphrodites) and the monoecy (or paradioecy) pathway, in which the intermediate is monoecious (species having both female and male flowers on the same plant) [42]. Theory indicates that the gynodioecy pathway should proceed with two successive mutations on two different genes, a male-sterile mutation producing females and a female-sterile mutation producing males [43,44]. No population genetic model has been developed for the monoecy pathway. It is possible that dioecious plants which evolved through the monoecy pathway depend more on epigenetics for sex determination than dioecious plants evolved through the gynodioecy pathway. Indeed, in a monoecious plant, two types of flowers can be produced, either male or female. It seems reasonable to expect that the evolution of separate male and female individuals (dioecy) from monoecious plants would only require a slight change in the regulation of the gene network already in place that controls the spatially separated development of male and female flowers. The findings in persimmons, willows and poplars suggest sex determination in plants can rely on a single gene and often involve epigenetics [45,46]. Interestingly, persimmons and Salicaceae may have followed the monoecy pathway [8,47]. By contrast, two or more sex-determining genes have been found in *Asparagus*, date-palm, grapes, kiwifruit and strawberries [48–55], and these species may have followed the gynodioecy pathway [8,47]. Therefore, it is possible that the monoecy pathway of dioecy evolution relies more on epigenetics and the gynodioecy pathway on two or more genes, but more species need to be studied to test this hypothesis.

3. The epigenetics of Y degeneration

All non-recombining regions of sex chromosomes accumulate repetitive sequences: transposable elements (TEs) and tandem repeats such as satellites [2]. Repeat accumulation happens even in recently evolved sex chromosomes [56–58]. This is probably a consequence of recombination suppression which (i) lowers the efficacy of selection owing to Hill–Robertson interferences, and (ii) prevents the deletion of TEs through ectopic recombination [59].

The movement of transposable elements can lead to insertional mutations and genomic instability, and epigenetic silencing of repeats ensures that their deleterious consequences are minimized [60]. Repetitive sequences are usually silenced by DNA methylation and/or histone modifications and are the source of multiple evolutionary changes in sex chromosomes. For example, repeats cause the heterochromatization of the Y chromosome and contribute to the morphological diversification of sex chromosomes, called sex chromosome heteromorphy. Repeat accumulation can also change the epigenetic balance between sexes (that is, epigenetic modifications differ between male and female), and can affect sex-specific phenotypes.

(a) Accumulation of repetitive DNA, Y heterochromatinization and recombination suppression

Accumulation of TEs and satellite DNA has been well documented in *Drosophila* thanks to neo-sex chromsomes in different species. These chromosomes are formed through fusion of a sex chromosome (either the X or the Y) to an autosome. In *Drosophila* there is no recombination in males and therefore neo-Y chromosomes instantly stop recombining and start degenerating along their entire length. *Drosophila* species containing newly evolved neo-Y chromosomes of varying age show a gradient of repeat accumulation that inversely correlates with age and the amount of gene decay. For example, the very recently formed neo-Y chromosome of *Drosophila albomicans* (less than 0.1 Myr old) has most of its ancestral genes intact. It only shows a modest increase in repeat density [56,61], but no global increase in H3K9me3, a histone modification associated with silencing heterochromatin [61]. *Drosophila miranda*'s neo-Y chromosome was formed about 1.5 Ma, and about half of its ancestral genes have become pseudogenized or lost [56,62,63]. Strikingly, it shows a drastic accumulation of transposable elements, and its neo-Y chromosome has expanded in size almost threefold compared to its homologue neo-X, which is mainly driven by the accumulation of repetitive DNA [63,64]. Repeat accumulation is associated with a global change in chromatin structure, and the *D. miranda* neo-Y shows a dramatic increase in H3K9me3 levels along its length [65,66]. Older neo-Y chromosomes, such as those of *Drosophila pseudoobscura* (greater than 15 Myr old), have lost almost all of their ancestral genes [67,68], and consist almost entirely of repetitive TE-derived and satellite DNA [67,68]. These older neo-Y chromosomes are typically entirely heterochromatic [66].

In papaya, *Rumex* and *S. latifolia*, some TEs have accumulated specifically on the Y or the X [69,70]. Older Y chromosomes seem to have accumulated more Y specific TEs compared to younger Y chromosomes, although there might be a bias in the amount of research done on different systems. These TE insertions in Y chromosomes are associated with the formation of heterochromatin in various species [70]. One exception is the large *S. latifolia* Y which is prevalently hypomethylated [71], but is nonetheless depleted of histone marks typical of active transcription [72].

It has been proposed that the accumulation of TEs might play an active role in recombination suppression [73]. Indeed, recombination initiation is inversely correlated with heterochromatin and DNA methylation mutants in various organisms show increased recombination rates [73]. At a more local scale, recombination initiation sites can be disrupted by DNA methylation [73]. According to the two-gene model of sex chromosome evolution, recombination is first suppressed on the Y to avoid recombination between the recessive male sterility and the dominant female sterility loci because it would otherwise generate sterile individuals [44]. After this initial recombination suppression, TEs are expected to accumulate owing to the reduced efficacy of selection through Hill–Robertson interference. Silencing of these TEs might then directly lead to recombination reduction, owing to the antagonism between recombination initiation and heterochromatin. Until now, the sexually antagonistic hypothesis had been the favoured hypothesis to explain the spread of recombination suppression along the Y. It relies on the accumulation of mutations that are beneficial for males and deleterious for females on the Y to drive further recombination suppression [74,75]. However, if indeed TE accumulation alone can cause recombination suppression through the formation of heterochromatin, this phenomenon could explain the spread of recombination suppression along the Y. Future investigation of recombination rates in TE silencing mutants in species with sex chromosomes will allow us to test this hypothesis [73].

(b) Y chromosomes and heterochromatin sinks

Recent studies in *Drosophila* have shown unexpected consequences of heterochromatin accumulation on Y chromosomes [66,76,77]. Old Y chromosomes often consist almost entirely of repetitive DNA and may act as epigenetic sinks that sequester heterochromatin components [78,79]. Indeed, the fully heterochromatic Y chromosome of *Drosophila melanogaster* harbours only a handful of genes but affects the gene expression of thousands of genes, probably by acting as a heterochromatin sink, which could lead to a genome-wide redistribution of chromatin marks [80,81]. In *D. melanogaster*, sex is determined by the ratio of X chromosomes to autosomes, which allows for the generation of males that lack a Y chromosome (X0 males) and females that harbour a Y (XXY females) [82]. Direct evaluation of the heterochromatin landscape between *D. melanogaster* males and females that differ in their sex chromosome karyotype (XX and XXY females, and XY, X0 and XYY males) showed that additional Y chromosomes indeed sequester heterochromatin components, which resulted in reduced levels of heterochromatin along other repeat-rich regions in the genome [76]. Intriguingly, a large number of genes that are differentially expressed between wild-type males and females of *D. melanogaster* are also differentially expressed between wild-type XY males and X0 males, or wild-type XX females and XXY females [76]. This suggests that sex-specific expression differences can simply result from global differences in the epigenome between sexes [76].

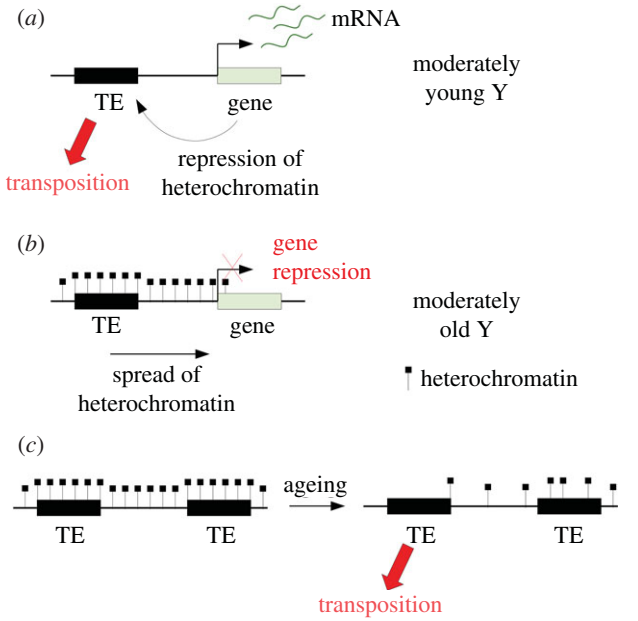

Figure 2. Epigenetics of Y degeneration and Y toxicity. (*a*) In moderately young Y chromosomes, numerous actively transcribed genes prevent the formation of heterochromatin on nearby TEs. This may lead to active TE transposition. (*b*) In moderately old Y chromosomes, few Y genes are surrounded by TEs. Heterochromatin marks spread to genes and prevent their expression, leading to further Y degeneration. (*c*) Heterochromatin marks get lost through ageing leading to active transposition of TEs. This phenomenon will be particularly prevalent in males with a Y chromosome and lead to Y toxicity. (Online version in colour.)

(c) Repetitive DNA and epigenetic conflict on the Y

Evolving Y chromosomes, i.e. those that still contain an appreciable number of ancestral genes but also a high repeat content (such as the neo-Y of *D. miranda*) may face a unique challenge: functional genes still need to be transcribed, while adjacent repeats need to be epigenetically silenced. Active transcription is known to antagonize the formation of silencing heterochromatin [83], and these competing forces may create a conflict between genic expression and TE silencing on a nascent Y [66] (figure 2*a*). Indeed, the comparison of TE expression in two *Drosophila* species with neo-Ys of different ages and different levels of degeneration supports the idea of an epigenetic conflict on evolving Y chromosomes [66]. The younger neo-Y of *D. miranda* is gene- and repeat-rich [63,64], while the older neo-Y of *D. pseudoobscura* consists almost entirely of repeats with only a handful of genes [67,68]. Heterochromatin is established during early embryogenesis in *Drosophila*, simultaneously with genome-wide activation of zygotic genes [84,85]. Males of both species show a surge of expression of Y-linked TEs during very early embryogenesis [66]. As heterochromatin starts to mature, *D. pseudoobscura* males (which have an old neo-Y) successfully suppress their Y-linked TEs, while *D. miranda* males (which have a young neo-Y) are ineffective to suppress their Y-linked TEs throughout development [66]. The expression of adjacent neo-Y genes was shown to impede heterochromatin formation and silencing of neo-Y linked TEs in *D. miranda*, resulting in elevated TE expression in males relative to females [66] (figure 2*a*). Higher levels of TE expression in *D. miranda* males was found to result in increased rates of somatic TE movement in males, suggesting that the neo-Y creates a mutational burden in males [66]. Epigenetic conflicts on evolving Y chromosomes may select for adaptive degeneration of remaining Y genes, to allow proper TE silencing and reduce the mutational burden of the Y chromosome.

In plants, TEs are typically methylated in the three contexts (CG, CHG and CHH) owing to their targeting by the RNA-directed DNA methylation pathway which silences TE expression [86]. It is known that TE methylation can spread to nearby genes and impact their expression level [87] (figure 2*b*). This phenomenon could be particularly prevalent on the Y chromosome. Indeed, in *S. latifolia* several Y-linked genes having a lower expression level than their X-linked homologues showed evidence for intronic TE insertion [88,89]. Rodríguez Lorenzo *et al.* [90] studied the methylation levels of six *S. latifolia* X/Y gene pairs to test whether Y expression degeneration is caused by the spread of nearby TE methylation. However, the results linking gene methylation and expression levels were inconclusive and data on more genes with annotated nearby TE insertions will be necessary to answer this question in plants.

(d) Y/W chromosome toxicity

Heterochromatin is established in early embryos to safeguard the genome, but studies in diverse organisms—ranging from yeast, to worms, flies and mammals—have shown that ageing is associated with a loss of heterochromatin [91–93]. Age-associated heterochromatin loss can result in an increase in TE expression and mobilization of TEs in old individuals [94,95]. Comparative studies have shown that males and females often differ in their lifespan, and the sex that contains the heteromorphic sex chromosomes often lives shorter (that is, males in species with XY sex determination and females in ZW systems) [96,97].

These observations led to the suggestion that Y chromosomes may be 'toxic', and contribute to a shorter lifespan in males [96,97]. A direct link between faster ageing, heterochromatin loss and the presence of a Y chromosome was again suggested in *D. melanogaster*: male *D. melanogaster* typically live shorter lives than females [98], and aged male flies lose H3K9me2 marks at their pericentromere and the Y chromosome to a greater extent than females [77]. This loss of heterochromatin in males resulted in an upregulation of TEs in old males but not females (figure 2*c*). Intriguingly, the introduction of a Y chromosome into females (XXY) decreased their lifespan, while males with two Y chromosomes (XYY) lived even shorter lives than wild-type males, and males without a Y (X0) outlived wild-type males [77]. This suggests that there is a direct link between the absence or presence of a Y chromosome and lifespan.

Y toxicity might differ among sex chromosome systems depending on how TE-rich the Y chromosome is. An analysis conducted on several animal species suggests that male longevity is more severely affected when the Y chromosome represents a larger part of the genome [99]. This could offer an explanation for why the Y chromosome is often much smaller than its X counterpart in old sex chromosome systems, an observation that is not well understood. In species in which male longevity is under selection and cannot get too different from that of females, deletions of large TE-rich portions of the Y chromosome might be beneficial and selected for as they will reduce Y toxicity. However, more studies will be necessary to confirm this hypothesis.

Y toxicity in plants might be worth investigating because in various species the Y chromosome is much larger than the X and potentially highly toxic (for example in *S. latifolia*, *Coccinia grandis* and *Rumex acetosa*), a situation which is much rarer in animals [12,100,101]. In other plant species, the X and the Y are usually homomorphic including in some relatively old systems [102,103]. Plants also exhibit extreme differences in longevity with herbs often being short-lived (annual or living a few years) and trees being long-lived (up to several centuries). Interestingly, sex chromosomes can be found in both herbs and trees [12]. In annual and young perennial plants, individuals might not live long enough for Y repeats to become active with age. Y toxicity might not be an issue for these species, potentially allowing the Y to expand and become larger than the X.

4. Meiotic sex chromosome inactivation

During meiosis in eutherians and marsupials, the X and Y chromosomes undergo meiotic sex chromosome inactivation (MSCI), in which most sex-linked genes are inactivated [104–108]. This process is mediated by epigenetic modifications, through chromatin condensation and heterochromatin formation, and the X and Y chromosomes are packaged into a compact structure, called the sex body [104–108]. MSCI is initiated at meiotic prophase I and is retained during late spermatogenesis, repressing most sex-linked genes during sperm differentiation. The function of MSCI is not known, but studies across the evolutionary tree are now providing clues.

(a) Meiotic sex chromosome inactivation and silencing of unpaired chromatin

Degeneration and sequence divergence of the Y or W chromosome creates a unique challenge during meiosis, when homologues pair and exchange genetic information to form crossovers. Pairing (synapsis) and recombination require a homologous template sequence, but in the case of the X or Z chromosome, no such template exists in the heteromorphic sex. Silencing of unsynapsed chromosomes has been observed in *Neurospora* [109] and *Caenorhabditis elegans* [110]. Furthermore, studies showed that in mice, unsynapsed autosomes are also silenced during meiosis [111,112]. This led to the hypothesis that meiotic silencing originated early in evolution, and that in therians the XY pair succumbed to this ancient silencing mechanism as they diverged. In eutherians [113] and birds [114], synapsis and recombination occur at the terminal PAR, thereby creating an obligatory crossover that facilitates accurate metaphase I chromosome segregation. In marsupials, no PAR exists, and the XY pair is instead thought to be tethered and segregated via a specialized structure called the dense plate [115,116]. Work in mice has shown that defective synapsis or meiotic double-strand break (DSB) repair on autosomes trigger distinct checkpoints that cause germ cell arrest [117,118]. Why the unsynapsed regions of the X/Z, or the unresolved meiotic DSBs located on them do not trigger the synapsis and recombination checkpoint remains a major unanswered question in meiosis.

However, functional studies have revealed mechanistic differences in meiotic silencing between species. For instance, meiotic silencing in *Neurospora* and *C. elegans* involves the RNAi pathway [119,120]. By contrast, it is triggered in mice by meiotic DSBs [121–123], which triggers the DNA-repair pathway to ultimately induce repressive chromatin modifications [108]. Furthermore, the DSB-dependent meiotic silencing mechanism observed in eutherians and marsupials is absent in monotremes (egg-laying mammals including platypus and echidna) and birds [124–126], indicating that it evolved after the split between monotremes and therian mammals (marsupials and eutherians, figure 3*b*). This observation means that the mechanism of MSCI evolved alongside the XY pair which is common to all therians (monotremes have a different sex chromosome system). This information implicates an XY-specific function for meiotic silencing in therian mammals.

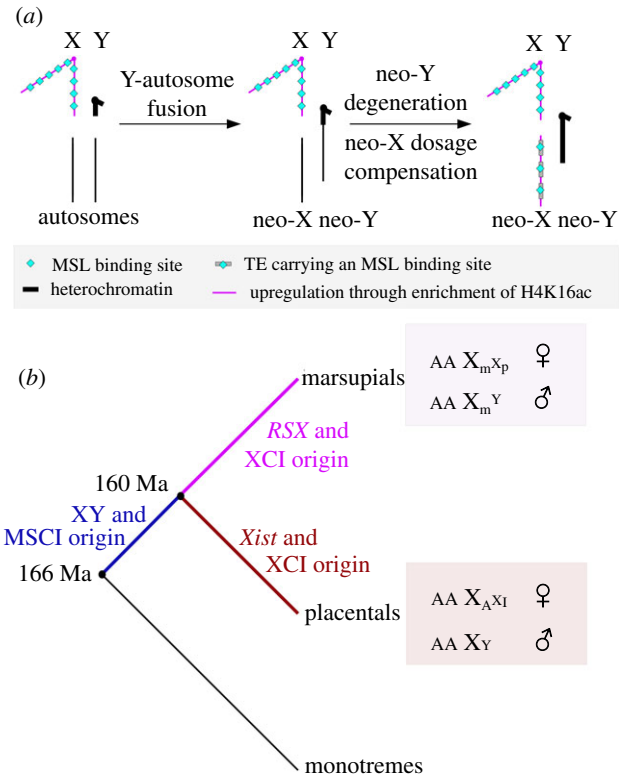

Figure 3. Evolution of the epigenetics of dosage compensation in *Drosophila* and mammals. (*a*) In *D. miranda*, the neo-X chromosome evolved dosage compensation through transposition of a TE that carries an MSL-binding site. (*b*) In mammals, XCI evolved twice convergently in eutherians and marsupials through different mechanisms relying on different ncRNA (X-inactive specific transcript (*Xist*) and RNA-on-the-silent X (*RSX*)). In marsupials, XCI is imprinted where the paternal X (X_p) is inactivated while the maternal X (X_m) is upregulated compared to the autosomes (A). In eutherians, the active X (X_A) is upregulated compared to autosomes and the inactive X (X_I) is randomly picked between X_m or X_p in most cases. However, in mice, XCI is imprinted in the preimplantation embryo and in the extraembryonic lineages (see text). (Online version in colour.)

(b) Meiotic sex chromosome inactivation as a defence against segregation distortion

One possible function for MSCI could be to control meiotic drive, the competition that promotes the transmission of one allele over another. Sex chromosomes are more likely than autosomes to experience meiotic drive, i.e. to accumulate transmission distorters [127,128]. MSCI could suppress meiotic drive by silencing the expression of XY transmission distorters, thereby retaining a balanced sex ratio in offspring. Research on the X-linked *Slx* and Y-linked *Sly* ampliconic

gene families has provided experimental evidence that perturbing XY silencing causes transmission distortion. *Slx* and *Sly* encode proteins that competitively bind to sex-linked gene promoters, with SLX promoting and SLY repressing expression [129–131]. Males deficient in *Sly* sire an excess of daughters [131], while males deficient in *Slx* sire an excess of sons [130,132]. Males deleted for both gene families sire equal numbers of females and males [130], demonstrating that *Slx* and *Sly* have mutually antagonistic properties. *Slx* and *Sly* are two of many highly amplified gene families on the X and Y chromosomes [133–135], some of which may also regulate XY silencing and transmission distortion in mice.

While old Y chromosomes in the genus *Drosophila* only harbour a handful of genes, young *Drosophila* neo-sex chromosomes often contain multiple co-amplified gene families on their neo-X and neo-Y chromosomes [136]. Detailed comparative and functional analysis of the *D. miranda* neo-sex chromosomes has uncovered about 100 different gene families that co-amplified on both its neo-X and neo-Y chromosomes [137]. These genes are highly transcribed during spermatogenesis, typically have functions related to chromosome segregation, chromatin condensation or RNAi, and generate endo-siRNAs [137]. This suggests that, similar to *Slx*/*Sly* in the mouse, co-amplified genes in *Drosophila* are involved in a conflict over sex chromosome transmission. Similar to mammals, the X of *Drosophila* is specifically inactivated in primary spermatocytes [138], but the molecular mechanisms that result in downregulation of the X are not yet understood in flies. Young *Drosophila* neo-X chromosomes are still actively transcribed during spermatogenesis [56]. These observations are consistent with the idea that MSCI evolved as a defence mechanism to silence sex chromosome drive systems [139]: sex chromosomes are a hotspot for the recurrent invasion of meiotic drivers and their suppressors, selecting for the transcriptional inactivation of sex chromosomes during spermatogenesis.

The meiotic drive hypothesis is also superior to others in explaining why MSCI occurs in therians but not birds [108]. Indeed, the opportunity for meiotic drive is greater during spermatogenesis than oogenesis because in therians, communication between the X and Y occurs throughout spermatogenesis via cytoplasmic bridges, while in birds, communication between the Z and W in oogenesis ceases at metaphase I with the formation of the polar body. In monotremes, where MSCI is absent, spermatogenesis has not been extensively characterized [140,141]. It would be interesting to establish whether monotreme male germ cells exhibit cytoplasmic bridges, and if sharing of sex-linked gene products occurs to the same extent in these species as it does in therians. If indeed MSCI evolved owing to meiotic drive, monotremes would be expected to have less meiotic drive than other mammals, maybe because of less gene product circulation through cytoplasmic bridges during spermatogenesis.

5. The epigenetics of dosage compensation

Following Y expression degeneration, males can suffer from insufficient dosage of their X-linked genes compared to females. This is expected to particularly affect X/Y genes that encode proteins which interact with autosomal proteins in large complexes [142]. In some species, this lack of expression in the heterogametic sex is compensated on a gene-by-gene basis, where only dosage-sensitive genes are balanced between the sexes. However, in a few cases, the expression of the entire X chromosome evolved to acquire dosage compensation, often through epigenetic mechanisms [143]. Several strategies have been described: upregulation of the single X in males (as found in *Drosophila* and *Anolis*), partial downregulation of both X chromosomes in females (as in *C. elegans*), or more elaborate combinations of both (as in mammals).

(a) X upregulation in insect and green anole lizard males

The mechanism of dosage compensation has been studied extensively in *D. melanogaster* and involves the upregulation of the single X in males [144]. This is achieved by a specific ribonuclear protein complex (the male specific lethal (MSL) complex) that recognizes particular sequence elements that are enriched on the X (the MSL recognition element (MRE) sites, which is a GA-rich motif), which results in global hyperacetylation of the X chromosome in males (an enrichment of the H4K16ac mark along with genes on the male X chromosome) [144]. A very similar mechanism convergently evolved in the green anole lizard where male-specific chromatin machinery leads to global hyperacetylation of H4K16 specifically on the male X chromosome [145].

Drosophila neo-sex chromosomes of different ages have allowed the study of the acquisition of dosage compensation on evolving X chromosomes [146]. Concordant with the degeneration of the neo-Y chromosomes, their former homologues, the neo-Xs, have evolved dosage compensation independently in dozens of species [146]. Neo-X chromosomes are dosage compensated by co-option of the MSL complex by acquiring new MRE binding sites to recruit the MSL complex [147,148]. The evolution of dosage compensation on newly evolved neo-X chromosomes was first studied in detail in *D. miranda*. The neo-X of this species shows intermediate levels of dosage compensation and has acquired a few hundred binding sites for the MSL complex since its formation about 1.5 Ma [147]. Intriguingly, a large number of dosage compensation binding sites were distributed along the neo-X by a TE that acquired an MSL-binding site, which allowed for the rapid evolution of dosage compensation on the neo-X chromosome of this species [147,149] (figure 3*a*).

Comparative analysis in other *Drosophila* species with independently evolved neo-sex chromosomes has shown the recurrent evolution of dosage compensation on neo-X chromosomes. Interestingly, TEs were shown to be involved in other species with high TE content to distribute MRE sites along neo-X chromosomes, while the GA-rich MSL-binding sites were gained by repeat expansions in species that contained a large number of microsatellites in their genome [148].

While dosage compensation is best understood in *Drosophila*, other Diptera species are also known to globally upregulate their X in males [150], but the molecular mechanisms by which expression levels are modulated chromosome-wide are unknown. Butterflies, where females are the heterogametic sex, also have chromosome-wide dosage compensation in many taxa [151]. A recent analysis in monarch butterflies, a species that has a recently formed a neo-Z chromosome in addition to its ancestral Z, showed an unexpected dichotomy of dosage compensation between its ancestral and neo-Z chromosome. Ancestral Z expression is downregulated by nearly twofold in ZZ males, while neo-Z

expression is upregulated by twofold in ZW females [152]. H4K16ac (the activating histone mark also enriched on the X chromosome of *D. melanogaster* males) was found to be enriched on the neo-Z in females, but depleted on the ancestral Z in males [152]. Dosage compensation also exists in many other insects (in beetles and many Diptera [150,153]), but the molecular mechanisms of how gene expression is equalized in males and females has not been identified yet.

(b) X inactivation and upregulation in mammals

Mammals are especially intriguing regarding dosage compensation, because they deploy two mechanisms to balance X to autosomal output: X-chromosome upregulation and X-chromosome inactivation. X-upregulation operates in both sexes and increases expression from the active X twofold to match that of the autosomes, while X-inactivation takes place for one X in females, equalizing the dose of X-genes with males. X-upregulation and X-inactivation occur in eutherians [154–161] and marsupials [162,163]. Neither process has been observed in monotremes [164,165], but this should be re-evaluated when the multiple XY pairs in these mammals are fully sequenced. Ohno proposed that X-upregulation in both males and females was the initial evolutionary adaptation to the loss of genes on the Y chromosome, serving to maintain dosage equality in males [166]. He posited that X-upregulation in females resulted in a twofold excess in X-gene dosage, and that X-inactivation evolved subsequently to reinstate X : A balance in this sex. It is unclear why mammals did not simply limit X-upregulation to males (like flies), thereby removing the need to evolve X-inactivation in females. In the case of male-specific X upregulation (as in *Drosophila*), expression in females happens through two X-alleles. Importantly, modelling has demonstrated that the expression level of a gene is more variable when it arises from two stochastically firing alleles than a single, upregulated allele [167]. Therefore, it is possible that the mammalian dosage compensation system with both X upregulation and X inactivation evolved to allow for less variable X expression in females, which might be deleterious [168]. What is more, having two active Xs in females would lead to different amounts of euchromatin between males and females and therefore differences in nuclear and cell volumes between the sexes, which could be deleterious [168].

While X-upregulation and X-inactivation cooperate to balance gene expression, not all X-genes are affected equally by these two processes. This point is important from an evolutionary and analytical perspective. Degeneration of a given Y-homologue does not necessitate in all cases that the corresponding X-gene is upregulated twofold. Indeed, X-upregulation preferentially affects broadly expressed, dosage-sensitive genes with housekeeping functions, rather than tissue-specific genes [142,169,170]. This consideration is crucial when calculating X : A ratios, because the X chromosome is enriched relative to the autosomes in genes expressed only in the testis [133,134,171] or ovary [171], and therefore not predicted to require X-upregulation. Including such genes in expression analyses has led to the wrongful conclusion that in male and female somatic tissues the X : A ratio is under one, i.e. that X-upregulation does not occur in mammals [172]. The number of X-genes subject to upregulation has not been systematically determined, and few functional studies have addressed how X-upregulation is mediated. However, increased transcription initiation, associated with enrichment of PolII-S5p, H2AZ and MOF-mediated H4K16Ac, as well as increased RNA stability are probably important factors [160,173–175].

Like X-upregulation, X-inactivation does not affect all X-genes. In humans, 23 to 30% of X-genes escape X-inactivation, and in mice 2 to 7% [176–179]. Escapees include genes with extant Y homologues [180–182], which exhibit no male–female imbalance and escape silencing in most tissues, and genes without Y homologues, which exhibit tissue- and age-specific escape from X-inactivation. Variable escapees have received much interest recently, given their potential to create phenotypic differences between females and between the sexes [176,179,183]. In eutherians, X-inactivation is initiated by the non-coding RNA (ncRNA) X-inactive specific transcript (*Xist*) [184,185], while in marsupials it is mediated by the ncRNA RNA-on-the-silent X (*RSX*) [186]. *Xist* arose after the eutherian—marsupial divergence from pseudogenization of *Lnx3*, a gene that in other amniotes, including marsupials, retains protein-coding potential [187]. Similarly, although the evolutionary origin of *RSX* is unknown, it is found only in marsupials and probably also arose after the eutherian—marsupial split [186]. X-inactivation in the therian ancestor was presumably achieved via a *Xist* – *RSX* independent mechanism, or may not have evolved yet, given the minimum degree of Y-chromosome degeneration at that point in evolution. Despite their distinct evolutionary origins and primary sequence, *Xist* and *RSX* show intriguing similarities in motif composition and nonlinear sequence similarity [188,189]. This observation suggests that *Xist* and *RSX* evolved convergently and enforce X-inactivation via similar mechanisms (figure 3*b*). Thanks to the development of genetic screens and assays that identify RNA-binding proteins (RBPs) [190–194], our knowledge of how *Xist* induces silencing is now more clear (reviewed in detail elsewhere [195,196]). The emerging theme is that different functional elements in *Xist* recruit distinct RBPs (e.g. SPEN, RMB15 and hnRNPK), which via binding of chromatin-modifying complexes (e.g. PRC1 and PRC2) enforce repressive histone marks (e.g. H3K27me3 and H2AK119Ub) and, ultimately, DNA methylation at CpG promoters. However, equivalent studies of *RSX* are lacking, and the epigenetic similarities between X-inactivation in eutherians and marsupials remain unclear.

Analysing the timing of X-inactivation during eutherian and marsupial embryogenesis has provided insight into the evolution of imprinted versus random X-inactivation. X-inactivation in humans, rabbits, pigs and cows initiates at the blastocyst stage, and is random, affecting the paternal or maternal X with equal probability [197–202]. Random X-inactivation is preceded by a phase in which *Xist* is expressed biallelically, and in rabbits this causes silencing of both X chromosomes [197]. However, in mice, X-inactivation initiates earlier, at the four-cell stage, and is imprinted, affecting the paternal X chromosome [203,204]. Paternal X-inactivation is retained in the extraembryonic lineages (such as the placenta) but erased in the epiblast, where random X-inactivation ensues [203,204]. Given its short gestation (19 days), it is not surprising that X-inactivation in mice initiates early, but why should it be imprinted and not random, as in other eutherians? Biallelic *Xist* expression, leading to silencing both X chromosomes, appears not to be tolerated early in development. Indeed, in androgenetic mice, which carry two paternal X chromosomes, the expression of *Xist* from both X chromosomes is associated

with developmental delay and embryonic lethality [205,206]. An imprint silencing one *Xist* allele would prevent biallelic *Xist* expression, thereby averting this outcome [197]. Support for this model has arisen from work in the opossum, a marsupial. Like mice, marsupials exhibit a shorter gestation (14 days in the opossum) and paternal X-inactivation. Interestingly, *RSX* expression and X-inactivation in the opossum also initiates early, at the 8-cell stage [163]. Imprinted X-inactivation therefore appears to have evolved multiple times to protect organisms with early X-inactivation from the deleterious effects of silencing both X chromosomes. It should be noted that this model is agnostic to which X is silenced.

Specific silencing of the paternal X is likely to be related to the genomic conflict theory of imprinting: in cases where females carry multiple offspring from potentially different fathers, a conflict arises between the two parents where the mother is under selection to provide the same amount of resources to every progeny individual, while the father is under selection to sire individuals that maximize resource uptake from the mother. This conflict is resolved when growth suppressors are paternally silenced and growth enhancers maternally silenced either in the embryo or its nourishing tissues such as the placenta [207]. This differential expression of the two alleles of a gene depending on their parental origin is called imprinting and relies on epigenetic marks transmitted from the parents. Genes suppressing embryonic growth are predicted to accumulate on the X chromosome because the X spends two-thirds of its time in females and is therefore expected to accumulate genes that favour mothers. Silencing of the paternal X as observed in the placenta of some mammals and in eutherians (figure 3*b*) may promote embryonic growth and could have been selected as an advantage to fathers [208]. It has been proposed that imprinted X chromosome inactivation could have evolved prior to dosage compensation in mammals to resolve parental conflicts, and later have been recruited for dosage compensation [209]. The order of events that led to the evolution of dosage compensation in mammals and the validity of Ohno's hypothesis (X upregulation followed by X inactivation) are still open questions.

(c) Dosage compensation in plants

Dosage compensation has been described in different plant species: *S. latifolia* [210–213], *Silene otites* [214], *Coccinia grandis* [215], *Rumex rothschildianus* [216] and *Cannabis sativa* [217]. It was inferred either (i) by using the ratio of male to female expression, which is close to one for dosage compensated sex-linked genes in spite of Y expression degeneration, or (ii) by studying the ratio of X expression in males to autosomal expression in an outgroup without sex chromosomes. In all studied species, dosage compensation did not affect all genes in the same way. For instance, X-hemizygous genes which lack an expressed Y copy tended to be less dosage compensated than X/Y genes with a degenerated but partially expressed Y copy [33,218]. It therefore remains unclear whether dosage compensation mechanisms affecting the entire X chromosome are at play in plants. Better genome assemblies will be necessary to answer this question in order to know the precise location of genes and test whether dosage compensation happens on entire regions along the X or gene-by-gene.

In *S. latifolia*, the expression of X and Y alleles in males and females was compared to orthologous autosomal expression in outgroups without sex chromosomes and the results indicated that dosage compensation could be linked to imprinting, in a similar but slightly different way to marsupials [212]. Indeed, the maternal X chromosome in *S. latifolia* was upregulated in both males and females, while the paternal X maintained its ancestral expression in females. However, this pattern was not confirmed by an independent study using a slightly different methodology and a cross from a different population [213], suggesting that either dosage compensation mechanisms vary among *S. latifolia* populations or that methodological issues need to be addressed. In any case, epigenetic studies in *S. latifolia* found that the two X chromosomes of *S. latifolia* females vary in terms of epigenetic marks. Immunodetection of 5-methylcytosine in chromosome staining of *S. latifolia* showed that one arm of one X chromosome is hypermethylated in females, while the same arm is hypomethylated in the second X of females and the unique X in males [71]. These results have recently been partially confirmed using immunolabelling and fluorescence *in situ* hybridization [72]: one X chromosome in females had higher levels of methylation along its entire length compared to the other female X and the male unique X. Histone marks showed a similar pattern, especially for the active transcription marks H3K9ac and H3K4me2 which were strongly enriched on one female X [72]. The identity of the maternal and paternal X in these epigenetic studies remains, however, unknown and will be required to test for the existence of imprinting and its role in dosage compensation in *S. latifolia*.

6. Conclusion and perspectives

Epigenetics can play a role in every step of sex chromosome evolution, from the evolution of sex determination to Y degeneration and dosage compensation. An important characteristic of epigenetic phenomena is their lability and flexibility in comparison to genetic phenomena. As such, epigenetics could play an important role in the adaptation of species to changing environments through sex reversals and sex lability that allow reproductive insurance and survival of the species. Research has shown that even in species where the sex of individuals is determined genetically, epigenetics can later override this genetic information. This is particularly important in plants where individuals cannot move to find a mate and population density has to be high enough to allow reproduction of dioecious plants. However, in cases where epigenetics allows for the appearance of hermaphrodites, these individuals could benefit from reproduction assurance through selfing and allow range expansion at the borders of the species' geographical distribution.

Epigenetics could also potentially explain why sex chromosome turnovers are so frequent in some groups. Indeed, in some poplars, sex is determined by siRNAs that originate from Y-specific duplicated copies of the *ARR17* gene. These Y-linked non-functional duplicates of *ARR17* might diverge through time, limiting the interaction of their siRNA with the original autosomal or pseudoautosomal copy of *ARR17*. As a consequence, the Y chromosomes of Salicaceae species may be doomed to disappear as they lose homology between *ARR17* and its duplicates. This might explain why the Salicaceae family (poplars and willows) has such an impressive diversity in terms of sex chromosome pairs and why these sex chromosomes are young and homomorphic. Alternatively,

homology between *ARR17* and its duplicated pseudogenes may be maintained through time by stabilizing selection, allowing for the conservation of ancient gene fragments shared between multiple species [40]. In that case, frequent sex chromosome turnover in Salicaceae would rather be explained by the movement of duplicated gene fragments in the genome, maybe facilitated by TEs. Future sequencing in this plant family will help investigate these two hypotheses further.

Throughout this review, we have repeatedly shown how the epigenetics of sex chromosome evolution is tightly linked to TEs. Indeed, TEs are responsible for Y heterochromatinization which leads to an epigenetic conflict between TE silencing and Y gene expression. The cost of not silencing TEs could eventually select for Y gene loss and accelerate Y degeneration. Epigenetics could therefore play an active part in Y degeneration, on top of the well-known phenomena of genetic interference in the absence of recombination. Intriguingly, epigenetics could also be responsible for the evolutionary shrinking of Y chromosomes. Indeed, heterochromatin tends to be lost through ageing which activates Y TEs and lowers male longevity. This deleterious effect could potentially select for Y deletions that mitigate Y toxicity.

In marsupials and in the plant *S. latifolia*, imprinting and dosage compensation evolution seem to be intrinsically linked. It remains unclear, however, whether imprinting evolved first owing to parental conflicts and was later co-opted for dosage compensation, or whether imprinting was selected for dosage compensation from the start.

Data accessibility. This article has no additional data.

Authors' contributions. D.B. wrote paragraphs on insects; J.M.A.T. on mammals; G.M. on plant sex determination and plant Y toxicity; A.M. on plant Y degeneration, plant dosage compensation, imprinting, general introduction and conclusion. A.M. and G.M. designed the figures. A.M. combined the different sections, streamlined the text and formatted the manuscript. All authors gave final approval for publication and agreed to be held accountable for the work performed therein.

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