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Review

Insect sex chromosome evolution: conservation, turnover, and mechanisms of dosage compensation

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Sex chromosomes have evolved many times throughout the tree of life, and understanding what has shaped their unusual morphological, sequence, and regulatory features has been a long-standing goal. Most early insights into insect sex chromosome biology came from a few model species, such as the fruit fly *Drosophila melanogaster*, which limited broad-scale evolutionary inferences. More recently, extensive comparative genomics studies have uncovered several unexpected patterns, which we highlight in this review. First, we describe the conservation of the ancestral X chromosome over 450 million years but also its recurrent turnover (i.e. its reversal to an autosome when a new X chromosome arose) in at least one order. We then summarize classical and more recent findings on how insects modulate the expression of X-linked genes following the degradation of the Y chromosome and how the diverse mechanisms of dosage compensation identified may elucidate important principles of sex chromosome regulatory evolution.

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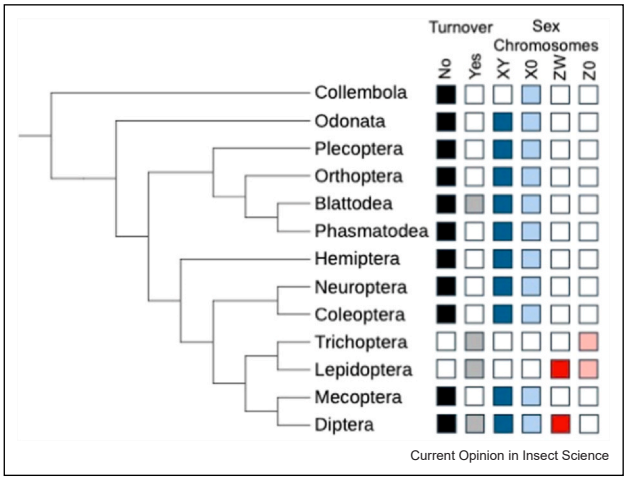
More than half of the described species are insects, making them among the most speciose groups on the planet [1]. Accordingly, they use a remarkable diversity of methods to determine sex, including chromosomal sex determination, haplodiploidy, and paternal genome elimination, all of which have evolved more than once across multiple orders [2]. Chromosomal sex determination, however, is the most widespread, known to occur in all orders except Hymenoptera [2]. Within insects, male heterogamety (XY males and XX females) is more common than female heterogamety (ZZ males and ZW females) and is thought to be the ancestral state of sex determination [2,3].

Chromosomal sex determination evolves when an autosome acquires a sex-determining locus. The canonical model of sex chromosome evolution predicts that recombination between the chromosome pair may become suppressed, potentially as a mechanism to link sexually antagonistic alleles (which have differential fitness effects in each sex) to the sex-determining locus, such that male-beneficial alleles occur more often in males and female-beneficial alleles occur more often in females. However, achiasmy, where recombination is absent in one or both sexes, has been detected in multiple insect orders, including Orthoptera, Mantodea, Hemiptera, Coleoptera, Lepidoptera, Trichoptera, Mecoptera, and Diptera (reviewed in Ref. [4]). In insects, achiasmy is limited to the heterogametic sex; specifically, females lack recombination in Lepidoptera and Trichoptera, which are female heterogametic, and males lack recombination in all other known achiasmic insect species, which are male heterogametic. This results in suppression of recombination across the entire sex-specific chromosome, accelerating the degeneration through inefficient selection on linked loci. The sex-specific chromosome undergoes large-scale deletions, gene loss, and accumulation of repetitive sequences, which eventually can result in structural distinctions between the sex chromosomes that are visible within a karyotype. Furthermore, the sudden, chromosome-wide degradation may select for a compensation mechanism on the Z or X to maintain functionality of dosage-sensitive genes on the sex chromosome. Eventually, in systems with dosage-dependent sex-determining genes (located on the X or Z), the sex-specific chromosome may be so degraded that it is lost altogether, leading to an X0 or Z0 system. It has been hypothesized that these advanced stages of sex chromosome evolution may function as a largely irreversible 'evolutionary trap' [5], as returning highly specialized X and Y (or Z/W) chromosomes to an autosomal state likely incurs strong fitness costs (for instance, due to their sex-specific regulatory architecture). Why some clades have highly conserved ancient sex

Figure 1



Insect sex chromosome conservation and turnover. The tree shows the phylogenetic relationship of insect orders for which the homology of the X has been assessed. The boxes highlight orders where turnover has been detected their associated sex chromosome complement(s).

chromosomes while others undergo frequent sex chromosome turnover is still an open question, to which insect studies have greatly contributed (Figure 1).

While initial genomic investigation into the evolutionary history of insect sex chromosomes concluded the sex chromosomes of insects are independently evolved [6], this analysis included the X chromosome of Drosophila, which was later shown to be the result of sex chromosome turnover within Dipterans [7]. Another chromosome, known as Muller Element F or the 'dot chromosome', is the ancestral X chromosome in this order [7,8]. Subsequent analyses of the German cockroach (*Blatella germanica*; Blattodea) and the blue-tailed Damselfly (*Ischnura elegans*; Odonata) determined the X chromosomes of these taxa were homologous to the ancient X chromosome of Dipterans [9,10], suggesting long-term conservation of the X or convergent recruitment of gene content. The tremendous amount of gene movement across such long time scales made distinguishing between these two hypotheses a challenge. Additionally, gene movement preferentially involves the X chromosome across many taxa with differentiated sex chromosomes, including several insect species [11–15], further generating variation and contributing to difficulty in assessing shared ancestry versus convergent gene recruitment. More recent systematic analyses using chromosome-level assemblies from across insects showed that the X chromosomes of Orthoptera, Coleoptera, Neuroptera, Hemiptera, Plecoptera, Phasmatodea, and Mecoptera were also homologous to the ancestral Dipteran X [16–18]. Intriguingly, the X chromosome of two species of springtails, which are members of the order Collembola and an outgroup to Class Insecta, is also homologous to the insect X chromosome [17]. This places the origin of the insect X chromosome at more than 450 million years ago, prior to the rise of insects [17], making it among the most ancient sex chromosome systems known.

In contrast to the retention of an ancient X chromosome across most insect groups, sex chromosome turnover is widespread in Diptera, with at least eight independent transitions from the ancient X0 system to new XY chromosomes and 1×0 to ZW turnover in Tephritidae [8]. It is puzzling that an X chromosome that had been conserved for hundreds of million years, exemplifying the 'evolutionary trap' model, should suddenly start undergoing recurrent turnover. One potential explanation is the finding that the gene content of the X chromosome shrank greatly in the ancestor of Diptera (from 1000 to ~200 genes) [17,18]. The dysregulation that likely occurs when the X reverts to an autosome should have much smaller fitness effects when only a small number of X-linked genes are concerned, and this may have facilitated the conversion of an ancient, highly modified X chromosome into an autosome [17,18]. In contrast, the large size of the ancient X chromosomes (> 1000 genes) of other insect orders may prevent turnover from occurring, resulting in the 'evolutionary trap' of highly differentiated sex chromosomes [5,17–19].

Elsewhere in insects, only two additional turnover events have been detected. The common ancestor of Trichoptera and Lepidoptera transitioned to a female heterogametic system around 210 million years ago [20]. Interestingly, all taxa examined thus far in Trichoptera are Z0, as well as the earliest diverging lineages in Lepidoptera, suggesting that either the common ancestor of these two orders also lacked a W or the ancestral W was lost in parallel in both orders [2,21]. An additional turnover from the ancient X0 to a new XY system has been identified in the Isoptera (order Blattodea) [22]. In contrast to Dipterans, it appears this turnover has occurred only once, as there are three closely related termite species that lack the ancestral insect X. Of the three termite species investigated, two (*Cryptotermes secundus* and *Reticulitermes flavipes*) have undifferentiated sex chromosomes and one species (*Macrotermes natalensis*) has differentiated XY chromosomes [22], and several other termite species have undifferentiated or complex sex chromosome systems [2]. Importantly, X-linked homologs from *Blatella germanica* are autosomal in termite species analyzed in [22], indicating a reversion of the ancient X chromosome to an autosome [22].

Beyond these documented turnover events, variation within sex chromosome systems can be generated through chromosomal rearrangements involving the

ancestral X (or Z in Lepidoptera), including fusions, fissions, and large-scale translocations. X-A fusions resulting in neo-sex chromosomes have been documented in Coleoptera [23,24], Odonata [24–26], Orthoptera [27], and Hemiptera [28] and hypothesized in Phasmatodea and Plecoptera [2], despite long-term conservation of the ancient X in these orders [16,23,25,29,30]. The ancestral Coleopteran X is preferentially involved in fusions [31], and it has been suggested that the Odonate X might be as well [24]. Similarly, the Z chromosome in Lepidoptera is the most commonly fused chromosome, having fused to an autosome at least 30 times [32], and unique W chromosomes have arisen several times independently in different lineages [2]. Fissions of sex chromosomes are thought to be more rare than fusions but have been documented in Lepidoptera [33], Hemiptera [34,35], and Coleoptera [36] and have also been suggested as a source of sex chromosome variation in Coleoptera more broadly [2].

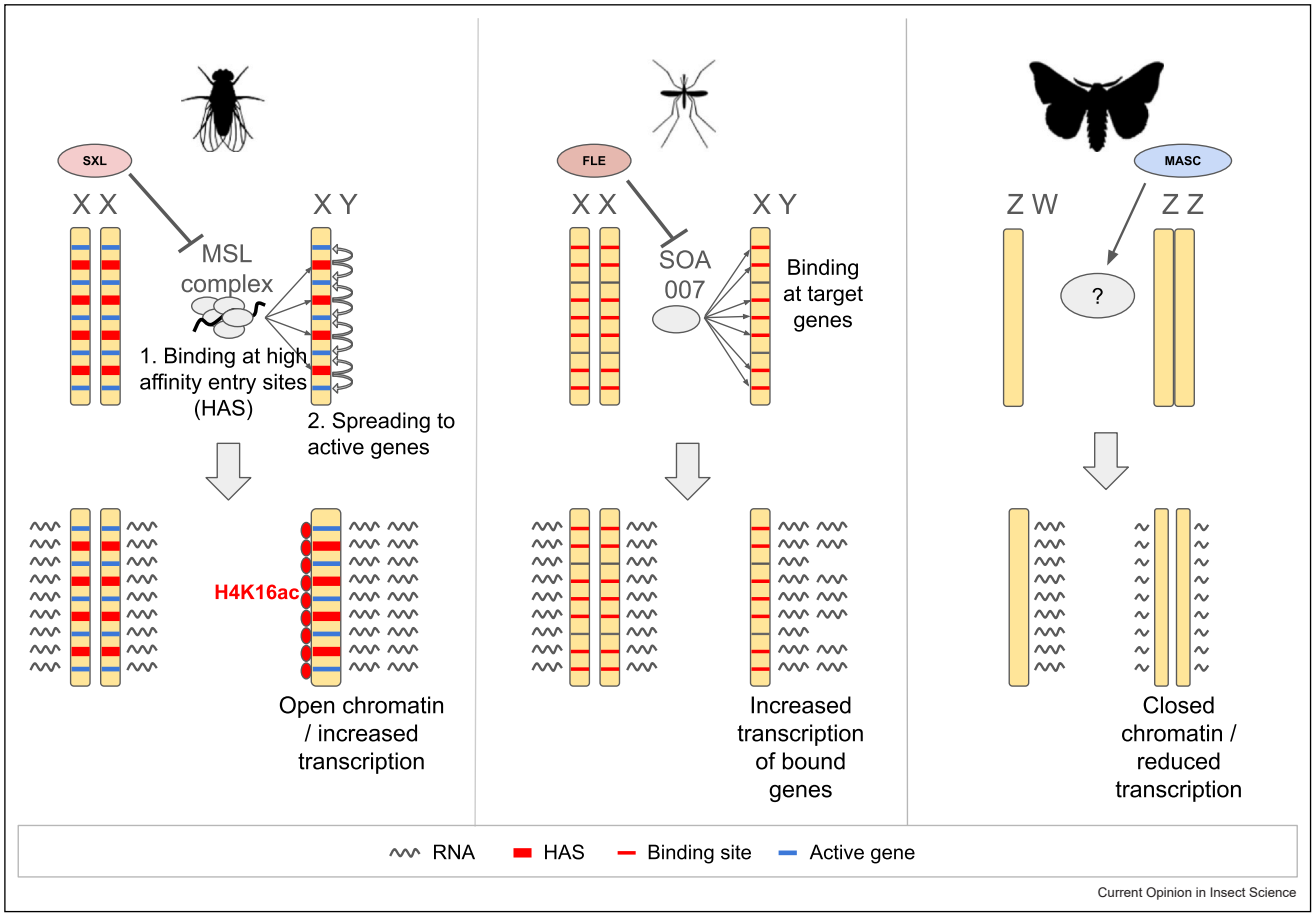
As genes are lost from degenerating (neo-)Y or W chromosomes, imbalances in expression arise in XY males or ZW females (as they now express only a single copy of their X/Z-linked genes but two copies of their autosomal genes). Such imbalances are thought to be deleterious and consequently select for molecular mechanisms that regulate the expression of X-linked genes to re-establish dosage balance, known as mechanisms of 'dosage compensation' [37]. While dosage compensation of the whole X chromosome is present in some clades (such as mammals), most genes remain uncompensated in others (e.g. some reptiles), at least at the transcriptional level. It is currently unclear what drives these different outcomes [38]. The many independent acquisitions of new X chromosomes and of additional neo-X arms through X:autosome fusions described above makes insects a promising clade for investigating how and when dosage compensation evolves.

Insect dosage compensation was first described in *D. melanogaster*, where a riboprotein complex composed of at least five protein subunits and two noncoding RNAs (*roX1* and *roX2*) binds to the male X chromosome and upregulates transcriptional rates to match those of the autosome [39]. The individual proteins of this dosage compensation complex were primarily identified through mutational screens through their male-specific lethality (the complex is also known as the Male-Specific Lethal complex, or MSL complex) [40], supporting the harmful effects of global underexpression of the X chromosome. Some of the MSL proteins are found as a regulatory complex in many organisms, including humans and other insects, but are not involved in dosage compensation in those clades, showing that an ancestral pathway was co-opted for this purpose in Drosophilids [41]. Indeed, most of the MSL proteins are expressed in both sexes, suggesting that other regulatory roles have been maintained. On the other hand, the translation of *Male-Specific Lethal 2* (*msl-2*) is suppressed in females by the female-specific Sex lethal protein (Sxl, a key component of the sex determination pathway) [42]. The presence of Msl-2 in males allows for the formation of the full MSL complex, which then targets the X chromosome through a two-step process. First, binding occurs at specific 'high-affinity entry sites' specified by the presence of a GA-rich motif [43,44]. Second, spreading to genes undergoing active transcription occurs through the affinity of the MSL protein Msl-3 to H3K36me3 [45], an epigenetic modification associated with high transcriptional activity, as well as 3D interactions between the high-affinity binding sites and transcriptionally active regions of the X [46–48]. Spreading ensures that expressed genes on the X are globally upregulated, that is, dosage compensation occurs chromosome wide. Finally, the MSL complex modulates the chromatin landscape of the X chromosome through acetylation of lysine 16 of histone H4 (H4K16ac), opening the chromatin and consequently increasing transcription [49–52].

While much less is known in other insects, recent developments in sequencing and genetic manipulation technologies have started to shed light on the prevalence and evolution of dosage compensation throughout the clade. In species of many orders (including Diptera, Coleoptera, Odonata, Hemiptera, Phasmatodea, Mecoptera, Orthoptera, recently reviewed in Ref. [53]), RNA-sequencing of male and female somatic tissues has shown that despite the presence of a single X in males, X-linked genes are expressed at similar levels in the two sexes. This suggests that global balancing of expression (i.e. the balancing of most X-linked genes) is a typical feature of insect sex chromosome evolution. However, the characterization of the underlying mechanisms in the mosquito *Anopheles gambiae* and in the moth *Bombyx mori* has uncovered unexpected diversity (Figure 2). In *A. gambiae*, a gene of previously unknown function (named *SOA* and *007* by the groups who independently described it [54,55]) was shown to be directly responsible for dosage compensation. Unlike the chromatin remodeling complex of *Drosophila*, *SOA/007* appears to function as a transcription factor, as it binds directly to the promoter region of the X-linked genes it upregulates. In its absence, this subset of X-linked genes becomes downregulated, but, unlike in *Drosophila*, this is not lethal to males (although developmental delays are observed). This demonstrates that gene-by-gene acquisition of transcription factor–binding sites is a viable mechanism for dosage compensation in insects and that this mechanism can evolve even when the fitness effects of dosage imbalance are relatively modest.

Unlike most insects, which have XY/X0 sex determination, all Lepidoptera are female heterogametic (i.e.

Figure 2



Diverse mechanisms are used by insects to achieve dosage compensation. The three panels represent the putative mode of action of dosage compensation in *D. melanogaster*, *A. gambiae,* and *B. mori*. SXL, FLE, and MASC are members of the sex-determining cascade of these clades (the first two are female-determining and inhibit dosage compensation, while MASC is a male determinant that promotes dosage compensation of the Z chromosome).

males have two Z chromosomes and females are ZW or Z0). The *B. mori* dosage compensation mechanism is directly under the control of the male-determining gene *Masculinizer (Masc)* and seems to lower the expression of the Z chromosome in ZZ males, as MASC-depleted male embryos overexpress Z-linked genes [56]. While this reduction in male expression leads to similar transcriptional output of the Z in males and females, Z-linked genes have overall lower expression than autosomes in both sexes [57,58], reminiscent of the compensation mechanisms of mammals and nematodes. Although the effector of dosage compensation is not known, several lines of evidence point toward a contribution of chromatin remodeling. First, FISH cytological visualization of the *B. mori* chromosomes and analysis of ATAC-seq data (Assay for Transposase-Accessible Chromatin using sequencing), which provide global measures of chromatin openness and accessibility, show that the two male Z chromosomes have less open chromatin than the autosomes [59]. Second, in another Lepidoptera species, the monarch butterfly *Danaus plexippus*, the male Z is depleted for the active histone mark H4K16ac [60*]. In this species, an autosome has fused to the Z to create a neo-Z chromosome. The neo-Z chromosome seems to be regulated differently from the ancestral part of the Z, with the female neo-Z carrying an excess of H4K16ac and being upregulated, reminiscent of dosage compensation in Drosophila. While more work is needed to fully understand this complex regulatory mode and to identify the molecular mechanisms at play, remodeling of the chromatin seems to at least contribute to both Z and neo-Z compensation.

Interestingly, Lepidoptera, *Anopheles*, and *Drosophila* all happen to have undergone sex chromosome turnover. The diversity of mechanisms uncovered in these groups therefore raises the question of whether dosage compensation is generally labile or simply changes when the

sex chromosomes do. Some insights into this question have come from studies of neo-sex chromosomes, where the old and new sex chromosomes coexist, and their respective mechanisms of dosage compensation can be directly compared. The two neo-X chromosomes of *Drosophila miranda* acquired novel-binding sites for the ancestral MSL complex [61,62], showing that an ancestral mechanism of compensation can in principle be co-opted by a new sex chromosome. On the other hand, the ancestral and neo-Z chromosomes of the monarch butterfly have opposite modes of compensation (see previous section). This dual mechanism may suggest that when ancestral compensation occurs through repression of the sex chromosomes of the homogametic sex, its cooption for a new sex chromosome is not favored, as it will simply extend dosage imbalances to both sexes. If the ancestral insect X was repressed in females, this repression may similarly have favored the evolution of novel mechanisms of compensation after turnover. While a systematic understanding of compensation of the ancestral X is still lacking, work in one species suggests that it may indeed involve the repression of the female X. In the Australian Sheep Blowfly *Lucilia cuprina*, which still carries the ancestral X, suppression of the gene *no blokes* (*nbl*) leads to downregulation of X-linked genes in both sexes [63], in line with a complex mechanism that combines non-sex-specific upregulation and secondary female downregulation. Similar studies in other insect species that have maintained the ancestral X chromosome, combined with the many events of turnover found throughout Diptera, hold great promise to shed light on how and when gene regulation evolves once a new sex chromosome arises.

Data Availability

No data were used for the research described in the article.

Declaration of Competing Interest

The authors have no interests to declare.

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mode of action of SOA/007 and the relatively modest fitness effects of its removal stand in contrast to the well-known mechanism of Drosophila melanogaster.

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