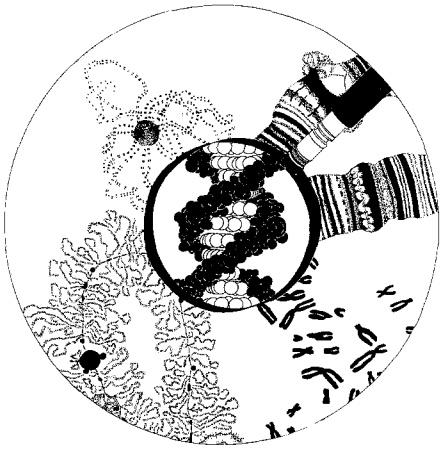
Chromosoma (1993) 102:71–80

CHROMOSOMA

Chromosoma Focus



Sex chromosomes, recombination, and chromatin conformation

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Received August 28, 1992/Accepted September 8, 1992

Abstract. We review what is known about the transcriptional inactivation and condensation of heteromorphic sex chromosomes in contrast to the activation of homomorphic sex chromosomes during meiotic prephase in animals. We relate these cytological and transcriptional features to the recombination status of the sex chromosomes. We propose that sex chromosome condensation is a meiotic adaptation to prevent the initiation of potentially damaging recombination events in nonhomologous regions of the X and Y chromosome.

During meiotic prophase the X–Y chromosome pair of many animal species is transcriptionally inactive and assumes a condensed chromatin configuration known as the sex body, whereas the X–X chromosome pair of female meiocytes is transcriptionally active and shows no such chromatin differentiation. We relate these cytological features to the recombination status of the sex chromosomes in the two sexes: in females the two X chromosomes pair and recombine while in males much of the length of the heteromorphic X–Y pair is unpaired and recombinationally inactive. In contrast to previous hypotheses regarding the function of sex chromosome inactivation in male meiocytes, we propose that sex chromosome condensation is a meiotic adaptation to prevent the initiation of potentially damaging recombination events in the differentiated X and Y chromosomes. This hypothesis is consistent with evidence on the taxonomic distribution of sex chromosome inactivation, on the timing of meiotic prophase events, and on the relation of chromatin configuration to meiotic recombination.

Sexual dimorphism in meiosis

Recently, attention has been focused on sexual differences in rates and distribution of meiotic recombination events and on their possible relationships with meiotic patterns of transcription (Fischer Lindahl 1991; Thomas and Rothstein 1991). In this paper, we review an extreme but informative case of sexual dimorphism in meiotic chromosome behavior: the euchromatic conformation and transcriptional activity of sex chromosomes in oocytes vis a vis the heterochromatic conformation and transcriptional inactivity of the sex chromosomes in spermatocytes of the same species. Meiotic sex chromosome inactivation (MSCI) is distinct from the more familiar somatic X inactivation, which functions in mammalian dosage compensation; the former is widespread in heterogametic male animals and is limited to germ cells, while the latter is known only in female mammals and occurs in the soma and oogonia but not in meiocytes. While it is possible that the two phenomena are mechanistically related in mammals, there is no evidence for this. Instead, we propose that the dimorphism in meiotic activity of sex chromosomes is related to the different status of the sex chromosomes with respect to pairing and recombination. The homologous X chromosomes of homogametic females must pair and recombine to ensure X chromosome segregation at anaphase I and to prevent the accumulation of mutations, whereas the heteromorphic X and Y chromosomes of heterogametic males must be prevented from unrestricted meiotic recombination because exchange events initiated within the differential regions could result in ectopic crossovers or in unrepaired chromosome damage. We suggest that

the euchromatic conformation of the sex chromosomes in oocytes facilitates chromosome pairing and recombination and that the heterochromatic conformation of the X and Y chromosomes in spermatocytes prevents promiscuous recombination. We argue that accessibility of DNA to transcriptases and recombinases depends on similar features of chromatin conformation and that, therefore, the difference in transcriptional activity of sex chromosomes in spermatocytes and oocytes is a secondary consequence of the dimorphism in commitment to recombination.

We first review the evidence for dimorphism in the behavior of sex chromosomes in meiocytes, then develop the hypothesis that this dimorphism results from the differential recombination status of the sex chromosomes in heterogametic and homogametic organisms, then evaluate evidence relevant to the hypothesis.

Sex chromosome behavior during meiosis

Sex chromosome meiotic behavior in many animals shows remarkable sexual dimorphism. Both of the homomorphic sex chromosomes are decondensed and transcriptionally active, as are the autosomes, during female meiosis, whereas the heteromorphic sex chromosomes are transcriptionally inactive and heterochromatic, unlike the autosomes, in male meiosis.

Female meiosis

In mammalian oogonia, as in somatic cells, X chromosome dosage compensation is achieved by having one X chromosome active and the other heterochromatic and transcriptionally inactive. Premeiotic germ cells from human female fetuses that are heterozygous *GpdA/GpdB* express only AA and BB forms, indicating activity of only one X chromosome per cell (Gartler et al. 1975). These data are consistent with the demonstration of a heterochromatic chromosome in mitotic oogonia (Gartler et al. 1980). However, coincident with meiotic prophase, the heterochromatic X chromosome is reactivated, so that in distinction to all other cells of the body, oocytes have two X chromosomes active. Three kinds of observations have provided the evidence for this. First, quantitative differences in the amount of X-encoded proteins are found in oocytes of XX individuals compared with those of XO female mice (Epstein 1969; Andina 1978; Monk and McLaren 1981; Gartler and Rivest 1983). Second, heteropolymeric forms of X-encoded enzymes can be detected in oocytes of both heterozygous mice (Kratzer and Chapman 1981; Johnston 1981) and humans (Gartler et al. 1972, 1975). Finally, a heterochromatic chromosome is not observed in oocytes (Ohno 1964). In conclusion, both X chromosomes in oocytes are transcriptionally active and in a chromatin conformation that is indistinguishable from that of the autosomes.

Male meiosis

In striking contrast to the behavior of the X chromosomes during female meiosis, the X and Y chromosomes of male germ cells in many animals are inactive at meiotic prophase. The earliest observations were cytological, documenting the presence of heterochromatic sex chromosomes (Mohr 1916 translated by Mittwoch 1983; Painter 1924; Ohno and Makino 1961). Sachs (1954) first coined the term "sex vesicle" to described the structure assumed by the sex chromosomes. The term is misleading because it implies a vesicular structure rather than simply the different chromatin conformation assumed by the sex chromosomes in spermatocytes. The structure and behavior of this nuclear domain, more appropriately termed the "sex body" or the "XY body" has been thoroughly and elegantly described by Solari (1974, 1989); it consistently exhibits differential staining and behavior by comparison with the autosomes. The evidence for transcriptional inactivation derives primarily from autoradiography following incorporation of [^{3}H]uridine in both insects and mammals (Henderson 1964; Monesi 1965; Utakoji 1966; Kierszenbaum and Tres 1974a, b): the sex body does not incorporate uridine while the autosomal chromosomes do. The precise time of MSCI is not known but it evidently occurs some time after the commitment to meiosis, since the X may be late replicating by the preleptotene S-phase (Kofman-Alfaro and Chandley 1970; Odartchenko and Pavillard 1970; however, see also Latos-Bielenska and Vogel 1992), and transcriptionally inactive at early meiotic prophase when the sex body is first seen.

Consequences for the male germ cell of X chromosome inactivation

It has been proposed that MSCI is an essential feature of gametogenesis in the heterogametic sex (Lifschytz and Lindsley 1972), and that X-encoded products are inhibitory to spermatogenesis (Forejt 1982). However, there is no evidence that any of the large number of known X-encoded proteins is detrimental to germ cells. In fact, spermatogenic cells seem to have devised several means to ensure the availability of products normally encoded by the X chromosome. One such coping strategy is the presence of autosomal "back-up" genes encoding enzyme variants expressed only in meiotic and post-meiotic spermatogenic cells. Autosomal back-up genes have been documented for PGK and the E1α subunit of pyruvate dehydrogenase. In the case of the *Pgk-1* gene, both functional enzyme and transcripts decline in meiotic prophase spermatocytes as the gene for a variant product, *Pgk-2*, located on mouse chromosome 17 (human chromosome 6), is activated (Gold et al. 1983; McCarrey and Thomas 1987; Singer-Sam et al. 1990). The PGK-2 protein is found only in meiotic and postmeiotic spermatogenic cells. The E1α subunit of pyruvate dehydrogenase is encoded on the X chromosome, but there is an autosomally encoded variant expressed only in the testis (Takakubo and Dahl 1992). However, for some X-linked

genes, such as that encoding HPRT, there is no functional autosomal back-up gene. Instead, the germ cell copes with inactivation by stabilization of gene products; Handel et al. (1992) found that levels of HPRT activity do not decrease markedly in spermatocytes and spermatids despite low levels of transcript in spermatocytes. Interestingly, this study (as well as that of Singer-Sam et al. 1990) found that the abundance of the transcript increases at the onset of meiotic prophase, decreases to exceedingly low levels in pachytene spermatocytes, then increases in postmeiotic cells, consistent with X chromosome inactivation being related to events of meiotic prophase, not to spermatogenesis generally.

Studies in male insects suggest the possibility of a compensatory hyperactivation of the X chromosome before meiosis. In grasshoppers, the X is heavily condensed during meiotic prophase, indicative of meiotic inactivation. However, in many species, it is diffuse and weakly stained relative to the autosomes during at least some of the premeiotic spermatogonial mitoses (White 1973). In spermatogonial interphase in *Brachysola magna*, the X chromosome, which accounts for only 6.5% of the metaphase chromosome length, underlies 17% of the silver grains following [^{3}H]uridine incorporation. This suggests that the X is hyperactivated in spermatogonial interphase to compensate for its subsequent inactivation (Church 1979).

The evidence for compensatory mechanisms to ensure the availability of X-encoded products in both mammalian and insect spermatogenesis makes it unlikely that sex chromosome inactivation evolved to suppress the production of gene products poisonous to spermatocytes. It is equally difficult to account for the reactivation of the inactive X in oocytes in terms of special transcriptional requirements of germ cells; although it is formally possible, there is no evidence that oocytes require a higher ratio of X to autosomal gene products than do oogonia or somatic cells. The failure to explain the peculiar behavior patterns of the sex chromosomes in gametocytes of either sex in terms of special transcriptional requirements suggests that these patterns reflect some other, more fundamental process. The fact that both sex chromosome reactivation in females and inactivation in males coincide temporally with events of meiotic prophase points to homologous pairing and recombination, the defining events of meiotic prophase, as the keys to understanding meiotic sex chromosome transcriptional behavior.

Meiotic pairing, recombination, and sex chromosome behavior

In organisms with heteromorphic sex chromosomes, the pairing/recombinational status of the sex chromosomes is fundamentally different in the two sexes. In the homogametic sex, the sex chromosomes are fully homologous and recombine freely, while in the heterogametic sex they are largely non-homologous and, therefore, incapable of full homologous pairing and recombination. The sexual differences in sex chromosome conformation and transcriptional activity in meiotic cells may be related to this dimorphism in the capacity of the sex chromosomes to recombine homologously. This idea is consistent with a considerable body of evidence that heterochromatin and euchromatin differ in their capacity to recombine as well as to be transcribed. Genetic data from *Drosophila* indicate a virtual absence of crossing over in the centric heterochromatin (Baker 1958; Roberts 1965; Carpenter and Baker 1982). In addition, cytological data from a wide variety of organisms document the absence of chiasmata in major heterochromatic blocks (reviewed in John 1988).

X reactivation and the benefits of recombination

The lack of recombination in heterochromatin implies that maintenance of the heterochromatic conformation of the inactive X in mammalian oogonia throughout meiosis would interfere with X–X recombination. In support of this is the observation that the two X chromosomes in tetraploid locust spermatocytes, which remain condensed throughout meiotic prophase, fail to form a chiasma (White 1933). The failure of X–X recombination could have at least two deleterious consequences. First, since the chiasmata that result from crossovers are important in ensuring accurate homologous segregation at anaphase I (Hawley 1988), disruption of X chromosome disjunction would result from failure of the X to assume a chromatin configuration compatible with chiasma formation. Second, chromosome regions that do not recombine regularly tend to accumulate nonfunctional sequences such as simple repeats and transposable elements (Miklos et al. 1988; Charlesworth and Langley 1989). Theoretical considerations suggest that recombination may oppose mutational decay by facilitating both selection against deleterious mutations and removal of repetitive DNA (Charlesworth and Langley 1989; Charlesworth 1989). Thus, reactivation of the previously inactive X in mammalian oocytes may function to allow X chromosomes to "reap the benefits" of recombination.

Sex chromosome inactivation as a means to prevent promiscuous recombination

By contrast, the X and Y chromosomes in many organisms are too divergent to reap anything but chaos from recombination. There are at least two reasons why participation of non-homologous sex chromosomes in homologous recombination might be detrimental.

Ectopic exchange

Sex chromosome recombination might lead to ectopic exchange between repeated sequences on the X and Y leading to rearrangements and aneuploidy. In yeast, meiotic exchange occurs between dispersed repeated sequences located on the same or non-homologous chro-

mosomes at frequencies comparable to those of allelic exchange (Petes and Hill 1988; Haber et al. 1991). Ectopic exchange between dispersed repeats also occurs in *Drosophila* meiosis (Montgomery et al. 1991). The frequency is substantially higher in heterozygous than in homozygous individuals, suggesting the suppression of ectopic exchange by homologous pairing. Dispersed repeated sequences are abundant in mammalian genomes and there is suggestive evidence for involvement of such sequences in both allelic and ectopic exchange (Stoppa-Lyonnet et al. 1990; Yen et al. 1990; Fischer Lindahl 1991). A number of sequence families are shared between the X and Y (Avner et al. 1987). These observations suggest that ectopic intra- and inter-chromosomal exchange might occur on heteromorphic sex chromosomes at unacceptably high frequencies, if there were no means to suppress it. Thus, one plausible function of MSCI would be to prevent ectopic exchanges within or between the X and Y chromosomes.

Double-strand breaks

A second possible function of MSCI is to suppress the *initiation* of recombination so as to prevent the accumulation of unrepaired chromosome damage such as double-strand breaks. The possibility of such damage is suggested by recent evidence that double-strand DNA breaks accompany the initiation of meiotic recombination in yeast (Sun et al. 1989; Cao et al. 1990). Apparently the occurrence of double-strand breaks does not depend upon prior establishment of homology since they are seen at comparable frequencies in individuals homozygous or heterozygous for a 2.5 kb insertion containing a recombination initiation site (Cao et al. 1990). This raises the possibility that if heteromorphic X and Y chromosomes were recombinationally active, double-strand breaks would occur in sequences that are heterologous and therefore incapable of recombining homologously.

The fate of meiotic double-strand breaks not repaired by homologous recombination is unknown. The most benign fate would be recombinational repair using the sister chromatid as template. Meiotic sister chromatid exchange (SCE) is negligible in *Drosophila* (Gatti 1982) and in other insects (reviewed in John 1990) but does occur in yeast (Game et al. 1989), where it is stimulated by lack of a homolog (Wagstaff et al. 1985), consistent with the possibility that SCE functions as a back-up repair system. However, the products include a very high frequency of unequal SCEs, suggesting that it may not be a very accurate back-up system. No comparable data are available from higher eukaryotes. The alternatives to recombinational repair by SCE – ectopic recombination, restitution of the break, and failure to repair – are considerably less benign. Ectopic recombination leads to rearrangements and aneuploidy. Direct religation of broken ends would likely lead to deletions since the recessed 5′ ends generated by breakage and resection during initiation (Sun et al. 1991) cannot be filled in by any known polymerase. Unrepaired double-strand breaks would likely cause either meiotic arrest or zygotic dominant lethality. If unrepaired double-strand breaks are at all common in meiosis, one might expect a "checkpoint" system to be operative in meiosis analogous to that in mitotic cells, which functions to halt cell cycle progression in cells with unrepaired chromosome damage such as double-strand breaks (Hartwell and Weinert 1989). Meiotic arrest would be a relatively benign outcome as long as the level of damage were not too high, since the loss of reproductive output could be easily compensated for by generating additional meiocytes. Indeed, several recent studies involving interactions among meiotic mutants have documented the existence of one or more checkpoints in meiotic prophase (Weber and Byers 1992; Bishop et al. 1992). However, such a checkpoint system would likely be swamped by the damage resulting from unrestricted recombination initiation involving non-homologous sex chromosomes.

Thus we propose that MSCI in spermatocytes of heterogametic males is a device to ensure that the non-homologous sex chromosomes are not involved in meiotic exchange. This prevents both ectopic exchange and chromosomal damage via double-strand breaks associated with the initiation of meiotic recombination. Viewed in this way, meiotic transcriptional inactivation is a secondary consequence of a chromatin configuration that prevents access of recombinatory enzymes. Conversely, the reactivation of the X chromosome in oocytes is not a transcriptional necessity but a consequence of a chromatin conformation permissive for recombination.

Tests of the hypothesis

Three predictions follow from the hypothesis that MSCI functions to prevent participation of heterologous sex chromosomes in meiotic recombination. The first is that in organisms in which a region of the X–Y pair remains homologous and recombinationally active, that region may be spared inactivation. The second prediction is that MSCI should be restricted to organisms with heteromorphic sex chromosomes, since if the sex chromosomes are largely homologous, there would be no need to suppress X–Y exchange. The third prediction is that MSCI should be restricted to organisms with meiotic exchange, because it would not be needed in "achiasmatic" organisms.

Failure to inactivate "pseudoautosomal" sequences

Male mice and humans provide good tests of the first prediction, because in both species, the X–Y pair, although largely diverged, has retained a limited region of homology. These pseudoautosomal regions (PARs), which are located at the distal end of the short arms of the X and Y chromosomes in humans and at the distal end of the long arms of the two sex chromosomes in mice (Ellis and Goodfellow 1989), pair regularly in meiosis and undergo one or more obligatory exchange events (Rouyer et al. 1986; Soriano et al. 1987; Hale

et al. 1991), which apparently function to facilitate X–Y segregation.

Although there is no direct evidence for transcriptional activity in the pairing region, there is evidence based on enzyme activity that the pseudoautosomal gene *Sts* is not inactivated in mouse spermatocytes (Raman and Das 1991). Furthermore, there are some data that this region exhibits a more open chromatin configuration than the rest of the X and Y chromosomes during male meiosis. In situ nick-translation revealed a region of DNase I sensitivity in the X–Y pairing region of the human X (Chandley and McBeath 1987), but there were conflicting results for the pairing region when this technique was applied to the mouse, some finding DNase I sensitivity (Richler et al. 1987; Raman et al. 1988), and others failing to (Separovic and Chandley 1987). Thus, there is suggestive evidence, but not yet proof, that the X–Y pairing region has a more open chromatin configuration than the differentiated segments that do not pair and recombine.

Sex chromosome inactivation and sex chromosome homology

If MSCI is a solution to the problem of recombination between heteromorphic sex chromosomes, then it should be unnecessary in organisms that lack heteromorphic sex chromosomes. The available taxonomic data are consistent with this prediction. The organisms in which MSCI has been thoroughly documented, such as mammals (Solari 1989) and grasshoppers (White 1973) all have heteromorphic sex chromosomes, either XY or XO. A survey of the literature failed to find any exceptions to this association. Moreover, there are some clear examples of organisms with homomorphic sex chromosomes that lack MSCI, especially among the mosquitoes and their close relatives. The only mosquitoes in which MSCI has been reported are Anophelines and these are also the only mosquitoes with an obviously heteromorphic XY pair (Stevens 1911; Rishikesh 1959; Mukherjee et al. 1970; Narang et al. 1972; Kitzmiller 1976). In other well-studied mosquitoes such as *Culex* and *Aedes* (White 1980), as well as in the related midges and blackflies (Bull 1983), the sex chromosomes are not readily distinguishable. There have been no reports of MSCI in these groups and in some cases there is clear evidence for its absence (Stevens 1911; Martin 1967; Mukherjee and Rees 1970; Mukherjee et al. 1970; Jost 1971; Bhalla 1971). This does not reflect a lack of sex chromosomes: XY systems have been documented in several mosquitoes, black flies and midges by genetic and/or by special staining methods and are considered to be universal in these groups (White 1980). Instead, the absence of MSCI more likely reflects extensive sex chromosome homology in the heterogametic sex.

However, not all species with differentiated sex chromosomes are characterized by meiotic formation of typical sex body chromatin, the most notable exceptions being non-mammalian vertebrates such as birds (Solari 1977, 1992), reptiles (Becak and Becak 1981) and amphibians (Kezer et al. 1989). In the case of birds, the heteromorphic sex chromosomes of oocytes undergo apparently non-homologous synapsis and extensive synaptic rearrangement (Solari 1992), which may somehow provide an alternative mechanism to suppress non-homologous sex chromosome recombination. In the case of some amphibian spermatocytes, even though the sex chromosomes do not organize the typical sex body, they do exhibit a condensation pattern that is different from that of the autosomes (Kezer et al. 1989), which may serve to prevent promiscuous sex chromosome recombination. There is much that is not known that could clarify these systems, such as the degree of homology between the differentiated sex chromosomes, whether or not there is any genetic evidence for exchange between the sex chromosomes, the meiotic pattern of transcription of both autosomes and sex chromosomes, and the relationship of the molecular events of meiosis to the observed cytological events. In the context of the hypothesis advanced here, it is especially important to learn whether these species have alternative methods to prevent recombination between differentiated sex chromosomes.

Sex chromosome inactivation and achiasmatic meiosis

Insects also provide a good test of the third prediction since achiasmy has been documented in the heterogametic sex in members of eight insect orders (White 1973; John 1990). A partial survey of the extensive insect cytogenetic literature indicates a strong although imperfect association between chiasmy versus achiasmy on the one hand and presence or absence of X inactivation on the other. Most Orthopteran, Dictyopteran and Heteropteran males are chiasmatic and sex chromosome inactivation appears to be the rule in these groups, even in the achiasmatic species (White 1938, 1965a, b, 1973; Nokkala and Nokkala 1983, 1984, 1986a, b). In the Diptera, by contrast, achiasmy is widespread and many species lack detectable heteropycnosis of the sex chromosomes despite having heteromorphic sex chromosomes. These include Drosophilidae (Stevens 1908; Cooper 1950; Kremer et al. 1986), Trypetidae (Emmart 1935), robber flies (Metz and Nonidez 1924; Ribbands 1941), batflies (Cooper 1941), and Phrynidae (Wolf 1950). Other Dipterans show clear evidence of sex chromosome heteropycnosis in spermatogenesis, including both chiasmatic forms such as the Tipulidae (John 1957) and achiasmatic forms such as the Mycetophilidae (Le Calvez 1947; Fahmy 1949). There have been no reports of sex chromosome heteropycnosis in Lepidopterans in which oogenesis is universally achiasmatic (Fisk 1989), despite the fact that most species have heteromorphic sex chromosomes. Thus the insect cytogenetic data support an association between achiasmy and lack of sex chromosome heteropycnosis. Chiasmatic insects typically show sex chromosome heteropycnosis while many (though not all) achiasmatic insects do not. The pattern is consistent with the idea that achiasmatic insects evolved from ancestral, chiasmatic forms with sex chromosome inactivation;

some achiasmatic groups have subsequently lost sex chromosome inactivation while others have retained it.

Both genetic and molecular data on *Drosophila* spermatogenesis support the hypothesis that achiasmy in the heterogametic sex is permissive for sex chromosome activity in meiotic prophase. After the completion of the premeiotic S-phase and chromosome pairing, both of which occur very quickly after the last spermatogonial mitosis in spermatocytes of *D. melanogaster* (Cooper 1950; Olivieri and Olivieri 1965) and *D. hydei* (Kremer et al. 1986), the chromosomes then decondense and remain so throughout the spermatocyte growth period (Cooper 1950; Kremer et al. 1986). Transcription occurs at high rates in both the nucleus and nucleolus of young primary spermatocytes as determined by autoradiography following [^{3}H]uridine incorporation (Hennig 1967; Gould-Somero and Holland 1974); transcription rates decline as spermatocytes age, ceasing as the chromosomes recondense for the meiotic divisions. The behavior of the X chromosome is not much different from that of the autosomes. The X euchromatin decondenses fully and is indistinguishable from autosomal euchromatin throughout most of the primary spermatocyte growth phase; moreover, [^{3}H]uridine incorporation is as intense over the X domain as over the autosomal domains (Hennig 1967; Kremer et al. 1986). In *D. hydei*, the X euchromatin begins condensation slightly in advance of the autosomal euchromatin (Kremer et al. 1986). However, this difference is relatively minor and does not contradict the conclusion that the behavior of the X and autosomes in *Drosophila* male meiosis is fundamentally similar.

The behavior of the Y chromosome is even more strikingly inconsistent with sex chromosome inactivation. Decondensation of the Y in the early primary spermatocyte is accompanied by development of large "lampbrush loops" (Hennig 1987; Bonaccorsi et al. 1988), which are intensely transcribed, as shown by Miller spreading, [^{3}H]uridine incorporation, and both RNA blot and transcript in situ hybridization using cloned loop sequences (reviewed in Hennig 1987; Bonaccorsi et al. 1990).

The identification of large numbers of genes required for spermatogenesis on the X and Y chromosomes of *Drosophila* is also difficult to reconcile with the idea of meiotic sex chromosome inactivation. The Y chromosomes of both *D. melanogaster* and *D. hydei* contain several loci essential for male fertility and normal spermatogenesis (reviewed in Hennig 1988) at least some of which coincide with the lampbrush loop-forming loci. Mutational analyses have also identified numerous X-linked genes required for spermatogenesis. There is no apparent difference between the X and autosomes in density of male sterile mutations (Lindsley and Tokuyasu 1980). Moreover, DNA sequences that are transcribed abundantly in testes appear to be randomly distributed among the chromosome arms, based on analysis of genomic clones homologous to enriched testis RNA (Joslyn 1988).

Thus the available data strongly indicate that *Drosophila* sex chromosomes are transcriptionally active in meiotic cells despite being extensively heteromorphic. This, as well as the lack of MSCI in organisms with homomorphic sex chromosomes, is inconsistent with the Lifschytz and Lindsley (1972) proposal that X inactivation is a universal requirement of spermatogenesis. Their proposal was based on the male sterility of most X-autosome translocations in both mammals and *Drosophila*, which they explained in terms of a disruption of the normal timing of X versus autosomal inactivation. However, there is no direct evidence for a link between MSCI and X-autosome translocation sterility in any organism. Whatever the explanation for X-autosome translocation sterility turns out to be, the lack of evidence for MSCI in *Drosophila* is consistent with the hypothesis that sex chromosome inactivation is a device to prevent the participation of largely non-homologous sex chromosomes in meiotic recombination.

Chromatin conformation and recombination

In addition to providing an explanation for the otherwise puzzling behavior of sex chromosomes in early meiosis, the findings reviewed here suggest that adjusting chromatin conformation may be a mechanism for regulating the distribution of recombination events. It has long been known that constitutive heterochromatin is inactive in meiotic recombination, but it has not been clear whether this reflects an intrinsic non-recombinogenicity of the sequences in such regions, which are mostly simple tandem repeats and transposable elements (John 1988), or is a consequence of the condensed conformation. If normally euchromatic sequences such as those on the X can be prevented from recombining by heterochromatization, as has been suggested here, then regulation of recombination by chromatin conformation is implied. This is consistent with recent evidence that at least some tandemly repeated sequences and transposable elements are intrinsically capable of recombination. Several studies have implicated such sequences as hotspots for meiotic recombination when located in the recombinationally permissive euchromatin (Fischer Lindahl 1991).

The idea that recombination events are regulated by chromatin conformation is also consistent with molecular studies of recombination hotspots. In both yeast (Nicolas et al. 1989; Sun et al. 1989; Stapleton and Petes 1991) and mice (Shenkar et al. 1991; Fischer Lindahl 1991), hotspots for meiotic recombination have been mapped to sites coincident with gene promoters or enhancers. A hotspot in the mouse H-2 locus overlaps with sites of DNase hypersensitivity that correspond to binding sites for known transcriptional activators (Shenkar et al. 1991). A plausible explanation for these findings is that the open (non-nucleosomal) chromatin conformation of promoter/enhancer regions (Grunstein 1990) favors accessibility of recombinases as well as transcriptases. If this interpretation is correct, the suppression of sex chromosomal transcriptional activity in spermatocytes may result from overlap in the chromatin features recognized by transcriptases and recombinases, open chromatin conformations favoring both recombination

and transcription and condensed conformations inhibiting both. This does not mean that transcription and recombination are closely co-regulated. Meiotic transcription and recombination play largely different roles in gametogenesis and are likely subject to very different selective pressures. An open conformation does not guarantee transcription; the appropriate transcription factors must also be present. Similarly, euchromatic regions exhibit large and predictable variations in recombination frequency (Lindsley and Sandler 1977), suggestive of regulatory control of recombination over and above the level of chromatin conformation. Thus, there is no reason to expect that recombination events would be restricted to sites of meiotic transcription, as has recently been suggested (Thomas and Rothstein 1991). However, where selection has favored heterochromatization as a means to prevent recombination throughout a chromosome pair, interference with meiotic transcription may be inevitable.

Possible mechanism for sterilizing effects of pairing failure

Although the hypothesis outlined above was developed to explain MSCI during gametogenesis, it also suggests a mechanism for the partial or complete sterility often associated with the failure of meiotic pairing in a chromosome or part of a chromosome. This phenomenon is common in heterozygotes for chromosome rearrangements and in hybrids between closely related species (see reviews in Gillies 1989). In most cases, sterility is associated with meiotic prophase arrest, often at pachytene or just before metaphase. Miklos (1974) has postulated that sterility in these cases results from "unsaturated" pairing sites, i.e., pairing sites that fail to find a partner during early prophase. This idea accounts formally for a substantial body of data, but there has been no mechanism linking the saturation state of pairing sites with sterility. If recombination events initiated in regions prevented from homologous pairing can result in unrepaired double-strand breaks, as suggested above, these may be the molecular basis of the unsaturated pairing sites of Miklos. Recent studies in yeast have documented that double-strand breaks at recombination hotspots appear very early in meiotic prophase, prior to or coincident with the initiation of synapsis (Padmore et al. 1991), suggesting that they play a role in the pairing process itself. Thus, the failure to achieve full homologous pairing, either because of a partial lack of homology or because of topological constraints imposed by rearrangement heterozygosity, could leave one or more double-strand breaks unrepaired. If meiotic SCE does not occur at sufficient levels to repair the resulting double-strand breaks, then a meiotic checkpoint to screen them out would be adaptive. Sterility associated with meiotic arrest in hybrids and in heterozygotes for structural rearrangements may then result from the detection of double-strand breaks by a meiotic "quality control" mechanism.

Summary and perspective

We have reviewed evidence for the sexually dimorphic behavior of heteromorphic sex chromosomes in gametocytes. In our view, this dimorphism, namely, X chromosome reactivation in mammalian female gametocytes and inactivation of both the X and Y chromosomes in spermatocytes of a wide range of animals, relates to the differing recombination status of the sex chromosomes in the two sexes. In order to ensure disjunction and to avoid the accumulation of mutations, the homologous X chromosomes in females must be in a chromatin conformation compatible with free recombination. In mammalian females, this requires reactivation, or decondensation, of the inactive X prior to or coincident with early meiotic prophase. In heterogametic males, the heteromorphic sex chromosomes are condensed, or inactivated, at meiotic prophase in order to prevent recombination events that would likely lead to rearranged or damaged sex chromosomes. Thus, in this view, sex chromosome transcriptional activity vs inactivity is a secondary consequence of an early meiotic event establishing chromatin configurations that are either permissive or nonpermissive for recombination. We have shown that this hypothesis is consistent with a substantial body of cytological and molecular data on the relationship between MSCI and other features of meiosis, such as sex chromosome heteromorphy and meiotic exchange.

Although this hypothesis is based on the exceptional behavior of sex chromosomes at meiosis, it provides a framework for investigation of the relationship between chromatin configuration and meiotic recombination in general. This hypothesis will almost certainly be modified as we learn more about molecular and comparative aspects of meiosis. However, it does focus on key issues concerning meiosis in higher eukaryotes, including timing of meiotic prophase events, the regulation of the initiation and distribution of recombination events, and the chromatin requirements of recombination. Experimental investigations of these issues are essential to enhance our knowledge of meiotic processes in general and the sexually dimorphic behavior of sex chromosomes at meiosis in particular.

Acknowledgements. We acknowledge NIH grants GM 40489 and GM 00522 (B.D.M.) and NSF grant DMB-8905117 (M.A.H.) for supporting work in our laboratories.

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