AN EFFECT OF CENTROMERE FUNCTION ON THE BEHAVIOR OF RING-*X* CHROMOSOMES IN *DROSOPHILA MELANOGASTER*[1]

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ABSTRACT

It is shown that under the influence of an autosomal meiotic mutant that causes abnormalities in meiotic centromere function (*mei-S332*), ring-*X* chromosomes are frequently nonrecoverable. Evidence is presented that this nonrecoverability is caused by a failure of sister ring-chromatids to successfully effect an equational separation with resultant dominant lethality. Because *mei-S332* results in meiotic abnormalities only after replication has been completed, and because ring chromosomes are normally transmitted with approximately the same efficiency as rod chromosomes, it is suggested that during replication in normal meioses, sister ring-chromatids form mutually interlocked ring complexes that are resolved without genetic consequences at anaphase II, with the resolution owing at least in part to normal centromere function.

SIMPLE three-dimensional considerations suggest that ring-shaped chromosomes should, as a consequence of replication, form mutually interlocked ring complexes; these, in turn, ought to result in either ring-chromosome loss or lethality. In fact, however, in Drosophila, ring chromosomes are generally at most only marginally less stable, both mitotically and meiotically, than are rod-shaped chromosomes.* This implies either that replication occurs in such a way that interlocked complexes are not formed or that, once formed, ring chromosomes can extricate themselves from such complexes without detectable genetic consequences. Some evidence favoring the latter alternative and suggesting that the centromere plays an essential role in effecting the resolution of interlocked complexes comes from an examination of ring-chromosome behavior in meiosis under the influence of a meiotic mutant that causes abnormalities in centromere function.

MATERIALS AND METHODS

The three sets of experiments, the results of which are reported below, monitor the behavior of various sex-chromosome types under the influence of the meiotic mutant *mei-S332*. This mutant is an autosomal euchromatic point mutant located at about 95 on the right arm of chromosome *2*. In *mei-S332* homozygotes of either sex there is a high frequency of precocious separation

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* There are a number of exceptions to this generality in Drosophila, and apparently some very important differences in ring-chromosome behavior among different forms. A detailed consideration of the meiotic mechanics of ring chromosomes is found in SANDLER (1964).

of sister centromeres late in meiosis I, resulting in correspondingly high frequencies of equational nondisjunction at anaphase II of all chromosomes in the complement. There is, in addition, frequent meiotic chromosome loss. Recombination, however, is normal. It is not known whether *mei-S332* causes a defect in meiotic centromere structure or in the regulation of the separation of sister centromeres, but in either event the meiotic mutant self-evidently results in abnormal meiotic centromere behavior. Because *mei-S332* has normal recombination and abnormal segregation, we will, in this report, suppose that early meiosis is unaffected by the meiotic mutant and therefore that its normal allele is not important then. While this seems reasonable, it should be explicitly noted that it may not be true and that the anomalous behavior of ring chromosomes in mutant meiocytes (see below) may be caused by mutant effects other than abnormal centromere behavior during the equational separation. For example, if *mei-S332*+ were involved in centromere replication, then ring chromosomes might become interlocked in mutant, but not in normal, meiocytes. The evidence for, and a discussion of, the cytogenetic properties of *mei-S332* is found in DAVIS (1971).

The sex-chromosome types in the first two sets of experiments to be reported are a ring-*X* chromosome (X^c) marked by the recessives *y*, *sn* and *g* and an identically marked rod chromosome that resulted from a spontaneous opening out of a ring. The rod chromosome is in inverted sequence, has a heterochromatic short arm and a distal heterochromatic segment. It is cytogenetically very similar to *In(1)EN* (see LINDSLEY and GRELL 1968). The ring chromosome was recovered from a newly constructed tandem metacentric compound-*X* chromosome (see below), while the *EN*-like rod derivative is from a ring originally recovered from an identically constructed tandem metacentric compound (by LINDSLEY and SANDLER 1965).

The last experiments to be reported involve a tandem metacentric compound-*X* chromosome that resulted from an exchange between the long arm of the *Y* chromosome of $X{\cdot}Y^L$, $In(1)sc^{4L}$ EN^R and the basal heterochromatin of a normal *X* chromosome. This type of construction is described in detail by LINDSLEY and SANDLER (1965).

All other chromosomes and all mutants used in these experiments are described in LINDSLEY and GRELL (1968), except *FM7*, a multiply inverted *X* chromosome marked by y^{s1d} w^a v^o *B*, that is described by MERRIAM (1969).

RESULTS

To examine the behavior of ring chromosomes with misbehaving centromeres, females heterozygous for the multiply inverted *X* chromosome, *FM7*, and either the ring-*X* chromosome or the *EN*-like rod derivative, and either heterozygous or homozygous for the meiotic mutant, *mei-S332*, were crossed to wild-type males. The results are presented in Table 1. In these experiments the inversions completely eliminate recombinants so that only two regular egg classes are produced: *FM7*-bearing and *X*- or X^c-bearing. Primary nondisjunction can be detected as matroclinous females (y^{s1d} *B*) or patroclinous males (+). The equational nondisjunction characteristic of *mei-S332* is detected as diplo-*FM7* females (y^{s1d} w^a *v B*), diplo-*X* or -X^c females (*y sn g*), and patroclinous males.

It is clear that the distribution of heterochromatin in, and the two-armed configuration of, the rod-*X* do not affect its response to *mei-S332*. Thus *FM7*-bearing and *X*-bearing eggs are equally frequent in heterozygous and homozygous *mei-S332* females; similarly, in homozygotes, diplo-*FM7* and diplo-*X* eggs are recovered approximately equally. The meiotic loss of chromosomes in meiotic-mutant-bearing females is seen by the excess of nullo-*X* eggs over the diplo exceptions. The few exceptions recovered in the control reflect the slight dominance of *mei-S332* (DAVIS 1971).

TABLE 1

Behavior of a ring-X chromosome in females under the influence of mei-S332

Results of crosses of females carrying the multiply inverted balancer, *FM7*, $y^{s1d}\ w^a\ v^o\ B$ and either a rod-shaped ring-derivative ($= X$) marked with *y sn g* or a ring-*X* chromosome ($= X^c$) marked with *y sn g* by *Canton-S* males.

The females are either heterozygous (Control) or homozygous (Experimental) for *mei-S332*.

		X/FM7				*X^c/FM7*			
		Control		Experimental		Control		Experimental	
Egg type	Phenotype	Number	Freq.	Number	Freq.	Number	Freq.	Number	Freq.
FM7	*B* ♀♀	5635	1.00	1455	1.00	2019	1.00	634	1.00
	$y^{s1d}\ w^a\ v\ B$ ♂♂	4276	0.76	1213	0.83	1520	0.75	511	0.81
	+ ♀♀	5353	0.95	1463	1.01	1810	0.90	424	0.67
*X**	*y sn g* ♂♂	4645	0.82	1250	0.86	1526	0.76	332	0.52
*FM7/X**	$y^{s1d}\ B$ ♀♀	9	<.01	31	0.02	10	<.01	3	<.01
FM7/FM7	$y^{s1d}\ w^a\ v\ B$ ♀♀	13	<.01	283	0.19	0	<.01	141	0.22
X/X**	*y sn g* ♀♀	8	<.01	224	0.15	1	<.01	29	0.05
0	+ ♂♂	84	0.01	1245	0.86	64	0.03	423	0.67

* *X* or X^c according to the cross.

From the ring controls it can be seen that the ring is only marginally, if at all, less transmissible than the rod. Under the influence of *mei-S332*, however, ring recovery is markedly reduced. Thus X^c-bearing eggs are recovered only two-thirds as often as *FM7*-bearing eggs, while diplo-*FM7* eggs are about four times more frequent than diplo-X^c-bearing ova. A ring that is not recovered might have been eliminated during the meiotic divisions to give rise to a nullo-*X* egg or it might have been included in the egg nucleus in such a way as to cause the death of the resulting zygote (i.e., have become a dominant lethal). The former will result in a relative increase in the nullo-*X* class corresponding to the decrease in the frequency of ring classes while the latter will not. The nullo-*X* class in the X^c experimental set is, if anything, relatively smaller than in the corresponding rod experiment.

It is concluded, therefore, that ring-*X* chromosomes in homozygous *mei-S332* females are not recovered with expected frequencies because a fraction of them become dominantly lethal. It is possible that the true situation is more complex than mere dominant lethality because the relative recovery of nullo-*X* eggs is in fact lower in the ring experimental set than in the rod experimental set. Whether this is relevant to ring chromosome behavior, however, is impossible to determine because there is considerable, and not understood, experiment-to-experiment variation in the recovery of the various gametic classes in *mei-S332* homozygotes (Davis 1971). In this report, therefore, we will ignore this difference; this will not affect the qualitative conclusions drawn, but may result in some error in estimating the proportion of rings that become dominantly lethal.

A set of experiments to examine ring recovery under the influence of *mei-S332* in males was performed. In this case, males carrying a *Y* chromosome marked by a y^+ allele translocated from an *X* chromosome ($= y^+Y$) and either the ring-*X* chromosome or the rod derivative and either heterozygous or homozygous for

TABLE 2

*Behavior of a ring-*X *chromosome in males under the influence of* mei-S332

Results of crosses of males carrying the y^+Y and either a rod-shaped ring-derivative ($=X$) marked with *y sn g* or a ring-X chromosome ($=X^c$) marked with *y sn g* by females carrying an attached-X chromosome homozygous for *y pn v* and no other sex chromosome. The males are either heterozygous (Control) or homozygous (Experimental) for *mei-S332*.

		X/Y				X^c/Y			
		Control		Experimental		Control		Experimental	
Sperm type	Phenotype	Number	Freq.	Number	Freq.	Number	Freq.	Number	Freq.
Y or YY	*pn v* ♀ ♀	8483	1.00	8985	1.00	2935	1.00	2362	1.00
X^*	*y sn g* ♂ ♂	7001	0.83	7473	0.83	1843	0.63	1832	0.78
X^*/Y	*sn g* ♂ ♂	4	<.01	112	0.01	6	<.01	31	0.01
X^*/X^*	*y sn g* ♀ ♀	2	<.01	1433	0.16	0	<.01	138	0.06
0	*y pn v* ♀ ♀	18	<.01	3723	0.41	53	0.02	912	0.39

* X or X^c according to the cross.

mei-S332 were crossed to females carrying an attached-X chromosome and no other sex chromosome. The results are presented in Table 2. In these experiments, the regular Y-bearing sperm are not distinguishable from the equational nondisjunctional diplo-Y bearing sperm. However, nullo-XY sperm, equational nondisjunctional diplo-X or diplo-X^c sperm, and primary nondisjunctional XY-bearing sperm can be detected (as *y pn v* ♀ ♀, *y sn g* ♀ ♀ and *sn g* ♂ ♂, respectively).

In the case of the rod X chromosome, it is clear that *mei-S332* does not affect the recovery of the X relative to the Y and there are many diplo-X sperm produced. Meiotic chromosome loss is evidenced by the large nullo-XY class.

In the case of the ring, however, the data are unfortunately less straightforward. A comparison of the ring and the rod experimental results suggests that ring behavior under the influence of *mei-S332* in males parallels that in females. Thus, diplo-X^c sperm are recovered, relative to Y-or-YY-bearing sperm, only about one-third as frequently as are diplo-X sperm, and there is no corresponding increase in the nullo-XY class. The X^c-bearing class may be reduced relative to X-bearing sperm but, if so, much less markedly than the diplo-X^c reduction. The X^c control, however, is anomalous since in that case ring recovery is lower than in any other cross; the reason for this is not clear.

It seems, therefore, most likely that ring behavior in *mei-S332* males is similar to ring behavior in females, but, owing to the uncertainties introduced by the ring control, we will concentrate on meiosis in the female in the analysis to follow.

In females it is clear that some fraction of ring chromosomes, because of their ring structure, becames dominantly lethal under the influence of *mei-S332*. The most obvious physical interpretation of this lethality is that it is caused by a failure of sister ring-chromatids to successfully separate from one another at the second meiotic division. A direct test of this proposition is to examine the anaphase II separation of a ring chromatid from a non-ring chromatid in *mei-S332* homozygotes. This can be accomplished by use of a tandem metacentric compound-X chromosome. Tandem metacentrics are two euchromatically complete X chromo-

TABLE 3

The behavior of a tandem metacentric compound-X chromosome (TM) *under the influence of* mei-S332

Results of crosses of females carrying tandem metacentric compound-*X* chromosomes homozygous for *y* and heterozygous for *v* and also carrying a *Y* chromosome with *y*+, either without (Control) or with (Experimental) *mei-S332*, by males carrying an attached-*XY* chromosome marked by *y B* and no other sex chromosome [= $Y^{S}X{\cdot}Y^{L}$, *In(1)EN, y B/0*].

Egg type	Phenotype	Control		Experimental	
		Number	Frequency	Number	Frequency
Y or *YY*	*B* ♂ ♂	4827	1.00	217	1.00
TM (?/+)	*y* ♀ ♀	1300	0.27	47	0.22
TM (*v*/*v*)	*y v* ♀ ♀	76	0.02		
X^{c} (*v* or +)	*y B* ♀ ♀	1410	0.29	57	0.26
	y ♂ ♂	1296	0.27	34	0.16
nullo-*XY*	*y B* ♂ ♂	244	0.05	240	1.11
TM/*Y*	*y*+ *B*+ ♀ ♀	4	<.01	1	<.01
X^{c}/*Y*	*y*+ *B* ♀ ♀	7	<.01	0	0.00
	y+ ♂ ♂	7	<.01	1	<.01

somes attached to a single medially located centromere and arranged in tandem so that the synaptic configuration is a spiral (NOVITSKI 1954). Exchange between the two elements of the compound results (from one-half of the single exchanges and one-quarter of the double exchanges) in a dyad composed of one single ring-*X* chromatid and one compound-*X* chromatid; it is the fate of these single rings that we wish to examine. The results of crosses of compound-bearing females with and without *mei-S332* are given in Table 3.

Two major complications prevent a direct comparison of ring recovery between *mei-S332* homozygotes and controls. First, NOVITSKI (1951) has shown that the disjunction of *TM*-X^{c} asymmetric dyads is nonrandom such that the ring chromatid is preferentially included in the functional egg nucleus. He demonstrated, furthermore, that nonrandom disjunction is a general property of asymmetric dyads; the smaller chromatid in any such dyad is included in the egg nucleus nonrandomly frequently. This phenomenon almost certainly depends upon the orientation of asymmetric dyads on the metaphase plate, which itself must depend upon the normal structure and function of unseparated sister centromeres. In *mei-S332* meiocytes it is precisely this situation that is abnormal, and therefore the extent of nonrandom disjunction in such meioses cannot be directly inferred from control values. The second complication is that one-half of the single exchanges and three-eighths of the double exchanges produce anaphase II bridges. Such bridges are normally lethal. However, this lethality most probably depends on normal centromere function, and therefore the fate of anaphase bridges may be abnormal in *mei-S332* meioses. Thus the experimental and control data in Table 3 are not directly comparable in this respect also.

The genetic consequences of exchange in tandem metacentric compound-*X*

chromosomes are set out in detail in LINDSLEY and SANDLER (1965). If E_i is the frequency of tetrads of exchange rank i, if $E_0 + E_1 + E_2 = 1$, if c is the probability of recovering a ring chromosome from a TM-X^c asymmetric dyad and if we use only one X^c class (i.e., the $y\ B\ ♀\ ♀$), then, in relative frequencies,

$$\begin{aligned}\text{Heterozygous } TM &= E_0 + \tfrac{1}{2}(1-c)E_1 + 1/8E_2\\ \text{Homozygous } TM &= 1/8(3-2c)E_2\\ X^c &= \tfrac{1}{2}\,c\,E_1 + 1/8(1+2c)E_2\\ \text{Lethal + nullo-}X &= \tfrac{1}{2}\,E_1 + 3/8\,E_2\ .\end{aligned}$$

In the controls we use 0.04 as the value for homozygous TM; this is twice the observed v homozygotes to account for undetected v^+ homozygotes. The total frequency of homozygosis will be only slightly underestimated by this procedure (LINDSLEY and SANDLER 1965). Heterozygous TM is, therefore, 0.25. The X^c class is directly 0.29. The lethal + nullo-X class is the total number of eggs that should have received an X centromere ($= B\ ♂\ ♂$) less the observed number that did receive one ($= y\ ♀\ ♀ + y\ v\ ♀\ ♀ + y\ B\ ♀\ ♀$) which, as a frequency, is 0.42. These equations, then, solve as $E_0 = 0.11$, $E_1 = 0.70$, $E_2 = 0.19$, and $c = 0.67$.

We turn now to the experimental set. First, we note four technical points. The data are very few because of the extreme sterility caused by the high frequency of aneuploidy owing both to the compound-X and to *mei-S332*. Secondly, because of the paucity of offspring per parental female, it was not possible to determine whether any particular parental female was or was not heterozygous for v; consequently homozygosis was not monitored in the experimental set. Thirdly, the effect of the meiotic mutant is evident in the large nullo-XY class, and in the small number of first division nondisjunctional types ($y^+\ B^+\ ♀\ ♀$, $y^+\ B\ ♀\ ♀$ and $y^+\ ♂\ ♂$); the equational exceptions characteristic of *mei-S332*, however, are virtually all lethal in tandem metacentric crosses. Finally, it can be seen that single-ring-bearing males ($y\ ♂\ ♂$) are not recovered as frequently as ring-bearing females in the experimental set. The reason for this is not understood, but these compounds have exhibited this same effect in the absence of *mei-S332*. We will, therefore, use the X^c-bearing females as a measure of the recovery of single ring-X chromosomes.

Because of the analytic complications caused by the many lethal classes and the uncertainty, already alluded to, about the fate of anaphase II bridges, we confine our attention here to the least problematic comparison that is informative with respect to the recoverability of single ring-X chromosomes: the ratio of tandem-metacentric-bearing females to single-ring-bearing females. From the equations given earlier, it can be seen that this ratio depends only on the exchange values and c. Moreover, since the exchange values are not affected by *mei-S332* we may use those from the control; thus this ratio is $(0.556 - 0.4c) \div (0.024 + 0.4c)$ which is, of course, 1.00 for $c = 0.67$. If, in the case of *mei-S332* females, nonrandom disjunction were lower, or rings became dominantly lethal, this ratio would increase (e.g., for $c = 0.50$, the ratio would be 1.6). In fact, as can be seen from Table 3, the ratio does not change, implying very strongly that single ring-X chromosomes under the influence of the meiotic mutant do not,

themselves, become dominantly lethal; it is, rather, a *pair* of separating sister-ring chromatids that results in dominant lethality.

DISCUSSION

From the foregoing it is clear that, in meiosis in females, ring-*X* chromosomes under the influence of *mei-S332* frequently become dominantly lethal. This dominant lethality is almost surely the consequence of the ring structure itself because the *EN*-like rod that was derived from a ring and is similar to a ring in having heterochromatic segments on both sides of the centromere does not exhibit any special properties in *mei-S332* meiocytes. Moreover, it seems most probable that the *mei-S332*-induced dominant lethality of ring chromosomes is caused by a failure of sister ring-chromatids to properly effect an equational separation because when, in the case of tandem metacentric compound-*X* chromosomes, the equational separation involves a ring from a non-ring, the ring does not appear to become dominantly lethal.

These observations, taken together with those of DAVIS (1971) showing that *mei-S332* causes meiotic anomalies only after the completion of replication and recombination (when ring chromosomes would be expected to become interlocked, implying that probably *mei-S332*$^+$ is not important at those early times), suggest that normally in meiosis ring chromosomes form mutually interlocked complexes that are resolved without genetic effects by proper centromere function. It is this resolution that often fails in *mei-S332* meiocytes owing to faulty centromere function.

If this general interpretation is accepted, then it is possible to make some very approximate estimates of the frequencies with which rings become interlocked and some inferences about the fate of such complexes. We begin by examining the behavior of *FM7* under the influence of *mei-S332* (Table 1, second column). Here, the recoveries were:

FM7-bearing eggs = 1,213
FM7/FM7-bearing eggs = 283
nullo-*FM7* eggs = 512 ($= \frac{1}{2} \times 1245 \times 0.83 \div 1.01$),

where the nullo-*FM7* class is estimated as one-half the nullo-*X* eggs grossly corrected for the viability difference between mutant and + flies. DAVIS (1971) has shown that it is convenient to separate the behavior of any chromosome at anaphase II under the influence of *mei-S332* into a fraction r that are not affected by the meiotic mutant and the remaining $(1-r)$ that are. Among the $(1-r)$ affected chromosomes, it is supposed that the two chromatids proceed to the anaphase II poles at random with any chromatid failing to be included in a daughter nucleus with probability p. Then,

FM7-bearing eggs $= r + \frac{1}{2}(1-r)(1-p^2)$
FM7/FM7-bearing eggs $= \frac{1}{4}(1-r)(1-p)^2$
nullo-*FM7* eggs $= \frac{1}{4}(1-r)(1+p)^2$,

which solve as $r = 0.216$ and $p = 0.144$.

Turning now to the behavior of the ring-X chromosome in homozygous *mei-S332* females (Table 1, last column), the results, treated as before and with respect to the two sex chromosomes separately, are:

Egg type	*FM7*	X^c
X	511	332
XX	141	29
0	174	174
	826	535

The *FM7* results are almost identical to those in the control, and therefore we adopt the values of r and p already computed.

There were 826 meioses that should have given rise to eggs with one ring, two rings or no ring of which 0.216 (= 178) were normal (i.e., produced an X^c-bearing egg). The remaining 648 (826 − 178) second division ring segregations are abnormal in that the two sister centromeres orient at random and each is lost p of the time. The special complication that we are now considering is that this can happen only in a fraction w of the cases in which the rings are not interlocked; in the remaining $(1-w)$ meiocytes there is some probability of dominant lethality. It seems reasonable to suppose that recoverable diplo-X^c-bearing eggs come (virtually) only from the noninterlocked fraction. Thus, if there were no interlocking and no ring loss, then $\frac{1}{4}(1-r)$ or 162 (648 ÷ 4) diplo-X^c-bearing eggs would have been recovered; only 29 were. This recovery, $29/162 = 0.179$, is therefore, $w(1-p)^2$, so that $w = 0.25$. That is, in three-quarters of meiocytes, sister ring-chromatids are interlocked. The 162 noninterlocked meioses, $w(1-r)$, will produce, after loss, 80 X^c-bearing and 54 nullo-X^c eggs in addition to the 29 diplo-X^c bearing eggs. This leaves 486 meiocytes in which the rings are interlocked and the centromeres misbehaving; these meiocytes produced 74 X^c-bearing and 120 nullo-X^c eggs. In one-half of these 486 meiocytes, the sister centromeres would be oriented to the same pole, giving 122 nullo-X^c eggs and 122 products that are evidently dominant lethals; this accounts for the nullo-X^c class. The 74 X^c-bearing eggs yet to be explained most probably represent cases in which among the separating sister centromers, the single rings pull free of the interlocked complex; in the remaining cases of this kind the interlocked complex apparently behaves like an anaphase II bridge—that is, it is dominantly lethal.

To summarize, in meiocytes in which the ring centromeres behave normally, sister ring chromatids are recovered as efficiently as rod chromatids. In those meiocytes in which ring-chromosome centromeres misbehave, the rings become dominantly lethal owing to unresolved interlocked complexes in two different ways: when sister centromeres separate, interlocked rings behave like anaphase II bridges; when an interlocked complex is included in the egg nucleus, lethality presumably results from anaphase bridge-like behavior in early cleavage divisions. That the behavior of centromeres in the early cleavage divisions in progeny of *mei-S332* homozygotes probably is abnormal has been observed by DAVIS (1971).

As noted above, an unexplained decrease in ring recovery in males without *mei-S332* makes any detailed analysis of the male experimental data meaningless. The one reasonably certain quantitative conclusion is that in *mei-S332* males, as in females, the diplo-X^c class is decreased and the nullo-X^c class is not increased. One calculation may be instructive. If the rod-X with *mei-S332* (Table 2, second column) is used to establish the parameters of the meiotic mutant, the results are that $r = 0.38$ and $p = 0.07$. If, in the experimental X^c set, the total number of meioses that should receive two, one or no rings is taken as the Y or YY class plus one-half of the nullo-XY class ($= 2818$), then $\frac{1}{4}(1-r)$ of these ($= 437$) should have been diplo-X^c, but only 138 were. As in the case of the female, $138/437 = w(1-p)^2$, so that $w = 0.34$. That is, by this analysis about two-thirds of rings in males are interlocked, a figure comparable to that in females.

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