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Relationships among chromatid interchanges, sister chromatid exchanges, and meiotic recombination in *Drosophila melanogaster*

(recombination-defective meiotic mutants/x-ray-induced aberrations in neuroblast cells)

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ABSTRACT **Repair- and recombination-defective mutations at two loci (*mei-9* and *mei-41*) of *Drosophila melanogaster* have been examined for their effects on the induction of chromosome aberrations by x-rays and the formation of sister chromatid exchanges (SCEs). Irradiation of larval neuroblast cells during the S phase with x-rays showed that mutants at both of these loci are about 10 times more sensitive than wild type to the induction of chromosome aberrations. The pattern of induced aberrations was characteristic for each mutant locus: in cells bearing *mei-9* mutations most breaks were chromatid deletions, whereas in the presence of *mei-41* mutations similar frequencies of chromatid and isochromatid deletions were observed. Furthermore, chromatid interchanges could not be induced in cells carrying *mei-9* alleles; therefore these mutations define a step necessary for chromatid rejoining. *mei-41* alleles also define a function involved in the formation of chromatid interchanges; total exchanges were less frequent than expected from nonmutant controls; and the proportion of exchanges arising by symmetrical rejoining was markedly reduced. These data indicate that chromatid and isochromatid deletions have different molecular steps in their formation, and that different molecular mechanisms are also involved in the symmetrical and unsymmetrical rejoining in chromatid interchanges. Neuroblast cells of larvae bearing *mei-9* and *mei-41* alleles were also treated for 13 hr with 5-bromodeoxyuridine at 9 μg/ml in order to differentiate sister chromatids for the scoring of SCEs. Whereas *mei-41* had a normal level of SCEs, *mei-9* exhibited a frequency of SCEs that was about 70% that of the control. Because both *mei-9* and *mei-41* mutations result in defective meiotic recombination, these data suggest that they define steps shared by symmetrical interchange formation and meiotic recombination that do not participate in the formation of most SCEs.**

Although the formation of chromosome aberrations, sister chromatid exchanges (SCEs), meiotic and mitotic recombinants, and many DNA repair processes all involve breakage and rejoining of DNA, the relationships among these processes are poorly understood. For example, although it has been well established that chromatid interchanges, SCEs, and meiotic recombination involve physical exchanges between whole chromatids, it is not known whether these exchanges occur via the same molecular mechanisms.

One approach to gaining insight into these relations is by a mutational dissection of the processes involved. This approach has been exploited with several rare inherited human diseases that affect DNA metabolism and mitotic chromosome stability. Cytological studies in Bloom syndrome, Fanconi anemia, and ataxia telangiectasia have shown that these conditions all increase the frequency of spontaneous chromosome aberrations (1–3). Whereas Fanconi anemia and ataxia telangiectasia do not affect the frequency of SCEs (4–6), in Bloom syndrome there is a dramatic increase in the incidence of SCEs (6). These results thus suggest that some chromosome aberrations and SCEs arise by mechanisms that are, at least in part, different.

In *Drosophila melanogaster* the past several years have witnessed a veritable explosion in the discovery of mutations that affect metabolism of chromsomal DNA (7–16). Two classes of mutants, meiotic mutants (mutants with altered recombination, chromosome segregation, or both during meiosis), and mutagen-sensitive mutants (mutants hypersensitive to killing by mutagens), have been shown to be rich sources of lesions in processes that are necessary for maintaining the integrity of mitotic chromosomes (10, 11, 17–19). In the present investigation we have studied the frequencies and patterns of x-ray-induced chromosome aberrations and the frequencies of SCEs in mutants with alterations at two of these loci (*mei-9* and *mei-41*). Mutations at the *mei-9* locus: decrease the frequency of meiotic recombination without altering the position of exchange events (7, 20); increase the frequency of spontaneous chromosome aberrations in somatic cells (11, 17–19), producing mostly chromatid deletions (18); do not increase the frequency of spontaneous mutations (A. T. C. Carpenter, personal communication); confer sensitivity to a wide range of mutagens and carcinogens (11, 12, 15, 17, 21); and reduce both repair replication and the rate of pyrimidine dimer excision (10, 13). Mutations at the *mei-41* locus: decrease the frequency of meiotic recombination and also alter the distribution along the chromosomes of exchange events (7); increase the frequency of spontaneous chromosome aberrations in somatic cells (11, 17, 18), producing both chromatid and isochromatid deletions (18); increase the frequency of both spontaneous and induced mutations (9); confer sensitivity to the same mutagen-carcinogens as *mei-9* (11, 12, 15, 17, 21); and are deficient in a caffeine-sensitive pathway of postreplication repair (14). Recent electron microscopic studies of meiosis in *mei-9*- and *mei-41*-bearing females have helped to delimit the roles of these loci in meiotic recombination (22).

MATERIALS AND METHODS

The mutant genes examined were *mei-9*^{a}, *mei-9*^{AT1}, *mei-41* and *mei-41*^{195} (7, 15, 18, 19). All these mutations are X-linked and were kept balanced over the multiply-inverted *FM7* chromosome (23). The wild-type Oregon-R stock was used as a control. All stocks were grown on standard *Drosophila* medium at 25 ± 1°C.

We dissected male third instar larvae in saline (0.7% NaCl) in order to obtain neural ganglia for examination of mitotic metaphases. After dissection the neural ganglia were transferred to petri dishes (Falcon, 35 × 10 mm) containing 2 ml of saline and irradiated with different doses of x-rays [180 kV, 6 mA, 3 mm Al, and 88 roentgens/min (1 roentgen = 2.58 × 10^{-4} coulombs/kg)], incubated at 25°C for 2 hr in saline followed by 2 hr in 10 μM colchicine, then fixed and squashed in ace-

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tic-orcein with our usual procedure (24). The slides were scored for the presence of chromatid deletions, isochromatid deletions, and chromatid interchanges. Aberrations produced by intrachromosomal events (e.g., rings, inversions, interstitial deletions) are not found in wild-type *Drosophila* (24, 25) and were also not observed in any of these mutants. It has been suggested that somatic pairing, by conferring rigidity on the paired homologues, prevents the formation of chromosome loops, which are prerequisite for the formation of intrachanges (24, 25).

To ensure that both the mutant and control metaphases collected in this manner came from cells irradiated during the S phase, samples of ganglia (both mutants and controls) were pulse labeled for 10 min with 5 μCi/ml (1 Ci = 3.7×10^{10} becquerels) of tritiated thymidine, washed three times in saline, irradiated, incubated 2 hr in saline followed by 2 hr in 10 μM colchicine, and then squashed under a siliconized coverslip. The coverslip was removed by dry ice and the slides, after air drying, were dipped in Kodak NTB2 emulsion. After 2 weeks of exposure at 4°C, the slides were developed for 2 min with Kodak D19, stained with 4% Giemsa (Merck) in phosphate buffer, and mounted in Euparal. These preparations were used only for scoring the frequency of labeled metaphases; chromosome aberrations were scored in slides not treated with tritiated thymidine.

In order to differentiate sister chromatids for the scoring of SCEs, ganglia were incubated in sterile saline supplemented with 20% fetal calf serum containing BrdUrd at 9 μg/ml for 13 hr and then processed according to the procedure of Gatti *et al.* (26).

RESULTS

Chromosome Aberrations. Our initial experiment addresses three questions with respect to the functions specified by the *mei-9*$^+$ and *mei-41*$^+$ loci. First, do the products of the normal alleles of *mei-9* and *mei-41* loci function in repair processes that reduce the probability that chromosome aberrations will be formed after mutagen damage? Second, what is the cause of different proportions of spontaneous chromatid vs. isochromatid breaks that occur in the presence of mutations at these two loci? Third, do the products of the wild-type alleles of these loci, which are utilized in meiotic recombination, also function in the generation of induced interchanges in mitotic cells? We approached these questions by x-irradiating cells during the S phase and determining the frequencies and types of chromosome aberrations found at the next metaphase (4 hr after irradiation). The results from two alleles at both the *mei-9* and *mei-41* loci as well as nonmutant controls are presented in Table 1. That the cells scored at metaphase were in fact in the S phase when irradiated is established by the fact that in all cases more than 90% of these cells were incorporating tritiated thymidine at the time irradiated (Table 1).

Mutations at both the *mei-9* and *mei-41* loci confer an extreme sensitivity to the induction of aberrations by x-rays. The frequencies of aberrations induced in these mutants are about an order of magnitude higher than those found in nonmutant controls irradiated with the same dose (Table 1). Thus the wild-type alleles of these loci normally function to remove x-ray-induced lesions that, if unrepaired, can lead to the production of chromosome aberrations.

Because nearly all aberrations observed in mutant cells irradiated with 220 roentgens are induced (Table 1) and arise as a consequence of the defects in chromosomal metabolism produced by the *mei-9* and *mei-41* mutations, these data can also be used to investigate the origin of the different patterns of spontaneous chromatid and isochromatid breaks occurring in the presence of *mei-9* and *mei-41* alleles (Table 1, ref. 18). These different patterns of breakage could be due to the spontaneous lesions that are the substrates of the products of these loci having very different probabilities, if unrepaired, of giving rise to chromatid and isochromatid breaks. Alternatively, different patterns of breakage could arise if the wild-type alleles of the *mei-9* and *mei-41* loci functioned during different portions of the cell cycle: whereas chromatid breaks must arise during S or G_2, isochromatid breaks can occur either via the duplication of a G_1 break or directly during S or G_2. The present data argue strongly against the latter possibility. Mutations at both loci confer hypersensitivity to the induction of chromatid aberrations by x-rays during the S phase, implying that products of the wild-type alleles normally function during this time. Moreover, the breaks induced by x-rays during the S phase in *mei-9* and *mei-41* exhibit the same proportions of chromatid and isochromatid deletions as found among spontaneous breaks in these mutants (Table 1): mostly chromatid deletions in *mei-9* alleles and similar frequencies of chromatid and isochromatid deletions in *mei-41* alleles. Because the array of primary lesions produced by x-rays is almost certainly the same in *mei-9*- and

Table 1. Chromosome aberrations produced by x-irradiating S-phase mitotic cells of meiotic-mutation-bearing males of *D. melanogaster*

Genotype	Dose, roentgens	Labeled cells, %	No. of cells	Breaks, % A	Breaks, % B	A/B	Exchanges C	Exchanges D, symmetrical	Exchanges E, asymmetrical	D/(D+E), %	Total exchanges, %	Total aberrations, %
Oregon-R	0	—	5000*	0.12	0.20	—	0	1	0	—	0.02	0.34
Oregon-R	220	93	500	4.00	10.20	0.39	0	1	4	—	1.00	15.20
Oregon-R	1320	92	1000	27.50	25.40	1.08	9	50	122	29.1	18.10	71.00
FM7	0	—	500†	—	0.20	—	0	0	0	—	0	0.20
FM7	220	94	2036	5.75	8.89	0.65	0	7	9	—	0.79	15.43
FM7	1320	94	1000	30.10	26.90	1.12	13	56	124	31.1	19.30	76.30
mei-9^a	0	—	1500*	7.00	1.57	4.77	0	0	0	—	0	8.47
mei-9^a	220	93	1000	117.80	13.70	8.60	0	1	0	—	0.10	131.60
mei-9^{AT1}	0	—	3000*	3.00	0.37	8.18	0	0	0	—	0	3.47
mei-9^{AT1}	220	92	1000	81.80	13.60	6.01	0	1	2	—	0.30	95.70
mei-41	0	—	1250*	4.32	3.04	1.42	0	0	0	—	0	7.36
mei-41	220	94	1000	50.50	46.00	1.10	4	12	86	12.3	10.20	106.60
mei-41^{195}	0	—	1600*	6.13	4.06	1.51	0	0	1	—	0.06	10.25
mei-41^{195}	220	91	1000	58.90	52.20	1.13	5	8	110	6.8	12.30	123.40

Column A, chromatid breaks per cell; column B, isochromatid breaks per cell; column C, triradials plus dicentrics.

* Data from ref. 24.

† Data from ref. 18.

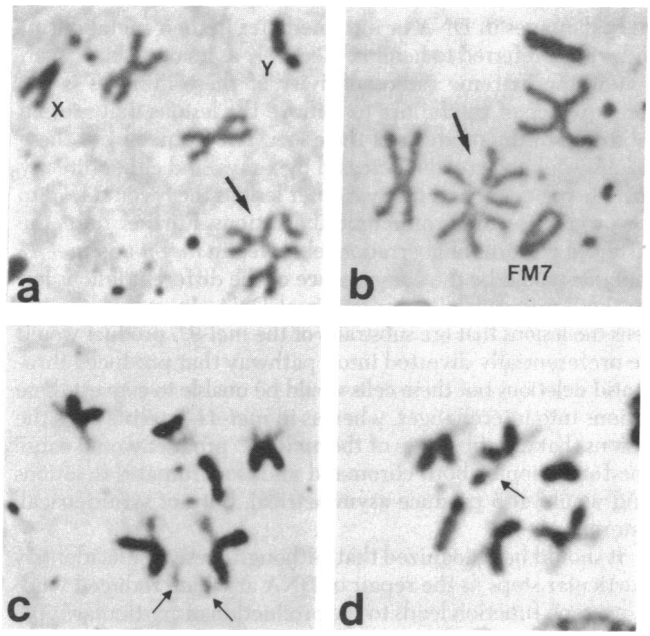

FIG. 1. Examples of interchanges and SCEs in neuroblast metaphases of *D. melanogaster*. (*a*) Asymmetrical interchange between autosomes; (*b*) symmetrical interchange between autosomes; (*c* and *d*) neuroblast cells treated with BrdUrd for two rounds of DNA replication and stained with fluorescence plus Giemsa technique. In *c* the arrows point to chromatid deletions involving the bifilarly substituted chromatids; in *d* the arrow points to a SCE.

mei-41-bearing cells, the finding of different patterns of x-ray-induced breakage in these mutants suggests that the types of lesions repaired by the normal alleles of these two loci lead to different spectra of aberrations if they are not repaired.

The final topic these data let us address is whether the *mei-9*$^+$ and *mei-41*$^+$ functions are needed for the production of chromatid interchanges in mitotic cells as well as meiotic exchange. An inspection of Table 1 reveals that chromatid interchanges cannot be induced in cells carrying either *mei-9* allele examined; thus the function specified by *mei-9*$^+$ is necessary for chromatid rejoining. These data also show that cells carrying *mei-41* alleles have a lower frequency of chromatid interchanges than would be expected on the basis of the results with control cells. Thus in Oregon-R males irradiated with 1320 roentgens there are 18% interchanges when the frequency of breaks (chromatid plus isochromatid deletions) is 53%. Similarly, in *FM7* males, irradiated with the same dose, there are 19% interchanges and 57% breaks. In *mei-41*, on the other hand, there are only 10% interchanges at a frequency of breaks of 96%; and in *mei-41*^{195} there are 12% interchanges and 111% breaks. Because the incidence of interchanges is expected to increase approximately as the square of the frequency of breaks, these data indicate that *mei-41*$^+$ function is also involved in chromatid rejoining.

Two types of interchanges—symmetrical (or X-type) and asymmetrical (or U-type)—are distinguishable (Fig. 1). A comparison of the relative proportions of these two types of interchanges found in cells bearing *mei-41* alleles to those found in control cells (Table 1) reveals a second way in which *mei-41* mutations affect interchanges. In both Oregon-R and *FM7* cells about 30% of the interchanges are symmetrical, whereas in *mei-41*- or *mei-14*^{195}-bearing cells symmetrical interchanges are only 12.3% and 6.8%, respectively, of the total interchanges. Thus it appears that mutations at the *mei-41* locus preferentially affect the formation of symmetrical interchanges. That the formations of symmetrical and asymmetrical exchanges are affected to comparable extents in *mei-9* mutants is suggested by the fact that of the four interchanges detected in cells carrying *mei-9* alleles two were symmetrical and two asymmetrical.

SCEs. To inquire whether the products of these loci are required for the formation of SCEs as well as meiotic recombination and the induction of interchanges, the frequencies of SCEs were determined in mutant and control cells after exposure to BrdUrd at 9 μg/ml for 13 hr. The results (Table 2; Fig. 1) show that in the presence of mutations at the *mei-41* locus the frequency of SCEs is the same as that found in the *FM7* cells used as controls. The frequency of SCEs in Oregon-R males exposed to the same concentration of BrdUrd is almost identical (11%) (26). On the other hand, in cells carrying the mutant alleles at *mei-9* the frequency of SCEs is about 70% of the control rate. Thus mutants at the *mei-9* locus are slightly defective in the formation of SCEs.

By scoring cells containing BrdUrd-substituted chromosomes for the presence of chromosome aberrations we could also inquire whether these mutations rendered the cells hypersensitive to damage by BrdUrd. Cells with mutant alleles of *mei-9* exposed to BrdUrd have a frequency of chromosome aberrations similar to that observed in untreated cells (cf. Table 1), whereas cells with mutant alleles at *mei-41* exhibit about twice as many aberrations as untreated cells. Thus *mei-41* mutants, in contrast to *mei-9* mutants, appear to be sensitive to the induction of aberrations by BrdUrd. A comparison of Table 2 with Table 1 shows that the BrdUrd increases both chromatid and isochromatid breaks in *mei-41* cells. Interestingly, most of the chromatid breaks scored in *mei-41* involve the BrdUrd bifilarly substituted chromatids, giving further support to the specific sensitivity of *mei-41* to BrdUrd.

These data also show that most of the chromatid deletions

Table 2. SCEs and chromosome aberrations in meiotic mutants exposed to BrdUrd (9 μg/ml) for two rounds of DNA replication

Genotype	Cells scored	SCEs		Chromatid deletions*					Isochromatid deletions		Total aberrations, %	Chromatid/ isochromatid deletions
		No.	%	A	B	C	Total	%	No.	%		
FM7/Y	678	74	10.91	1	0	0	1	0.14	2	0.29	0.43	—
mei-9^a*/Y*	605	45†	7.44	19	26	3	48	7.93	6	0.99	8.92	8.00
mei-9^{AT1}*/Y*	624	44‡	7.05	19	14	2	35	5.60	4	0.64	6.24	11.00
mei-41/Y	658	69	10.48	55	17	5	77	11.70	39	5.92	17.62	1.97
mei-41^{195}*/Y*	837	91	10.87	101	12	1	114	13.62	70	8.36	21.98	1.63

At least 15 ganglia were examined for each genotype.

* Columns A and B, true chromatid deletions without SCE at the level of the break, involving the bifilarly and the unifilarly substituted chromatids, respectively. Column C, incomplete SCEs.

† Significantly different from the control in χ^2 test ($\chi^2 = 4.59$; $P < 0.05$)

‡ Significantly different from the control in χ^2 test ($\chi^2 = 5.88$; $P < 0.025$)

observed in *mei-9* and *mei-41* mutants are true chromatid breaks and not incomplete SCEs. Wolff and Bodycote (27), examining Chinese hamster cells, found 376 true deletions and 32 deletions resulting from incomplete SCEs. In mutants at *mei-9* and *mei-41* there is an even smaller proportion of deletions resulting from incomplete SCEs, but the lack of pertinent controls does not allow us to determine whether these mutations affect the frequency of incomplete SCEs.

DISCUSSION

Chromosome Aberrations. The two loci—*mei-9* and *mei-41*—at which we used mutants to investigate the origin of chromosome aberrations are among the best-characterized repair-defective loci in *Drosophila*. Mutants at the *mei-9* locus reduce both repair replication and the rate of pyrimidine dimer excision and are defective in a postincision step of excision repair (10, 13, 28). *mei-41* mutants are defective in a caffeine-sensitive pathway of postreplication repair (14). The present data show that concomitant with these repair defects both *mei-9* and *mei-41* mutations confer hypersensitivity to the induction of chromosome aberrations by x-rays. After irradiation, total chromosome aberrations are about an order of magnitude more frequent in both *mei-9* and *mei-41* mutants than they are in controls. However, strikingly different patterns of chromosome aberrations are induced in the presence of mutations at these two loci. In the presence of *mei-9* alleles most induced breaks are chromatid deletions and chromatid interchanges are not inducible, whereas in the presence of *mei-41* alleles equivalent frequencies of chromatid and isochromatid deletions are produced and the formation of X-type chromatid interchanges is preferentially reduced. Alleles show the same pattern of chromosome aberrations, demonstrating that the patterns of aberrations are properties of the loci.

Many types of chromosome aberrations are the end products of a complex series of DNA metabolic events (29). There are several general ways in which mutations such as *mei-9* and *mei-41* can be imagined to result in the formation of unique patterns of chromosome aberrations after mutagen damage.

One way in which mutations at different DNA repair loci can effect the production of different patterns of chromosome aberrations is by being defective in different portions of the cell cycle. In the present case the data, as discussed above, clearly establish that this is not the explanation for the different patterns of aberrations produced in *mei-9* and *mei-41* mutants.

An alternative mechanism by which mutations might affect the production of chromosome aberrations is by altering the spatial arrangement of chromosomes. For example, Revell (30) suggested that both chromatid and isochromatid deletions may originate from complete or incomplete intrachanges occurring in looped regions of chromosomes, and considerations of the origins of symmetrical and asymmetrical exchanges in other systems have led to suggestions that the spatial arrangement of chromosomes may also affect the types of exchange events produced (31). However, because (*i*) our observations suggest somatic pairing is normal in these mutants and (*ii*) both *mei-9* and *mei-41* mutants have well-defined lesions in DNA repair processes, it is not necessary to postulate an additional effect of these mutations on the arrangement of interphase chromosomes in order to account for the patterns of aberrations produced.

A final way in which we can conceive of mutations affecting the types of aberrations that are generated after mutagen damage is by altering the metabolism of lesions in DNA. Thus we assume that *mei-9*$^+$ and *mei-41*$^+$ function in the removal of spontaneous as well as x-ray-induced abnormalities in chromosomal DNA. These abnormalities could be either primary damages in DNA or intermediates in their metabolism, and will be referred to herein collectively as lesions. Under such a view the extreme radiosensitivity of these mutants is the consequence of the failure to remove the lesions that are the substrates of the products of these loci. The frequency of these lesions would be greatly increased by x-rays, and either directly or by being converted into yet other lesions they would lead to the production of chromosome aberrations. Furthermore, the different patterns of aberrations observed in *mei-9* and *mei-41* mutants would be the consequence of the different lesions left by these mutations in chromosomal DNA. In *mei-9*-bearing cells the lesions that are substrates of the *mei-9*$^+$ product would be preferentially diverted into a pathway that produces chromatid deletions but these cells would be unable to convert these lesions into interchanges, whereas in *mei-41*-bearing cells the lesions that are substrates of the *mei-41*$^+$ product would cause the formation of both chromatid and isochromatid deletions and would also produce asymmetrical, but not symmetrical, interchanges.

It should be recognized that, although these results identify particular steps in the repair of DNA at which reduced wild-type gene function leads to the production of particular types of aberrations, this does not tell us whether there is one or more than one pathway of DNA metabolism by which cells can generate a particular type of aberration.

These data provide some insights into the relationships between the processes that lead to the generation of chromosome aberrations. The different proportion of chromatid and isochromatid deletions observed in *mei-9* and *mei-41* mutants strongly suggests that the mechanisms by which these two types of breaks arise differ in at least some steps. Similarly, the fact that *mei-41* mutations preferentially affect the formation of symmetrical exchanges provides strong evidence for different origins of X- and U-type exchanges. Moreover, it is striking that *mei-9* and *mei-41* mutants are both defective in carrying out meiotic recombination and also in producing mitotic interchanges.

SCEs. In *D. melanogaster* SCEs are induced by the BrdUrd treatments used to detect them, because they are not found after treatments with low concentrations of BrdUrd (1 μg/ml) but are found after exposure to higher concentrations (e.g., 9 μg/ml) (26).

At the concentration of BrdUrd used in our studies (9 μg/ml), *mei-9* and *mei-41* mutants, which exhibit an about 30-fold increase in the frequency of spontaneous chromosome aberrations, do not show a corresponding large increase in the frequency of SCEs. Indeed, the level of SCEs in *mei-41* mutants does not differ from that found in nonmutant controls, whereas in *mei-9* mutants SCEs occur at about 70% of control rates.

Discordance between effects on chromosome aberrations and SCEs are also found in a number of other circumstances. Thus, an increase in the frequency of SCEs is not observed in the human diseases ataxia telangiectasia and Fanconi anemia (4, 6), which cause high levels of spontaneous chromosome aberrations (1–3), although in Bloom syndrome there is a concomitant increase in both aberrations and SCEs (1–3, 6). Furthermore, in a series of experiments involving chemical and physical mutagenesis, many cases were found in which substantial increases in the frequency of chromosome aberrations were not paralleled by an increase in the frequency of SCEs (for review see refs. 32 and 33). Taken as a whole, these data indicate that the chromosomal lesions responsible for the formation of SCEs are generally different from those that cause chromosome aberrations. Additional support for this conclusion is provided by the observation that mutants at other loci (*mus-102, mus-105,* and *mus-109*) that produce elevated frequencies of chromo-

some aberrations in nonmutagenized somatic cells (18) do not produce a concomitant increase in the frequency of SCEs (unpublished observation).

In early studies of SCEs, it was postulated that the formation of SCEs depended upon some form of postreplication repair (32, 33). However, subsequent studies showed that normal levels of SCEs were present in the variant forms of xeroderma pigmentosum with normal excision repair ability but defective in postreplication repair (34, 35). Our data show that *mei-41* mutants, which are defective in a caffeine-sensitive pathway of postreplication repair (14), have normal levels of SCEs. A normal SCE level has been also observed in *mus-104* (unpublished observations), which is defective in a caffeine-insensitive pathway of postreplication repair (14). This supports the notion that formation of SCEs is not a cytological manifestation of postreplication repair.

mei-9 mutants, which are defective in a postincision step of excision repair, do exhibit a slight reduction in the level of SCEs. However, the forms of xeroderma pigmentosum defective in the first steps of excision repair have normal frequencies of SCEs (34). The other characteristics of the *mei-9* mutants that distinguish them from excision-defective xeroderma pigmentosum mutants (34, 36) are: (*i*) their effects on somatic chromosome stability (11, 17, 18); (*ii*) their extreme sensitivity to methyl methane-sulfonate and ionizing radiations (11, 13, 15, 17); and (*iii*) their effects on the frequency of meiotic recombination (7, 20). Taken as a whole, these data indicate that *mei-9*$^+$ specifies a function different from the functions defective in patients with xeroderma pigmentosum.

Mutations at *mei-9* have dramatic effects on meiotic crossing over (reduced to 8% of the wild-type) (7) and are severely defective in the formation of chromatid interchanges after x-irradiation; however, they produce only a slight decrease in the frequency of SCEs (70% of the wild-type). This suggests that *mei-9*$^+$ may have only a peripheral role in the formation of SCEs. Alternatively, if, as proposed by Kato (35, 37), SCEs arise via two mechanisms—one operating at replicating points at DNA and the other acting postreplicationally in a fashion similar to meiotic crossing over—then mutations at *mei-9* could inhibit the formation of those SCEs that arise by the latter mechanism.

Meiotic crossing over, symmetrical chromatid interchanges, and SCEs all involve X-type physical exchanges of whole chromatids, and, at least superficially, might be expected to be generated by similar, if not identical, sequences of events. Nevertheless, our data clearly demonstrate that these three phenomena do not have common molecular mechanisms of formation. *mei-9* and *mei-41* mutants, which are both defective in meiotic recombination, exhibit a parallel defect in X-type rejoining in interchanges, but do not greatly affect the incidence of SCEs. Thus it can be suggested that symmetrical chromatid interchanges, but not SCEs, arise with mechanisms similar to those of meiotic recombination.

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