Proc. Natl. Acad. Sci. USA
Vol. 77, No. 1. pp. 503–507, January 1980
Genetics

The *RAD*52 gene is required for homothallic interconversion of mating types and spontaneous mitotic recombination in yeast

(recombination deficiency/radiation sensitivity/mating type switching/*Saccharomyces cerevisiae*)

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Communicated by Franklin W. Stahl, August 13, 1979

ABSTRACT **The *rad*52-1 mutation prevents homothallic mating type interconversion and reduces mitotic recombination in yeast. It has been previously reported that *rad*52-1 abolishes meiotic recombination. These data suggest either that a generalized recombination function(s) is required for mating type switching or that generalized recombination and specific homothallic functions are jointly controlled by the *RAD*52 gene. The *rad*52-1 mutation affects the interconversion of the two yeast mating types (*a* and *α*) differently, suggesting that the interconversion process is not equivalent for both mating types. This type of asymmetry is not predicted by current models of homothallic switching.**

The yeast *Saccharomyces cerevisiae* exhibits both heterothallic and homothallic life cycles, which are controlled by a number of specific genes. In the heterothallic life cycle, the two haploid cell mating types (*a* and *α*) are stable and can efficiently mate with one another to form nonmating (N) *a*/*α* diploids. Diploid *a*/*α* cells can grow vegetatively or be induced by the appropriate conditions (e.g., nitrogen and glucose starvation) to undergo meiosis and sporulation giving rise to asci containing 2 *a* and 2 *α* haploid ascospores. Tetrad analysis indicates that mating phenotype is controlled by two alleles of the *MAT* locus, designated *MATa* and *MATα*, located 25 map units from the centromere of chromosome III.

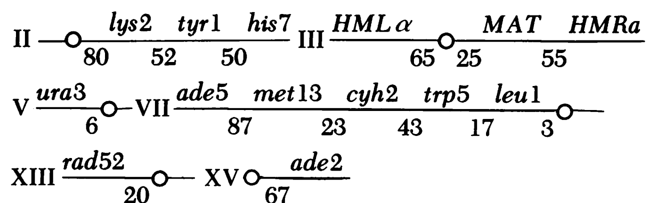
In contrast to the stability of mating type in heterothallic strains, homothallic cells frequently switch from one mating type to the other (1, 2). The high frequency of mating type interconversion is promoted by a dominant allele of the homothallism locus, *HO*. In the presence of *HO*, interconversion of mating types occurs repeatedly until haploids of opposite mating type mate to form N *a*/*α* diploids in which the *HO* allele no longer causes switching (1, 2). The changes in mating type result from heritable alterations at the *MAT* locus. The newly expressed mating type allele is indistinguishable from the normal *MATa* or MAT*α* alleles and is stable when *HO* is removed by outcrossing to heterothallic *ho* strains. Sporulation of *HO*/*HO* homothallic diploids gives rise to 2 *a* and 2 *α* haploid spores; within a few generations of germination, mating type interconversion and mating between cells of opposite type lead to spore clones that contain predominantly N *a*/*α* diploids (3).

In addition to the *HO* locus, two loci located on chromosome III, *HMLα* and *HMRa*, are required for mating type switching (3, 4). A number of lines of evidence (1, 4–6) have led to the proposal that *HMLα* and *HMRa* are copies of the *MATα* and *MATa* alleles that are not expressed, but which act as repositories of information that can be inserted into the *MAT* locus in the presence of the *HO* allele. This evidence indicates that the original *MAT* information is lost and the *HMLα* and *HMRa* loci remain unchanged. One specific model for the informational exchange, the "cassette" model (5), proposes that a copy of the *HMLα* or *HMRa* locus is made and subsequently transposed into the *MAT* locus by a mechanism analogous to that proposed for bacterial transposition (7, 8).

Genetic recombination appears to be involved in the control of gene expression in a number of other systems [e.g., immunoglobulin production in mammalian cells (9), phase variation of flagellar proteins in *Salmonella* (10), and controlling elements in maize (11)]. These observations support the notion that recombination may be an important process in cell differentiation. The purpose of the present study was to determine whether generalized recombination functions might be involved in the specific control of cell type during homothallic switching in yeast. To alter recombination we used *rad*52-1, originally isolated as a mutation conferring x-ray sensitivity and reduced sporulation (12), which has recently been reported to abolish meiotic recombination (13, 14). We therefore asked whether the *RAD*52 gene product was required for mating type interconversion.

MATERIALS AND METHODS

Strains. The relevant genotypes of the strains used are shown in Table 1. The *rad*52-1 mutation was obtained from strain LP582-3D, kindly sent by L. Prakash. Segregation of *rad*52-1 was followed by inability to grow on plates containing methyl methanesulfonate (MMS). To develop relatively isogenic *rad*52-1 and *RAD*52 strains, we performed three rounds of backcrosses between our *RAD*52 laboratory stocks and *rad*52-1 segregants. Complementation tests indicated that the *rad*52-1 mutation used in our experiments was allelic to a *rad*52-1 mutation obtained from the Berkeley Yeast Genetic Stock Center (strain g160/2d). Most of the experiments described were performed in two different, though related, genetic backgrounds to minimize artifacts due to strain differences. The linkage relationships of the genetic loci used are shown below:



Roman numerals refer to the chromosome number; numbers below the line refer to map distances between loci (15). Gene symbols are defined in Plischke et al. (16), except for *MAT*, *HO*, *HMLα*, and *HMRa*, which are defined in the text, according to conventions adopted by the Ninth International Conference

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Abbreviations: N, nonmating, sporulating; MMS, methyl methanesulfonate.

Table 1. Relevant genotypes of strains used

Strain	Relevant genotype	Source
RM27	*a RAD52 HO ade2-1* / *α RAD52 HO ade2-1*	This study
RM37	*a RAD52 HO ade2-1* / *α rad52-1 ho ade2-1*	This study
RM37-1D	*a rad52-1 HO*	
RM38	*a RAD52 HO ade2-1* / *α rad52-1 ho ade2-1*	This study
RM39	*a rad52-1 HO ade2-1* / *α RAD52 HO ade2-1*	This study
RM40	*a rad52-1 HO ade2-1* / *α RAD52 HO ade2-1*	This study
RM41	*a rad52-1 ho* / *α rad52-1 ho*	This study
RM42	*a rad52-1 ho* / *α rad52-1 ho*	This study
TI	*a ade1*	This study
TII	*α ade1*	This study
W223-1D	*a asp5*	R. Rothstein
W223-9A	*α asp5*	R. Rothstein
W224-1C	*a his6 leu2*	R. Rothstein
W224-1D	*α his6 leu2*	R. Rothstein

The auxotrophic mutations shown were used to select for diploids in mating type tests; all strains contained various other auxotrophic mutations as well.

on Yeast Genetics and Molecular Biology, Rochester, NY, 1978; the position of the centromere is indicated by a circle.

Media and Techniques. The recipes for all media used have been described (17). MMS plates are YPD plates containing 0.008% MMS (Eastman Kodak). Standard techniques were used for sporulation, dissection, testing of auxotrophic requirements, and prototroph selection of diploids (18, 19). Strains of *MATa* or *MATα* genotype are defined as those that mate exclusively with haploid *MATα* or *MATa* mating type testers, respectively. The term *nonmating* (N) has been used to encompass a range of mating responses seen in *a/α* vegetative diploid cells, ranging from complete nonmating to a variable degree of "bisexual" mating with both mating type testers.

Determination of Mitotic Recombination Frequencies. Single colonies from a recently constructed diploid were picked into 1 ml of sterile water and cell concentration was determined by hemocytometer count. Approximately 500 cells per ml were inoculated into 20 ml of YPD medium and the culture was grown at 25°C until a cell concentration of about 2×10^7 cells per ml was obtained. Each culture was started from an independent colony. Cells were washed twice in an equal volume of sterile water and plated at various dilutions on complete media, media lacking an auxotrophic requirement, and complete media containing cycloheximide. Plates were counted after 3 days of incubation at 30°C.

Table 3. Mating phenotypes of *rad52-1* and *RAD52* spores

Spore genotype	Mating phenotypes of spores: Whole tetrads*			Total viable spores†		
	a	*α*	N‡	*a*	*α*	N‡
rad52-1	71	45	0	103	62	0
RAD52	14	25	69	48	49	112
Total	85	70	69	151	111	112

* Data from the same 60 tetrads described in Table 2 minus four tetrads that became contaminated prior to tests for MMS sensitivity.

† Data from all viable spores from 125 asci of RM37 and RM38, including those from whole tetrads.

‡ All nonmaters were capable of sporulation.

Isolation of MMS-Resistant Revertants of *rad52-1*. A single colony of RM37-1D was picked into 1 ml of sterile water and cell concentration was determined by hemocytometer count. Approximately 10^5 cells were plated on a YPD plate and allowed to grow into a lawn at 30°C. The lawn was replica plated to an MMS plate and 11 normal-sized colonies were picked from a background of many tiny colonies. These colonies were purified and analyzed further. From the original water suspension, 10^4 cells were also plated on each of 10 MMS plates and no MMS-resistant colonies were observed. This result suggests that no MMS-resistant colonies were present in the 10^5 cells that formed the YPD lawn, and implies that most of the MMS-resistant revertants arose independently.

RESULTS

Homothallic Switching Is Prevented by the *rad52-1* Mutation. To determine the effect of *rad52-1* on the *HO* allele, two diploids (RM37 and RM38) were constructed, each heterozygous for *rad52-1* and *HO*. Analysis of the segregation of mating type in such diploids showed that the majority of tetrads (40/60) failed to segregate as expected for an *ho/HO* diploid (i.e., 2 maters: 2 nonmaters, see Table 2). Instead, an excess of maters was observed. Furthermore, analysis of the mating phenotypes of *rad52-1* and *RAD52* spore clones indicated that there were no *rad52-1* nonmaters (Table 3). These data suggested that *rad52-1* prevents the expression of the *HO* gene. We therefore predicted that in tetrads containing only one N spore (i.e., *RAD52 HO*), the other *HO* allele must be present in one of the two *rad52-1* spores. To test this prediction, both *rad52-1* segregants from tetrads containing one N spore clone were outcrossed to wild-type heterothallic (*RAD52 ho*) haploids of opposite mating type (Table 4). In every case, one of the

Table 2. Mating type segregation in *a/α HO/ho* diploids

Diploid	Genotype	Mating phenotypes* of tetrads: 2 M:2 N			3 M:1 N		4 M:0 N
		2 *a*:2 N	2 *α*:2 N	1 *a*:1 *α*:2 N	2 *a*:1 *α*: 1 N	1 *a*:2 *α*:1 N	2 *a*:2 *α*
RM37	*RAD52/rad52-1*	0	2	5	6	5	0
RM38	*RAD52/rad52-1*	4	2	7	18	11	0
	Total	4	4	12	24	16	0
Wild type†	*RAD52/RAD52*	7	5	24	0	0	0

Data were obtained from asci with 4 viable spores. Mating phenotypes were determined by crosses with all three mating type tester pairs (TI, TII; W223-1D, W223-9A; W224-1C, W224-1D). All spore clones were examined for ability to sporulate; all N spore clones (and only N spore clones) were capable of sporulation.

* M refers to maters with either *a* or *α* phenotype.

† Wild-type data were provided by S. Klapholz from dissections of two diploids that are closely related to the *RAD52* strains used to construct RM37 and RM38.

Table 4. Outcrosses of *rad*52-1 spores from tetrads containing only one N spore to test for the presence of a cryptic *HO* gene

*rad*52-1 spores	Mating phenotype	Outcrosses to *a* and *α* mating testers: Tetrads dissected	Spore viability, %	Spore mating phenotype: *a*	*α*	N
Strain RM37						
1A*	*α*	5	60	6	6	0
1D*	*a*	5	75	8	4	3
15A	*a*	5	75	8	2	5
15C	*α*	5	80	8	8	0
17B	*α*	5	85	10	7	0
17C	*a*	5	65	6	2	5
Strain RM38						
5A†	*α*	5	90	9	9	0
5B†	*a*	5	55	3	4	4
6A†	*a*	5	85	7	5	3
6B†	*a*	5	90	9	9	0
17A	*α*	5	90	10	8	0
17B	*a*	5	65	7	3	3
18A	*a*	5	66	6	3	3
18C	*α*	5	79	7	6	0
20A	*α*	5	55	6	5	0
20C	*a*	5	74	7	3	4
61C	*a*	5	80	8	4	4
61D	*α*	5	85	8	9	0
64A	*a*	25	81	29	25	24
64C	*α*	25	89	41	46	0

All outcrosses were made with *RAD*52 heterothallic haploid testers. Crosses were done with TI or TII unless otherwise noted. All spores produced in outcrosses were also tested for sporulation, and all N spore clones were capable of sporulation. The presence of N sporulating segregants in an outcross indicates a cryptic *HO* gene in the *rad*52-1 spore.

* Outcrosses to W223-1D, W223-9A.

† Outcrosses to W224-1C, W224-1D.

*rad*52-1 segregants harbored a cryptic *HO* allele. It should be emphasized that in these outcrosses, as in RM37 and RM38, only *RAD*52 spore clones showed a N phenotype. Segregation of mating phenotypes in the outcrosses of *rad*52-1 *HO* × *RAD*52 *ho* was completely consistent with the segregation pattern in Table 2. All *rad*52-1 spores containing the cryptic *HO* gene were stable haploids. More than 800 colonies from 11 *rad*52-1 *HO* spore clones were tested for mating type and sporulation ability, and all retained their haploid mating phenotypes and did not sporulate. In a similar experiment with colonies obtained from *RAD*52 *HO* spore clones, all (100/100) had a N sporulating phenotype (data not shown).

Spores of Genotype *rad*52-1 *α* *HO* Are Inviable. The data in Table 3 indicate that *rad*52-1 *a* segregants exceed *rad*52-1 *α* segregants by a factor of about 1.6. Moreover, the data in

Table 5. Evidence that spores of genotype *rad*52-1 *α HO* are inviable

A. Spore mating phenotypes from asci with three viable spores

*rad*52-1 spores: *a*	*α*	N	*RAD*52 spores: *a*	*α*	N
31	17	0	24	31	39

B. Tetrad types containing one N spore

	rad a *rad a* *RAD α* *RAD* N	*rad a* *rad α* *RAD α* *RAD* N	*rad a* *rad α* *RAD a* *RAD* N	*rad α* *rad α* *RAD a* *RAD* N
Number	11	12	15	0
Expected	8	11	11	8

Data were obtained from dissection of RM37 and RM38 *rad*52-1/*RAD*52 *α/a ho/HO*. The expected values are calculated by using the known map distances of the *RAD*52 and *MAT* loci from their centromeres on chromosomes XIII and III, respectively. For the calculation it was assumed that second-division segregation frequency was twice the map distance and that *rad*52-1 *α HO* spores were viable. The expected ratio of parental:nonparental:tetratype asci for *rad*52 and *MAT* is 1:1:3. The probability that the differences between the observed and the expected are due to random chance is less than 0.025 ($\chi^2 = 10.8$).

Table 4 show that in all tetrads containing one N spore clone, where one *rad*52-1 segregant was *a* and the other *α*, the *a* spore always contained the cryptic *HO* allele. Because the *MAT* locus and *rad*52-1 are on different chromosomes, the probability that all nine *rad*52-1 *HO* spores would contain the *a* allele is $(1/2)^9$ or 0.002. Both these observations suggested that spores of genotype *rad*52-1 *α HO* are inviable. Two additional observations from the analysis of RM37 and RM38 supported this contention. First, among those tetrads with only three viable spores, *rad*52-1 *a* spores exceeded *rad*52-1 *α* spores by approximately 2 to 1 (Table 5A). Second, among the four expected segregation patterns for tetrads containing one N spore, in which one *rad*52-1 spore must harbor a cryptic *HO* allele, tetrads in which both *rad*52-1 spores were *α* were not observed (Table 5B). To prove unequivocally that the genotype *rad*52 *α HO* was inviable, two diploids of genotype *rad*52-1/*RAD*52 *a*/*α HO*/*HO* were analyzed. The spore viability patterns obtained were exactly those predicted (see Table 6). Furthermore, *RAD*52 spores exceeded *rad*52-1 spores by a factor of 2, and all *rad*52-1 spores had the *a* mating phenotype. We conclude that cells of the genotype *rad*52-1 *α HO* are inviable.

Revertants of *rad*52-1. In order to rule out the possibility that homothallic switching was inhibited by a mutation tightly linked to *rad*52-1, rather than *rad*52-1 itself, we isolated 11 revertants of *rad*52-1 *a HO* that were resistant to MMS; the majority of these should have been independent. Each revertant exhibited a N phenotype, sporulated, and generated viable spores (Table 7). Each of the spore clones derived from the revertants had a N phenotype and sporulated. These results are

Table 6. Segregation data from *rad*52-1/*RAD*52 *a*/*α HO*/*HO* diploids

Diploid	Tetrad survival patterns, Viable:inviable spores: 4:0	3:1	2:2	1:3	0:4	% viable	Mating phenotypes of spore clones, *rad*52-1 spores: *a*	*α*	N	*RAD*52 spores: *a*	*α*	N
RM39	3	10	5	0	1	68	17	0	0	0	0	35
RM40	2	14	2	0	0	75	15	0	0	0	0	39
Total	5	24	7	0	1	72	32	0	0	0	0	74
Expected*	7.4	22.2	7.4	0	0	75	35	0	0	0	0	70

RM39 and RM40 were made by crossing *rad*52-1 *a HO* × *RAD*52/*RAD*52 *a*/*α HO*/*HO* spores.

* Expected tetrad survival and mating phenotypes are calculated as in Table 5 except that spores of genotype *rad*52-1 *α HO* are assumed to be inviable ($\chi^2 = 0.71$, $P = 0.70$).

Table 7. Properties of MMS-resistant revertants isolated from a *rad*52-1 *HO a* haploid

Name	Phenotype*	Mating phenotype	Sporulation, %	Spore viability, %
R-1	MMS^r	N	15	100
R-2	MMS^r	N	75	50
R-3	MMS^r	N	88	100
R-4	MMS^r	N	35	90
R-5	MMS^r	N	68	95
R-6	MMS^r	N	61	85
R-7	MMS^r	N	78	90
R-8	MMS^r	N	4	88
R-10	MMS^r	N	61	95
R-11	MMS^r	N	59	95
R-12	MMS^r	N	52	90
RM-37-1D	MMS^s	*a*	0	—
RM41	MMS^s	N	11	<1

MMS-resistant revertants were isolated from RM37-1D as described in the text. RM41 (*rad*52-1/*rad*52-1 *a*/α *ho*/*ho*) is shown for comparison.

* MMS^r, MMS-resistant; MMS^s, MMS-sensitive.

expected if the revertant diploids were homozygous for the *HO* gene. Because reversion of the *rad*52-1 phenotype led in every case to successful mating type interconversion, we conclude that the *rad*52-1 mutation, and not a closely linked mutation, prevents homothallic switching.

Mitotic Recombination Is Reduced by *rad*52-1. The *rad*52-1 mutation has been reported to abolish meiotic recombination in several genetic intervals (13, 14) and to reduce induced mitotic recombination (20, 21). Its effect on spontaneous mitotic recombination has not been examined as extensively, although in one interval *rad*52-1 appeared to reduce exchange (13). Because our studies demonstrated that *rad*52-1 prevented homothallic switching during mitotic growth, we considered it important to determine whether the *rad*52-1 mutation generally reduced mitotic recombination. To answer this question, two diploids were constructed; each contained several heteroallelic loci and one heterozygous recessive drug resistance locus (cycloheximide, cyh) to monitor intragenic and intergenic recombination, respectively (Table 8). The data indicate that at every heteroallelic locus except one (*met*13) prototroph production was substantially reduced; intergenic exchange in the *cyh*2–centromere region was similarly reduced. Furthermore, virtually all of the *MET*13 prototrophs can be attributed to an increased reversion frequency of *met*13-c in the presence of *rad*52-1 (data not shown).

DISCUSSION

The homothallic mating type interconversion system in yeast provides an example of how one cell type can specifically change to another. The cassette model for the swtiching process proposes that copies of the silent mating type information located at *HML* α and *HMRa* are made and then transferred into the *MAT* locus, where they are expressed (22). The model suggests that this exchange may occur by a mechanism analogous to bacterial transposition (8). However, mating type interconversion differs in several respects. For example, the "transposition" event occurs at a specific locus, it involves replacement rather than insertion, and the silent loci do not appear to code for functions necessary for the transfer itself (22). We have demonstrated that there may be an additional difference between bacterial transposition and yeast mating type interconversion. Bacterial transposition does not require generalized recombination functions (7, 23, 24), whereas the data presented in this paper indicate that a mutation (*rad*52-1) that reduces meiotic and mitotic recombination also prevents homothallic switching. These observations are consistent with the hypothesis that a component of the generalized recombination system (either the *RAD*52 product or a function under its control) is used in mating type interconversion. An alternative hypothesis is that the *RAD*52 gene regulates both generalized recombination functions and a separate specific function required for mating type interconversion. A third view is that *rad*52-1 is a polar mutation that prevents expression of a gene downstream required for homothallic switching. This last hypothesis seems unlikely because as yet no polycistronic operons have been found in yeast; the "polar" effects that have been observed have been in genes (e.g., *his*4ABC) that appear to code for polypeptides with several enzymatic activities (25). A final possibility is that the *rad*52-1 lesion leads to DNA damages competing for functions that normally would participate in homothallic switching. This hypothesis suggests that x-ray (or MMS) damage might prevent switching in wild-type strains. We favor the first hypothesis that a general recombination function is required for switching [perhaps via a gene conversion mechanism (29)], because we feel it is the simplest interpretation of the data.

Other mutations have been found that reduce the efficiency of homothallic switching (e.g., *swi*1-1); it is not known whether

Table 8. Mitotic recombination frequencies in *rad*52-1/*rad*52-1 diploids

		Mean frequency of recombinants* × 10^5							
		Intragenic (prototrophs)							Intergenic
Diploid	Genotype	*leu*1-c / *leu*1-d	*trp*5-c / *trp*5-d	*met*13-c / *met*13-d	*ura*3-1 / *ura*3-313	*lys*2-1 / *lys*2-2	*tyr*1-1 / *tyr*1-2	*his*7-1 / *his*7-2	*cyh*2^r / *CYH*2^s
RM41	*rad*52-1/*rad*52-1	0.037	0.084	5.8†	0.057	0.024	0.0095	0.058	5.4
RM42	*rad*52-1/*rad*52-1	0.020	0.037	8.5†	0.082	0.079	0.0030‡	0.037	9.9
Combined mean§		0.028	0.056	7.1	0.069	0.044	0.0095	0.046	7.3
RM27	*RAD*52/*RAD*52	7.5	3.9	3.8	0.65	0.35	0.30	0.29	94
Relative decrease¶		268	88	0.54	9.4	9.8	31.6	6.3	13.4

* Mean frequency of recombinants refers to the geometric mean of (prototrophs/ml ÷ total viable cells/ml) for three cultures of RM41 and RM42 and two cultures of RM27.

† The frequencies for the *met*13 locus in *rad*52-1 diploids are inflated by a high reversion frequency (see text).

‡ RM42 is homoallelic for *tyr*1-1, and this value represents a reversion frequency rather than a recombination frequency. The combined mean of *tyr*1 is taken as the value from RM41 alone.

§ The combined mean refers to the geometric mean of all six cultures of *rad*52-1 diploids.

¶ The relative decrease in recombination frequency is determined by dividing the combined mean for a locus into the mean frequency of RM27.

these affect generalized recombination (26). Preliminary results indicate that the *rad*6-1 mutation, which confers UV and x-ray sensitivity and has been reported to reduce meiotic recombination (13, 27), does not substantially reduce levels of mitotic recombination and has no effect on homothallic switching. These results suggest that, if mating type interconversion requires a generalized recombination pathway, it is likely to be the mitotic rather than the meiotic system that is utilized.

The data in this paper further demonstrate that the interconversion process is not identical for the *MATa* and *MAT*α loci. In the presence of the *rad*52-1 mutation *a HO* spores produce clones of stable haploids, whereas α *HO* spores are inviable. This type of asymmetry contrasts with all previous data, which indicate that *MATa* and *MAT*α behave similarly in the interconversion process. The nature of the lethal event in *rad*52-1 α *HO* spores is not yet defined, nor has it been determined whether the structure or information content of the MATα locus is responsible for the inviability. Lethal events may also occur in *rad*52-1 *a HO* cells, although if they occur, they clearly must take place at a lower rate than in *rad*52-1 α *HO* cells. Initial examination of cell death in mitotic pedigrees of several homo- and heterothallic *rad*52-1 *a* strains indicates a somewhat higher rate of lethal events in the homothallic lines. However, the pattern of cell death cannot be correlated with the known specific pattern of mating type interconversion (1, 2).

Although it is clear that the *rad*52-1 mutation reduces mitotic recombination frequencies, the actual reductions may be even larger than those shown in Table 8. Because mutation frequencies were not determined in homoallelic *rad*52-1/*rad*52-1 diploids, it is conceivable that many, or all, of the prototrophs observed were the result of mutation. There are three observations that suggest that *rad*52-1 may increase mutation frequency: (*i*) The *met*13-c mutation, which is leaky in wild type, reverts at high frequency in our *rad*52-1 strains. (*ii*) Weak suppressors of the ochre alleles *lys*2-1 and *lys*2-2 occur at a frequency 10–20 times that in *RAD*52 (data not shown). (*iii*) The frequency of *tyr*1-1 reversion in RM42 was 3×10^{-8} (see Table 8); this is approximately 10-fold higher than the frequency measured in a related *RAD*52 homoallelic diploid (28).

Genetic recombination is being increasingly implicated as a method of control of gene expression (29). In prokaryotes, transposition of insertion elements, phage P2 integration and excision, and phase variation in *Salmonella* are examples of recombination events that can modify gene expression, and that appear to be independent of generalized recombination functions. It is not known whether the recombination events involved in such processes as immunoglobulin production in mammalian cells or controlling element regulation in maize are catalyzed by general or specific recombination systems. The evidence presented here suggests that the events leading to specific mating type interconversion in the eukaryote *S. cerevisiae* depend upon a gene that is also required for generalized recombination. Although the multiple phenotypes of the *rad*52-1 mutation (deficiencies in the repair of x-ray induced double strand breaks, mitotic and meiotic recombination, and homothallic mating type switching) might suggest that it is a defect in a control function, the pleiotropic phenotype of *recA*$^-$ mutations in *Escherichia coli* (30) provides a precedent for the possibility that the *RAD*52 gene product directly participates in all of these processes. It remains to be determined whether mating type interconversion occurs exclusively via a generalized system of exchange and derives its specificity from the structural properties of the loci involved, whether only homothallism-specific recombination functions are required, or whether both types of functions are utilized in the switching event.

Note Added in Proof. After 10 days of incubation on YPD at 30°C, about 5% very small slow-growing clones appeared on the dissection plates of *rad*52/*RAD*52 *a*/α *HO*/*ho*. Some of these clones have a *rad*52 α phenotype.

We thank Sue Klapholz for many helpful experimental suggestions and for her comments on the manuscript. We also express our appreciation to Joe Wagstaff for his critical review of the paper and to Eric Holte for excellent technical assistance. R.E.M. was supported by National Institutes of Health Postdoctoral Fellowship PHS GM-05965-03. This research was supported by National Institutes of Health Grant PHS GM-23277-02 and University of Chicago Cancer Research Center Grant PHS CA 19265-03/Project 508.

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