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Genetics

Lack of DNA homology in a pair of divergent chromosomes greatly sensitizes them to loss by DNA damage

MICHAEL A. RESNICK*, METTE SKAANILD†, AND TORSTEN NILSSON-TILLGREN†

*Yeast Genetics/Molecular Biology Group, Cellular and Genetic Toxicology Branch, National Institute of Environmental Health Sciences, Research Triangle Park, NC 27709; and †Institute of Genetics, University of Copenhagen, O.Farimagsgade 2A, DK-1353 Copenhagen K, Denmark

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ABSTRACT **Chromosomal DNA is considered *a priori* to be a target for the induction of numerical (whole chromosome) aneuploidy in mitotic cells. If true, DNA repair would be expected to contribute to genome stability. One type of repair that appears to play an important role in the response of many organisms to DNA-damaging agents involves recombination. Using the yeast *Saccharomyces cerevisiae* containing a pair of DNA divergent (homoeologous) chromosomes, we have been able to determine the importance of recombinational repair of DNA damage in the maintenance of chromosome number. Specifically, the induction of aneuploidy by ionizing radiation has been examined in diploids that had one chromosome III replaced by a divergent chromosome from *Saccharomyces carlsbergensis*. The chromosomes are functionally equivalent but lack precise DNA homology over one-half their length. The absence of homology, and thus the opportunity for recombinational repair (presumably of DNA double-strand breaks) in the divergent chromosomes, results in high levels (5–10%) of aneuploidy for chromosome III at doses of radiation resulting in almost no killing. For homologous chromosomes, the frequency of loss is 20–50 times lower.**

Chromosomal segregation in mitotically growing cells is an accurate process with an error frequency that varies from approximately 10^{-2} to 10^{-4} per chromosome in human cells to as low as 10^{-5} in yeast (summarized in ref. 1). While much of the segregation apparatus is expected to be a target for aneuploidy induction, there is a paucity of information about processes leading to aneuploidy or the mechanisms of action by reported aneuploidogens (1). Evidence is generally lacking that chromosomal DNA is a target for the induction of numerical (whole chromosome) aneuploidy in mitotic cells.

In the yeast *Saccharomyces cerevisiae*, considerable progress has been made in the genetic characterization of the segregational apparatus and systems required for chromosome stability. Mutations include those affecting cell division cycle (2), repair and recombination (3, 4), specific and general chromosome stability (5, 6), the centromere (summarized in ref. 7), topoisomerase II (8), and α-tubulin (9). We are using the yeast *S. cerevisiae* to identify the components of the mitotic apparatus that are targets for aneuploidy induction as well as the processes that lead to aneuploidy (10).

Chromosomal DNA is a likely target for induction of numerical aneuploidy, and DNA repair would be expected to contribute to genome stability. Recombinational repair plays an important role in the response of many organisms to DNA damage. The repair of radiation-induced double-strand breaks (DSBs) is an efficient process in yeast, where it occurs through recombination (11, 12). In this paper, we address the role of recombinational repair in maintaining genomic stability following ionizing radiation exposure and the consequences when recombination is prevented due to lack of homology.

Radiation-induced aneuploidy has been examined in *S. cerevisiae* diploids that had one chromosome III replaced by a divergent chromosome from the related yeast *Saccharomyces carlsbergensis* (13). While the two chromosomes were functionally equivalent and exhibited the same gene order, the lack of precise DNA homology in half the length of a chromosome pair (ref. 13; see Fig. 1 and *Materials and Methods*) was expected to prevent recombinational repair processes in this region. The inability to repair ionizing radiation-induced DNA damage (presumably DSBs) in this region via recombination results in high levels of chromosome loss rather than chromosome deletions or malsegregation at nonlethal doses.

MATERIALS AND METHODS

Strains. Strains 230283BI-57 and 021281AI-6 are derived from the Cold Spring Harbor collection (Table 1). The his^- alleles in each diploid strain are complementing (i.e., HIS^+). Strains 300686C-2, 300686H-45, and 290986C-34U are *S. cerevisiae* haploids with chromosome III replaced by a divergent chromosome from *S. carlsbergensis* (13). The *his4* alleles in the *S. carlsbergensis* chromosomes were induced by ethyl methane sulfonate (T.N.-T., unpublished data). The alleles belong to the *HIS4A* and the *HIS4C* region (T.N.-T., unpublished data) based on complementation patterns with known *S. cerevisiae his4* alleles.

S. carlsbergensis chromosome III is functionally homologous to chromosome III of *S. cerevisiae* but genetic as well as molecular analyses indicate that the chromosome is composed of two different sections (13, 14) with the left part being divergent from and the right part homologous to the *S. cerevisiae* chromosome (see Fig. 1). No meiotic recombination occurs in the region from *HML* (near the left telomere) to *MAT*. This appears to result from nucleotide sequence differences in this region, as shown for four loci (*HML*, *HIS4*, *LEU2*, and *MAT* exhibit about 80–90% DNA homology; ref. 14). In the region to the right of *MAT*, the recombination levels are normal for the *MAT–THR4* interval and the molecular structure of *SUP61* and *HMR* appears identical to those of *S. cerevisiae* (14).

Noncomplementing heteroallelic diploids carrying one *S. carlsbergensis* allele and one *S. cerevisiae* allele exhibit spontaneous and ultraviolet light-induced mitotic recombination levels that are both 100–1000 times lower than in similar pure *S. cerevisiae* strains. Since recombination is greatly reduced, stable diploids with complementing heteroalleles can be constructed. The appearance of histidine auxotrophs in such diploids is likely to signal genetic events other than recombination.

Growth Conditions and Irradiation. Media and growth procedures have been described (15). Cells were grown in

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Abbreviation: DSB, double-strand break.

Table 1. Genotypes of strains

Strain	Chromosome	Genotype
D-VG	(*S. cerevisiae*) 021281AI-6 300686C-2 (*S. carlsbergensis*)	*his4-15 leu2 MATa thr4* / *his4-S3 + MATα +* — *ade2* / + — + / *ade1* — *cyh2* / + — *+ ura3* / *can1 +* — + / *lys2* — + / *ura4*
D-VGG	Same as D-VG except the strain is disomic for the *S. carlsbergensis* chromosome	
H-VV	021281AI-6 230283BI-57 (*S. cerevisiae*)	*his4-15 leu2 MATa thr4* / *his4-290 + MATα +* — *ade2* / + — *cyh2* / + — *ura3* / + — + / *lys1*
H-GG	(*S. carlsbergensis*) 300686H-45 290986C-34a (*S. carlsbergensis*)	*his4-S7 + MATa* / *his4-S3 + MATα* — *ade1* / + — *lys2* / + — *can1 +* / *+ ura3*

histidineless medium for 2–3 days. Since ≈95% of the cells lacked buds, only 5% were in the S or G_2 phase of the cell cycle. Cells were washed with water, resuspended at 5×10^4 cells per ml, and irradiated at 0°C in a Shepherd Mark I ^{137}Cs irradiator (model 68-A) at a dose rate of 3.6 krad/min (1 rad = 0.01 Gy). Cells were diluted and plated to yeast extract/peptone/dextrose (YEPD) and grown at 30°C. Colonies were replicated to the appropriate medium to determine genotype.

Genetic Analysis. Standard tetrad analysis methods were used. To investigate whether strains expressing the *MAT***a** or *MATα* mating type were monosome or euploid for chromosome III, they were crossed to appropriately marked diploids. For isolates expressing the *S. carlsbergensis*-specific markers (*his4-S3* and *MATα*) the tester strain was a diploid monosomic for chromosome III (*his4-15 leu2 MAT***a** *thr4*). For isolates expressing the *S. cerevisiae* specific markers (*his4-15 leu2 MAT***a** and *thr4*) the tester strain carried two copies of the *S. carlsbergensis* chromosomes III (*his4-S3 MATα*). The resulting tetraploids were sporulated and dissected. Based on the mating characteristics of spore colonies from the tetrads and the segregation of the *his4* and *leu2* markers, it was possible to assess whether the original diploids were monosome or euploid. Because homologous chromosomes (*S. cerevisiae* or *S. carlsbergensis*; unpublished data) preferentially disjoin in meiosis and there is no recombination between the linked genes *HIS4*, *LEU2*, and *MAT*, this linkage group segregates in the first meiotic division.

Physical Analysis of Chromosomes. Chromosomes were separated according to size using pulse field gel electrophoresis methods (16).

RESULTS

Radiation-Induced Loss of Genetic Markers in Divergent vs. Homologous Pairs of Chromosome III. In yeast, the repair of radiation-induced DSBs, as well as other double-strand damage involves recombination (11, 12), and a reduction in homology would be expected to reduce repair. To examine the consequences of reducing the opportunity for recombination, we developed diploid strains in which all but 1 (chromosome III) of the 16 pairs of chromosomes are homologous. The remaining pair is divergent (i.e., homoeologous); one chromosome is derived from *S. carlsbergensis* and the other is from *S. cerevisiae*. Nearly half of the chromosome III pair exhibits no or greatly reduced recombination in both meiosis and mitosis (from *MAT* to the left telomere); a high level of DNA homology exists in the other half (Fig. 1; see *Materials and Methods*; ref. 13). The system we developed to detect possible damage-induced genetic changes was based on complementing mutations in the *HIS4* locus at different functional regions of the locus (19). Loss of an allele results in histidine auxotrophy and can be detected by replica-plating colonies that arise on rich medium to histidineless medium. At high levels of survival, this also allows sectored vs. whole colony events to be discriminated.

Exposure of the divergent chromosome III strain to nonlethal doses of radiation induced high frequencies of his$^-$ colonies. After only 5 krad, the histidine auxotroph frequency was ≈3%, and this increased linearly to ≈20 krad (Table 2). The induction of his$^-$ colonies was much lower in homologous strains. Over 95% of the his$^-$ colonies derived from the divergent strain also expressed a mating-type allele. Nearly half were *MAT***a** and expressed *leu2* and *thr4*; the

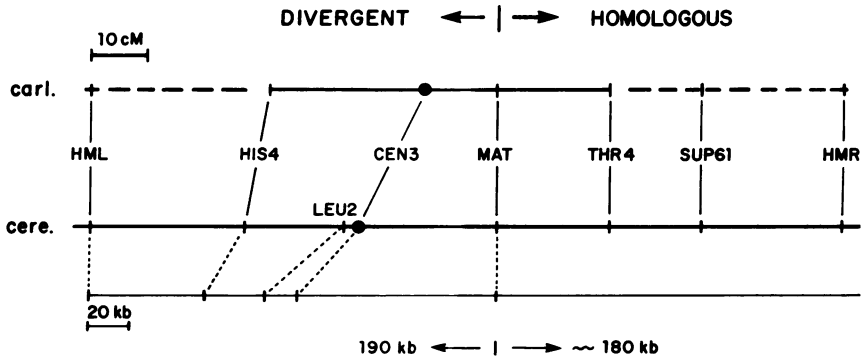

FIG. 1. The genetic maps of chromosome III from *S. carlsbergensis* (carl.) and *S. cerevisiae* (cere.; summarized from refs. 17 and 13, respectively); dashed line, unmapped region. Lower line, physical map of the *S. cerevisiae* chromosome (16, 18).

Table 2. Induction of aneuploidy in strains that are divergent (D-VG) or homologous (*S. cerevisiae*, H-VV; *S. carlsbergensis*, H-GG) for chromosome III

Homologous (H) or divergent (D) strain	Dose, krad	Total colonies	% his⁻*	% chromosome lost†	
				α	a
H-VV	0	842[a]	<0.1	0	0
H-VV	0	1370[b]	<0.1	0	0
H-GG	0	1213[a]	<0.1	0	0
D-VG	0	454[a]	<0.2	0	0
	0	1088[b]	<0.1	0	0
D-VGG‡	0	1118	<0.1	0	0
D-VG	5	303[a]	2.7	1.7	1.0
D-VG	5	382[b]	3.5	1.1	2.4
H-VV	10	414[a]	0.5	0	0.2
H-VV	10	1620[b]	0.2	0	0.06
H-GG	10	1168	0.4	0	0
D-VG	10	321[a]	5.6	3.4	2.2
D-VG	10	650[b]	5.4	2.5	2.8
D-VGG‡	10	688	2.0	0	1.9
D-VG	15	424[b]	10.6	3.3	6.4
H-VV	20	429[a]	0.7	0.2	0.2
H-VV	20	2785[b]	1.1	0.18	0.29
H-GG	20	2597	1.0	0.19	0.16
D-VG	20	274[a]	9.9	6.6	2.9
D-VG	20	390[b]	8.0	2.1	5.4
D-VGG‡	20	382	3.7	0	3.4
D-VG	25	244[b]	11.1	7.0	4.1
H-VV	30	373[a]	1.1	0.3	0.6
H-VV	30	1047[b]	1.2	0.1	0.6
H-GG	30	1284	1.6	0.16	0.4
D-VG	30	328[a]	12.5	6.1	5.5
D-VG	30	397[b]	7.8	3.5	2.8
D-VGG‡	30	382			(4.0)
H-VV	40	287[a]	0	0	0
H-VV	40	1184[b]	1.6	0.17	0.68
H-GG	40	1148	1.4	0.26	0.43
D-VG	40	309	12.3	6.1	5.8
D-VG	40	252	15.5	7.5	6.4
D-VGG‡	40	380			(3.4)

Superscripts a and b indicate two experiments done on different days.

*Frequency of total colonies that require histidine for growth. In the controls (0 krad), no his⁻ colonies were detected.

†Frequency of total colonies that are due to loss of the *S. carlsbergensis* chromosome III and are, therefore, his⁻ leu⁻ *MAT***a** thr⁻ or due to loss of the *S. cerevisiae* chromosome III and are, therefore, his⁻ *MATα*.

‡Strain disomic for the *S. carlsbergensis* chromosome III. Results in parentheses correspond to the total frequency of his⁻ colonies. Based on results with 10 and 20 krad, most of these are likely to be due to loss of the *S. cerevisiae* chromosome.

other half expressed *MATα*. Since *HIS4* and *MAT* are located on either side of the centromere, the radiation efficiently induced aneuploidy and/or malsegregation of the *S. carlsbergensis* chromosome. As discussed below, the events are primarily due to chromosome loss. The lack of genetic markers on the *S. carlsbergensis* chromosome might render analysis of the remaining his⁻ colonies somewhat less accurate. However, the comparable frequency of his⁻ *MATα* and his⁻ leu⁻ *MAT***a** thr⁻ colonies (Table 2) suggests that events involving the *S. cerevisiae* chromosome occur with similar frequency (even when there is an additional copy of the *S. carlsbergensis* chromosome; see D-VGG in Table 2 and Fig. 3).

We conclude that low doses of ionizing radiation (Fig. 2) can be efficient inducers of chromosome loss. Few if any events could be explained by multiple reciprocal recombination events since the frequency of the his⁻ only category is low (histidine auxotrophs not expressing mating type; Table 3). Furthermore, the cells were predominantly (>95%) in the G_1 phase of the cell cycle when irradiated, which would preclude the detection of reciprocal exchange events.

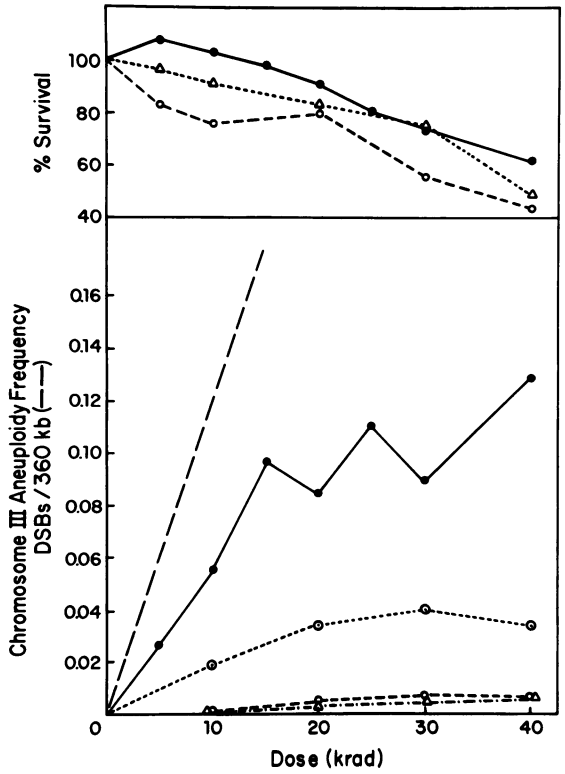

FIG. 2. The induction by ionizing radiation of chromosome III aneuploidy in strains that are divergent (●), homologous *S. cerevisiae* (○), or homologous *S. carlsbergensis* (△) for chromosome III. Also included are results with a trisomic chromosome III strain that has two copies of the *S. carlsbergensis* chromosome III and one copy of the *S. cerevisiae* III (⊙). Presented is total aneuploidy for chromosome III based on the data in Table 1. The two results for the divergent experiment are averaged; the results for the homologous experiments are pooled between experiments (because of the small number of events). Also shown (---) is the expected induction of DSBs as a function of dose (12) in a 360-kb stretch of DNA (180 kb × 2); this corresponds to the divergent portion of the chromosomes.

Table 3. Expression of recessive markers in colonies from irradiated (10 and 20 krad) cells of divergent (D-VG) or homologous (H-VV or H-GG) strains

Strain	Dose, krad	Colonies examined	% his⁻ only	% thr⁻ only	% ade⁻ only
D-VG	10	971	0.1 (1)*	0.2 (2)	2.2
D-VG	20	664	0.2 (1)	0.8 (5)	4.3
H-VV	10	2034	0.1 (2)	0.2 (4)	2.1
H-VV	20	3214	0.6 (18)	0.2 (7)	3.8
H-GG	10	1168	0.4 (5)	—	1.2
H-GG	20	2597	0.6 (16)	—	1.4

Among the colonies arising from unirradiated cells (see Table 2), none expressed the recessive markers described in this table.

*Numbers in parentheses correspond to the number of colonies. The ade⁻ colonies were observed from a much larger sample and therefore the numbers of colonies are not presented. The divergent strain is +/*ade1* +/*ade2*; the H-VV strain is +/*ade2*; the H-GG strain is +/*ade1*. The distances to the centromere of the *ADE2* and *ADE1* genes are ≈65 and 5 centimorgans, respectively, which accounts for the differences in response between the H-VV and H-GG strains.

The chromosome III loss frequency in the homologous strains was 20–50 times lower than for the divergent strains (Fig. 2 and Table 2). Based on the data in Tables 2 and 3, the low level of *MAT***a** or *MATα* histidine auxotrophs found in the homologous chromosome experiments could not be explained by recombination on both sides of the centromere. Thus, precise homology greatly reduces the potential for radiation-induced chromosome loss.

Mechanism of Chromosome Loss. The above results could have arisen by nondisjunction of a sister chromatid pair resulting in a monosomic and a trisomic daughter cell, nondisjunction of pairs of sister chromatids resulting in two daughter cells both euploid for chromosomes III, or chromosome loss so that the progeny would only be monosomic. If the first hypothesis were true, the colonies containing his^- cells should be sectored (his^-/HIS^+). If the second hypothesis were true, the colonies would be entirely his^- but they would be sectored for the associated mutations on chromosome III. Only 5% of the his^- colonies showed evidence of his^-/HIS^+ sectors; the rest were whole his^- colonies. The lack of sectoring is not due to a growth advantage by either his^- or HIS^+ cells (unpublished results) or lethal sectoring, since nonlethal doses were used. We conclude that the radiation-induced appearance of his^- colonies in the divergent strain is largely the result of chromosome loss in the G_1 cells.

Chromosome loss was examined further genetically and by karyotype analysis using pulse field gel electrophoresis methods to display chromosomes (16). Eleven his^- leu^- *MAT***a** thr^- strains were crossed with a diploid that was carrying two copies of the *S. carlsbergensis* chromosome III found in strain 300686C-2. After meiosis, the tetrads contained two his^- *MATα* cells and two HIS^+ nonmaters (*his4-15* and *his4-S3* are complementing). Since all the cells were also LEU^+ and THR^+, the tested strains were monosomic for chromosome III, presumably from *S. cerevisiae*. This was confirmed by pulse field gel electrophoresis analysis (Fig. 3, lanes 6 and 7; unpublished data; the intensity of the chromosome III band was approximately half that of the chromosome VI band). Thus, when the *S. cerevisiae* chromosome is retained, the radiation-induced loss of a divergent chromosome results in monosomy.

When the *S. carlsbergensis* chromosome III is retained, the situation is somewhat different. Nine his^- LEU^+ *MATα* THR^+ isolates were tested genetically by crossing to a diploid monosomic for a his^- *S. cerevisiae* chromosome III. Four produced tetrads containing only his^- spores of either *MAT***a** or *MATα* mating types and were monosomic for chromosome III. The remaining five strains were euploid for chromosome III since they yielded tetrads in which HIS^+/his^- segregated 2:2 and the HIS^+ strains were nonmaters. Pulse field gel electrophoresis analysis confirmed euploidy for three strains in Fig. 3 (lanes 8–10). The intensity of the *S. carlsbergensis* chromosome III band approximately equals the intensity of the chromosome VI band (migrating slightly faster than chromosome III). It is possible that euploidy results as a consequence of a secondary event following loss of the *S. cerevisiae* chromosome and is selected during clonal outgrowth.

Induction of Other Genetic Events. Among the his^- colonies arising from the divergent strains after low doses, nearly all were associated with the appearance of other genetic markers (Table 3). Of 358 his^- colonies recovered from all doses in two experiments, all but 20 could be attributed to chromosome loss. Seven of the 20 were his^- and 5 of these were examined with the pulse field gel electrophoresis system. Three appeared to contain a *S. cerevisiae* chromosome III with reduced mobility (one of these corresponds to lane 3 in Fig. 3). The other two did not exhibit chromosome rearrangements (lanes 2 and 4). The origin of the genetic change in these cells remains unknown; it is possible that a rare gene conversion may have occurred even though there is limited homology. Among the remaining 13 colonies, 7 could be explained by chromosome loss and associated recombination between *MAT* and *THR4*. One colony appears to have resulted from a break or recombinational event between *LEU2* and the centromere. The other 5 colonies remain unexplained.

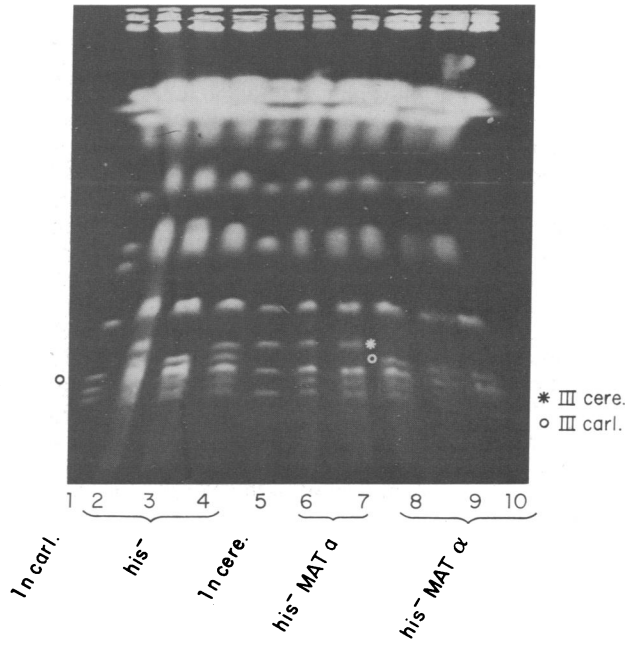

FIG. 3. Pulse field gel electrophoresis analysis of chromosomal DNA extracted from his^- haploid parents and radiation-induced his^- isolates of strain D-VG (divergent; see Table 1). Lanes: 1, haploid parent 300686C-2 (*S. carlsbergensis*); 5, haploid parent 021281AI-6 (*S. cerevisiae*); 2–4, his^- (only) isolates from strain D-VG; 6 and 7, his^- leu^- *MAT***a** thr^- isolates of strain D-VG; 8–10, his^- *MATα* isolates of strain D-VG. The chromosomes III of the diploid parent D-VG migrate as expected based on the haploid parents (data not shown). * and o, correspond to positions of chromosome III from *S. cerevisiae* and *S. carlsbergensis*, respectively.

While the total frequency of his^- colonies was much lower in the homologous strains, the frequency of the "his^- only" category among these colonies was much higher, presumably because of recombination. Somewhat comparable numbers of colonies that were only thr^- occurred with both types of strains; they probably arose by recombination between the *MAT* and *THR4* loci.

Events on other chromosomes were similar between the various strains (ade^-, Table 3; ura^-, data not shown). Comparable levels of homozygosis would be expected to occur by recombinational repair between homologous chromosomes.

DISCUSSION

Recombination requires sufficient homology to enable productive DNA interactions. We showed (13) that some chromosomes or portions of chromosomes derived from *S. carlsbergensis* would not undergo meiotic recombination with their *S. cerevisiae* counterparts because of insufficient DNA homology (13, 14, 20, 21), although they were functionally homologous. The repair of ionizing radiation-induced DSBs requires recombination either between homologous chromosomes (in G_1 or G_2) or sister chromatids (in G_2; ref. 22; summarized in ref. 23). We have shown that the reduction of homology that results in loss of meiotic reciprocal recombination in one-half of chromosome III has a profound effect

on the recovery of this chromosome after irradiation of mitotic cells. More than 10% of the cells lose one or the other copy of chromosome III. Because loss in strains that are homologous for chromosome III is 20–50 times less frequent while the survival is comparable, we conclude that the absence of opportunity for chromosomal interactions due to limited homology prevents recombinational repair of DNA damage, which, in turn, leads to chromosome loss. The unrepaired damage does not lead to the deletion of portions of chromosomes although a few cases of chromosome alterations have been found (cf. Fig. 3, lane 3).

The lesions responsible for the radiation-induced aneuploidy are presumed to be DSBs; they require repair via a recombination mechanism. Approximately 25–50 DSBs (corresponding to 20–40 krad) are efficiently repaired in logarithmically growing diploid cells (12). DSBs induced in stationary (G_1) cells are repaired once the cells are incubated in fresh nutrient medium (24). The frequency of DSBs induced in the divergent regions of the two chromosomes has been estimated from the length of the region (Fig. 1) and the efficiency of DSB induction (12). As shown in Fig. 2, the DSB frequency is within a factor of 2 of the induced aneuploidy frequency at low doses. The "tailing off" in aneuploidy induction at higher doses could be due in part to DSBs being induced in both chromosomes in the divergent regions, resulting in lethality.

Thus unrepaired DSBs appear to have two biological consequences. In a *rad52* mutant lacking DSB repair, they have a dominant lethal effect (12, 25). The dominant lethal effect of DSBs in *rad52* mutants could result from an unresolved recombinational event between two chromosomes (as discussed in ref. 12). Consistent with this, *rad52* has been shown to be defective in an intermediate step in meiotic recombination (26). We propose a second genetic consequence for unrepaired DSBs—namely, the induction of chromosome loss, when recombination is prevented by a lack of homology. Possible reasons for the loss include degradation of the chromosome or inability to replicate the chromosomes in the absence of a telomere.

Previously, it was shown (3) that low radiation doses administered to a *rad52* diploid mutant caused a large increase in the already high spontaneous aneuploidy levels. The frequency of chromosome loss far exceeded that of DSBs and chromosome number approached near-haploid levels after several generations. The mechanism involved in the secondary aneuploidy is not understood, but it may be related to the generally poor growth of *rad52* mutants and the decrease in an essential nuclease (27, 28). We do not find evidence of aneuploidy for multiple chromosomes in our repair-proficient strains. Among the monosomic colonies for chromosome III, there was no increase in homozygosis for ade^-.

There are several inferences that can be derived from the present observations. (*i*) The consequences of damage in nonhomologous regions is only important in G_1 cells, since repair can occur between sister chromatids in G_2 (22). (*ii*) Given the efficiency of induction of aneuploidy, it may be possible to determine the size of the divergent region between two chromosomes using just one genetic marker; chromosome loss should be proportional to size. (*iii*) The mapping of genes to specific chromosomes would be greatly facilitated by divergent chromosomes. This approach may account for the ability to develop linkage maps in the yeast *Pichia pinus* (29). (*iv*) Other damage requiring recombinational repair may also lead to chromosome loss of divergent chromosomes. (*v*) It is possible that even in homologous chromosomes there may be small regions of relatively low homology. Damage induced in these regions would not be subject to recombinational repair and could therefore lead to aneuploidy. (*vi*) Our results may be relevant to observations with a human chromosome/CHO cell hybrid. Waldren *et al.* (30) demonstrated that low radiation doses efficiently induced inactivation of a gene associated with the human chromosome. An alternative explanation is that the radiation damage in the human chromosome induced chromosome loss, possibly due to lack of opportunity for interaction with a homologous chromosome.

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