One of the most common microsatellites in eukaryotes consists of tandem arrays of the dinucleotide GT. Although the study of the instability of such repetitive DNA has been extremely fruitful over the last decade, no biological function has been demonstrated for these sequences. We investigated the genetic behavior of a region of the yeast Saccharomyces cerevisiae genome containing a 39-CA/GT dinucleotide repeat sequence. When the microsatellite sequence was present at the ARG4 locus on homologous chromosomes, diploid cells undergoing meiosis generated an excess of tetrads containing a conversion of the region restricted to the region of the microsatellite close to the recombination-initiation double-strand break. Moreover, whereas the repetitive sequence had no effect on the frequency of single crossover, its presence strongly stimulated the formation of multiple crossovers. The combined data strongly suggest that numerous recombination events are restricted to the initiation side of the microsatellite as though progression of the strand exchange initiated at the ARG4 promoter locus was impaired by the repetitive sequence. This observation corroborates in vitro experiments that demonstrated that RecA-promoted strand exchange is inhibited by CA/GT dinucleotide tracts. Surprisingly, meiotic instability of the microsatellite was very high (>0.1 alterations per tetrad) in all the spores with parental and recombinant chromosomes.

[Key Words: Microsatellite; homologous recombination; double-strand break repair; genome instability; meiosis; Saccharomyces cerevisiae]
served in the different species tested, inhibition of strand exchange by microsatellites could be a general process that may modify the recombination activity in the vicinity of the microsatellite. To test this hypothesis we analyzed the effect of a tract of 39 GT/CA dinucleotide repeats on meiotic recombination in *S. cerevisiae*. Because the amount of meiotic double-strand breaks (DSBs) is correlated with the frequency of gene conversion, it is assumed that meiotic insertion is one of the site of initiation of recombination events [Alani et al. 1990]. Thus, during meiosis, it is possible to identify the site of initiation of one recombination event and to analyze strand-exchange progression and its resolution.

**Results**

**Introduction and analysis of a CA/GT microsatellite at the ARG4 locus**

To analyze the effects on recombinational events around *ARG4* due to microsatellites, we introduced a sequence of 39 CA/GT dinucleotide repeats (MS) into the *ARG4* gene (Fig. 1) at a locus close to a well-characterized meiotic hotspot for recombination [Nicolas et al. 1989; Sun et al. 1989]. This hot spot of meiotic recombination is located upstream of the *ARG4* coding sequences and is associated with meiosis-specific DSBs that occur in this area. DSBs are detected as transient and heterogeneous DNA fragments in wild-type *RAD50* strains, but accumulate as discrete bands in *rad50S-K181* mutant strains [Cao et al. 1990]. The presence of a microsatellite sequence in the *ARG4* coding sequence does not affect the location or the frequency of the breaks induced during meiosis in the area [Fig. 2]. Moreover, the processing of DSBs at the *ARG4* promoter, estimated by the disappearance of the fragments during incubation, is similar in *RAD50* strains carrying or not carrying the microsatellite (data not shown).

To monitor recombination events induced at meiosis we introduced two genetic markers (*URA3* and *TRP1*), and two modifications of restriction sites in the flanking regions of the microsatellite (Fig. 1). During some constructions the microsatellite insertion on the chromosome carrying the *URA3* and *TRP1* markers lost one repeat. We used this opportunity to monitor the events of instability and recombination at the microsatellite locus. Two diploid strains carrying the microsatellite sequence were used: strains MS[38/39], carrying a one-repeat heterology in the microsatellites and strain MS[39/39], with fully homologous microsatellites. The meiotic products were analyzed for the expression of the *URA3* and *TRP1* genes on selective media and for the presence of restriction sites by digestion of PCR-amplified DNA fragments. Two kinds of recombination events were monitored: crossovers (CO) that give rise to a reciprocal exchange of homologous chromosome regions (new segregation 2:2) and conversions that result from the correction of the heteroduplex intermediate, which are characterized by three spores carrying the same marker (segregation 3:1). As a control, we inserted a random non-repetitive 50% GC-rich sequence (RS) in the *ARG4* locus with a length identical to that of the microsatellite and with no apparent secondary structure.

High frequency of short conversions do not pass the microsatellite sequence

Tetrad analysis shows that the total number of *BstZ171*...
and AgeI conversion events, measured by digestion of PCR-amplified fragments, is similar in the two strains containing the microsatellite insert and in the strain with the random insert (Table 1). However, strains differ in the number of the short conversions that are restricted to the BstZ171 marker and do not encompass the AgeI marker. As a matter of fact, the number of short conversions is higher in MS diploids (11%–12%) than in RS diploids (3%). After statistical analysis of these values, we found that the difference between short conversion frequencies of the MS and RS diploids was highly significant ($\chi^2 = 8.2, P \leq 0.002$; Table 1). Although the total number of conversions was not significantly higher in the MS strains ($\chi^2 = 0.52, P = 0.13$), we do not exclude that the extra short conversions observed in both MS strains result from rare new initiation events. Moreover, there was no apparent bias in the direction of the BstZ171 conversion. Both chromosomes were donors or recipients for the converted sequence as expected if initiation can occur indifferently on each chromosome. The one-repeat heterology in the MS(38/39) diploid did not seem to have any specific effect on the conversions in the MS diploids.

The size of the microsatellite sequence for the spores of the converted tetrads in the MS(38/39) strain was analyzed by PCR amplification and sequencing gel electrophoresis. As expected, the microsatellite sequence was always converted with the AgeI and BstZ171 markers in the 18 spores with large conversions that we analyzed. In contrast, among the 11 spores with BstZ171 short conversions that we analyzed, only 2 had converted the microsatellite. This reduction in the number of co-conversion of the BstZ171 marker and the microsatellite suggests that some conversion events would be restricted to the region between the initiation site and the microsatellite and would not be able to extend across the repetitive sequence.

Short conversions without associated crossovers are more frequent in the MS strains

During recombination, strands of homologous chromosomes exchange and form Holliday junctions that are resolved by specific resolvases. According to the junction resolutions, the resulting conversions are associated (+CO) or not (−CO) with an exchange of the adjacent regions. The chromosome reciprocal exchanges in the ARG4 region were first monitored by the segregation of the URA3 and TRP1 markers. Few double crossover events that restore the parental segregation for these markers were also observed (Table 1). We compared the

Table 1. Number of conversion events in strains homozygous for the RS and MS sequences in the ARG4 gene

| Insert   | Short conversiona | Long conversionb | Total number of tetrads analysed |
|----------|-------------------|------------------|---------------------------------|
|          | Bst+ conversion   | Bst− conversion  | Total number frequency          | Bst+ Age− coconversion | Bst− Age+ coconversion | Total number frequency |
| RS       | 3 (1)             | 4 (2)            | 7 [3] 3%                        | 7 [1]                 | 33 (14)               | 40 (15) 21%            | 205                     |
| MS [38/39] | 12 [3*]          | 12 [3*]         | 24 [6] 11%                     | 14 [8]                | 22 [8*]               | 36 [14] 17%            | 215                     |
| MS [39/39] | 10 [2*]          | 12 [3*]         | 22 [5] 12%                     | 7 [4]                 | 21 [14]               | 30 [18] 16%            | 188                     |

Numbers in brackets correspond to conversion events associated with crossover.

aShort tract conversion covering only the BstZ171 site (Bst).
bLong tract conversion encompassing the BstZ171 (Bst) and AgeI (Age) sites including the inserted sequence. The chromosome carrying the URA3 and TRP1 genetic markers and the AgeI restriction site is either the recipient or the donor in ARG4 gene conversion events.

One conversion event is associated with a double crossover.

**Two conversion events are associated with a double crossover.
Four-strand events (three MS(38/39) tetrads and nine MS(39/39) tetrads). Values in brackets correspond to the percentage of recombinant tetrads. Some double crossovers involve more than two strands.

MS 14 4 22 40 (21%) 22

RS 17 1 24 42 (20%) 6 4 0 10 (5%) 205

Insert

| Insert | Number of tetrads | Total number of tetrads analysed |
|--------|-------------------|---------------------------------|
|        | URA-Bst | Bst-Age | Age-TRP | Total |
| RS     | 17      | 1       | 24      | 42 (20%) |
| MS     | 15      | 5       | 20      | 40 (19%) |
| MS(38/39) | 14 | 4       | 22      | 40 (21%) |
| MS(39/39) | 15 | 4       | 22      | 40 (21%) |

MS strains were highly significant ($\chi^2 = 12, P < 0.0002$). It is interesting to note that it was the only difference observed between the MS(39/39) and the MS39/38) strains.

### Crossovers resolved preferentially at the side of the microsatellite close to the initiation site

Diploid cells with the MS insert generated at meiosis an excess of tetrads containing reciprocally recombined product in the BstZ171 and AgeI area: 9% in the MS(38/39) and 16% in the MS(39/39) tetrads had resolved at least one crossover between the BstZ171 and AgeI restriction sites whereas only 3% of the RS tetrads displayed a crossover at this interval (Table 1). In the MS(38/39) strain, the 5 tetrads with a single crossover and 14 tetrads with a double crossover that had one crossover located in the insert region between the BstZ171 and AgeI restriction sites were analyzed more precisely. We measured the length of the microsatellite associated to the exchange to locate the crossover in relation to the microsatellite sequence. All but two events resolved in the area limited by the BstZ171 site and the microsatellite sequence corresponding to the side of the microsatellite close to the ARG4 initiation DSB. Interestingly, the two crossovers that resolved at the other side of the microsatellite correspond to spores that have undergone double crossovers in which the second crossover is located in the AgeI-TRP1 area. These events could result from repair of DSBs generated at the other side of the microsatellite. It is possible that a small number of meiotic DSBs could occur in the TRP1 region (see Fig. 1).

### Instability of the repetitive sequence is increased during meiotic divisions

During the study of the MS(38/39) tetrads we measured the length of the microsatellite to analyze the recombination events. We compared the frequency of microsatellite alterations in the different types of recombinant spores (Table 3). We found that dinucleotide repeat tract alterations were not more frequent in spores having un-
undergone conversion or crossovers than in spores that displayed parental segregation. However, the rate of microsatellite meiotic instability was very high as 3 tetrads out of 32 contained at least one spore with an altered tract length. None of the tetrads displayed the same microsatellite changes on the two copies of one parental chromosome, as would be expected if instability had resulted from a mitotic event. Moreover, we found a frequency of 1/197 tract alterations in the MS diploid cells used for this study. The difference between the pre- and post-sporation instability frequencies could indicate that, at the ARG4 chromosome locus, the meiotic instability is high relative to the mitotic instability. As already observed in analysis of dinucleotide repeats instability [Henderson and Petes 1992], the changes in length were small [one or two repeats]. The number of tract changes was underestimated as we eliminated changes that would generate a 3:1 segregation of the microsatellite, which cannot be distinguished from microsatellite gene conversion (Table 3).

Discussion

When the microsatellite sequence was introduced into homologous chromosomes at the ARG4 locus, conversion and crossovers were induced in the area between the BstZ171 site and the microsatellite sequence. With a random sequence inserted at the same position there were few events restricted to this small area (129 bp). Interestingly, this region corresponds to the side of the microsatellite close to the DSB initiation site. In MS strains, crossovers located near the microsatellite were mainly observed in tetrads having undergone two crossovers. The increase of multiple events induced by the microsatellite sequence has been already reported by Treco and Arnheim [1986]. However, the diploid strain used did not further the precise location of the events. We found that most of the double crossovers in the MS[39/39] strain involved one resolution in the area between observed and calculated frequencies is not significant and could reflect the underestimation of the cross-overs. The observation of four-strand double crossovers were slightly higher for the two MS strains (1.4% and 4.8%). This difference between observed and calculated frequencies is not significant and could reflect the underestimation of the crossovers in this area. For example, recombination events leading to a double crossover URA–Bst/Bst–Age associated with a BstZ171 conversion would be detected as a short conversion not associated with crossovers. We found an excess of short conversions that were not associated with single crossovers. Given the high frequency of double crossovers in this region, we cannot exclude that part of the short conversions were associated with undetectable double crossovers. Several mechanisms have been proposed to generate conversion events not associated with a reciprocal exchange of the flanking regions [Gilbertson and Stahl 1996]. Resolution of DSB repair intermediates can involve the cleavage of two, one, or no Holliday junctions. In the first case, the intermediates should be processed by resolution of the two Holliday junctions, in the same orientation, either both vertically or both horizontally to avoid reciprocal exchange of the distal markers. This model implies that the microsatellite induces a distal constraint and influences the resolution of the Holliday junction formed at the other side of the initiation site. However, this model is attractive as it applies both to the double crossovers and to the conversion not associated to crossovers.

Table 3. Rates of instability and types of alterations for the microsatellite sequences in parental and recombinant spores

| Genotype of spores | Rate of tract instability | Number of spores with additions or deletions of base pairs |
|-------------------|---------------------------|--------------------------------------------------------|
| Parental          | 1.3 × 10⁻²                | -2 0 +2 +4 Total: 76                                    |
| Recombinant       | 7.7 × 10⁻²                | 0 75 1 0 Total: 76                                    |

Recombinant spores include crossing-over and conversion events encompassing the BstZ171 and/or AgeI restriction sites. The asterix indicates that four of the recombinants classified as microsatellite conversions could be mutants with alterations of the repetitive sequence: Three spores [-2] and one spore [+2].

To locate the second crossover in relation to the microsatellite, we used the MS[39/38] strain, which contains microsatellites at the ARG4 locus with a length differing by one repeat. Most of the crossovers resolved in the BstZ171–Agel region were located on the DSB initiation side of the microsatellite. Surprisingly, whereas the high frequency of short conversions and the excess of double crossovers were also observed in this strain, half of the second crossovers were resolved in the Agel–TRP1 intervals. This result suggests that the mismatched repeat could help the strand exchange to progress across the repeated sequence either by recruiting special proteins or by destabilizing the blocked recombination complex. The difference in crossover location was specific to the resolution of a second crossover as single crossovers showed the same distribution along the chromosome in the two MS strains. A large number of double crossovers occurring in the MS strains involved the four strands. Tetrads carrying three and four chromosome recombinations for a single interval have been already observed in chromosomes carrying microsatellite sequences [Treco and Arnheim 1986]. In all the MS tetrads with four recombinant strands resulting from two double crossovers located on each chromosomes, one crossover was located in the microsatellite region. In both MS strains, the high number of four-strand exchanges in the URA–Bst/Bst–Age regions can be explained simply by the random occurrence of two independent events that involve all four chromatids within the genetic interval monitored. As a matter of fact, double crossovers occurred at a frequency of 5.6% in MS[38/39] strain and 12% in the MS[39/39] strain so the two events should occur at frequencies of 0.3% and 1.3%, respectively. The observed frequencies of four-strand double crossovers were slightly higher for the two MS strains (1.4% and 4.8%). This difference between observed and calculated frequencies is not significant and could reflect the underestimation of the crossovers in this area. For example, recombination events leading to a double crossover URA–Bst/Bst–Age associated with a BstZ171 conversion would be detected as a short conversion not associated with crossovers. We found an excess of short conversions that were not associated with single crossovers. Given the high frequency of double crossovers in this region, we cannot exclude that part of the short conversions were associated with undetectable double crossovers. Several mechanisms have been proposed to generate conversion events not associated with a reciprocal exchange of the flanking regions [Gilbertson and Stahl 1996]. Resolution of DSB repair intermediates can involve the cleavage of two, one, or no Holliday junctions. In the first case, the intermediates should be processed by resolution of the two Holliday junctions, in the same orientation, either both vertically or both horizontally to avoid reciprocal exchange of the distal markers. This model implies that the microsatellite induces a distal constraint and influences the resolution of the Holliday junction formed at the other side of the initiation site. However, this model is attractive as it applies both to the double crossovers and to the conversion not associated to crossovers.
Whatever the resolution model, the high number of events that resolve before the repetitive sequence strongly suggest that progression of strand exchange is inhibited at this level. It may be inhibited by the binding of specific proteins or by a special effect of the sequence on the recombination proteins. This last hypothesis is in agreement with previous in vitro observations indicating that the recombination proteins do not exchange the strands of homologous DNA across such sequences [Dutreix 1997]. We found that the highly affinity of recombination proteins for the repeated sequences could prevent their extension and the increase of instability at meiosis on plasmid-carried microsatellites. It is unclear whether the lack of inhibition seems to be limited and such sequences would change nearby. It could be a region where homologous DNA segments are drawn together as the initial step for the meiotic recombination apparatus with a specific structure that could be a signal to initiate genetic exchange nearby. The most important question raised is that of the role of this highly repetitive element in the evolution of eukaryotic genomes. If a CA/GT tract inhibits progression of the strand exchange, then do the 50 to 100 copies of this repetitive sequence that are normally found in the yeast genome serve similar functions? If so, then strand exchange would be limited to regions between such sequences, and the genome would be divided into recombination units. During meiosis the extent of strand exchange seems to be limited and such sequences would have an effect only if they are located close to a DSB. At mitosis, during repair of damage on chromosomes it has been observed that the exchanged regions are longer. Repetitive sequences could prevent their extension and the loss of heterozygosity in large regions of the genome. To support this hypothesis, the effect of microsatellite sequences on mitotic recombination has to be demonstrated. Alternatively, recombination may be an activity that microsatellite sequences influence by virtue of their structure, but this activity may be unrelated to some other function that the repetitive sequence performs within eukaryotic cells.

The high levels of microsatellite instability at meiosis was unexpected. Our results differ from data obtained with a 49-repeat-length tract [Wierdl et al. 1997] or a 15-repeat-length [Strand et al. 1993] microsatellite carried by a plasmid. It is unclear whether the lack of increase of instability at meiosis on plasmid-carried microsatellites represents a chromosome–plasmid difference or an effect of flanking DNA sequences. However, we favor the hypothesis of a plasmid effect because Strand et al. [1993] have already observed that a 29-bp microsatellite has 3-fold higher instability and is 10-fold less sensitive to a defect in mismatch repair when carried by the chromosome rather than by the plasmid. The location and frequency of DSB initiation sites on these plasmids have not been studied and could play an important role in the meiotic instability of microsatellites. Two models have been proposed to explain the instability of simple repeats: unequal recombination [Smith 1973] or DNA polymerase slippage [Streisinger et al. 1996]. The first model implies that instability would be higher in recombinant spores. Our data do not allow us to confirm this hypothesis, and a study of a higher number of recombinant tetrads would be necessary to confirm or exclude the role of the recombination in meiotic microsatellite instability. However, several studies in bacteria [Levison and Gutman 1987] and yeast [Strand et al. 1993] indicate that slippage during replication seems to be the main mechanism of CA/GT repetitive tract instability. Our finding, that this process could be increased during meiosis, raises the questions of the fidelity of the replication complex formed and the efficiency of mismatch repair during meiotic divisions. Because expression of some genes involved in mismatch repair [MSH5, MSH4, and MSH2] and replication [RPA, POL30, POL1, POL3, and POL4] has been shown to be modified during meiosis, it is possible that one [or both] systems could change their fidelity and induce the instability of the microsatellite.

Materials and methods

Plasmids and strains

All plasmids were derived from the L1.1 plasmid. This plasmid is a derivative of the pt92 plasmid and contains the (poly1) substitution of the ARG4 promoter sequence [-316 bp to -139 bp] described previously by de Massy and Nicolas [1993]. Two types of large insert were used in this study: The MS [microsatellite insert]XbaI–PstI fragment from the bacteriophage M13mp19[CA/GT]39 containing a sequence of 39 CA/GT repeats [Dutreix 1997]; the RS insert, a random sequence corresponding to the PvuII–PstI fragment of the puc18 plasmid. MS and RS sequences were inserted (out of frame) into the EcoRV (+262 by) site in the ARG4-coding region of L1.1. In the MS constructions, the BstZ171 and AgeI restriction sites were modified by insertion of 2 and 4 bp. The modified ARG4 regions were introduced at the ARG4 locus on chromosome VIII of the strains ORD11-4B and ORD17-47C. Sequences of the constructions were checked by PCR amplification and sequencing using a ABI PRISM system. The poly[CA/GT] tract was oriented such that the poly[CA] repeats were on the transcribed strand.

The S. cerevisiae strains used in this study were derived from the strains ORD11-4B [Matα; ARG4Δ2060; ura3-52; trpl-28; leu2-3; ade2-10; dup KV[DED82-Arg2[ΔHpal]-YSY83] and ORD17-47C [Matα; ARG4Δ2060; his3Δ1; DED82:URA3; ORF83:TRP1; dupKV[DED82-Arg2[ΔHpal]-YSY83; Lichten et al. 1990]. These strains are derivatives of the strain S288c [N. Schultes, unpubl.]. DED82:URA3 and YSY83:TRP1 correspond to a 1.5-kb EcoRI fragment and a 1.2-kb HindIII fragment inserted into the DED82 BamHI site and the YSY83 BglII site, respectively. To complement deficiencies created upon disruption of the essential genes DED82 and YSY83,
a 12-kb fragment was inserted into ApaI–Stul of the URA3 gene at its normal chromosomal position on chromosome V. This insert, designed at dupKV [DED62-Arg(ΔHpaI)-YSC83], contains an ApaI–SnaBl fragment of the ARG4 region deleted of a 2-kb fragment from −316 bp to +1745 bp that carries the poly(I) substitution. The...duced into various strains by crosses with the strains ORT329 (MATα, ARG4Δ2060; ura3-52, trp1-289, ade2-101, his3Δ4; rad50::URA3) and ORT324 (Mat α, ARG4Δ2060; ura3-52, trp1-289, leu2-3, rad50::URA3) (de Massy and Nicolas 1993).

**Media, culture conditions, and genetic analysis**

Growth and sporulation of yeast cells were performed by standard methods (de Massy and Nicolas 1993). Cells were grown in YPD media. For sporulation, cells were grown at 30°C in presporulation media (SPS) to a concentration of 2 × 10⁷ to 4 × 10⁷ cells/ml, washed in water, and incubated at the same density in sporulation medium (1% potassium acetate supplemented with the required amino acids) at 30°C. The distribution and frequencies of meiotic recombination implicating the marker genes (URA3 and TRP1) and gene conversion events in the ARG4 gene were studied by tetrad analysis. The segregation of ARG4, URA3, TRP1, and at least four additional markers (LEU2, HIS3, ADE2, and the mating type locus MAT) were examined. All tetrad showing non-Mendelian segregation for URA3, TRP1, or ARG4 were tested for all the markers, using larger patches of cells.

**Analysis of the segregation of the restriction sites**

The segregation of the BstZ171 and Agel sites was studied by the polymerase chain reaction with primers complementary to positions +8 bp and +730 bp. DNA was amplified directly from colonies arising from individual spores. The PCR products were digested with the BstZ171 or Agel restriction enzymes and analyzed by agarose gel electrophoresis on 2% NuSieve GTG (FMC BioProducts, Rockland, Maine) agarose gels.

**Analysis of the length of repetitive tracts**

The lengths of the tracts in the spores were determined by PCR amplification directly on colonies with primers that flank the repeated tracts (positions +198 bp and +432 bp). The PCR products were run on 6% denaturing polyacrylamide gels with control DNA samples containing poly(GT) CTGs of 38 and 39 bp and transferred onto a nylon membrane (Amersham, N+). Membranes were prehybridized for 2 hr and hybridized for 24 hr at 65°C with the labeled probe (20 ng/ml). Probes were labeled by random priming [Readyprime Kit; Amersham] with [α-32p]dCTP, 3000 mCi/m mole, 110 TBq/m mole [Amersham]. Unincorporated nucleotides were separated by filtration on a ProbeQuant G-50 Micro column. The probe used in the hybridization as the 707-bp PCR product (primers complementary to positions +8 bp and +715 bp) internal to the ARG4-coding region. Quantification of DSB signals were performed as described previously (de Massy and Nicolas 1993) by use of a PhosphorImager (Molecular Dynamics, STORM 860) and the ImageQuant program.

**Statistical analysis**

All results were tested by statistical analysis. Fisher’s exact variant of the chi-square test was used for most comparisons and a P value of <0.05 was considered to be statistically significant.

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(CA/GT)$_n$ microsatellites affect homologous recombination during yeast meiosis

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