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38. We thank P. Philippsen and J. Gafner for providing the sequences of *Ty*1-B10 and *Ty*1-D15 and R. Davis for the S13 plasmid. Our work was supported by NIH grants GM15408 and CA23441. G.S.R. was supported by a fellowship from the Medical Research Council of Canada. D.T.C. was supported by training grant GM07617 from the National Institutes of Health.

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Recombination of Dispersed Repeated DNA Sequences in Yeast

Stewart Scherer and Ronald W. Davis

Dispersed, repeated gene families have been found to be a general feature of eukaryotic genomes. Some, such as the actin genes of *Drosophila* (*1*) or the yeast histone genes (*2*), are multiple copies of structural genes, while others are organized like the transposable elements of bacteria (*3*). This latter class, including the *copia* genes of *Drosophila* (*4*) and the *Ty*1 family in yeast (*5*), seems to be capable of relatively rapid movement throughout the genome of its host. The integrated copies of the RNA tumor viruses share many structural similarities with these mobile dispersed families (*6*).

Summary. Yeast transformation can be used to insert new sequence arrangements into a variety of chromosomal locations by homologous recombination. These newly inserted sequences can recombine with similar sequences located on other chromosomes. In these events, information is duplicated without being lost at the site from which it is derived. Similar mechanisms might be utilized by cells to provide new functions during development or differentiation.

Recombination among the members of tandemly repeated sequence families has been proposed as a major mechanism for their evolution (*7*). However, the mechanisms that have been proposed for maintenance of sequence homogeneity among the members of the tandemly repeated families are not suited to the problem of the dispersed family. It has been suggested that reciprocal recombination between the members of a dispersed repeated sequence family may play a role in the inversions, translocations, and deletions of eukaryotic chromosomes.

Analysis of multigene families at the molecular level is complicated by the duplication of genetic information and by the hybridization between the DNA sequences coding for the various members of the family. A mutation in a single member of a large family may have no scorable phenotype. It is also difficult to assess the relative levels of transcription of each member of the family, as the transcripts are often indistinguishable except at the level of nucleotide sequence.

Transformation of yeast with DNA containing new sequence arrangements provides a mechanism for addressing many questions involving dispersed, repeated gene families. One can construct molecules that have selectable markers within or adjacent to a cloned, dispersed repeated element. This permits identification of a particular member of such a family. Also, one can introduce additional copies of sequences of known function to construct new dispersed gene families.

We have found that *Ty*1 sequences can recombine homologously during transformation experiments. Since *Ty*1 elements are dispersed throughout the yeast genome, the inclusion of *Ty*1 sequences in the transforming DNA allows one to introduce a particular sequence into a variety of chromosomal locations. Unusual genetic behavior by these novel sequence arrangements may provide approaches for such problems as position effects and the influence of transposable elements on the expression of neighboring genes.

Here we show that sequences introduced at several chromosomal locations can recombine with homologous sequences on a different chromosome. The events we observed are asymmetric (gene conversion); information is duplicated without being lost from its original location. The recombinational events occur when one copy of the sequences contains a deletion or a rearrangement. This suggests that the generalized recombination systems of the host can be utilized to transfer sequence information from one chromosome to another. These results also show that the recombination of dispersed repeated sequences is not limited to those organized as transposable elements. In many organisms there are examples of similar unlinked copies of structural genes coding for a wide variety of enzymes. Recombination of dispersed, related coding sequences might be an additional mechanism for providing new functions for a cell during development or in evolutionary time.

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Yeast Transformation Experiments

Since the original demonstration of transformation of yeast cells with DNA by Hinnen *et al.* (*8*), several mechanisms for the maintenance of the newly inserted sequences have been described. The basic method for introducing DNA molecules into yeast cells, however, has remained largely unchanged, and a similar procedure has proven successful for *Neurospora* (*9*). Briefly, the yeast cell wall is removed enzymatically and the resulting spheroplasts are incubated with DNA in the presence of calcium chloride. Polyethylene glycol is added to stimulate the uptake of DNA, and the spheroplasts are plated under conditions that stabilize them until fully viable cells can be regenerated.

The fraction of cells that becomes transformed is small. If the DNA molecules being used can be replicated by the cell, between 10^{-3} and 10^{-4} of the regenerated spheroplasts become transformed. Autonomous replication of circular DNA is made possible by addition of a segment of the endogenous yeast plasmid (*10*) or a chromosomal origin of replication to the transforming DNA (*11*). If the transforming DNA cannot replicate autonomously but has homology to the yeast chromosomal sequences, it can be integrated by homologous recombination. This occurs in about 10^{-7} of the viable cells in a typical experiment.

Because the fraction of regenerated spheroplasts that become transformed is small (especially when the transforming DNA cannot replicate), a strong selection must be applied to identify the transformed cells. The vector usually carries a wild-type biosynthetic gene (*ura*3 in these experiments) and the host carries a nonreverting mutation for that function (in this case a deletion, *ura*3-52). The vector used here, YIp5 (Fig. 1), contains a small fragment of DNA with the *ura*3 gene inserted into a nonessential region of the commonly used *Escherichia coli* vector pBR322. Yeast strains containing the *ura*3-52 deletion are missing most of the yeast sequences contained in YIp5. The remaining homology between the vector and the yeast genome is sufficiently low that no transformants have been detected when YIp5 is used to transform yeast strains containing the *ura*3-52 deletion. Without any inserted sequences, YIp5 will not replicate autonomously in yeast cells. We use this plasmid to determine whether the inserted sequences are sufficiently homologous with the chromosomes to allow integration of the transforming DNA and for selecting transformants containing new sequence arrangements.

Transformation with an Intact *Ty*1 Element (D15)

The *Ty*1 element of yeast described by Carmeron *et al.* (*5*) contains a 5300-base pair (bp) internal region flanked by direct repeats of about 350 bp. These end repeats are called δ sequences and are found at many additional sites in the yeast genome not associated with *Ty*1 sequences. The function of the *Ty*1 sequences in yeast is unknown.

Several intact *Ty*1 elements have been isolated from yeast as Hind III fragments cloned in phage λ (*5*). Each of these cloned *Ty*1 fragments has a small fragment of unique yeast DNA at each end of the *Ty*1 sequences.

A prototype *Ty*1 element, D15, was inserted into YIp5 at the Hind III site of the vector. The hybrid molecules transform a *ura*3-52 yeast strain, YNN36, to Ura$^+$ at a low frequency ($\sim 10^{-6}$ viable cells). The transformants are relatively stable, a phenotype strongly correlated with integration of the transforming DNA into a chromosome (*8*). Thus the *Ty*1 sequences in D15 do not replicate autonomously and, therefore, apparently do not contain a yeast chromosomal origin of replication (*11*, *12*). In related work involving other YIp5-*Ty*1 recombinant molecules, we examined the genetic behavior of the transforming DNA (*13*). In crosses with an appropriately marked strain, the *ura*3 gene in the vector sequences showed the segregation pattern expected from integration of the transforming DNA into the chromosomes.

Twelve independent transformants were analyzed by the method of Southern (*14*) to determine the site of integration of the transforming DNA into the chromosomes. The DNA of the transformants was cleaved with Hind III endonuclease and the fragments were resolved by agarose gel electrophoresis. (Most *Ty*1 elements do not have sites for Hind III endonuclease.) After transfer to nitrocellulose, this DNA was hybridized with ^{32}P-labeled DNA of cloned internal *Ty*1 sequences. In this set of transformants, the transforming DNA was integrated into the yeast genome at eight distinguishable sites. In six, the DNA was clearly integrated into a restriction fragment containing *Ty*1 sequences because the integration event changed the size of one restriction fragment hybridizing with a *Ty*1 probe. Some transformants simply contained an additional fragment homologous with a *Ty*1 hybridization probe, while others showed no obvious change in the *Ty*1 hybridization pattern; however, they did contain the vector DNA sequences.

In the cases in which the transformation event altered a restriction fragment containing *Ty*1 sequences, we demonstrated that the integration event was mediated by *Ty*1 sequences. The genomic DNA of the transformants was cleaved with an enzyme that cuts within both the *Ty*1 sequences and the vector

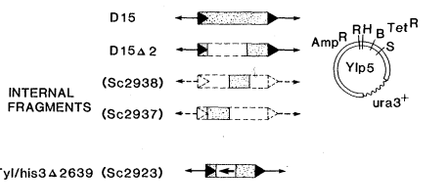

Fig. 1. Structure of the molecules used in the experiments. D15 is a prototype *Ty*1 element; it is a Hind III fragment of 8.45 kb. The darkened arrows represent the δ sequences at the ends of *Ty*1 and the spotted areas are the internal sequences. D15 was cloned into YIp5 (*16*), shown at right at the Hind III site; the δ sequences point clockwise. D15Δ2 was constructed by deletion of the two internal Bgl II fragments, Sc2937 and Sc2938. The two internal fragments were cloned into the Bam HI site of YIp5. The *Ty*1*his*3 hybrid element was constructed by insertion of a Bam HI fragment containing a promoterless *his*3 gene, Δ2639 (*22*), at the remaining Bgl II site of YIp5-D15Δ2. The *his*3 gene is transcribed counterclockwise in YIp5-Sc2923, as is the major *Ty*1 transcript (*15*). The restriction endonuclease cleavage sites indicated for YIp5 are *R*, Eco RI; *H*, Hind III; *B*, Bam HI; *S*, Sal I.

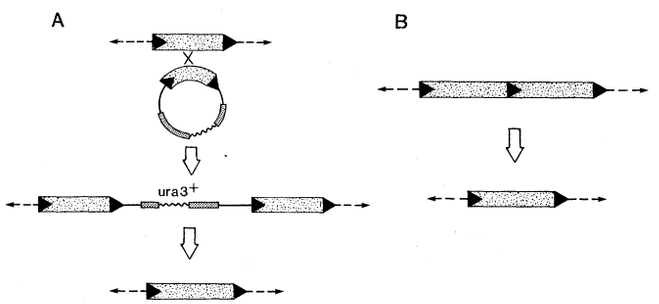

Fig. 2. Recombination of tandem *Ty*1 elements in a chromosome. (A) The structure generated when the YIp5-D15 hybrid molecule recombines with a *Ty*1 element in a chromosome. The duplicated *Ty*1 sequences are separated by the vector sequences containing the *ura*3 gene. The bacterial sequences are shown as a double line. Recombination between the tandem *Ty*1 elements restores the untransformed configuration. (B) The structure of certain tandem *Ty*1 elements found in the yeast genome. One might expect these structures to recombine at a rate similar to that for the nontandem elements shown in (A).

sequences (Eco RI or Pst I). Fragments identical in size with those of the transforming DNA were observed. If the recombinational event that integrated the transforming DNA involved nonhomologous DNA, this would not have been the case. In addition, *Ty*1 is polymorphic with regard to the number of Eco RI sites in the element. Some of the transformants showed the hybridization pattern expected on integration of the transforming DNA by *Ty*1 homology into known *Ty*1 variants (*13*).

None of the transformants integrated the transforming DNA via the unique flanking sequences in D15. Strain YNN36 does not have a *Ty*1 element at the homologous chromosomal location of D15. However, it probably has one δ sequence at this site (*15*). Integration at the D15 locus by homologous recombination of the sequences flanking the *Ty*1 in D15 would produce a fragment identical in size with the cloned D15 segment. The fact that no such fragment was found indicates that the transforming DNA did not integrate into these sequences.

Analysis of this type is complicated by the large number of preexisting *Ty*1 sequences, the unknown restriction endonuclease cleavage patterns of the DNA flanking the various *Ty*1 elements in yeast, sequence polymorphism within *Ty*1 (*5*), and the possibility of coincidentally sized fragments. The transformants with DNA not readily assigned to *Ty*1 sites may have DNA integrated by *Ty*1 homology and may not have been detected for any of these reasons. Alternatively, the transforming DNA might have been integrated at one of the many δ sequences not adjacent to a *Ty*1. Nonhomologous recombination cannot be excluded by the data presented here, but it is probably not the major mechanism for integration of the transforming DNA.

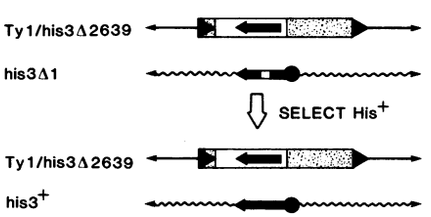

Fig. 3. Recombination between unlinked *his*3 sequences. The *his*3 sequences in the *Ty*1*his*3 hybrid recombine with the *his*3 sequences at the normal chromosomal location, *his*3-Δ1. Selection for His$^+$ allows identification of the cells where the event occurred. All revertants tested were indistinguishable. A mitotic gene conversion event occurred that resulted in an intact *his*3 gene on chromosome XV with no change in the *Ty*1*his*3 sequences. The functional *his*3 promoters are indicated with circles; the *his*3 coding sequences, with bars. The wavy line indicates the sequences adjacent to *his*3 on chromosome XV. Other symbols are described in the legend to Fig. 1.

Integration by *Ty*1 sequence homology should be a reversible process. Accordingly, one of the transformants obtained with YIp5-D15 that had clearly been integrated by *Ty*1 homology was tested for the ability to revert spontaneously to Ura$^-$. After ten generations of nonselective growth, three of 1000 colonies tested were Ura$^-$. Hybridization analysis revealed that all three had exactly reversed the original transformation event. This event is outlined in Fig. 2A. Evidence has been obtained for similar direct repeats of *Ty*1 elements in the yeast genome by identification of clones containing circularly permuted *Ty*1 sequences (*5*). One would expect such structures to delete an intact element (Fig. 2B). If these *Ty*1 elements lack an origin of replication (as did the clone tested here) and these circular products fail to integrate back into the genome, they would be diluted out of the population. Either there is a selective advantage for yeast strains with tandem *Ty*1 sequences, or some mechanism must exist to generate them at a high frequency.

Transformation with Internal Segments of *Ty*1

The experiments described above show that the *Ty*1 sequences can recombine homologously during transformation. The δ sequences at the ends of *Ty*1 or the internal *Ty*1 sequences could be mediating these events. Evidence for the recombination of δ sequences during mitotic growth has been obtained by examination of spontaneous deletions of a transfer RNA gene (*16*). We tested two internal restriction fragments of *Ty*1, Sc2937 and Sc2938 (Fig. 1), for the ability to provide homology to integrate YIp5. Both gave "stable" transformants at a frequency slightly lower than the intact D15 fragment. Therefore, the internal *Ty*1 sequences can recombine during mitotic growth of yeast cells.

Transformation with a *Ty*1*his*3 Hybrid Element

To avoid the complexity of the analysis of the transformants generated with YIp5-D15, a hybrid element, Sc2923, was constructed (Fig. 1). It contains the ends of *Ty*1 and a *his*3 gene with a deletion of its promoter (*13*). The *his*3 sequences replace a large internal segment of *Ty*1. After this hybrid element is introduced into yeast, the location and transcription of this particular *Ty*1 element can be distinguished from other *Ty*1 elements in experiments in which *his*3 sequences are used as the hybridization probe. The transformants now contain two distinguishable *his*3 genes, one at the normal chromosomal location and the other at any of the sites where the *Ty*1 sequences in the hybrid element can recombine during transformation.

The hybrid element was used to generate transformants of YNN36 or YNN37, another yeast strain with the *ura*3-52 mutation. The *his*3 gene in YNN36 contains a deletion of ~ 150 bp in the structural gene (defined as *his*3-Δ1). Strain YNN37

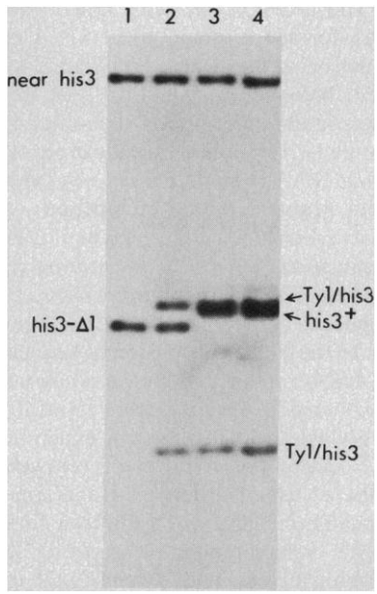

Fig. 4. Hybridization to *his*3 sequences in strains where the unlinked *his*3 sequences have recombined. All DNA samples were cleaved with Pst I endonuclease, electrophoresed in a 0.7 percent agarose gel, transferred to nitrocellulose, and probed with sequences from the Bam HI fragment containing *his*3 (*23*). Since there is a Pst 1 site in the *his*3 Bam HI fragment, two fragments are labeled in lane 1, untransformed YNN36. The smaller fragment contains the *his*3 sequences of *his*3-Δ1, and the large fragment contains sequences beyond the 3′ end of the *his*3 gene. Lane 2 is DNA of a transformant of YNN36 with YIp5-Sc2923. Two new bands appear. The smaller fragment contains the *his*3 coding sequences in the hybrid element (identical in size with the transforming DNA) and the other derives from sequences beyond the 3′ end of *his*3 in the hybrid element. The remaining lanes contain DNA from His$^+$ revertants selected from the strain shown in lane 2. The sequences derived from the *his*3 locus on chromosome XV have increased in size; the Δ1 allele has been gene-converted to wild type. The fragments derived from the hybrid element are unchanged; therefore, the event was asymmetric. These digests do not determine whether a reciprocal translocation occurred. Appropriate digests are shown in Fig. 6.

has a rearrangement at the *his*3 locus consisting of a substitution of 2.55 kbp of DNA from the *GAL* 1, 7, 10 region on chromosome II for the same 150 bp deleted in YNN36 (defined as *his*3-R1) (*17*). As was the case with the normal *Ty*1 element, the hybrid element integrates into a variety of sites in the yeast genome. Transformants of YNN36 or YNN37 with YIp5-Sc2923 are His$^-$, except in the rare event that integration has occurred at the *his*3 locus and an intact *his*3 gene is reconstructed.

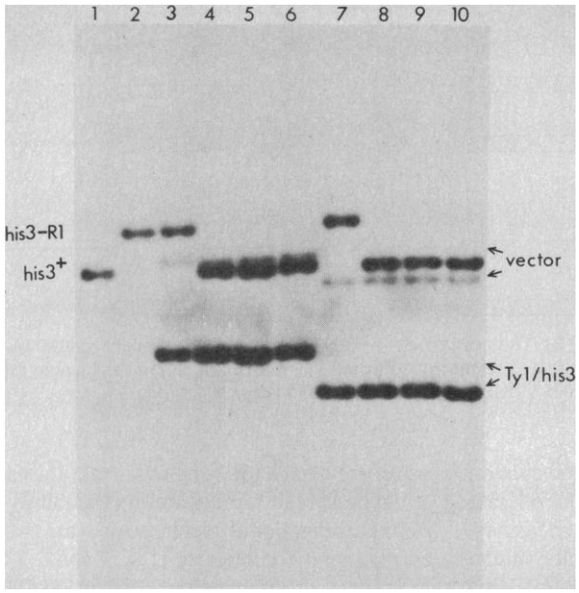

Fig. 5. Gene conversion of a mutation that is a substitution of nonhomologous DNA. The DNA used here was digested with Eco RI and treated as described in the legend to Fig. 4 (*23*). Lane 1 shows the size of the wild-type *his*3 gene. Lane 2 shows the larger *his*3-R1 allele fragment. Lane 3 is DNA from a transformant of YNN37 with YIp5-Sc2923. Lanes 4 through 6 contain DNA from revertants of the strain shown in lane 3. The fragment with sequences from the normal *his*3 locus has been gene-converted to wild type, while the band arising from the hybrid element is unchanged. Lane 7 shows DNA from another transformant of YNN37 generated with YIp5-Sc2923. The fragments arising from the integration of the transforming DNA are of a different size than those in lane 3, indicating integration at a different site in the yeast genome. The remaining lanes show DNA from three revertants derived from the second transformant.

The *Ty*1*his*3 Hybrid Converts Deletions and Rearrangements at *his*3

All transformants of YNN36 or YNN37, with one copy of YIp5-Sc2923 integrated at a variety of chromosomal locations, revert spontaneously to His$^+$ at a frequency of about 10^{-7} cells in an exponential population. This even has been characterized by a variety of techniques. First, the level of *his*3 expression has been assessed approximately by the observation that yeast strains with a wild-type *his*3 gene are resistant to the histidine analog aminotriazole (*18*). Cells that express *his*3 at a low level are sensitive to the drug. Second, the functional *his*3 gene was mapped by genetic techniques. The *his*3 and *ura*3 genes of yeast are normally on different chromosomes. If the *his*3 gene in the hybrid element had become functional, His$^+$ and Ura$^+$ would be tightly linked in a cross with an appropriately marked strain. This result was not found; the functional *his*3 gene was not linked to the *ura*3 gene in the vector. Finally, since the two *his*3 genes are marked by deletions and rearrangements, the sizes of the transcription products and the restriction fragments containing the coding sequences are easily distinguished.

All the lines of evidence lead to a single conclusion. The two unlinked *his*3 genes recombined and reconstructed a functional gene at the normal *his*3 locus by mitotic gene conversion (Fig. 3). The data presented in Fig. 4 show that the recombinational event was not symmetric. The fragment containing the *his*3 sequences on chromosome XV increased in size by the expected 150 bp, while the fragments from the *Ty*1*his*3 hybrid element remains unchanged. Similar results are obtained with the *his*3-R1 allele in YNN37 (Fig. 5).

Fink and Styles (*19*) examined gene conversion of deletions at *his*4. In their experiments, recombination was largely asymmetric, and outside markers were exchanged in about half of the events. Hybridization experiments (Fig. 6) have not identified any translocation-containing strains arising from the events described here; however, the relative directions to the centromeres from the *his*3 gene on chromosome XV and from the *his*3 gene in the hybrid element are unknown. The exchange of outside sequences might produce dicentric and acentric chromosomes and be a lethal event.

Interchromosomal Recombinational Events Not Involving *Ty*1 Sequences

In all the experiments described above, one of the *his*3 genes was located within a *Ty*1 element. This configuration is not required for the interchromosomal recombinational events to occur. Two other types of configurations were tested. First, the same *his*3 fragment that was used to construct the hybrid element was inserted outside instead of within the D15Δ2 sequences (Fig. 1). The *his*3 sequences in this molecule are located ~ 2000 bp from the end of the *Ty*1 sequences. This hybrid molecule can insert into a variety of sites in the yeast genome on transformation. Three transformants of YNN36, containing this new plasmid integrated into different chromosomal sites, gave rise to His$^+$ recombinants at the same frequency as with the *Ty*1*his*3 hybrid. Second, the same promoterless *his*3 fragment was cloned into a YIp5 recombinant containing sequences from

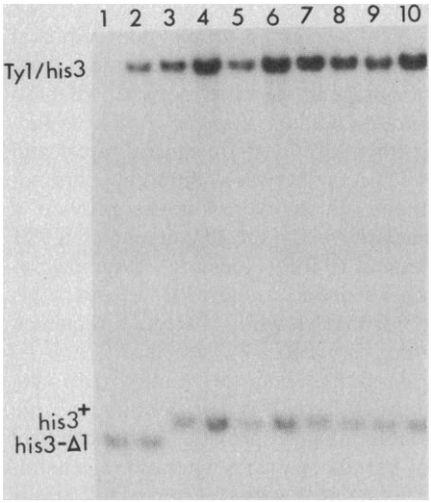

Fig. 6. The interchromosomal recombinational events were not associated with reciprocal translocations. The DNA in this figure was cleaved with Bam HI endonuclease, electrophoresed, transferred to nitrocellulose, and probed with pBR322-Sc2676 (the *his*3 Bam HI fragment). Lane 1 contains DNA from YNN36 and shows the size of the Bam HI fragment containing the *his*3-Δ1 allele. Lane 2 is a transformant of YNN36 with YIp5-Sc2923. The remaining lanes contain DNA from revertants of the strain shown in lane 2. The revertants have had an increase in size of the Bam HI fragment on chromosome XV to that of wild type (1.75 kbp). The large fragment containing sequences from the hybrid element is greater than 10 kbp. If a reciprocal translocation had occurred, a fragment of about 8 kbp would be expected near the center of the gel. (The structure of the integrated DNA was determined with other hybridization experiments. The predicted 8-kbp fragment would derive from the 5′ end of the *his*3 locus on chromosome XV and the 3′ end of the hybrid element extending to the Bam HI site in YIp5.)

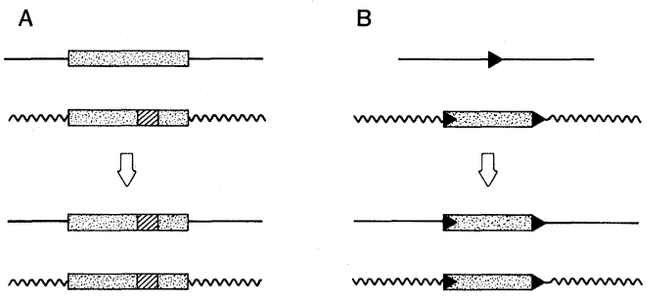

Fig. 7. Possible recombinational events involving dispersed repeated gene families. (A) The means by which a copy of a dispersed repeated sequence (shaded area) containing a mutation (striped area) could recombine asymmetrically with another member of the family and convert it to the altered form. (B) The means by which an intact *Ty*1 element could recombine with an isolated δ sequence and result in additional *Ty*1 in the cell. The event would be analogous to the gene conversion of a deletion mutation of *his*3 (Fig. 3).

chromosome II near the *gal* gene cluster. This new plasmid was introduced into yeast and integrated near the *gal* genes. These transformants give results similar to those obtained with the *Ty*1*his*3 hybrid element in reversion experiments (*13*).

Discussion

Recombination of dispersed, repeated DNA sequences provides a mechanism for gross chromosomal rearrangements. Such recombinational events may play a major role in the generation of deletions, inversions, and translocations in eukaryotic chromosomes. Cameron *et al.* (*5*) gave evidence for tandem *Ty*1 elements in the yeast genome. If such tandem repeats delete at a frequency similar to that measured for nontandem repeats here, there must be a mechanism to generate new tandem *Ty*1 elements at an equally high frequency, or some unknown selective pressure to maintain them.

Mobile dispersed sequences can move genetic information to new sites in the genome by transposition. The mobile elements of eukaryotes are characterized by short direct repeats at their ends. One possibility for movement of the element involves recombination through these repeats and excision of the element from the chromosome. Such movement might be facilitated by replication of the excised elements. We have found that the intact *Ty*1 element does not appear capable of promoting autonomous replication during DNA transformation of yeast.

When the recombinational events involving dispersed repeated sequences are not reciprocal, a mechanism is provided to maintain sequence homology between the various members of the gene family. Deleterious mutations could be corrected and beneficial mutations could be spread rapidly among the family by recombinational mechanisms (for example, gene conversion) (Fig. 7A).

Several chromosomes contain *Ty*1's (*15*). It is unlikely that the second *his*3 gene would be on the same chromosome as the normal *his*3 locus when it is introduced into yeast through *Ty*1 homology. In experiments in which the second *his*3 gene is inserted on chromosome II, however, the chromosomal locations of both *his*3 genes are known. In these experiments, the gene conversion event must involve sequences on two different chromosomes.

One possible mechanism for the interaction of the *his*3 sequences on one chromosome with the *his*3 sequences at their normal location involves the excision of the transforming DNA from the first location. Although these excision events are easily detected, we do not believe they are involved in the events we have observed. In thirty independent events, the original inserted *Ty*1*his*3 hybrid was retained when the intact *his*3 gene was reconstructed. Also, the reconstruction of *his*3 was not associated with an insertion of the vector sequences at *his*3.

As shown in this article, nonreciprocal recombination or mitotic gene conversion can involve several kilobase pairs of nonhomologous sequences (deletions, additions, or substitutions) and can occur between different chromosomes. Such events might provide a mechanism for the movement of a *Ty*1 element to a new location containing only a δ sequence. Figure 7B illustrates this movement, in which a single δ sequence is converted to a *Ty*1 element.

Recombination of homologous sequences flanked by or containing large nonhomologies provides a mechanism for certain sequence alterations generally associated with "illegitimate" transposition events. Spontaneous mating type interconversion in yeast would be one example of such an event (*3*, *20*). The recently described structures of the α and *a* mating type sequences show two regions of homology at the ends separated by nonhomologous sequences (*20*). The low-frequency, spontaneous switch of the information at the mating type locus is analogous to the recombinational events described here involving the *his*3*Ty*1 hybrid and the *his*3-R1 allele. The three copies of the mating type information recombine reciprocally and produce large deletions or ring chromosomes (*21*). Also, complex recombinational events are required for the construction of the mature immunoglobin genes in lymphocytes. Some of these events may involve the recombination of short homologous sequences. Asymmetric events would not require that information be lost during development. Information could be duplicated to the various sites in the genome where it is required.

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23. The fragments used for hybridization probes (the gift of J. Jaehning) were nick-translated after purification on a preparative sucrose gradient. As a result, they hybridized weakly to fragments containing the vector sequences from which they were separated.
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