Possible Loss of Length Conservation and Reciprocity During Recombination or Conversion in Tandem Arrays

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ABSTRACT

Recombination or conversion between arrays of repeated sequences need not be conservative for length because two single strands of DNA from one chromatid may form heteroduplexes in different registers on the other participating duplex. This can cause an overall change in repeat number. Loss of length conservation is equally possible whether models of recombination initiated by single-strand transfer or double-strand break are applicable. Length changing conversion will frequently produce a characteristic insertion within a deletion, often appearing as a double deletion such as are frequently found in new variants of human minisatellite MS32. There is no apparent means of preserving parity during length-changing conversion or recombination, and if the changes are biased then the overall copy number will increase or decrease according to that bias. The observation that arrays persist suggests that any bias in these arrays will be toward gains. An equilibrium may be reached where gains, which may be largely independent of array length, equal losses from the array-length-dependent processes of intrachromatid recombination and repeated unequal sister chromatid exchanges.

UNEQUAL crossovers between misaligned arrays can cause variation in array length by producing matched deletions and tandem duplications which are length conservative (Figure 1), however JEFFREYS *et al.* (1990) found that 7/49 new short variants in human minisatellite MS32 were double deletions, the ends of the array surrounding a segment from the middle. This frequency was a minimum because many possible double deletions would have been unresolvable, and they were too frequent to be products of two independent deletions. The most probable explanation is that the apparent double deletions were produced by a single length-changing conversion between two arrays. Recombination or conversion between unique sequences is necessarily conservative for length, because the exchanged single strands can form heteroduplex in one position only. During the formation of Holliday intermediate structures between arrays of repeats it appears to be possible for the two exchanged single strands to form heteroduplex in different registers. This is especially easy to envisage if the repeats are short, say dinucleotides, but could also occur with larger repeat units hundreds or thousands of base pairs long. Resolution of the Holliday structure can then cause an overall change in repeat number by mismatch repair or infilling synthesis. This loss of length conservation will occur in certain conditions in single-strand nick mechanisms of recombination, and in many situations in double-strand break repair recombination. Conversion without crossing over will produce an insertion within a deletion. This will appear as a double deletion, as seen in MS32, if the insertion is homologous to part of the larger deleted

region, but since this need not be the case, the more general term "insertion-in-a-deletion" is used here to describe accurately the molecular patching process.

MODELS OF RECOMBINATION

Models of recombination have developed as experimental evidence has shown up their deficiencies. There are two basic types of recombination model, which may be classified as the single-strand nick type and the double-strand break type.

Single-strand nick models: The earliest model of recombination (HOLLIDAY 1964) was elegantly simple. It envisaged symmetrical transfer between chromatids of single DNA strands of the same polarity nicked at homologous sites. Evidence from analysis of fungal asci suggested that the transfer was not entirely symmetrical, and the chromatid initiating recombination was the recipient of information during conversion [see WHITEHOUSE (1973), CATCHESIDE (1977), SZOSTAK *et al.* (1983) and THALER and STAHL (1988) for reviews]. These requirements can be met (Figure 2) by supposing that one molecule is digested on the recipient (initiating) chromatid leaving a single-strand gap. The remaining single strand invades the homologous donor duplex, capturing the complementary strand (RADDING 1982). One end of the gapped molecule eventually transfers to the donor chromatid, completing the Holliday structure. Gaps are filled by synthesis and ends ligated. There are other variations on this theme, but in all of them, only one strand is transferred at the initiation site. The second strand is exchanged at a distance, probably independently, and the outcome is as shown in Figure 2B.

FIGURE 1.—Length conservative unequal crossover (a) gives a tandem duplication matching a corresponding deletion (b). Many short variant minisatellites apparently have pairs of deletions (c), which do not fit this mechanism.

The possibility therefore exists for the two strands to transfer in different registers, giving the potential for non-reciprocity and a change in total length.

Figure 3 shows how length increases may occur. The Holliday intermediate has a heteroduplex with one strand longer than the other by a number of whole repeat units. If the short strand is cleaved during resolution of the Holliday intermediate, or DNA replication precedes mismatch excision repair, an increase in total copy number will result. The result of excision repair of the loop after resolution of the Holliday structure depends on whether the excess loop is cut, restoring the original copy number, or the shorter strand is cleaved, leading to an overall length increase. The excess DNA will always be on one of the two exchanged strands, and could be shuffled between the donated and the displaced strands. The shorter non-exchanged strands will receive an insert complementary to the loop, and the exact effect will depend on where the loop stops, which could be a considerable distance from the initial event. The single-strand loop can migrate by rotary diffusion but may be arrested by regions of non-homology. Substantial migration through mismatched sites could lead to jumbling of sequences by excision repair of individual mismatches. All the duplex transversed by the loop will have mismatches arising from variation between repeats, because the two single molecules will be displaced sideways by the number of repeats in the loop. Arbitrary correction, or non-correction, in this region could completely jumble the sequences. It is conceivable that two or more loops form and are corrected independently, giving multiple insertions. Conversion without crossing over yields an insertion in a smaller deletion if mismatch repair uses the transferred strand as a template for conversion or DNA synthesis precedes repair (Figure 3, E and F). This could appear as a duplication (but with two break points) if part of the

FIGURE 2.—The single-strand nick model of recombination. (A) A single strand of DNA from the donor chromatid (P-Q, thick lines) hybridizes to the recipient (p-q, thin lines) replacing a strand of the same polarity which may already be degraded. (B) The displaced strand eventually hybridizes to the donor chromatid replacing the donated strand. Any loss by degradation of the displaced strand is replaced by synthesis on the donor chromatid, and gives a region of asymmetric transfer (from PQ to pq) and possible gene conversion. Branch migration can change the size of the adjacent region of symmetric transfer. (C) If the exchanged strands are cut and re-ligated continuity can be restored (D) with potential for symmetric (Sym.) and asymmetric (Asym.) conversion. (E) Isomerization can occur to give a symmetric "Holliday intermediate." This potentially gives equal probability of the exchanged or non-exchanged strands being cut and re-ligated, although in practice the chromosome structure may restrict the outcome. (F) Isomerization followed by cutting and religation of the non-exchange strands gives a classic reciprocal crossover, exchanging outside markers (G) with adjacent symmetric and asymmetric heteroduplex at the site of crossover. The absolute and relative lengths of these heteroduplex regions may vary between events and species.

inserted sequence was homologous to the deleted sequence.

A loss of copies occurs if the second transferred strand is out of register in the other direction. This again gives a length mismatch on one or both chromatids (Figure 4). In these cases, however, excision of the excess loop will give an overall loss of copy number, and length will only be conserved if the short strands are enlarged or no repair occurs before DNA synthesis. If the loop migrates laterally, followed by cutting of the short strand, there will be a duplication at the incision, matched in size by a deletion elsewhere. The deletion actually arises at the point where the 3' end of the transferred strand primes synthesis in the adopted chromatid. Again, the duplex between the origin of the loop and its final correction will contain a trail of mismatches between laterally displaced single strands. Repair of these could give very complex changes in the sequence. Conversion without crossing over can give a short insertion within a larger deletion. This would appear as a double deletion, as found in short variants of MS32, if the insertion was homologous to part of the deletion, which would have to be the case if the deletion extended to most of the array.

FIGURE 3.—Amplification during single-strand nick recombination. (A) The displaced strand hybridizes to the donor out of register, giving a single-strand loop (units 5 and 6 in this example) while (g) and (h) are replaced by synthesis. (B) The loop is more clearly seen in the symmetric cross configuration. (C) If the crossover is completed and the short (original p-q) strand is cut, replication of the loop amplifies units 5 and 6. The presence of the loop may bias resolution of the intermediate ensuring or preventing crossing over. (D) If the exchanged strands are cut and re-ligated then the original arrangement of outside markers (PQ/pq) is maintained, but there is still a loop mismatch which may migrate. Loops on both chromatids are possible. (E) Mismatch repair cutting the short (original length) strand will give an amplification during conversion. Co-conversion will replace units 7 and 8 with units e, f, g and h, appearing as an insertion of 4 units within a smaller deletion (2 units). (F) A similar result is achieved if DNA synthesis precedes mismatch repair. In all cases excision of the loop restores length conservation, and there is no possibility of overall loss. Letters and numbers represent repeat units in the arrays. The letters may be homologous to particular numbers, or represent a laterally displaced region of the array, or represent different alleles. Thin dashed lines between strands show regions of heteroduplex.

Differences in the frequency of occurrence of the various types of single-strand misalignment, and also preferential excision cleavage of either excess loops or short strands at length mismatches will tend to bias the process to either increase or reduce the overall copy number. Similarly, length mismatches may also affect the relative frequency with which conversions are accompanied by reciprocal crossover of flanking markers. The loop adjacent to the Holliday structure may always cause, or always prevent, crossing over. Bias could be identified if length-changing conversions were monitored for accompanying crossovers in G_1 or meiosis, but sister chromatid exchanges are not detectable genetically, only physically, *e.g.*, in ring chromosomes. Conversions between chromosomes could be detected if the repeat units in the homologous arrays differed by detectable point mutations. Production of new length variants of variable number tandem repeat arrays is rarely accompanied by detectable crossing over (WOLFF *et al.* 1991;

JEFFREYS *et al.* 1990), which suggests sister chromatid exchange or conversion. It is also interesting to note that arrays of highly repeated sequences are typically found in heterochromatin where recombination is suppressed. This suggests that if recombination intermediates are formed there, recombination is prevented and they are resolved as conversions.

Double-strand break repair models: Double-strand break repair by recombination was proposed by RESNICK (1976) who also suggested that double-strand breaks might initiate recombination in meiosis. Recombination, using another double helix as the information-bearing template, is the only error-free mechanism of repairing double-strand breaks, where all information is lost on the damaged duplex. It is essential for this that DNA from the donor bridges the gap in the recipient strand. Detailed observations led to an amended double-strand break model of recombination (SZOSTAK *et al.* 1983; THALER and STAHL 1988; both publications review

FIGURE 4.—Loss of repeats in single-strand break recombination. The displaced strand can hybridize to the donor chromatid to give single-strand loops in the non-exchanged strands. These loops may be on the donor chromatid (a), both chromatids (b), or the recipient (c). The derivatives of this are similar to those in Figures 2 and 3, but because the strands with excess DNA loops represent the originals, removal of the loop causes overall loss. Conservation of length requires mismatch excision repair to cut the short strand(s) and replicate from the loop DNA template. If the exchanged strands religate to the original continuity, a length decreasing conversion can occur if DNA replication precedes mismatch repair or correction favors the intruding sequence. This gives a small insertion in a larger deletion. This resembles a double deletion if the insert has homology to part of the deleted sequences, *i.e.*, in f, if *def* was homologous to 345, 2 and 6 would appear to have been deleted.

the supporting evidence). Physical evidence for short lived double-strand breaks in *Saccharomyces cerevisiae* chromosomes early in meiosis is evident from pulsed field gel analysis (GAME *et al.* 1989; BISHOP *et al.* 1992). The single-strand nick models of recombination are inadequate to explain recombination in *S. cerevisiae*.

In the double-strand break repair model (Figure 5), one chromatid is broken enzymatically (or by radiation prior to mitotic recombination repair). The gap is bridged by DNA from another chromatid, either from the sister chromatid or the homologous chromosome. This must involve hybrid DNA at both sides of the gap, but it is only essential on the broken chromatid. In an array of repeated sequences the two broken ends can interact independently with the donor. It seems to be difficult for the strand from the donor to match the break or gap exactly because of ambiguity from both exonuclease digestion and relative movement of the broken ends. This difficulty arises regardless of the molecular details of the recombination repair process. Length conservation would only be possible if the two intact chromatids were held together in homologous alignment *before* the break was made. This might be normal in meiosis or mating type conversion, but the cell cannot predict where X-rays will cause breaks, and it seems unlikely that the chromosomes or chromatids are

always paired along their length. In unique sequences there is only one possible alignment, but in a tandem array of repeats the majority of events might be non-conservative for length (Figure 6), the chance of errors increasing as the repeat unit length decreases. All conversion by double-strand break repair without crossing over will give an insertion within a deletion or double deletion. The overall change in copy number is the difference in size between the inserted patch and the deletion.

Three other potentially length changing modifications of double-strand break repair exist (Figure 7).

Modification 1: If the ends of the broken chromatid cross before invading the intact duplex the outcome is problematic. The extending ends will never meet, and if such a meeting as shown in Figure 5 is a stimulus for resolution of the Holliday structure(s), then the broken ends could be extended by synthesis to the end of the chromosome, at least in yeast which has small chromosomes. This would be replacement of both chromatid ends (independently) by conversion. The originally intact chromatid might survive, giving an extra third chromatid, or be destroyed in the process. Alternatively the two (crossed) invading ends might independently recombine and ligate into the intact duplex maintaining ploidy with two chromatids, each with a unique deletion.

FIGURE 5.—The double-strand break repair model of recombination. A break is made in one chromatid (A). The break may be enlarged, and the 5' end is resected (BISHOP *et al.* 1992). The 3' single-strand ends invade the intact donor chromatid (B) and prime synthesis (C, open arrows) extending across the break. Each end of the filled gap has a Holliday structure with one single strand unligated. If both ends are resolved in the same way conversion occurs without crossing over (D). If they are resolved differently a crossover occurs (E) recombining outside markers.

This crossed-ends event is analogous to “ends-out” integration of a gapped plasmid, which occurs at about one half to one third the frequency of “ends-in” integration, in conditions of equal homology (HASTINGS *et al.* 1993). This means that either integration of one end roughly doubles the chance of the other end integrating facing it, perhaps because the duplex is opened up; or the two ends are independent, both types of resolution of the two Holliday junctions are equally likely, and so the combination of one crossover + one conversion required for ends-in integration is twice as likely as the two crossovers needed for ends-out integration. Conversion in the ends-out situation restores the original broken end, possibly extended, and this could reinitiate the repair cycle. Similarly, recombination generates a free end on the originally intact chromatid.

Modification 2: If the two sections of chromatid either side of the break attack two different intact duplexes in a diploid in G_2 , the two ends could be completely replaced by conversion, again giving an extra chromatid. Ploidy could only be maintained if one end was restored by conversion/resynthesis using the intact chromatid as template, and the other end of the broken chromatid was lost. If both ends recombine into the two donor chromatids they effectively break both of them, leaving two ends as before, with potential for further rounds of repair.

Modification 3: A related situation could arise if the section to one side of a double-strand break was lost

because of enzymatic degradation, or it simply failed to “find” a homologous chromatid. In this case it would be necessary to replace the lost end section by conversion and to maintain the donor chromatid to keep the correct number of chromatids. The combination of end replacement by conversion and integration by recombination required to maintain ploidy differs between these three cases, and there is no obvious way for the cell to distinguish them, so aneuploidy is likely to result in some cases. For example, if replacement of a lost end (required in 3) were applied to the situation in (1) and (2) then they would each generate an extra chromatid. The cases where the broken ends attack different intact chromatids, or one end is lost (2 and 3) could also occur in unique sequences, and there is experimental evidence that the entire acentric end of the chromosome is sometimes replaced during repair of double-strand breaks induced by *HOT1* in yeast (VOELKEL-MEINHAM and ROEDER 1990). It must be remembered that yeast chromosomes are minute compared to those of most multicellular organisms.

DISCUSSION

It is clear that crossovers or conversions in arrays could lead to an overall change in copy number. Any bias will systematically amplify or remove repeats from individual chromatids, and from the whole population. There are two pertinent questions to ask.

1. Do the single-strand nick and double-strand break models differ in their predicted products to allow distinction between them?: The products of both the single-strand nick and double-strand break models are similar. Crossing over to give exchange of outside markers will produce two chromatids which seem to originate from crossing over at different points (incidentally confusing fine-structure mapping in genes containing a repeat motif). Conversion without crossing over can give an insertion within a deletion, the overall length change being the difference in the number of repeats between the deletion and the insertion. The single-strand nick models can give insertions within deletions (or double deletions) if DNA replication precedes mismatch repair or mismatch repair uses the intruding strand as a template. If the length mismatch loops envisaged in the single-strand nick models are allowed to migrate laterally, and especially if multiple loops form, the rearrangements produced could be very complex. Excision of a laterally displaced loop could give a deletion in that strand, compensated by a duplication at the original site of strand transfer. Excision of multiple loops could give double or multiple deletions. The final sequence could be complicated by any combination of mismatch repair, whereas the double-strand break models should give relatively simple products. The single-strand nick models always give a heteroduplex intermediate on both chromatids, although these are asymmetric and may be

FIGURE 6.—Non-conservation of length during double-strand break recombination. (a) Following the introduction of a double-strand break the ends of the recipient chromatid may become displaced laterally. (b) If the ends move apart (left hand section) then the gap bridged will be less than the length of the bridging strand from the donor. Similarly, if excessive degradation of the edges of the gap occurs, and the ends move together the bridging strand will be shorter than the material lost from the gap, giving an overall decrease in length (right hand section). (c) Crossing over gives an overall length change, the two chromatids appearing to have been produced by crossovers in different points in the array. (d) Conversion without crossing over leaves the donor chromatid intact, but the recipient has an insert from the donor which may be longer or shorter than the repaired gap, thus changing the length of the array on the recipient chromatid. The converted chromatid will look like a double deletion if the bridging strand came from the region homologous to the center of the gap. For example, if *cd* in the decreased chromatid *1cd6* were actually units 3 and 4 from a sister chromatid, then *1cd6* would be *1346*, apparently having units 2 and 5 deleted.

FIGURE 7.—Movement of the ends of a broken chromatid can produce abnormal repair configurations. (a) The ends could cross before invading the array on the donor. Ploidy is only maintained if both ends recombine into the donor. Loss of repeats would occur. (b) The ends could invade different chromatids in a diploid in G_2 . (c) One end of the broken chromatid may be lost.

of very unequal length. The exact outcome depends on the manner of resolution of the Holliday structure, the direction of mismatch repair or the occurrence of DNA replication before repair. The double-strand break models may give very little heteroduplex (post meiotic segregation is typically rare in yeast) and all the change could be on the recipient chromatid. In this case, assuming equal frequencies of conversion alone and crossing over, one quarter of participating chromatids, or one third of changed chromatids, should show the in-

section in a deletion effect. Another possible difference is that the single-strand loop required for overall length change in the single-strand nick/gap models will bias the ratio of conversion to crossing over for length changing compared to length conservative events. No special bias in the conversion/recombination ratio would be expected to accompany overall length changes by the double-strand break repair models.

Cells probably have the means to perform both types of recombination, and there are dangers in expecting a single unifying solution. The classes of events are likely to vary between arrays within species, and between species. The size of repeat unit, array length, chromosomal position, and the relative activity of the proteins involved [mismatch recognition, endonuclease, exonucleases, polymerase, ligase, topoisomerases, strand transfer (RecA type) proteins, single-strand binding/stabilizing proteins] in specific strains, will all affect the recombination/conversion events. It is very difficult to definitively identify the mechanisms of recombination (THALER and STAHL 1988). The single-strand models are more sensitive to mismatch repair mutants because they have more extensive heteroduplex than the double-strand break models. This could aid discrimination, but only if the heteroallelic mutants are fully understood. Many genetic markers produce allele-specific outcomes to recombination events because their presence modifies the processes. Both models can explain the high frequency of double deletions reported in new short variants of minisatellite MS32 (JEFFREYS 1990) as a consequence of length decreasing conversion. Both models

also predict the occurrence of increased length arrays carrying a large insertion in a small (possibly undetectable) deletion, and predict that the insertion may come entirely from sequences which do not overlap the deletion. Further analysis of minisatellite variation may reveal these products. As a rule in biology, anything that seems biologically possible (and much that does not) is likely to occur somewhere.

Deletions and duplications are also produced by replication slippage. These should always be simple independent events, never associated with recombination, but they may occur at a high frequency in a few cells, thus appearing in complex combinations. It seems likely that replication slippage is most frequent in short repeat units, involving small absolute changes in number of base pairs, whereas the effects of length-changing conversion or recombination can occur in large repeats and change substantial portions of the array. Observations of reciprocal products of changes in variable number tandem repeats in congenic cell lines which contain different combinations of recombination and mismatch repair deficiencies would help to answer these questions, but such observations are obviously difficult to obtain.

2. Is there evidence to suggest that bias exists, and in which direction?: Arrays of repeats may be misaligned during recombination, giving unequal crossovers (UCO). The sequence of deletions and tandem duplications will reduce the variability between the sequences of adjacent repeat units (SMITH 1973, 1976). Since these length changes are the mechanism of homogenization, the potential loss of conservation of total length during recombination has no effect on the proposed homogenization. The variation in length so produced is important, because homogenization rate is proportional to the harmonic mean length. Selection will maintain the length of functional sequences, but many arrays evolve very rapidly and have no coding or other known function. The continued existence of such unselected arrays suggests a bias toward amplification by some mechanism, because there are four ways hypothesized in which UCO can remove repeats, but only the transient effect of drift can give an increase:

Mechanism i: The length of any particular array lineage will undergo a random walk through time. There is only one stable end-point, which is when the arrays becomes too short to undergo further UCO, possibly when they are reduced to a single copy. In a finite population, all arrays will eventually walk into this trap (PERELSON and BELL 1977).

Mechanism ii: It is not reasonable to assume that very long arrays, even of "junk" DNA, will be selectively neutral. With successive UCO, variation in length, and hence maximum length, can increase indefinitely. At the upper limit, the longest arrays will impose a cost in terms of constituents and energy for replication, and will be removed by selection. Unequal crossing over pro-

duces variation which selection can act on, and removal of the longest arrays must reduce the mean array length (CHARLESWORTH *et al.* 1986; STEPHAN 1986).

Mechanism iii: If recombination occurs *within* an array (intrachromatid), that is between repeats on the same DNA molecule, the region between the sites of recombination will be deleted as a closed circle (WALSH 1987) and lost. If the circle contained an origin of replication, could replicate extrachromosomally, and if copies of it could reintegrate, it would give a possible amplification mechanism. The overall effect depends on the frequencies of the alternative fates of each excised circle.

Mechanism iv: Repeated unequal sister chromatid exchange will skew the distribution of array lengths if longer arrays tend to have greater absolute misalignment in crossovers than short arrays (OHTA 1981; FLETCHER and RAFFERTY 1993). If the root of the mean square misalignment is a fraction a of the array length, the median and modal length decreases by a^2 in two unequal crossovers. After n unequal crossovers the median (modal) length decreases

$$\text{from } L_0 \text{ to } L_0(1 - a)^{n/2}(1 + a)^{n/2}$$

having had equal numbers ($n/2$) of increases and decreases (FLETCHER and RAFFERTY 1993). Arrays as long as, or longer than, the original become very rare.

There are still many arrays of repeated sequences under no obvious maintaining selection, and WALSH (1987) proposed an equilibrium between their removal by UCO and amplification by another unspecified mechanism. Given the effectiveness of intrachromatid crossovers (mechanism iii) and unbiased sister chromatid exchange (mechanism iv) combined with selection against very long arrays (mechanism ii), above, in removing repeats, it seems that arrays can only survive if there is such a mechanism for amplification, and bias in the crossover/conversion mechanism itself is a good candidate for this mechanism. Both intrachromatid recombination and the skewing effect (iii and iv) are potentially length dependent, causing faster absolute reduction in longer arrays. Loss of length conservation in single-strand nick recombination will depend on the recombination mechanism and physical constraints on the displacement of the DNA strands, and could be largely independent of array length. Similarly in the double-strand break model, loss or gain of repeats appears to depend on physical movement or digestion of the ends of the break, and could be constrained independently of array length, (although in both cases array length might impose the upper limit on non-reciprocity). This leads directly to an equilibrium between length reduction by length dependent mechanisms (ii, iii and iv) and amplification by biased displacement errors (partially or largely length independent) in the crossover mechanism itself. If the non-conservative crossovers were biased toward reduction, or

even neutral, then unselected arrays would quickly shorten. Some powerful, and as yet undetermined, amplification mechanism is needed to maintain unselected arrays subjected to UCO, and amplification during crossing over or conversion could be that mechanism.

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