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Commentary

Induction of DNA rearrangement and transposition

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The study of mammalian transposition has been hampered tremendously by the lack of an experimental system in which transposition can be induced and observed directly. Almost all of the conclusions and models involving mammalian transposition events have been inferred from structural comparisons to transposons studied in the bacterial, yeast, or *Drosophila* genomes or from models based on a few structural characteristics of the elements themselves along with evolutionary analysis of the accumulation of these elements in the mammalian genomes. The creation of an inducible system that allowed transposition of TY1 elements in yeast (1) provided researchers with the basic tool to begin to study the enzymology and regulation of the transposition process (reviewed in ref. 2). Furthermore, the finding of active transposable elements has opened up new opportunities for helping to introduce genetic modifications to genomes as in *Drosophila* (reviewed in ref. 3), as well as to use the laboratory generated transposition events to generate "tagged" mutation sites (reviewed in refs. 3 and 4). Thus, transposition on a laboratory "time scale" not only allows investigations to be carried out to understand the transposition process but also allows investigators to turn those transposons into useful laboratory tools. A number of attempts have been made to devise such a system to study transposition of mammalian transposons, with little success. The best we have are a few naturally occurring transposons that have caused specific genetic diseases (5, 6), but at such low frequencies that they are of no use for direct studies or as molecular genetic tools.

The article by Bucala *et al.* (7) utilizes a fairly standard shuttle vector assay to look at the effect of nonenzymatic treatment of DNA with advanced glycosylation endproducts (AGE) on DNA damage in mammalian cells. AGE have been previously demonstrated to be mutagenic in *Escherichia coli* (8) and have been hypothesized as a factor in age-related cellular degenerations (9). In the shuttle vector assay, the vector DNA is exposed to the AGE followed by transfection into a mouse lymphocyte cell line. The treated DNA is then subject to DNA repair processes in the cell, and the repaired DNAs are rescued and transfected into *E. coli*, where the nature of the mutations can be assayed readily. Such assays have been used in the past with several different reporter plasmids and using various mutagenic treatments (10–12). Treatment of the DNA with AGE in this study led to as much as a 300-fold increase in the mutation rate in the mouse cells. A large proportion of the mutant plasmids generated in the study by Bucala *et al.* (7) corresponded to relatively large insertions, deletions, and rearrangements. Similar results have been seen with other shuttle vector systems and mutagens (10), although other similar systems have found most mutations to be small deletions and point mutations (11). Although the AGE increased all classes of mutation in this assay, the most striking effect was the increase in insertional mutations. Several of the insertions were characterized and found to be derived from mouse cellular DNA. Strikingly, a significant portion of these mutations in all experiments, and a much higher rate in the AGE-treated cells, carried essentially identical inserts, with a sequence termed INS-1 being by far the most commonly found sequence. If this represents transposition events, then it both provides a basic assay for studying the transposition process and also suggests that the mammalian transposition processes may be occurring at a much higher rate than previously had been suspected.

The INS-1 sequence has several interesting and surprising characteristics, some of which are consistent with a transposable element and several of which are difficult to rationalize with such an element. Analysis of four separate INS-1 insertions showed that they each involved different deletions of some of the vector sequence while one of them also had some sequences of unknown origin appended to the 5′ end of the INS-1 sequence. Thus, if this is a transpositional event, it seems likely that the structure is unstable and undergoes recombination involving the flanking sequences either during or after the transposition. The sequence data on the INS-1 insert do not show any direct repeats that would be associated with most transposition events, and there is no evidence of open reading frames that might suggest protein coding capacity of a transposon. Although there is a B1 short interspersed nuclear element (SINE) repeat in the INS-1 element, there is no obvious connection between this B1 repeat and the transposition event, as none of the normal features of a retroposition event that would be associated with a B1 insertion (reviewed in ref. 13) are associated with the INS-1 element. Thus, the B1 element is more likely to be a disrupting sequence in the INS-1 sequence rather than a contributing factor in its transposition.

Thus, the INS-1 insertions either represent a unique type of mamamalian transposing element or have inserted by an alternate mechanism altogether. One might consider the possibility that the lymphocyte cell line used in these experiments is crucial to the results, as contrasted with other studies seeing few if any insertions (11). It may have large amounts of specific circular DNAs derived from the genomic DNA that may be more readily available for recombination with the shuttle vector or express crucial recombination or transposition-specific enzymes. It is well known that DNA transfected into mammalian cells is highly subject to ligations and recombinations. It may be that other episomal DNAs are able to take part in such recombinations with the shuttle vector or simply that transfected DNAs are more subject to transpositional events than normal chromosomal DNA. Different cell lines have been found to have different amounts and classes of sequences involved in such circular DNAs. Other investigators have also shown a high proportion of deletions and insertions using similar shuttle vector systems (10), but to my knowledge none demonstrated large numbers of them involving incorporation of cellular DNAs. Certainly more work will be needed to track down the nature of these inserted sequences. Even more interesting will be a characterization of these sequences in the genomic DNA to determine whether this is an element that has transposed or duplicated in the normal cellular genome or whether it is only available to episomal DNAs. Whatever the nature of the process, the way is now open to dissection of mechanism and regulation.

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