MOBILE ELEMENTS AS A SOURCE OF ENVIRONMENTALLY SENSITIVE GENETIC INSTABILITY

A Distinguished Lecture

By

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Abstract: Mobile elements represent a major intrinsic form of genetic instability in mammalian genomes. There is at least one mobile element insertion in every 20 new human births, resulting in about 0.2% of new genetic diseases. In addition, new reports show high levels of activity in some somatic tissues and tumors, suggesting that their insertion continues to contribute to degenerative processes, such as aging and cancer. We have previously shown that mobile element activity is stimulated by several environmental stimuli, including heavy metals, as well as by light pollution (alterations of the circadian clock). Others have found that ionizing radiation and other DNA damaging agents are similar stimuli. Thus, we have been developing tools to look at mobile element expression using RNASEQ to assess their impact on somatic tissues under different environmental stimuli. After insertion, mobile elements, particularly Alu, continue to contribute to genetic instability as a major source of non-allelic homologous recombination (NAHR). We have created a reporter-gene system that measures the rate of NAHR between two Alu elements that can be inserted in single copy in the genome. This system gives us a unique approach to measuring the influence of Alu element on resolution of environmentally caused double-strand breaks. We have measured the influence of mismatches between two Alu elements and find that even very low levels of mismatch cause Alu-mediated NAHR to go down to very low levels. However, as mismatch levels increase, our system shows higher levels of Alu-mediated deletions, but this seem to be caused by micro-homology directed NHEJ. Our data suggest the homology between the mismatched Alu elements directs recombination events to occur in their vicinity in response to double-strand breaks. This process is dependent on at least some of the mismatch repair response and suggests that the influence of Alu elements contribute a great deal to human genetic instability, but their influence is complex. Using this reporter-gene system, we have also shown that expression of L1 elements triggers Alu/Alu NAHR at a very high frequency, in an L1 endonuclease-dependent and endonuclease target-site-dependent manner. These studies demonstrate that the DSBs caused by L1 are likely to contribute a major source of DNA DSBs that create DNA damage that has not previously been associated with mobile element activity.