L1 ELEMENTS AS A SOURCE OF ENVIRONMENTALLY SENSITIVE GENETIC INSTABILITY

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Abstract: LINE-1 is the only active autonomous human non-LTR retroelement. The expression and activity of these elements contribute to human genomic instability. LINE-1 elements comprise 17% of the human genome, which translates into about $5 \times 10^5$ L1 copies, the majority of which are defective due to truncations at their 5’ end. L1 elements cause extensive genetic instability, through insertional mutagenesis, some recombination, and through double-strand DNA breaks that we show lead to apoptosis, cell checkpoints, as well as a senescence-like state. In addition, L1 drives the amplification of Alu elements that represent another 11% of the human genome with over 1 million copies per genome. These elements also contribute to insertional mutagenesis, as well as a higher proportion of Alu/Alu non-allelic homologous recombination. We have found that portions of the normal DNA repair surveillance, notably the ERCC1/XPF 3’ flap endonuclease that is required in nucleotide excision repair, are capable of blocking the activity of L1 elements. Thus, individuals with lowered capacity for this enzyme activity are likely to be more subject to the extensive DNA damage caused by these elements. A number of environmental exposures, notably heavy metals, ionizing radiation, and various hormonal exposures, have been shown to increase the level of L1 expression and/or activity. We have now demonstrated that this L1 expression not only leads to high levels of L1-induced double-strand breaks, but that these breaks then stimulate Alu/Alu non-allelic homologous recombination. We hypothesize that environmental stimulation of human mobile element activity leads to previously unrecognized levels of cellular and DNA damage that might cause cancer and cellular aging.

Key words: genetic instability; DNA repair; mobile elements; endonuclease; DNA damage

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