L1 ELEMENTS AS A SOURCE OF ENVIRONMENTALLY SENSITIVE GENETIC INSTABILITY

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Abstract: LINE-1 is the only active autonomous non-LTR human 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 5x10^5 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. 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. We note that some key components of the nucleotide excision repair pathway are subject to inhibition by heavy metals, notably XPA. We have previously shown that L1 activity is significantly stimulated by the heavy metals, cadmium and nickel. Thus, a likely mechanism for this environmental stimulation of L1-induced damage might be through their ability to block nucleotide excision repair, or similar DNA surveillance system that might then block the ability of ERCC1/XPF to inhibit L1 insertions. 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.

Keywords: Genetic instability; DNA repair; mobile elements; endonuclease; DNA damage

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