Investigating the chromosomal instability signature of LINE-1 retrotransposition

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Abstract

Long interspersed element-1 (LINE-1) is the only active, protein-coding transposon in humans that can self-propagate via RNA intermediates. LINE-1 overexpression and somatically-acquired LINE-1 copies are commonly detected in human cancers with *TP53* mutations. A recent pan-cancer analysis found associations between somatically-acquired LINE-1 insertions and chromosomal rearrangements, suggesting that LINE-1 retrotransposition activity may represent a major source of chromosomal instability in cancer genomes. To address this hypothesis, we have developed a Tet-On system to induce LINE-1 expression in *TP53* deficient retinal pigment epithelial (RPE-1) cells, which are nearly diploid cells. Using this system, we examined the genotoxicity and mutational consequences of LINE-1 expression in cells. Consistent with previous studies, we find LINE-1 expression robustly activates the DNA damage response, causes chromosomal breaks, results in micronuclei formation, and induces DNA replication stress. To assay the impact of LINE-1 expression on genome integrity, we performed whole genome sequencing (WGS) of single cells or clonal outgrowths to comprehensively assay the genomic alterations generated after induction of LINE-1 expression. We have found that single cells or clonal outgrowths induced with LINE-1 expression contain one or multiple *de novo* DNA copy-number alterations, including copy-number losses and gains, and whole chromosome losses. We have also detected a variety of short and long-range genomic rearrangements with one or multiple breakpoints attributed to LINE-1-encoded ORF2p endonuclease, demonstrating a direct role of LINE-1 in creating large structural rearrangements. Strikingly, we have found that cells exposed to LINE-1 expression also contain complex chromosomal rearrangements such as chromothriptic chromosomes, suggesting that LINE-1 expression can elicit chromothripsis. These studies highlight the scope of LINE-1-mediated genome instability, providing insights into how LINE-1 deregulation in malignancies may broadly contribute to cancer genome evolution via chromosomal instability.

Keywords: LINE, 1, chromosomal instability, DNA damage

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