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Detecting hot-activity of retrotransposons in human tumours using a novel targeted sequencing-based method

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Long interspersed nuclear element 1 (LINE-1, or L1) retrotransposons are widespread repetitive elements in the human genome, representing 17% of the entire human reference genome DNA content. Using a combination of cellular enzymes and self-encoded proteins with endonuclease and reverse transcriptase activity, L1 elements copy and insert themselves at new genomic sites, a process called retrotransposition. Our research group has recently shown (Rodriguez-Martin et al. 2018 Nature Genetics, in press) that aberrant integration of L1-retrotransposons may cause large, Megabase-size deletions, which occasionally remove tumour suppressor genes. Somatic retrotranspositions can also initiate braking-fusion-bridge cycles, leading to high-level amplification of oncogenes. Hence, this mutational process mediated by L1 retrotransposons may have important implications in the development of some human tumours (especially in oesophagus cancer, lung cancer, colorectal cancer (CRC), and head and neck cancer (HNSCC)). Interestingly, from the nearly 500,000 widespread L1 loci in our genome, only a small subset (~124 copies or “source elements”) is responsible for the activity causing such dramatic structural remodelling with oncogenic potential (Tubio et al. 2014 *Science*).

Given the oncogenic roles that these L1 loci may play in some human tumours, a molecular test for the detection of their activity at diagnosis would be very valuable for the identification of the mutations and mutational processes involved in the origin and/or development of a given tumour. For that reason, we developed a novel targeted sequencing-based method for the detection of high-activity rates of individual L1 source elements in cancer samples. The method relies on the identification of L1-mediated transductions, which are the result of an aberrant L1 retrotransposition mechanism (Tubio et al. 2014 *Science*) that mobilizes and integrates non-repetitive, unique, DNA regions originally located immediately downstream to a given L1 source element. Because the detection of L1-transductions would allow the identification of the source element whence they derive, we designed specific probes for target capturing, using the SureSelectXT Target Enrichment System (Agilent), and sequencing of the 5kb region immediately downstream to each one of the 124 L1 source elements with potential activity in cancer. We first tested our approach on different lung cancer cell-lines with known different rates of somatic retrotransposition, validating its ability of detection. Then, using cell lines, frozen, and Formalin-Fixed Paraffin Embedded tumor tissues from HNSCC, CRC and lung cancer patients, the bioinformatic analysis of the results confirmed the usefulness of this tool to identify L1-mediated transductions acquired somatically during tumour development, irrespective of the tumor tissue sample.

Therefore, this promising tool opens new avenues to study the molecular consequences of L1 activation in tumor initiation and development. We believe that its clinical application could change cancer diagnosis and would help oncologists for personalized treatments.

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