GENETICS, BIOINFORMATICS, AND SYSTEMS BIOLOGY COLLOQUIUM

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EXTENSIVE MOSAICISM BY SOMATIC L1 RETROTRANSPOSITION IN NORMAL COLORECTAL EPITHELIUM

Over the course of an individual's lifetime, genomic alterations accumulate in somatic cells. However, the mutational landscape by retrotranspositions of long interspersed nuclear element-1 (L1), a widespread mobile element in the human genome, is poorly understood in normal cells. Here, we explored the whole-genome sequences of 892 single-cell clones established from various tissues collected from 28 individuals. Remarkably, 88% of colorectal epithelial cells acquired somatic L1 retrotranspositions, referred to as soL1Rs, carrying ~3 events per cell on average with substantial intra- and inter-individual variances, which was accelerated at least 10-fold during tumourigenesis. Breakpoints of soL1Rs suggested that a few variant mechanisms can be involved in the L1 retrotransposition processes. Fingerprinting of donor L1s using source-specific unique sequences revealed 34 hot L1s, 44% of which were newly discovered in this study, and many ultra-rare hot L1s in the human population showed higher retrotransposition potential in somatic lineages than common sources. Multi-dimensional analysis of soL1Rs with early embryonic developmental relationships, genome-wide methylation, and gene expression profiles of the clones demonstrated that (1) soL1Rs occur from early embryogenesis at a substantial rate, (2) epigenetic activation of hot L1s is stochastically acquired during the wave of early global epigenomic reprogramming, rather than by the sporadic loss-of-methylation at the late stage, and (3) most L1 transcripts in the cytoplasm do not generate soL1Rs in somatic lineages. In summary, this study provides insights into the retrotransposition dynamics of L1s in the human genome and the resultant somatic mosaicism in normal human cells.