Locus-level L1 DNA methylation profiling reveals the epigenetic and transcriptional interplay between L1s and their integration sites.

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Abstract

LINE-1 (L1) retrotransposons represent an abundant and repetitive fraction of the human genome and are implicated in human disease and evolution. Epigenetic mechanisms, such as DNA methylation, suppress their activity in most somatic tissues, but they are transcribed and eventually mobilized in many cancers. Consistently, loss of bulk L1 DNA methylation is a common cancer biomarker, and demethylating agents used in cancer therapy further increase L1 expression, contributing to the establishment of a viral mimicry state. However, given the repetitive nature and the dispersion of L1 sequences throughout the genome, deciphering the regulation of individual copies has been challenging. Here, we combine short- and long-read sequencing to unveil L1 methylation variation across cell-types, families and individual loci and elucidate key principles involved. We find that the youngest primate L1 families are specifically hypomethylated in pluripotent stem cells and the placenta, but not in most tumors. Locally, intronic L1 methylation is intimately associated with gene transcription. Conversely, the L1 methylation state can propagate to the proximal region up to 300 bp. This phenomenon is accompanied by the binding of specific transcription factors, which drive the expression of L1 and chimeric transcripts. Finally, L1 hypomethylation alone is typically insufficient to trigger L1 expression due to redundant silencing pathways. Together, our results highlight the reciprocal influence of L1 retrotransposons and their integration sites with respect to DNA methylation and expression, and reveal unanticipated layers of cell-type-specific epigenetic regulation. This work was supported by Agence Nationale de la Recherche (ANR-11-LABX-0028; ANR-11-LABX-0071; ANR-15-IDEX-0001; ANR-16-CE12-0020; ANR-18-IDEX-0001; ANR-19-CE12-0032; ANR-21-CE12-0001), Fondation pour la Recherche Médicale (DEQ20180339170), Institut National Du Cancer (INCa PLBIO 2020-095), Fondation ARC (PGA1/RF20180206807), and other grants from the Canceropôle PACA, INCa and the Region Sud (Projet Emergence), INSERM (GOLD Cross-cutting Program on Genomic Variability), and CNRS (GDR 3546).

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