Revealing the uniqueness of repeated sequences

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Transposable elements (TEs) are abundant, dispersed repetitive sequences in the human genome. Although various classes and families are present and transcriptionally active, only the long-interspersed element 1 (LINE-1 or L1) is capable of autonomous mobilization in modern humans. This process allows L1s to act as potent endogenous mutagens in somatic and germline cells, contributing to cancer, aging and genetic diseases. Beyond insertional mutagenesis, TEs can influence nearby gene regulation and expression, and trigger inflammation through viral mimicry. Studying these dispersed sequences at individual loci has been challenging due to their repetitive nature and extreme insertional polymorphism. Consequently, fundamental questions about L1 biology remained unanswered: Does high L1 activity in specific cell types arise from a few deregulated copies, or widespread activation? Are all silenced L1s methylated, and conversely, are all expressed L1s unmethylated? We will discuss strategies developed in our laboratory to overcome these challenges, revealing the remarkable heterogeneity of L1 expression and regulation, even within the same family, and the interplay between L1s and their genomic environment.

Work in the lab of GC is or was supported by Agence Nationale de la Recherche (ANR-11-LABX-0028; ANR-15-IDEX-0001; ANR-16-CE12-0020; ANR-19-CE12-0032; ANR-21-CE12-0001), Fondation pour la Recherche Médicale (DEQ20180339170), Institut National du Cancer (INCa PLBIO 2020-095), Canceropôle PACA, INSERM (GOLD Cross-cutting Program on Genomic Variability), and CNRS (GDR 3546).