HERVH protects the human genome from transposition of young retroelements in the early embryo

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Abstract

The ancestor of human endogenous retrovirus H (HERVH) was among the plethora of retroviruses, invaded primate genomes. HERVH integrated into the primate germline after the divergence of New- and Old-World monkeys (_˜40 MYA). As a result of successful endogenization and transposition, HERVH is represented by about 1,200 genomic copies in the human genome. Although HERVH no longer transposes, several HERVH-containing genomic loci are transcribed in the early human embryo. Indeed, HERVH is an example of co-option by the host. HERVH-derived transcripts form a transcriptional regulatory network that supports pluripotency in humans. HERVH-supported functions (e.g. pluripotency) add primate-specific features to evolutionarily conserved biological. In our recent study, we observed increased retrotransposition of LINE-1 and the occurrence of *de novo* integration of non-autonomous Alu and SVA elements in HERVH-depleted hESCs, suggesting that HERVH is involved in the protection of genome stability. We have shown that a copy inserted upstream of APOBEC3G inhibits retrotransposition of evolutionarily young (< 7MY) retrotransposable elements (REs). Interestingly, HERVH appears to protect genome stability in more than one way. Here, we report a subcluster of HERVH copies (_˜300; HERVH-lin) that has an expression profile opposite to that of young REs and exhibits a tandemly repeated binding motif for the LIN28A protein. LIN28A is an RNA-binding protein, and inhibits the maturation of the miRNA Let-7. The "binary dance" of LIN28A and Let-7 is an evolutionarily conserved regulatory pathway that and establishes a delicate balance between pluripotency and differentiation. Let-7 targets multiple mRNAs, including those encoding pluripotency factors, but also inhibits retrotransposition of LINE-1. Thus, HERVH-lin promotes Let-7-based suppression of LINE-1 retrotransposition (and other non-autonomous retroelements such as Alus and SVAs). Our data suggest that HERVH-lin recruits an evolutionarily conserved regulatory pathway via sponging on LIN28A and integrates Let-7 into the genome protection programme of human pluripotent stem cells.

Keywords: endogenous retrovirus HERVH genome stability LINE, 1 LIN28A Let, 7

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