Repression of HERV-K negatively impacts astrocyte development

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Abstract

One of the major challenges towards deciphering the blueprint of life is to understand how functional elements of the genome influence key biological processes. However, the functions of large parts of the human genome including human endogenous retroviral (HERV) elements remain elusive. We could recently show that activation of one specific HERV family, namely HERV-K(HML-2), negatively impacts cortical neuronal development. However, thorough analyses of a larger number of HERV groups are missing to understand their functional contribution to the development of diverse brain cell types beside neurons.

Transcriptomics analysis of post-mortem patient samples demonstrated that HERV groups are differentially expressed between astrocytes and neurons. In particular, we uncovered a substantial upregulation of several HERV-K elements in astrocytes compared to neurons. To unravel the functional contribution of HERV-K to astrocyte development, we applied CRISPR-interference targeting multiple LTRs of the HERV-K group in neuronal progenitor cells. Excitingly, inhibition of HERV-K resulted in a significant decrease in the astrocytic markers GFAP and AQP4 upon differentiation into astrocytes. In contrast, transcriptional repression of HERV-K LTRs had had no effect on neuronal differentiation. HERV-K transcriptional repression also influenced the expression of several cellular genes involved in astrocytic development. In particular, we revealed a C2H2-type ZNF as a promising downstream target, and transcriptional downregulation of the C2H2-type ZNF also resulted in impaired astrocyte development providing mechanistic insight into the identified HERV-K-astrocyte differentiation axis.

In conclusion, our study unveils a previously unknown function of HERV-K in astrocyte development, with implications for brain-specific cellular differentiation. These findings contribute to a deeper understanding of the intricate regulatory mechanisms governing astrocyte differentiation and neurodevelopmental processes.

Keywords: Astrocyte development, HERV, CRISPR interference

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