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Epigenetic regulation of retroviruses in embryogenesis, oncogenesis and neurodegeneration

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Background: Nearly 50% of the human genome is composed of retroviral elements which are remnants of prior retroviral infections that occurred over millions of years. Of these, about 8% are nearly intact retroviruses.
Rationale: The most recently incorporated retrovirus is the human endogenous retrovirus-K (HERV-K). There are multiple copies throughout the genome, many with intact open reading frames. Retroviral elements are highly activated in embryogenesis however the role of HERV-K in early stages of development is unknown.
Hypothesis: HERV-K plays a critical role in human embryogenesis and is tightly controlled. Dysregulation of these genes lead to tumorigenesis or degeneration of terminally differentiated cells.
Results: The envelope protein of HERV-K located in chromosomes 12 and 19 was expressed on the surface of pluripotent stem cells. The protein signals via interactions with CD98HC which interacts with beta-1 integrin. This activates m-TOR pathway that is linked to lysophosphatidylcholine acyltransferase which regulates epigenetic changes in the chromosome. These interactions are critical for stemness and cell adhesion. Silencing of HERV-K leads to cell dissociation and differentiation along neuronal pathways. Persistent activation of HERV-K was found in embryonic brain tumors. Induction of the *env* in terminally differentiated neurons caused cell death and in transgenic animals it caused loss of motor neurons. Serum and autopsy brain tissue from patients with ALS showed activation of the *env*.
Discussion: Endogenous retroviral elements play a critical role in embryogenesis. Once organogenesis has occurred, these genes are epigenetically silenced. Reactivation causes degeneration of terminally differentiated neurons and oncogenesis in progenitor cells.