SnapShot: Human endogenous retroviruses

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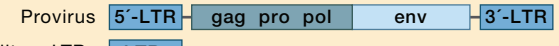
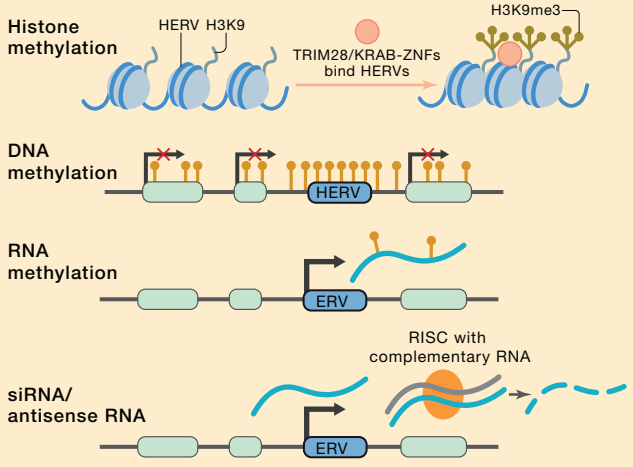
BASIC PRINCIPLES

HERV elements



	HERV-groups	LTR (RepBase name)	Solitary LTRs/proviruses (estimated in the human genome)
Class I γ-retroviruses	HERV-H	LTR7	1000/1000
	ERV9	LTR12,PTR5	5000/300
	HERV-W	LTR17	1100/40
	HERV-I	LTR10	1000/250
	HERV-E	LTR2,2B,2C	1000/250
	HERV-F	LTR19	550/45
	S71	LTR6A,B	400/80
Class II β-retroviruses	HERV-K(HML-2)	LTR5Hs,LTR5A,LTR5B	944/91
	HERV-K(C4)	LTR14	100/10
	HERVK14C	LTR14C	120/15
	HML-1	LTR14A,14B	350/70
	HML-3	MER9	700/150
	HML-4	LTR13	800/10
	HML-6	LTR3,3B	400/50
Class III spumaviruses	HERV-L	MLT2A1,2A2,MLT2B1,2B2	6000/200
	HERV-16	LTR16A,16A1,16C,16D	25/15
	HERV-S	LTR18,18B	150/50
	HERV74	MER74,74A,74B,74C	200/25
	HERV40	LTR40,40B,40C	300/10
	HERV57	LTR57	200/30

HERV regulation control mechanisms



Reactivation

Infections
- Herpesviridae (e.g. HSV, EBV)
- Influenza
- HTLV-1
- HIV-1
- Prions

Radiation
- UV
- γ-radiation

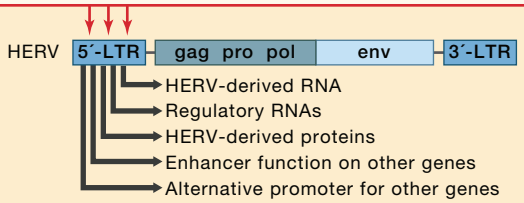
Mitogens
- Phytohemagglutinin
- Concanavalin A
- Phorbol ester

Cytokines
- IL-1 (α,β)
- TNF-α
- IFN-α

Aging
- Senescence
- Inflammation

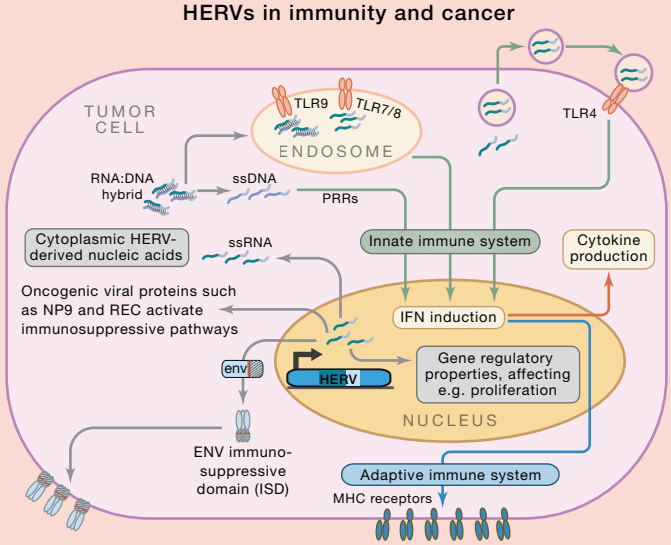
Epigenetic drugs
- 5-azacytidin
- Valproic acid
- HDACi

Steroid hormones
- Estrogen
- Progesterone
- Dexamethason

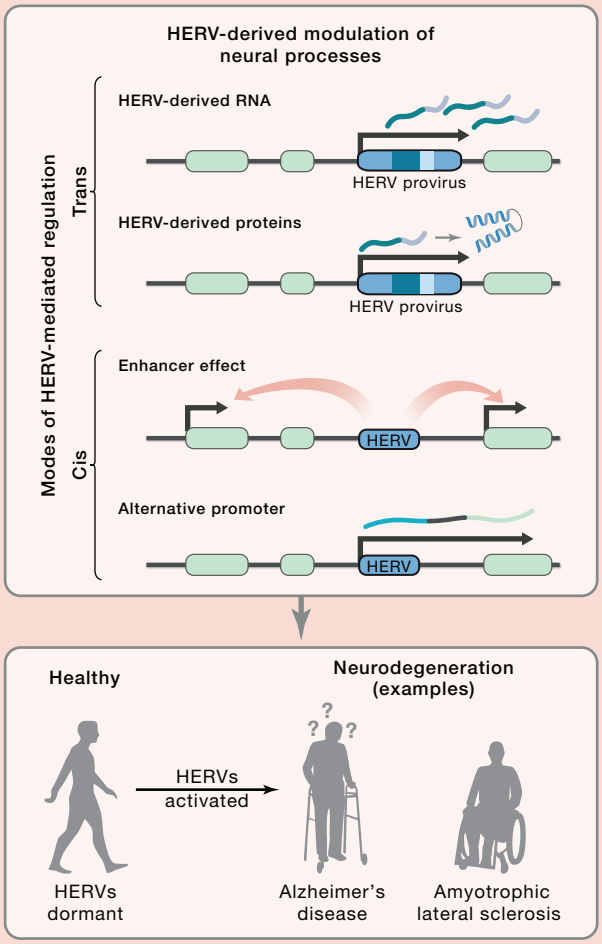


FUNCTIONAL IMPACT ON DISEASE OUTCOME

HERVs in immunity and cancer



HERVs in neurological disorders



Abbreviations: **HERV**, human endogenous retrovirus; **TLR**, toll-like receptor; **PRRs**, pattern recognition receptor; **MHC**, major histocompatibility complex; **IFN**, interferon; **RISC**, RNA-induced silencing complex; **TNF**, tumor necrosis factor; **HDACi**, histone deacetylase inhibitor.

  DOI https://doi.org/10.1016/j.cell.2021.12.028

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One of the most surprising findings of the human genome project was that at least 50% of the human genome consists of transposon-derived sequences, including a sizable fraction of human endogenous retroviruses (HERVs). For decades, HERVs were considered genomic parasites, but recent studies provide compelling evidence that HERVs critically influence biological processes and implicate HERV dysregulation in human disease.

Basic principles

HERV elements

HERVs are relics of infectious retroviruses in our ancestors, whose proviruses have invaded the germline and expanded via retrotransposition and reinfection (Mager and Medstrand, 2003). Approximately 8% of the human genome consists of HERVs (over 500,000 individual elements) (Mager and Medstrand, 2003). A HERV provirus is composed of the proviral genes *gag*, *pro*, *pol* and *env* flanked by two long terminal repeats (LTRs), which provide regulatory functions including promoter, enhancer, or primer binding sites. Recombination has led to most elements existing as solitary LTRs, but around 4,000 full-length HERVs remain intact in our genome. HERVs have three major classes defined by sequence similarities in their polymerase (*pol*)-gene. Class I HERVs show sequence similarities to γ-retroviruses, class II HERVs to β-retroviruses, and the class III HERVs to human spumaviruses (Mager and Medstrand, 2003). HERV classes are subdivided into several groups according to the sequence similarity of their primer binding site (pbs), with the corresponding complementary sequence of tRNAs (e.g., HERV-W has a pbs matching the 3′ end of the tRNA for W, tryptophan). Each HERV group not only differs in sequence homology but also varies in the number of sequences distributed at distinct loci in the human genome (Mager and Medstrand, 2003; Subramanian et al., 2011).

HERV regulation

Control mechanisms. HERVs may be silenced by mutations and are subject to layers of epigenetic control, resulting in low transcriptional activity in most cell types. In adult human tissues, HERVs are covered by DNA methylation, which is associated with transcriptional silencing. Repressive heterochromatin at HERVs is established by KRAB-containing zinc finger proteins, which bind to specific sequences within HERVs. This leads to recruitment of the docking platform TRIM28 (aka KAP1), which attracts heterochromatin proteins and epigenetic modifiers such as the histone methyltransferase SETDB1 (Jönsson et al., 2020). RNA-mediated targeting is also involved in silencing mammalian ERVs (Jönsson et al., 2020). Although several such mechanisms have only been described in mice or different human transposon classes, they likely provide a further layer of control for HERVs. m6A RNA methylation represses ERVs in mouse embryonic stem cells (Chelmicki et al., 2021). ERV families may also be silenced by a Dicer-dependent small interfering RNA (siRNA)-based pathway or by antisense transcripts. Finally, the PIWI-interacting RNA (piRNA) pathway can also be responsible for ERV regulation.

Reactivation. Environmental stimuli can modify epigenetic mechanisms and thus reactivate HERV expression. There is emerging literature suggesting that HERVs can be reactivated by multiple environmental factors such as infectious agents, exogenous viruses, radiation, aging-associated processes, epigenetic drugs, cytokines, or mitogens (Küry et al., 2018). Reactivation of HERVs results in the production of viral transcripts and viral proteins and can impact host gene expression as HERV LTRs can serve as alternative promoters or enhancers. These events can impact important biological functions of the host or contribute to the development of certain diseases.

Functional impact on disease outcome

HERVs in immunity and cancer

Aberrant transcriptional activation of HERVs has been linked to cancer. HERVs are an integral part of transcriptional networks, so their dysregulation can have broad consequences. Here, HERV LTRs can serve as alternative promoters, a phenomenon that can drive oncogene expression (Jönsson et al., 2020). Importantly, expression of HERVs may activate innate immune responses via induction of viral defense pathways through the cell's misinterpretation of HERV elements (DNA, RNA, or peptides) as an exogenous viral infection (Jönsson et al., 2020). HERV-based viral mimicry has recently been exploited for the development of new cancer therapies. Epigenetic therapies, such as DNA methyltransferase inhibitors, can activate HERV expression and thereby provoke an anti-tumor immune response. However, other transposons such as *Alus* and LINE-1 elements may also be involved, and further work is required to resolve the relationships between transposons and their immunogenic potential.

HERVs in neurological disorders

Our genetic information is organized in regulatory networks involving *cis*-regulatory sequences and *trans*-acting genes. Their interplay is the basis for cellular plasticity and evolution. HERV sequences comprise many regulatory elements and can regulate host gene activity at different expression levels via multiple mechanisms. Several recent studies indicate that the tight regulation of endogenous retroviruses is essential for a healthy brain and that dysregulation may be associated with neurodegenerative diseases. RNAs, peptides, and proteins derived from full-length HERV-K and HERV-W elements have been described to cause neurotoxicity (Küry et al., 2018) and induce an inflammatory response (Jönsson et al., 2020, 2021; Küry et al., 2018). This leads to neuronal injury and has been linked to disorders like Alzheimer's disease (Dembny et al., 2020), amyotrophic lateral sclerosis (ALS), (Li et al., 2015) or psychosis (Johansson et al., 2020). Beside inducing an inflammatory response via HERV-derived proteins or RNAs, the activation of HERV-K impacts cortical neuronal development by influencing the expression of neighboring genes, such as the developmental factor NTRK3 (Padmanabhan Nair et al., 2021). This influence on gene expression may occur at a considerable genomic distance via HERVs acting as enhancers. Notably, this mechanism does not necessarily require transcriptional activation of the actual HERV, but when HERVs get reactivated they can act as alternative promoters for neighboring genes.

In summary, future research on HERVs will likely yield many new insights into exact mechanisms and consequences of HERV regulations that contribute to human development and disease pathogenesis.

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  DOI https://doi.org/10.1016/j.cell.2021.12.028