



# Human endogenous retroviruses in development and disease

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## ABSTRACT

Human endogenous retroviruses (HERVs) represent ~8% of human genome, deriving from exogenous retroviral infections of germ line cells occurred millions of years ago and being inherited by the offspring in a Mendelian fashion. Most of HERVs are nonprotein-coding because of the accumulation of mutations, insertions, deletions, and/or truncations. It has been long thought that HERVs were “junk DNA”. However, it is now known that HERVs are involved in various biological processes through encoding proteins, acting as promoters/enhancers, or lncRNAs to affect human health and disease. In this review, we summarized recent findings about HERVs, with implications in embryonic development, pluripotency, cancer, aging, and neurodegenerative diseases.

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## 1. Introduction

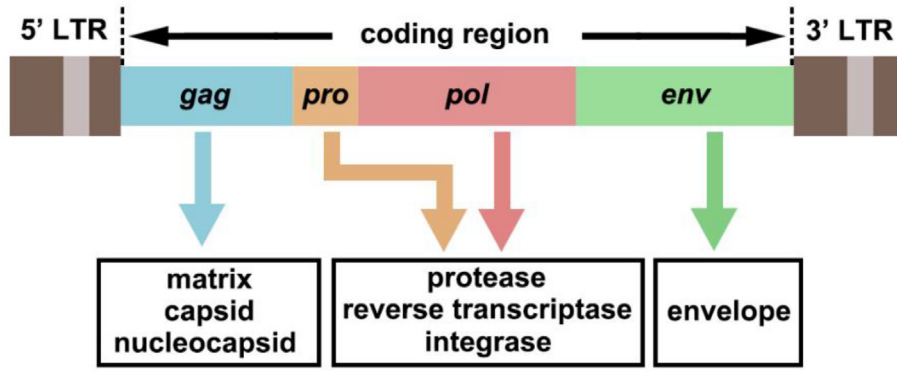
Reverse-transcribing viruses, which synthesize a copy of genomic DNA from an RNA template, are widespread in animals, plants, algae, and fungi. Among reverse-transcribing viruses, betapoviruses, metaviruses, pseudoviruses [better known as Bel/Pao, Ty3/Gypsy, and Ty1/Copia long terminal repeat (LTR) retrotransposons, respectively], and retroviruses typically encapsidate single-stranded RNA (ssRNA) genomes and frequently integrate into the host genomes as part of their replication cycles (Baltimore class VI) [1]. In fact, endogenous retroviruses (ERVs) and LTR retro-

transposons represent a considerable part of their host genomes [2]. Human ERVs (HERVs), which integrated into the human genome via exogenous retroviral infections of germ line cells over millions of years ago [3], account for ~8% of the human genome [4]. The complete genomic structure of HERVs is composed of *gag*, *pro*, *pol*, and *env*, flanked by two LTRs (Fig. 1). Among them, *gag* encodes capsid, nucleocapsid, and matrix protein, *pro* encodes protease, *pol* encodes reverse transcriptase and integrase, and *env* encodes envelope protein [5]. LTR is non-coding region that comprises many regulatory functions [promoter, enhancer, primer-binding site (PBS) for reverse transcription, polyA signal, and others]. However, most of HERVs are nonprotein-coding because of the accumulation of mutations, insertions, deletions, and/or truncations [6,7].

HERVs are divided into three main classes based on sequence similarity with the exogenous members: class I

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**Fig. 1.** The genomic structure of HERVs. The general structure of a full-length HERV provirus is represented: the two long terminal repeats (LTRs) flank the *gag*, *pro*, *pol*, and *env* genes that encoded matrix, capsid, nucleocapsid; proteinase, reverse transcriptase, integrase; and envelop, respectively. Although full-length HERVs exist, HERVs DNA sequences are often truncated, and contain mutations, insertions, or deletions.

(Gammaretrovirus- and Epsilonretrovirus-like), class II (Betaretrovirus-like) and class III (Spumaretrovirus-like) while no Alpha-, Deltaretrovirus- or Lentivirus-like elements were detectable in human genome [7]. In other species, endogenous Alpharetrovirus, avian leukosis virus (ALV) in the domestic fowl (*Gallus gallus*), is one of the first discovered ERVs [8]. An endogenous Deltaretrovirus, MINERVA, was identified in the germline of long-fingered bats (*Miniopteridae*) [9] and the first endogenous lentivirus, RELIK, was discovered and characterized in the European rabbit (*Oryctolagus cuniculus*) [10]. Notably, Chong *et al.* revealed a new class of ERV, ERV4, which appears to be common to crocodylians and turtles, is phylogenetically distinct from the other ERV classes and currently has no characterized exogenous counterpart [11]. Recently, Vargiu *et al.* classified the HERVs by analyzing the phylogenetic relationships among all the well-conserved HERV sequences in human genome and provided a comprehensive HERV classification and characterization approach, which should be applicable for classification of all ERVs [7]. Based on the tRNA binding to the viral PBS to prime reverse transcription, HERVs are further classified into several groups. For instance, HERV-K implies a group of proviruses that utilize a lysine (K) tRNA, no matter their relationship to one another [12]. In some cases, the PBS sequence was not available when novel elements were first discovered, leading to the names based on neighboring genes (e.g. HERV-ADP), clone number (e.g. HERV-S71), or amino acid motifs (e.g. HERV-FRD) [13]. Over the span of millions of years, the genomes of vertebrates have accumulated thousands, even hundreds of thousands of ERV loci [3]. Thus, a unified system for naming ERV loci is needed to assist genome annotation and facilitate the research on ERVs. Recently, a nomenclature both providing unique identifiers for individual loci and denoting orthologous relationships between ERVs in different species has been proposed [13]. In this nomenclature, an ERV loci is assigned standard, unique IDs composed of three elements, each separated by a hyphen, in a “Category – Taxonomic group. Numeric ID – Species ID” format [13]. For example, ERV-K(HML2).4352-Hsa refers to human copy HERV-K (HML2) at chromosome 4q35.2. Currently, several databases containing all the transposable elements (TEs, HERVs included) coordinates in human genome, including RepBase [14], RepeatMasker [15], and Dfam [16], have been established. Software tools have also been developed specifically to assist in the identification and characterization of ERVs, such as RetroTector [17,18]. Benefit from the new resources in genetics, several works collected and analyzed the coordinates of specific HERV families, including HERV-K (HML-2) [19], HERV-K (HML-6) [20], HERV-K (HML-7) [21], HERV-K (HML-10) [22], and HERV-W [23]. Furthermore, a recent study provided a reference of global population

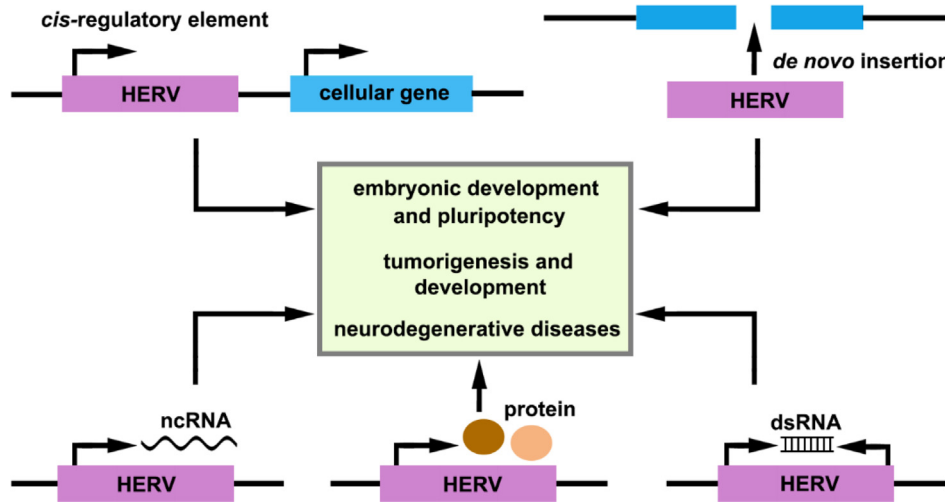
diversity in HERV-K proviruses at all currently known polymorphic loci in the human genome and revealed notable differences in the prevalence of HERV-Ks in different global populations and in the total number of HERV-Ks currently known to be polymorphic within a person’s genome [24].

HERVs have been considered as “junk DNA sequences” for a long time. Accumulating evidence now reveals that HERVs play a role in normal physiologic processes and have been implicated in several diseases (Fig. 2). In this review, we will discuss the physiological and pathological functions of these long-misunderstood elements.

## 2. HERVs in embryonic development and pluripotency

The envelope proteins encoded by *env* are involved in the morphogenesis of placenta in mammals, which is one of the best characterized biological functions [25]. Syncytin-1 and syncytin-2, which are envelope proteins encoded by HERV-W and HERV-FRD respectively, are specifically expressed in the placenta and with cell–cell fusogenic activities, contributing to the formation of the placenta syncytiotrophoblast layer at the materno-fetal interface [26,27]. Likewise, the envelope proteins syncytin-A and syncytin-B with similar expression specificity and function are found in mouse [28]. Therefore, capture of retroviral envelope genes may have played a role in the emergence of placental mammals.

ERVs and other types of TEs have been revealed as regulatory sequences for many host genes in a wide range of cell types throughout mammalian evolution by their *cis*-regulatory element activities [29]. As LTRs harbor the regulatory regions required for proviral transcription, generally including various transcription factor binding sites (TFBSs), they are able to recruit cellular transcription factors and enhance the transcription of their neighboring genes in specific cell types [30]. TEs contribute ~20% of TFBSs across the genome [31]. Among them, LTR elements tend to contribute more than other TE types, probably because LTRs are more likely to possess and to retain their ancestral *cis*-regulatory activities [32]. The *cis*-regulatory element activities of ERVs during embryonic development have been deeply studied in mouse cleavage and 2-cell stage. Briefly, after fertilization, the 1-cell zygote undergoes a series of cleavage cell divisions, during which the embryo increases cell numbers while maintaining overall size [33]. The initial phases of cleavage rely on maternally inherited mRNAs and proteins, but cannot be accomplished without transcription from the embryonic genome. Thus a process known as zygotic genome activation (ZGA) occurs [33]. Mouse ZGA is prominent at 2-cell stage [34] and activation of MuERVs (e.g., murine endogenous retrovirus with leucine tRNA primer [MuERV-L]) [35]



**Fig. 2.** Mechanistic actions of HERVs in human development and diseases. HERVs are involved in physiological and pathological processes through several mechanisms: HERVs may act as promoters or enhance cellular gene expression through LTR *cis*-regulatory elements; insertion of HERV sequences can induce chromosomal rearrangements and genome instability; HERVs can encode ncRNAs, proteins, and dsRNAs.

and stage-specific genes (e.g., *Zscan4*, *Tcstv1/3*) [36,37] are unique features of ZGA [34]. In fact, MuERV-L are transiently activated and produce ~ 3% of the transcribed messenger RNAs at the 2-cell stage [35]. The pattern of MuERV-L expression overlaps with hundreds of 2-cell-specific genes, which have co-opted regulatory elements from these retroviruses to initiate transcription, indicating that MuERV-L serve as functional promoters in the activation of their transcription [35]. For example, MT2, an LTR derived from MuERV-L family, acts as promoters for over five hundred 2-cell-specific gene transcripts [30]. Although activated MuERVs and other non-LTR TEs have been found at mouse 2-cell stage, their regulatory mechanism and biological function remain largely unknown.

In human, HERVs are systematically transcribed during human early embryogenesis in a stage-specific manner, and HERVs expression is a hallmark of cellular identity and cell potency that characterizes the cell populations in early human embryos [38]. Specifically, HERV-K (HML-2) has been reported to be transcribed during normal human embryogenesis, beginning with embryonic genome activation at the eight-cell stage, and continuing through the emergence of epiblast cells in preimplantation blastocysts [39]. Such proviral RNAs lead to the production of viral-like particles and Gag proteins in human blastocysts, indicating that early human development proceeds in the presence of retroviral products [39]. Interestingly, the envelope protein of HERV-K (HML-2) from loci in chromosomes 12 and 19 is highly expressed on the cell membrane of human pluripotent stem cells (hPSCs), and critical in maintaining the stemness via mammalian target of rapamycin (mTOR) pathway [40]. Down-regulation or epigenetic silencing of HML-2 Env resulted in dissociation of the stem cell colonies and enhanced differentiation along neuronal pathways, suggesting that HML-2 regulation is critical for human embryonic development and neural differentiation [40]. HERV-H, which is a primate-specific ERV and accounts for 2% of all poly-A RNAs in human embryonic stem cells (hESCs), is essential for maintenance of pluripotency in human stem cells [41]. Based on evidence observed so far, HERV-H has several roles, including as functional long non-coding RNAs (lncRNAs), enhancers or alternative promoters, and markers of topologically associating domain (TAD) boundaries [41]. Considering the length and transcriptional activity, HERV-H themselves can be considered as lncRNAs [41], and depletion of HERV-H RNA in hESCs by short hairpin RNA (shRNA) leads to loss

of self-renewal, downregulation of hallmark pluripotency transcription factors OCT4, SOX2, and NANOG, and upregulation of differentiation markers [42,43]. Although a general knockdown of HERV-H is sufficient to impair pluripotency, individual HERVH-derived lncRNAs with unique chimeric sequences also play specific roles in hPSCs, such as *ESRG* [42], *linc-ROR* [44], *LINC00458* [45], and *HPAT* [46]. However, a recent study showed that *ESRG* is dispensable for pluripotency maintenance by a complete excision of the entire *ESRG* region [47]. The disagreement between these studies could be attributed to the different methods, Wang *et al.* using an RNAi knockdown [42] while Takahashi *et al.* using CRISPR/Cas9 knockout [47]. In addition, HERV-H LTRs contain binding sites for the LTR-binding protein 9 (LBP9) [42], OCT4 [43], and NANOG [48] to recruit these pluripotency factors. Moreover, HERV-H is involved in establishing TAD boundaries in hPSCs [49]. TADs represent a physical compartmentalization of the genome, and two regions within a TAD associate on average more frequently with each other than with regions outside of the TAD [50]. HERV-H sequences affect gene regulatory programs by creating new hPSC-specific TAD boundaries that shape the chromatin architecture, providing a new insight into how these elements may impact gene regulatory networks [49]. Recently, an eutherian-specific multicopy retrogene, human *DUX4* and its mouse ortholog, *Dux*, were identified to share central roles in driving cleavage-specific gene expression (including *ZSCAN4*, *KDM4E* and *PRAMEF*-family genes), ERVL-family retrotransposon transcription, and chromatin remodeling, suggesting that *DUX4* resides at the top of a transcriptional hierarchy initiated at embryonic genome activation (EGA) and is implicated in developmental events during mammalian embryogenesis [51].

### 3. HERVs in cancer

The transcriptional activation of HERVs is a common feature in human cancers, involving HERVs as causative elements or cofactors contributing to the onset and progression of human cancer [52]. So far, several studies have demonstrated the presence of HERVs transcripts, proteins, and viral-like particles in various human cancers (Table 1).

Given to the potential transposable ability of retrotransposon, it is believed that the tumorigenicity of HERVs could depend on retroviruses movement and consequently disrupting the stability

**Table 1**  
HERVs expression in tumors.

Tumor type	HERVs Detected	HERVs-Products/Oncogenic Mechanisms
Breast	HERV-K (HML-2)	Env induces EMT and activates the ERK pathway [61] Env [81,111] Env splice variants [112] Reverse Transcriptase [113]
	HERV-H	Env [111] LTR7, etc. contribute to lncRNA linc-ROR [75]
	HERV-R	Env [111]
	HERV-P	Env [111]
	ERVW-1/syncytin-1 ERVMER34-1/HEMO	Syncytin-1-mediated cancer-endothelial cell fusions [60] Env [114]
Cervical	HERV-H	LTR as alternative promoter for <i>GSDML</i> [115,116]
Colon	HERV-H	Non-coding spliced transcripts [117] More active HERV-H loci [117] HERV-H is associated with the microsatellite and nodal status [118]
Head and Neck Hepatocellular	HERV-H	Transcripts [83]
	HERV-K (HML-2)	Transcripts [119]
	HERV-H	LTR7, etc. contribute to lncRNA linc-ROR [77]
Kidney	ERV-9	LTR12C contributes to lncRNA PRLH1 [120]
	HERV-E	Env [84]
	HERV-H	<i>HHLA2</i> in tumor immune suppression [121]
Leukemia	HERV-K (HML-2)	Np9 as a critical molecular switch of multiple signaling pathways [70]
Lung	HERV-R	Env [122,123]
	HERV-P	Env [123]
	HERV-H	Env [123]
	HERV-K (HML-2)	Env [123]
	HERV-K (HML-2)	Novel insertion polymorphisms [124] Env [125] Gag [126] Transcripts [127]
Lymphoma	HERV-K (HML-2)	Transcripts [127]
	HERV-W	Transcripts [127]
	MaLR	LTR as alternative promoter for <i>CSF1R</i> [54]
Melanoma	HERV-K (HML-2)	Env-mediated intercellular fusion [58] Rec [128] Virus-like particles [129] anti-HERV-K antibodies in patient [129] Maintaining CD133+ melanoma cells with stemness features [130]
	ERV3	Env [131]
	HERV-K (HML-2)	Env [131] Gag [132] Hypomethylation [133]
	HERV-W	Transcripts [134]
	HERV-E	Env [131]
Pancreatic	ERVMER34-1/HEMO	Env [114]
	HERV-K (HML-2)	Env [62] Reverse transcriptase [62] Virus-like particles [62] anti-HERV-K antibodies in patient [62]
	HERV-H	LTR7, etc. contribute to lncRNA linc-ROR [76]
	HERV-K (HML-2)	Env [82] Gag [82] Transcripts [135]
Sarcoma	HERV-E	Env [136]
	ERV3	Env [136]
	HERV-K (HML-2)	Transcripts [137]
Seminoma	HERV-F	Transcripts [137]
	ERVW-1/syncytin-1	Env [138]
Teratocarcinoma	HERV-K (HML-2)	HERV-K-specific T cells in patients [139]
	HERV-K (HML-2)	Virus-like particles [140] Np9 [141]
Urothelial	HERV-K (HML-2)	Hypomethylation [142]
	HERV-H	LTR7Y and HERV-H contribute to lncRNA <i>UCA1</i> [72] <i>HHLA2</i> in tumor immune suppression [143]
	HERV-E	Modulating <i>PLA2G4A</i> transcription [144]
	ERVW-1/Syncytin-1	Env [145]

of the host genome [52]. Actually, new insertions of TEs, especially HERVs, have been described in several tumors [53]. LTRs can act as alternative promoter or enhancer, leading to the deregulation of proto-oncogenes or tumor suppressor genes. In Hodgkin's lymphoma, *CSF1R* transcription does not originate from its own promoter, but instead initiates at an LTR element of the MaLR

THE1B family, located ~ 6.2 kb upstream of the normal promoter [54]. An HERV type C inserted in Pleiotrophin (PTN) between its 5' untranslated and coding regions generates an additional promoter with trophoblast-specific activity, resulting in fusion transcripts between HERV and PTN (HERV-PTN) specifically expressed in human trophoblast cell cultures and trophoblast-

derived choriocarcinoma cell lines, suggesting that the tissue-specific expression of PTN due to the HERV insertion supports the highly aggressive growth of human choriocarcinoma and possibly of the human trophoblast [55]. However, it should be noted that the LTRs activity can have an anti-oncogenic effect by driving the expression of tumor suppressor genes. For example, *TP63* and *TNFRSF10B*, encoding the p63 homologue of the tumour suppressor p53 and death receptor 5 (DR5), respectively, are regulated by upstream LTRs belonging to the ERV9 group of HERVs [56,57].

HERVs can exert a direct action through their own proteins in cancer. The envelop proteins of HERVs contribute to tumorigenesis and development by inducing cell–cell fusion or epithelial to mesenchymal transition (EMT) in melanoma [58], endometrial carcinoma [59], and breast cancer [60,61]. In pancreatic cancer, HERV-K (HML-2) Env protein was reported to play an integral role in pancreatic cancer proliferation, tumorigenesis, and metastasis formation by both regulating KRAS through hyperactivation of the RAS/MEK/ERK pathway and upregulating p70S6 Kinase/JNK/C-Jun signalling [62]. Another mechanism of Env in tumor progression is involved in the promotion of the immune escape, as the immunosuppressive domain (ISD) of Env can abolish the anti-oncogenic cytolytic immune response [63]. For example, tumor cells expressing Env protein of HERV-H are able to escape the immune rejection and to proliferate when injected into immunocompetent mice [64], and the knockdown of HERV-H Env in tumor cells improves immune responses *in vitro* and *in vivo* accompanied by tumor regression [65], suggesting that HERV-H is a critical determinant of immune escape in cancer. In addition, HERV proteins Rec and Np9 encoded by HERV-K (HML-2) may act oncogenically by derepressing *c-MYC* through the inhibition of promyelocytic leukemia zinc finger protein (PLZF) [66], and Rec alone is able to overcome the direct transcriptional repression by testicular zinc-finger protein (TZFP) of the *c-MYC* gene promoter [67]. In addition, Rec can form a trimeric complex with TZFP and androgen receptor (AR) [67], or bind to the human small glutamine-rich tetratricopeptide repeat protein (hSGT) [68], relieving the repression of AR activity. Np9 is also a tumor-specific biomarker, it can interact with ligand of Numb protein X (LNx, a RING-type E3 ubiquitin ligase), affecting tumorigenesis through the LNx/Numb/Notch pathway [69], and act as a critical molecular switch for co-activating  $\beta$ -catenin, ERK, Akt and Notch1, promoting the growth of human leukemia stem/progenitor cells [70].

Long noncoding RNAs (lncRNAs) have critical roles in various biological processes, such as cancer progression. Strikingly, 75–83% of lncRNAs contain TE sequences, especially ERVs [71]. Several HERVs-derived lncRNAs have been described. *UCA1*, a lncRNA consists of LTR7Y and HERV-H, promotes proliferation, motility, and invasion of bladder cancer [72]. The HERVs-derived lncRNAs *SAMMSON* and *BANCR* are involved in melanoma progression [73,74]. Additionally, linc-ROR derived from LTR7, HERVH-int, etc., has been reported to contribute to the progression, metastasis or chemoresistance in breast cancer [75], pancreatic cancer [76] and hepatocellular carcinoma [77].

It has been reported that the expression of HERVs is associated with the modulation of innate immune response in different physiological and pathological conditions [52]. In the context of tumorigenesis and development, HERVs may have opposite effects on modulating immune response. They may be involved in both anti-tumor defense and oncogenic process. On the one hand, DNA methyltransferase inhibitors (DNMTis) upregulate HERVs in tumor cells to induce a growth-inhibiting immune response. High expression of the genes associated with the anti-viral response seems to potentiate a response to immune checkpoint therapy [78,79]. On the other hand, the double-stranded RNA (dsRNA) transcribed from HERVs can induce immune-suppressed

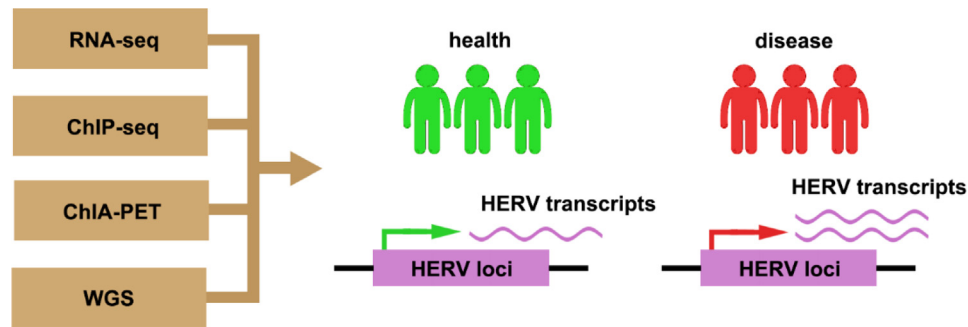
microenvironment of tumors, with important implications for cancer immunotherapy [80].

Considering the activation of HERVs in many human cancers, HERVs can be used as biomarkers for tumor diagnosis and/or prognosis [52]. For example, in breast cancer patients, HERV-K (HML-2) Env expression is closely associated with tumor size, TNM stage, and lymph node metastases [81]. Moreover, breast cancer patients with high expression of HERV-K (HML-2) Env protein is a novel candidate prognostic marker for breast cancer [81]. A study in prostate cancer reported that the combination testing of HERV-K (HML-2) with traditional prostate-specific antigen may improve the efficacy of prostate cancer detection, specifically among older men and smokers who tend to develop a more aggressive disease [82]. Recently, Kolbe *et al.* performed the first locus-specific analysis of HERVs expression in head and neck cancer and found that members of the HERV-H family are highly expressed in tumor tissues and may serve as biomarkers for disease progression [83]. In this view, HERVs have the potential to be targets for new cancer therapeutic opportunity. A recent study revealed that CT-RCC HERV-E envelope-encoding peptides, which are expressed in the majority of ccRCC tumors but not in normal tissues, are immunogenic and capable of stimulating CD8<sup>+</sup> T cells *in vitro* that recognize CT-RCC HERV-E-expressing ccRCC tumors, suggesting that HERV-E Env can represent an excellent target for T cell-based immunotherapy for kidney cancer [84]. Another study reported that anti-HERV-K (HML-2) Env antibodies inhibited growth and induced apoptosis of breast cancer cells *in vitro* and reduced growth of xenograft tumors in mice [85]. Consistently, HERV-K Env-specific CAR<sup>+</sup> T cells are able to lyse melanoma tumor cells in an antigen-specific manner *in vitro* and *in vivo* [86]. In addition, DNMTis activate the viral recognition and interferon response pathway by inducing dsRNAs transcribed by HERVs, which can potentiate the response to immune checkpoint therapy [78,79].

#### 4. HERVs in aging and neurodegenerative diseases

In general, ERVs are largely transcriptionally silenced through a heterochromatic structure, which is established by histone modification and DNA methylation mechanisms [87]. However, there may be a net loss of heterochromatin with ageing, resulting to the abnormal activation of retrotransposons, including ERVs, in aging individuals [88,89]. In aging mouse, the MuERV intracisternal A-particle (IAP) becomes active [90], and an increase in the RNA transcription and copy number of MusD is detected [91]. In human, HERV-K (HML-2) and HERV-W exhibit different expression patterns in young and old individuals [92]. The expression of HERV-H and HERV-W in human peripheral blood mononuclear cells (PBMCs) shows a significant positive correlation with age over 30 years old [93]. Notably, the expression of HERV-W shows a significant increase in individuals over 40 years old, and neurodegenerative diseases such as multiple sclerosis (MS) also occur around this range of age [93]. It has been recognized that the reactivation of HERVs is related to the occurrence and development of human aging-related diseases [94,95].

Currently, abnormal activation of HERVs has been detected in certain neurodegenerative diseases [5]. For example, elevated HERV-W envelope protein expression is detected in muscle cells of amyotrophic lateral sclerosis (ALS) patients [96]. HERV-K (HML-2) is expressed in cortical and spinal neurons of ALS patients, but not in neurons from control healthy individuals, and its envelope protein may contribute to neurodegeneration [97]. MS is another neurodegenerative disease associated with HERVs abnormal expression. HERV-W envelope protein was detected in MS brains and specially in lesions [98], and HERV-W Env-mediated



**Fig. 3.** Advanced technologies provide opportunities to explore HERVs in health and disease. The application of advanced technologies such as high-throughput sequencing provides opportunities for identifying functional HERV loci in patients versus healthy individuals.

microglial polarization contributes to neurodegeneration in MS [99]. In fact, a recently completed clinical study in MS patients, which used monoclonal neutralizing antibodies against the HERV-W envelope protein, showed that the antibody-mediated neutralization exerts neuroprotective effects [99]. In neurodevelopmental disorder autistic spectrum disorder (ASD), HERV-H and HERV-W are differentially expressed in ASD patients and healthy controls, with HERV-H being more abundantly expressed while HERV-W having lower abundance in PBMCs from ASD patients compared to healthy controls [100]. Furthermore, HERV-H exhibits a statistically significant higher expression in ASD patients with severe disease development [100]. Moreover, it has been reported that expression of HEMO (ERVMER34-1) is altered in ASD patients and may be useful for the disease diagnosis [101]. Therefore, HERVs expression could be considered as a biomarker, which is easily detectable in blood and potentially contributing to an early diagnosis. In addition, several HERVs and non-LTR TEs are activated in Alzheimer's disease (AD) [102], and some HERV-W and HERV-H loci are transcriptionally upregulated in postmortem brain samples from schizophrenic and bipolar patients [103]. Taken together, these studies suggest that the activation of HERVs may be a mechanistic link between aging and neurodegeneration.

## 5. Conclusion and perspective

HERVs are involved in various biological processes through encoding proteins, acting as promoters/enhancers, or lncRNAs to affect human health and disease. In addition to the discoveries mentioned above, HERVs are also involved in neurodevelopment [104,105], HIV-1 infection [106], chronic hepatitis C virus (HCV) infection [107], and type 1 diabetes [108,109]. Although there are a large number of studies focusing on the expression of whole HERVs families, most of these works did not detect the individual coordinates of the expressed loci, or measure the expression of a single locus. Recently, the application of omics approaches has allowed to solve these problems, for instance, high-throughput sequencing, which allows the obtaining of important information about the individual HERV loci, can be used to investigate the contribution of HERVs to human development and diseases [110] (Fig 3). Previously, due to the technical difficulties in analyzing these highly repetitive elements, HERVs have not received enough attention. With the development of novel technologies, such as high-throughput sequencing, single-cell RNA-seq, genome editing technology, and integration of big data, etc., the mystery of HERVs is being further uncovered. Nonetheless, there are still more questions about these ancient remnants than definite answers, such as the identification of specific HERV loci associated with specific diseases. This provides a promising opportunity to enrich our knowledge for HERVs, the complex genomic elements that make up ~ 8% of human genome.

## CRediT authorship contribution statement

**Jian Mao:** Conceptualization, Writing – review & editing. **Qian Zhang:** Writing – review & editing. **Yu-Sheng Cong:** Conceptualization, Writing – review & editing.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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