

Decoding Neurological Mysteries: The Potential Impact of Endogenous Retroviruses on Brain Health

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ABSTRACT

Endogenous retroviruses (ERVs), remnants of ancient viral invasions, make up a significant part of the mammalian genomes. ERVs are typically held in check by complex epigenetic mechanisms, which serve to limit their expansion and potential adverse effects on the genome. However, ERVs can become aberrantly activated in response to stressful challenges, contributing to progression in pathological conditions, including cancer, inflammation, auto-immune disorders, and aging, through various mechanisms. Notably, ERV activation is also detected in the brain and is increasingly recognized as an important factor in neuropsychiatric disorders. In this review, we encapsulate the general understanding of ERVs in both physiological and pathological states and compiled evidence for ERV activation across a spectrum of neuropsychiatric disorders, along with current studies exploring the underlying mechanisms. Despite the accumulating body of evidence, research in this field remains in its infancy and faces substantial challenges. Further studies are warranted to enhance our understanding of ERV activation mechanisms and their roles in neuropsychological conditions, potentially contributing to the development of innovative therapeutic interventions.

1 Introduction

Transposable elements (TEs), also known as “transposons,” are genetic sequences capable of changing their position within the genome. They are found in all species and constitute nearly 40% of the mammalian genome [1]. TEs are primarily categorized into the following two types: Class I transposons or retrotransposons, and class II transposons or DNA transposons.

Retrotransposons use a “copy-and-paste” mechanism, transcribing into RNA and then reverse-transcribing back into DNA, which is then integrated back into the genome. This mechanism allows retrotransposons to amplify their own copy number, making them the predominant TEs in the genome. Meanwhile, DNA transposons utilize a “cut-and-paste” method, accounting for only 1%–2% of the mammalian genome. Despite their different mechanisms, all TEs

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can potentially create mutations, rearrange the genome, and influence the genome size. Apart from these potentially harmful effects, TEs can also have beneficial impacts on fostering genetic diversity and have remarkably shaped genome evolution [2].

Retrotransposons can be further categorized into the following two main types: long terminal repeat (LTR) and non-LTR retrotransposons. Although a detailed classification of these elements is beyond the scope of this review and has been covered elsewhere [3], in this paper, we will focus our discussion on endogenous retroviruses (ERVs), which represent a subset of LTR retrotransposons. ERVs are pervasive across species, not only appearing in all vertebrates but also spanning in the entire animal kingdom. They co-evolve with their hosts and exhibit relatively lower evolutionary rates; hence, they are considered “molecular fossils” and serve as phylogenetic markers for linkage analysis [4, 5]. ERVs can be further categorized into different classes and families, distinguished by more specific sequence characteristics. For instance, based on the similarity with exogenous viruses, ERVs can be classified as classes I, II, and III. Besides, the specificity of their primer binding sites (PBSs) for certain tRNAs, a crucial element in initiating reverse transcription during retroviral infection, is a defining feature [6]. As an example, the human ERV families HERV-W and HERV-K belong to the ERV1 and ERV2 classes, respectively. The “W” in HERV-W stands for tryptophan and the “K” in HERV-K stands for lysine, reflecting the tRNA specificity of their PBSs. However, classifying ERVs can be complex and sometimes inconsistent owing to their diversity, the complexity of these elements, and the varying criteria used by different studies or databases. For instance, HERV-K, also known as Human MMTV-like 2 (HML-2), is named as such because

of the sequence homology it shares with the Mouse Mammary Tumor Virus (MMTV), a type of beta-retrovirus [7]. This naming convention illustrates the intricate relationships and evolutionary history that ERVs share with exogenous retroviruses.

ERVs originated from ancient retroviral infections occurring in germline cells. These retroviral sequences were integrated into the host species’ genome and have been passed down through generations. ERVs structurally resemble exogenous retroviruses, containing cassettes that encode typically viral components. In full-length ERVs, besides the LTRs located at both ends, there are three primary retroviral genes, which are as follows: *GAG*, *PRO/POL*, and *ENV* [3]. The *GAG* gene encodes the virus’s capsid proteins, whereas the *PRO/POL* genes encode proteases that are essential for the virus’s replication, integration, and cleavage during host infection. The *ENV* gene encodes envelope glycoproteins that dictate viral infection specificity. The LTRs control retroviral gene transcription and are crucial for integrating the retroviral DNA into the host genome. Nevertheless, similar to other TEs, most ERVs are defective due to the accumulation of mutations, frameshifts, and deletions, with some ERVs retaining only solo LTRs. Meanwhile, the host organism actively suppresses the ERVs’ activity in the genome through various epigenetic regulatory mechanisms, as the invasion and recombination process of ERVs can increase the host genome’s instability. However, some ERVs have retained some activities through selection during the evolutionary process and play an important regulatory role in mammals [3]. Their aberrant activation is also closely linked to a range of pathological conditions, including tumors, immune diseases, aging, and neuropsychological disorders [3, 8].

Studies on ERVs have garnered increasing

attention in recent years, with many focusing on cancer and immune diseases. However, a comprehensive understanding of ERVs in the field of neuroscience, particularly their involvement in brain disorders, has only begun to emerge. In this review, in addition to providing a general introduction of ERVs and their activity under both physiological and pathological conditions, we particularly discuss their role in the brain and potential implications for various neuropsychiatric disorders. We begin by describing the primary epigenetic mechanisms involved in silencing ERVs, with a specific focus on histone H3K9 trimethylation (H3K9me3) and DNA methylation. Then, we discuss the role of ERVs in transcriptional regulation under physiological conditions. We then explore the de-repression of ERVs when subjected to various stressors, and its consequences, including the induction of cancer, inflammation, auto-immune responses, and aging. To conclude our review, we highlight recent studies that present evidence of the involvement of ERVs in neuropsychological disorders, including Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), autism spectrum disorder (ASD), schizophrenia (SCZ), bipolar disorder (BD), and others.

2 Epigenetic mechanisms in ERV regulation

As previously mentioned, active ERVs, while driving host genome diversity and evolution, also introduce instability into the host genome. To minimize these risks, hosts have developed various strategies employing epigenetic modifications to counteract ERVs' activity. Among these strategies, SETDB1-mediated H3K9me3 and DNA methylation are the two most commonly used epigenetic mechanisms. These two mechanisms often operate synergistically

to silence ERVs. Additionally, other epigenetic mechanisms reportedly play important roles in ERV regulation.

2.1 SETDB1-mediated H3K9me3 and its co-regulators

SET Domain, Bifurcate 1 (SETDB1) operates as a histone methyltransferase, with its *in vivo* activity specifically toward the repressive histone mark, H3K9me3. In this section, we primarily focused on presenting evidence for SETDB1's role in silencing ERVs across various systems, including the brain. Beyond ERVs, SETDB1 also exerts a significant regulatory influence on other genes crucial for the functioning of the central nervous system (CNS), a topic which has been extensively reviewed by our team and others [9, 10]. A landmark study by Matsui and colleagues [11] highlighted the critical function of SETDB1, also referred to as ESET, in silencing both endogenous and exogenous retroviral elements within the embryonic stem cells (ESCs). Their findings showed that a reduction in SETDB1 led to a considerable reactivation of ERVs, specifically impacting classes I and II, but not class III or non-LTR retrotransposons. Notably, only H3K9me3, not H3K9me2, was affected on ERVs that were targeted by SETDB1, thereby underscoring the importance of H3K9me3 [11].

Although SETDB1 contains a methylated CpG binding-domain, it has not been directly shown to bind to ERVs or any other genomic DNA sequences. Instead, it functions as an integral component of a well-characterized transcriptional repressive complex, known as SETDB1/KAP1/KRAB-ZFPs. The Krüppel-associated box zinc-finger proteins (KRAB-ZFPs) represent the largest transcription factor family in higher vertebrates. They recognize and bind to specific DNA sequences through their zinc-finger structures, enabling them to identify the PBSs of various ERV families [12]. A notable example is ZFP809

in mice, which suppresses the Moloney murine leukemia virus by recognizing PBS-Pro [13, 14]. The evolution of the host ZFP family is believed to have been driven by the integration of new ERVs [15]. Each integration of new ERVs coincides with the emergence of a corresponding new ZFP family. This diversification of ZFPs allows them to target and inhibit the activity of the newly integrated ERVs [16, 17]. To enable their silencing effect, KRAB-ZFPs recruit the transcriptional co-repressor KAP1 (KRAB-associated protein 1) and SETDB1 [18]. Along with the heterochromatin protein HP1, they establish an H3K9me3-mediated heterochromatic environment and impose the inhibitory effect on the ERV sites [18]. This mechanism is observed in the early embryos, pre/pro B cells, neural progenitor cells (NPCs), and neurons, and the deletion of this complex results in H3K9me3 loss and ERV activation [18-22]. Interestingly, despite HP1 being recognized as an H3K9me3 reader, its deletion alone does not cause considerable ERV activation [11, 18], suggesting the existence of other H3K9me3 readers. For instance, a most recent study identified the trinucleotide-repeat-containing 18 (TNRC18), which is a new H3K9me3 reader that selectively mediates class I ERV silencing [23].

Beyond loss-of-function studies, unbiased screening studies have further highlighted the pivotal role of SETDB1 in ERV silencing, while also unveiling new associating partners. Yang et al. utilized a siRNA screening system to systematically identify factors that influence ERV silencing in embryonic cells [24]. They identified several SUMOylation factors, including SUMO2, UBE21, SAEL, UBA2, and SENP6, in addition to the well-studied SETDB1/KAP1/ATF7IP complex. Interestingly, SUMO2, a central player in the SUMOylation process, impacts the same range of ERVs as SETDB1 or KAP1, and these ERVs were remarkably enriched for H3K9me3. Furthermore,

SUMO2 directly binds to and mediates the SUMOylation of SETDB1 and KAP1, promoting their recruitment to ERVs [25, 26]. Subsequently, Fukuda and colleagues conducted a CRISPR/Cas9 screening to identify genes involved in MLV silencing in mouse ESCs [27]. Their findings revealed that the top 100 genes were highly enriched for chromatin modification and remodeling complexes. Notably, *SETDB1* and its binding partner *ATF7IP* topped the list. Moreover, most of the other genes, including those in the *BAF* family and HUSH complex, either directly interact with SETDB1 or are involved in SETDB1-associated protein complexes. The involvement of the HUSH complex was also reported in an independent study that utilized a non-lethal forward genetic screening in near-haploid KBM7 cells [28]. Interestingly, a minimal overlap was noted between Fukuda's and Yang's lists, with only eight genes appearing in both studies among the top 100. These genes could be grouped into the following three protein complexes: SETDB1/KAP1/ATF7IP, SWI/SNF complex (SMARCA4, SMARCB1, and SMARCC1), and SUMOylation factors (SUMO2/SAE1). This further emphasizes the indispensable role of SETDB1 in regulating ERVs, while also highlighting the specificity of more refined regulatory pathways tailored to the ERV-type and host species.

2.2 DNA methylation

DNA methylation, typically occurring at 5-cytosine of CpG in mammals, is a well-studied repressive epigenetic mechanism that mediates TE silencing [29]. DNA methylation participates in ERV silencing in multiple cell types and systems, including the brain [21, 30, 31]. The finely-orchestrated establishment and deletion of DNA methylation signal on ERVs involve a series of methyltransferases (DNMT1, DNMT3A/3B/3C/3L) [31-34] and demethylases (TET1/2/3, TDG) [35, 36].

Additionally, other epigenetic regulators also assist in the DNA methylation-mediated silencing of ERVs, particularly those that catalyze the repressive histone mark, H3K9 methylation, including SETDB1 [37] and G9A/GLP [38].

The pattern of DNA methylation on ERV repression is highly dynamic during early embryonic development. From fertilization to the morula stage, ERVs undergo active DNA demethylation, mediated by TET1/2/3 and TDG [35, 36]. An exception is the intracisternal A-particle (IAP), a subgroup of rodent ERVs that are partially shielded from demethylation [39]. DNMT1, including its oocyte (DNMT1o) and somatic (DNMT1s) forms, has been implicated in the maintenance of IAPs methylation throughout preimplantation, achieved via binding to the 5'LTR of IAPs [39, 40]. DNMT1 plays a crucial role in maintaining the methylation patterns following DNA replication [32, 39]. It is recruited to the replication fork by the PCNA/NP95/G9A complex [41], where it maintains IAP methylation in cleavage embryos by methylating the symmetrical CpG on the newly synthesized DNA strand [42]. As development progresses, ERVs undergo *de novo* DNA methylation from the blastocyst to the post-implantation period by DNMT3A/B [43], which form a complex with DNMT3L [44]. DNMT3A/B also form a protein complex with NP95 and G9A to initiate ERV body silencing [41]. During the peri- and post-implantation stages, zygotic DNMT1s is highly expressed and continues to maintain IAP methylation [40], with the aid of histone H3K9 methyltransferase G9A and SETDB1 [38, 45]. Interestingly, early studies highlighted the dispensable role of DNA methylation on ERV repression in ESCs, as most ERV remained silenced in *Dnmt1/Dnmt3a/Dnmt3b* triple-knockout ESCs [11]. However, subsequent research revealed the crucial interplay between DNA methylation and H3K9me3 in ERV silencing in ESCs.

Specifically, ectopic NP95 binding after *Dnmt1* knockout caused an expansion of hemimethylated DNA, inhibiting SETDB1-dependent repression and leading to transient IAP expression [46]. However, after gradual dilution of hemimethylated DNA, SETDB1-mediated repression machinery was recovered and IAP was silenced again [46].

Differentiation brings about more complex regulatory mechanisms of ERVs. DNA methylation, which is canonically stable and fixed, was considered essential for creating large silent domains that suppress ERV in differentiated cells [29, 47]. However, recent studies have shed light on the cooperative interaction between DNA methylation and H3K9me3 in maintaining ERV silencing. In the embryonic endoderm, DNA methylation inhibits IAP activity in both visceral endoderm (VE) and definitive endoderm, whereas SETDB1-mediated H3K9me3 only controls IAP in VE [48]. In the differentiated human cell lines, DNA methylation represses young ERVs enriched in CpG, whereas H3K9me3 primarily regulates the intermediate-aged ERVs [49]. In the developing brain, *DNMT1* loss in telencephalic NPCs resulted in considerable DNA hypomethylation and induced the production of IAP protein in the dorsal cortex, contributing to cortical degeneration and defects in neuronal maturation [50]. Additionally, the depletion of H3K9me3 methyltransferase SETDB1 triggered an abnormal IAP expression, accompanied with CpG demethylation in the LTR of IAPs [21]. This underscores the intricate interplay between DNA methylation and H3K9me3 in regulating the ERV activity during cellular differentiation and brain development.

2.3 Others

In addition to SETDB1, other proteins, including SUV39H, also mediate H3K9me3 modification in mammals. However, the role of SUV39H in ERV silencing remains a topic of debate. SUV39H

is well recognized for its role in constitutive heterochromatin formation, and SUV39H-mediated H3K9me3 is involved in suppressing class II ERVs in ESCs. However, ERVs maintain silence in ESCs and NPCs even in the absence of SUV39H [51]. Apart from H3K9me3, G9A-mediated H3K9me2 has also been implicated in ERV regulation, specifically targeting MERVL, a class III ERV [52]. Notably, Yang's screening identified another complex, CHAF1A/B, which primarily targets Class III ERVs. Interestingly, CHAF1A/B targets exhibit low signals for H3K9me3 but are enriched for active histone modifications, including H3K4me2, H3K9ac, and H3K27ac [24]. Further pull-down experiments identified KDM1A and HDAC1/2 as binding components within the CHAF1A/B complex [24]. CHAF1A/B are core components of the chromatin-assembling factor complex CAF1, which is also a binding partner of SETDB1 [53]. H3K27me3, another important repressive histone mark, is also involved in ERV silencing, although its role appears to be limited to class I ERVs [54]. The histone variant H3.3 also plays a role in ERV regulation [55]. Collectively, these studies suggest a complex interplay of multiple epigenetic mechanisms in the control of ERVs.

3 ERV activation and its biological implications

Although the majority of ERVs within the mammalian genome are typically silenced due to genetic mechanisms, it is essential to appreciate the remarkable roles that certain ERVs play in host physiological functions.

3.1 Encode functional proteins

ERV-derived proteins play important functions in the placenta, early embryo, and brain. Two proteins derived from ERV-env, Syncytin-1

(originating from HERV-W) and Syncytin-2 (originating from HERV-FRD), are responsible for facilitating cell fusion and syncytiotrophoblast formation, which are essential for placental development. [56, 57]. Additionally, proteins derived from ERV-ENV can restrict retroviral infection across various mammalian species, including humans. A prime example is the gene suppressyn (*SUPYN*), derived from the *ENV* of HERV-F, which is highly expressed in the placental trophoblast and can inhibit mammalian D-type retroviral infection [58, 59]. ERV-encoded protein also enhance resistance to viral invasions during embryonic development. HERV-K, for example, encodes the accessory protein REC, which can bind to host cell RNA, regulate its nucleosome occupancy, and inhibit viral infection by amplifying the cell surface expression of the IFN-induced viral restriction factor IFITM1 [60]. Methyltransferase 6 (*Prmt6*) generates a chimeric transcript with *Mt2b2*, a member of MERVL, in mouse preimplantation embryos. This transcript undergoes translation, giving rise to the PRMT6MT2B2 chimeric protein upon zygotic genome activation. PRMT6MT2B2 exhibits distinct functionality characterized by a more substrate-specific behavior and reduced histone arginine methylation activity as compared to the conventional PRMT6. This unique protein variant plays a pivotal role in orchestrating cell differentiation during the blastocyst stage [61]. There are also instances from the brain. Arc, a post-synaptic protein originating from the Ty3/Gypsy retrotransposon family, plays a crucial role in excitatory synapses and is essential for learning and memory [62]. The arc protein can assemble into virus-like capsids, demonstrating biochemical properties reminiscent of retroviral GAG proteins. These capsids play a role in facilitating the intercellular transfer of Arc mRNA among neurons [63, 64].

3.2 Serve as regulatory elements

ERVs can function as regulatory elements for gene expression. During the developmental phase that precedes embryo implantation, a unique DNA hypomethylated environment allows ERVs to temporarily escape repression. In this context, MERVL/HERVL serves as an alternative promoter, driving the expression of chimeric transcripts and playing a pivotal role in regulating cell state transitions [65, 66]. MERVL transcripts are essential for accurately regulating the host transcriptome and chromatin state during preimplantation development [67]. ERVs also participate in gene regulation in placental development. This is substantiated by studies conducted on rodent trophoblast stem cells (TSCs) that found considerable enrichment of ERVs in TSC-specific enhancers [68]. One example is the mouse-specific ERV, RLTR13D5, which functions as an enhancer, associates with the core factors of the TSC regulatory network, and influences the expression of adjacent genes [68]. Furthermore, ERVs act as evolving enhancers, orchestrating immune gene regulation, and coordinating transcriptional responses to interferons in both humans and mice. A case in point is the primate-specific MER41, which acts as an IFN-inducible enhancer, interacts with *STAT1*, and activates proximal IFN-stimulated genes in CD14 macrophages upon IFN exposure [69].

3.3 Participate in 3D genome organization

ERVs also play an instrumental role in organizing the three-dimensional (3D) genome structure, facilitating distant chromatin interactions and gene regulation. For instance, HERV-H establishes the boundaries of topologically associating domains (TADs) in human pluripotent stem cells (hPSCs) and is involved in TAD remodeling during cardiomyocyte differentiation [70]. When HERV-H is removed, the corresponding TAD boundaries disappear, leading to a decrease in

the transcription of genes located upstream of these boundaries. Importantly, species without these HERV-H elements do not have these TAD boundaries, suggesting HERV-H's role in shaping cell-type- and species-specific chromatin structures. Further evidence on the role of ERVs in 3D genome organization comes from a study focusing on cell type-specific 3D epigenomics during human cortical development. It identified super-interactive promoter groups (SIPGs), which are areas that demonstrated enhanced interaction between promoters and their distal interacting regions. ERVL-MaLR elements are significantly enriched in SIPGs, contributing to gene expression regulation and lineage specification during development [71].

4 ERV activation under pathological conditions

Although ERV expression is usually minimal in healthy tissues, accumulating evidence suggests that various pathological conditions, including cancer, infections, immunoinflammation, and aging, can trigger the transcription of proviral elements and subsequent protein production.

4.1 Cancer

The activation of ERVs is a phenomenon extensively observed in various cancer models and patients, with some studies even reporting the presence of viral-like particles [72, 73]. A notable increase in HERV-K expression has been identified in malignant tissues, which includes germ cell tumors, melanoma, ovarian cancer, leukemia, and prostate cancers, in contrast to its minimal expression in healthy tissues [74-78]. For melanomas, ERV activation resulted in the expression of various viral proteins, including GAG, ENV, REC, NP9, and RT, which are absent in melanocytes or normal lymph nodes [79, 80]. Furthermore, ERV activation appears to play a

role in promoting tumor progression. Activated ERVs can trigger an IFN response and stimulate the expression of chemokines, including CXCL10. This subsequently results in the infiltration of specific T cells, including Th2 and Treg cells, which contribute to the establishment of an immunosuppressive microenvironment within the tumor. This environment can potentially facilitate tumor initiation and progression [81].

4.2 Infection

Previous studies have highlighted that HERVs can be activated in response to viral and microbial infections. For example, the presence of HERV-K RNA, protein, and virus-like particles has been identified in the plasma of HIV-1 patients [82]. In addition to HERV-K, HIV-1 infection activates several other types of HERVs, including HERV-E, HERV-T, and ERV9 [83, 84]. Interestingly, the interplay between HIV-1 and HERV viral production appears to counteract each other. HIV-1 infections stimulate the ERV9 member LTR12C, which subsequently triggers the expression of IFN-inducing genes *GBP2* and *GBP*. This action limits the production of HERV-K virus particles [85]. Conversely, the envelope protein of HERV-K108 potentially inhibits the production of HIV-1 virus particles [86]. Additionally, in individuals infected with HIV-1, HERV-K-specific viral T cells can be detected. These specific CD8⁺ T cells are capable of recognizing and eliminating cells that present homologous peptides, a consequence of HIV-induced HERV protein expression [87]. This mechanism plays a pivotal role in the natural immune response to HIV [88].

4.3 The infections beyond HIV can also influence ERV activation

For instance, in mice infected with the herpes family virus EBV, an increase in ERV transcription

was observed in mouse lymphocytes, leading to an auto-immune response [89]. Additionally, an increase in the mRNA levels of the HERV-env was detected in peripheral white blood cells infected by the Coxsackie B virus *in vitro* [90]. Apart from the viruses, bacterial infections can also prompt ERV activation [91]. For example, the microbiota in mice can initiate ERV transcription, resulting in T-cell accumulation in the skin. This process promotes an antibacterial inflammatory response and assists in tissue repair [91].

4.4 Immunoinflammation

Long-term studies have established a reciprocal relationship between ERV expression and inflammation. It is well understood that inflammatory triggers can stimulate ERV expression. The promoters of ERVK, for instance, contain interferon-stimulated response elements and binding sites for pro-inflammatory transcription factors, such as NF- κ B [92]. When exposed to bacterial endotoxins or specific pro-inflammatory cytokines, ERV expression increases in both mouse and human cells and tissues [92-94]. Early exposure to inflammatory factors can induce lasting changes in ERV expression, which, in turn, can influence disease susceptibility among individuals. For example, maternal exposure to virus-like acute phase reactions elevates the mRNA levels of *IL-6* and several ERVs in the placenta and fetal brain [95]. Moreover, ERV activation itself have pro-inflammatory effects [95]. HERV expression has also been closely associated with many auto-immune diseases [96]. An early study has established a strong link between HERVs and the incidence of rheumatoid arthritis (RA) [97]. This study compared the sera obtained from RA patients and those from healthy controls, revealing a high proportion of RA patients with antibodies

specific to envelope proteins from HERV-K10 and IDDMK1. Further analysis using RT-qPCR showed an elevated expression of HERV-K10 GAG in peripheral blood mononuclear cells (PBMCs) from RA patients as compared to healthy controls [98, 99]. In patients with inflammatory bowel disease (IBD), *SETDB1* expression is significantly reduced in the intestinal stem cells. This reduction leads to diminished H3K9me3 levels on ERVs, which, in turn, triggers ERV activation [100]. In summary, the interplay between inflammation and ERV expression is complex and bidirectional, with potential long-term implications for disease susceptibility and progression.

4.5 Aging

ERV activation is reportedly connected to cellular senescence and tissue aging [101]. Various cellular senescence models have demonstrated ERV activation due to factors such as the loss of epigenetic transcriptional silencing, shifting in heterochromatin/euchromatin compartments, profound epigenetic resetting, and aberrant activation of enhancers associated with the senescence-related gene [102-104]. ERV expression is expected to maintain the establishment of a senescence-associated secretory phenotype, which, in turn, reinforces the aging response [102, 105]. This correlation has been observed across multiple species, including yeast, flies, and rodent [106-108]. In the human hippocampus, a trend toward an increase in microbial burden with age was observed. This overall infectious burden is directly related to the abundance of retroelements, primarily HERVs [109]. Furthermore, an increased expression of HERV-K and HERV-W was noted in the PBMCs and skeletal muscle of aging individuals, as well as in the frontal lobe of aging primates [110, 111]. This change has been associated with DNA hypomethylation at the HERV loci [112-114]. Additionally, HERV-K

upregulation in human cells and primate tissues has been linked to programmed aging, providing another layer of evidence for the role of ERVs in the aging process [101, 111, 115].

5 Biological consequence of ERV activation

Three primary mechanisms have been proposed to explain how ERV activation can disrupt host homeostasis, leading to pathological responses (Figure 1). Firstly, ERVs can serve as alternative promoters or enhancers. Upon activation, they can either influence adjacent gene expression or establish long-range chromatin interactions for distal gene regulation. Secondly, the activated ERVs can generate a large volume of transcripts that form double-stranded RNAs (dsRNAs), which can induce inflammatory responses by activating the nucleic acid sensors. Lastly, some ERVs retain intact coding sequences, enabling them to produce functional viral proteins, such as GAG and ENV. These proteins hold the potential to assemble into viral-like particles, particularly in loci that still harbor full-length ERVs. The presence of these functional viral proteins or particles can initiate immune responses, mimicking the process of exogenous retroviral infection. In certain scenarios, they might even be secreted extracellularly, thereby impacting the surrounding healthy cells.

5.1 Serve as alternative promoters or enhancers

Emerging from cancer research is the pioneering concept that ERVs can serve as regulatory elements for gene expression. During tumorigenesis, aberrant TE activation can stimulate the expression of certain proto-oncogenes. Thus, in this context, activated ERVs or LTRs can function as alternative promoters, initiating the expression of genes in their proximity [116]. For example, in Hodgkin's lymphoma, an aberrantly activated LTR from the MALR family acts as

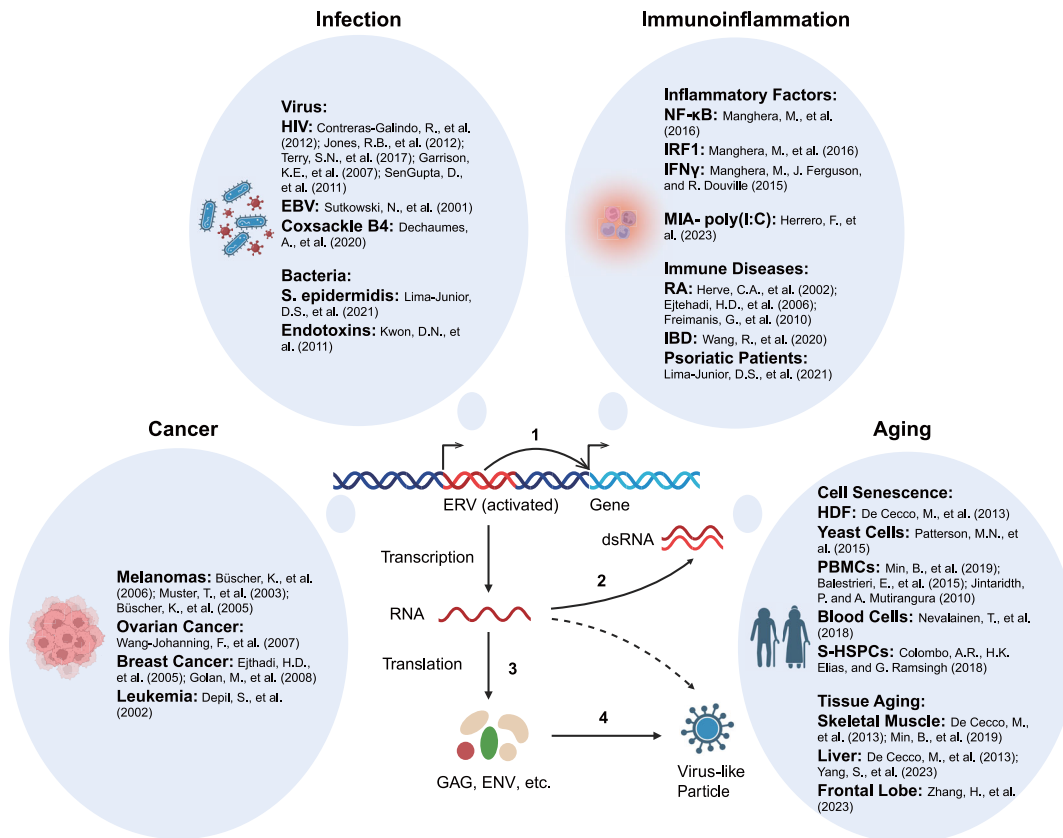


Fig. 1 Stimuli that activate ERVs and their biological consequence. ERVs can be activated under pathological conditions, including cancers, infections, immunoinflammatory disorders, and aging. Upon activation, ERVs can 1) function as alternative promoters or enhancers influencing gene expression. In addition, the transcripts from ERVs can 2) form dsRNAs or 3) translate into functional viral proteins, which may further 4) assemble into virus-like particles. HIV, human immunodeficiency virus; EBV, Epstein-Barr virus; MIA, maternal immune activation; RA, rheumatoid arthritis; IBD, inflammatory bowel disease; HDF, human diploid fibroblasts; PBMCs, peripheral blood mononuclear cells; S-HSPCs, senescent human stem and progenitors; GAG, group-specific antigen gene; ENV, envelope.

a promoter, triggering proto-oncogene *CSF1R* expression [117]. Further evidence of this regulatory role comes from studies on acute myeloid leukemia, where at least six classes of ERV family members were identified as enhancers. These ERVs regulate the expression of nearby leukemia-associated genes. A notable instance is *APOC1* regulation by LTR2, a process crucial for cancer cell proliferation [116]. Such regulatory mechanisms have also been studied in the context of neural development. In NPCs, the genetic ablation of *SETDB1* or its binding partner *KAP1* triggers a massive ERV activation, leads to long noncoding RNA production, and coincides with the upregulation of adjacent gene expression [20, 21, 118]. The causal effect and

biological consequences of this mechanism, focusing on interneuron development, were further established in a recent study [20]. The researchers identified a class I ERV locus, RMER21B, located downstream of the *Htr3a* gene, which encodes the important type 3 serotonin receptor subunit A. They provided evidence of chromatin interaction between the RMER21B and *Htr3a* promoter, demonstrating the enhancer activity of RMER21B that contributes to the regulation of the *Htr3a* gene, which is an important marker gene for cortical interneurons. The study showed that RMER21B activation disrupts the development of *Htr3a*⁺ interneurons in mouse cortex, contributing to mood dysregulation [20].

5.2 Activation of nucleic acid sensors

Certain effector molecules, classified into four groups, are tasked with monitoring aberrant nucleic acids within the cells. First, Toll-like receptors (TLR3/7/8/9) in the endosomal membrane recognize viral nucleic acids. Second, the cytoplasmic DNA sensor, cyclic GMP-AMP synthetase (cGAS), identifies pathogenic and excess host DNA. Third, retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs) serve as cytoplasmic RNA sensors [119]. Lastly, Z-DNA Binding Protein 1 (ZBP1), a nuclear RNA sensor, detects abnormal dsRNAs exhibiting a left-handed conformation [100]. Upon activation, ERVs can trigger the immune responses primarily through the aforementioned pathways. For instance, dsRNA produced by the activated ERVs initiates the TLR3-mediated antiviral signaling pathway, a process observed in breast cancer and melanoma. This activation subsequently activates the type I IFN response via the MyD88 and TRIF pathways [120]. There are also alternative mechanisms where cytoplasmic dsRNA activates RIG-1/MDA-5 and dsDNA initiates the cGAS-STING pathway. These activations, found in various cancer cell lines, typically stimulate the classical antiviral IFN pathways [121]. In addition to triggering an inflammatory response, ERV activation can also induce cell death. In intestinal epithelial cells, genetic ablation of *SETDB1* activates the ERVs and generates conformationally aberrant Z-RNAs, leading to necroptosis in a ZBP1-dependent manner [100]. A similar mechanism was observed in Schwann cells, a type of glial cell found in the peripheral nervous system [122]. The expression of nucleoporin *Seh1*, a component of the nuclear pore complex, decreases with aging. In Schwann cells, the loss of *Seh1* results in immune activation and ZBP1-mediated cell necroptosis. This process is SETDB1/KAP1 dependent and can be alleviated by a reverse transcriptase inhibitor [122].

5.3 Generation of viral proteins or particles

ERV activation not only involves dsRNA formation but also leads to functional viral protein generation, which, in turn, can directly stimulate an immune response. An earlier study has shown that the viral ENV protein derived from the HERV-W stimulates innate immunity via the CD14/TLR4 pathway, thereby promoting Th1-like responses [123]. Additionally, in a recent study, the Major Histocompatibility Complex class I (MHC-I) presentation pathway was identified to mediate T-cell activation induced by MuLV-derived peptides [124]. Further, ERVs can influence other cells through exosomes. As an illustration, MuLV aids in the intercellular transmission of misfolded proteins, a phenomenon also observed in astrocytes from AD patients [125]. Besides the envelope proteins, GAG proteins from ERVs also play a pivotal role in immune response. In a diabetic mouse model, these proteins serve as antigens for T-cell activation and auto-immune response [126]. In neurons, GAG proteins produced due to ERV activation following the loss of *KAP1*, aggregate within the cells, triggering a substantial microglial activation [22]. Moreover, electron microscopy has revealed the production of virus-like particles in mouse neurons exhibiting massive ERV activation due to *Setdb1* depletion, a process also accompanied by reactive gliosis [127]. Aging is an important factor that induces ERV activation, which has been validated in both *in vitro* and *in vivo* studies [101] [111]. Activated ERVs in senescent fibroblasts can form virus-like particles, which are then secreted extracellularly and induce senescence in proximate young cells [101]. In a recent multi-omics profiling study of the frontal lobe in aged primates, a specific deterioration of the nuclear lamina was identified in neurons. This degeneration coincided with ERV activation and virus-like particle formation, which instigated inflammation via the cGAS signaling pathway

[111]. Notably, this previous study highlighted that abacavir, a nucleoside reverse transcriptase inhibitor, could alleviate aging-related changes in human IPS-induced neurons and aged mice [111].

Additionally, alongside their toxic impacts, ERV proteins can also confer protective effects. HERV-K particles, released from human teratocarcinoma cells, demonstrate immunosuppressive capabilities through the HERV-K-enveloped TM proteins. These proteins inhibit immune cell proliferation and promote the release of the anti-inflammatory cytokine IL-10 [128]. Furthermore, activated ERVs exert neuroprotective effects by upregulating NGF and BDNF in the cultured neuronal cells during an HIV infection [129]. Additionally, in an immunodeficient mouse model, transfection of HERV-K-ENV into the neural stem cells led to suppression of TNF- α expression and microglia activation, accompanied by improved neurobehavioral outcomes [129].

6 Recent insights on ERVs in brain diseases

It is essential to recognize that ERVs play active roles in brain functioning, in both healthy and pathological conditions. One study utilizing the GTEx RNA-seq dataset obtained from 948 individuals reported that HERV-K transcripts are most abundant in the brain, particularly in the cerebellum, pituitary, and cortex, among 54 different tissues [130]. Moreover, polymorphic HERV-K insertions were identified in over 2,000 human whole genomes, exhibiting considerable enrichment for tissue-specific gene expression and complex phenotypes, notably associated with neurological and immunological diseases [131]. In line with this, a growing body of evidence from clinical and preclinical investigations has recently emerged, highlighting the correlation between ERV activation and various brain disorders (Table 1), including neurodegenerative

diseases and neurodevelopmental and psychiatric disorders. These studies have illuminated potential pathogenic mechanisms, paving the way for future investigations and offering valuable insights into novel targets for disease treatment.

6.1 Neurodegenerative diseases

AD, the most common cause of dementia, is a progressive neurodegenerative disorder. It is characterized by the accumulation of amyloid-beta plaques and hyperphosphorylated Tau tangles within the brain [132]. AD models in *Drosophila* and mice with Tau pathology have shown a remarkable upregulation of TE expression, especially ERVs [133, 134]. A clinical research study involving 103 AD patients and 45 healthy controls reported that differentially expressed HERVs were dispersed throughout the entire genome and associated with the dysregulated gene expression in AD [135]. Recent studies have made progress in understanding how ERVs trigger AD [136-139]. For instance, HML-2 can specifically activate human TLR8 or mouse TLR7 through the sequence 5'-GUUGUGU-3' within its *ENV* gene, trigger neuroinflammation through the NF- κ B pathway, and ultimately activate caspase-3, leading to neuronal apoptosis. Coculture of neurons with microglia will accelerate this process *in vitro* [136]. One research group using *Drosophila* models has shown that mutations in the *flamenco* gene, which encodes piwi-interacting RNA (piRNA), or piRNA inhibition, can lead to a considerable upregulation of certain ERVs, which can result in neuronal death and symptoms similar to those seen in AD. Conversely, piRNA overexpression or ERV transposition activity inhibition can alleviate some of these symptoms [139]. Moreover, an increase in dsRNA and the activation of corresponding immune sensing mechanisms were observed in the astrocytes in both *Drosophila* and mouse AD models, as well as in postmortem brain

Table 1 Neuropsychological disorders with detectable alternations of HERV expressions.

Type	Disorders	Alternation of ERVs	Reference
Neurodegenerative diseases	AD	Upregulated ERVs including HERV-K	[135, 138]
	ALS	Upregulated HERV-K at RNA (<i>POL</i>) and protein level (<i>ENV</i>)	[141-143]
		Upregulated antibody level to specific epitope of HERV-H	[148]
	MS	Upregulated HERV-W in RNA and protein level (syncitin-1/HERV-W <i>ENV</i>)	[141, 155-157,161]
Psychiatric disorders	SCZ	Upregulated HERV-W in RNA (<i>POL</i> , <i>GAG</i> , <i>ENV</i>) and protein level (<i>ENV</i>)	[163-167, 185-186]
		Downregulated HERV-W <i>GAG</i>	[168]
		Upregulated HERV-K10 transcripts with reduction of methylation	[178-179]
		Upregulated ERV9 <i>POL</i>	[180, 185]
	BD	Upregulated HERV-W <i>ENV</i> transcripts	[166,186]
		Downregulated HERV-W <i>GAG</i>	[168]
		Upregulated HERV-K10 transcripts	[178]
		Upregulated ERV9 <i>POL</i>	[180]
	MDD	Downregulated HERV-W <i>GAG</i>	[168]
	SAD	Upregulated HERV-W	[164]
Neurodevelopmental disorders	ADHD	Upregulated HERV-H transcripts	[191]
	ASD	Upregulated HERV-H <i>ENV</i> transcripts	[194]
		Upregulated HERV-W <i>ENV</i> transcripts	[195]
Others	CIDP	Upregulated HERV-W transcripts (<i>ENV</i> , <i>POL</i>)	[201]
	MOG-IgG	Upregulated HERV-W <i>ENV</i>	[202]
	SBMA	Upregulated ERV-K proteins (<i>GAG</i> , integrase)	[204]
	CFS	Upregulated HERV-K <i>ENV</i> transcripts	[207]

AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; MS, multiple sclerosis; SCZ, schizophrenia; BD, bipolar disorder; MDD, major depressive disorder; SAD, schizoaffective disorder; ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; MOG-IgG, MOG-IgG-associated demyelinating disorders; SBMA, spinal and bulbar muscular atrophy; CFS, chronic fatigue syndrome.

samples from AD patients [137]. In *Drosophila*, the increased expression of ERVs corresponded to dsRNA formation, along with the disrupted heterochromatin formation, which is believed to cause neuroinflammation [137]. In another line of research, scientists used pluripotent stem cells (iPSCs) and cerebral organoids derived from the hippocampal tissue of AD patients. They observed abnormal neuronal proliferation and differentiation, accompanied by increased expression of HERV-K and DNA-RNA hybrids. This led to further activation of the cGAS-STING pathway and its downstream effector caspase-3, causing neuronal apoptosis. Remarkably, the

degradation of c-JUN, an upstream factor of this signaling pathway, significantly alleviated the AD phenotype [138].

ALS is a debilitating disease characterized by motor neuron degeneration, leading to progressive muscle weakness and ultimately resulting in respiratory failure [140]. The activation of HERV-K reportedly is linked to ALS, with numerous studies reporting higher levels of HERV-K antibodies and transcripts in the serum and cerebrospinal fluid (CSF) of ALS patients than in healthy controls [141-143]. However, some studies report no significant difference in the HERV-K transcripts between ALS patients

and healthy controls, suggesting potential heterogeneity in the disease [144, 145]. The pathogenesis of ALS is often associated with the TAR-DNA-Binding protein (TDP-43), which plays a critical role in maintaining the physiological function of motor neurons [146]. In *Drosophila*, both TDP-43 function loss and gain can trigger an ALS-like phenotype, highlighting its critical role and dosage sensitivity in disease progression [146]. A higher expression of HERV-K and TDP-43 was detected in the postmortem brain tissue of patients with HIV infection than in the control group with chronic systemic illness [147]. The amount of HERV-H and TDP-43 antibodies binding to different epitope fragments in the plasma of ALS patients increased significantly as compared to that of the healthy controls, and as the disease progressed, the two antibodies showed a positive correlation [148]. The interaction between TDP-43 and Dicer-2 is key in repressing ERVs in the *Drosophila* motor system [146]. Interestingly, the neurotoxic effect of TDP-43 overexpression is stronger in glial cells than in neurons [149, 150]. In cases of ALS progression, ERV and TDP-43 can stimulate each other, exacerbating disease progression [151]. Moreover, researchers have shown that full-length ERV, along with excessive TDP-43, can spread from one lesion to other locations *in vitro*. This migration can initiate the onset of disease in cells that were previously healthy [151], potentially contributing to disease progression.

MS is an auto-immune demyelinating disease characterized by chronic neuroinflammation [152]. A research using a mouse model revealed that HERV-W ENV overexpression negatively impacts the demyelination and regeneration process [153]. Further studies have shown that HERV-W ENV can activate the microglia, increase the inflammatory factors, reduce the levels of neuroprotective factors, and impair the ability of microglia to clear myelin debris,

suggesting a potential pathological link between HERV-W and MS [154]. Clinical studies have shown that HERV-W specific RNAs were significantly higher in autopsied brain tissues from MS patients than in the healthy controls [155]. The antigenic peptides of HERV-W were elevated in the serum of MS patients, and the syncytin-1 levels were also increased in the PBMCs of MS patients [156, 157]. Moreover, numerous studies have suggested that exogenous viral infections participate in the onset of MS, and also interact with ERV activation [158-161]. For instance, a clinical study has shown that MS patients had elevated HERV-W ENV levels in immune cells as compared to healthy donors. Additionally, this study found a significant correlation between the titers of human herpesvirus 6 (HHV-6) antibodies and HERV-W ENVs in the immune cells of these MS patients [161], suggesting a potential interaction between exogenous viral infections and ERV activation in MS pathogenesis.

6.2 Schizophrenia and other psychiatric disorders

A hypothetical model proposed that psychiatric symptoms could result from ERV activation triggered by traumatic experiences or viral infections [162]. Recent research has made promising progress in unveiling the association between ERVs and psychiatric disorders, with SCZ providing the most compelling evidence. HERV-W, distinct from other HERVs, is implicated in SCZ pathogenesis, as detectable HERV-W expression has been reported in the CSF and plasma of SCZ patients. This included transcripts with coding potentials such as *POL* [163], *GAG* [164], and *ENV* [165]. Besides body fluids, researches on the postmortem brain of SCZ patients have identified an elevated transcription level of HERV-W in the frontal cortex [163], anterior cingulate cortex (ACC), hippocampus,

and orbitofrontal cortex [166]. In addition to the changes in the transcriptional level, the expression of both the GAG and envelope proteins of HERV-W was detected in the serum in some cases [167]. However, contrasting reports exist, with one study indicating a reduction in HERV-W GAG protein expression in the neurons and astrocytes of the ACC and hippocampus in SCZ patients [168]. These conflicting findings underscore the complex role of HERV-W in psychiatric disorders and highlight the need for further investigation.

As previously discussed, the de-repression of ERVs is tightly linked to inflammation and immune responses. This association is also evident in the context of psychiatric disorders. In SCZ, patients can be categorized into inflammatory subgroups based on the presence of HERV-W ENV antigenemia, which is associated with a distinct disease onset and symptom profiles [169]. Another study has reported a correlation between HERV-W GAG and ENV antigenemia levels, C-reactive protein levels, and cognitive impairment among SCZ patients [167]. From a mechanistic perspective, recent research in neuronal cells has unveiled the role of the linc01930/cGAS/STING pathway in the immune activation triggered by HERV-W ENV in recent-onset SCZ [170]. Furthermore, HERV-W induces a calcium ion influx *in vitro* by elevating the expression of small conductance Ca^{2+} -activated K^+ type 2 channels (SK2) [171], small conductance Ca^{2+} -activated K^+ channel protein 3 (SK3) [172], and transient receptor potential cation channel subfamily C member 3 (TRPC3) [173], which are factors closely linked to SCZ [174, 175]. Beyond these impacts on the ion channels, ERVWE1 has been demonstrated to modify the density and morphology of dendritic spines through the inhibition of Wnt/JNK non-canonical pathway in SCZ [176]. A recent study also revealed that ERVWE1 may be implicated in the

pathophysiology by inducing ferroptosis [177]. These findings provide a deeper understanding of the complex molecular mechanisms underlying the role of ERVs in SCZ.

Besides HERV-W, several other ERVs have been implicated in SCZ, either through their own expression or by influencing adjacent genes. For instance, HERV-K10, a subgroup of the HML-2 family, is considerably overexpressed in the brains of SCZ patients [178]. This observation aligns with the findings of an independent study that reported lower DNA methylation levels of HERV-K in the blood cells of SCZ patients [179]. Moreover, the ERV9 *POL* gene expression has been detected in patients with recent-onset SCZ [180]. Apart from the expression aspect, genetic evidences were reported on the relationship between HERV and SCZ, which implicate the potential mechanisms. For example, HsERV was identified as an enhancer that regulates the expression of the *PRODH* gene [181], a candidate gene for SCZ [182], which encodes proline dehydrogenase. HERV-K102, known for its transcriptional activity in the brain, overlaps with loci susceptible to SCZ [183]. Furthermore, an earlier onset of SCZ is associated with a higher frequency of HERV-K115 insertions [184].

Notably, some of the results including the expression difference and mechanisms, have also been established in patients with BD [166, 168, 178, 185, 186], major depression disorder [168], and schizoaffective disorder [164], suggesting a more general effect of ERVs in the mental homeostasis. These findings collectively highlight the multifaceted roles of ERVs in the pathogenesis of psychiatric disorders. The role of antipsychotics in regulating HERV expression provides further evidence of their involvement in SCZ. Chlorpromazine is a typical medication for SCZ, and it has been shown to increase the DNA methylation levels in HERV-K in a dose-dependent manner in patients with multi-episode SCZ [179].

Additionally, as the antiviral activity has been validated on both chlorpromazine [187] and VPA [188], it would be interesting to consider whether their therapeutic effects include influences on ERV activity. It is interesting to note that evidence suggests RNA deaminases, such as APOBECs, play protective roles against ERV activation in both human and mouse cells [189] [190], indicating a potential for future therapeutic development.

6.3 Neurodevelopmental disorders

Neurodevelopmental disorders (NDDs) are thought to emerge from the intricate interplay of genetic susceptibility, maternal immune activation, and environmental risk factors. The unique role of ERVs in orchestrating these elements implies their potential importance in the pathogenesis of NDDs. Indeed, substantial evidence has established a correlation between ERVs and NDDs. For instance, in patients with attention deficit hyperactivity disorder (ADHD), a common NDD characterized by the executive dysfunction and persistent inattention, the HERV-H expression is elevated in the PBMCs of these patients [191]. Intriguingly, treatment with methylphenidate results in reduced transcriptional activity of HERV-H, coinciding with the observed improvement in ADHD symptoms [192, 193].

Similarly, differential expression of HERVs has also been observed in ASD. ASD is a pervasive developmental disorder with major symptoms of deficits in social interaction and communication. In ASD patients, the abnormality of ERVs activity is manifested as an elevation of HERV-H expression [194, 195] and a reduction in HERV-W expression in PBMCs [195]. Moreover, a high expression of HERV-H has been linked to severe speech and motor deficits [195], whereas an anti-HERV-W immune response negatively correlates with social and adaptive competence in individuals with ASD [196]. These findings

have been preliminarily validated in two commonly used ASD mouse models, BTBR T+tf/J inbred mice and CD-1 outbred mice with in-utero treatment of valproic acid (VPA). These models exhibit a relatively high expression of two murine ERVs, IAPs and Type II early transposons (ETns), at the whole embryo level, which persists in the brain and blood in adulthood [197]. Notably, the study has shown transgenerational inheritance via maternal lineage in mice [198], aligning with the observation that human ASD patients and their mothers share abnormal ERV expression patterns [199]. Most importantly, ERV and cytokine expression in PBMCs from ASD patients and their parents can be modulated upon drug exposure [200]. Given the abovementioned evidence, ERVs hold promise as both biomarker and therapeutic targets for NDDs.

6.4 Others

Beyond the neuropsychiatric disorders mentioned previously, ERV activation has also been detected in a range of other brain disorders, including progressive supranuclear palsy [139], chronic inflammatory demyelinating polyradiculoneuropathy [201], MOG-IgG-associated demyelinating disorders [202], and sporadic Creutzfeldt-Jakob disease [203], a rare and fatal neurodegenerative disorder. ERVs are also associated with spinal and bulbar muscular atrophy [204] and myalgic encephalomyelitis, also known as chronic fatigue syndrome [205-207]. These findings highlight the extensive influence of ERV activation across a wide spectrum of disease processes associated with neuronal dysfunction.

7 Conclusion and perspectives

ERVs are the remnants of ancient viral invasions and constitute a significant portion of mammalian

genomes. Throughout evolution, host organisms have developed intricate epigenetic strategies, notably the interplay between SETDB1-mediated H3K9me3 and DNA methylation, to suppress the activity of ERVs. This suppression controls their expansion and potential destabilization of the genome. Simultaneously, certain ERVs have evolved to serve beneficial roles for the host, contributing to the development of other physiological processes. However, under challenging or pathological conditions, ERVs can become aberrantly activated and contribute to disease progression. Why are ERVs induced by stress or infection? This question can be approached from two perspectives. Firstly, considering HERV integration into the human genome as ancient viruses, it implies a certain adaptability, especially among evolutionarily young HERVs that may retain regulatory elements responsive to environmental cues, particularly those associated with infections or inflammation. This aspect may help explain some of HERV's beneficial roles, such as their involvement in immune defense mechanisms. Secondly, HERVs are primarily silenced by epigenetic mechanisms. Therefore, environmental stressors that can alter or compromise these epigenetic restrictions may contribute to HERV activation or de-repression. This, in turn, may lead to pathological consequences and contribute to the development of neuropsychological disorders.

Another critical question revolves around the molecular mechanisms underlying HERV activation. According to the literature, inflammation pathways play an important role in HERV activation, but their involvement can be both causal and consequential. One of the most compelling pieces of evidence supporting the potential causal role of the inflammatory pathway in HERV activation comes from bioinformatic analyses on the LTR regions of HERVs,

particularly HERVKs. These analyses have revealed the enrichment of inflammatory transcription factor sites, and these LTRs can be transcriptionally activated by inflammatory factors, contributing to ERV activation under pathological conditions. Nevertheless, there is also evidence suggesting that ERV activation, in turn, can induce an inflammatory response, thus activating the related molecular pathways such as Toll-like receptor signaling. Thus, a complex interplay exists between the inflammatory pathways and ERV activation. Identifying the causal molecular pathway underlying ERV activation in response to stress is imperative for future studies in the field.

Upon activation, HERVs can act as transcriptional regulatory elements, generate dsRNAs/dsDNAs, and form functional viral proteins or viral-like particles. The outcomes of HERV activation vary depending on the involved tissue and cell types. Studies on intestinal stem cells [100] and Schwann cells [122] have shown that cell death following ERV activation through ZBP1-dependent necroptosis. Additionally, the direct introduction of HERV-K RNA into the CSF induces neurodegeneration [136]. Although these studies provide evidence for cell death following ERV activation, many other studies lack direct evidence of cell death, but inflammation appears to be a commonly observed event. The brain, an organ with heightened ERV activity, often exhibits neuroinflammation, a common feature in many neuropsychiatric disorders. ERV activation is increasingly recognized as a significant contributor to the pathogenesis of several such conditions.

One intriguing contemplation is whether HERV activation events would be considered as an organismal defense system by eliminating stressed or infected cells, or as a potential self-escape mechanism from unfavorable conditions. As mentioned previously, there is evidence

indicating that ERV activation can lead to cell death. However, whether this serves as a defense mechanism or as a pathological consequence remains an open question. In exogenous viruses, such as the herpes virus, DNA damage can stimulate or even create a conducive environment for viral replication [208]. For HERVs, evidence from an *in vitro* aging model indicates the production of retrovirus-like particles (RVLPs) and their transmission from senescent cells to younger cells [101]. Thus, conducting further studies first to ascertain whether such transmission occur *in vivo* is essential. Only then can we consider whether such activation represents an “escape” mechanism or an “infection” event.

In this review, we have gathered evidence for ERV activation across a broad spectrum of neuropsychiatric disorders, including AD, ALS, MS, ASD, SCZ, BD, and others. Beyond mere correlation, recent studies have begun to unravel the underlying mechanisms and seek intervention targets for potential therapeutic exploration. However, numerous challenges still persist in this field. One such challenge is the species specificity of ERVs during evolution. Rodents, commonly used as animal models for mechanistic studies, harbor abundant ERVs (IAPs, Mulv, and so on) not present in humans, thus limiting the applicability of the findings from rodent models to human diseases. Secondly, ERVs, like other TEs, exist in multiple copies within the genome. Even with advanced bioinformatic analysis, accurately pinpointing the precise location of a given ERV in the genome remains a problem that warrants further attention and improvement. Third-generation sequencing may offer a future solution. Lastly, despite the advances in genomic editing technology, manipulating the activity of any specific type of ERVs, particularly in the brain, remains a formidable task.

Deepening our understanding of the ERV activation mechanisms and their roles in these disorders could shed light on the developmental and progression pathways of these conditions, potentially paving the way for the development of novel therapeutic interventions.

Declaration of conflicting interests

The authors declare no conflict of interest.

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JL, LL, and XL prepared the first draft of the manuscript, and they share corresponding authorship. YZ, DS, CZ participated in writing and revision. YJ participated in and supervised the study throughout. All authors commented on previous versions of the manuscript and approved the final version.

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There is no data for this review.

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- [1] Han, M., Perkins, M. H., Novaes, L. S., Xu, T., Chang, H. Advances in transposable elements: From mechanisms to applications in mammalian genomics. *Frontiers in Genetics*, **2023**, 14: 1290146.
- [2] Chuong, E. B., Elde, N. C., Feschotte, C. Regulatory activities of transposable elements: From conflicts to benefits. *Nature Reviews Genetics*, **2017**, 18(2): 71–86.
- [3] Mager, D. L., Stoye, J. P. Mammalian endogenous retroviruses. *Microbiology Spectrum*, **2015**, 3(1): p. MDNA3-0009-2014.
- [4] Duffy, S., Shackelton, L. A., Holmes, E. C. Rates of evolutionary change in viruses: Patterns and determinants. *Nature Reviews Genetics*, **2008**, 9(4): 267–276.
- [5] Zheng, J. L., Wei, Y. T., Han, G. Z. The diversity and evolution of retroviruses: Perspectives from viral “fossils”. *Virologica Sinica*, **2022**, 37(1): 11–18.
- [6] Gifford, R. J., Blomberg, J., Coffin, J. M., Fan, H., Heidmann, T., Mayer, J., Stoye, J., Tristem, M., Johnson, W. E. Nomenclature for endogenous retrovirus (ERV) loci. *Retrovirology*, **2018**, 15: 59.
- [7] Garcia-Montojo, M., Doucet-O’Hare, T., Henderson, L., Nath, A. Human endogenous retrovirus-K (HML-2): A comprehensive review. *Critical Reviews in Microbiology*, **2018**, 44(6): 715–738.
- [8] Giménez-Orenga, K., Oltra, E. Human endogenous retrovirus as therapeutic targets in neurologic disease. *Pharmaceuticals*, **2021**, 14(6): 495.
- [9] Zhu, Y. Y., Sun, D. J., Jakovcevski, M., Jiang, Y. Epigenetic mechanism of SETDB1 in brain: Implications for neuropsychiatric disorders. *Translational Psychiatry*, **2020**, 10: 115.
- [10] Markouli, M., Strepkos, D., Chlamydas, S., Piperi, C. Histone lysine methyltransferase SETDB1 as a novel target for central nervous system diseases. *Progress in Neurobiology*, **2021**, 200: 101968.
- [11] Matsui, T., Leung, D., Miyashita, H., Maksakova, I. A., Miyachi, H., Kimura, H., Tachibana, M., Lorincz, M. C., Shinkai, Y. Proviral silencing in embryonic stem cells requires the histone methyltransferase ESET. *Nature*, **2010**, 464(7290): 927–931.
- [12] Gautam, P., Yu, T., Loh, Y. H. Regulation of ERVs in pluripotent stem cells and reprogramming. *Current Opinion in Genetics & Development*, **2017**, 46: 194–201.
- [13] Wolf, G., Yang, P., Fuchtbauer, A. C., Fuchtbauer, E. M., Silva, A. M., Park, C., Wu, W., Nielsen, A. L., Pedersen, F. S., MacFarlan, T. S. The KRAB zinc finger protein ZFP809 is required to initiate epigenetic silencing of endogenous retroviruses. *Genes & Development*, **2015**, 29(5): 538–554.
- [14] Wolf, D., Goff, S. P. Embryonic stem cells use ZFP809 to silence retroviral DNAs. *Nature*, **2009**, 458(7242): 1201–1204.
- [15] Jacobs, F. M. J., Greenberg, D., Nguyen, N., Haeussler, M., Ewing, A. D., Katzman, S., Paten, B., Salama, S. R., Haussler, D. An evolutionary arms race between KRAB zinc-finger genes ZNF91/93 and SVA/L1 retrotransposons. *Nature*, **2014**, 516(7530): 242–245.
- [16] Thomas, J. H., Schneider, S. Coevolution of retroelements and tandem zinc finger genes. *Genome Research*, **2011**, 21(11): 1800–1812.
- [17] Imbeault, M., Helleboid, P. Y., Trono, D. KRAB zinc-finger proteins contribute to the evolution of gene regulatory networks. *Nature*, **2017**, 543(7646): 550–554.
- [18] Rowe, H. M., Jakobsson, J., Mesnard, D., Rougemont, J., Reynard, S., Aktas, T., Maillard, P. V., Layard-Liesching, H., Verp, S., Marquis, J. et al. KAP1 controls endogenous retroviruses in embryonic stem cells. *Nature*, **2010**, 463(7278): 237–240.
- [19] Tie, C. H., Fernandes, L., Conde, L., Robbez-Masson, L., Sumner, R. P., Peacock, T., Rodriguez-Plata, M. T., Mickute, G., Gifford, R., Towers, G. J. et al. KAP1 regulates endogenous retroviruses in adult human cells and contributes to innate immune control. *EMBO Rep*, **2018**, 19(10): e45000.
- [20] Li, J. Q., Zheng, S. H., Dong, Y. H., Xu, H., Zhu, Y. Y., Weng, J., Sun, D. J., Wang, S. Y., Xiao, L., Jiang, Y. Histone methyltransferase SETDB1 regulates the development of cortical Htr3a-positive interneurons and mood behaviors. *Biological Psychiatry*, **2023**, 93(3): 279–290.
- [21] Tan, S. L., Nishi, M., Ohtsuka, T., Matsui, T.,

- Takemoto, K., Kamio-Miura, A., Aburatani, H., Shinkai, Y., Kageyama, R. Essential roles of the histone methyltransferase ESET in the epigenetic control of neural progenitor cells during development. *Development*, **2012**, 139(20): 3806–3816.
- [22] Jönsson, M. E., Garza, R., Sharma, Y., Petri, R., Södersten, E., Johansson, J. G., Johansson, P. A., Atacho, D. A., Piracs, K., Madsen, S. et al. Activation of endogenous retroviruses during brain development causes an inflammatory response. *EMBO J*, **2021**, 40(9): e106423.
- [23] Zhao, S., Lu, J. W., Pan, B., Fan, H. T., Byrum, S. D., Xu, C. X., Kim, A., Guo, Y. R., Kanchi, K. L., Gong, W. D. et al. TNRC18 engages H3K9me3 to mediate silencing of endogenous retrotransposons. *Nature*, **2023**, 623(7987): 633–642.
- [24] Yang, bin xia, EL Farran, C., Guo, hong chao, Yu, T., Fang, hai tong, Wang, hao fei, Schlesinger, S., Seah, Y., Goh, G., Neo, S. et al. Systematic identification of factors for provirus silencing in embryonic stem cells. *Cell*, **2015**, 163(1): 230–245.
- [25] Tessier, S., Ferhi, O., Geoffroy, M. C., González-Prieto, R., Canat, A., Quentin, S., Pla, M., Niwa-Kawakita, M., Bercier, P., Rérolle, D. et al. Exploration of nuclear body-enhanced sumoylation reveals that PML represses 2-cell features of embryonic stem cells. *Nature Communications*, **2022**, 13: 5726.
- [26] Rosendorff, A., Sakakibara, S., Lu, S. X., Kieff, E., Xuan, Y., DiBacco, A., Shi, Y. J., Shi, Y., Gill, G. NXP-2 association with SUMO-2 depends on lysines required for transcriptional repression. *Proceedings of the National Academy of Sciences of the United States of America*, **2006**, 103(14): 5308–5313.
- [27] Fukuda, K., Okuda, A., Yusa, K., Shinkai, Y. A CRISPR knockout screen identifies SETDB1-target retroelement silencing factors in embryonic stem cells. *Genome Research*, **2018**, 28(6): 846–858.
- [28] Tchasovnikarova, I. A., Timms, R. T., Matheson, N. J., Wals, K., Antrobus, R., Göttgens, B., Dougan, G., Dawson, M. A., Lehner, P. J. Epigenetic silencing by the HUSH complex mediates position-effect variegation in human cells. *Science*, **2015**, 348(6242): 1481–1485.
- [29] Walsh, C.P., J.R. Chaillet, and T.H. Bestor. Transcription of IAP endogenous retroviruses is constrained by cytosine methylation. *Nat Genet*, **1998**, 20(2): 116–117.
- [30] Lei, H., Oh, S. P., Okano, M., Jüttermann, R., Goss, K. A., Jaenisch, R., Li, E. *De novo DNA cytosine methyltransferase activities in mouse embryonic stem cells*. *Development*, **1996**, 122(10): 3195–3205.
- [31] Barau, J., Teissandier, A., Zamudio, N., Roy, S., Nalesso, V., Hérault, Y., Guillou, F., Bourc'h, D. The DNA methyltransferase DNMT3C protects male germ cells from transposon activity. *Science*, **2016**, 354(6314): 909–912.
- [32] Min, B., Park, J. S., Jeong, Y. S., Jeon, K., Kang, Y. K. Dnmt1 binds and represses genomic retroelements via DNA methylation in mouse early embryos. *Nucleic Acids Research*, **2020**, 48(15): 8431–8444.
- [33] Chen, T. P., Ueda, Y., Dodge, J. E., Wang, Z. J., Li, E. Establishment and maintenance of genomic methylation patterns in mouse embryonic stem cells by Dnmt3a and Dnmt3b. *Molecular and Cellular Biology*, **2003**, 23(16): 5594–5605.
- [34] Bourc'h, D., Bestor, T. H. Meiotic catastrophe and retrotransposon reactivation in male germ cells lacking Dnmt3L. *Nature*, **2004**, 431(7004): 96–99.
- [35] Ito, S., D'Alessio, A. C., Taranova, O. V., Hong, K., Sowers, L. C., Zhang, Y. Role of Tet proteins in 5mC to 5hmC conversion, ES-cell self-renewal and inner cell mass specification. *Nature*, **2010**, 466(7310): 1129–1133.
- [36] He, Y. F., Li, B. Z., Li, Z., Liu, P., Wang, Y., Tang, Q. Y., Ding, J. P., Jia, Y. Y., Chen, Z. C., Li, L. et al. Tet-mediated formation of 5-carboxylcytosine and its excision by TDG in mammalian DNA. *Science*, **2011**, 333(6047): 1303–1307.
- [37] Leung, D., Du, T. T., Wagner, U., Xie, W., Lee, A. Y., Goyal, P., Li, Y. J., Szulwach, K. E., Jin, P., Lorincz, M. C. et al. Regulation of DNA methylation turnover at LTR retrotransposons and imprinted loci by the histone methyltransferase Setdb1. *Proceedings of the National Academy of Sciences of the United States of America*, **2014**, 111(18): 6690–6695.
- [38] Dong, K. B., Maksakova, I. A., Mohn, F., Leung, D., Appanah, R., Lee, S., Yang, H. W., Lam, L. L., Mager, D. L., Schübeler, D. et al. DNA methylation in ES cells requires the lysine methyltransferase G9a but not its catalytic activity. *The EMBO Journal*, **2008**, 27(20): 2691–2701.
- [39] Gaudet, F., Rideout, W. M. III, Meissner, A., Dausman, J., Leonhardt, H., Jaenisch, R. Dnmt1 expression in

- pre- and postimplantation embryogenesis and the maintenance of IAP silencing. *Molecular and Cellular Biology*, **2004**, 24(4): 1640–1648.
- [40] Kurihara, Y., Kawamura, Y., Uchijima, Y., Amamo, T., Kobayashi, H., Asano, T., Kurihara, H. Maintenance of genomic methylation patterns during preimplantation development requires the somatic form of DNA methyltransferase 1. *Developmental Biology*, **2008**, 313(1): 335–346.
- [41] Sharif, J., Muto, M., Takebayashi, S. I., Suetake, I., Iwamatsu, A., Endo, T. A., Shinga, J., Mizutani-Koseki, Y., Toyoda, T., Okamura, K. et al. The SRA protein Np95 mediates epigenetic inheritance by recruiting Dnmt1 to methylated DNA. *Nature*, **2007**, 450(7171): 908–912.
- [42] Rowe, H. M., Trono, D. Dynamic control of endogenous retroviruses during development. *Virology*, **2011**, 411(2): 273–287.
- [43] Okano, M., Bell, D. W., Haber, D. A., Li, E. DNA methyltransferases Dnmt3a and Dnmt3b are essential for *de novo* methylation and mammalian development. *Cell*, **1999**, 99(3): 247–257.
- [44] Suetake, I., Shinozaki, F., Miyagawa, J., Takeshima, H., Tajima, S. DNMT3L stimulates the DNA methylation activity of Dnmt3a and Dnmt3b through a direct interaction. *Journal of Biological Chemistry*, **2004**, 279(26): 27816–27823.
- [45] Rowe, H. M., Friedli, M., Offner, S., Verp, S., Mesnard, D., Marquis, J., Aktas, T., Trono, D. *De novo* DNA methylation of endogenous retroviruses is shaped by KRAB-ZFPs/KAP1 and ESET. *Development*, **2013**, 140(3): 519–529.
- [46] Sharif, J., Endo, T., Nakayama, M., Karimi, M., Shimada, M., Katsuyama, K., Goyal, P., Brind'Amour, J., Sun, M. A., Sun, Z. X. et al. Activation of endogenous retroviruses in Dnmt1^{−/−}ESCs involves disruption of SETDB1-mediated repression by NP95 binding to hemimethylated DNA. *Cell Stem Cell*, **2016**, 19(1): 81–94.
- [47] Groh, S., Schotta, G. Silencing of endogenous retroviruses by heterochromatin. *Cellular and Molecular Life Sciences*, **2017**, 74(11): 2055–2065.
- [48] Wang, Z. Y., Fan, R., Russo, A., Cernilogar, F. M., Nuber, A., Schirge, S., Shcherbakova, I., Dzhylyanova, I., Ugur, E., Anton, T. et al. Dominant role of DNA methylation over H3K9me3 for IAP silencing in endoderm. *Nature Communications*, **2022**, 13: 5447.
- [49] Ohtani, H., Liu, M. M., Zhou, W. D., Liang, G. N., Jones, P. A. Switching roles for DNA and histone methylation depend on evolutionary ages of human endogenous retroviruses. *Genome Research*, **2018**, 28(8): 1147–1157.
- [50] Hutnick, L. K., Golshani, P., Namihira, M., Xue, Z. G., Matynia, A., Yang, X. W., Silva, A. J., Schweizer, F. E., Fan, G. P. DNA hypomethylation restricted to the murine forebrain induces cortical degeneration and impairs postnatal neuronal maturation. *Human Molecular Genetics*, **2009**, 18(15): 2875–2888.
- [51] Bulut-Karslioglu, A., De La Rosa-Velázquez, I., Ramirez, F., Barenboim, M., Onishi-Seebacher, M., Arand, J., Galán, C., Winter, G., Engist, B., Gerle, B. et al. Suv39h-dependent H3K9me3 marks intact retrotransposons and silences LINE elements in mouse embryonic stem cells. *Molecular Cell*, **2014**, 55(2): 277–290.
- [52] Maksakova, I. A., Thompson, P. J., Goyal, P., Jones, S. J., Singh, P. B., Karimi, M. M., Lorincz, M. C. Distinct roles of KAP1, HP1 and G9a/GLP in silencing of the two-cell-specific retrotransposon MERV1 in mouse ES cells. *Epigenetics & Chromatin*, **2013**, 6(1): 15.
- [53] Loyola, A., Tagami, H., Bonaldi, T., Roche, D., Quivy, J. P., Imhof, A., Nakatani, Y., Dent, S. Y. R., Almouzni, G. The HP1α-CAF1-SetDB1-containing complex provides H3K9me1 for Suv39-mediated K9me3 in pericentric heterochromatin. *EMBO Reports*, **2009**, 10(7): 769–775.
- [54] Leeb, M., Pasini, D., Novatchkova, M., Jaritz, M., Helin, K., Wutz, A. Polycomb complexes act redundantly to repress genomic repeats and genes. *Genes & Development*, **2010**, 24(3): 265–276.
- [55] Elsässer, S. J., Noh, K. M., Diaz, N., Allis, C. D., Banaszynski, L. A. Histone H3.3 is required for endogenous retroviral element silencing in embryonic stem cells. *Nature*, **2015**, 522(7555): 240–244.
- [56] Sugimoto, J., Sugimoto, M., Bernstein, H., Jinno, Y., Schust, D. A novel human endogenous retroviral protein inhibits cell-cell fusion. *Scientific Reports*, **2013**, 3: 1462.
- [57] Esnault, C., Priet, S., Ribet, D., Vernochet, C., Bruls, T., Lavalie, C., Weissenbach, J., Heidmann, T. A placenta-specific receptor for the fusogenic, endogenous

- retrovirus-derived, human syncytin-2. *Proceedings of the National Academy of Sciences of the United States of America*, **2008**, 105(45): 17532–17537.
- [58] Frank, J. A., Singh, M., Cullen, H. B., Kirou, R. A., Benkaddour-Boumzaouad, M., Cortes, J. L., Garcia Pérez, J., Coyne, C. B., Feschotte, C. Evolution and antiviral activity of a human protein of retroviral origin. *Science*, **2022**, 378(6618): 422–428.
- [59] Johnson, W. E. Origins and evolutionary consequences of ancient endogenous retroviruses. *Nature Reviews Microbiology*, **2019**, 17(6): 355–370.
- [60] Grow, E. J., Flynn, R. A., Chavez, S. L., Bayless, N. L., Wossidlo, M., Wesche, D. J., Martin, L., Ware, C. B., Blish, C. A., Chang, H. Y. et al. Intrinsic retroviral reactivation in human preimplantation embryos and pluripotent cells. *Nature*, **2015**, 522(7555): 221–225.
- [61] Honda, S., Hatamura, M., Kunimoto, Y., Ikeda, S., Minami, N. Chimeric PRMT6 protein produced by an endogenous retrovirus promoter regulates cell fate decision in mouse preimplantation embryos. *Biol Reprod*, **2024**: ioae002.
- [62] Zhang, W. C., Wu, J., Ward, M., Yang, S., Chuang, Y. A., Xiao, M. F., Li, R. J., Leahy, D., Worley, P. Structural basis of arc binding to synaptic proteins: Implications for cognitive disease. *Neuron*, **2015**, 86(2): 490–500.
- [63] Pastuzyn, E. D., Day, C. E., Kearns, R. B., Kyrke-Smith, M., Taibi, A. V., McCormick, J., Yoder, N., Belnap, D. M., Erlendsson, S., Morado, D. R. et al. The neuronal gene arc encodes a repurposed retrotransposon gag protein that mediates intercellular RNA transfer. *Cell*, **2018**, 172(1–2): 275–288.e18.
- [64] Ashley, J., Cordy, B., Lucia, D., Fradkin, L. G., Budnik, V., Thomson, T. Retrovirus-like gag protein Arc1 binds RNA and traffics across synaptic boutons. *Cell*, **2018**, 172(1–2): 262–274.e11.
- [65] Hendrickson, P. G., Doráis, J. A., Grow, E. J., Whiddon, J. L., Lim, J. W., Wike, C. L., Weaver, B. D., Pflueger, C., Emery, B. R., Wilcox, A. L. et al. Conserved roles of mouse DUX and human DUX4 in activating cleavage-stage genes and MERV1/HERV1 retrotransposons. *Nature Genetics*, **2017**, 49(6): 925–934.
- [66] MacFarlan, T. S., Gifford, W. D., Driscoll, S., Lettieri, K., Rowe, H. M., Bonanomi, D., Firth, A., Singer, O., Trono, D., Pfaff, S. L. Embryonic stem cell potency fluctuates with endogenous retrovirus activity. *Nature*, **2012**, 487(7405): 57–63.
- [67] Sakashita, A., Kitano, T., Ishizu, H., Guo, Y. J., Masuda, H., Ariura, M., Murano, K., Siomi, H. Transcription of MERV1 retrotransposons is required for preimplantation embryo development. *Nature Genetics*, **2023**, 55(3): 484–495.
- [68] Chuong, E. B., Karim Rumi, M. A., Soares, M. J., Baker, J. C. Endogenous retroviruses function as species-specific enhancer elements in the placenta. *Nature Genetics*, **2013**, 45(3): 325–329.
- [69] Chuong, E. B., Elde, N. C., Feschotte, C. Regulatory evolution of innate immunity through co-option of endogenous retroviruses. *Science*, **2016**, 351(6277): 1083–1087.
- [70] Zhang, Y., Li, T., Preissl, S., et al. Transcriptionally active HERV-H retrotransposons demarcate topologically associating domains in human pluripotent stem cells. *Nat Genet*, **2019**, 51(9): 1380–1388.
- [71] Song, M., Pebworth, M. P., Yang, X. Y., Abnoui, A., Fan, C. X., Wen, J., Rosen, J. D., Choudhary, M. N. K., Cui, X. K., Jones, I. R. et al. Cell-type-specific 3D epigenomes in the developing human cortex. *Nature*, **2020**, 587(7835): 644–649.
- [72] Downey, R. F., Sullivan, F. J., Wang-Johanning, F., Ambs, S., Giles, F. J., Glynn, S. A. Human endogenous retrovirus K and cancer: Innocent bystander or tumorigenic accomplice? *International Journal of Cancer*, **2015**, 137(6): 1249–1257.
- [73] Kassiotis, G. Endogenous retroviruses and the development of cancer. *The Journal of Immunology*, **2014**, 192(4): 1343–1349.
- [74] Büscher, K., Hahn, S., Hofmann, M., Trefzer, U., Özel, M., Sterry, W., Löwer, J., Löwer, R., Kurth, R., Denner, J. Expression of the human endogenous retrovirus-K transmembrane envelope, Rec and Np9 proteins in melanomas and melanoma cell lines. *Melanoma Research*, **2006**, 16(3): 223–234.
- [75] Wang-Johanning, F., Liu, J. S., Rycak, K., Huang, M., Tsai, K., Rosen, D. G., Chen, D. T., Lu, D. W., Barnhart, K. F., Johanning, G. L. Expression of multiple human endogenous retrovirus surface envelope proteins in ovarian cancer. *International Journal of Cancer*, **2007**, 120(1): 81–90.

- [76] Ejthadi, H. D., Martin, J. H., Junying, J., Roden, D. A., Lahiri, M., Warren, P., Murray, P. G., Nelson, P. N. A novel multiplex RT-PCR system detects human endogenous retrovirus-K in breast cancer. *Archives of Virology*, **2005**, 150(1): 177–184.
- [77] Golan, M., Hizi, A., Resau, J. H., Yaal-Hahoshen, N., Reichman, H., Keydar, I., Tsarfaty, I. Human endogenous retrovirus (HERV-K) reverse transcriptase as a breast cancer prognostic marker. *Neoplasia*, **2008**, 10(6): 521–IN2.
- [78] Depil, S., Roche, C., Dussart, P., Prin, L. Expression of a human endogenous retrovirus, HERV-K, in the blood cells of leukemia patients. *Leukemia*, **2002**, 16(2): 254–259.
- [79] Muster, T., Waltenberger, A., Grassauer, A., Hirschl, S., Caucig, P., Romirer, I., Födinger, D., Seppel, H., Schanab, O., Magin-Lachmann, C. et al. An endogenous retrovirus derived from human melanoma cells. *Cancer Research*, **2003**, 63(24): 8735–8741.
- [80] Büscher, K., Trefzer, U., Hofmann, M., Sterry, W., Kurth, R., Denner, J. Expression of human endogenous retrovirus K in melanomas and melanoma cell lines. *Cancer Research*, **2005**, 65(10): 4172–4180.
- [81] Mao, J., Zhang, Q., Wang, Y., Zhuang, Y., Xu, L., Ma, X., Guan, D., Zhou, J., Liu, J., Wu, X. et al. TERT activates endogenous retroviruses to promote an immunosuppressive tumour microenvironment. *EMBO Rep*, **2022**, 23(4): e52984.
- [82] Contreras-Galindo, R., Kaplan, M. H., Contreras-Galindo, A. C., Gonzalez-Hernandez, M. J., Ferlenghi, I., Giusti, F., Lorenzo, E., Gitlin, S. D., Dosik, M. H., Yamamura, Y. et al. Characterization of human endogenous retroviral elements in the blood of HIV-1-infected individuals. *Journal of Virology*, **2012**, 86(1): 262–276.
- [83] Jones, R. B., Garrison, K. E., Mujib, S., Mihajlovic, V., Aidarus, N., Hunter, D. V., Martin, E., John, V. M., Zhan, W., Faruk, N. F. et al. HERV-K-specific T cells eliminate diverse HIV-1/2 and SIV primary isolates. *Journal of Clinical Investigation*, **2012**, 122(12): 4473–4489.
- [84] Vincendeau, M., Göttendorfer, I., Schreml, J. M., Wetie, A. G., Mayer, J., Greenwood, A. D., Helfer, M., Kramer, S., Seifarth, W., Hadian, K. et al. Modulation of human endogenous retrovirus (HERV) transcription during persistent and *de novo* HIV-1 infection. *Retrovirology*, **2015**, 12: 27.
- [85] Srinivasachar Badarinarayan, S., Shcherbakova, I., Langer, S., Koepke, L., Preising, A., Hotter, D., Kirchhoff, F., Sparrer, K. M. J., Schotta, G., Sauter, D. HIV-1 infection activates endogenous retroviral promoters regulating antiviral gene expression. *Nucleic Acids Research*, **2020**, 48(19): 10890–10908.
- [86] Terry, S. N., Manganaro, L., Cuesta-Dominguez, A., Brinzevich, D., Simon, V., Mulder, L. C. F. Expression of HERV-K108 envelope interferes with HIV-1 production. *Virology*, **2017**, 509: 52–59.
- [87] Garrison, K. E., Jones, R. B., Meiklejohn, D. A., Anwar, N., Ndhlovu, L. C., Chapman, J. M., Erickson, A. L., Agrawal, A., Spotts, G., Hecht, F. M. et al. T cell responses to human endogenous retroviruses in HIV-1 infection. *PLoS Pathog*, **2007**, 3(11): e165.
- [88] SenGupta, D., Tandon, R., Vieira, R. G. S., Ndhlovu, L. C., Lown-Hecht, R., Ormsby, C. E., Loh, L., Jones, R. B., Garrison, K. E., Martin, J. N. et al. Strong human endogenous retrovirus-specific T cell responses are associated with control of HIV-1 in chronic infection. *Journal of Virology*, **2011**, 85(14): 6977–6985.
- [89] Sutkowski, N., Conrad, B., Thorley-Lawson, D. A., Huber, B. T. Epstein-barr virus transactivates the human endogenous retrovirus HERV-K18 that encodes a superantigen. *Immunity*, **2001**, 15(4): 579–589.
- [90] Dechaumes, A., Bertin, A., Sane, F., Levet, S., Varghese, J., Charvet, B., Gmyr, V., Kerr-Conte, J., Pierquin, J., Arunkumar, G. et al. Cocksackievirus-B4 infection can induce the expression of human endogenous retrovirus W in primary cells. *Microorganisms*, **2020**, 8(9): E1335.
- [91] Lima-Junior, D. S., Krishnamurthy, S. R., Bouladoux, N., Collins, N., Han, S. J., Chen, E. Y., Constantinides, M. G., Link, V. M., Lim, A. I., Enamorado, M. et al. Endogenous retroviruses promote homeostatic and inflammatory responses to the microbiota. *Cell*, **2021**, 184(14): 3794–3811.e19.
- [92] Manghera, M., Ferguson-Parry, J., Lin, R. T., Douville, R. N. NF- κ B and IRF1 induce endogenous retrovirus K expression via interferon-stimulated response elements in its 5' long terminal repeat. *Journal of Virology*, **2016**, 90(20): 9338–9349.
- [93] Kwon, D. N., Lee, Y. K., Greenhalgh, D. G., Cho, K. Lipopolysaccharide stress induces cell-type specific production of murine leukemia virus type-endogenous

- retroviral virions in primary lymphoid cells. *Journal of General Virology*, **2011**, 92(2): 292–300.
- [94] Manghera, M., Ferguson, J., Douville, R. ERVK polyprotein processing and reverse transcriptase expression in human cell line models of neurological disease. *Viruses*, **2015**, 7(1): 320–332.
- [95] Herrero, F., Mueller, F. S., Gruchot, J., Küry, P., Weber-Stadlbauer, U., Meyer, U. Susceptibility and resilience to maternal immune activation are associated with differential expression of endogenous retroviral elements. *Brain, Behavior, and Immunity*, **2023**, 107: 201–214.
- [96] Magiorkinis, G., Belshaw, R., Katzourakis, A. ‘There and back again’: Revisiting the pathophysiological roles of human endogenous retroviruses in the post-genomic era. *Philosophical Transactions of the Royal Society B: Biological Sciences*, **2013**, 368(1626): 20120504.
- [97] Herve, C. A., Lugli, E. B., Brand, A., et al. Autoantibodies to human endogenous retrovirus-K are frequently detected in health and disease and react with multiple epitopes. *Clin Exp Immunol*, **2002**, 128(1): 75–82.
- [98] Ejtehadi, H. D. The potential role of human endogenous retrovirus K10 in the pathogenesis of rheumatoid arthritis: A preliminary study. *Annals of the Rheumatic Diseases*, **2006**, 65(5): 612–616.
- [99] Freimanis, G., Hooley, P., Davari Ejtehadi, H., Ali, H. A., Veitch, A., Rylance, P. B., Alawi, A., Axford, J., Nevill, A., Murray, P. G. et al. A role for human endogenous retrovirus-K (HML-2) in rheumatoid arthritis: Investigating mechanisms of pathogenesis. *Clinical and Experimental Immunology*, **2010**, 160(3): 340–347.
- [100] Wang, R. C., Li, H. D., Wu, J. F., Cai, Z. Y., Li, B. Z., Ni, H. X., Qiu, X. F., Chen, H., Liu, W., Yang, Z. H. et al. Gut stem cell necroptosis by genome instability triggers bowel inflammation. *Nature*, **2020**, 580(7803): 386–390.
- [101] Liu, X. Q., Liu, Z. P., Wu, Z. M., Ren, J., Fan, Y. L., Sun, L., Cao, G., Niu, Y. Y., Zhang, B. H., Ji, Q. Z. et al. Resurrection of endogenous retroviruses during aging reinforces senescence. *Cell*, **2023**, 186(2): 287–304.e26.
- [102] Paluvai, H., Di Giorgio, E., Brancolini, C. The histone code of senescence. *Cells*, **2020**, 9(2): 466.
- [103] Di Giorgio, E., Paluvai, H., Dalla, E., Ranzino, L., Renzini, A., Moresi, V., Minisini, M., Picco, R., Brancolini, C. HDAC4 degradation during senescence unleashes an epigenetic program driven by AP-1/p300 at selected enhancers and super-enhancers. *Genome Biology*, **2021**, 22(1): 129.
- [104] Colombo, A. R., Elias, H. K., Ramsingh, G. Senescence induction universally activates transposable element expression. *Cell Cycle*, **2018**, 17(14): 1846–1857.
- [105] Guan, Y. T., Zhang, C., Lyu, G. L., Huang, X. K., Zhang, X. B., Zhuang, T. H., Jia, L. M., Zhang, L. J., Zhang, C., Li, C. et al. Senescence-activated enhancer landscape orchestrates the senescence-associated secretory phenotype in murine fibroblasts. *Nucleic Acids Research*, **2020**, 48(19): 10909–10923.
- [106] De Cecco, M., Criscione, S. W., Peterson, A. L., Neretti, N., Sedivy, J. M., Kreiling, J. A. Transposable elements become active and mobile in the genomes of aging mammalian somatic tissues. *Aging*, **2013**, 5(12): 867–883.
- [107] De Cecco, M., Criscione, S. W., Peckham, E. J., Hillenmeyer, S., Hamm, E. A., Manivannan, J., Peterson, A. L., Kreiling, J. A., Neretti, N., Sedivy, J. M. Genomes of replicatively senescent cells undergo global epigenetic changes leading to gene silencing and activation of transposable elements. *Aging Cell*, **2013**, 12(2): 247–256.
- [108] Patterson, M. N., Scannapieco, A. E., Au, P. H., Dorsey, S., Royer, C. A., Maxwell, P. H. Preferential retrotransposition in aging yeast mother cells is correlated with increased genome instability. *DNA Repair (Amst)*, **2015**, 34: 18–27.
- [109] Hu, X., Chris-Anne, M., Colin, S., et al. The remarkable complexity of the brain microbiome in health and disease. *BioRxiv*, **2023**: p. 2023.02.06.527297.
- [110] Min, B., Jeon, K., Park, J. S., Kang, Y. K. Demethylation and derepression of genomic retroelements in the skeletal muscles of aged mice. *Aging Cell*, **2019**, 18(6): e13042.
- [111] Zhang, H., Li, J. M., Yu, Y., Ren, J., Liu, Q., Bao, Z. S., Sun, S. H., Liu, X. Q., Ma, S., Liu, Z. P. et al. Nuclear lamina erosion-induced resurrection of endogenous retroviruses underlies neuronal aging. *Cell Reports*, **2023**, 42(6): 112593.

- [112] Nevalainen, T., Autio, A., Mishra, B. H., Marttila, S., Jylhä, M., Hurme, M. Aging-associated patterns in the expression of human endogenous retroviruses. *PLoS One*, **2018**, 13(12): e0207407.
- [113] Balestrieri, E., Pica, F., Matteucci, C., Zenobi, R., Sorrentino, R., Argaw-Denboba, A., Cipriani, C., Bucci, I., Sinibaldi-Vallebona, P. Transcriptional activity of human endogenous retroviruses in human peripheral blood mononuclear cells. *Biomed Res Int*, **2015**, 2015: 164529.
- [114] Jintaridth, P., Mutirangura, A. Distinctive patterns of age-dependent hypomethylation in interspersed repetitive sequences. *Physiological Genomics*, **2010**, 41(2): 194–200.
- [115] Yang, S., Liu, C., Jiang, M., Liu, X., Geng, L., Zhang, Y., Sun, S., Wang, K., Yin, J., Ma, S. et al. A single-nucleus transcriptomic atlas of primate liver aging uncovers the pro-senescence role of SREBP2 in hepatocytes. *Protein Cell*, **2024**, 15(2): 98–120.
- [116] Jansz, N., Faulkner, G. J. Endogenous retroviruses in the origins and treatment of cancer. *Genome Biology*, **2021**, 22(1): 147.
- [117] Lamprecht, B., Walter, K., Kreher, S., Kumar, R., Hummel, M., Lenze, D., Köchert, K., Bouhrel, M. A., Richter, J., Soler, E. et al. Derepression of an endogenous long terminal repeat activates the CSF1R proto-oncogene in human lymphoma. *Nature Medicine*, **2010**, 16(5): 571–579.
- [118] Fasching, L., Kapopoulou, A., Sachdeva, R., Petri, R., Jönsson, M. E., Männe, C., Turelli, P., Jern, P., Cammas, F., Trono, D. et al. TRIM28 represses transcription of endogenous retroviruses in neural progenitor cells. *Cell Reports*, **2015**, 10(1): 20–28.
- [119] Lin, H. Y., Cao, X. T. Nuclear innate sensors for nucleic acids in immunity and inflammation. *Immunological Reviews*, **2020**, 297(1): 162–173.
- [120] Chen, R., Ishak, C. A., De Carvalho, D. D. Endogenous retroelements and the viral mimicry response in cancer therapy and cellular homeostasis. *Cancer Discovery*, **2021**, 11(11): 2707–2725.
- [121] Cuellar, T. L., Herzner, A. M., Zhang, X. T., Goyal, Y., Watanabe, C., Friedman, B. A., Janakiraman, V., Durinck, S., Stinson, J., Arnott, D. et al. ---Silencing of retrotransposons by SETDB1 inhibits the interferon response in acute myeloid leukemia--. *Journal of Cell Biology*, **2017**, 216(11): 3535–3549.
- [122] Wu, M., Li, M., Liu, W., Yan, M. B., Li, L., Ding, W. C., Nian, X. M., Dai, W. X., Sun, D., Zhu, Y. Q. et al. Nucleoporin Seh1 maintains Schwann cell homeostasis by regulating genome stability and necroptosis. *Cell Reports*, **2023**, 42(7): 112802.
- [123] Rolland, A., Jouvin-Marche, E., Viret, C., et al. The envelope protein of a human endogenous retrovirus-W family activates innate immunity through CD14/TLR4 and promotes Th1-like responses. *J Immunol*, **2006**, 176(12): 7636–7644.
- [124] Griffin, G. K., Wu, J., Iracheta-Vellve, A., et al. Epigenetic silencing by SETDB1 suppresses tumour intrinsic immunogenicity. *Nature*, **2021**, 595(7866): 309–314.
- [125] Liu, S., Heumüller, S. E., Hossinger, A., Müller, S. A., Buravlova, O., Lichtenthaler, S. F., Denner, P., Vorberg, I. M. Reactivated endogenous retroviruses promote protein aggregate spreading. *Nature Communications*, **2023**, 14: 5034.
- [126] Dai, Y. D., Dias, P., Margosiak, A., Marquardt, K., Bashratyan, R., Hu, W. Y., Haskins, K., Evans, L. H. Endogenous retrovirus Gag antigen and its gene variants are unique autoantigens expressed in the pancreatic islets of non-obese diabetic mice. *Immunol Lett*, **2020**, 223: 62–70.
- [127] Chandrasekaran, S., Espeso-Gil, S., Loh, Y. E., et al. Neuron-specific chromosomal megadomain organization is adaptive to recent retrotransposon expansions. *Nat Commun*, **2021**, 12(1): 7243.
- [128] Morozov, V. A., Dao Thi, V. L., and Denner, J. The transmembrane protein of the human endogenous retrovirus--K (HERV-K) modulates cytokine release and gene expression. *PLoS One*, **2013**, 8(8): e70399.
- [129] Bhat, R. K., Rudnick, W., Antony, J. M., Maingat, F., Ellestad, K. K., Wheatley, B. M., Tönjes, R. R., Power, C. Human endogenous retrovirus-K(II) envelope induction protects neurons during HIV/AIDS. *PLoS One*, **2014**, 9(7): e97984.
- [130] Burn, A., Roy, F., Freeman, M., Coffin, J. M. Widespread expression of the ancient HERV-K (HML-2) provirus group in normal human tissues. *PLoS Biology*, **2022**, 20(10): e3001826.
- [131] Wallace, A. D., Wendt, G. A., Barcellos, L. F., de Smith, A. J., Walsh, K. M., Metayer, C., Costello, J. F., Wiemels, J. L., Francis, S. S. To ERV is human: A phenotype-wide scan linking polymorphic human

- endogenous retrovirus-K insertions to complex phenotypes. *Front Genet*, **2018**, 9: 298.
- [132] Scheltens, P., De Strooper, B., Kivipelto, M. et al., Alzheimer's disease. *The Lancet*, **2021**, 397(10284): 1577-1590.
- [133] Guo, C., Jeong, H. H., Hsieh, Y. C., et al. Tau Activates Transposable Elements in Alzheimer's Disease. *Cell Reports*, **2018**, 23(10): 2874-2880.
- [134] Ramirez, P., Zuniga, G., Sun, W., Beckmann, A., Ochoa, E., DeVos, S. L., Hyman, B., Chiu, G., Roy, E. R., Cao, W. et al. Pathogenic tau accelerates aging-associated activation of transposable elements in the mouse central nervous system. *Prog Neurobiol*, **2022**, 208: 102181.
- [135] Dawson, T., Rentia, U., Sanford, J., Cruchaga, C., Kauwe, J. S. K., Crandall, K. A. Locus specific endogenous retroviral expression associated with Alzheimer's disease. *Frontiers in Aging Neuroscience*, **2023**, 15: 1186470.
- [136] Dembny, P., Newman, A. G., Singh, M., Hinz, M., Szczeppek, M., Krüger, C., Adalbert, R., Dzaye, O., Trimbuch, T., Wallach, T. et al. Human endogenous retrovirus HERV-K(HML-2) RNA causes neurodegeneration through Toll-like receptors. *JCI Insight*, **2020**, 5(7): 131093.
- [137] Ochoa, E., Ramirez, P., Gonzalez, E., De Mange, J., Ray, W. J., Bieniek, K. F., Frost, B. Pathogenic tau-induced transposable element-derived dsRNA drives neuroinflammation. *Sci Adv*, **2023**, 9(1): eabq5423.
- [138] Scopa, C., Barnada, S. M., Cicardi, M. E., Singer, M., Trotti, D., Trizzino, M. JUN upregulation drives aberrant transposable element mobilization, associated innate immune response, and impaired neurogenesis in Alzheimer's disease. *Nature Communications*, **2023**, 14: 8021.
- [139] Sun, W. Y., Samimi, H., Gamez, M., Zare, H., Frost, B. Pathogenic tau-induced PiRNA depletion promotes neuronal death through transposable element dysregulation in neurodegenerative tauopathies. *Nature Neuroscience*, **2018**, 21(8): 1038-1048.
- [140] Brown, R. H., and Al-Chalabi, A., Amyotrophic Lateral Sclerosis. *N Engl J Med*, **2017**, 377(2): 162-172.
- [141] Arru, G., Mameli, G., Deiana, G. A., Rassu, A. L., Piredda, R., Sechi, E., Caggiu, E., Bo, M., Nako, E., Urso, D. et al. Humoral immunity response to human endogenous retroviruses K/W differentiates between amyotrophic lateral sclerosis and other neurological diseases. *Eur J Neurol*, **2018**, 25(8): 1076-e84.
- [142] Douville, R., Liu, J. K., Rothstein, J., Nath, A. Identification of active loci of a human endogenous retrovirus in neurons of patients with amyotrophic lateral sclerosis. *Annals of Neurology*, **2011**, 69(1): 141-151.
- [143] Garcia-Montojo, M., Simula, E. R., Fathi, S., McMahan, C., Ghosal, A., Berry, J. D., Cudkowicz, M., Elkahouloun, A., Johnson, K., Norato, G. et al. Antibody response to HML-2 may be protective in amyotrophic lateral sclerosis. *Annals of Neurology*, **2022**, 92(5): 782-792.
- [144] Garson, J. A., Usher, L., Al-Chalabi, A., Huggett, J., Day, E. F., McCormick, A. L. Quantitative analysis of human endogenous retrovirus-K transcripts in postmortem premotor cortex fails to confirm elevated expression of HERV-K RNA in amyotrophic lateral sclerosis. *Acta Neuropathologica Communications*, **2019**, 7(1): 45.
- [145] Mayer, J., Harz, C., Sanchez, L., Pereira, G. C., Maldener, E., Heras, S. R., Ostrow, L. W., Ravits, J., Batra, R., Meese, E. et al. Transcriptional profiling of HERV-K(HML-2) in amyotrophic lateral sclerosis and potential implications for expression of HML-2 proteins. *Molecular Neurodegeneration*, **2018**, 13(1): 39.
- [146] Romano, G., Klima, R., Feiguin, F. TDP-43 prevents retrotransposon activation in the Drosophila motor system through regulation of Dicer-2 activity. *BMC Biology*, **2020**, 18(1): 82.
- [147] Douville, R. N., Nath, A. Human endogenous retrovirus-K and TDP-43 expression bridges ALS and HIV neuropathology. *Frontiers in Microbiology*, **2017**, 8: 1986.
- [148] Simula, E. R., Arru, G., Zarbo, I. R., Solla, P., Sechi, L. A. TDP-43 and HERV-K envelope-specific immunogenic epitopes are recognized in ALS patients. *Viruses*, **2021**, 13(11): 2301.
- [149] Chang, Y. H., Dubnau, J. The Gypsy endogenous retrovirus drives non-cell-autonomous propagation in a drosophila TDP-43 model of neurodegeneration. *Current Biology*, **2019**, 29(19): 3135-3152.e4.

- [150] Krug, L., Chatterjee, N., Borges-Monroy, R., Hearn, S., Liao, W. W., Morrill, K., Prazak, L., Rozhkov, N., Theodorou, D., Hammell, M. et al. Retrotransposon activation contributes to neurodegeneration in a *Drosophila* TDP-43 model of ALS. *PLoS Genet*, **2017**, 13(3): e1006635.
- [151] Chang, Y. H., Dubnau, J. Endogenous retroviruses and TDP-43 proteinopathy form a sustaining feedback driving intercellular spread of *Drosophila* neurodegeneration. *Nature Communications*, **2023**, 14: 966.
- [152] Marcus, R. What is multiple sclerosis? *JAMA*, **2022**, 328(20): 2078.
- [153] Gruchot, J., Lewen, I., Dietrich, M., Transgenic expression of the HERV- W envelope protein leads to polarized glial cell populations and a neurodegenerative environment. *Proc Natl Acad Sci U*, **2023**, 120(38): e2308187120.
- [154] Kremer, D., Gruchot, J., Weyers, V., Oldemeier, L., Göttle, P., Healy, L., Ho Jang, J., Kang T Xu, Y., Volsko, C., Dutta, R. et al. pHERV-W envelope protein fuels microglial cell-dependent damage of myelinated axons in multiple sclerosis. *Proceedings of the National Academy of Sciences of the United States of America*, **2019**, 116(30): 15216–15225.
- [155] Mameli, G., Astone, V., Arru, G., Marconi, S., Lovato, L., Serra, C., Sotgiu, S., Bonetti, B., Dolei, A. Brains and peripheral blood mononuclear cells of multiple sclerosis (MS) patients hyperexpress MS-associated retrovirus/HERV-W endogenous retrovirus, but not Human herpesvirus 6. *The Journal of General Virology*, **2007**, 88(Pt 1): 264–274.
- [156] Garcia-Montojo, M., Rodriguez-Martin, E., Ramos-Mozo, P., Ortega-Madueño, I., Dominguez-Mozo, M. I., Arias-Leal, A., García-Martínez, M. Á., Casanova, I., Galan, V., Arroyo, R. et al. Syncytin-1/HERV-W envelope is an early activation marker of leukocytes and is upregulated in multiple sclerosis patients. *European Journal of Immunology*, **2020**, 50(5): 685–694.
- [157] Mameli, G., Cossu, D., Cocco, E., Frau, J., Marrosu, M. G., Niegowska, M., Sechi, L. A. Epitopes of HERV-Wenv induce antigen-specific humoral immunity in multiple sclerosis patients. *Journal of Neuroimmunology*, **2015**, 280: 66–68.
- [158] Alvarez-Lafuente, R., García-Montojo, M., De Las Heras, V., Domínguez-Mozo, M. I., Bartolome, M., Benito-Martin, M. S., Arroyo, R. Herpesviruses and human endogenous retroviral sequences in the cerebrospinal fluid of multiple sclerosis patients. *Multiple Sclerosis*, **2008**, 14(5): 595–601.
- [159] Charvet, B., Reynaud, J. M., Gourru-Lesimple, G., Perron, H., Marche, P. N., Horvat, B. Induction of proinflammatory multiple sclerosis-associated retrovirus envelope protein by human herpesvirus-6A and CD46 receptor engagement. *Front Immunol*, **2018**, 9: 2803.
- [160] Meier, U. C., Cipian, R. C., Karimi, A., Ramasamy, R., Middeldorp, J. M. Cumulative roles for epstein-barr virus, human endogenous retroviruses, and human herpes virus-6 in driving an inflammatory cascade underlying MS pathogenesis. *Frontiers in Immunology*, **2021**, 12: 757302.
- [161] Pérez-Pérez, S., Domínguez-Mozo, M. I., García-Martínez MÁ, García-Frontini, M. C., Villarrubia, N., Costa-Frossard, L., Villar, L. M., Arroyo, R., Álvarez-Lafuente, R. Anti-human herpesvirus 6 A/B antibodies titers correlate with multiple sclerosis-associated retrovirus envelope expression. *Front Immunol*, **2021**, 12: 798003.
- [162] Canli, T. A model of human endogenous retrovirus (HERV) activation in mental health and illness. *Medical Hypotheses*, **2019**, 133: 109404.
- [163] Karlsson, H., Bachmann, S., Schröder, J., McArthur, J., Torrey, E. F., Yolken, R. H. Retroviral RNA identified in the cerebrospinal fluids and brains of individuals with schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America*, **2001**, 98(8): 4634–4639.
- [164] Karlsson, H., Schröder, J., Bachmann, S., Bottmer, C., Yolken, R. H. HERV-W-related RNA detected in plasma from individuals with recent-onset schizophrenia or schizoaffective disorder. *Molecular Psychiatry*, **2004**, 9(1): 12–13.
- [165] Huang, W., Li, S., Hu, Y., Yu, H., Luo, F., Zhang, Q., Zhu, F. Implication of the env gene of the human endogenous retrovirus W family in the expression of BDNF and DRD3 and development of recent-onset schizophrenia. *Schizophrenia Bulletin*, **2011**, 37(5): 988–1000.
- [166] Li, F., Sabunciyan, S., Yolken, R. H., Lee, D., Kim, S., Karlsson, H. Transcription of human endogenous

- retroviruses in human brain by RNA-seq analysis. *PLoS One*, **2019**, 14(1): e0207353.
- [167] Perron, H., Mekaoui, L., Bernard, C., Veas, F., Stefas, I., Leboyer, M. Endogenous retrovirus type W GAG and envelope protein antigenemia in serum of schizophrenic patients. *Biological Psychiatry*, **2008**, 64(12): 1019–1023.
- [168] Weis, S., Llenos, I. C., Sabunciyan, S., Dulay, J. R., Isler, L., Yolken, R., Perron, H. Reduced expression of human endogenous retrovirus (HERV)-W GAG protein in the cingulate gyrus and hippocampus in schizophrenia, bipolar disorder, and depression. *Journal of Neural Transmission*, **2007**, 114(5): 645–655.
- [169] Tamouza, R., Meyer, U., Foiselle, M., Richard, J. R., Wu, C. L., Boukouaci, W., Le Corvoisier, P., Barrau, C., Lucas, A., Perron, H. et al. Identification of inflammatory subgroups of schizophrenia and bipolar disorder patients with HERV-W ENV antigenemia by unsupervised cluster analysis. *Translational Psychiatry*, **2021**, 11(1): 377.
- [170] Li, X., Wu, X., Li, W., Yan, Q., Zhou, P., Xia, Y., Yao, W., Zhu, F. HERV-W ENV induces innate immune activation and neuronal apoptosis via linc01930/cGAS axis in recent-onset schizophrenia. *Int J Mol Sci*, **2023**, 24(3): 3000.
- [171] Wu, X. L., Yan, Q. J., Liu, L. Z., Xue, X., Yao, W., Li, X. H., Li, W. S., Ding, S., Xia, Y. R., Zhang, D. Y. et al. Domesticated HERV-W env contributes to the activation of the small conductance Ca^{2+} -activated K^{+} type 2 channels via decreased 5-HT₄ receptor in recent-onset schizophrenia. *Virologica Sinica*, **2023**, 38(1): 9–22.
- [172] Li, S., Liu, Z. C., Yin, S. J., Chen, Y. T., Yu, H. L., Zeng, J., Zhang, Q., Zhu, F. Human endogenous retrovirus W family envelope gene activates the small conductance Ca^{2+} -activated K^{+} channel in human neuroblastoma cells through CREB. *Neuroscience*, **2013**, 247: 164–174.
- [173] Chen, Y. T., Yan, Q. J., Zhou, P., Li, S., Zhu, F. HERV-W env regulates calcium influx via activating TRPC3 channel together with depressing DISC1 in human neuroblastoma cells. *Journal of NeuroVirology*, **2019**, 25(1): 101–113.
- [174] Grube, S., Gerchen, M. F., Adamcio, B., Pardo, L. A., Martin, S., Malzahn, D., Papiol, S., Begemann, M., Ribbe, K., Friedrichs, H. et al. A CAG repeat polymorphism of *KCNN3* predicts SK3 channel function and cognitive performance in schizophrenia. *EMBO Molecular Medicine*, **2011**, 3(6): 309–319.
- [175] El-Hassar, L., Simen, A. A., Duque, A., Patel, K. D., Kaczmarek, L. K., Arnsten, A. F. T., Yeckel, M. F. Disrupted in schizophrenia 1 modulates medial prefrontal cortex pyramidal neuron activity through cAMP regulation of transient receptor potential C and small-conductance K^{+} channels. *Biological Psychiatry*, **2014**, 76(6): 476–485.
- [176] Yao, W., Zhou, P., Yan, Q. J., Wu, X. L., Xia, Y. R., Li, W. S., Li, X. H., Zhu, F. ERVWE1 reduces hippocampal neuron density and impairs dendritic spine morphology through inhibiting Wnt/JNK non-canonical pathway via miR-141-3p in schizophrenia. *Viruses*, **2023**, 15(1): 168.
- [177] Zhang, D., Wu, X., Xue, X., Li, W., Zhou, P., Lv, Z., Zhao, K., Zhu, F. Ancient dormant virus remnant ERVW-1 drives ferroptosis via degradation of GPX4 and SLC3A2 in schizophrenia. *Virol Sin*, **2024**, 39(1): 31–43.
- [178] Frank, O., Giehl, M., Zheng, C., Hehlmann, R., Leib-Mösch, C., Seifarth, W. Human endogenous retrovirus expression profiles in samples from brains of patients with schizophrenia and bipolar disorders. *Journal of Virology*, **2005**, 79(17): 10890–10901.
- [179] Mak, M., Samochowiec, J., Frydecka, D., Pełka-Wysiecka, J., Szmida, E., Karpiński, P., Sasiadek, M. M., Piotrowski, P., Samochowiec, A., Misiak, B. First-episode schizophrenia is associated with a reduction of HERV-K methylation in peripheral blood. *Psychiatry Res*, **2019**, 271: 459–463.
- [180] Huang, W. J., Liu, Z. C., Wei, W., Wang, G. H., Wu, J. G., Zhu, F. Human endogenous retroviral pol RNA and protein detected and identified in the blood of individuals with schizophrenia. *Schizophrenia Research*, **2006**, 83(2–3): 193–199.
- [181] Suntsova, M., Gogvadze, E. V., Salozhin, S., Gaifullin, N., Eroshkin, F., Dmitriev, S. E., Martynova, N., Kulikov, K., Malakhova, G., Tukhbatova, G. et al. Human-specific endogenous retroviral insert serves as an enhancer for the schizophrenia-linked gene *PRODH*. *Proc Natl Acad Sci USA*, **2013**, 110(48): 19472–19477.
- [182] Willis, A., Bender, H. U., Steel, G., Valle, D.

- PRODH variants and risk for schizophrenia. *Amino Acids*, **2008**, 35(4): 673–679.
- [183] Nakamura, A., Okazaki, Y., Sugimoto, J., Oda, T., Jinno, Y. Human endogenous retroviruses with transcriptional potential in the brain. *Journal of Human Genetics*, **2003**, 48(11): 575–581.
- [184] Otowa, T., Tochigi, M., Rogers, M., Umekage, T., Kato, N., Sasaki, T. Insertional polymorphism of endogenous retrovirus HERV-K115 in schizophrenia. *Neuroscience Letters*, **2006**, 408(3): 226–229.
- [185] Diem, O., Schäffner, M., Seifarth, W., Leib-Mösch, C. Influence of antipsychotic drugs on human endogenous retrovirus (HERV) transcription in brain cells. *PLoS One*, **2012**, 7(1): e30054.
- [186] Perron, H., Hamdani, N., Faucard, R., Lajnef, M., Jamain, S., Daban-Huard, C., Sarrazin, S., LeGuen, E., Houenou, J., Delavest, M. et al. Molecular characteristics of Human Endogenous Retrovirus type-W in schizophrenia and bipolar disorder. *Transl Psychiatry*, **2012**, 2: e201.
- [187] Otręba, M., Kośmider, L., Rzepecka-Stojko, A. Antiviral activity of chlorpromazine, fluphenazine, perphenazine, prochlorperazine, and thioridazine towards RNA-viruses. A review. *European Journal of Pharmacology*, **2020**, 887: 173553.
- [188] Andreu, S., Ripa, I., Bello-Morales, R., López-Guerrero, J. A. Valproic acid and its amidic derivatives as new antivirals against alphaherpesviruses. *Viruses*, **2020**, 12(12): E1356.
- [189] Esnault, C., Millet, J., Schwartz, O., Heidmann, T. Dual inhibitory effects of APOBEC family proteins on retrotransposition of mammalian endogenous retroviruses. *Nucleic Acids Research*, **2006**, 34(5): 1522–1531.
- [190] Esnault, C., Priet, S., Ribet, D., Heidmann, O., Heidmann, T. Restriction by APOBEC3 proteins of endogenous retroviruses with an extracellular life cycle: *Ex vivo* effects and *in vivo* “traces” on the murine IAPe and human HERV-K elements. *Retrovirology*, **2008**, 5: 75.
- [191] Balestrieri, E., Pitzianti, M., Matteucci, C., D’Agati, E., Sorrentino, R., Baratta, A., Caterina, R., Zenobi, R., Curatolo, P., Garaci, E. et al. Human endogenous retroviruses and ADHD. *The World Journal of Biological Psychiatry*, **2014**, 15(6): 499–504.
- [192] D’Agati, E., Pitzianti, M., Balestrieri, E., Matteucci, C., Sinibaldi Vallebona, P., Pasini, A. First evidence of HERV-H transcriptional activity reduction after methylphenidate treatment in a young boy with ADHD. *The New Microbiologica*, **2016**, 39(3): 237–239.
- [193] Cipriani, C., Pitzianti, M. B., Matteucci, C., D’Agati, E., Miele, M. T., Rapaccini, V., Grelli, S., Curatolo, P., Sinibaldi-Vallebona, P., Pasini, A. et al. The decrease in human endogenous retrovirus-H activity runs in parallel with improvement in ADHD symptoms in patients undergoing methylphenidate therapy. *Int J Mol Sci*, **2018**, 19(11): E3286.
- [194] Balestrieri, E., Cipriani, C., Matteucci, C., et al. Transcriptional activity of human endogenous retrovirus in Albanian children with autism spectrum disorders. *New Microbiol*, **2016**, 39(3): 228–231.
- [195] Balestrieri, E., Arpino, C., Matteucci, C., Sorrentino, R., Pica, F., Alessandrelli, R., Coniglio, A., Curatolo, P., Rezza, G., Macciardi, F. et al. HERVs expression in Autism Spectrum Disorders. *PLoS One*, **2012**, 7(11): e48831.
- [196] Carta, A., Manca, M. A., Scoppola, C., Simula, E. R., Noli, M., Ruberto, S., Conti, M., Zarbo, I. R., Antonucci, R., Sechi, L. A. et al. Antihuman endogenous retrovirus immune response and adaptive dysfunction in autism. *Biomedicines*, **2022**, 10(6): 1365.
- [197] Cipriani, C., Ricceri, L., Matteucci, C., De Felice, A., Tartaglione, A. M., Argaw-Denboba, A., Pica, F., Grelli, S., Calamandrei, G., Sinibaldi Vallebona, P. et al. High expression of Endogenous Retroviruses from intrauterine life to adulthood in two mouse models of Autism Spectrum Disorders. *Scientific Reports*, **2018**, 8: 629.
- [198] Tartaglione, A. M., Cipriani, C., Chiarotti, F., Perrone, B., Balestrieri, E., Matteucci, C., Sinibaldi-Vallebona, P., Calamandrei, G., Ricceri, L. Early behavioral alterations and increased expression of endogenous retroviruses are inherited across generations in mice prenatally exposed to valproic acid. *Molecular Neurobiology*, **2019**, 56(5): 3736–3750.
- [199] Balestrieri, E., Cipriani, C., Matteucci, C., Benvenuto, A., Coniglio, A., Argaw-Denboba, A., Toschi, N., Bucci, I., Miele, M. T., Grelli, S. et al. Children with autism spectrum disorder and their mothers

- share abnormal expression of selected endogenous retroviruses families and cytokines. *Front Immunol*, **2019**, 10: 2244.
- [200] Cipriani, C., Giudice, M., Petrone, V., Fanelli, M., Minutolo, A., Miele, M. T., Toschi, N., Maracchioni, C., Siracusano, M., Benvenuto, A. et al. Modulation of human endogenous retroviruses and cytokines expression in peripheral blood mononuclear cells from autistic children and their parents. *Retrovirology*, **2022**, 19(1): 26.
- [201] Faucard, R., Madeira, A., Gehin, N., Authier, F. J., Panaite, P. A., Lesage, C., Burgelin, I., Bertel, M., Bernard, C., Curtin, F. et al. Human endogenous retrovirus and neuroinflammation in chronic inflammatory demyelinating polyradiculoneuropathy. *EBioMedicine*, **2016**, 6: 190–198.
- [202] Arru, G., Sechi, E., Mariotto, S., Zarbo, I. R., Ferrari, S., Gajofatto, A., Monaco, S., Deiana, G. A., Bo, M., Sechi, L. A. et al. Antibody response against HERV-W in patients with MOG-IgG associated disorders, multiple sclerosis and NMOSD. *J Neuroimmunol*, **2020**, 338: 577110.
- [203] Jeong, B. H., Lee, Y. J., Carp, R. I., Kim, Y. S. The prevalence of human endogenous retroviruses in cerebrospinal fluids from patients with sporadic Creutzfeldt–Jakob disease. *Journal of Clinical Virology*, **2010**, 47(2): 136–142.
- [204] Rex, C., Nadeau, M. J., Douville, R., Schellenberg, K. Expression of human endogenous retrovirus-K in spinal and bulbar muscular atrophy. *Frontiers in Neurology*, **2019**, 10: 968.
- [205] De Meirleir, K. L., Khaiboullina, S. F., Frémont, M., Hulstaert, J., Rizvanov, A. A., Palotás, A., Lombardi, V. C. Plasmacytoid dendritic cells in the duodenum of individuals diagnosed with myalgic encephalomyelitis are uniquely immunoreactive to antibodies to human endogenous retroviral proteins. *In Vivo*, **2013**, 27(2): 177–187.
- [206] Singh, S., Stafford, P., Schlauch, K. A., Tillett, R. R., Gollery, M., Johnston, S. A., Khaiboullina, S. F., De Meirleir, K. L., Rawat, S., Mijatovic, T. et al. Humoral immunity profiling of subjects with myalgic encephalomyelitis using a random peptide microarray differentiates cases from controls with high specificity and sensitivity. *Molecular Neurobiology*, **2018**, 55(1): 633–641.
- [207] Rodrigues, L. S., da Silva Nali, L. H., Leal, C. O. D., Sabino, E. C., Lacerda, E. M., Kingdon, C. C., Nacul, L., Romano, C. M. HERV-K and HERV-W transcriptional activity in myalgic encephalomyelitis/chronic fatigue syndrome. *Autoimmunity Highlights*, **2019**, 10(1): 12.
- [208] Volcy, K. and Fraser, N.W. DNA damage promotes herpes simplex virus-1 protein expression in a neuroblastoma cell line. *J Neurovirol*, **2013**, 19(1): 57–64.



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