Molecules and Cells

Minireview

Human Endogenous Retroviruses as Gene Expression Regulators: Insights from Animal Models into Human Diseases

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The human genome contains many retroviral elements called human endogenous retroviruses (HERVs), resulting from the integration of retroviruses throughout evolution. HERVs once were considered inactive junk because they are not replication-competent, primarily localized in the heterochromatin, and silenced by methylation. But HERVs are now clearly shown to actively regulate gene expression in various physiological and pathological conditions such as developmental processes, immune regulation, cancers, autoimmune diseases, and neurological disorders. Recent studies report that HERVs are activated in patients suffering from coronavirus disease 2019 (COVID-19), the current pandemic caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) infection. In this review, we describe internal and external factors that influence HERV activities. We also present evidence showing the gene regulatory activity of HERV LTRs (long terminal repeats) in model organisms such as mice, rats, zebrafish, and invertebrate models of worms and flies. Finally, we discuss several molecular and cellular pathways involving various transcription factors and receptors, through which HERVs affect downstream cellular and physiological events such as epigenetic modifications, calcium influx, protein phosphorylation, and cytokine release. Understanding how HERVs participate in various physiological and pathological processes will help develop a strategy to generate effective therapeutic approaches targeting HERVs.

Keywords: cancer, COVID-19, human endogenous retrovirus, neurological disease, syncytin-1, toll-like receptor

INTRODUCTION

Endogenous retroviruses (ERVs) are found in the genomes of all vertebrates and are therefore considered remnants of ancestral infections (Dewannieux and Heidmann, 2013; Hayward et al., 2015). Since many different species can share endogenous retroviral sequences, exogenous retrovirus might have infected common ancestors and gotten fixed in the genome before species diverged or been later spread via a cross-species transmission (Hayward et al., 2013) (Supplementary Fig. S1). Human endogenous retroviruses (HERVs) were first discovered more than 40 years ago by screening human tissue with non-stringent blot hybridization probes derived from murine leukemia virus (MuLV), revealing the presence and cloning of the first endogenous retroviral sequences present in human DNA (Escalera-Zamudio and Greenwood, 2016; Martin et al., 1981). HERVs and their derivative sequences comprise at least 8% of the human genome (Mager and Medstrand, 2005). While a majority of these sequences are mostly defective, several phylogenetically distinct HERVs are still transcriptionally active and competent to produce some retroviral proteins (Bannert and Kurth,
HERV IN DISEASES

HERVs involve in the pathology of various diseases, including cancers (Burns, 2017; Fischer et al., 2016; Gao et al., 2021; Kassiotis, 2014; Mullins and Linnebacher, 2012; Yu et al., 2013), autoimmune diseases (Anand et al., 2017; Balada Giménez-Orenga and Oltra, 2021; Goldsmith et al., 2016; Perron et al., 2012). This is likely to a continuing and growing list of diseases in which HERVs are involved in the pathology.

External factors: UV, smoking, infections, and chemicals

UV radiation, especially UVB and UVC, stimulates transcription of retroviral env and pol genes of HERV-K in melanoma (Reiche et al., 2010; Schanab et al., 2011) and keratinocyte cell lines (Hohenadl et al., 1999), which suggests that HERV-K may specifically contribute to UV radiation-related pathogenesis of skin cells. Smoking also affects the expression of HERVs, because the level of HERV-derived transcripts is higher in smokers than in non-smokers (Bergallo et al., 2019; Gabriel et al., 2010; Wallace et al., 2014).

Infection of parasites such as Toxoplasma gondii is also reported to upregulate transcription of certain HERV elements in human neuroepithelial cells (Frank et al., 2006). Viral infections by Epstein–Barr virus (EBV) (Sutkowski et al., 2004), human immunodeficiency virus 1 (HIV-1) (Contreras-Galindo et al., 2007), herpes simplex virus 1 (HSV-1) (Lee et al., 2003), coxsackievirus-B4 (CV-B4) (Dechaumes et al., 2020), Kaposi’s sarcoma-associated herpesvirus (KSHV) (Dai et al., 2018), dengue virus serotype 2 (DENV-2) (Wang et al., 2020a), cytomegalovirus (CMV) (Bergallo et al., 2015), human herpesvirus 6B (HHV-6B) (Turcanova et al., 2009), or influenza A (Nelläker et al., 2006) have been shown to increase the level of transcripts from diverse classes of HERVs. Recently, HERV-W Env is reported to be highly expressed in the leukocytes of COVID-19 patients infected by SARS-CoV-2 (Balestrieri et al., 2021).
Chemical elements such as hydroquinone (HQ) (Conti et al., 2016), cupric ion (Karimi et al., 2019), and silver nanoparticles (Alqahtani et al., 2016) are found to influence the expression of HERVs (H, K, and W) in several tumor cell lines. HQ is a benzene-derived metabolite that is connected with the risk of acute myelogenous leukemia. After treatment with HQ, three human retrotransposons, long interspersed element 1 (LINE-1, L1), alu and syncytin-1, the HERV-W ENV protein, display increased expression levels in monocytic leukemia cell line THP-1 and hematopoietic stem cells (Conti et al., 2016). Upon copper sulfate (CuSO4) exposure, the expression of HERV-H env is decreased, whereas that of env genes of HERV-K and HERV-W is increased in human skin malignant melanoma cell line SK-MEL-37. However, the expression of both HERV-K and HERV-W env genes seems to decrease as the concentration of CuSO4 increases (Karimi et al., 2019). Finally, silver nanoparticles (AgNPs) increase mRNA and protein levels of syncytin-1 of HERV-W in both human T-lymphoblastic leukemia MOLT-4 and Fanconi anemia acute myeloid leukemia (FA-AML1) cells (Alqahtani et al., 2016).

Internal factors: morphogens, hormones, and cytokines

Retinoic acid, a vitamin A metabolite that functions as a morphogen (Ono et al., 1987) during early embryogenesis, is also reported to transcriptionally activate retinoic acid-responsive human ERV-I (RRHERV-I), a type of HERV-I, in teratocarcinoma cells (Kannan et al., 1991). HERV-K expression is stimulated by a sequential treatment of female hormones, progesterone after estradiol, in human breast cancer cell line T47D (Ono et al., 1987). On the other hand, HERV-R expression in human vascular endothelial cells is upregulated by treatment of various cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 alpha (IL-1α) and IL-1β, but downregulated by that of interferon-gamma (IFNγ) (Katsumata et al., 1999). These observations indicate that HERV-R expression may be up-or down-regulated at sites of inflammation in human vessels and play a role in inflammatory vascular diseases. Various transcription factors and cellular signaling pathways are downstream of these internal factors and discussed below.

Epigenetic factors: DNA methylation and histone modification

Transcription of HERV-K and methylation level of their LTRs are associated with each other in the teratocarcinoma cells (Florl et al., 1999). DNA demethylation of HERV LTRs triggers upregulation of HERV expression. A low level of DNA methylation in HERV-K and -W regions has been reported in urothelial cell carcinoma (UCC) (Menendez et al., 2004) and ovarian cancer (Stengel et al., 2010). HERVs harbor binding sequences for KRAB-containing zinc finger proteins (KRAB-ZFPs), and histone modifications are induced by the interaction of KRAB-ZFPs to those binding sites. KRAB-ZFPs bind to transcription factor binding site (TFBS) within HERV elements, recruiting the co-repressor KRAB-associated protein 1 (KAP1), which is also called TRIM28 (Giménez-Orenga and Oltra, 2021). In another study, it is shown that HERV-K is repressed by KAP1 (TRIM28) in undifferentiated human embryonic stem cells (hESCs) and differentiated cell lines HeLa and 293T cells, adult peripheral blood mononuclear cells (PB-MCs), and CD4+ T cells (Tie et al., 2018). HERV-S and HERV-T are overexpressed in KAP1 (TRIM28) knockout HeLa cells, and the KAP1 (TRIM28) depletion also results in a decrease in H3K9me3 level at HERV-K regions, which supports KAP1 (TRIM28)’s repression on HERVs. These results indicate that the KRAB-ZFP/KAP1 (TRIM28) pathway involves regulating HERV activation presumably via epigenetic controls. Knockdown of KAP1 (TRIM28) in human neural progenitor cells (NPCs) generally upregulates various HERV gene expressions (Brättès et al., 2017). A gene regulatory network based on HERVs may participate in the control of gene expression of protein-coding transcripts necessary for proper development of nervous systems (Lee et al., 2019b; 2021b; Zhang et al., 2019a).

CRISPR/Cas9-based deletion of KAP1 (TRIM28), an epigenetic co-repressor protein, results in upregulation of ERVs in mouse NPCs in vitro (Jönsson et al., 2021). However, there is no activation of ERVs in adult neurons, in case a vector targeting KAP1 (TRIM28) is injected into the forebrain of adult Cas9-GFP mice (Lee et al., 2020b). KAP1 (TRIM28) is required to silence ERVs during brain development in both humans and mice, and the results indicate that the suppression of ERVs by KAP1 (TRIM28) remains in the adult brain. In vivo depletion of KAP1 (TRIM28) in cortical NPCs during mouse brain development later results in upregulation of ERVs in excitatory neurons in the adult brain. In addition, activated microglia are found in the cortex where excitatory neurons lack KAP1 (TRIM28). Expression of ERV in neurons is linked to the activation of microglia, which demonstrates that activation of ERV in neurons results in an inflammatory response in the nervous system.

TIP60 is a histone acetyltransferase and functions as a haploinsufficient tumor suppressor (Gorrini et al., 2007). Tumors from colorectal and breast cancer patients show a decrease in the expression of TIP60, suggesting a link between downregulation of TIP60 and tumor progression (Gorrini et al., 2007; Mattera et al., 2009). TIP60 positively regulates the expression of histone methyltransferases (HMTs), SETDB1, and SUV39H1, loss of TIP60 results in a global decrease in H3K9me3 level (Rajagopalan et al., 2018). TIP60 silences HERV-L, HERV-K, HERV-1, and HERV-W, dependent on bromodomain-containing protein 4 (BRD4), an epigenetic reader recognizing histone proteins (Zhou et al., 2020), through regulation of histone H3K9me3 in colorectal cancer cells. HERVs are repressed in colorectal cells overexpressing TIP60. In addition, the nonobese diabetic/severe combined immunodeficient (NOD-SCID) mouse model, which is injected with colorectal cancer cells overexpressing TIP60, exhibits a reduction in tumor growth. ChIP assay reports TIP60 occupancy at LTR regions of HERVs (Rajagopalan et al., 2018).

**HERVs IN TRANSGENIC ANIMAL MODELS**

HERVs can regulate the expression of host cellular genes through their cis-regulatory elements predominantly localized in their LTRs. These features play a critical role in the commencement and progression of diseases in several ways involving genetic instability, hypomethylation, transactivation,
and RNA interference (Yu et al., 2013). Thus, it is crucial to understand how LTRs participate in gene expression processes. Utilizing animal models provides research platforms to test LTR activities and their interacting factors in various contexts, thereby helping understand the potential roles of LTR in human physiological and pathological conditions (Fig. 1).

**Caenorhabditis elegans**

*C. elegans* is a free-living, non-parasitic, and transparent nematode about 1 mm in length. *C. elegans* is the first multi-cellular organism and animal to have its whole genome sequenced, and its genome contains approximately 20,000 genes and shares high genetic homology of 60% to 80% with humans (C. elegans Sequencing Consortium, 1998). *C. elegans* is a versatile model with a powerful genetics due to many advantages such as easy lab maintenance, a large brood size with approximately 300 offspring within a reproductive cycle of only three days and the short lifespan of three weeks in a typical culture condition, and practically no ethical concerns (Menéely et al., 2019). Therefore, *C. elegans* has been widely used to study various questions asking principles in biological sciences and human diseases (Chung et al., 2020; Kim et al., 2019; Lee et al., 2021a; Levine and Lee, 2020).

Promoter activity of HERV-K LTR that is assessed by expressing GFP is reported in free-living soil worms *C. elegans* (Durnaoglu et al., 2020). Expression of GFP is mainly observed in vulval muscle, and LTR activation is dependent on che-1, a sensory neuron driver, and lin-15b, a negative regulator of RNAi and germline gene expression. CHE-1 is a C2H2 zinc-finger transcription factor and has various homologs detected in human, murine, and fly genomes. The GLASS transcription factor required for photoreceptor cell differentiation in *Drosophila melanogaster* and human ZNF500 shares the highest homology with the CHE-1 domain (Etchberger et al., 2007; Moses et al., 1989; Uchida et al., 2003).

**Drosophila melanogaster**

The fruit fly, *D. melanogaster*, has been used as a genetic model organism for over a century to study various biological processes such as inheritance, embryonic development, and aging (Jennings, 2011). *Drosophila* can be easily cultured in a laboratory condition, have a short life cycle of around ten days at 25°C, a large number of laid eggs, approximately 100 eggs per day, and a relatively short lifespan of 2 to 3 months. The genome of *Drosophila* contains about 13,600 genes, 60% homologous to the human genome (Adams et al., 2000). *Drosophila* develop most major organs found in...
humans, including heart, hematopoietic system, and compartmented nervous system, thus serving as a useful simple model for studying circulation and behavior (Lee and Kim, 2021; Rimal et al., 2020; Vlisidou and Wood, 2015).

TAR DNA-binding protein 43 (TDP-43) is abnormally expressed in many ALS patients (Chen-Plotkin et al., 2010), and it has been reported to directly bind to HERV-K LTR (Li et al., 2015). There are five binding sites for TDP-43 in HERV-K LTRs. CHIP assay revealed that TDP-43 binds to HERV-K LTR, indicating that it may have a role as a regulator of HERV-K expression and involve in neurodegeneration. Fruit flies Drosophila expressing human TDP-43 (hTDP-43) induce retrotransposable element (RTE) expression in neurons and glia (Krug et al., 2017). hTDP-43 expression in glia causes regulatory control loss in the specific RTE, the ERV gypsy. The fly glia expressing hTDP-43 degenerate, and those transgenic flies show severely impaired locomotion. The toxicity of glial hTDP-43 is rescued by either RNAi against gypsy or pharmacologically inhibiting RTE reverse transcriptase activity by tenofovir disoproxil fumarate (TDF), zidovudine (AZT), and stavudine (d4T). Altogether, the studies suggest that RTE activity may contribute to neurodegeneration in TDP-43-mediated diseases.

Zebrafish
The zebrafish Danio rerio is a freshwater fish easily cultured in regular fish tanks. A single female zebrafish lays up to 200 eggs per week (Gutiérrez-Lovera et al., 2017). The zebrafish genome contains about 26,000 protein-coding genes and shows approximately 70% of homology with the human genome, including 82% of orthologous human disease-related genes (Howe et al., 2013). The transparent model organism is particularly useful in studies directly observing ongoing events inside the live vertebrate animal body, providing detailed information in organ and neural development (Choe et al., 2020; Jung et al., 2019; 2020b; Lee et al., 2020c; Oh and Park, 2019).

Transgenic zebrafish is generated to test whether ERV-9 (also known as HERV-W) LTR drives GFP expression (Pi et al., 2004). LTR activated GFP expression in transgenic zebrafish shows a maternal effect. In the study, fluorescence level in embryos decreased 48 hours after post-fertilization, which indicates ERV-9 LTR enhancer was active during oogenesis but not active during spermatogenesis or early embryogenesis. In situ hybridizations also confirmed that ERV-9 LTR was involved in the primordial oocytes but not in spermatozoa. ERV-9 LTR was similarly active in human oocytes and stem/progenitor cells but not active in spermatozoa and differentiated somatic cells. These results indicate that ERV-9 LTR may play a role in synthesizing maternal mRNAs required for early embryogenesis.

A zebrafish reporter line of zebrafish endogenous retrovirus (ZFERV) is recently described (Hamilton et al., 2021). It5, the promoter of zerv1a, is used to drive GFP expression, and ZFERV is activated in the thymus and brain. Interestingly, the expression of zerv1a is specific to T-cells, suggesting a potential role for ZFERV in lymphocyte development, immunity, and neurological diseases. ZFERV knockout is also generated by deleting LTRs of ZFERV with CRISPR/Cas9 (Yang et al., 2018). ZFERV-deficient zebrafish embryos exhibit spinal abnormality in early embryonic development, and expression of both Delta D and Notch1 is significantly lower in zebrafish with abnormal spines than normal fish. The results suggest that ZFERV may involve in vertebral development by regulating Notch1/Delta D signaling pathway.

Murine models
Murine models such as mice and rats are widely studied mammalian models due to their small size and fast reproduction cycle of three weeks (Walsh et al., 2017). Murine ESCs are available and easily subjected for genetic manipulation: thus various humanized murine models are generated to study human diseases and health (Saito et al., 2019). Transgenic animals overexpressing HERV ENVs have been studied in multiple contexts to examine the activities of HERVs. Also, studies using murine models show that maternal effect factors affect activities of endogenous murine retroviral elements, influencing early development.

HERV genes and LTRs in murine models
HERV-R env gene expression is reported in salivary glands of transgenic rats in which the transgenes carry the complete provirus genome of ERV3 (Tanaka, 2000; Tanaka et al., 2003). The transgenic rats carrying HERV-R under the control of their own promoter also express HERV-R transcripts in the placenta, where HERV-R is highly expressed in humans. Also, immunohistochemistry results show the specific expression of ENV glycoprotein in acinar cells of the Harderian glands, but not in duct epithelial cells indicating the protein expression of HERV-R is under the control of host cell regulation. Still, the transgenic rats do not show any significant pathology.

Transgenic mice expressing the lacZ gene under the control of HERV-K LTRE3, which is active in cancer developments, are generated (Casau et al., 1999). The highest expression levels are mainly restricted to the undifferentiated spermatocytes of adult testes. HERV-K LTRE3 also drives the expression of reporters in testicular teratocarcinoma cell lines but not in other cell lines of transformed kidney cell line, breast carcinomas, an osteosarcoma, and lung and colon adenocarcinomas (Bae et al., 2020; Kim et al., 2020). The results indicate that HERV-K LTRE3 is specifically compatible with the transcriptional machinery of testes cells.

Many germ cell tumor (GCT) patients are young men, and HERV-K rec gene, a variant of the env gene, is highly expressed in GCTs (Galli et al., 2005). Transgenic mice expressing HERV-K rec gene show disturbed germ cell development and are prone to developing testicular carcinoma (Lee et al., 2019c). Transgenic mice expressing the HERV-K env gene in their neurons develop motor dysfunction, exhibiting selective loss of volume of the motor cortex, decreased synaptic activity in pyramidal neurons, dendritic spine abnormalities, and nucleolar dysfunction (Li et al., 2015). TDP-43’s binding to the LTRs regulates the expression of HERV-K, which is presumably responsible for the increased expression level of HERV-K env in the postmortem brain tissue of some ALS patients.

HERV-W env has been detected in the serum, PBMCs, and pancreata of type-1 diabetes (T1D) patients. Also, there is a
correlation between HERV-W env expression and infiltration of macrophages in the exocrine pancreas. Transgenic mice expressing HERV-W env decrease insulin level, displaying hyperglycemia and immune cell infiltration in the pancreas. The results suggest that HERV-W env may contribute to T1D pathogenesis (Levet et al., 2017).

Maternal effect factors
stella is a gene coding a protein containing an SAP-like domain and a splicing factor motif-like structure, showing maternal effect (Payer et al., 2003). stella is required for early embryonic development and found to affect maternal-to-zygotic transition (MZT) (Huang et al., 2017). stella M/Z KO 2-cell embryos have reduced activation of the LTR-ERVL family, specifically mouse endogenous retrovirus type-L (MuERV-L) elements which encode a canonical retroviral gag and pol, flanked by 5' and 3' LTR. MuERV-L knock-down in embryos by microinjecting MuERV-L siRNA into the cytoplasm of zygotes hinders developmental progression. stella may involve in the regulation of transposable elements in 2-cell embryos and the activation of MuERV-L. The study suggests that there is a possibility that mammalian maternal effect factors may participate in early developments by regulating retroviral elements.

Hybrid model of humans and mice
Multiple sclerosis-associated retrovirus (MSRV) is a HERV-W-related retroelement and found in cell cultures isolated from patients with MS, the human inflammatory demyelinating disease (Antony et al., 2011). In order to address the pathogenicity of MSRV retroviral particles, a hybrid model of humans and mice is used (Firouzi et al., 2003). SCID model mice grafted with primary human lymphocytes obtained from healthy blood donors are humanized SCID (hu-SCID) mice. hu-SCID intraperitoneally injected with MSRV virions exhibit neurological symptoms such as partial or generalized paralysis and eventually die bleeding in the brain. Pro-inflammatory T cell cytokines such as TNF-α and IFN-γ are overexpressed in severely ill animals. Thus, MSRV particles have potent immune-pathogenic properties mediated by T cells.

Experimental autoimmune encephalomyelitis (EAE) is the most commonly used experimental model for MS, and it has been shown that MSRV-ENV protein, a HERV-W ENV-derived protein, can induce EAE in C57/BL6 mice when administered in emulsion together with myelin oligodendrocyte glycoprotein (MOG) peptides (Perron et al., 2013). The clinical and histopathological features of MSRV-ENV-induced disease are indistinguishable from standard EAE, supporting the HERV-W ENV protein pathogenicity in vivo.

Tumor xenograft models
Several tumor xenograft studies testing oncogenic properties of HERVs have been reported. Syncytin-1, an envelope protein encoded by the HERV W env gene, is highly expressed in human hepatocellular carcinoma (HCC) (Zhou et al., 2021). Tumor xenograft assay reveals that NIH3T3 cells overexpressing syncytin-1 induce tumor formation in nude mice. Phosphorylation of MEK1/2 and ERK1/2 and expression of syncytin-1 are upregulated in HCC, which indicates MEK/ERK pathway is likely to be crucial in syncytin-1-promoted hepatocarcinogenesis. Syncytin-1-transfected human uroepithelial cells (SV-HUC-1) also develop into UCC in xenograft nude mice, too (Yu et al., 2013).

Expression of HERV-K ENV protein is higher in various cancers, including colorectal cancer than in normal tissues (Jo et al., 2016). A tumor is not formed, or even if formed, its size is significantly reduced in nude mice injected with human DLD-1 colorectal cancer cells in which HERV-K env is knocked out using the CRISPR-Cas9 system (Ko et al., 2021a). In another study, shRNA targeting HER-V-K env RNA (shRNAenv) is transfected into pancreatic cancer (PC) cells to suppress the expression of HERV-K env and then grafted into mice, which eventually show the reduced size of tumors when compared with controls (Li et al., 2017). The results indicate that HERV-K ENV protein participates in cell proliferation and tumor growth.

Acute lymphocytic leukemia cells, Raji, overexpressing Np9 are used for tumor xenograft in NOD-SCID mice and found to promote the growth of the xenograft leukemia cells (Chen et al., 2013). Kaposi’s sarcoma-associated herpesvirus (KSHV) infection can trans-activate HERV-K, particularly the encoded oncogenic Np9 expression worsens Kaposi’s sarcoma pathogenesis and KSHV-induced tumorigenesis in endothelial cells (Dai et al., 2018). Kaposi’s sarcoma xenograft model, mice injected with cells, in which Np9 is stably knockdown by shRNA, significantly suppresses the tumorigenesis of Kaposi’s sarcoma in vivo.

Porcine models
Pigs share many characteristics with humans such as anatomy, physiology, and metabolism, making it useful for an alternative organ donor for xenotransplantation (Gutierrez et al., 2015). PERVs are, in contrast to HERVs, still active to produce virion particles, which are infectious (Denner, 2016). Thus, there is a potential risk of cross-species transmission of porcine endogenous retroviruses (PERV), which can infect the recipient’s cells. Anti-PERV shRNAs method is shown to be highly effective to knock-down the expression of pol and gag genes of PERVs in pigs (Ramsoondar et al., 2009).

TRANSCRIPTION FACTORS BINDING HERV LTRs
The association between LTR sequence and cell line-specific expression suggests that certain sequence-specific elements, such as TFBSs, play a pivotal role in determining differential promoter activity. Identification of TFBSs and of their actual interactors is essential to assess the promoter activity of HERV LTRs, which drives gene expression in various situations, including human diseases (Montesion et al., 2018) (Table 1).

Double Homeobox 4 (DUX4) is a transcription factor, and its misexpression in skeletal muscle results in facioscapulohumeral muscular dystrophy (FSHD), an inherited muscle disease. DUX4 binds to the LTRs of HERV-L in rhabdomyosarcoma (RD) cells (Mitsuhashi et al., 2021), while it binds to those of HERV-K in myoblast cell lines (Young et al., 2013). DUX4 induces several HERV fusion transcripts and might significantly contribute to the pathology of FSHD.

SLE is an autoimmune disease and the most common type
| Type of HERV | Transcription factor Type | Disease/physiology | Type of model | Confirmation method | Reference |
|-------------|--------------------------|-------------------|---------------|---------------------|-----------|
| HERV-L, HERV-K, HERV-1 | DUX4, MIFAT1, ERα, MIFAT2 | Kidney cancer | ChIP, RNA-seq | Mitsuhashi et al., 2021; Young et al., 2019 |         |
| HERV-E | OCT4, Sox2 | Kidney cancer | ChIP, EMSA | Young et al., 2013 |         |
| HERV-K | HOX-1, CEBP | Kidney cancer | ChIP, EMSA | Yu et al., 2013 |         |
| HERV-W | NF-Y, OCT-1, C/EBP | Kidney cancer | ChIP, EMSA | Fuchs et al., 2011 |         |
| HERV-L, HERV-K | HNF-1, TIP60, BRD4 | Kidney cancer | ChIP, EMSA | Rajagopalan et al., 2018 |         |
| HERV-K | NF-κB, IRF1 | ALS | ChIP | Manghera et al., 2016 |         |
| HERVs (HERV-1) | Unknown | Brain tumor | RNA-seq | Yuan et al., 2021 |         |

**Table 1.** Transcription factors, which have been experimentally shown to influence HERV LTR activity.

DUX4, double homeobox 4; MIFAT1, ERα, MIFAT2, nuclear factor of activated T cells 1; ERα, estrogen receptor α; NF kB, nuclear factor κB; IRF1, interferon regulatory factor 1; TIP60, transcriptional intermediary factor 60; NF-κB, nuclear factor κB; TIP60, transcriptional intermediary factor 60; BRD4, bromodomain containing 4; MFT, microphthalmia-associated transcription factor; NF-kB, nuclear factor kappa-B; TIP60, transcriptional intermediary factor 60; BRD4, bromodomain containing 4; MFT, microphthalmia-associated transcription factor; bHLH, basic-helix-loop-helix; bHTH, basic helix–turn–helix; bHLH-LZ, basic helix-loop-helix leucine-zipper; FSHD, facioscapulohumeral muscular dystrophy; ALS, amyotrophic lateral sclerosis; SLE, systemic lupus erythematosus; RD, rhabdomyosarcoma; EMSA, electrophoretic mobility shift assay.
of lupus, and it is reported that high level of HERV-E clone 4-1 mRNA is detected in CD4+ T cells from SLE patients (Wang et al., 2019). Both nuclear factors of activated T cells 1 (NFAT1) and estrogen receptor-α (ER-α) bind to HERV-E clone 4-1LTRs where DNAs are hypomethylated. Therefore, HERV-E in CD4+ T cells can be activated by abnormal inflammatory responses in SLE.

Hypoxia-inducible transcription factor 2α (HIF-2α) binds to HIF response elements (HRE) localized in proviral LTRs of HERV-E in the clear cell histological subtype of renal cell carcinoma (ccRCC) and activates HERV-E expression (Cherkasova et al., 2011). The expression of a novel transcript derived from HERV-E provirus named CT-RC HERV-E is restricted to ccRCC, which is characterized by inactivation of the von Hippel-Lindau (VHL) tumor-suppressor gene. Transfection of a ccRCC tumor line with a plasmid expressing functional VHL significantly reduces the expression of CT-RC HERV-E transcripts. The results suggest that inactivation of tumor suppressor VHL may be associated with HERV-E expression in ccRCC.

HIFs, HIF-1α, HIF-2α, and HIF-1β, are all reported to bind to the LTRs of class I HERVs and HERV-K families, and HIF-bound LTRs show a promoter-like activity driving expression of POU5F1 (OCT4), a stem cell transcription factor, in RCCs (Moon et al., 2020; Siebenthall et al., 2019). POU5F1 is consistently upregulated in tumor cells in Cancer Genome Atlas (TCGA) cohorts. Progesterone receptor (PR) and OCT4 bind progesterone-response element (PRE) and an octamer motif, respectively, in a long terminal repeat LTRSHS of HERV-K, activating transcription downstream of the LTRSHS in human breast cancer cells T47D, in which the activation of HERV-K by female hormones have been reported (Nguyen et al., 2019; Ono et al., 1987).

A specific mutation in HERV-W LTRs is significantly associated with the pathology of UCC and with synctin-1 overexpression. c-Myb binds to 3′-LTRs of HERV-W, which depends on 142T > C mutation (Yu et al., 2013). The mutant 3′-LTR acts as an enhancer for synctin-1 gene expression, stimulated by c-Myb in UCC. The results indicate that the HERV-W 3′-LTRs can be a regulatory element affecting synctin-1 gene expression, participating in tumor development. On the other hand, HOXA5 is shown to bind normal HERV-W 3′-LTR, also regulating synctin-1 gene expression.

In colorectal cancer cells, hepatocyte nuclear factor 1 (HNF-1) binds to the LTR of HERV-L, which acts as an alternative promoter for the human p1,3-galactosyltransferase 5 gene (Dunn et al., 2003). It is found that the HERV-L LTR is a dominant promoter in the colon and has a significant impact on the gene expression of β3Gal-T5.

HERV-K expression is upregulated in neural tissues from ALS patients. Independent and synergistic upregulation of HERV-K by interferon regulatory factor 1 (IRF1), NF-κB isoforms p50 and p65 are observed in ALS patients’ astrocytes and neurons (Manghera et al., 2016). Treatment with cytokines TNF-α and LIGHT (the lymphotixin-like inducible protein that competes with glycoprotein D for herpes virus entry on T cells) increase the levels of HERV-K transcript and protein through the direct interaction between both interferon regulatory factor 1 (IRF1) and NF-κB and the interferon-stimulated response elements (ISREs) located in the HERV-K LTRs. Cytokine-mediated IRF1 and NF-κB binding to the HERV-K LTR is in a cell-type-dependent manner. TNF-α increases HERV-K protein levels in neurons, whereas LIGHT induces HERV-K in astrocytes.

Several transcriptional initiator (Inr) sites in the HERV-K LTRs are detected by rapid amplification of complementary DNA ends (5′ RACE) (Katoh et al., 2011). The most potent Inr is associated with a TATA box and three binding motifs of microphthalmia-associated transcription factor (MITF). Both chromosomal HERV-K and the cloned LTRs are strongly activated in HEK293, which are transfected with MITF-M, a melanocyte/melanoma-specific isoform of MITF. In malignant melanoma lines, HERV-K transcription is enhanced when compared with normal melanocytes.

Gel shift assay shows that binding complexes, which are formed on the enhancer sequence by protein extracts of HERV-K-expressing teratocarcinoma cell lines GH and Tera2 form, are different from those of HeLa and HepG2 cells, both of which do not express HERV-K (Knössl et al., 1999). Combined results obtained from competition gel shift assay, Dnase I footprinting, and supershift experiments indicate that the binding site of these complexes is a 20-bp sequence within HERV-K enhancer, and the transcription factor YY1 was one component of the HERV-K enhancer-bound complex.

Transcription factors Sp1 and Sp3 also interact with HERV-K LTRs (Fuchs et al., 2011). Both mutating specific GC boxes, which are binding sites for Sp proteins, and knocking down Sp1 and Sp3 with small interfering RNA (siRNA) significantly interfere with the promoter activity of HERV-K LTRs in human melanoma and teratocarcinoma cells.

Gliomas originated from astrocytes, oligodendrocytes, and ependymal cells attributes more than 70% of all brain tumors (Ohgaki and Kleihues, 2005). Glioblastoma multiforme (GBM) arises from the uncontrolled proliferation of astrocytes and is one of the most aggressive types of malignant brain tumors (Buckner et al., 2007; Kim et al., 2021; Ostrom et al., 2015). The analyses of the various genome and transcriptome data sets generated from GBM tissues and normal brain tissues identify some differentially expressed repetitive elements (Jung et al., 2020a; Yuan et al., 2021). Forty-eight of those repetitive elements are LTR elements, of which 46 are derived from HERV elements. Forty-three out of the 46 differentially expressed HERV elements are upregulated, and 34 significantly changed HERV elements belong to the class I superfamily. The LTR elements from HERVs are potential biomarkers for immunotherapy to treat GBM. Expression levels of these elements could be monitored as biomarkers to treat GBM.

The Rec protein of HERV-K interacts with human small glutamine-rich tetraticopeptide repeat (TPR)-containing protein (hSGT) which is a cellular androgen receptor (AR) inhibitor (Hanke et al., 2013). This interaction was confirmed by co-immunoprecipitation, pull-down assays, and colocalization experiments. Rec interference with hSGT induces AR activity. Rec also acts as a transactivator by enhancing AR-mediated activation of the HERV-K LTR promoter. Rec-driven hyper-activation of the AR leads to increased cell proliferation and
inhibition of apoptosis and eventually to tumor induction or promotion.

An atypical teratoid rhabdoid tumor (AT/RT) is an embryonal central nervous system (CNS) cancer often characterized by loss of SMARCB1 (SWI/SNF Related, Matrix Associated, Actin Dependent Regulator of Chromatin, subfamily B, Member 1). SMARCB1 is a tumor suppressor gene and essential during development. AT/RTs contain undifferentiated cancer cells (Nemes and Frühwald, 2018). The repression of HERV-K env retains stem cell features and enhances neuronal differentiation (Wang et al., 2020a). In AT/RT cell lines, loss of SMARCB1 in neural stem cells (NSCs) results in upregulation of HERV-K env, but restoration of SMARCB1 leads to down-regulation of HERV-K env (Doucet-O’Hare et al., 2021). In the absence of SMARCB1, c-Myc binds to HERV-K LTR and increases HERV-K expression. However, SMARCB1 interferes with c-Myc, binds to HERV-K LTR, and represses HERV-K expression, when overexpressed. HERV-K activation in the development of undifferentiated tumors in AT/RT suggests it may play a critical role in human embryonic and neurodevelopment.

**MOLECULAR AND CELLULAR EVENTS CONTROLLED BY HERV ELEMENTS**

HERV elements actively control multiple molecular and cellular events in different cells including neurons, glia, cancer and stem cells in various physiological and pathological conditions (Table 2).

**Toll-like receptor (TLR) signaling: TLR-3 and TLR-4**

Elevated levels of TLR-3 and IL-6 are detected in syncytin-1-overexpressing human microglia cell line CHME-5 and astrocyte cell line U251 (Wang et al., 2018). The syncytin-1-overexpressing human microglia cell line CHME-5 and... 

### Table 2. Roles of HERV elements in signaling pathways

| HERV elements | Signaling pathways | Effects | Reference |
|---------------|--------------------|---------|-----------|
| MSRV-Env      | TLR4 pathway       | - Acts as agonist of human TLR-4 - Impairs human OPC maturation to myelinating oligodendrocytes - Induces TLR4-dependent pro-inflammatory stimulation of immune cells - Induces over-expression of ICAM-1 and stimulates inflammatory factors in BBB in vitro model | Madeira et al., 2016 Duperay et al., 2015 |
| MSRV-Env-SU   | CD14 and TLR-4 pathway | - Triggers maturation process in human dendritic cells - Induces human monocytes to produce major pro-inflammatory cytokines through CD14 and TLR4 | Rolland et al., 2006 |
| HERV-W-env    | TLR4/MyD88 pathway | - Upregulates the expressions of inflammatory cytokines through TLR4/MyD88 pathway in glial cells | Wang et al., 2021 |
|               | BDNF signaling     | - Increases the expression of BDNF, NTRK2, and DRD3 that contribute to the pathogenesis of the schizophrenia | Huang et al., 2011 |
| Syncytin-1    | TRPC3 channel SK3 channel | - Induces Ca2+ influx through TRP3 channel and regulates DISC1 | Chen et al., 2019 Li et al., 2013 Zhou et al., 2021 |
|               | MEK/ERK pathway    | - Promotes cell proliferation, metastasis, and tumorigenicity in human hepatocellular carcinoma (HCC) | Wang et al., 2018 |
|               | TLR3 pathway       | - Activates TLR-3 signaling and induces the production of CRP in microglia and astrocytes | |
| HERV-K env    | TGF-β signaling    | - Proliferation and cell-cell fusions | Strick et al., 2007 Zhou et al., 2016 Ko et al., 2021a Wang et al., 2020b Lemaître et al., 2017 |
|               | Ras signaling      | - Promotes tumorigenesis in breast cancer (BC) | |
|               | TGF-β signaling    | - Tumor proliferation, invasion, migration in colorectal cancer | |
|               | mTOR pathway       | - Interacts with CD98HC, triggers mTOR and regulates of stem cell function/neuronal differentiation | |
|               | ERK1/2 pathway     | - Induces epithelial to mesenchymal transition (EMT) | |
| HERV-K LTR    | NTRK3 signaling pathway | - Induces NTRK3 expression and impairs cortical neuron development | Padmanabhan Nair et al., 2021 Li et al., 2010 |
| HERV-K gag and env | MEK-ERK and p16INK4A-CDK4 pathways | - Potential regulator of BRAF-MEK-ERK and p16INK4A-CDK4-RB during melanoma pathogenesis | Chen et al., 2013 |
| HERV-K Np9    | β-catenin, ERK, Akt and Notch1 signaling | - Activates β-catenin, ERK, Akt and Notch1 signaling pathways and regulates the growth of human leukemia stem/progenitor cells | |

MSRV-Env, multiple sclerosis associated retrovirus envelope protein, member of the W family of HERV (HERV-W); MSRV-Env-SU, the surface unit of the MSRV envelope protein; OPC, oligodendrocyte precursors cells; PBMC, peripheral blood mononuclear cells; BBB, blood-brain barrier; ICAM-1, intercellular adhesion molecule 1; BDNF, brain-derived neurotrophic factor; DISC1, disrupted-in-schizophrenia 1; CREB, cAMP response element-binding protein; CRE, cAMP response element; CD98HC, a heterodimeric amino acid transporter; NTRK3, neurotrophic tyrosine receptor kinase 3.
Overexpression of syncytin-1 upregulates brain-derived neurotrophic factor (BDNF), neurotrophic tyrosine kinase receptor type 2 (NTRK2), and dopamine receptor D3, and phosphorylation of CAMP (cyclic adenosine monophosphate) response element-binding (CREB) protein in human glioma cells (Huang et al., 2011). Syncytin-1 interacts with BDNF promoter, enhancing transcription. In human neuroblastoma cells, syncytin-1 activates the promoter of small conductance Ca²⁺-activated K⁺ channel protein 3 (SK3), depending on both CREB and CAMP response element (CRE) (Li et al., 2013). In neuroblastoma cells, syncytin-1 overexpression induces Ca²⁺ influx through transient receptor potential cation channel subfamily M member 3 (TRPM3) channels by directly regulating its expression or by downregulating the gene disrupted-in-schizophrenia 1 (DISC1) (Chen et al., 2019; Dhakal and Lee, 2019). These conditions contribute to the pathogenesis of schizophrenia: thus, HERV-W may also involve in the development of psychotic disorders.

**HERV coding proteins affect signaling pathways in cancers**

Syncytin-1 promotes cell proliferation, metastasis, and tumorigenicity in HCC by activating MEK/ERK pathway. It is shown that syncytin-1 upregulates MEK/ERK downstream proteins such as c-Myc, c-Fos, c-Jun, CDK1, and CDK4 in HCC (Zhou et al., 2021). HERV-K ENV induces epithelial to mesenchymal transition (EMT), which promotes cell motility in human breast epithelial cells, activating the ERK1/2 pathway (Lee et al., 2019a; Lemaitre et al., 2017). The downstream events include increased expression of various transcription factors such as EGR1, ZCCHC12, ETV4, and ETV5, which are tightly related to oncogenesis. HERV-K ENV is also reported to increase Ras-induced ERK activation in human breast cancer cells and promote tumorigenesis (Wang et al., 2020c; Zhou et al., 2016). These findings lead to a therapeutic approach using anti-HERV-K ENV, which is potential for immunotherapy of breast cancer. A chimeric antigen receptor (CAR) specific for HERV-K ENV protein (K-CAR) has an anti-metastatic activity, inhibiting cell proliferation in vitro and tumorigenesis in vivo (Zhou et al., 2015). A recent study shows that CRISPR-Cas9 mediated knock-down of the HERV-K ENV gene in DLD-1 colorectal cancer showed reduced proliferation, invasion, migration, and tumor colonization by activating the ROS-NUPR1 pathway (Ko et al., 2021b).

Syncytin-1 expression is significantly increased in endometrial carcinomas (EnCa) (Strick et al., 2007). Treatment with steroid hormone estrogen induces syncytin-1 expression in primary EnCa cells and increases cell proliferation. DNA binding assays reveal that ER binds explicitly to the syncytin-1 ERE, an estrogen response element located in the LTR of HERV-W. Therefore, steroid hormones directly regulate syncytin-1 gene expression. In addition, syncytin-1 is also upregulated in EnCa cells treated with the SP isomer of CAMP (SP-cAMP), and those EnCa cells undergo proliferation and cell-cell fusion, which are blocked by silencing of syncytin-1 gene expression. The addition of purified TGF-β1 or TGF-β3 proteins to SP-cAMP treated EnCa cells inhibits cell-cell fusion while the high level of syncytin-1 is unchanged. The result indicates that TGF-β treatment can rework syncytin-1-mediated cell-cell fusions, which may provide a therapeutic option in endome-
rial cancers.

Both HERV-K GAG and ENV are highly expressed in melanoma cells, in which phosphorylation of ERK is also increased. In contrast, p16INK4a suppresses tumors by inhibiting cyclin-dependent kinases CDK4 and CDK6 (Quelle et al., 1995) and is detected in mostly nevus cells rather than melanoma cells (Li et al., 2010). These studies show a positive correlation between the levels of HERV-K GAG and ENV proteins with activation of MEK/ERK pathway and loss of p16INK4A-CDK4 activities in melanoma cells.

Overexpression of HERV-K type 1-encoded Np9 induces the growth of leukemia cells, whereas knock-down of Np9 expression inhibits the growth of myeloid and lymphoblastic leukemia cells (Chen et al., 2013). These results indicate that Np9 is essential for the survival and growth of myeloid and lymphoblastic leukemia cells. Overexpression of Np9 is also reported to increase the protein levels of β-catenin, ERK, Akt, and Notch1 signaling molecules, whereas silencing of Np9 causes a significant decrease of expression levels of c-Myc, pERK1, phospho-Akt (pAkt), and cleaved Notch1 in leukemia cells.

**ENVs in stem cells**

HERV-K ENV is reported to be expressed in the cell membrane of pluripotent stem cells and interact with a heterodimeric amino acid transporter CD98HC (Wang et al., 2020b). The interaction leads to triggering mammalian targets of rapamycin (mTOR) and lysophosphatidylcholine acyltransferase (LPCAT1) pathways that regulate stem cell function. Down-regulation of HERV-K ENV was shown to promote neuronal differentiation of stem cells.

LTR promoter of HERV-K is activated in hESCs by the CRISPR activation (CRISPRa) method (Padmanabhan Nair et al., 2021). HERV-K activated hESCs are differentiated into cortical neurons. Those cortical neurons display a drastic reduction in microtubule-associated protein 2 (MAP2) expression, which is a neuron-specific cytoskeletal protein and a marker for neuronal cells (Dinsmore and Solomon, 1991). These cortical neurons exhibit shorter axons with fewer branches. Activated HERV-K LTR also robustly upregulates neurotrophic tyrosine receptor kinase 3 (NTRK3), critical in cortical neuron development (Bartkowska et al., 2007). The knock-down of NTRK3 in HERV-K LTR-activated cortical neurons reverts the observed phenotypes, suggesting that HERV-K activation impairs NTRK3-dependent cortical neuron development, which ultimately results in abnormal brain development (Padmanabhan Nair et al., 2021).

**HERVs in COVID-19**

Recently, several studies report that HERVs are activated in COVID-19 infection. IFN-1, IFN-2, TRIM28, SETDB1, and viral genes of HERV-H, -K, and -W families are upregulated in peripheral blood from children between 4-8 years suffering from COVID-19 with mild symptoms, whereas downregulated in severe cases (Tovo et al., 2021). The correlative expression of these genes according to the severity of COVID-19 suggests that there are distinct phases of the disease, for which the differentially regulated genes may serve as prognostic markers. The syncytin-1 protein level is high in blood samples from adult COVID-19 patients (Balestrieri et al., 2021; Garcia-Montojo and Nath, 2021). The expression of syncytin-1 is also correlated with the markers of T-cell differentiation such as IL-6, IL-10, IL-17, IL-17RA, MCP1, and CXCR1. Syncytin-1-positive lymphocytes and inflammatory markers are correlated with the severity of pneumonia in COVID-19 patients.

A recombinant baculovirus expressing the envelope of HERV-W (AcHERV) is constructed as a DNA vaccine system against Middle East respiratory syndrome coronavirus (MERS-CoV) and the severe acute respiratory syndrome coronavirus-2 (SARS-CoV2), responsible for COVID-19 (Cho et al., 2021; Shah and Woo, 2021). Baculoviruses possess a nuclear transport signal which enables an efficient gene expression of inserted full-length S, S1 subunit, or RBD antigens of MERS-CoV or SARS-CoV2 with multiple boosting. The AcHERV-COVID19-S vaccine induces serum IgG, neutralizing antibody, and antigen-specific IFN-γ secretion, indicating high cellular immunity. AcHERV-MERS-S1 also prompts high levels of IgG, neutralizing antibody, and T-cell immune responses. AcHERV-DNA vaccines provide increased protection against MERS-CoV and SARS-CoV2 in animal models, supporting the feasibility of AcHERV-MERS or AcHERV-COVID19 vaccines in preventing pandemic spreads of viral infections.

**CONCLUSION**

HERVs are ancient sequences of exogenous retroviruses integrated into the human genome and are considered viral “fossils”. Although most HERVs have accumulated mutations and lost their coding capability, they still retain some activities in terms of HERV-mediated regulation of host gene expression. Many studies have revealed that abnormal activation and expression of HERV genes can lead to severe illnesses like cancers, autoimmune diseases, and neurological diseases. Various endogenous transcription factors regulating cell proliferation and differentiation bind to specific motifs in HERV LTRs, which act as a promoter or an enhancer. Downstream events include activation of various signaling pathways such as TLR-4 and MEK/ERK. While a number of stimulators are known to activate HERV genes inadequately, the recent report shows that expression patterns of HERV genes fluctuate in the progress of COVID-19. The more profound insight into the mechanisms explaining the roles HERV activities in various biological contexts will help develop clinical applications targeting HERVs and set up diagnostic and prognostic biomarkers for related diseases, even unprecedented pandemic illness of COVID-19.

*Note: Supplementary information is available on the Molecules and Cells website (www.molcells.org).*

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01373, Artificial Intelligence Graduate School Program [Hanyang University]). We sincerely apologize to our colleagues in case we unwittingly omit their valuable works in this review.

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CONFLICT OF INTEREST
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