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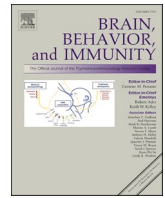
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# Interplay between activation of endogenous retroviruses and inflammation as common pathogenic mechanism in neurological and psychiatric disorders

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## ABSTRACT

Human endogenous retroviruses (ERVs) are ancestral retroviral elements that were integrated into our genome through germline infections and insertions during evolution. They have repeatedly been implicated in the aetiology and pathophysiology of numerous human disorders, particularly in those that affect the central nervous system. In addition to the known association of ERVs with multiple sclerosis and amyotrophic lateral sclerosis, a growing number of studies links the induction and expression of these retroviral elements with the onset and severity of neurodevelopmental and psychiatric disorders. Although these disorders differ in terms of overall disease pathology and causalities, a certain degree of (subclinical) chronic inflammation can be identified in all of them. Based on these commonalities, we discuss the bidirectional relationship between ERV expression and inflammation and highlight that numerous entry points to this reciprocal sequence of events exist, including initial infections with ERV-activating pathogens, exposure to non-infectious inflammatory stimuli, and conditions in which epigenetic silencing of ERV elements is disrupted.

## 1. Introduction

Endogenous retroviruses (ERVs) are inherited genetic elements derived from exogenous retroviral infections occurring throughout the evolution of the genome. In general, ERVs belong to a retrotransposon subgroup of mobile genomic elements and comprise 5–8 % of the human genome (Lander et al., 2001). In other mammalian genomes, ERVs are similarly abundant and comprise, for example, approximately 10 % of the mouse genome (Stocking & Kozak, 2008). It is thought that multiple independent infectious events generated a unique genomic ERV content in different species, with additional genetic recombination leading to more than 100,000 ERV loci known in humans with extensive inter-individual variations (Nellaker et al., 2012; Thomas et al., 2018).

ERVs are traditionally classified into three classes (I, II and III), based on relatedness to the exogenous *Gammaretrovirus*, *Betaretrovirus* and

*Spumaretrovirus*, respectively. Within this classification individual ERV lineages are referred to as “families”, and comprise groups of ERVs that are assumed to derive from a single germline invasion event (Gifford et al., 2018).

While human ERVs are often regarded as genomic parasites, their ancestral embedding in our genomes suggests a certain degree of domestication and symbiosis (Küry et al., 2018). An illustrative example of positive evolutionary selection are syncytin 1 and 2, which represent envelope (Env) genes of the ERVW-1 and ERVFRD-1, respectively. The encoded proteins play an important role in placentogenesis and might also be involved in foetal-maternal immune tolerance (Xiang & Liang, 2021). A similar functional domestication emerged for ERV-encoded group specific antigens (GAGs), some of which pertain to key processes of memory consolidation in the mammalian brain, including long-term potentiation and long-term depression (Pastuzyn et al., 2018).

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Whereas most human ERVs (HERVs) appear to be inherently inactivated, multiple studies revealed activation of some of these elements in neurodevelopmental disorders such as autism spectrum disorder (ASD) or attention deficit hyperactivity disorder (ADHD), psychiatric disorders such as schizophrenia (SZ) and bipolar disorder (BD), and neuro-inflammatory/neurodegenerative disorders such as multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS). While all these clinical conditions differ in terms of overall disease pathology and causalities, a common feature is that they are all associated with different degrees of (subclinical) chronic inflammation. Based on these commonalities, we aim at discussing the potential relationships between ERV activation and expression along the induction of inflammatory processes, thereby examining whether a direct sequence of events can be deduced.

## 2. Human endogenous retroviruses as a central element of neurodevelopmental, psychiatric and neuroinflammatory disorders

### 2.1. Neurodevelopmental disorders

Autism spectrum disorder (ASD) was one of the first neurodevelopmental disorders in which abnormal retroviral activity was identified. It is a pervasive developmental disorder, affecting 1 in every 160 children worldwide, characterized by three main core symptoms, namely impairments in social interaction, deficits in verbal and non-verbal communication, and presence of restricted and repetitive behaviours (Santos et al., 2022). It was shown to involve immunological dysfunction with several ASD risk genes encoding components of the immune system (Meltzer & Van de Water, 2017). Signs of microglia activation and increased production of inflammatory cytokines and chemokines, including interferon (IFN)- $\gamma$ , interleukin (IL)-1 $\beta$ , IL-6, IL-12p40, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and chemokine C-C motif ligand (CCL)-2, in the brain parenchyma and cerebral spinal fluid (CSF) were described (Onore et al., 2012). Furthermore, elevated levels of pro-inflammatory cytokines in plasma were identified in medication-free ASD patients from the ages of 2 to 5 compared to age-matched, normally developing and healthy control children and to children with other developmental disabilities (Ashwood et al., 2011). The overproduction of peripheral cytokines in ASD children was further associated with impaired communication skills and aberrant behaviours (Ashwood et al., 2011).

Env gene expression of HERV-H, HERV-K, HERV-W and HEMO (different subtypes of human ERVs) was investigated in peripheral blood mononuclear cells (PBMCs) from ASD children, their parents and from corresponding healthy controls. ASD patients showed significantly higher HERV-H Env transcript levels as compared to healthy children (Balestrieri et al., 2019). Intriguingly, PBMCs from mothers of ASD children also showed significantly higher levels of HERV-H Env transcripts in comparison to mothers of the control group (Balestrieri et al., 2019). Similar findings were obtained for HERV-K and HEMO Env gene expression. On the contrary, the transcriptional activity of HERV-W Env was significantly lower in ASD children as compared to healthy controls, but significantly higher in their mothers and fathers compared to the corresponding control group (Balestrieri et al., 2019).

Abnormally high expression levels of ERV components were also reported in two distinct mouse models of ASD (Cipriani et al., 2018b). The first mouse model involved BTBR T + tf/J inbred mice, which corresponds to an idiopathic ASD model capturing several ASD-related behavioural traits, including impairments in social interaction, communication, and cognitive flexibility, as well as high levels of repetitive behaviours. The second model was based on CD-1 outbred mice which were prenatally treated with the anticonvulsant and histone deacetylase inhibitor valproic acid (VPA). These animals show ASD-like behavioural alterations, including early motor hyperactivity, social deficits, and cognitive impairments. Both models showed consistently increased transcriptional activity of several ERV families in whole

embryos, as well as in postnatal blood and brain samples (Cipriani et al., 2018b). Moreover, expression levels of pro-inflammatory cytokines and toll like receptors (TLRs) were also significantly elevated after prenatal VPA treatment (Cipriani et al., 2018b).

ERVs also seem to be implicated in attention deficit hyperactivity disorder (ADHD), a neurodevelopmental condition usually detected before the onset of late adolescence or early adulthood. ADHD is characterized to a varying degree by difficulties in maintaining sustained attention and executive functions, motor hyperactivity, and impulsivity (American Psychiatric Association, 2013). As the majority of children with ADHD have a high prevalence of allergic diseases, it is likely that immune- and inflammation responses are involved in the aetiology of this disorder (Tsai et al., 2013). When PBMCs of 30 subjects with ADHD and 30 healthy controls were analysed, increased expression of HERV-H was found in PBMCs of ADHD subjects, with Env transcript levels correlating positively with inattention and hyperactivity (Balestrieri et al., 2014). Furthermore, drug-naïve ADHD patients showed a reduction in HERV-H Env mRNA levels in response to administration of methylphenidate, a commonly used drug for treating ADHD symptoms (Cipriani et al., 2018a).

### 2.2. Psychiatric disorders

Abnormal ERV expression was also identified in schizophrenia (SZ), a major psychiatric disorder affecting up to 1 % of the world's population (Charlson et al., 2018). It is characterized by varying degrees of cognitive impairments, emotional aberrations, and behavioural anomalies, which together undermine basic processes of perception, reasoning, and judgment. Typically, the onset of full-blown SZ is in early adulthood and includes a myriad of symptoms. These symptoms can be referred to as positive symptoms (e.g. visual and/or auditory hallucinations, delusions, paranoia, psychomotor agitation), negative symptoms (e.g. social withdrawal, apathy, deficits in motivation and reward-related functions), and cognitive symptoms (e.g. deficits in executive functioning, working memory, and attention) (Owen et al., 2016).

Increasing evidence suggests that the immune system is involved in the pathogenesis and pathophysiology of SZ. Support for this notion includes epidemiological findings of increased risk of SZ following early-life exposure to infectious pathogens or inflammatory stimuli (Brown & Meyer, 2018), along with post-mortem and imaging studies demonstrating glial anomalies and increased expression of cytokines and other mediators of inflammation in the brain and periphery in people with SZ (Miller et al., 2011; Trepanier et al., 2016). Noticeable inflammatory abnormalities, however, are evident only in a subgroup of SZ cases (Fillman et al., 2013; Fillman et al., 2016; Purves-Tyson et al., 2021) and may predict poorer clinical outcomes and treatment responses (Hoang et al., 2022; Mondelli et al., 2015).

Furthermore, it was recently demonstrated that patients with SZ or bipolar disorder (BD) can be stratified into subgroups with differing inflammatory and clinical profiles based on HERV-W Env protein antigenemia and cytokines (Tamouza et al., 2021). In this study, two main clusters of patients were identified which were best predicted by the presence or absence of the HERV-W Env protein. HERV-W expression was associated with increased serum levels of inflammatory cytokines and higher childhood maltreatment scores. Furthermore, patients with SZ expressing the HERV-W Env protein showed more manic symptoms and higher daily chlorpromazine equivalents. These findings add to a previous study identifying retroviral polymerase gene sequences of the HERV-W family in the CSF of 29 % of individuals with recent-onset SZ or schizoaffective disorder (Karlsson et al., 2001). Transcripts from HERV-W family genes were also found to be upregulated in the frontal cortex of brains from individuals with SZ (Karlsson et al., 2001). A more recent publication found that patients with first-episode psychosis displayed lower levels DNA methylation at HERV-K loci, whereas chronic patients with SZ did not differ from matched controls with regards to HERV-H methylation (Mak et al., 2019). In addition, it was found that HERV-K

methylation levels correlated positively with the chlorpromazine equivalents, indicating that antipsychotic medications may contribute to the normalization of aberrant HERV-H methylation patterns along the clinical course of schizophrenia (Mak et al., 2019).

Abnormal ERV expression was found in BD, a heterogeneous psychiatric disorder characterized by fluctuating symptoms involving episodes of mania and depression and intermittent periods of euthymia. The number of episodes and duration of each state varies markedly between individuals. Manic episodes typically include a reduced need for sleep, increased energy, rapid speech, increased libido, reckless behaviour, grandiose thoughts, and elevations in mood. In severe episodes, psychotic symptoms such as delusions and hallucinations may also be present. While the precise etiopathology of BD is still ill-defined (Harrison et al., 2018), several studies indicate that it involves changes in the innate and adaptive immune system including inflammation. For example, patients with BD often show increased serum concentrations of interleukins and C-reactive protein (CRP), a protein which rises in response to inflammation. Moreover, inflammatory alterations have been detected in the brain parenchyma of patients with BD (Harrison et al., 2018). Similarly to SZ, HERV-W transcripts and proteins were repeatedly found to be elevated in the blood, CSF and brains of patients with BD (Li et al., 2019; Perron et al., 2012; Tamouza et al., 2021). Intriguingly, a recent study showed that patients with BD who were positive for HERV-W Env protein had increased serum levels of IL-1 $\beta$  and an earlier disease onset as compared to patients were negative for HERV-W Env protein (Tamouza et al., 2021), suggesting that differential HERV-W activity may define distinct subgroups in bipolar disorder.

### 2.3. Neurological disorders

Human ERVs have long been speculated to be involved in the aetiology and pathophysiology of neurological disorders, especially in multiple sclerosis (MS) (Perron et al., 1989). MS is characterized by a primary attack to oligodendrocytes, the myelinating glial cells of the central nervous system (CNS), and by the subsequent demyelination of axons and axonal degeneration. These neurodegenerative processes eventually result in irreversible loss of sensory, motor, and cognitive functions. Infiltrating lymphocytes, monocytes/macrophages, activated astrocytes and microglia represent some of the key pathological features of MS, whereas their contribution varies between acute, relapsing/remitting and chronic, progressive disease stages (Matthews, 2019). Nevertheless, despite the plethora of studies conducted over the last decades, the precise aetiology of MS remains elusive.

Since the initial discovery of retroviral elements in the leptomeningeal cells of MS patients (Perron et al., 1989), MS has been repeatedly associated with human retroviral elements in general, and with the HERV-W Env gene in particular. These associations further involved pro-inflammatory effects on innate and adaptive immune cells, impacts on endothelial cells of the blood–brain-barrier (BBB), impaired regenerative responses of remyelinating oligodendroglial precursor cells, as well as activation and polarisation of microglial towards an axon-damaging phenotype (Küry et al., 2018). Hence, there is converging evidence suggesting a broad impact of ERV activation and expression in the development and progression of MS. A pathological involvement of the HERV-W Env protein in the aetiology of MS has recently been confirmed by a clinical trial, in which a therapeutic Env-neutralizing antibody was administered to MS patients. The clinical outcome revealed reduced brain atrophy rates as well as stabilized radiological markers of white matter integrity thus an impact on neurodegeneration as well as on repair activities (Hartung et al., 2022).

Following the thread of neurological disease associated with the expression of human ERVs, we find amyotrophic lateral sclerosis (ALS) with an estimated prevalence of 4 to 8 cases per 100.000 persons (Longinetti & Fang, 2019). This disease is characterized by a progressive loss of cortical and spinal motor neurons, resulting in motor dysfunction and motor cortex volume loss (Li et al., 2015a; Mathis et al., 2017). On

the immunological aspect, ALS involves microglia and astrocyte activation as well as T cell infiltration and inflammatory cytokine overproduction (Liu and Wang, 2017).

A study conducted among 23 ALS patients and 21 patients suffering from other neurological diseases serving as controls, found the presence of reverse transcriptase (RT) activity in the sera of 56 % of the ALS patients versus in 19 % of the control group (MacGowan et al., 2007). It was furthermore observed that non-symptomatic blood relatives of ALS patients also had increased RT activity in comparison to the ALS patient's spouses, which served as control group (Steele et al., 2005). These findings thus support the notion that the RT proteins derive from an endogenous origin rather than from an exogenous viral infection. Furthermore, all major genetic components of the HERV-K genome, i.e., Gag, Pol and Env, were found to be elevated in post-mortem brain samples from ALS patients (Li et al., 2015b). While the detection and involvement of HERV-K in ALS is still debated, studies on cultured neurons showed that both, the entire genome and the Env gene caused a similar decrease in cell numbers and retraction of neurites in a dose-dependent manner. Likewise, transgenic overexpression of the HERV-K Env protein in motor neurons provided strong evidence that this leads to pathological hallmarks of ALS, including progressive motor dysfunction and motor cortex volume loss (Li et al., 2015b). Moreover, 24 weeks of antiretroviral therapy on 29 ALS patients resulted in a progressive decrease of copy numbers of HML-2 (subtype of HERV-K) and the majority of participants (82 %) revealed to be “responders”. Among the responders, respiratory function and motor neuron dysfunction was ameliorated, indicating a slower progression of the disease. This outcome supports a possible role for HERV-K in the clinical course of the disease (Garcia-Montojo et al., 2021).

Taking together, an intricate interaction between endogenous retroviral elements and inflammation-related immune responses appear to play a role in the onset and/or progression of these neurological conditions. However, it is currently unclear to what degree endogenous retroviruses act in a unified way in all these disorder and whether inflammation acts as a trigger of ERV activation or, the other way round, whether immune processes are specifically initiated and supported by ERVs. These questions are addresses in the subsequent section, where the relationship between epigenetic control mechanisms, ERV expression and inflammation are discussed in more detail.

### 3. (Re-)Awakening of endogenous retroviruses

Under physiological conditions, the majority of endogenous retroviruses, particularly those with primarily pathological functions, are thought to be in a dormant state and suppressed by molecular mechanisms of epigenetic silencing. Upon certain events, however, such epigenetic repression can break down, leading to a (re)activation of these retroviral entities, possibly initiating disease onsets and/or accelerating disease progression. We therefore aim at summarizing the current knowledge regarding the epigenetic mechanisms that maintain repression and facilitate activation of pathological ERVs.

Based on the current state of evidence, it appears that various epigenetic processes are relevant for controlling ERV expression, including localisation of proviruses in the heterochromatin, blocking long terminal repeat (LTR) access, CpG methylation and histone deacetylation. The predominant view is that these epigenetic processes assure overall ERV silencing, whereas small leakages at transcription levels can still occur (Leung & Lorincz, 2012).

Most CpG islands are found to be methylated throughout the human genome, including those encompassing ERVs (CGIs) (Deaton et al., 2011). In this regard, a genome-wide microarray approach identified human ERV families to be heavily methylated in healthy tissues (Szpakowski et al., 2009). Furthermore, differences in silencing modes were associated with the evolutionary age of ERV insertions. Indeed, evolutionary “young” LTRs are CpG rich and amenable to DNA methylation, whereas the expression of evolutionary “old” ERVs appear to be

controlled mostly via histone modifications (Ohtani et al., 2018). This distinction was confirmed by a study showing a correlation between HERV-K (HML-2) 5' LTR methylation and transcriptional suppression of its provirus in the Tera-1 cell line (Lavie et al., 2005).

Histone acetylation blocks the positive charges on lysine residues, which destabilises chromatin and favours transcriptional activation. Thus, histone deacetylation represents another epigenetic silencing mechanism with relevance to ERVs (Bannister & Kouzarides, 2011). Acetylation of lysine residues in histones is catalysed by histone acetyltransferases (HATs) and counteracted by histone deacetylases (HDACs). As the use of HDAC inhibitors alone did not significantly induce ERV expression in humans (HERV-K [HML-2], HERV-W, HERV-FRD) in cell lines with the dormant HIV-1 virus or primary T cells infected with HIV-1 (Hurst et al., 2016), it is unlikely that histone deacetylation alone may be the primary epigenetic mechanism underlying ERV repression, but it nevertheless may act in combination with CpG methylation to do so. This hypothesis is supported by the observation that the combination of the HDAC inhibitor trichostatin A and the DNA methylation inhibitor 5'-azacytidine increased HERV-Fc1 expression in human embryonic kidney cells, whereas trichostatin A alone did not (Laska et al., 2012).

In addition to histone acetylation, histone methylation appears to be another epigenetic mechanism relevant for controlling ERV expression. In support of this notion, an enrichment of repressive histone marks such as trimethylation of histone 3 lysine 9 (H3K9) or H4K20 was described for mouse ERVs (Day et al., 2010; Mikkelsen et al., 2007) and for HERV-K (Campos-Sánchez et al., 2016). Furthermore, during early embryonic development, Krüppel-associated box zinc finger proteins (KRAB-ZFP) are critical for establishing and maintaining histone methylation and heterochromatin formation. Human KRAB-ZFP binding sites are highly concentrated within transposons, mainly retrotransposons, including human ERVs. Most of these transposable elements have lost their transposable potential, indicating that the KRAB-ZFP has silenced them by curbing them in heterochromatin (Imbeault et al., 2017; Thomas & Schneider, 2011). Of note, LTR-containing retrotransposons seemed to have co-evolved with KRAB-ZFP genes, as the integration of each family of human ERVs coincided with a new KRAB-ZFP (Lukic et al., 2014; Thomas & Schneider, 2011). Binding of KRAB-ZFP to chromatin leads to the recruitment of other proteins via the KRAB domain, forming larger protein complexes that modify histones (Thomas & Schneider, 2011). This includes the scaffold protein TRIM28/KAP1, DNA methyltransferases (DNMT)-1 and DNMT3a/b, as well as the histone lysine methyltransferase SETDB1. The latter was found to be critical for global repression of ERVs, as supported by findings in SETDB1 knock-out mice showing increased ERV expression in B-lymphocytes as compared to wild-type mice (Collins et al., 2015).

Finally, nucleosome positioning has been hypothesised by some authors to regulate ERV transcription (Fuchs et al., 2011). The binding of transcription factors, specificity protein (Sp)1 and Sp3 Sp1 to the LTR, would free the transcription starting sites from nucleosomes, allowing the genetic expression. HERV-K (HML-2) sequences were described to lack the classical TATA box element of common RNA polymerase II promoters, necessary for transcriptional initiation. These authors found that HERV-K LTR sequences contain alternative transcription starting sites. They showed that Sp1 and Sp3 have three binding sites within the LTRs of HERV-K proviruses and when knocked down, the promoter activity was significantly reduced (Fuchs et al., 2011).

Thus, while various molecular mechanisms mediating epigenetic silencing of ERVs have been identified, there are also several processes that can re-awake these retroviral elements from their dormant state. For example, ultraviolet (UV) radiation exposure, which is known to be associated with epigenetic modifications such as alterations in DNA methylation, DNA methyltransferase activities and histone acetylation, was shown to lead to transcriptional activation of the HERV-K pol gene as well as to enhance expression of Env protein in melanoma cells (Schanab et al., 2011). Likewise, several nutritional factors have been

shown to affect human ERV repression. One example is B-carotene, which was shown to increase DNA methylation of HERV-W (Bollati et al., 2014). Furthermore, vitamin C was identified to be an important cofactor for DNA methyltransferase inhibitors (DNMTis) in treating neoplasia. Combined application of DNMTi and vitamin C resulted in diminished ERV DNA methylation and subsequent increases in ERV expression (Liu et al., 2016).

In addition, certain drugs are known to modulate the silencing of ERVs by acting on epigenetic regulators. HDAC inhibitors such as valproic acid (VPA) have extensively been used in the treatment of neurological and psychiatric disorders, and in this context, an upregulation of several class I and class II human ERV elements by VPA in a dose-dependent manner was described in brain cell lines (Diem et al., 2012). Moreover, upregulation of HERV-W and ERV9 transcription was detected in post-mortem brains of schizophrenic patients that were undergoing chronic VPA treatment (Diem et al., 2012). The HDAC inhibitor vorinostat was also found to modulate ERV expression. Elements belonging to the ERV-L and HERV-9 families were found to be predominantly down- and upregulated, respectively in CD4<sup>+</sup> T cells, after vorinostat treatment (White et al., 2018). Furthermore, treatment with the DNMTi 5-aza-deoxycytidine was found to increase HERV-E mRNA expression in CD4 + T cells in patients with systemic lupus erythematosus (Wu et al., 2015). Altered DNA methylation has also been associated in human leukaemia cell lines and hematopoietic stem cells upon decitabine and hydroquinone exposure, resulting in elevated ERV expression (Conti et al., 2016).

A couple of recent publications have also shed light onto a different mechanism involving the histone variant H3.3 for the (re)awakening of ERVs. They showed that the loss of the histone variant H3.3 leads to a reduction of suppressing H3K9me3 marks at ERV elements. This in turn would open up binding sites for the interferon regulatory factor family of transcription factors (Guo et al., 2022). Furthermore, another publication described that the H3.3 chaperone death-associated protein 6 (Daxx), alpha-thalassaemia X-linked mental retardation (Atrx) lead to derepression of ERVs via histone acetylation and/or methylation (Gerber et al., 2021).

Of particular interest is the capability of viruses to change the epigenetic landscape of host cells to ensure proper replication (summarized in (Tsai & Cullen, 2020)). Importantly, some viral infections represent a risk factor in the development of certain HERV-associated diseases, including for example Epstein bar virus (EBV) and human *Herpesviridae* (HHV)-6 and herpes simplex viruses (HSV)-1 in MS (Römer, 2021). Thus, viral exposures could be one of the environmental factors linking altered ERV activity/expression to neurological and psychiatric disorders. In support of this notion, exposure of B cells to EBV was found to cause a genome-wide activation of LTR sequences (Leung et al., 2018) in these cells. The EBV-mediated activation of LTRs further coincided with local DNA hypomethylation (Leung et al., 2018). Moreover, EBV infection is thought to change host epigenetics on the long-term, thereby counteracting the immune reaction and further unlocking endogenous retroviral elements (Buschle & Hammerschmidt, 2020). Similar observations were made upon infection of primary fibroblast cells with influenza A virus, which led to the transactivation of the Env gene in the HERV-W locus ERVWE1 (Li et al., 2014). This induction was likely triggered by an in infection-mediated decrease in the repressive histone mark H3K9me3 as well as by lowered SETDB1 expression (Li et al., 2014).

Taken together, there is strong evidence that endogenous retroviral elements need to be epigenetically unlocked before they can be activated. Several environmental factors, including infections, nutrition, and certain drugs are thought to play key roles in the process of epigenetic unlocking. However, these processes are only partially understood to date, such that additional longitudinal studies are warranted to decipher the temporal sequences of molecular events acting on inserted viral elements and leading to their release – prior or concomitant to disease development.

#### 4. Activation of ERV expression

While epigenetic de-repression of endogenous retroviral elements itself can already induce mild expression levels, epigenetic mechanisms alone do not explain why ERVs are highly expressed in certain disorders. Thus, abnormally high ERV expression in some pathological contexts is likely to be the result of intricate interactions between epigenetic de-repression and other factors. As discussed below, various environmental factors, such as microorganisms, nutrients, and stress, as well as intrinsic components, such as cytokines and hormones, have been identified to act on ERV expression. For example, human ERV expression is known to be modifiable by hormones, both under physiological and pathological conditions. In females, basal HERV-K fluctuates as a function of the menstrual cycle, suggesting a regulation of HERV-K by the sex hormones progesterone and estradiol (Mueller et al., 2018). These findings are corroborated by the recent publication showing that progesterone and estradiol synergistically activate HERV-K involving binding of progesterone receptor and the octamer-binding transcription factor 4 (OCT4) to HERV-K LTRs (Nguyen et al., 2019).

While in the context of ALS strong evidence support the TDP43 protein as activator of HERV-K expression (Li et al., 2015b) there is also converging evidence supporting a direct impact of systemic inflammation on ERV expression, likely also via acting on flanking LTR sequences (Kovalskaya et al., 2006). LTR sequences feature strong gene regulatory sequences and contain many binding sites for transcription factors, including sites for the pro-inflammatory nuclear factor kappa light chain enhancer of activated B-cells (NF- $\kappa$ B) (Manghera & Douville, 2013; Thompson et al., 2016). Given that NF- $\kappa$ B regulates various aspects of innate and adaptive immunity and can be activated by numerous pro-inflammatory cytokines such as TNF $\alpha$ , IL-1 $\beta$ , IL-6 and IFN $\gamma$ , binding of NF- $\kappa$ B to flanking LTR sequences may readily provide a direct mode of action of how inflammation can drive human ERV transcription (Liu and Wang, 2017). In this context, IFN $\gamma$  was shown to induce the expression of the HERV-K Gag-Pro-Pol polyprotein as well as of the reverse transcriptase in human astrocytes and neurons (Manghera et al., 2015). In the same cells, however, TNF $\alpha$  was found to induce HERV-K transcription through interferon regulatory factor-1 (IRF1) and NF- $\kappa$ B binding to the interferon-stimulated response elements (ISRE) (Manghera et al., 2016). Similarly, exposure to TNF $\alpha$ , IFN $\gamma$ , IL-6 or IL-1 was shown to boost the activity of the ERVWE1/syncytin promoter via NF- $\kappa$ B in human U-87MG astrocytes (Mameli et al., 2007). Moreover, TNF $\alpha$  also appears to shift the open reading frame of the HERV-K Env gene, thereby giving rise to the conotoxin-like protein (CTXLP). This protein is similar to the neurotoxic conotoxin protein of marine snails and, more importantly bears similarities to the human immunodeficiency virus (HIV) tat protein. CTXLP can act in a positive feedback loop via binding to ISREs within the HERV-K promoter, thereby further stimulating its expression. CTXLP was also demonstrated to enhance nuclear NF- $\kappa$ B p65 expression, which then tunes into HERV-K transcription (Curzio et al., 2020).

Of note, a recent transcriptome study supports the notion that inflammation leads to ERV induction in humans, as revealed by correlations between the expression of various endogenous retroviruses with different injuries such burn, trauma and septic shock (Mommert et al., 2020; Tabone et al., 2018). Whereas none of these injuries are primarily associated with the common risk factors for developing neurological disorders, all of them are associated with a strong inflammatory reaction and a concomitant upregulation of at least five different human ERVs. Additional evidence supporting a primary role of inflammation in stimulating ERV transcription can be obtained from a clinical investigation using PBMCs derived from ADHD children. As outlined above, children with ADHD who were treated with methylphenidate displayed decreased HERV-H expression in PBMCs (Cipriani et al., 2018a). Notably, ex vivo induction of HERV-H in drug-naïve PBMCs was then shown to occur in response to a T cell activation cocktail, containing IL-2 and phytohemagglutinin, but was not observed in PBMCs from drug-treated ADHD children and healthy controls (Cipriani et al., 2018a).

Besides inflammatory responses, infections with viruses, the intestinal microbiota, and protozoans can also modulate ERV expression (Küry et al., 2018). Indeed, numerous viral infections, including HIV-1, the *Herpesviridae* HSV-1, HHV6 and EBV as well as SARS-CoV2, have repeatedly shown to directly induce the transcription of endogenous retroviral elements (summarized in (Küry et al., 2018), see also (Bales-trieri et al., 2021)).

One of these mentioned viral infections is the EBV infection. We previously mentioned that EBV is likely to overcome the epigenetic barriers and change the host epigenetic landscape on the long term, resulting in the evasion of the immune system. *In vitro* studies showed EBV glycoprotein 350 (EBVgp350) induction of the HERV-W Env expression in astrocytes, B cells and monocytes of MS patients. This process showed to be NF- $\kappa$ B signalling dependent (Mameli et al., 2012). This finding was further corroborated by a clinical study showing increased HERV-W expression in patients with EBV dependent mononucleosis (Mameli et al., 2013). Recent reports have reinforced the causal involvement of EBV in MS aetiology (Bjornevik et al., 2022; Lanz et al., 2022), additionally supporting an active participation of HERV-W in the development and progression of MS. Similar effects are shown with respect to HERV-K18. EBV latent membrane proteins 1 and 2A, but also EBV itself, through interaction with its cellular receptor complement receptor 2 (CD21) induce HERV-K18 expression in resting B lymphocytes (Hsiao et al., 2006; Sutkowski et al., 2001).

Following human herpes virus (HHV) 6A infection, HERV-W Env expression is induced through the transmembrane glycoprotein CD46, while no induction was observed upon exposure to HHV6B or the measles virus vaccine strain (Charvet et al., 2018). On the other hand, both subtypes HHV6A and HHV6B were found to activate HERV-K18 in B cells and PBMCs, respectively (Tai et al., 2009; Turcanova et al., 2009). In this context, a recent publication discusses accumulating evidence supporting the view that EBV, HHV6 and HERV-W can influence each other, eventually leading to dysregulation of the immune response (summarized in (Meier et al., 2021)).

Although it has been proposed that ERV-inducing viruses act via increasing the affinity of transcription factors to LTR binding sites (Manghera & Douville, 2013), it is important to point out that the NF- $\kappa$ B signalling pathway can also be directly activated by viral infections (Santoro et al., 2003). Hence, a direct induction of ERV expression by viral infections is indistinguishable from an indirect activation through inflammatory i.e., NF- $\kappa$ B signalling pathways in terms of its end product. Furthermore, most of available studies were correlative in nature, and therefore, they fall short in answering the question whether infectious agents exert direct effects on ERV expression, or whether these effects are indirectly mediated by pro-inflammatory pathways and/or epigenetic unlocking processes discussed above. Indeed, because systemic inflammation and viral infections share similar signalling pathways, it is difficult to distinguish temporally between those two ERV effectors. Moreover, none of the available studies ascertained the epigenetic *status quo*. Therefore, for ERV activation to occur in response to infection and/or inflammation, it remains unknown whether prior epigenetic de-repression is a necessary step in order to turn cells susceptible to ERV responses.

It is also worth considering that the activation of ERVs could also be beneficial in some conditions. A certain degree of ERV expression could potentially contribute to inherent host defence mechanism by inducing resistance against superinfections (Villarreal, 2011). Indeed, such beneficial effects of ERVs may arise because endogenous and exogenous entities reveal high similarities in their protein and nucleic acid sequences (Grandi & Tramontano, 2017) and/or because ERV proteins might interact with the same receptors as the exogenous viral proteins (Spencer et al., 2003). This might also explain why ERV sequences have survived the evolutionary purge.

## 5. Induction of inflammation-related processes by ERVs

While inflammation is one of the factors that can stimulate ERV expression, endogenous retroviral proteins can induce inflammatory responses in different cell types as well. Hence, ERVs themselves appear to have pro-inflammatory effects. One of the first studies supporting this hypothesis demonstrated that the HERV-W Env protein is capable of activating the TLR4 pathway in human monocytes (Rolland et al., 2006). The authors also revealed that dendritic cells were similarly triggered by HERV-W Env protein, leading to the promotion of Th1 differentiation. Additional evidence for the involvement of TLR4 signalling after HERV-W Env protein exposure was then provided using genetically modified HEK-Blue cells (Charvet et al., 2018). A similar pro-inflammatory polarisation was also shown for primary human and rat microglia, which displayed elevated pro-inflammatory cytokine and chemokine production as well as nitric oxide levels after exposure to HERV-W Env protein. This polarisation was further associated with an axon-damaging microglial phenotype (Kremer et al., 2019). Moreover, Env protein activated microglial cells were also shown to mediate synaptic NMDA-receptor dispersal – a molecular process associated with psychosis (Johansson et al., 2020).

Oligodendroglial precursors are cells with generally low immunocompetence (Kremer et al., 2010) yet they are critically involved in the MS pathology. They can provide replacement of lost oligodendrocytes and myelin sheaths – cells and structures that represent primary targets of the autoimmune reaction in MS – hence they represent one of the few regeneration conferring cells of the adult CNS. HERV-W Env protein stimulation of TLR4 was shown to promote nitrosative stress generation in these glial cells, leading to an impaired differentiation reaction and reduced axonal myelination. It was therefore suggested that endogenous retrovirus activation is restricting naturally occurring repair activities (Kremer et al., 2013). Furthermore, HERV-W Env inhibition by its neutralizing GNBAC1/Temelimab antibody, as well as TLR4 blockage by different pharmaceutical TLR4 inhibitors reduced the Env-mediated effects, suggesting that they were indeed dependent on Env and TLR4 (Göttle et al., 2019; Göttle et al., 2021; Kremer et al., 2015). Of note, an involvement of HERV-W Env in microglial axon damage as well in constraining myelin regeneration was later supported indirectly by the clinical examination of the anti-Env antibody GNBAC1/Temelimab (Hartung et al., 2022), adding up to the numerous effects of HERV-W in the context of MS the observation of an inflammatory response in endothelial cells upon stimulation with HERV-W Env protein. Furthermore, a weakening of the BBB was suggested, as intercellular adhesion molecule (ICAM)-1 was induced, a major mediator of leukocyte adhesion to endothelial cells which is also associated with BBB permeability (Abadier et al., 2015; Duperray et al., 2015).

Another study showed that HERV-W Env overexpression in a human glioma cell line increases the TNF $\alpha$ /IL-10 ratio, in a TLR4 dependent manner. Furthermore, this study describes that myeloid differentiation primary response-88 s (MyD88s) mRNA levels (a splice variant of MyD88 acting as a downstream negative regulator of TLR4) were decreased by HERV-W Env. When MyD88s was overexpressed however, the inflammatory pathway stimulated by HERV-Env was down-regulated, counteracting the HERV-W initial effect (Xiang & Liang, 2021).

The expression of HERV-W Env protein showed to correlate with cytokine levels in PBMCs derived from patients suffering from chronic inflammatory demyelinating polyradiculoneuropathy (CIPD) – an autoimmune condition of the peripheral nervous system (PNS). Likewise, human Schwann cells exposed to or transfected with HERV-W Env presented increased IL-6 and CXCL10 expression levels (Faucard et al., 2016), supporting that a pro-inflammatory response of immune- and neural cells to HERV-W Env is not restricted to the CNS. Beside the well-described interaction with TLR4, it is proposed that human ERVs also interact with and activate other receptors such TLR2, MFSD2, ASCT1/Slc1a4, ASCT2/Slc1a5 and MCT-1/Slc16a1 (Antony et al., 2007; Blanco-

Melo et al., 2017; Blond et al., 2000; Esnault et al., 2008; Reuven et al., 2014). All of them are thought to be involved in pro-inflammatory responses but functional analyses related to potential interactions with ERVs are mostly missing.

In the context of HERV-K, it was recently described that the HERV-K encoded deoxyuridine triphosphate nucleotidohydrolase (dUTPase) is expressed in circulating monocytes and macrophages of patients with pulmonary arterial hypertension. Furthermore, HERV-K dUTPase was shown to induce the expression of the pro-inflammatory cytokine IL-6 in pulmonary arterial endothelial cells (Saito et al., 2017), which was proposed to be also dependent on TLR4 as well as on melanoma cell adhesion molecule signalling pathways (Otsuki et al., 2021). Of note, as the human leukocyte antigen (HLA) cluster represents one of the main genetic risk factors for the development of autoimmune diseases, the observation that HERV-K9 elements are located in the proximity as a result of the so-called hitchhiking effect (Kulski et al., 2008), is of further interest. Likewise, the HLA-8.1 ancestral haplotype, which is known to be protective against schizophrenia, was not found to contain the HERV-K element as compared to other pro-inflammatory ancestral haplotypes (Stewart et al., 2004), providing another link between retroviral elements and inflammation in psychiatric disorders.

Immune dysregulation and the modulated immune cell polarization present yet other mechanisms through which endogenous retroviruses can foster a pro-inflammatory environment. In this context, Superantigens (Sag) are known as inflammatory triggers that can stimulate much larger numbers of T cells than ordinary antigens. On that account, they become of specific interest in the context of autoimmune diseases such as MS. A large number of studies indeed describe HERV-K18 dependent Sag effects (Hsiao et al., 2006; Tai et al., 2009). Although not in that detail, similar effects are described for other ERVs such as HERV-Fc1, mouse mammary tumor virus (MMTV) and HERV-W (Gröger et al., 2020; Perron et al., 2001; Xu et al., 1996). In the context of SAGs, it was shown that viral HERV-W particles isolated from MS derived cells or via application of recombinant HERV-W Env protein, can induce polyclonal V $\beta$ 16 T-lymphocyte activation (Perron et al., 2001). Similar effects are described for HERV-K18, as it was shown that HERV-K18 Sags induce V $\beta$ 7 T cell activation (Stauffer et al., 2001).

More general evidence for a functional implication of ERVs in immune dysregulation can be deduced from observations on the HERV-W Env protein acting as an adjuvant and thereby activating CNS autoinflammation (experimental autoimmune encephalomyelitis). In this context, a direct involvement of the encoded Env protein was shown, given the observed rescue effect upon application of the neutralising antibody termed GNBAC1/Temelimab (Perron et al., 2013).

An indirect scenario is suggested, upon the discovery of the epigenetic de-repression of IFN $\gamma$ , a Th1 related gene. This gene becomes transcriptionally active once its endogenous retroviral neighbour becomes transcriptionally active too. This transactivation leads to changes in the expression profiles of differentiated Th2 cells, rendering them transcriptionally similar to Th1 cells (Adoue et al., 2019). Of note, in physiological conditions upon Th2 differentiation, Th1 related genes become epigenetically silenced and vice versa (Sanders, 2006). Similar effects were identified by a transcriptome study, showing an activation of the HERV-neighbouring gene CD55 in monocytes and neutrophils of patients with various injuries such as burn, trauma and septic shock (Mommert et al., 2020; Tabone et al., 2018). CD55 encodes a glycoprotein involved in the regulation of the complement cascade, suggesting a modulatory role of human ERVs in the immune response during an ongoing inflammatory process.

Beyond traditional, mainly MS-related inflammatory scenarios, emerging observations in the context of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) have further corroborated the concept of ERVs fostering inflammatory processes. HERV-W was found to be specifically induced in a cohort of 30 COVID-19 patients, with peripheral HERV-W Env protein levels even exceeding increased levels, which have been previously observed in MS patients (Balestrieri et al.,

2021). Interestingly, as opposed to myeloid cells being main producers of HERV-W Env in MS, lymphocytes were identified to express HERV-W Env in these COVID-19 patients. In parallel, using an *ex vivo* healthy donor PBMC stimulation approach, a temporal correlation between inflammatory markers and the ERV expression was established. This study revealed that the induction of Env expression by SARS-CoV-2 spike protein occurs prior to the expression of IL-6 (3 h and 24 h, respectively), with IL-6 representing a key marker of the inflammatory response, which eventually can amount to cytokine storms. Hence, it was concluded that HERV-W induction might indeed contribute to critical, overshooting immune reactions and therefore lead to more severe disease courses in COVID-19 patients. Likewise, such a scenario might also account for chronic low inflammation in sub-acute patients suffering from long-term consequences of COVID-19 (Balestrieri et al., 2021).

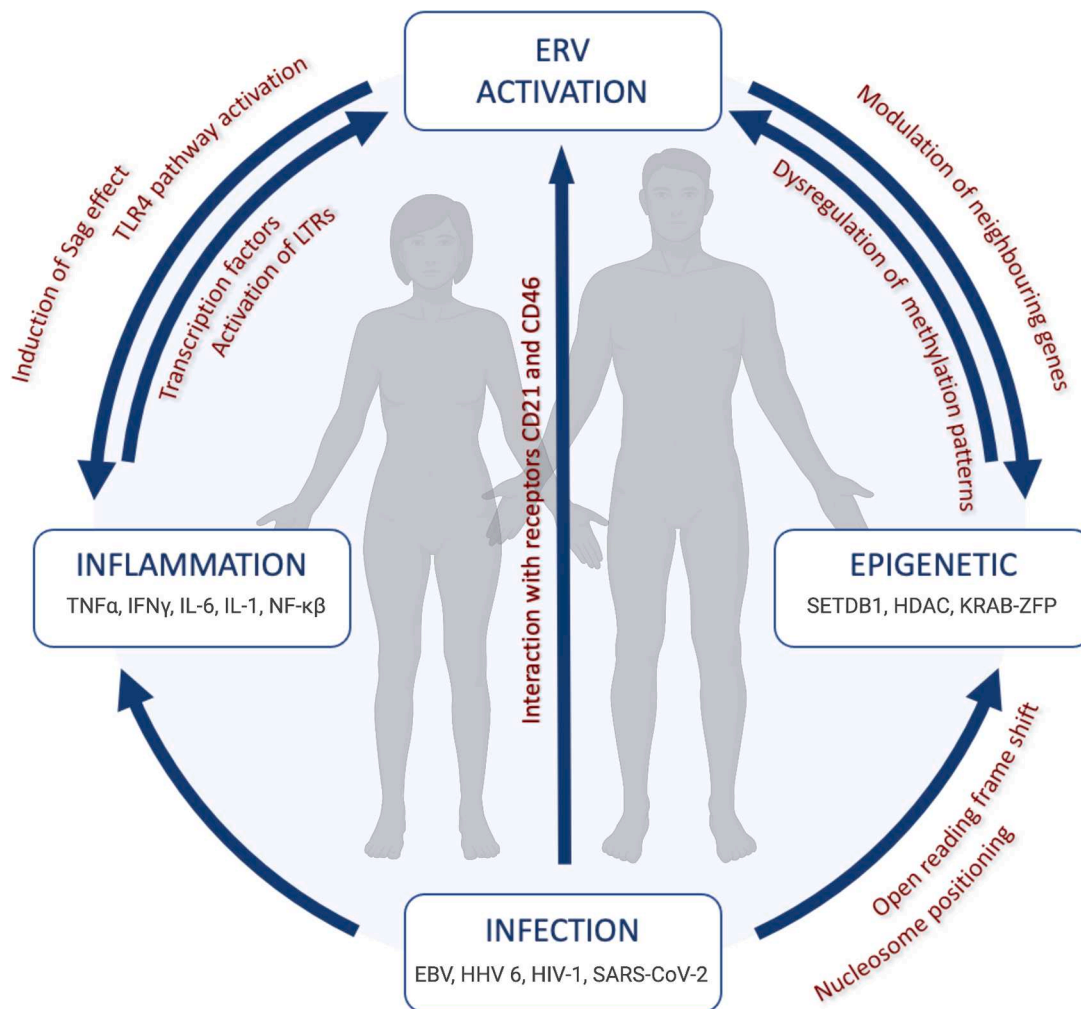
**6. Concluding remarks**

Although endogenous retroviral elements have long been detected and described in health and disease, ERV research is still at infancy when it comes to the evaluation of their precise etiopathological role in neurological, neurodevelopmental, neurodegenerative, or psychiatric disorders. The presence of abnormal ERV expression in multiple brain disorders suggests that abnormal activation of endogenous retroviral elements may reflect a common mechanism for shared pathologies, including (but possibly not limited to) inflammation. Recent studies

aiming at neutralizing ERV proteins in pathological contexts such as MS provide initial evidence that ERVs are not simply incidental phenomena, but instead they are pathologically relevant. The current view is that ERVs can trigger inflammatory processes through multiple pathways of the innate and adaptive arms of the immune system. At the same time, inflammatory signals may drive the (re-)activation and/or maintain the expression of ERVs, leading to a sequence of reciprocal cause and effect (Fig. 1). Based on the current state of research, it is likely that the numerous entry points to this reciprocal sequence of events exist, including initial infections with ERV-activating pathogens, exposure to non-infectious inflammatory stimuli such as trauma or burn, and conditions in which epigenetic silencing of ERV elements are disrupted. With regards to the latter, epigenetic factors may be crucial for determining the susceptibility towards developing ERV-associated pathologies, and therefore, determining epigenetic factors interacting with endogenous retroviral elements should become a research priority. In addition, more longitudinal and mechanistic studies are warranted in order to further corroborate the pathological relevance of ERV expression in neurological and psychiatric disorders.

**Declaration of Competing Interest**

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



**Fig. 1.** Relationship between ERV activation, inflammation, infection and epigenetic processes. Multiple processes such as inflammation, epigenetic unlocking as well as exposure to certain infections can lead to the activation of ERVs. Upon ERV activation, feedback signals can amplify inflammatory processes and alter epigenetic programs. The figure summarizes some of the molecular factors and processes involved in each of these relationships.



## Data availability

No data was used for the research described in the article.

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