JEMI-PEARLS

Human Endogenous Retroviruses Type W (HERV-W): an Epiphenomenon or the Missing Link in Schizophrenia?

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BACKGROUND INFORMATION

Schizophrenia (SZ) is a multifactorial psychiatric disorder, with a complex genetic background interacting with environmental factors [1]. One of the leading causes of disability worldwide, SZ costs US$40–60 billion per year in the US and accounts for more than 25% of mental health costs and 33% of hospital bed occupancy [1, 2].

The diagnosis and treatment of SZ still remain poor. Since Emil Kraepelin's first scientific classification of mental diseases in 1896, hardly any advances have been made with diagnosis of psychiatric disorders [3]. The current classification system relies heavily on symptoms and clinical presentation [3]. No quantitative or experimental tests are in place to formulate a correct diagnosis [3]. Such an approach is problematic as there are significant overlaps of symptoms and clinical presentations among psychotic illnesses [3]. Also, the current treatment for SZ only serves to provide symptomatic improvements, and does not affect the overall disease progression [3]. Such pitfalls in diagnosis and treatment strategies call for a new paradigm on how we view SZ and its etiopathogenesis. Novel molecular biomarkers to diagnose and monitor

the disease progression are needed, and new therapeutic avenues must be sought out to achieve improvements in disease outcome [3].

To improve the diagnosis and treatment of schizophrenia, it is therefore necessary to gain a better understanding of the disease etiology. Various epidemiological studies suggest that SZ pathogenesis involves a complex interplay of environmental risk factors and genetic susceptibility [1]. Many different environmental risk factors have been identified, including living in urban areas, births during specific seasons, and maternal infections by various microbial agents, including rubella, influenza virus and *Toxoplasma gondii* [4, 5]. Prenatal infections with such agents in animal models have revealed neurocognitive and neurophysiological abnormalities that are characteristic of SZ [6, 7]. For example, in monkeys infected with influenza virus during pregnancy, the offspring presented SZ-like abnormalities beyond one

year of age [8]. Other studies have found that infections later in life, during childhood and adulthood, can present secondary risk factors associated with SZ [1].

On the genetic level, SZ-susceptible genotypes in common alleles of the major histocompatibility complex have also been identified [9]. This aligns with the findings of genome-wide association studies showing that loci responsible for immunity are involved in SZ development [10].

However, how these various factors contribute to the pathophysiology of SZ remains unanswered. The exact mechanisms responsible for increased SZ susceptibility upon exposure to certain environmental factors and susceptible genotypes remain elusive. In recent years, human endogenous retrovirus type W (HERV-W) has emerged as the potential bridge in SZ research [11]. It has been established that certain infectious agents can activate HERV-W elements, including envelope protein, which can induce neurotoxicity, leading to the symptomatic onset of SZ [11]. Therefore, HERV-W has been suggested to be the missing link between infectious events and SZ pathogenesis [11]. As HERV-W comes to the forefront of SZ research, it may lead to exciting new avenues for diagnosis as well as treatment. This article aims to describe how HERV-W may serve as the missing link between these various environmental risk factors and the exact etiopathogenesis mechanism of SZ.

RESEARCH QUESTIONS

Elucidating the exact molecular mechanisms of this severe and debilitating disease has been given a high priority, as its burden on developed economies is estimated to 1.65% of the gross domestic product and is projected to rise [2]. Determining the exact etiopathogenesis of SZ may open doors for new diagnostic tools. The discovery of new biomarkers for the disease that can be further developed to diagnose psychiatric diseases, in particular SZ, will provide immense benefits. Such biomarkers will aid drug development for SZ as they allow for a method to track and monitor the progress of the disease. Also, new

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therapeutic targets could be identified, which would drastically improve the outcome of treatment and could affect the overall disease progression, rather than simply alleviating the symptoms, as is the case for current SZ treatment strategies.

Three questions are to be addressed to elucidate the role of HERV-W in SZ etiopathogenesis. First, the biology of HERVs and their biological significance must be illuminated. Then, it is important to address the evidence supporting the association between HERV-W and SZ. Finally, the proposed molecular and immunological mechanisms involving HERV-W and timing of events leading to SZ pathogenesis must be investigated. By answering these three key questions, this article aims to better illuminate the role of HERV-W in SZ and demonstrate how HERV-W may serve as a bridge to fill in the gap in our current understanding of SZ and its etiopathogenesis.

PROJECT NARRATIVE

HERV Biology and Physiological Significance of HERVs

In order to explore the link between HERVs and human diseases, such as SZ, it is important to first develop a better understanding of HERV biology. HERVs are endogenous viral elements that are remnants of ancient germline infections by exogenous retroviruses. The first infection event of a human ancestor by an exogenous retrovirus is dated to around 100 million years ago, and many more retroviral integration events have taken place, resulting in HERVs comprising 8% of the human genome. [12]

HERVs can be subdivided into three classes: I, II, and III, based on their molecular resemblance to different infectious retroviruses [13]. For instance, Class I resembles mammalian type C viruses, class II mammalian type A, B and D viruses, and class III the foamy virus [13]. Each class is further subdivided into families, classified by the one-letter code of the amino acid denoting the primer tRNA binding site [13]. HERV-W is primed by tRNA-tryptophan, HERV-K is primed

by tRNA-lysine, and HERV-H is primed by tRNA-histidine.

Intact HERVs are composed of at least three genes, *gag, pol,* and *env*, flanked by two long terminal repeats (LTRs) [13]. LTRs contain promoter and enhancer sequences necessary for transcription [13]. The genes *gag, pol,* and *env* encode the different proteins needed for the retroviral life cycle [13], with *pol* coding for the viral enzymes including the reverse transcriptase, *gag* encoding the structural capsid, and *env* encoding the viral envelope protein (Fig. 1) [13].

Over the course of evolution, most HERVs have undergone various inactivating mutations, rendering them unable to form infectious virions or retrotranspose [13]. These mutations include point and frameshift mutations as well as epigenetic silencing mechanisms such as methylation [13]. However, although previously dubbed "junk DNA" and thought to be inactive in the human genome, many significant biological functions of HERVs have been elucidated in recent years. For instance, HERV LTRs have been incorporated into regulatory sites of human genes, where they can serve as promoters [12]. HERVs can also be transcribed into RNA, which can then be translated and perform essential functions [12]. For example, the HERV-W element on chromosome 7q21 contains an *env* gene, which encodes syncitin [13]. Syncitin is a protein that is essential in the development of the placenta, as it mediates the fusion of trophoblasts [12]. Some HERV components, such as syncytin, have therefore been "domesticated" over evolution and now serve essential functions in humans [13].
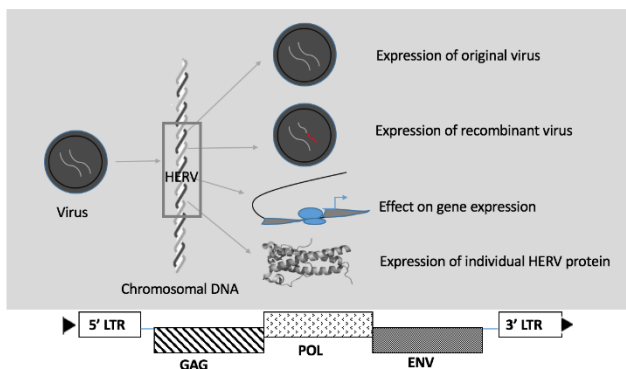

FIG. 1 Expression of HERV elements and HERV structure: *Above* Diagram depicting integration of exogenous retrovirus into host genome and expression of HERVs into original virus, recombinant virus, and individual HERV proteins. *Below* Genomic structure of HERV elements. Composed of *gag, pol* and *env* genes flanked by two long terminal repeats. Gag proteins are structural, *env* encodes envelope protein and *pol* retroviral enzymes.

However, in other species, including mice and cats, some endogenous retroviruses are established pathogens. In humans, despite some HERVs serving an essential biological role in the host, notable HERV families have been implicated in a range of human diseases [12]. HERVs have been implicated in autoimmune diseases, such as rheumatoid arthritis, neurodegenerative diseases, including multiple sclerosis and amyotrophic lateral sclerosis, and certain types of cancer [14, 15]. Human endogenous retroviruses have pathogenic potential both as genes and gene products, and as retroviruses [12]. Although a clear role of HERVs in etiopathogenesis has not yet been unequivocally demonstrated, HERVs may be considered as emerging pathogens.

The association between HERV-W and SZ

Hypotheses regarding the potential role of retroviruses in the pathophysiology of SZ have been suggested many decades back, but the first study which demonstrated this association was a study of three monozygotic twin pairs discordant for SZ, and it showed that HERV-W sequences were present in increased quantities in affected twins compared to healthy twins [16].

Transcriptome studies on HERV-W in SZ further support this link. A study of brain tissue obtained from SZ subjects revealed 45% of transcripts in schizophrenia subjects were homologous to HERV-W, as opposed to 10% in controls [17]. Another study which analyzed CSF samples from 35 subjects with recent-onset SZ and a healthy control group found that HERV-W RNA was detected in 10 subjects of the SZ-affected group, while none were detected in the healthy control group [18]. Other independent studies on post-mortem cerebral RNA, as well as on RNA in circulating blood, confirmed increased HERV-W expression in certain patients with SZ [18, 19]. When other HERV families were tested for any abnormal expression, only HERV-W showed significant and differential expression in SZ [18].

In another study, peripheral blood mononuclear cells (PBMCs) of 30 SZ subjects were analyzed for the presence of HERV-W sequences. HERV-W *gag* transcripts were elevated by two-fold in subjects with SZ as opposed to healthy controls [19].

Also, antigenemia, the presence of antigen in the blood, was studied for HERV-W Gag and Env proteins in the serum of 49 SZ-affected individuals and 49 healthy subjects [20]. Positive antigenemia for both Env and Gag protein was found in more than 50% of the patients, whereas in control patients, only about 3–4%

had positive antigenemia for either antigen [20]. In the same study, HERV-W antigenemia and C-reactive protein levels was found to be strongly correlated, which hints at an inflammation-mediated pathophysiology [20].

In a recent study that proposed a pathological link of HERV-W *env* elements with SZ, plasma mRNA sequences homologous to the HERV-W *env* gene were found in 36% of SZ subjects, but none were detected in control participants [21]. Real-time polymerase chain reaction (rtPCR) analysis also revealed increased reverse transcriptase activity in SZ subjects as opposed to controls [20]. This corroborates an earlier study that found significantly increased reverse transcriptase activity in cerebellum SZ compared to healthy controls [18].

More importantly, it was found that in human U251 glioma cells, overexpression of HERV-W *env* upregulates neurotrophic tyrosine kinase receptor type 2 (TrkB), dopamine receptor D3 (DRD3), and brain-derived neurotrophic factor (BDNF) [21]. This study provided strong support for the direct effect of the HERV-W Env protein on genes associated with SZ. It was also found that phosphorylation of the cyclic adenosine monophosphate response element-binding (CREB) protein was also increased [21]. This is significant since the CREB protein has been discovered to be required for BDNF expression [21]. Therefore, the HERV-W Env protein leads to a cascade event, leading

to the activation of the promoter of BDNF and ultimately overexpression of BDNF (Fig. 2) [21].

In summary, an increasing body of research suggests that there exists a sub-group of SZ patients which is associated with abnormal expression of HERV-W and the concomitant elevated levels of systemic inflammation. Also, some studies suggest a potential effect of HERV-W overexpression on certain elements that have strong links to SZ pathogenesis, including BDNF and DRD3.

Proposed molecular mechanisms involving HERV-W and specific timing of environmental events leading to SZ pathogenesis

As mentioned previously, different viral infections have been identified as etiological agents for SZ [1]. However, it is becoming increasingly clear that a single infectious cause cannot directly account for the etiology of the disease. Prenatal maternal infections by pathogens including influenza, rubella, herpes simplex virus type 2, and *T. gondii* pose a high risk for SZ, but specific infections later in life are also associated with an increased risk for the disease [1]. The link between viral infections and SZ remains to be bridged, and HERV-W is an excellent candidate to bridge this missing link [11].

HERV elements are not usually expressed, due to inactivating mutations and epigenetic silencing mechanisms. However, certain infections have been demonstrated to activate HERV-W elements in the human genome [11]. Reactivation of these HERV-W
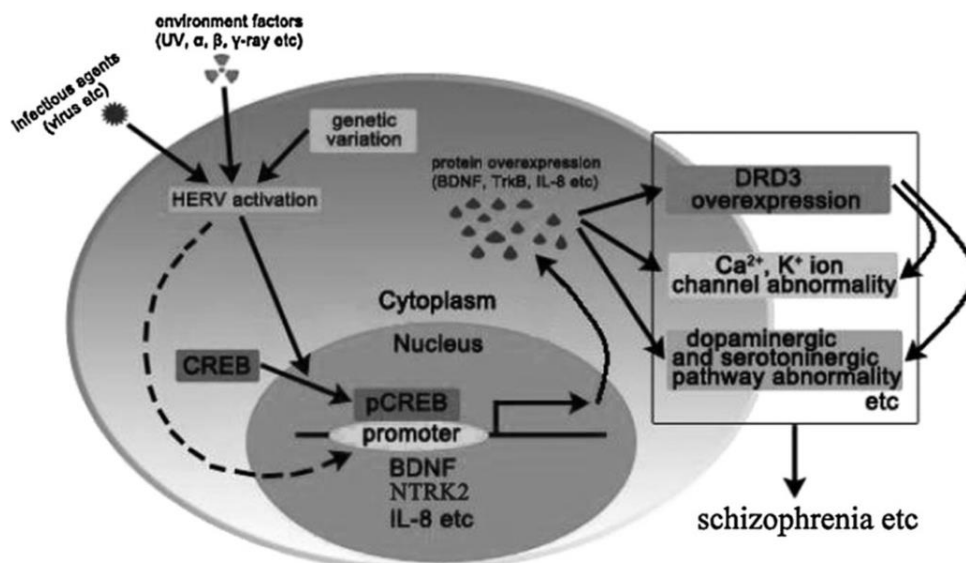

FIG. 2 Effect of HERV-W Env expression on SZ-related elements, BDNF, DRD3 and TrkB. HERV-W env is expressed by infectious agents and environmental factors. Expressed HERV-W proteins increase the promoter activation of specific genes, leading to overexpression of BDNF, TrkB and DRD3 in neuroglia cells. This abnormal expression contributes to SZ (21).

elements, including potent activators of the innate immune system and other SZ-associated elements like the Env protein, may then trigger SZ.

Prenatal influenza infection has been associated with increased risk for SZ by three-fold [22, 23]. Influenza virus has been demonstrated to activate HERV-W elements [24]. It has been suggested that HERV-W elements are transactivated by exogenous influenza A via reduction of the repressive histone mark, H3K9me3 [13]. This prenatal activation of HERV-W elements can lead to reverse transcriptase activity as reported in SZ patients [20]. This activated reverse transcriptase activity can then produce more copies of HERV-W, which can be retroinserted into embryonic DNA via retrotransposition [13]. This retrotransposition could explain the DNA modifications reported in SZ patients [25]. Such genetic modifications as well as neuroinflammation from activation of HERV-W may encourage abnormal neurodevelopment and favour later onset of SZ [13].

Herpesviridae, *T. gondii* and cytomegalovirus (CMV) infections during adult life are also associated with increased risk of SZ [13]. They have been shown to trigger reactivation of HERV-W elements in the human genome [13]. For example, infection by herpes simplex type 1 (HSV-1) stimulates HERV-W expression in meningeal cells from multiple sclerosis (MS) patients, but not in healthy subjects [26]. Increased transcriptional activity of HERV-W elements has also been reported in cells infected with *T. gondii* [27]. In another study, CMV infection increased expression of HERV-W [28].

Once activated following such infection events, HERV elements can produce the Env protein, which may lead to neuroinflammation and neurotoxicity [13]. HERV-W Env protein is a potent activator of innate immunity, stimulating production of proinflammatory cytokines, including TNFα and interleukins via CD14 and Toll-like receptor 4 (TLR-4) [13]. Activation of innate immunity in the CNS via the TLR-4 pathway has been shown to lead to neurodegeneration, which may precipitate symptoms of SZ [13]. Positive antigenemia for HERV-W proteins was concomitant with elevated C-reactive protein (CRP), a biomarker of systemic inflammation [20]. As the HERV-W Env protein is an established proinflammatory agent, elevated CRP most likely indicates that the inflammation is mediated by HERV-W Env protein [20]. Furthermore, elevated serum levels of CRP were associated with the severity of cognitive impairment in individuals with SZ [29].

The presence of HERV-W Env also leads to overexpression of BDNF, DRD3 and TrkB [21]. In animal models, abnormal expression of these three elements has been established as a risk factor for SZ and these elements are thought to play an important role in SZ pathogenesis [30]. This suggests that HERV-W is likely closely linked to SZ-associated BDNF and DRD3 abnormalities [13].

HERV-W also uses the amino acid transporters ASCT (alanine serine cysteine transporter)-1 and ASCT-2, as receptors [13]. In SZ, a notable reduction in ASCT-1 immunoreactivity in the cingulate cortex has been reported [13]. It has been hypothesized that the HERV-W Env protein can block these receptors, leading to decreased immunoreactivity and decreased uptake of amino acids required for neurotransmitter production [13]. This may account for the dopaminergic dysfunction which is characteristic of SZ [13].

SZ has been classically explained within the context of the two-hit hypothesis: a first hit disrupts some aspect of brain development and establishes increased vulnerability to a second hit that occurs later in life, finally precipitating disease symptoms and leading to onset of full clinical SZ [31]. In this article, a prenatal infection event (e.g. influenza) is presented as the first hit, which activates HERV-W elements and results in "genetic priming" for SZ; later infections during adulthood, including CMV, HSV and *T. gondii*, can serve as the second hit, activating HERV-W elements, particularly the Env protein, and leading to inflammation and neurotoxicity (Fig. 3). This novel
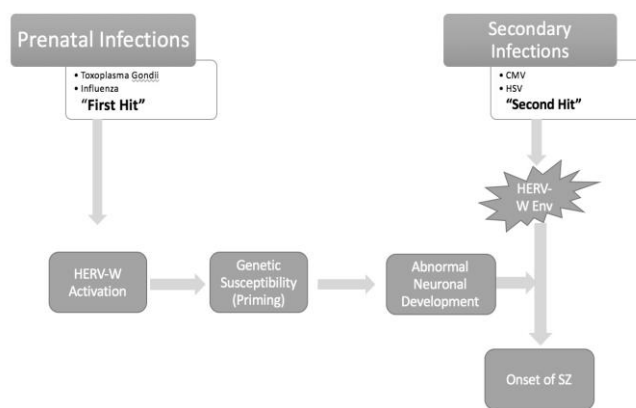

FIG. 3 Model for SZ etiopathogenesis involving HERV-W. This model is framed as two-hit scenario, where a prenatal infectious agent, such as influenza, induces HERV-W activation and leads to DNA modification that sets a path for abnormal neurodevelopment, thereby creating genetic susceptibility. Secondary infection reactivates HERV-W elements, leading to Env protein production and onset of SZ. Adapted from *(11)*.

framework of prenatal viral infections, HERV-W activation and SZ disease pathogenesis aligns well with the classical two-hit hypothesis of SZ [13].

SUMMARY AND CONCLUSION

HERVs are viruses within our genome that are highly responsive to environmental influences, such as hormones, UV radiation, and microbes. Therefore, HERV elements are placed at the gene-environment interface characteristic of complex multifactorial diseases such as MS and SZ. This article explores the association between HERV-W and SZ, and presents a model which treats HERV-W as the sought-after missing link in SZ etiopathogenesis.

Studies that support the association between HERV-W and SZ still remain limited in number. However, in following years, HERV biology may emerge at the forefront of SZ molecular research, calling for further experimental evidence to support the model presented in this article. Once it is established that SZ is indeed a HERV-mediated pathology, this opens up novel therapeutic avenues for SZ treatment, with the potential to dramatically improve upon current treatment approaches which are limited to alleviating symptoms and have highly reported side effects [3].

Efficacy of antiretroviral therapy in SZ has not yet been studied extensively. Because HERV-W Env is linked with potential neurotoxicity and SZ-associated elements, such as BDNF, it makes the Env protein an appealing target for HERV-W-directed therapy. Neutralization of this protein by a specific monoclonal anti-Env antibody could be an effective approach that should be explored. As HERV-W Env levels was concomitant with elevated levels of systemic inflammation, and such inflammation was associated with the increasing severity of cognitive impairments in a subgroup of SZ patients [29], anti-inflammatory medications may also be effective in reducing symptom severity. Interferon (IFN)-β therapy and other anti-retroviral treatments are potential treatment avenues that have found moderate success in retroviral-mediated diseases, such as ALS-like syndromes [32], and may be applicable to SZ treatment strategies. Also, recent evidence shows that in MS patients, IFN-β treatment reduced HERV-W RNA, as well as circulating antigens and antibodies against HERV-W [33]. These clinical precedents may be further translated into research on SZ etiopathogenesis and treatments, and such findings can serve as a model that can be extended to other HERV-mediated human diseases.

Not only could HERV-W research in the context of SZ inform potential treatment strategies, it could also improve the current diagnostic system for the disease (Fig. 4). Currently, there is no single test that can definitively and absolutely diagnose SZ, and the diagnosis is made on the basis of symptoms and presentation, which can be problematic due to the lack of natural boundaries between disorders, such as SZ, schizoaffective disorders and bipolar disorders [3]. Reliable biomarkers have yet to be identified for SZ, and further HERV-W studies may lead to discovery of novel SZ biomarkers. For instance, elevated levels of *gag* transcripts have been identified in PBMC from SZ, and this cell population could be potentially useful in identifying biomarkers of the disease [30]. Novel biomarkers will improve prevention and treatment, as
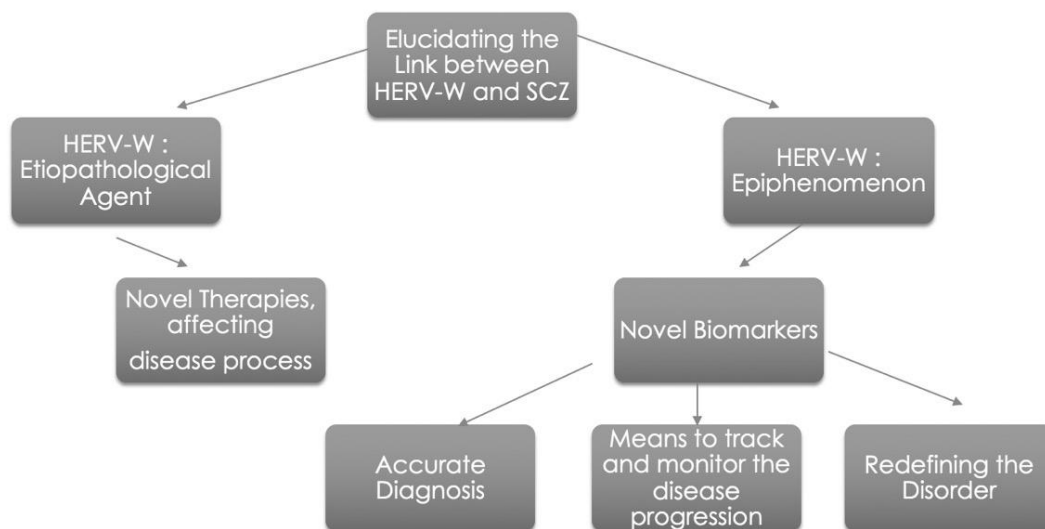

FIG. 4 Future directions for SZ research. This is a flowchart depicting future directions for SZ research. Once the link between HERV-W and SCZ are elucidated and HERV-W's roles determined, it can lead the field towards exciting new avenue towards novel therapies and biomarkers.

it will allow for a system to accurately diagnose, track and monitor the disease progression in SZ patients. It may even open up a new definition of SZ, as we become equipped with the ability to cluster patients based on their biomarker profiles.

Future studies should focus on experimentally proving whether there is truly an overlap between patients with abnormal HERV-W expression, patients with a history of infectious events during both prenatal stage and adulthood, and patients with elevated systemic inflammation, marked by high CRP levels [13]. Also, the pathological mechanisms of HERV-W presented in this article should be further investigated and proven within the context of SZ. On the other hand, other environmental influences still remain to be explored within the context of SZ, such as steroid hormone, which has been shown to enhance expression of HERV elements [34]. SZ incidence peaks between 15–24 years of age for both males and females, and females display a second peak at age 55–64 [35]. These periods are times of important hormonal shifts, and therefore, the hormonal influence on HERV expression and SZ pathogenesis may prove to be a valuable area of research that is yet to be explored. Also, the existence of HERV-W negative SZ patients must be acknowledged [31], which merits further research into other etiological agents and development of alternative models of SZ pathogenesis.

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ACRONYMS

Schizophrenia (SZ), human endogenous retrovirus (HERV), human endogenous retrovirus type W (HERV-W), herpes simplex virus (HSV), cytomegalovirus (CMV), long terminal repeats (LTR), neurotrophic tyrosine kinase receptor type 2 (TrkB), dopamine receptor D3 (DRD3), and brain-derived neurotrophic factor (BDNF), toll-like receptor 4 (TLR-4), peripheral blood mononuclear cells (PBMC), C-reactive protein (CRP), cyclic adenosine monophosphate response element-binding protein (CREB)