9 Human Endogenous Retrovirus as Missing Link in the Global Etiopathogenesis of Schizophrenia and Bipolar Disorder

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9.1 Introduction

Schizophrenia (SZ) and bipolar disorder (BD) are severe psychiatric disorders involving complex interactions between genetic and environmental factors [1–5].

Environmental factors, such as winter birth, urban environment, and maternal infection during pregnancy, in particular caused by Influenza virus, Herpesviruses or T. gondii, are associated with an increased risk for SZ and for BD [6–9]. Viruses or parasites have been associated with the pathogenesis of SZ or BD, but most studies were based on serology that essentially detects an immunological scar, i.e., specific immunoglobulin G antibody [10–12]. Nonetheless, though the period of infection can be debated, epidemiological data provide arguments for critical periods in life when they may have a significant impact, along with associated immune-mediated inflammation: (a) the perinatal period encompassing the embryonal development and the postnatal final steps of neurodevelopment and (b) the young adulthood period when infections with, e.g., Herpesviruses occur. These periods were further thought to correspond to the early acquisition of a

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M. Berk et al. (eds.), *Immuno-Psychiatry*, https://doi.org/10.1007/978-3-030-71229-7_9

"neurodevelopmental risk", followed by some triggering effects of new infections and/or particular stress factors in teenagers or young adults [12–17]. As illustrated in Fig. 9.1, such a lifelong scenario may integrate perinatal "priming" event(s) and "boosting" events later in life, which could be synergistic or substitutable, with a critical period for teenagers and young adults.

Genetic studies revealed a potential contribution of loci involved in the inflammatory/immune pathways, including the major histocompatibility complex region, in both SZ and BD [18–21], among other candidate genes [22, 23]. Structural genomic studies also highlighted significant modifications in psychotic patients, including copy number variations, deletions, or somatic modifications of the genomic DNA [24–26].

Nonetheless, the mechanisms possibly underlying interactions between genetic and environmental risk factors contributing to the clinical onset and/or to the progression of psychotic disorders remain to be understood. Moreover, the significant observations made in studies addressing different aspects from various disciplines should require a unifying, but missing, link to allow a global understanding.

Rather recently, the involvement of multicopy genetic elements of the human genome, such as Human Endogenous Retroviruses (HERVs), has been reported in SZ and BD [9, 13, 27].

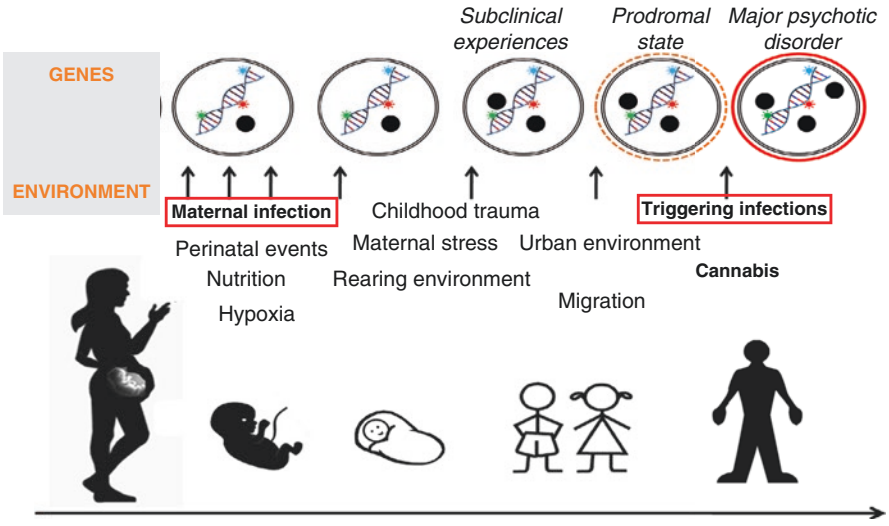

Fig. 9.1 Lifelong exposure to environmental factors impacting epigenetics and gene expression. Environmental triggers may influence gene expression but no direct link with disease was identified, nor directly targeted or involved genes. Epidemiological studies point to most critical periods of exposure to infectious factors, during the embryonal/postnatal period and during the teenage/young adult period. Black circles represent cumulated events having potentially impacted genomic regulation or structures. Colored stars on the drawing for DNA double helix represent potentially susceptible DNA sequences. Adapted from Rutten & Mills Sch. Bull. 2009

9.2 HERVs Represent a Disregarded but Important Part of the Human Genome with Original Genetic Features

HERVs are multicopy families of polygenic structures, represent 8% of the human genome and have retained characteristics of retroviruses. They entered the genome of species from ancient germ-line infections by exogenous retroviruses that have integrated their DNA genomic copy (cDNA) into the DNA of such host cells. Integration of retroviral genome cDNA reverse-transcribed from the virion RNA is a common characteristic of retroviruses, mediated by their encoded enzymes, reverse transcriptase, and integrase. Thus, nonlethal infection and integration of a retroviral genome within a chromosomal region that may not affect embryonal and adult development following gametes fusion, can lead to a hereditary transmission to the offspring. Multiple similar events, called "endogenization", with various retroviruses during evolution, led to multiple families of endogenous retroviruses (ERVs) within the genomes of species ending with numerous mutations, recombination events, and deletions within integrated sequences (provirus), as illustrated in Fig. 9.2.

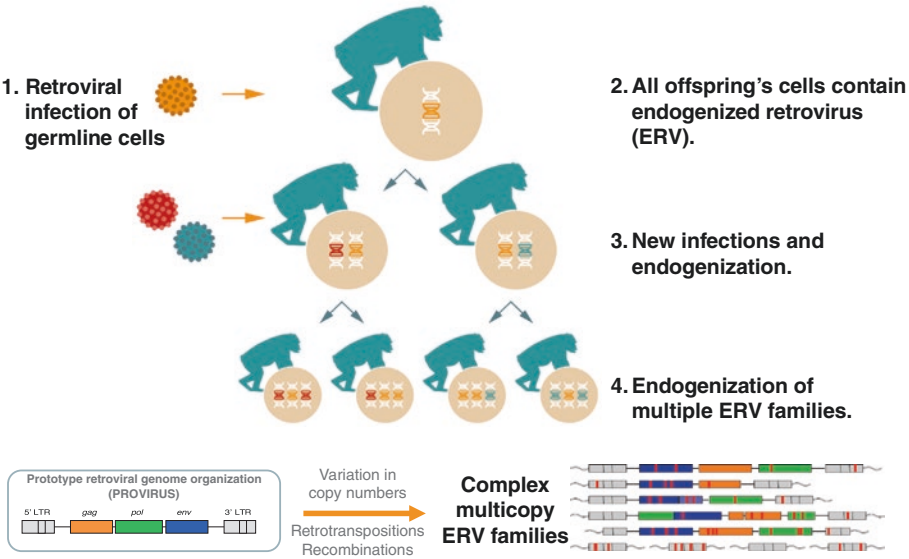

Fig. 9.2 Retroviral endogenizations and transmission to offspring. This illustration depicts the successive steps of retroviral endogenization in species, starting from infection of gametes, integration of a DNA retroviral copy (provirus) in a chromosome giving birth to a viable individual inheriting and retaining this copy in the DNA of all cells and transmitting it to its offspring. Throughout successive generations and species evolution, both endogenous retrotranspositions and re-infections of the germ line of certain individuals (as long as the exogenous strain is persisting in the environment) generate multiple and variable copy numbers in a final population. As shown in the lower panel, retroviral genomes integrated as proviruses are originally composed of two flanking long terminal regions of repeated sequences (LTR), with gag, pol, and env genes, respectively encoding viral capsid proteins, retroviral enzymes, and the envelope protein. They may undergo many somatic modifications during inheritance over generations and most elements are modified or inactivated. Nonetheless, few proviruses from various families may retain coding potential for proteins, if not for complete retroviral expression

HERVs, like other ERVs, belong to the superfamily of repeated and transposable elements (transposons, retrotransposons, and endogenous retroviruses) and altogether represent over 42% of the human genome. They were shown to have played a role in inter- and intra-species gene transmission between individuals. At the individual level, they are responsible of somatic modifications such as intracellular gene retro-transposition or recombination, and may undergo changes under selective environmental pressure or interactions with infectious pathogens.

HERVs are therefore components of the human genome that can be transmitted to subsequent generations through gametes, but have evolved differently from other host genes [28]. They have significant inter-individual copy number variations within the genome of healthy humans from different ethnic origins or simply between individuals [29–32], which would suggest inter-individual differences in potentially related genetic susceptibility.

9.3 HERVs in Schizophrenia and Bipolar Disorder

Interestingly, considering observed somatic rearrangements and copy number variation in psychotic patients' DNA, HERVs may generate such genetic rearrangements linked to their properties of mobile genetic elements [33]. This could even be triggered by microbial agents activating the expression of certain HERV copies or families [34–38]. Interestingly, structural modifications in the major histocompatibility complex (MHC) C4 gene were associated with characteristics of HERVs [29] and numerous HERV sequences were also found in the chromosomal region corresponding to MHC class II genes [39, 40]. In addition, the role of HERV inserts in the regulation of schizophrenia-linked genes has been described [41] and genomic differences between affected and nonaffected homozygous twins identified a differentially amplified HERV copy from the twin with SZ [42].

Thus, HERVs may link many observed genetic features in psychoses such as schizophrenia, while providing an explanation for an underlying mechanism driven by these remnants of "mobile genetic elements" in the human genome, since still functionally interacting with environmental pathogens.

However, a potentially unifying role should not be limited to the genomic level, as HERV-encoded proteins with well characterized and relevant pathogenic mode of action [43] were shown to be expressed in SZ or BD [44–49].

Although most of the contemporary copies of HERVs were inactivated by mutations or deletions or silenced by epigenetic modifications, as schematized in Fig. 9.2, their plasticity and potential responsiveness to environmental triggers are of particular relevance for gene–environment interactions [50]. Under certain conditions, undisrupted HERV sequences or copies may be expressed and display viral protein properties [51–53].

In schizophrenia, a sequence homologous to a human endogenous retrovirus originally identified in MS and previously named "Multiple Sclerosis-associated Retroviral element" (MSRV), was identified from differential DNA amplification in homozygote twins discordant for the disease [42]. MSRV sequences later permitted

to unravel a previously unknown HERV family, now named HERV-W [54–56]. MSRV/HERV-W proteins or elevated RNA levels were further detected in patients with schizophrenia from different world areas and in independent studies [45, 47, 49]. Significantly elevated HERV-W transcriptional activity, though with different expression patterns, was also reported in patients with SZ or BD [44].

The HERV-W family and copies corresponding to its MSRV element, have now consistently been shown to be activated by infectious agents [35, 57–59]. In particular, HERV-W elements have been reported to be activated by T. gondii [60] as well as by Influenza virus in human cell lines [37], which is relevant for environmental infections incriminated in elevated risk, for e.g., schizophrenia. Such pathogenic activation of HERV-W elements [45, 61–63] may result in the production of its envelope protein (HERV-W Env) that strongly stimulates a pro-inflammatory cascade through the TLR4 receptor pathway [64] and displays neurotoxicity [43].

At the neuronal level, altered NMDA receptor (NMDAR) signaling plays a central role in psychosis [65] and this glutaminergic system has been extensively described to be part of several key physiological processes, such as synapse maturation [61, 62], spinogenesis [63, 66], and learning/memory [67]. Moreover, the regulation of NMDA receptor signaling is highly dependent on the surface diffusion of the receptor and its dynamic anchoring within postsynaptic densities [68]. A recent study showed that the effect of HERV-W-encoded envelope protein (HERV-W ENV) on glutamatergic NMDAR signaling was not mediated through direct action on channel physiology, but on its trafficking in the plasma membrane at the level of neuronal synapses [43]. This showed a potent link between exposure to HERV-W ENV and NMDAR surface dynamics with a pattern of response that was unique to HERV-W Env compared to all other tested compounds, including LPS, another TLR4 agonist. The effect also uniquely targeted gluN2B and not gluN2A receptors. The fact that these effects were not observed under glia-free conditions also suggested the implication of glia-dependent pathways in this process. The study showed the potential impact of HERV-W env expression, beyond its pro-inflammatory effects, on neuroreceptor dysregulation as observed in psychoses such as schizophrenia and bipolar disorder. Moreover, these specific effects were reproduced using HERV-W ENV serum from patient.

Most interestingly, this study also showed that consistent psychotic behavior was induced in an animal model consisting in rats expressing HERV-W ENV protein in hippocampal neurons transfected with *ENV* gene expressing plasmids in vivo. In addition, a specific monoclonal antibody targeting HERV-W ENV not only inhibited HERV-W ENV pathogenic effects in vitro but also significantly prevented abnormal behavioral signs in antibody-treated rats using intraperitoneal injections in this animal model, versus mock-transfected controls. This not only confirmed the specificity of the neuropathogenic effects of HERV-W ENV and of its behavioral correlates in vivo, but importantly paves the way toward a new therapeutic avenue with antibodies neutralizing this HERV protein.

Thus, HERVs should not only provide a link with previously described genomic features of SZ or BD but also with the abnormal expression of pathogenic endogenous proteins activated by environmental factors, in particular HERV-W envelope

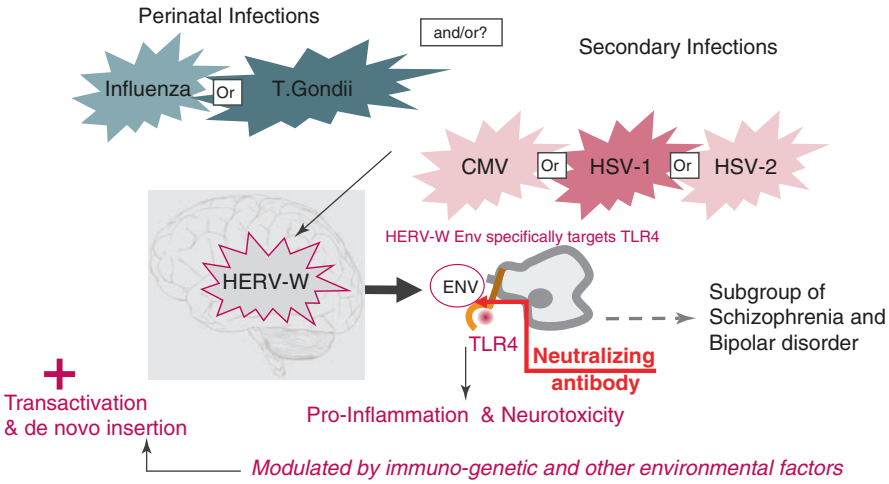

Fig. 9.3 Human Endogenous retroviruses (HERV-W): the missing link? As previously presented, infectious agents were associated with increased risk for schizophrenia or bipolar disorder but, according to their tropism and corresponding periods of infection, they can activate HERV-W elements as already shown in vitro. They would however have a relevant impact in two different periods of life. The early perinatal infections would mostly involve influenza virus or Toxoplasma gondii, while viruses from the Herpesvirus family (e.g., Cytomegalovirus-CMV; Herpes simplex virus type 1 and type 2 -HSV-1 or 2) are commonly acquired in teenagers and young adults

protein with a now evidenced mode of action on the distribution of neuronal receptors at the synapse level. Therefore, the involvement of certain HERV elements appears consistent with the previously evoked missing link between known features of these psychotic diseases and it may provide a global understanding of their pathogenesis, with gene-environment interactions and resulting endogenous neuropathogenic effector molecules. A global scenario summarizing the hypothesis resulting from the present data on the role of HERV-W envelope protein is proposed in Fig. 9.3.

9.4 Conclusion and Perspectives

In conclusion, a lifelong scenario of a detrimental interaction between infectious agents and HERV-W genes may decipher the actual development and course of schizophrenia or bipolar disorder. But, after the preclinical proof of concept provided with a monoclonal antibody neutralizing the pathogenic effects of HERV-W ENV in an animal model, further research and development followed by clinical studies are needed to find out if such a specific treatment strategy could neutralize the pathogenic effects of HERV-W ENV and/or reduce the expression of HERV-W, with appropriate endpoints in patients with schizophrenia or with bipolar disorder. Time may come when new therapeutic strategies targeting pathogenic and non-physiological agonists would allow treating, or possibly preventing, such psychiatric diseases without impairing physiological functions mediated by neuroreceptors and neurotransmitters.

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