A model of human endogenous retrovirus (HERV) activation in mental health and illness

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ABSTRACT

Despite strong evidence for the heritability of major depressive disorder (MDD), efforts to identify causal genes have been disappointing. Furthermore, although there is strong support for life stress as a major predictor of MDD, there are also considerable individual differences in susceptibility and resilience that remain poorly understood. Efforts to identify specific gene-by-environment risk factors produced results that were initially encouraging, but that were not supported by later large-scale studies. Here I propose a novel mechanism that could address the “missing heritability” of MDD, the role of environmental risk factors, and individual differences in susceptibility and resilience. This mechanism focuses on a class of transposable elements, Human Endogenous Retroviruses (HERVs), which make up approximately 8% of the human genome as the result of ancient retroviral infections that entered mammalian germ lines throughout the course of evolution. My primary hypothesis is that exposure to either exogenous viruses or traumatic experiences can activate HERVs in the brain to cause depressive (and possibly other psychiatric) symptoms. My secondary hypothesis is that individual differences in vulnerability or resilience result from the balance of activated HERVs with pathogenic versus protective functions in the brain. Future research can test these hypotheses by analysis of postmortem human brain tissue from donors with known viral or trauma histories; animal studies manipulating HERV expression; cell culture studies examining regulatory mechanisms of HERV expression; and from brain imaging studies of individuals with known HERV-expression. Such research may reveal novel functions of HERVs in neural tissue and may lead to a new generation of psychiatric interventions designed to target aberrant HERV activation.

Background

Major depressive disorder (MDD) is a debilitating yet common illness that has a lifetime prevalence rate of 16% in the United States [1]. Worldwide, depression is ranked first in terms of disability-adjusted life years (DALYs), accounting for 41% of the 184 million DALYs, according to the Global Burden of Diseases, Injuries, and Risk Factors Study 2010 [2]. Yet, depression treatment outcomes remain unsatisfactory, with lifetime recurrence rates for first- and second-episode patients at 50% and 80%, respectively [3].

Both genetic and environmental risk factors contribute to depression. The condition has a heritability of approximately 0.4 based on twin studies [4,5], and environmental risk factors include childhood adversity, life stress, social, and life style factors [6–8]. Efforts to identify specific candidate gene-by-environment risk factors produced results that were initially encouraging [9,10], but that were not supported by later large-scale studies [11–13]. Genome-wide association studies (GWAS) pursued an alternative hypothesis-free approach that initially also showed poor replicability, despite being conducted in samples that were orders of magnitude larger than in prior candidate-gene studies [14]. Even the largest recent GWAS, which produced a successful replication of 17 genome-wide significant single nucleotide polymorphisms (SNPs) across 15 genomic locations, only accounted for a small portion of the variance with heritability estimates of 0.06–0.07 [15]. Yet, current genetic analyses have excluded vast territories of human DNA from study, particularly the 45% of the human genome that contain transposable elements (TEs) including human endogenous retroviruses (HERVs) [16].

Hypothesis

An influential hypothesis articulated by Smith in this journal in 1991 proposed that the immune system may play a causal role in psychopathology [17]. Since then, evidence continued to accrue linking psychopathology (particularly depression) to inflammation [18,19], and I have previously discussed the potential role of pathogens such as parasites, bacteria, and viruses in the etiology of depression [20–22]. I speculated that “missing heritability” in depression may be represented in sections of the human genome that were overlooked in prior work, such as retroviral insertions, which represent a particular subclass of TEs. A retrovirus uses reverse transcription to integrate a DNA copy of viral RNA into the genomic DNA of its host. Integration in the germline lineage endogenizes the retrovirus (ERV, endogenous retrovirus) to become heritable. Human ERVs (HERVs) make up about 8% of human DNA and are comprised of 504 distinct families with approximately 520,000 individual
members [23]. Recent work suggests that 50% of some HERV families are transcriptionally active [24]. Despite their large numbers, HERVs have received only scant attention for their role in human health and disease.

The genomic structure of a full-length HERV (a provirus) consists of long terminal repeats (LTRs) that contain open reading frames (ORFs) and many regulatory sequences (such as transcription-factor binding sites, TFBSs; promoters, enhancers, splice sites, polyadenylation signals). These LTRs flank and regulate the expression of retroviral genes Gag, Prot, Env, and Pol. The expression of such HERV proteins can be quite common: for example, 30% of healthy individuals show expression of HERV-K Env proteins in blood [25]. Evolutionary recent HERVs have the most intact ORFs and retroviral structures, such as the HERV-K family with 54 proviruses that integrated between 14 and 19 million years ago (MYA) [26]. Most HERV-Ks are much more ancient (40–60 MYA) and lost their internal retroviral structure through recombination over the course of evolution. Yet, their remaining solitary LTRs can still be powerful regulators of their host’s genome through five mechanisms [23]: enhancers/repressors of neighboring genes; transcription of downstream genomic sequences to create new genes or non-coding RNAs; premature termination of read-through transcripts through LTR poladenylation sites; LTR splice sites that can alter their host’s exon-intron structure; and regulation through RNA interference mechanisms. Indeed, almost 800,000 HERV TFBSs have been identified [27], which enable them to regulate host genes in a tissue- and cell-type specific manner. Such flexibility and specificity could be relevant for psychopathology, which affects specific neural circuits and cellular components.

Based on data I review further below, my primary hypothesis is that genetic contributions to depression (and perhaps other psychiatric disorders) originate from HERVs embedded in the human genome that are environmentally activated by exogenous viruses or psychological trauma. My secondary hypothesis is that individual differences in vulnerability or resilience result from the balance of activated HERVs with pathogenic versus protective functions in the brain. In the following section, I will present the empirical evidence from which I generated these hypotheses.

Why HERVs?

Studies of schizophrenic patients suggest a role for HERVs in psychopathology

One postmortem brain RNA expression study of four schizophrenic patients and six controls reported elevated HERV-W expression in patients [28], although two other, similarly small, studies reported no [29] or reduced [30] HERV-W expression between schizophrenic patients and controls. An RNA expression study of the plasma of 118 patients with recent-onset schizophrenia and 106 controls reported expression of the HERV-W env gene in 36% of patients, but none of the controls [31]. These studies are intriguing, but it is unknown whether these transcripts would generate bioactive proteins that could play a pathogenic role.

HERVs can be activated by the same exogenous viruses that have been associated with depression

A meta-analysis on infectious agents and depression [32] reported significant associations with Epstein-Barr virus (EBV), varicella zoster virus (VZV), herpes simplex virus-1 (HSV-1), and Borna Disease Virus (BDV). EBV is a co-factor contributing to Multiple Sclerosis (MS) [33] through a mechanism that involves two members of the HERV-W family, MS-associated retrovirus (MSRV) and ERVWE1 [34], whose expression parallels patients’ active/remission phases and MS stages [35]. Interferon-beta (IFN-β) therapy in MS patients is associated with increased seroreactivity to EBV EBNA-1 and VZV in non-responders, and corresponding seroreactivities to envelope antigens for HERV-H and HERV-W [36]. HSV-1 activates HERV-K LTRs [37], and HERV-K is activated in patients with sporadic amyotrophic lateral sclerosis (ALS) [38].

HERVs can be regulated by epigenetic signals, which can also be activated by stressful or traumatic experiences

Epigenetic signals regulate gene expression through molecular mechanisms such as DNA methylation and histone modifications. DNA methylation refers to the addition of methyl primarily to cytosine (but also adenine) through DNA methyltransferases (DNMTs) [39]. This process occurs mostly at cytosines that precede a guanine nucleotide (called CpG sites), and tends to reduce gene expression by recruiting repressive proteins or interfering with transcription factors. Histones are proteins that contribute to the structural organization of the genome: an octamer of eight histones (two copies each of H2A, H2B, H3 and H4) forms one unit, called a nucleosome, around which 147 base pairs of DNA are coiled in approximately 1.7 turns [40]. Histone H1 then links multiple nucleosomes together to form chromatin. Port-translations modifications (PTMs) of histones include methylation, acetylation, phosphorylation, ubiquitylation, and sumoylation, which affect gene expression by recruiting histone modifiers or by altering the density of chromatin (euchromatin, which is less densely packed, and tends to not be transcribed or to be silenced by RNA-induced transcriptional silencing [41]; heterochromatin, which is condensed, and tends to not be transcribed by RNA-induced transcriptional silencing [42]).

Epigenetic repression is believed to be a principal protective mechanism against activation of potentially dangerous retrotransposons and endogenous retroviruses [43–47]. Conversely, removal of repressive epigenetic marks can promote endogenous retroviral LTR activation. For example, decreased DNA methylation (through DNA methylation inhibitors) or increased histone acetylation (through histone deacetylase inhibitors) can activate LTRs from theERV9/LTR12 family [48]. These results were further extended in a study of more than 450,000 HERV LTRs located within the intergenic regions of human somatic cell DNA [49]. Inhibition of DNA methylation produced 988 up-regulated LTRs, whereas inhibition of histone methyltransferases targeting histone H3 lysine 9 (H3K9) or lysine 27 (H3K27) methylation produced 791 up-regulated LTRs (a subset of 59 LTRs were regulated by both epigenetic signals). Subsequent analysis revealed that the differentiating factor was evolutionary age: relatively young LTRs were regulated by DNA methylation, whereas intermediate-age LTRs were regulated by histone methylation. This switch from one epigenetic silencing mechanism to another over evolutionary time likely reflects structural changes to LTRs: young LTRs tend to have abundant CpG sites regions that can be targeted by 5-methylcytosine (5mC) for DNA methylation, but these regions tend to be depleted over time due to progressive deamination of 5mC to thymine [50,51].

DNA methylation and histone modifications are also activated by stressful life experiences. In a seminal study conducted in rats [52], poor maternal care was associated with hypermethylation in the promoter region of the glucocorticoid receptor gene (nr3c1). This observation was later translated to humans, based on examination of gene expression profiles in postmortem hippocampal tissue in suicide
victims with a history of childhood [53]. Early adversity also has genome-wide differential methylation effects, as shown in rhesus macaques: compared to maternal-reared controls, peer-reared monkeys exposed to maternal separation had significantly different DNA methylation across 1373 distinct gene promoters in the prefrontal cortex (PFC), of which 835 were hyper-methylated and 538 hypo-methylated [54]. An additional modification to DNA methylation is the enzymatic catalysis to 5-hydroxymethylcytosine (5hmC) [55], and maternal separation in rhesus macaques was associated with genome-wide DNA hydroxymethylation changes in the PFC [56]. Surprisingly, although hydroxymethylation was generally associated with reduced gene expression, it was associated with increased gene expression in a subset of genes that had previously been associated with numerous disorders including autoimmune disease and inflammatory response.

Histone modifications are another epigenetic mechanism by which stressful life experiences can regulate gene expression. For example, histone H3 lysine 9 trimethylation (H3K9me3), which represses gene expression, was increased in the hippocampus of rats exposed to brief, acute restraint stress [57]. Remarkably, H3K9me3 was enriched at transposable element loci and was shown to repress expression of retrovirus elements, particularly the ERV Intracisternal-A particle (IAP). The authors speculated that this mechanism could function to contain genomic instability brought on by stress-induced transposon activation. Relatedly, histone H3 lysine 4 trimethylation (H3K4me3), which facilitates gene expression, was reduced in the oxytocin receptor gene OXTR (with corresponding reduced OXTR mRNA expression) in peer-reared rhesus macaques [58]. Loss of H3K4me3 through application of the histone de-methylase Kdm2a was shown to reduce expression of Intracisternal A particles, MurVY linked (IAP-Ey) [59], which is again consistent with the view that the link between stress and ERV regulation favors mechanisms that protect against genomic instability.

HERVs are polymorphic, possibly contributing to individual differences in disease vulnerability and resilience

For example, ERV-K is polymorphic and its variants confer differential disease vulnerability [60,61]. There are three alleles encoding the ERVK-18 envelope protein (K18.1, 2, and 3) and the K18.3 allele is associated with increased risk for MS. A risk haplotype comprised of two ERVK-18 SNPs (rs558648 and rs1090799) is associated with elevated risk for Type 2 diabetes among schizophrenic patients. Whole-genome sequencing data from the diverse 1000 Genomes Phase 3 population (n = 2,504) identified 46 polymorphic HERV-K SNP insertions that were associated with neurologic and immunologic disease phenotypes [62].

Putative pathogenic and protective mechanisms

HERV activation can be pathogenic through inflammatory processes or disruption of the blood-brain-barrier (BBB)

Inflammatory processes are illustrated by expression of the MSRV envelope protein (Env-ms) in HCMEC/D3 brain endothelial cells (a human BBB in vitro model), which stimulates pro-inflammatory cytokines IL-6 and IL-8 via the Toll-like receptor 4 (TLR4) [63]. This is relevant to depression (but also anxiety disorders like PTSD) because these conditions are associated with elevated levels of pro-inflammatory cytokines [64–70] and depression is associated with elevated TLR4 levels [71,72]. Disruption of the BBB is illustrated by the fact that the same system (MSRV in HCMEC/D3 brain endothelial cells) stimulates ICAM-1 (which mediates leukocyte adhesion to endothelial cells), and the transmigration of activated immune cells through a monolayer of endothelial cells [63]. This is relevant to depression and anxiety disorders like PTSD because both conditions are associated with BBB disruption. For example, changes in density and function of astrocytes and microglial cells are associated with depressive symptoms and recover their function in response to antidepressant treatments [73,74]. Damaged astrocytes release the growth and differentiation factor S100B, which is elevated in depression [75], childhood trauma [76], and combat training stress [77]. S100B is regulated by pro-inflammatory transcription factors (TFs) such as Nuclear Factor-Kappa Beta (NF-xB), which is dysregulated in depression and PTSD [78,79], and which activates HERV-K [60].

HERV activation can also be protective through anti-retroviral, neurotrophic, or immunosuppressive mechanisms

Anti-retroviral functions are illustrated by activation of HERV envelope (env) genes that act as restriction factors against related exogenous retroviruses [80,81], as HERV-K, which protects against the HIV-1 Vpr protein in neuroblastoma cells and in transgenic mice [82]. Another example is BDV (discussed above for its association with depression): activation of endogenous BDV sequences correlates with resistance to exogenous BDV exposure [83]. Neurotrophic functions are illustrated by HERV-K: in a human neuronal cell line, transfections with an HERV-K env expression construct induced expression of the neurotrophins nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) [82]. Relevant to depression and other psychiatric illnesses, meta-analyses confirmed that low concentration of serum BDNF is associated with depression [84], and that serum BDNF can be a biomarker for treatment success in depression and bipolar disorder [85]. PTSD is also associated with reduced BDNF [86], as well as hippocampal shrinking [87,88], and increased BDNF-methylation after combat exposure [89]. Immunosuppressive functions are illustrated by HERV-K, which activates the anti-inflammatory cytokine IL-10 [90], and the HERV-W env protein (ERVW-1)-encoded Syncytin, which is involved in placentation and maternal tolerance of the fetus through immunosuppression [23]. Relevant to depression, immunosuppressive therapy relieved depressive symptoms in patients with Inflammatory Bowel Disease [91,92]. Anti-inflammatory drugs such as the TNF-α receptor blocker Etanercept showed antidepressant effects in patients with moderate to severe psoriasis [93] and in patients with rheumatoid arthritis [94].

Summing up

The Balance Model (figure below) summarizes the preceding sections. Briefly, the model stipulates that stressful life experiences can activate HERVs in relevant brain regions through epigenetic signaling pathways. Stress-resilience may reflect underlying epigenetic mechanisms that protect against HERV-induced genomic instability, whereas stress-susceptibility may reflect the failure of such mechanisms. The model also stipulates a second pathway, by which exogenous viruses can activate HERVs in the brain by disrupting the BBB. Activation of specific HERV variants can then either have pathogenic effects via inflammation and additional BBB-disruptive signals, or have protective effects via neurotrophic or BBB-restorative effects. Individual differences in disease resilience or susceptibility reflect the balance of these two kinds of HERV activations.
Evaluation

The balance model predicts HERV activation in persons with exogenous virus exposure (particularly EBV, VZV, HSV-1, and BDV) or a history of stressful life experiences. Evidence for such activation could be obtained from postmortem brain samples of donors with known life histories, particularly in brain regions associated with stress processing or psychopathology. The model further predicts that the pattern of HERV activation will be different for individuals who developed depression (or other psychiatric illnesses) from those who were resilient. To maximize the opportunity to discover HERVs that are bioactive and may therefore play a causal role in psychiatric illness, postmortem tissue analysis should focus on the presence of HERV proteins (as opposed to mRNA).

HERV candidates identified from the postmortem study could be examined mechanistically at the cellular, neural, and behavioral level of analysis. At the cellular level, one could study the transcription profile of HERV-transfected neuronal cell cultures. At the neural level, one could manipulate HERV expression in vivo in behaving rodents. Such pre-clinical work could also begin evaluations of potential treatment strategies: for example, whether correcting aberrant HERV expression in the brain can restore normal behavior. Also at the neural level, one could use noninvasive magnetic resonance imaging (MRI) in patient and control cohorts with known infection and life stress histories and blood-based HERV expression profiles. These studies could directly test the hypothesis that HERV expression moderates BBB permeability, as is now possible with MRI [95]. Related imaging studies could use positron emission tomography and the [18F]-FEPPA radio ligand to quantitate translocator protein binding to image neuroinflammation [96] as a function of HERV expression and depressive status [97,98]. At the behavioral level, one could study cognitive, affective, and physiological stress responses as a function of HERV expression in patients and controls and HERV-targeted interventions.

In addition to these laboratory-based studies, one could conduct field studies in regions with considerable disease and trauma-burden, while at the same time delivering desperately needed clinical care to underserved populations. For example, Africa has the highest infection rates in the world [99], and refugees in Africa have endured significant amounts of psychological trauma. A study of 1210 respondents from 28 Northern Ugandan refugee camps [100] found that 75% witnessed the
mortality of a friend or family member, 56% experienced torture or beatings, and 58% experienced 8 or more of 16 trauma events; 54% met criteria for PTSD and 67% met criteria for depression. Furthermore, genetic diversity is greatest among African populations, maximizing the opportunity for discovery of causal variants [101]. African genetic diversity extends to HERVs. For example, ERV-K is polymorphic and the degree of variation varies across ethnicities [60,61], with the highest genetic diversity in African samples, compared to samples from Asia, Europe, and Papua New Guinea [61]. As stated earlier, HERV polymorphic variants can differ in functional consequences for imparting disease risk, as shown in MS and schizophrenic patients [60,61]. Such fieldwork could also enrich the African Genome Variation Project, which was conceived to serve as a resource for genomic studies in sub-Saharan Africa [102], but does not currently include data on mental health disorders or participants’ trauma history, and has not utilized genome-sequencing methods needed to capture HERV expression profiles.

Discussion

As discussed elsewhere, treatment success for major depression remains a matter of trial-and-error [20–22], and pharmacological approaches have not changed much over the course of decades, nor have recent medications proved superior to earlier ones [103–105]. Furthermore, the clinical effectiveness of drugs targeting alternative pathways has also been criticized across numerous meta-analyses [106–111]. HERVs represent an entirely new class of potential pharmacological targets for future interventions designed to correct aberrant HERV expression. Development of such interventions will face considerable technical challenges, such as off-target effects. Although the study of HERVs in psychopathology represents an enormous opportunity for discovery, their sheer number also represents a major challenge. There are about 520,000 individual HERV members, and in addition to main effects, there may be unknown numbers of interactions among them. One way to make sense of this complexity is to focus on the signaling pathways known to play a role in psychiatric disorders. Another approach is to focus on brain-region-specific or cell-specific expression profiles. Pathway analysis is one bioinformatics approach that integrates information about individual genes with known regulatory networks that can be filtered by disease or tissue.

In addition to treatment advances, the study of HERVs may also help better understand the heritability of depression and possibly other psychopathologies. Both candidate gene and GWAS approaches have fallen short of expectations and “missing heritability” in psychopathology remains a source of continued speculation. Yet, as noted by Olshansky and colleagues [49], “transposable elements including Alus, long interspersed nuclear elements (LINEs), and endogenous retroviruses (ERVs) make up >40% of the human genome, yet they have been refractory to mapping and epigenomic analysis due to their highly repetitive nature” (p. 1147). Recent advances in both sequencing technology and mapping software have now made it possible to conduct genome-wide studies of repetitive elements, which may turn out to be the equivalent of “dark matter”, within which heritable sequences associated with psychopathologies have been hiding.

Genomic studies across psychiatric disease categories suggest links that may explain disease comorbidity. Recent work by the Cross-Disorder Group of the Psychiatric Genetics Consortium discovered moderate-to-high (0.32–0.68) genetic correlations using common SNPs between MDD, schizophrenia (S), bipolar disorder (BD), and attention-deficit-hyperactivity disorder (ADHD) [112]. Similarly, the Brainstorm Consortium found significant correlations among MDD, S, BD, anxiety disorders, and ADHD [113]. These genetic analyses suggest a common underlying genetic architecture and yet-undiscovered pathogenic pathways across disorders. Considering that human DNA is composed of 8% HERVs and 40% transposable elements, it is possible that their functions contribute significantly to psychiatric comorbidity. To borrow another phrase from physics, such a “grand unifying theory” of psychiatric illness may be overly optimistic, but it is certainly experimentally verifiable. Perhaps more likely, there could be a plethora of different HERVs or other transposable elements acting through pleiotropic mechanisms to affect different disease outcomes. The study of such mechanisms would require combining the large-scale hypothesis-free discovery approach of GWAS with the best of the experimentally based candidate gene approach. Such consilience could transform not only psychiatry, genomics, and neuroscience, but may even lead to a new appreciation of what it means to be human in a viral world.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2019.109404.

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