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Human endogenous retroviruses (HERV) and non-HERV viruses incorporated into the human genome and their role in the development of autoimmune diseases

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ABSTRACT

Genomic incorporation of viruses as human endogenous retroviruses (HERVs) are components of our genome that possibly originated by incorporating ancestral of exogenous viruses. Their roles in the evolution of the human genome, gene expression, and the pathogenesis of autoimmune diseases (ADs) and neoplastic phenomena are the subject of intense research. This review analyzes the evolutionary and virological aspects of HERVs and other viruses that incorporate their genome into the human genome and have known role in the genesis of ADs. These insights are helpful to understand further the possible role in autoimmunity genesis of HERVs, other ancestral viruses no HERVs and modern viruses with the ability to incorporate into the human genome or interact with HERVs.

1. Introduction

The immune system can recognize its own antigens and not establish a response against them. This process is known as antigenic tolerance. When antigenic tolerance is lost, and an immune response against it is created, autoimmunity is initiated. If tissue/organ damage is generated due to this process, an autoimmune disease (AD) is constituted [1]. More than 100 autoimmune diseases have been described, ranging between 5% and 8% of the general population, with a higher prevalence in women [2].

ADs are a significant clinical problem, due to their complexity and chronicity. Its etiology is multifactorial, among which genetic, epigenetics, environmental, and infectious aspects stand out [3]. Among the most studied aspects are viral infections [4]. In recent years a possible implication of human endogenous retroviruses (HERVs) and other viruses that incorporate their genome into the human genome in the induction of autoimmunity has been raised [5].

This article reviews the virological, evolutionary, and pathogenic aspects of the association between HERVs presence in the human genome and autoimmunity. In addition, the possible role of other viruses incorporated into the human genome that could be involved in the pathogenesis of ADs is also described.

2. Retrovirus

Retroviruses are viruses with a protein envelope (about 100 nm in diameter), which contain as a genome a positive RNA chain (7–10 kb) that codes for an enzyme called reverse transcriptase (RT), which catalyzes the passage from RNA to DNA [6].

Retroviruses are classified as exogenous or endogenous. The current exogenous retroviruses of medical importance are human immunodeficiency viruses (HIV 1, HIV 2) and Human T-lymphotropic viruses (HTLV1, HTLV 2). The first two cause acquired immunodeficiency syndrome (AIDS), and the last two cause tropical spastic paraparesis, T-cell leukemia/lymphoma, and HTLV-1 – associated myelopathy (HAM) [7]. HTLV 3 and 4 have been discovered; however, their pathogenic role has not been evidenced [8].

HERVs are those that in previous stages of human evolution have integrated into the human genome and constitute 8% of the human genome [9]. Initially, HERVs were considered silent genomic sequences that lacked function; however, in recent years, multiple investigations have been carried out that have revealed their importance in human pathological processes such as cancer and autoimmunity and physiological processes such as embryogenesis [10–12].

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3. HERVS: Evolutionary, structure and classification aspects

The human genome comprises a small number of genes, and exons account for only 1% of our DNA. This small percentage stands in stark contrast to various types of repetition that take up almost half of our genome [13]. HERVs are part of these elements and probably are the remnants of ancient germ cell infection by exogenous retroviruses and are transmissible to the next generation in a Mendelian way [14]. The presence of HERVs is also postulated because of co-evolutionary processes [15]. Most HERVs invaded our genome at least 25 million years ago, except for the evolutionary young HERV-K group [16]. The role of this genetic information is unknown, and their ancestral effects on the function of own genes are under investigation, including the replication and insertion of new genomics structures (including genes of exogenous viruses) and the effects in the biological dynamics of adjacent or distant genes [17]. However, existing HERV loci may alter gene expression by providing alternative transcription initiation [18] or antisense inhibition [19]. Thus, these elements and others probably undiscovered could influence the evolution of genomes. Even though they seemed biologically silent and highly defective [20], some are still active, and their expression is regulated by different factors (UV radiation, inflammatory cytokines, steroid hormones, and exogenous virus products) [21].

HERVs have a similar genetic sequence to exogenous retroviruses. A complete sequence of HERVs is composed of *gag*, *pol*, *pro*, and *env* regions sandwiched between two long terminal repeats (LTRs). *Gag* codes for structural components of the matrix (MA), capsid (CA), and nucleocapsid (NC). The *pol* gene codes for integrase, reverse transcriptase, and RNAse. The *pro* gene codes for the protease and the *env* gene codes for the envelope (E) and transmembrane (TM) subunits [22,23].

HERVS are taxonomically classified into three categories according to their phylogenetic similarity: Class I (Gammaretrovirus, Epsilonretrovirus); class II (Deltaretrovirus, Alpharetrovirus, Lentivirus, Betaretrovirus); Class III (Spumaretrovirus) [24]. Therefore, those most implicated in autoimmunity are class I endogenous retroviruses.

4. Mechanism of autoimmunity induced by HERVs

Multiple mechanisms have been described by which autoimmunity can be induced by HERVs. Thus, there are some with the greatest biological plausibility and those with the most significant evidence.

4.1. Superantigens

Some HERVs can encode proteins that can act as superantigens, activating cells of the immune system, especially CD4 T lymphocytes [25]. In 2001, Sutkowsk et al., showed that Epstein-Barr virus (EBV) could transactivate the HERV-K18 that encodes a superantigen [26]. Transactivation is believed to occur through the major EBV envelope glycoprotein, gp350, the herpes virus binds to human CD21 (hCD21) and enters B cells by endocytosis [27]. The interaction between gp350 and hCD21 triggers signal transduction pathways that culminate in the activation of NF-kB and the up-regulation of IL-6 transcript [28]. Then the LMP-1 and LMP-2A (for latent membrane proteins 1 and 2A) of EBV, transactivate a HERV [29]. This creation of superantigens induced by the EBV could be a mechanism by which this virus generates autoimmunity.

Consistent with these findings, Sicat *et al* [30] demonstrated that HERV-K18 expression was significantly elevated in peripheral blood from patients with juvenile rheumatoid arthritis (mean ratio of HERV-K18 to 18S ribosomal transcripts 2.456, SD 2.122; $p = 0.014$), but not in patients with Systemic lupus erythematosus (SLE) (mean 0.997, SD 0.579; $p = 0.258$), compared to healthy controls (mean 0.749, SD 0.598). These findings suggest a possible mechanism for autoimmunity induction.

4.2. Molecular mimicry

The molecular mimicry theory proposes that proteins of microbial origin could share homologous peptide sequences with host proteins and that the immune system, by recognizing these exogenous sequences, can establish a cross-reactive response with its own and generate damage [31]. This mechanism has been described as an autoimmunity inducer in multiple viruses, among which are: EBV [32], Cytomegalovirus (CMV) [33], Parvovirus B19 [34], or in bacteria such as Group A Streptococcus [35].

In HERVs, it is proposed that these sequences can code for proteins that have regions like proteins encoded by the host genome. Due to loss of antigenic tolerance, antibodies can be generated against HERVs proteins, and by molecular mimicry, an antibody that is cross-reactive against a self-antigen is generated [36]. This finding was evidenced in a study of patients with SLE, in which antibodies against an endogenous retroviral element-encoded nuclear protein autoantigen, HRES-1, were more present in patients with SLE vs. controls (52% vs. 3%) and that these autoantibodies were cross-reactive with other antigens such as U1-ribonucleoprotein (RNP) [37].

4.3. DNA hypomethylation

DNA hypomethylation is an epigenetic mechanism of DNA regulation, involving the loss of the methyl group in the 5-methylcytosine nucleotide [38]. Methylation is a natural modification of DNA and mainly affects the cytosine base (C) followed by guanosine (G) in mammals (methylation). Hypomethylation can be applied to describe the unmethylated state of most CpG sites in a specific sequence that usually is methylated or as a general phenomenon affecting the bulk of the genome; this is a decrease in the proportion of methylated versus unmethylated cytosines [39,40]. DNA hypomethylation has been described in multiple diseases [41], especially neoplastic diseases [42]. Regarding autoimmunity, it has already been shown that hypomethylation can play a role in the pathogenesis of SLE [43,44]. In 2013, Nakkuntod et al. published a study that demonstrated HERV-E LTR2C methylation level in CD3 + CD4 + T lymphocytes of active SLE was significantly lower than inactive SLE and normal controls ($P = 0.023$ and 0.035, respectively). Furthermore, the hypomethylation of HERV-E LTR2C in CD3 + CD4 + T lymphocytes was positively correlated with lymphopenia in patients with active SLE [45].

Surprisingly, HERV-K LTR5_Hs hypomethylation was significantly detected in CD3 + CD4 + T lymphocytes from patients with inactive SLE compared with the active SLE and normal controls ($P = 0.027$ and 0.002, respectively). Demethylation of HERV-K LTR5_Hs in B cells was also detected compared with the normal controls ($P = 0.048$).

5. Autoimmune diseases where HERVs may be involved in their pathogenesis

There are multiple autoimmune diseases in which the involvement of HERVs in its pathogenesis has been implicated. The most important are described in Table 1.

5.1. Type 1 diabetes mellitus (T1DM)

Type 1 diabetes is an autoimmune disease in which there is the destruction of the beta cells of the pancreas, which are responsible for the production of insulin, with consequent hyperglycemia [46]. 80% of cases begin in childhood. There are many associated etiological factors, mainly genetic, environmental factors, and viral infections. Tovo et al. assessed the transcription levels of pol genes of HERV-H, HERV-K, and HERVW in peripheral leucocytes from 37 children and adolescents with new-onset T1DM and 50 age-matched control subjects. A real-time PCR amplification assay evaluated HERV transcripts. The expression levels of the HERV-H-pol gene and HERV-W-pol gene were significantly higher in

Table 1
Most representative human endogenous retroviruses (HERVs) associated with some autoimmune diseases and their most probable pathogenetic role.

Disease	HERVs Involved	Predominant Autoimmunity mechanism	References
Type 1 diabetes mellitus (T1DM)	HERV-H HERV-K HERVW	Molecular mimicry Superantigens	47,48,49
Multiple sclerosis (MS)	MSRV HERV-K HERVW	Superantigen	53, 56,57,58
Systemic Lupus Erythematosus (SLE)	HRES-1 HERV-K HERV-E	DNA hypomethylation Molecular mimicry	37,45,66
Rheumatoid Arthritis	HML-2	Molecular mimicry	68,69,70

diabetic patients than in control subjects [47]. One of the theories of the role of HERVS could be that a viral infection such as enterovirus induces transactivation of HERVs and thus induces autoimmunity [48].

The most convincing evidence of the relationship between HERVS and type 1 diabetes was given by Levet *et al* who in 2017 demonstrated that in patients with T1D, HERV-W-Env protein was detected in 70% of sera, and its corresponding RNA was detected in 57% of peripheral blood mononuclear cells. Studies on human Langerhans islets evidenced the inhibition of insulin secretion by HERV-W-Env, this endogenous protein was found to be expressed by acinar cells in 75% of human T1D pancreas. An immunohistological analysis revealed a significant correlation between HERV-W-Env expression and macrophage infiltrates in the exocrine part of human pancreas [49].

Antibodies directed against a peptide of HERV-K6 envelope protein have also been found elevated in a T1D patients. This was evidenced by Niegowska *et al* who demonstrated that patients with antibodies against *Mycobacterium avium* had an antibody against HERVS, showing a clear correlation between both antibodies and suggesting a pattern of molecular mimicry [50].

So far, the evidence has also been demonstrated in experimental animal models, in 2016 Bashratyan *et al* shown that NOD (non-obese diabetic) mice developed autoantibodies against ERV envelopes proteins, with antibody titers increasing with disease progression. ERV proteins encoded by the gag gene (retroviral capsid proteins) also appeared to be involved in pro-inflammatory responses and in the induction of autoreactive cells in NOD mice [51].

5.2. Multiple sclerosis (MS)

MS is a demyelinating autoimmune disease of the central nervous system characterized by multifocal areas of demyelination with loss of oligodendrocytes and astroglial scarring [52]. Considerable evidence supports the role of HERVs in MS pathogenesis. A HERVs in patients with MS was described in 1980, called Multiple Sclerosis- Associated Retroviral Agent (MSRV) [53,54]. This HERVs can activate monocytes and endothelial cells through CD14/TLR4 and activate the production of proinflammatory cytokines such as interleukin (IL) - 1β, IL-6, and tumor necrosis factor (TNF) –α [55].

Multiple studies show that MS patients have higher expression of HERVs compared to controls. This evidence was corroborated in a meta-analysis carried out by Morandi et al., where they analyzed 43 studies and showed an association between expression of HERVs, particularly the HERV-W family, and MS [56]. This association has even had therapeutic implications. Arru et al. showed that the use of Natalizumab in patients with MS inhibits the expression of HERVs of the W family [57]. However, the clinical implication of this finding is not yet clear.

In 2013, Kremer et al. demonstrated that human endogenous retrovirus type W (HERV-W) negatively affects oligodendroglial precursor cell (OPC) differentiation and remyelination via its envelope protein pathogenic HERV-W (pHERV-W) ENV (formerly MS-associated retrovirus [MSRV]-ENV [58].

The same research group found that in MS lesions, pHERV-W ENV is present in myeloid cells associated with axons. Focusing on progressive disease stages, demonstrated that pHERV-W ENV induces a degenerative phenotype in microglial cells, driving them toward a close spatial association with myelinated axons. Moreover, in pHERV-W ENV-stimulated myelinated cocultures, microglia were found to structurally damage myelinated axons. Taken together, data suggest that pHERV-W ENV-mediated microglial polarization contributes to neurodegeneration in MS [59].

These findings are extremely valuable and allowed the development of a monoclonal antibody directed against HERV-W envelope protein, this drug called initially GNbAC1 and then temelimab, showed reduction of the stress reactions resulting in a rescue of myelin expression *in vitro* [60].

In July 2021 the clinical study was published, a phase 2, double-blind, 48-week trial in relapsing-remitting MS with 48-week extension phase. The primary endpoint was the reduction of cumulative gadolinium-enhancing T1-lesions in brain magnetic resonance imaging (MRI) scans at week 24. Additional endpoints included numbers of T2 and T1-hypointense lesions, magnetization transfer ratio, and brain atrophy. In total, 270 participants were randomized to receive monthly intravenous temelimab (6, 12, or 18 mg/kg) or placebo for 24 weeks; at week 24 placebo-treated participants were re-randomized to treatment groups. The primary endpoint was not met. At week 48, participants treated with 18 mg/kg temelimab had fewer new T1-hypointense lesions ($p = 0.014$) and showed consistent, however statistically non-significant, reductions in brain atrophy and magnetization transfer ratio decrease, as compared with the placebo/comparator group. These latter two trends were sustained over 96 weeks. No safety issues emerged [61].

5.3. Systemic lupus erythematosus (SLE)

SLE is the prototype of systemic autoimmune diseases. It is characterized by the formation of autoantibodies and multi-organ compromise [62]. There is growing evidence showing the relationship between HERVS and SLE. As mentioned above, antibodies against an endogenous retroviral element-encoded nuclear protein autoantigen, HRES-1, were more present in patients with SLE vs. controls [37].

Piotrowski et al. showed that blood plasma concentrations of anti-U1 RNP and anti-Sm antibodies may correlate with PBMC transcript levels of HERV-E clone 4-1 gag sequence ($R = 0.775$, $p < 0.000001$; $R = 0.698$, $p < 0.000001$, respectively). These observations suggest that the expression of HERV-E clone 4-1 might be associated with production of anti-U1 RNP and anti-Sm antibodies in patients with SLE [63]. In addition to these results, Wang *et al* found that HERV-E clone 4–1 mRNA expression was upregulated in $CD4^+$ T cells from SLE patients and positively correlated with SLE disease activity. This is associated with the activation of Ca2+/calcineurin (CaN)/NFAT1 and E2/ER-α signaling pathway and DNA hypomethylation of HERV-E clone 4–1 5′LTR [64].

There is robust evidence showing that impaired methylation of HRES-1 occurring in B cells of SLE patients seems to be the key to understanding the mechanism underneath the hyper-expression [65]. In 2014 Fali et al. showed that blocking the autocrine-loop of IL-6 in SLE B cells with an anti-IL-6 receptor monoclonal antibody restores DNA methylation and control of HRES-1/p28 expression became effective [66].

5.4. Rheumatoid arthritis (RA)

RA is the most common systemic autoimmune disease. It is characterized by synovial inflammatory involvement [67]. Some evidence for HERVs has been found in the pathogenesis of RAs. Ejtehadi *et al*, in 2006, published a study showing higher HERV-K10 gag mRNA expression in

RA than in osteoarthritis ($p = 0.01$) or in the healthy controls ($p = 0.02$) [68]. These results have been replicated in other studies with other HERVs such as HML-2 [69,70].

On the other hand, In 1999, Seidl *et al* studied a solitary LTR element (DQ-LTR3) of the HERV-K family at the HLA-DQB1 locus for a possible disease association among 228 RA patients and 311 unrelated blood donors. The DQ-LTR3 was significantly more frequent among patients (76% vs 33%, OR = 5.07,$p < 0.0001$), with the majority of patients being heterozygous for the DQ-LTR3 (61% vs 22%, $p < 0.0001$). HLA-DRB1*04 positive patients did still differ for the presence of the DQ-LTR3 (88% vs 70%, OR = 3.03, $p < 0.001$), with an increase of both DQ-LTR3 homozygous and heterozygous patients, when compared to DRB1*04 positive controls ($p = 0.0015$) [71]. These findings suggest that this DQ-LTR3 enhances susceptibility to RA. In 2017, Mameli *et al* explored the role of humoral immune response against HERV-K as a potential pathogenetic mechanism in RA. They took four different peptides from the extracellular portion of the env protein of HERV-K (env-su19–37, env-su109–126, env-su164–186, env-su209–226) and quantify antibodies against those peptides on blood samples of 70 consecutive RA patients and 71 healthy controls. Serum autoantibodies against one of four tested peptides of HERV-K (env-su19–37) were significantly higher in RA than in healthy controls(19 versus 3%, P 0.0025). Subgroup analysis showed no association between anti-HERV-K peptide humoral response and clinical, serological and clinimetric RA disease descriptors [72].

6. Genomic incorporation of viruses other than retrovirus

Viruses such as herpesviruses (e.g., EBV), adenoviruses, parvoviruses, polyomaviruses, arenaviruses, bornaviruses, filoviruses, rhabdoviruses, and hepatitis B virus [73–78] can incorporate into the human genome.

It is hypothesized that to support immune memory, integrating sequences can boost adaptive B cell and T cell responses long after replicating viruses are cleared [79]. Could this form of activation of the immune response be involved in the pathogenesis of AD? The interaction of these viruses with HERVs or the very fact of incorporating its genes into the host genome through reverse transcription [80] or by other different mechanisms [81], is also a promising field in the study of AD pathogenesis. Physiopathologic evidence indicates that the pathologic mechanisms may be similar among diverse ADs including the infection, being these concepts part of the autoimmune tautology [82].

SARS-CoV-2 infection may be related to autoimmunity phenomena and several hypotheses have been proposed [83,84]. However, the proven incorporation of the virus into the human genome [85,86] and its possible role in the genesis of autoimmunity, remains to be elucidated.

7. Conclusions

Endogenous retroviruses are part of our genome, most likely originating from ancestral exogenous retroviruses that were incorporated. Other ancestral and modern nonretroviral viruses are also incorporated into our genome. These incorporations of genes of viral origin are an inherent phenomenon in our evolution. They are part of many research processes to understand their biological role in normal cell physiology and pathological processes such as ADs. The evidence is accumulating how HERVs participate in the pathogenesis of ADs, while the study of other nonretroviral viruses that are incorporated into our genome and that also participate in the genesis of AD, is a reason for posing hypotheses and possible future research.

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.

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