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HERVs in Multiple Sclerosis — From Insertion to Therapy

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<http://dx.doi.org/10.5772/61726>

Abstract

Genome-wide association studies (GWAS) have not been able to completely elucidate the genetic background of complex diseases. Part of it could lie in repetitive sequences not studied in the GWAS, as those corresponding to Human Endogenous Retroviruses (HERVs). In the present work, we aim to review the potential role of HERVs in the etiology of autoimmune diseases, especially in multiple sclerosis (MS); their potential pathogenic role and their putative consideration as a good target for new treatments. For this purpose, we carried out an in-depth literature review on HERVs, and we integrated our previous findings about HERV-W, HERV-K18, and HERV-Fc1 and MS susceptibility. The study was carried out by a systematic search from electronic databases using the keywords “HERV,” “Multiple sclerosis,” “HERV-W,” “MSRV,” “HERV-K,” “HERV-Fc1,” and “GNbAC1.”

Keywords: Multiple sclerosis, HERV, MSRV, GNbAC1

1. Introduction

1.1. HERVs

The endogenous retroviruses (ERVs) could be defined as “genetic parasites” of vertebrates [1], given that their origin is very different from the one displayed by the rest of the genome. Their existence in the genome of mammals is only known since 1970 [2], although, they resulted from ancestral infections by exogenous retroviruses millions of years ago. During an infection, the exogenous retroviruses are able to integrate one copy of their genome (provirus) into the genome of the host. Thus, they can stay permanently associated with the host and be transmitted horizontally by the creation of new virions (the typical spread of an infectious virus). Only when they infect a germ line cell, the integrated DNA can become part of the gene pool

and be transmitted in a Mendelian fashion like ERVs [1, 3-5], as shown in Figure 1. Those who are present in the human genome are named human endogenous retroviruses (HERVs).

The endogenization process profoundly impacts on the survival and evolution of the virus and the host. It results from the balance achieved between the immune surveillance and the virus virulence [6]. In this way, the HERVs must surpass the host's antiviral defense mechanisms and infect the germ cells without causing a cytotoxicity that would prevent persistence in the progeny of the host [6]. Furthermore, from this moment on, all host cells are carriers of an integrated provirus [6].

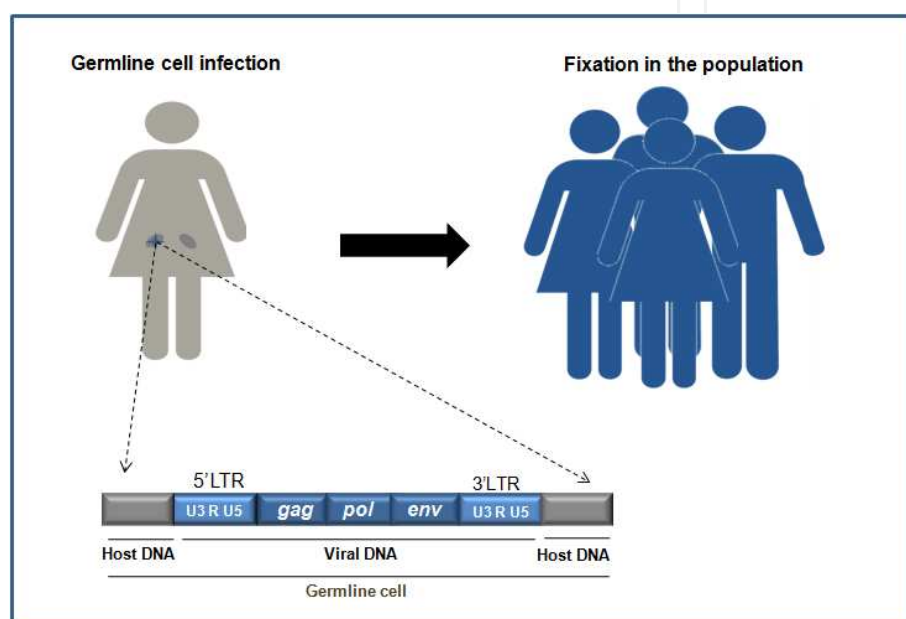


Figure 1. The endogenization process: once the retrovirus infects a germ line cell, vertical transmission in a Mendelian fashion occurs.

The retroviral insertion is aleatory, in the sense that no specific sites for retroviral integration exist in the host genome. Nonetheless, due to the epigenetic chromatin packaging, integrated HERVs elements are more commonly found within the transcriptionally active genome [6]. Currently, HERVs comprise nearly 8% of the human genome [7], distributed in approximately 31 independently acquired multigene families [8]. Even though no standard nomenclature has been defined for HERVs, they have been classified based on their homology with different groups of exogenous retroviruses. They are grouped as class I, class II, or class III retroviruses considering their homology with Gamma and Epsilon retroviruses, Betaretrovirus or Spumavirus, respectively [9, 10]. The family name is usually given by "HERV" followed by a one-letter amino acid code that corresponds to the tRNA specific of the site used to initiate reverse transcription [10]; consequently, the HERV-W family would use a tryptophan.

As mentioned, HERVs have a similar structure to proviruses of infectious retroviruses, with three principal genes, *gag*, *pol*, and *env*, flanked by two long terminal repeats (LTRs) [6]. The *gag* gene codes for the viral assembly proteins, including the nucleocapsid, matrix, and capsid

proteins. The *pol* gene codes for the viral replication proteins, yielding the reverse transcriptase, protease, ribonuclease, and integrase proteins. Finally, the *env* gene codes for a viral glycoprotein, with both a surface and a transmembrane subunit. However, important changes are observed in the HERVs expression compared to that of exogenous retroviruses. Most HERVs encode incomplete proteins and accumulate mutations and recombinations. Furthermore, most HERVs with functional LTRs remain in a latent state under homeostatic conditions, owing to the epigenetic silencing of the provirus in heterochromatin [11]. Exceptionally, specific HERVs have been selected during evolution, provided that their biological functions could be beneficial for the host. In these cases, HERVs suffer a “domestication,” meaning that a foreign gene can be used for cellular functions of the host [12]. In this group, we find proteins like Syncytin-1 from the HERV-W family, and Syncytin-2 from the HERV-FRD family [13]. These highly fusogenic envelope proteins are necessary to allow the formation of the placental syncytiotrophoblast layer; furthermore, they could be involved in the immune tolerance to the fetus [13].

In addition to these “domestic HERVs,” several studies show reactivation of HERVs under pathologic conditions, such as different types of cancer [14-20]; autoimmune diseases including multiple sclerosis (MS) [21-37], rheumatoid arthritis (RA) [38], psoriasis [39], or systemic lupus erythematosus (SLE) [40]; and other diseases like schizophrenia [41, 42]. Nonetheless, we do not know whether their reactivation or increased expression is a causal effect, or conversely, is an underlying consequence of the disease.

1.2. Potential expression mechanisms of HERVs

Many factors can interfere or modulate the expression of HERVs, such as recombination events between two or more replication-defective HERVs [43, 44], infectious agents like Human herpesvirus 6 (HHV6) [34, 45] and Epstein–Barr virus (EBV) [46, 47], several transcription factors [31, 48], and the epigenomic context of the HERVs [6, 49, 50].

- Recombination events

Two or more replication-defective HERVs can restore their own defects through recombination events, resulting in a replication-competent retrovirus [5]. Even though this is an infrequent event, a study in mice points to a significantly increased frequency in specific immune deficiencies [44]. Furthermore, it has been demonstrated that recombination between three HERV-K defective proviruses is possible, leading to an infectious retrovirus [5, 43].

- Infectious agents

A putative explanation about the preferential expression of HERVs found in human brain samples could be the tropism of specific viruses and bacteria to the central nervous system (CNS). Neurotropic agents like herpesvirus [29, 51], *Toxoplasma gondii* [52], or certain strands of influenza virus [53] are able to cross the hematoencephalic barrier into the CNS. Usually, they are intercepted by cerebral macrophages leading to an abortive infection, but their transient presence in the CNS could activate the HERVs expression as a consequence of their immediate-early (IE) genes expression [4]. The expression of the IE genes of herpes simplex

virus type 1 (HSV-1) and its interaction with the transcription factor binding sites situated in the U3 region of the LTR, such as AP-1 [54] and Oct-1 [55], lead to an activation of transcription in HERV-K and HERV-W families.

The herpesviruses are one of the best candidates: they may be neurotropic, remain latent, and can be reactivated. Furthermore, the expression of the Env epitopes in the surface of B cells and monocytes could be a consequence of the interaction between HERVs and herpesviruses [25]. Thus, the herpesviruses could play a dual role in neurodegenerative diseases, acting as pathological entities *per se* and as inducers of HERVs [6].

- Transcription factors

An important component of the antiviral innate immunity is the regulation of the expression and replication of HERVs by different transcription factors [48]. In HERV-W and HERV-K elements, both families previously related to multiple sclerosis (MS), different binding sites for transcription factors such as NF- κ B [31, 48] are located in their promoter regions and could drive an increased expression of HERVs during inflammation.

- Epigenomic context

The chromatin state as well as the methylation state of CpG islands within the HERV promoter and regulatory regions seem to be crucial factors in the control of HERVs expression [49, 50]. Both play an important role as a part of the defense system against the potential effects of inserted sequences. Previously published studies describe how proviruses and solitary LTRs are densely methylated under physiological conditions, but hypomethylated in placenta [49, 50]. Thus, DNA hypomethylation, as observed in certain types of cancer, could allow reactivation of retroelements. In MS, HERVs have been described as susceptible elements to undergo epigenetic modifications, mainly due to modifications in the methylation state, resulting in activation of their expression and, consequently, inappropriate activation of the immune system.

1.3. Pathogenic mechanisms of HERVs

Even though most inserted copies in the human genome are defective copies, some HERVs could maintain the potential to cause or contribute to disease by different mechanisms [5]. As mentioned, HERVs may alter cellular functions by two ways, either acting as a genetic element or as a viral pathogen [6].

- Gene disruption

HERVs, like transposons, are able to experience transposition, recombination, and integration cycles. Some HERVs families include a high number of copies in the genome. It is believed that these families have been spread around the genome through the reintegration of a provirus. However, each new integration process increases the risk of a harmful insertion. They can disrupt genes present in their integration sites, for example, HERV-K integrations have been identified into tumor suppressor genes like *BRCA2* and into the repair *XRCC1* gene [6, 56].

- Modulation of gene expression

Some HERVs conserve regulatory sequences that can operate as functional promoters, enhancers, or polyadenylation signals, so they could change the expression of adjacent or distal genes [4]. They can also form part of regulatory RNAs: microRNAs (miRNA), small interfering RNAs (siRNA), and long intergenic noncoding RNAs (lincRNAs), contributing to the complex regulatory network of gene expression [5]. Furthermore, HERVs integrated into introns can provide alternative transcription start and termination sites [5].

- Pattern recognition receptors (PRRs)

The HERVs expression products, both nucleic acids and proteins, can modulate immune responses. They have the potential to interact with components involved in the immune innate response and to activate proinflammatory signaling pathways [57, 58]. Therefore, certain HERVs proteins could directly interact with specific toll-like receptors (TLRs), for example with TLR4, resulting in the production of TNF α and proinflammatory cytokines [58-60]. The nucleic acids derived from HERVs may also activate cytosolic PRRs; in this way, both an increased expression of RNA and the presence of cDNA in a nonfamilial compartment like the cytosol could activate PRRs [60]. Nonetheless, the human being has coevolved with endogenous retroelements and this could have shaped the sensibility of DNA sensors of the innate immune system, leading to an increased cDNA detection threshold to avoid an immune response against them. The cDNA levels are restrained by the action of gene products like Trex1 or SAMHD1 [60] and a loss-of-function mutation in these enzymes could result in the cDNA accumulation and the consequent sensors activation. This process would lead to a chronic immune response with release of pathogenic type I IFN and inflammatory mediators, similar to those observed in autoimmune diseases [60].

- Viral proteins: molecular mimicry, superantigen activity, or immunosuppressive proteins

HERVs proteins hold epitopes to B and T cells and molecular mimicry between viral proteins and certain autoantigens may exist, resulting in an autoimmune response. Moreover, some HERVs sequences are able to encode for superantigens. Superantigens combine with MHC class-II molecules to form ligands that stimulate T cells [61], and this may end in an abnormal activation of autoreactive T lymphocytes [62].

Alternatively, evidences exist of the immunosuppressive activity of certain HERVs Env proteins [63, 64]. This activity is reminiscent of their exogenous antecessors, which in this way increased the viability of the virions in the host. This capacity has suffered an adaptation process, and nowadays it might be implicated in the materno-fetal tolerance and could also prevent the immune response to exogen pathogens and tumors [60].

- Retroviral help for B cells

HERVs can also help B cells to quickly produce antibodies directed against pathogenic antigens [65]. The bacterial polysaccharide antigens and the carbohydrates linked to viral glycoproteins have the ability to stimulate B cells in the absence of T-cell help. These antigens are called thymus-independent antigens (TI), and they can be classified into two types: TI-1 or TI-2 antigens. TI-2 antigens cause extensive cross-linking of the BCR, leading to a quick differentiation of B cells into plasma cells. Finally, these plasma cells secrete protective antibodies, IgM

and IgG [66]. However, the mechanism by which the TI-2 antigens activate B cells in the marginal zone without the help of T cells still remains poorly understood. It has been recently described that the cross-linking of B cells activates a signaling cascade, including the Bruton Tyrosine Kinase and the nuclear transcription factor NF- κ B, allowing transcription of endogenous retroviral DNA [66]. The retroviral RNA may activate B cells by two complementary but different pathways: first, it could activate the retinoic-acid-inducible gene 1 receptor (RIG-1), resulting in a mitochondrial antiviral-signaling (MAVS); second, the RNA can be converted into DNA and can activate the cyclic GMP-AMP synthase (cGAS, cGAMP synthase). Finally, both signaling pathways would finish in the antigen-specific B-cell activation [65, 66].

2. HERVs and autoimmune diseases

HERVs represent the immunological limit between the self and the foreign. Their peculiar origin is very different from that of other genome elements, as they can share properties with infectious agents. Indeed, in case they would produce particles, these would not be so different from those originated from exogenous retroviruses. Therefore, they could activate the immune system and would induce autoimmunity [67]. As it has been previously discussed, HERVs have been associated, among other infectious or neurologic diseases, with different autoimmune diseases like MS [21-37], RA [38], psoriasis [39], T1D [68], or SLE [40], as shown in Table 1. Genome-wide association studies (GWAS) showed the existence of a genetic basis shared between different autoimmune diseases, discovering new immunogenic mechanisms implicated, and HERVs could be part of these shared genetic elements.

Class	Family	PBS	Related diseases	Expression mechanisms	Pathogenic mechanisms
I	HERV-W	Trp	MS Schizophrenia HIV Osteoarthritis	Herpesviruses Transcription factors Toxoplasma gondii Influenza A virus	Pro-inflammatory Env protein Superantigen activity OPCs differentiation interference Altered glial function
I	HERV-F	Phe	MS	Demethylating agents	Superantigen activity
I	HERV-H	His	3q13.31 microdeletion syndrome	N/A	Genetic deletion by recombination
I	HERV-E	Glu	SLE	Hypomethylation	Immunosuppressor potential of Env
I	HERV-P	Pro	Cancer	Unkown	Unknown
II	HERV-K	Lys	MS ALS HIV	Herpersviruses HTLV-1 Type 1 IFN	Superantigen activity Neoepitopes Genes disruption

Class	Family	PBS	Related diseases	Expression mechanisms	Pathogenic mechanisms
			Schizophrenia		
			T1D	Transcription factors	
			RA	Hypomethylation	
			Juvenil arthritis		
			Cancer		

MS, multiple sclerosis; HIV, human immunodeficiency virus; SLE, Systemic lupus erythematosus; ALS, amyotrophic lateral sclerosis; T1D, type 1 diabetes; RA, rheumatoid arthritis, HTLV-1, human T-lymphotropic virus-1; IFN, interferon; Env, envelope; OPCs, oligodendrocyte precursor cells; N/A, not applicable. Based on Douville and Nath, 2014 [6].

Table 1. HERVs families associated with different diseases

3. HERVs and MS

MS is one of the conditions more frequently related with HERVs. It is a chronic progressive disease characterized by neuroinflammation in the CNS accompanied by demyelination, axonal damage, and progressive neurologic dysfunction [69]. It is a complex disease, originated from the interaction of genetic, environmental, and epigenetic factors [70]. Recently, its incidence seems to be increased; at present MS affects 2.3 million people in the world [71]. However, many aspects of its pathogenesis are still poorly understood. GWAS have not completely explained the MS genetic background [72-74], albeit including the ImmunoChip Project [75] a total of 110 single nucleotide polymorphisms (SNPs) have been associated with MS susceptibility. Even considering the strongest risk factor, the HLA-DRB1*15:01 allele, each SNP has a modest effect and all together are able to explain only 20–28% of MS heritability [75]. Part of the missing heritability could reside on HERVs, as repetitive regions were not analyzed in the GWAS. Those repetitive regions were previously considered as “junk DNA” because it was thought that they had little or no physiological role. However, nowadays we know that these sequences could play an important role in the development of autoimmune diseases, including MS.

In 1989, Perron et al. [76] described the presence of extracellular virions associated with reverse transcriptase activity in a culture of leptomeningeal cells (LM7) obtained from the cerebrospinal fluid (CSF) of an MS patient. In the beginning, it was thought that those virions could correspond to the human T-lymphotropic virus (HTLV-1) due to the similarities between the tropical spastic paraparesis (a demyelinating progressive disease) caused by HTLV-1, and MS. However, a new retroviral element called MSRV (Multiple-sclerosis-associated retrovirus) was identified, the founder of the HERV-W family [77]. This multicopy family, consisting of approximately 650 loci around the human genome [35], comprises a total of 311 inserts (more or less complete proviruses or pseudogenes) and 343 additional HERV-W LTRs [78].

Only the *env* gene mapping on chromosome 7, encoding Syncytin, presents a complete open reading frame (ORF) and has been selectively conserved [35]. The MSRV *env* sequence can be differentiated from the one corresponding to Syncytin-1 by a 12-nucleotide insertion in the

transmembrane moiety. Both genes are expressed in the brain of MS patients, but the MSRV-type *env* DNA copies were found sixfold more frequently in MS patients than in healthy controls, while comparable copy numbers of Syncytin-1 were observed [79]. Furthermore, Syncytin-1 is originated from the retroviral copy inserted in chromosome 7, and the pathogenic protein MSRV-type Env could be originated from several integrations in the human genome, or it could result from recombination events between insertions in different chromosomes [80, 81]. The genomic origin of HERV-W Env remains unknown although recent works consider the copy mapping to chromosome X one plausible candidate [4, 80, 81]. This copy, located on Xq22.3, would encode for an almost complete MSRV-type protein, truncated on its N-terminal end due to the presence of a stop codon mutation at position 39 [81]. *Ex vivo*, this copy still conserves coding capacity, as it is able to produce a truncated N-terminally Env protein [80]. Furthermore, the reversion of this stop codon would lead to a complete protein with signal peptide, expressed in the cellular surface in the same way that Syncytin [80].

Recently, a genetic screening was performed by specific PCR amplification followed by High Resolution Melting (HRM) analyses of the two MSRV-like *env* copies which show the ORF with the highest length similarity and homology to Syncytin (1614 bp), inserted in chromosome X (1428 bp) and in chromosome 20 (1419 bp). Both chromosomal origins show similar lengths of their respective ORFs, 10% shorter than the one measured for Syncytin, and could putatively originate functional proteins. The results pointed to the insertion in chromosome X, and not the one in chromosome 20, as an origin of MSRV. One polymorphism identified in chromosome X, rs6622139*T, was associated in women with MS susceptibility and severity [82], and it was also associated with higher MSRV-like *env* levels of expression (Mann–Whitney U test: $p=0.003$), while the two polymorphisms found in chromosome 20 did not show evidence of association [83].

Since it was described, several studies have associated the HERV-W family with MS: the presence of MSRV-type Env protein has been found in demyelinated acute lesions in MS patients [31], as well as an increased number of DNA copies [84] or a higher prevalence of MSRV-type RNA in serum and CSF of MS patients compared with patients suffering from other neurological diseases or healthy controls from all ethnic groups [24, 27, 28, 31, 84–86]. The MSRV presence in serum and CSF is correlated with the clinical progression, severity, and prognosis of MS [28, 46], while the absence of MSRV relates with a more stable course of the disease [28, 36]. The MSRV production is stimulated by cytokines like TNF α , IL6, and IFN γ [87], and current MS therapies like IFN- β and Natalizumab, which are able to reduce MS symptomatology, promote a diminution of MSRV virus load levels in blood [87–89].

HERV-W Env proteins, MSRV-type Env, and Syncytin have proinflammatory and superantigenic properties. They can cause neuroinflammation, neurodegeneration, immune system dysregulation, and endoplasmic reticulum stress [4, 21, 22, 58, 90, 91]. Their pathogenicity has been studied *in vitro* using different types of cell cultures and *in vivo* using a humanized Severe Combined Immunodeficiency Disease (SCID) animal model, showing neurotoxic effects in both settings [22, 92] and a reduced capacity of oligodendrocyte progenitor cells (OPC) differentiation, interfering in the remyelination process [57]. A recent study clarifies the possible pathogenic mechanisms of MSRV. In a human model of BBB, the endothelial cell line

HCMEC/D3, they show that MRSV-type Env interacts with TLR4 and induces a dose-dependent overexpression of ICAM1, as well as an induced IL6 and IL8 production; while the Env protein derived from Syncytin-1 did not show these effects [59]. Furthermore, they also described that the MSRV-type Env presence significantly stimulates the adhesion and migration of activated immune cells through the layer of endothelial cells. These results support the hypothesis that MSRV can be involved in MS pathogenesis, as well as in other chronic inflammatory diseases, at least in the maintenance of the underlying inflammatory condition [59]. Table 2 reflects the possible pathogenic mechanisms described for MSRV.

Cell type	Receptor	Pathogenic mechanisms
T lymphocytes	TCR	Superantigen activity, T lymphocytes proliferation and CK liberation
APC	TLR4	↑ pro-inflammatory CK ↑ costimulatory molecules
HCMEC/D3 endothelial cell line	TLR4	↑ ICAM1 expression IL6, IL8 expression
OPC	TLR4	OPCs differentiation interference (↑ iNOS, oxidative stress)

APC, antigen presenting cell; OPC, oligodendrocyte precursor cell; TCR, T-cell receptor; TLR4, toll-like receptor 4

Table 2. Known pathogenic mechanisms of MSRV

Even though the HERV-W family is one of the HERV families more related to MS, other families like HERV-K18 [37, 93] or HERV-Fc1 [29, 94, 95] have also been associated with MS susceptibility.

HERV-K is a multicopy family including approximately 332 copies dispersed through the human genome. It is the only known retroviral element that codes for all the structural and enzymatic proteins (Gag, Prt, Pol), as well as for the Env protein and for the accessory Rec protein [96]. This family has been related with different autoimmune diseases as MS [37], type-1diabetes (T1D) [68], or juvenile rheumatoid arthritis [38]; and different cancer types [14-17]. One specific member of this family, HERV-K18, has been associated with MS susceptibility and its expression is induced by herpesvirus [97, 98] and by EBV [99-102], both viruses previously proposed as potential environmental factors involved in MS development [45, 51, 97, 103-108]. Three different variants of the HERV-K18 copy mapping to chromosome 1 [37] have been described. They conform haplotypes within the first intron of CD48 that can be defined by two SNPs (18.1 SNP1*A/SNP2*A, 18.2 SNP1*G/SNP2*G, 18.3 SNP1*A/SNP2*G), all of them coding for an Env protein with superantigenic properties. However, only one of these variants (18.3) has been associated with a higher risk to MS [37] and with an overall higher susceptibility to autoimmune diseases, as described by a meta-analysis including a total of 2656 patients and 2016 controls [93].

Considering the HERV-Fc family, a total of 6 HERV-Fc elements and 11 LTRs have been identified across the human genome. Among them, only two elements correspond to a complete HERV-Fc provirus (Fc1env and Fc2master) [109]. Related to MS, it has been observed that the HERV-Fc1 RNA levels were significantly increased in the plasma of patients suffering from active MS, compared to nonactive MS or controls [30]. The HERV-Fc1 is an unusual provirus, because it includes a single copy in the genome, located on Xq21.33. Furthermore, it is a recent acquisition for the genome, only present in humans, chimpanzees, and gorillas [109]. Nexø et al. [94] were the first to describe that rs391745, located in the promoter region of HERV-Fc1, was associated with MS susceptibility in Danish cohorts and, then, a replication study was performed with a Norwegian cohort. The latter study also detailed that the association was only observed in the nonprimary-progressive MS forms [29], results validated in further studies [95]. Regarding the HERV-Fc1 expression mechanisms, it has been observed that the transcriptional expression levels of HERV-Fc1 RNA sequences are negatively correlated with the methylation levels of CpG islands on the 5' LTR region and, therefore, a higher HERV-Fc1 expression involves DNA demethylation [11, 110].

4. HERVs as future treatment options

An increased expression of HERVs in several autoimmune diseases [21-40, 68] and different types of cancer [14-20], along with the decreased expression levels observed in successfully treated patients with immunomodulatory therapies [88, 89] or chemotherapy [111] point to the potential pathogenic role of HERVs and their putative consideration as a good target for new treatments.

A humanized monoclonal antibody anti-Env-SU MSRV/HERV-W, GNBAC1, has been studied as a putative MS treatment due to its potential neuroprotector effects [112-115]. The results of a phase IIa clinical trial [114] show that the GNBAC1 treatment blocks the transcription of proinflammatory genes mediated by Env, prevents the formation of nitrosantine, and restores OPC differentiation. Furthermore, GNBAC1 has advantages compared to other MS treatments, because the patients retain all their immune capacity. This treatment has also been studied in other diseases like diabetes and schizophrenia.

The proteins encoded by HERV-K *env* have been proposed as therapeutic targets for different types of cancer, due to the fact that a general hypomethylation of HERVs sequences has been observed, as well as an increased expression of Np9 and Rec proteins originating from HERV-K in different cancer cells [116]. Both proteins bind to the PLZF protein, a transcriptional repressor of the C-MYC proto-oncogene. The inflammation and the deregulation of proto-oncogene signaling caused by the HERV-K protein results in a protumorigenic microenvironment, which favors cell proliferation and metastasis [116]. The use of monoclonal antibodies against HERV-K Env protein inhibits tumoral growth and induces apoptosis in breast cancer cells *in vitro* [116]; therefore, it could be considered a good candidate as a therapy used together with other cancer treatments.

In addition to autoimmune diseases and cancer, the human immunodeficiency virus (HIV) has been also related to HERVs, particularly with the HERV-K family, raising the issue of potential beneficial effects of a therapy directed against HERVs in AIDS. Some studies report an increased expression of HERV-K provirus in HIV patients compared to controls [117, 118] and show that the immune responses against HERV-K decrease the HIV-1 viral load. *In vitro*, the use of an antibody directed against the HERV-K transmembrane protein (HML-2), HA-137, was able to eliminate the cells that displayed the antigen in their surface. This was carried out by an antibody-dependent cell-mediated cytotoxicity (ADCC) mechanism by natural killer (NK) cells. It has been described that the HIV-infected cells display this membrane antigen in their surface [119]; therefore, they would be potential targets of the antibody. The possibility of finding a target epitope different from those of the HIV virus could open up opportunities to the development of vaccines against this disease; a field that has been very limited due to the high rate of mutation of the HIV [119].

5. Conclusion

This work aimed to provide a systematic revision of HERVs, with particular emphasis on their potential pathogenic role in MS. Although many aspects of the etiology of this disease remain to be solved, different works support the relevance that HERVs may have in the etiopathogenesis of autoimmune diseases, and specifically in MS. HERVs may contribute to both, disease onset and maintenance, through an exacerbated activation of the immune system. Recently, the results of a phase IIa clinical trial that studies the effectiveness of a human monoclonal antibody (GNbAC1) as a therapeutic target in MS have been published with promising outcome. Thus, evidences support the role of HERVs as potential therapeutic armory in different autoimmune diseases, cancer, and HIV.

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