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](image)

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 Spuma-virus, 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, \textit{gag}, \textit{pol}, and \textit{env}, flanked by two long terminal repeats (LTRs) [6]. The \textit{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 hematooencephalic 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-Kβ [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 GpC 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 innate immune 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 TNFα 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-Kβ, 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 | Herpesviruses          | Pro-inflammatory Env protein |
|       |        |     | HIV, Osteoarthitis| Transcription factors  | Superantigen activity  |
|       |        |     |                  | Toxoplasma gondii      |                      |
|       |        |     |                  | Influenza A virus      |                      |
| 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    | Herpesviruses, HTLV-1  | Superantigen activity, Neoepitopes |
|       |        |     |                  | Type 1 IFN            |                      |
|       |        |     |                  |                       |                      |

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### Table 1. HERVs families associated with different diseases

| Class            | Family | PBS  | Related diseases | Expression mechanisms | Pathogenic mechanisms |
|------------------|--------|------|------------------|-----------------------|-----------------------|
| Schizophrenia    |        |      |                  |                       |                       |
| T1D              |        |      |                  |                       |                       |
| RA               |        |      |                  |                       |                       |
| Juvenile 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, olygodendrocyte precursor cells; N/A, not applicable. Based on Douville and Nath, 2014 [6].

### 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 TNFα, IL6, and IFNγ [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 olygodendrocyte 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                                       |
| HCM/C3 endothelial cell line     | TLR4     | ↑ ICAM1 expression                                         |
| OPC                              | TLR4     | OPCs differentiation interference (↑ iNOS, oxidative stress) |

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-1 diabetes (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]. Nexo 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 G NbAC1 treatment blocks the transcription of proinflammatory genes mediated by Env, prevents the formation of nitrosantine, and restores OPC differentiation. Furthermore, G NbAC1 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-oncogen. The inflammation and the deregulation of proto-oncogen signaling caused by the HERV-K protein results in a protumorogenic 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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References

[1] Ribet D, Heidman T. Formation et évolution des rétrovirus endogènes. Virologie. 2010;14:141-50. DOI:10.1684/vir.2010.0294.
[2] Coffin JM. Structure, replication, and recombination of retrovirus genomes: some unifying hypotheses. *J Gen Virol.* 1979;42:1-26.

[3] Chuong EB. Retroviruses facilitate the rapid evolution of the mammalian placenta. *Bioessays.* 2013;35:853-61. DOI: 10.1002/bies.201300059.

[4] Perron H, Bernard C, Bertrand JB, Lang AB, Popa I, Sanhadji K, et al. Endogenous retroviral genes, Herpesviruses and gender in Multiple Sclerosis. *J Neurol Sci.* 2009;286:65-72.

[5] Young GR, Stoye JP, Kassiotis G. Are human endogenous retroviruses pathogenic? An approach to testing the hypothesis. *Bioessays.* 2013;35:794-803. DOI: 10.1002/bies.201300049.

[6] Douville RN, Nath A. Human endogenous retroviruses and the nervous system. *Handb Clin Neurol.* 2014;123:465-85. DOI:10.1016/B978-0-444-53488-0.00022-5.

[7] Lander ES, Linton LM, Birren B, Nusbaum C, Zody MC, Baldwin J, et al. Initial sequencing and analysis of the human genome. *Nature.* 2001;409:860-921. DOI: 10.1038/35057062.

[8] Belshaw R, Katzourakis A, Paces J, Burt A, Tristem M. High copy number in human endogenous retrovirus families is associated with copying mechanisms in addition to reinfection. *Mol Biol Evol.* 2005;22:814-7. DOI:10.1093/molbev/msi088.

[9] Voisset C, Weiss RA, Griffiths DJ. Human RNA "rumor" viruses: the search for novel human retroviruses in chronic disease. *Microbiol Mol Biol Rev.* 2008;72:157-96. DOI: 10.1128/MMBR.00033-07.

[10] Gifford R, Tristem M. The evolution, distribution and diversity of endogenous retroviruses. *Virus Genes.* 2003;26:291-315. DOI:10.1023/A:1024455415443.

[11] Laska MJ, Nissen KK, Nexo BA. (Some) cellular mechanisms influencing the transcription of human endogenous retrovirus, HERV-Fc1. *PLoS One.* 2013;8:e53895. DOI: 10.1371/journal.pone.0053895.

[12] Patel MR, Emerman M, Malik HS. Paleovirology - ghosts and gifts of viruses past. *Curr Opin Virol.* 2011;1:304-9. DOI:10.1016/j.coviro.2011.06.007.

[13] Dupressoir A, Heidmann T. [Syncytins – retroviral envelope genes captured for the benefit of placental development]. *Med Sci (Paris).* 2011;27:163-9. DOI:10.1051/medsci/2011272163.

[14] Buscher K, Trefzer U, Hofmann M, Sterry W, Kurth R, Denner J. Expression of human endogenous retrovirus K in melanomas and melanoma cell lines. *Cancer Res.* 2005;65:4172-80. DOI: 10.1158/0008-5472.CAN-04-2983

[15] Herbst H, Kuhler-Obbarius C, Lauke H, Sauter M, Mueller-Lantzsch N, Harms D, et al. Human endogenous retrovirus (HERV)-K transcripts in gonadoblastomas and go-
nadoblastoma-derived germ cell tumours. *Virchows Arch.* 1999;434:11-5. DOI:10.1007/s004280050298

[16] Lower R, Lower J, Frank H, Harzmann R, Kurth R. Human teratocarcinomas cultured in vitro produce unique retrovirus-like viruses. *J Gen Virol.* 1984;65 (Pt 5): 887-98.

[17] Wang-Johanning F, Liu J, Rycak K, Huang M, Tsai K, Rosen DG, et al. Expression of multiple human endogenous retrovirus surface envelope proteins in ovarian cancer. *Int J Cancer.* 2007;120:81-90. DOI:10.1002/ijc.22256.

[18] Florl AR, Lower R, Schmitz-Drager BJ, Schulz WA. DNA methylation and expression of LINE-1 and HERV-K provirus sequences in urothelial and renal cell carcinomas. *Br J Cancer.* 1999;80:1312-21. DOI: 10.1038/sj.bjc.6690524.

[19] Menendez L, Benigno BB, McDonald JF. L1 and HERV-W retrotransposons are hypomethylated in human ovarian carcinomas. *Mol Cancer.* 2004;3:12. DOI: 10.1186/1476-4598-3-12.

[20] Wentzensen N, Coy JF, Knaebel HP, Linnebacher M, Wilz B, Gebert J, et al. Expression of an endogenous retroviral sequence from the HERV-H group in gastrointestinal cancers. *Int J Cancer.* 2007;121:1417-23. DOI:10.1002/ijc.22826.

[21] Antony JM, Ellestad KK, Hammond R, Imaizumi K, Mallet F, Warren KG, et al. The human endogenous retrovirus envelope glycoprotein, syncytin-1, regulates neuroinflammation and its receptor expression in multiple sclerosis: a role for endoplasmic reticulum chaperones in astrocytes. *J Immunol.* 2007;179:1210-24. DOI: 10.4049/jimmunol.179.2.1210

[22] Antony JM, van Marle G, Opii W, Butterfield DA, Mallet F, Yong VW, et al. Human endogenous retrovirus glycoprotein-mediated induction of redox reactants causes oligodendrocyte death and demyelination. *Nat Neurosci.* 2004;7:1088-95. DOI:10.1038/nn1319.

[23] Antony JM, Zhu Y, Izad M, Warren KG, Vodjgani M, Mallet F, et al. Comparative expression of human endogenous retrovirus-W genes in multiple sclerosis. *AIDS Res Hum Retroviruses.* 2007;23:1251-6. DOI:10.1089/aid.2006.0274..

[24] Arru G, Mameli G, Astone V, Serra C, Huang YM, Link H, et al. Multiple Sclerosis and HERV-W/MSRV: A Multicentric Study. *Int J Biomed Sci.* 2007;3:292-7.

[25] Brudek T, Christensen T, Aagaard L, Petersen T, Hansen HJ, Moller-Larsen A. B cells and monocytes from patients with active multiple sclerosis exhibit increased surface expression of both HERV-H Env and HERV-W Env, accompanied by increased seroreactivity. *Retrovirology.* 2009;6:104. DOI:10.1186/1742-4690-6-104.

[26] Dolei A. MSRV/HERV-W/syncytin and its linkage to multiple sclerosis: the usability and the hazard of a human endogenous retrovirus. *J Neurovirol.* 2005;11:232-5. DOI: 10.1080/13550280590952899.
[27] Dolei A, Perron H. The multiple sclerosis-associated retrovirus and its HERV-W endogenous family: a biological interface between virology, genetics, and immunology in human physiology and disease. *J Neurovirol*. 2009;15:4-13. DOI: 10.1080/13550280802448451.

[28] Dolei A, Serra C, Mameli G, Pugliatti M, Sechi G, Cirotto MC, et al. Multiple sclerosis-associated retrovirus (MSRV) in Sardinian MS patients. *Neurology*. 2002;58:471-3. DOI:10.1212/WNL.58.3.471.

[29] Hansen B, Oturai AB, Harbo HF, Celsiu EG, Nissen KK, Laska MJ, et al. Genetic association of multiple sclerosis with the marker rs391745 near the endogenous retroviral locus HERV-Fc1: analysis of disease subtypes. *PLoS One*. 2011;6:e26438. DOI:10.1371/journal.pone.0026438.

[30] Laska MJ, Brudek T, Nissen KK, Christensen T, Moller-Larsen A, Petersen T, et al. Expression of HERV-Fc1, a human endogenous retrovirus, is increased in patients with active multiple sclerosis. *J Virol*. 2012;86:3713-22. DOI:10.1128/JVI.06723-11.

[31] Mameli G, Astone V, Arru G, Marconi S, Lovato L, Serra C, et al. Brains and peripheral blood mononuclear cells of multiple sclerosis (MS) patients hyperexpress MS-associated retrovirus/HERV-W endogenous retrovirus, but not Human herpesvirus 6. *J Gen Virol*. 2007;88:264-74. DOI: 10.1099/vir.0.81890-0

[32] Mameli G, Astone V, Khalili K, Serra C, Sawaya BE, Dolei A. Regulation of the syncytin-1 promoter in human astrocytes by multiple sclerosis-related cytokines. *Virology*. 2007;362:120-30. DOI:10.1016/j.virol.2006.12.019.

[33] Rolland A, Jouvin-Marche E, Saresella M, Ferrante P, Cavaretta R, Creange A, et al. Correlation between disease severity and in vitro cytokine production mediated by MSRV (multiple sclerosis associated retroviral element) envelope protein in patients with multiple sclerosis. *J Neuroimmunol*. 2005;160:195-203. DOI:10.1016/j.jneuroim.2004.10.019.

[34] Ruprecht K, Obojes K, Wengel V, Gronen F, Kim KS, Perron H, et al. Regulation of human endogenous retrovirus W protein expression by herpes simplex virus type 1: implications for multiple sclerosis. *J Neurovirol*. 2006;12:65-71. DOI: 10.1080/13550280600614973.

[35] Schmitt K, Richter C, Backes C, Meese E, Ruprecht K, Mayer J. Comprehensive analysis of human endogenous retrovirus group HERV-W locus transcription in multiple sclerosis brain lesions by high-throughput amplicon sequencing. *J Virol*. 2013;87:13837-52. DOI:10.1128/JVI.02388-13..

[36] Sotgiu S, Arru G, Mameli G, Serra C, Pugliatti M, Rosati G, et al. Multiple sclerosis-associated retrovirus in early multiple sclerosis: a six-year follow-up of a Sardinian cohort. *Mult Scler*. 2006;12:698-703. DOI:10.1177/1352458506070773
[37] Tai AK, O'Reilly EJ, Alroy KA, Simon KC, Munger KL, Huber BT, et al. Human endogenous retrovirus-K18 Env as a risk factor in multiple sclerosis. *Mult Scler*. 2008;14:1175-80. DOI:10.1177/1352458508094641.

[38] Sicat J, Sutkowski N, Huber BT. Expression of human endogenous retrovirus HERV-K18 superantigen is elevated in juvenile rheumatoid arthritis. *J Rheumatol*. 2005;32:1821-31.

[39] Moles JP, Tesniere A, Guilhou JJ. A new endogenous retroviral sequence is expressed in skin of patients with psoriasis. *Br J Dermatol*. 2005;153:83-9. DOI:10.1111/j.1365-2133.2005.06555.x.

[40] Wu Z, Mei X, Zhao D, Sun Y, Song J, Pan W, et al. DNA methylation modulates HERV-E expression in CD4+ T cells from systemic lupus erythematosus patients. *J Dermatol Sci*. 2015;77:110-6. DOI:10.1016/j.jdermsci.2014.12.004.

[41] Perron H, Mekaoui L, Bernard C, Veas F, Stefas I, Leboyer M. Endogenous retrovirus type W GAG and envelope protein antigenemia in serum of schizophrenic patients. *Biol Psychiatry*. 2008;64:1019-23. DOI:10.1016/j.biopsych.2008.06.028.

[42] Yao Y, Schroder J, Nellaker C, Bottmer C, Bachmann S, Yolken RH, et al. Elevated levels of human endogenous retrovirus-W transcripts in blood cells from patients with first episode schizophrenia. *Genes Brain Behav*. 2008;7:103-12. DOI:10.1111/j.1601-183X.2007.00334.x.

[43] Lee YN, Bieniasz PD. Reconstitution of an infectious human endogenous retrovirus. *PLoS Pathog*. 2007;3:e10. DOI: 10.1371/journal.ppat.0030010.

[44] Young GR, Eksmond U, Salcedo R, Alexopoulou L, Stoye JP, Kassiotis G. Resurrection of endogenous retroviruses in antibody-deficient mice. *Nature*. 2012;491:774-8. DOI:10.1038/nature11599.

[45] Alvarez-Lafuente R, Garcia-Montojo M, De Las Heras V, Dominguez-Mozo MI, Bartolome M, Benito-Martin MS, et al. Herpesviruses and human endogenous retroviral sequences in the cerebrospinal fluid of multiple sclerosis patients. *Mult Scler*. 2008;14:595-601. DOI:10.1177/1352458507086425.

[46] Mameli G, Madeddu G, Mei A, Uleri E, Poddighe L, Delogu LG, et al. Activation of MSRV-type endogenous retroviruses during infectious mononucleosis and Epstein-Barr virus latency: the missing link with multiple sclerosis? *PLoS One*. 2013;8:e78474. DOI: 10.1371/journal.pone.0078474..

[47] Mameli G, Poddighe L, Mei A, Uleri E, Sotgiu S, Serra C, et al. Expression and activation by Epstein Barr virus of human endogenous retroviruses-W in blood cells and astrocytes: inference for multiple sclerosis. *PLoS One*. 2012;7:e44991. DOI:10.1371/journal.pone.0044991.
[48] Manghera M, Douville RN. Endogenous retrovirus-K promoter: a landing strip for inflammatory transcription factors. Retrovirology. 2013;10:16. DOI: 10.1186/1742-4690-10-16.

[49] Matouskova M, Blazkova J, Pajer P, Pavlicek A, Hejnar J. CpG methylation suppresses transcriptional activity of human syncytin-1 in non-placental tissues. Exp Cell Res. 2006;312:1011-20. DOI:10.1016/j.yexcr.2005.12.010.

[50] Reiss D, Zhang Y, Mager DL. Widely variable endogenous retroviral methylation levels in human placenta. Nucleic Acids Res. 2007;35:4743-54. DOI: 10.1093/nar/gkm455.

[51] Hawkes CH, Giovannoni G, Keir G, Cunnington M, Thompson EJ. Seroprevalence of herpes simplex virus type 2 in multiple sclerosis. Acta Neurol Scand. 2006;114:363-7. DOI:10.1111/j.1600-0404.2006.00677.x.

[52] Frank O, Jones-Brando L, Leib-Mosch C, Yolken R, Seifarth W. Altered transcriptional activity of human endogenous retroviruses in neuroepithelial cells after infection with Toxoplasma gondii. J Infect Dis. 2006;194:1447-9. DOI:10.1086/508496.

[53] Li F, Nellaker C, Sabunciyan S, Yolken RH, Jones-Brando L, Johansson AS, et al. Transcriptional derepression of the ERVWE1 locus following influenza A virus infection. J Virol. 2014;88:4328-37. DOI:10.1128/JVI.03628-13.

[54] Kwun HJ, Han HJ, Lee WJ, Kim HS, Jang KL. Transactivation of the human endogenous retrovirus K long terminal repeat by herpes simplex virus type 1 immediate early protein 0. Virus Res. 2002;86:93-100.

[55] Lee WJ, Kwun HJ, Kim HS, Jang KL. Activation of the human endogenous retrovirus W long terminal repeat by herpes simplex virus type 1 immediate early protein 1. Mol Cells. 2003;15:75-80.

[56] Misra A, Chosdol K, Sarkar C, Mahapatra AK, Sinha S. Alteration of a sequence with homology to human endogenous retrovirus (HERV-K) in primary human glioma: implications for viral repeat mediated rearrangement. Mutat Res. 2001;484:53-9. DOI: 10.1016/S0027-5107(01)00240-8.

[57] Kremer D, Schichel T, Forster M, Tzekova N, Bernard C, van der Valk P, et al. Human endogenous retrovirus type W envelope protein inhibits oligodendroglial precursor cell differentiation. Ann Neurol. 2013;74:721-32. DOI: 10.1002/ana.23970.

[58] Rolland A, Jouvin-Marche E, Viret C, Faure M, Perron H, Marche PN. The envelope protein of a human endogenous retrovirus-W family activates innate immunity through CD14/TLR4 and promotes Th1-like responses. J Immunol. 2006;176:7636-44. DOI: 10.4049/jimmunol.176.12.7636.

[59] Duperray A, Barbe D, Ragueneau G, Weksler BB, Romero IA, Couraud PO, et al. Inflammatory response of endothelial cells to a human endogenous retrovirus associat-
ed with multiple sclerosis is mediated by TLR4. *Int Immunol.* 2015;27. DOI:10.1093/intimm/dxv025.

[60] Hurst T, Magiorkinis G. Activation of the innate immune response by endogenous retroviruses. *J Gen Virol.* 2014. DOI:10.1099/jgv.0.000017.

[61] Herman A, Kappler JW, Marrack P, Pullen AM. Superantigens: mechanism of T-cell stimulation and role in immune responses. *Annu Rev Immunol.* 1991;9:745-72. DOI: 10.1146/annurev.iy.09.040191.003525.

[62] Zhang J, Vandevyver C, Stinissen P, Mertens N, van den Berg-Loonen E, Raus J. Activation and clonal expansion of human myelin basic protein-reactive T cells by bacterial superantigens. *J Autoimmun.* 1995;8:615-32. DOI:10.1016/0896-8411(95)90012-8.

[63] Mangeney M, Renard M, Schlecht-Louf G, Bouallaga I, Heidmann O, Letzelter C, et al. Placental syncytins: Genetic disjunction between the fusogenic and immunosuppressive activity of retroviral envelope proteins. *Proc Natl Acad Sci U S A.* 2007;104:20534-9. DOI:10.1073/pnas.0707873105.

[64] Morozov VA, Dao Thi VL, Denner J. The transmembrane protein of the human endogenous retrovirus--K (HERV-K) modulates cytokine release and gene expression. *PLoS One.* 2013;8:e70399. DOI:10.1371/journal.pone.0070399.

[65] Grasset EK, Cerutti A. Immunology. Retroviral help for B cells. *Science.* 2014;346:1454-5. DOI:10.1371/journal.pone.0070399.

[66] Zeng M, Hu Z, Shi X, Li X, Zhan X, Li XD, et al. MAVS, cGAS, and endogenous retroviruses in T-independent B cell responses. *Science.* 2013;346:1486-92. DOI: 10.1126/science.346.6216.1486.

[67] Nexo BA, Villesen P, Nissen KK, Lindegaard HM, Rossing P, Petersen T, et al. Are human endogenous retroviruses triggers of autoimmune diseases? Unveiling associations of three diseases and viral loci. *Immunol Res.* 2015. DOI:10.1007/s12026-015-8671-z.

[68] Marguerat S, Wang WY, Todd JA, Conrad B. Association of human endogenous retrovirus K-18 polymorphisms with type 1 diabetes. *Diabetes.* 2004;53:852-4. DOI: 10.2337/diabetes.53.3.852

[69] Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. *N Engl J Med.* 2000;343:938-52.

[70] Oksenberg JR, Baranzini SE. Multiple sclerosis genetics--is the glass half full, or half empty? *Nat Rev Neurol.* 2010;6:429-37. DOI:10.1038/nrneurol.2010.91.

[71] Browne P, Chandraratna D, Angood C, Tremlett H, Baker C, Taylor BV, et al. Atlas of Multiple Sclerosis 2013: A growing global problem with widespread inequity. *Neurology.* 2013;83:1022-4. DOI:10.1212/WNL.000000000000768.
[72] IMSGC, Hafler DA, Compston A, Sawcer S, Lander ES, Daly MJ, et al. Risk alleles for multiple sclerosis identified by a genomewide study. *N Engl J Med.* 2007;357:851-62.

[73] IMSGC, Sawcer S, Hellenthal G, Pirinen M, Spencer CC, Patsopoulos NA, et al. Genetic risk and a primary role for cell-mediated immune mechanisms in multiple sclerosis. *Nature.* 2011;476:214-9. DOI:10.1038/nature10251.

[74] Gourraud PA, Harbo HF, Hauser SL, Baranzini SE. The genetics of multiple sclerosis: an up-to-date review. *Immunol Rev.* 2012;248:87-103. DOI: 10.1111/j.1600-065X.2012.01134.x.

[75] IMSGC, Beecham AH, Patsopoulos NA, Xifara DK, Davis MF, Kemppinen A, et al. Analysis of immune-related loci identifies 48 new susceptibility variants for multiple sclerosis. *Nat Genet.* 2013;45:1353-60. DOI:10.1038/ng.2770.

[76] Perron H, Geny C, Laurent A, Mouriquand C, Pellat J, Perret J, et al. Leptomeningeal cell line from multiple sclerosis with reverse transcriptase activity and viral particles. *Res Virol.* 1989;140:551-61.

[77] Perron H, Garson JA, Bedin F, Beseme F, Paranhos-Baccala G, Komurian-Pradel F, et al. Molecular identification of a novel retrovirus repeatedly isolated from patients with multiple sclerosis. The Collaborative Research Group on Multiple Sclerosis. *Proc Natl Acad Sci U S A.* 1997;94:7583-8.

[78] Pavlicek A, Paces J, Elleder D, Hejnar J. Processed pseudogenes of human endogenous retroviruses generated by LINEs: their integration, stability, and distribution. *Genome Res.* 2002;12:391-9. DOI:10.1101/gr.216902.

[79] Mameli G, Poddighe L, Astone V, Delogu G, Arru G, Sotgiu S, et al. Novel reliable real-time PCR for differential detection of MSRV env and syncytin-1 in RNA and DNA from patients with multiple sclerosis. *J Virol Methods.* 2009;161:98-106. DOI: 10.1016/j.jviromet.2009.05.024.

[80] Roebke C, Wahl S, Laufer G, Stadelmann C, Sauter M, Mueller-Lantzsch N, et al. An N-terminally truncated envelope protein encoded by a human endogenous retrovirus W locus on chromosome Xq22.3. *Retrovirology.* 2010;7:69. DOI: 10.1186/1742-4690-7-69.

[81] Laufer G, Mayer J, Mueller BF, Mueller-Lantzsch N, Ruprecht K. Analysis of transcribed human endogenous retrovirus W env loci clarifies the origin of multiple sclerosis-associated retrovirus env sequences. *Retrovirology.* 2009;6:37. DOI: 10.1186/1742-4690-6-37.

[82] Garcia-Montojo M, de la Hera B, Varade J, de la Encarnacion A, Camacho I, Domínguez-Mozo M, et al. HERV-W polymorphism in chromosome X is associated with multiple sclerosis risk and with differential expression of MSRV. *Retrovirology.* 2014;11:2.
[83] Varadé J, García-Montojo M, de la Hera B, Camacho I, García-Martínez MA, Arroyo R, et al. Multiple sclerosis retrovirus-like envelope gene: Role of the chromosome 20 insertion. *BBA Clin.* 2015;3:162-7. DOI:10.1016/j.bbacli.2015.02.002.

[84] Garcia-Montojo M, Domínguez-Mozo M, Arias-Leal A, García-Martínez A, De las Heras V, Casanova I, et al. The DNA copy number of human endogenous retrovirus-W (MSRV-type) is increased in multiple sclerosis patients and is influenced by gender and disease severity. *PLoS One.* 2013;8:e53623. DOI:10.1371/journal.pone.0053623.

[85] Garson JA, Tuke PW, Giraud P, Paranhos-Baccala G, Perron H. Detection of virion-associated MSRV-RNA in serum of patients with multiple sclerosis. *Lancet.* 1998;351:33. DOI:10.1016/S0140-6736(98)24001-3.

[86] Perron H, Germi R, Bernard C, Garcia-Montojo M, Deluen C, Farinelli L, et al. Human endogenous retrovirus type W envelope expression in blood and brain cells provides new insights into multiple sclerosis disease. *Mult Scler.* 2012;18:1721-36. DOI: 10.1177/1352458512441381.

[87] Serra C, Mameli G, Arru G, Gotti S, Rosati G, Dolei A. In vitro modulation of the multiple sclerosis (MS)-associated retrovirus by cytokines: implications for MS pathogenesis. *J Neurovirol.* 2003;9:637-43. DOI:10.1080/13550280390246462.

[88] Mameli G, Serra C, Astone V, Castellazzi M, Poddighe L, Fainardi E, et al. Inhibition of multiple sclerosis-associated retrovirus as biomarker of interferon therapy. *J Neurovirol.* 2008;14:73-7. DOI:10.1080/13550280701801107.

[89] Arru G, Leoni S, Pugliatti M, Mei A, Serra C, Delogu LG, et al. Natalizumab inhibits the expression of human endogenous retroviruses of the W family in multiple sclerosis patients: a longitudinal cohort study. *Mult Scler.* 2014;20:174-82. DOI: 10.1177/1352458513494957.

[90] Antony JM, Deslauriers AM, Bhat RK, Ellestad KK, Power C. Human endogenous retroviruses and multiple sclerosis: innocent bystanders or disease determinants? *Biophys Acta.* 2011;1812:162-76. DOI: 10.1016/j.bbadis.2010.07.016.

[91] Perron H, Jouvin-Marche E, Michel M, Ounanian-Paraz A, Camelo S, Dumon A, et al. Multiple sclerosis retrovirus particles and recombinant envelope trigger an abnormal immune response in vitro, by inducing polyclonal Vbeta16 T-lymphocyte activation. *Virology.* 2001;287:321-32. DOI:10.1006/viro.2001.1045.

[92] Firouzi R, Rolland A, Michel M, Jouvin-Marche E, Hauw JJ, Malcus-Vocanson C, et al. Multiple sclerosis-associated retrovirus particles cause T lymphocyte-dependent death with brain hemorrhage in humanized SCID mice model. *J Neurovirol.* 2003;9:79-93. DOI:10.1080/13550280390173328.

[93] de la Hera B, Varade J, Garcia-Montojo M, Lamas JR, de la Encarnacion A, Arroyo R, et al. Role of the human endogenous retrovirus HERV-K18 in autoimmune disease
susceptibility: study in the Spanish population and meta-analysis. *PLoS One.* 2013;8:e62090. DOI:10.1371/journal.pone.0062090.

[94] Nexo BA, Christensen T, Frederiksen J, Moller-Larsen A, Oturai AB, Villesen P, et al. The etiology of multiple sclerosis: genetic evidence for the involvement of the human endogenous retrovirus HERV-Fc1. *PLoS One.* 2011;6:e16652. DOI: 10.1371/journal.pone.0016652.

[95] de la Hera B, Varade J, Garcia-Montojo M, Alcina A, Fedetz M, Alloza I, et al. Human endogenous retrovirus HERV-Fc1 association with multiple sclerosis susceptibility: a meta-analysis. *PLoS One.* 2014;9:e90182. DOI:10.1371/journal.pone.0090182.

[96] Kraus B, Fischer K, Sliva K, Schnierle BS. Vaccination directed against the human endogenous retrovirus-K (HERV-K) gag protein slows HERV-K gag expressing cell growth in a murine model system. *Virol J.* 2014;11:58. DOI:10.1186/1743-422X-11-58.

[97] Turcanova VL, Bundgaard B, Hollsberg P. Human herpesvirus-6B induces expression of the human endogenous retrovirus K18-encoded superantigen. *J Clin Virol.* 2009;46:15-9. DOI:10.1016/j.jcv.2009.05.015.

[98] Tai AK, Luka J, Ablashi D, Huber BT. HHV-6A infection induces expression of HERV-K18-encoded superantigen. *J Clin Virol.* 2009;46:47-8. DOI:10.1016/j.jcv.2009.05.019.

[99] Hsiao FC, Lin M, Tai A, Chen G, Huber BT. Cutting edge: Epstein-Barr virus transactivates the HERV-K18 superantigen by docking to the human complement receptor 2 (CD21) on primary B cells. *J Immunol.* 2006;177:2056-60. DOI: 10.4049/jimmunol.177.4.2056

[100] Sutkowski N, Conrad B, Thorley-Lawson DA, Huber BT. Epstein-Barr virus transactivates the human endogenous retrovirus HERV-K18 that encodes a superantigen. *Immunity.* 2001;15:579-89. DOI:10.1016/S1074-7613(01)00210-2.

[101] Hsiao FC, Tai AK, Deglon A, Sutkowski N, Longnecker R, Huber BT. EBV LMP-2A employs a novel mechanism to transactivate the HERV-K18 superantigen through its ITAM. *Virology.* 2009;385:261-6. DOI:10.1016/j.virol.2008.11.025.

[102] Sutkowski N, Chen G, Calderon G, Huber BT. Epstein-Barr virus latent membrane protein LMP-2A is sufficient for transactivation of the human endogenous retrovirus HERV-K18 superantigen. *J Virol.* 2004;78:7852-60. DOI:10.1128/JVI.78.14.7852-7860.2004

[103] Buljevac D, van Doornum GJ, Flach HZ, Groen J, Osterhaus AD, Hop W, et al. Epstein-Barr virus and disease activity in multiple sclerosis. *J Neurol Neurosurg Psychiatry.* 2005;76:1377-81. DOI:10.1136/jnnp.2004.048504

[104] Christensen T. The role of EBV in MS pathogenesis. *Int MS J.* 2006;13:52-7.
[105] Nielsen TR, Pedersen M, Rostgaard K, Frisch M, Hjalgrim H. Correlations between Epstein-Barr virus antibody levels and risk factors for multiple sclerosis in healthy individuals. *Mult Scler.* 2007;13:420-3. DOI:10.1177/1352458506071470

[106] DeLorenze GN, Munger KL, Lennette ET, Orentreich N, Vogelman JH, Ascherio A. Epstein-Barr virus and multiple sclerosis: evidence of association from a prospective study with long-term follow-up. *Arch Neurol.* 2006;63:839-44. DOI:10.1001/archneur.63.6.noc50328.

[107] Hollsberg P, Kusk M, Bech E, Hansen HJ, Jakobsen J, Haahr S. Presence of Epstein-Barr virus and human herpesvirus 6B DNA in multiple sclerosis patients: associations with disease activity. *Acta Neurol Scand.* 2005;112:395-402. DOI:10.1111/j.1600-0404.2005.00516.x.

[108] Martinez A, Alvarez-Lafuente R, Mas A, Bartolome M, Garcia-Montojo M, de Las Heras V, et al. Environment-gene interaction in multiple sclerosis: human herpesvirus 6 and MHC2TA. *Hum Immunol.* 2007;68:685-9. DOI:10.1016/j.humimm.2007.05.005.

[109] Benit L, Calteau A, Heidmann T. Characterization of the low-copy HERV-Fc family: evidence for recent integrations in primates of elements with coding envelope genes. *Virology.* 2003;312:159-68. DOI:10.1016/S0042-6822(03)00163-6.

[110] Strissel PL, Ruebner M, Thiel F, Wachter D, Ekici AB, Wolf F, et al. Reactivation of codogenic endogenous retroviral (ERV) envelope genes in human endometrial carcinoma and prestages: Emergence of new molecular targets. *Oncotarget.* 2012;3:1204-19.

[111] Rhyu DW, Kang YJ, Ock MS, Eo JW, Choi YH, Kim WJ, et al. Expression of human endogenous retrovirus env genes in the blood of breast cancer patients. *Int J Mol Sci.* 2014;15:9173-83. DOI: 10.3390/ijms15069173.

[112] Kremer D, Forster M, Schichel T, Gottle P, Hartung HP, Perron H, et al. The neutralizing antibody GNbAC1 abrogates HERV-W envelope protein-mediated oligodendroglial maturation blockade. *Mult Scler.* 2014;21:1200-3. DOI: 10.1177/1352458514560926.

[113] Curtin F, Perron H, Kromminga A, Porchet H, Lang AB. Preclinical and early clinical development of GNbAC1, a humanized IgG4 monoclonal antibody targeting endogenous retroviral MSRV-Env protein. *MAbs.* 2015;7:265-75. DOI: 10.4161/19420862.2014.985021.

[114] Derfuss T, Curtin F, Guebelin C, Bridel C, Rasenack M, Matthey A, et al. A phase IIa randomised clinical study of GNbAC1, a humanised monoclonal antibody against the envelope protein of multiple sclerosis-associated endogenous retrovirus in multiple sclerosis patients. *Mult Scler.* 2014;21:885-93. DOI: 10.1177/1352458514554052.

[115] Curtin F, Lang AB, Perron H, Laumonier M, Vidal V, Porchet HC, et al. GNbAC1, a humanized monoclonal antibody against the envelope protein of multiple sclerosis-
associated endogenous retrovirus: a first-in-humans randomized clinical study. Clin Ther. 2012;34:2268-78. DOI:10.1016/j.clinthera.2012.11.006.

[116] Downey RF, Sullivan FJ, Wang-Johanning F, Ambs S, Giles FJ, Glynn SA. Human endogenous retrovirus K and cancer: Innocent bystander or tumorigenic accomplice? Int J Cancer. 2014;137:1249-57. DOI: 10.1002/ijc.29003.

[117] van der Kuyl AC. HIV infection and HERV expression: a review. Retrovirology. 2012;9:6. DOI:10.1186/1742-4690-9-6.

[118] Bhardwaj N, Maldarelli F, Mellors J, Coffin JM. HIV-1 infection leads to increased transcription of human endogenous retrovirus HERV-K (HML-2) proviruses in vivo but not to increased virion production. J Virol. 2014;88:11108-20. DOI:10.1128/JVI.01623-14.

[119] Michaud HA, SenGupta D, de Mulder M, Deeks SG, Martin JN, Kobie JJ, et al. Cutting edge: An antibody recognizing ancestral endogenous virus glycoproteins mediates antibody-dependent cellular cytotoxicity on HIV-1-infected cells. J Immunol. 2014;193:1544-8. DOI:10.4049/jimmunol.1302108.