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Review article

Endogenous retroviruses in multiple sclerosis: A network-based etiopathogenic model

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ABSTRACT

The present perspective article proposes an etiopathological model for multiple sclerosis pathogenesis and progression associated with the activation of human endogenous retroviruses. We reviewed preclinical, clinical, epidemiological, and evolutionary evidence indicating how the complex, multi-level interplay of genetic traits and environmental factors contributes to multiple sclerosis. We propose that endogenous retroviruses trans-activation acts as a critical node in disease development. We also discuss the rationale for combined anti-retroviral therapy in multiple sclerosis as a disease-modifying therapeutic strategy. Finally, we propose that the immuno-pathogenic process triggered by endogenous retrovirus activation can be extended to aging and aging-related neurodegeneration. In this regard, endogenous retroviruses can be envisioned to act as epigenetic noise, favoring the proliferation of disorganized cellular subpopulations and accelerating system-specific "aging". Since inflammation and aging are two sides of the same coin (plastic dis-adaptation to external stimuli with system-specific degree of freedom), the two conditions may be epiphenomenal products of increased epigenomic entropy. Inflammation accelerates organ-specific aging, disrupting communication throughout critical systems of the body and producing symptoms. Overlapping neurological symptoms and syndromes may emerge from the activity of shared molecular networks that respond to endogenous retroviruses' reactivation.

1. Pressing issues and controversies in multiple sclerosis

Multiple sclerosis (MS) is commonly defined as an autoimmune disease characterized by progressive demyelination and neuro-degeneration of the central nervous system (CNS) (Filippi et al., 2018). The complex nature of this pathological condition poses significant challenges to patients and clinicians. Several genetic and environmental risk factors have been indicated to influence disease progression (Dobson and Giovannoni, 2019). Autoimmunity and inflammation are central in the pathogenetic process, leading to the characteristic white and grey matter alterations of the brain and the spinal cord (McFarland and Martin, 2007). Autoimmunity and inflammation are also the primary targets of pharmacological interventions (McGinley et al., 2021; Robertson and Moreo, 2016). While disease-modifying therapies are available and novel remyelinating agents are on the way, the primary cause of the autoimmune process at the root of the disease is still largely unknown (Cunniffe and Coles, 2021).

In the last three decades, the Epstein-Barr virus (EBV) – a member of the *Herpesviridae* family – has emerged as a critical risk factor for MS (Bjornevik et al., 2022; Soldan and Lieberman, 2022). Several population studies confirmed its association with MS, but EBV is neither sufficient nor necessary for MS development. Although rarely, not all people with MS (pwMS) have a confirmed history of past EBV infection; moreover, not all individuals exposed to EBV develop MS (Maeda et al., 2009; Pakpoor et al., 2013). Besides, EBV seropositivity is highly diffuse in the general population (Dowd et al., 2013; Smatti et al., 2017) and other human herpesviruses (HHVs) have been linked to MS development (Grut et al., 2024; Rice et al., 2021; Thakolwiboon et al., 2020). Thus, it is likely that the individual genetic background —influenced by a plethora of environmental factors — shapes MS risk in a complex, intertwined process. In this perspective paper, we propose a model centered on (but not limited to) the action of specific exogenous and

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endogenous infective agents hypothesized to modulate the disease and promote its onset and progression.

2. Genetic background

The genetics of MS is still an uncharted territory. However, the last few years have provided valuable insights into the genetic factors contributing to MS development (Belbasis et al., 2020). Linkage studies identified associations between variations in the human leukocyte antigen (HLA) genes – crucial for immune response regulation – and increased risk of developing MS as well as response to interferon therapy (Bortolotti et al., 2022; Byun et al., 2008; Cénit et al., 2009; Fransen et al., 2020; Jacobs et al., 2020; Okolicsanyi et al., 2020). In addition, more than 200 non-HLA single nucleotide polymorphisms (SNPs) have been associated with variable MS susceptibility and severity. Of note, the functional role of these variants is largely unexplored since they were primarily found in intronic or intragenic regions (Gresle et al., 2020).

The polygenic nature of MS is further emphasized by the diverging prevalence of MS among different ethnic groups. Ancestrally diverse populations display markedly different susceptibilities to MS. However, the classical notion of a major predominance of MS among Caucasians and of a relatively low incidence in Afro-descendent groups is debated (Langer-Gould et al., 2013; Walton et al., 2020), with high heterogeneity resulting from geographical and socio-economic biases, including access to diagnostic procedures. Several studies examined the prevalence of MS in immigrant populations, emphasizing the role played by environmental factors, particularly when immigration occurs early in life (Gale and Martyn, 1995; Munk Nielsen et al., 2019; Pugliatti and Ferri, 2020).

Part of the global difference in MS prevalence seems to derive from European genetic ancestry (Beecham et al., 2022; Chi et al., 2019; Goodin et al., 2021). Recent investigations using ancient DNA revealed that the genetic risk for MS associated with the HLA haplotype arose among pastoral populations from the Pontic steppe and was brought into Europe through migration dated to approximately 5000 years ago. MS-associated immunogenetic variants underwent positive evolutionary selection within the steppe population and later in Europe (Barrie et al., 2024). Specifically, the selected alleles had protective associations with several HHVs and other infectious agents (Barrie et al., 2024). According to the authors, these genetic variants probably derived from a positive selection coinciding with the emergence of a pastoralist lifestyle in the Pontic-Caspian steppe. Coevolution of steppe populations and microbial zoonoses from cattle and other farming animals (i.e., *Brucella* and *Mycobacterium* spp.) may have resulted in the emergence of MS as a "byproduct" of this newly selected immune adaptation. The hypothesis is fascinating, but its investigation remains challenging (Cossu et al., 2017; Eisele, 1950; Ekundayo et al., 2022).

Other critical SNPs link immune responses in MS and infectious agents. Tripartite Motif (TRIM) is a superfamily of ubiquitin ligases that control molecular pathways involved in antiviral defense, including viral particle entry, uncoating, replication, and release (Giraldo et al., 2020). These retroviral restriction factors co-evolved with exogenous and endogenous infective agents associated with MS development (see also Section 3.2).

MS cases have also been reported in individuals of non-European ancestry, including Indigenous Americans (Mirsattari et al., 2001; Robers et al., 2023). These individuals showed an aggressive phenotype, suggesting a genetic predisposition to severe disease. It may also be speculated that in separate human populations, MS phenotypes with different clinical severity emerged independently from shared immune-related mechanisms.

Additional genetic factors beyond the HLA genes and the identified SNPs emphasize the intricate polygenicity of MS (Goris et al., 2022). In this context, specific melanin genotypes could explain the interaction between viral infections and sun exposure during childhood in shaping the risk of developing MS (Krone et al., 2009; Mykicki et al., 2016; Ostkamp et al., 2021; van der Mei, 2003). Skin melanin and nerve cells are profoundly intertwined, considering the shared origin of nerve cells and melanocytes from the neural crest (Behan and Chaudhuri, 2010) and their relation with several neurological conditions like oculocutaneous albinism type 1, type 1 neurofibromatosis, Gaucher's syndrome, Aicardi-Goutieres syndrome type 6, and Parkinson's disease (Kono et al., 2016; Kulcsarova et al., 2022). The role of melanin as an oxidative stress scavenger (through its interaction with transition metals) and in catecholamine synthesis is well established and has been implicated in MS pathology (Claudia et al., 2015; Krone and Grange, 2011; Marsden, 1961, 1965; Offen et al., 2004). While the mechanism through which melanin pathways and the immune response interact in MS pathology remains unknown, dysfunction of oxidative stress scavenging seems a central hub (Zucca et al., 2023).

In susceptible individuals, exogenous infections might disrupt the molecular organization of specific tissues, resulting in dysregulated immune-microbial interactions leading to inflammation, with neural crest-derived tissues particularly vulnerable in the context of MS (Fedorow et al., 2005).

3. Could HERVs play a role in multiple sclerosis?

3.1. Endogenous retroviruses: a brief introduction

Retroviruses are a family of RNA-based viruses. After infection of permissive cells, their replication cycle includes a reverse transcription of their single-stranded RNA (ssRNA) genome into a double-stranded DNA (dsDNA) copy, which then integrates into the chromosomal DNA of the host cell, forming a provirus. The provirus can replicate with the host cell genome, express viral genes, and produce newly synthesized viral genomic RNA molecules (Johnson, 2019).

Throughout evolution, exogenous retroviruses pervasively infected all vertebrate lineages, including humans, integrating into the host's germline as endogenous retroviruses (ERVs). Thus, ERVS are signatures of ancient retroviral infections inherited in Mendelian fashion (Dopkins and Nixon, 2023). ERV genomes evolve across generations within the host lineage, in most cases losing their coding potential through epigenetic silencing and/or accumulation of disruptive mutations (Domingo and Perales, 2019; Nowak, 1992; Ojosnegros et al., 2011). Independently from cell division, ERVs can duplicate as transposable elements (TEs), a class of mobile genetic sequences capable of changing position within the genome, or as viruses, moving within the genome or across cells after endogenous reinfections (Magiorkinis et al., 2012). TEs are abundant and, in mammals, comprise almost 50 % of the entire genome (Lawson et al., 2023). The distinct retroviral signature of the essential structural genes *gag*, *pol*, *pro*, and *env* flanked by long terminal repeat (LTR) sequences indicates that ~ 8 % of the human genome consists of genomic material of exogenous retroviral origin, which forms a specific subset of class I retrotransposons, the LTR retrotransposons (Griffiths, 2001, Dopkins and Nixon, 2023).

ERVs are thought to have been repurposed as a defense mechanism against exogenous viral infections, particularly in the early phases of embryonic development before the maturation of a functional immune system (Grow et al., 2015). Mechanistically, endogenous env expression counteracts exogenous virion entry through a competitive process termed receptor interference (Jangam et al., 2017; Malfavon-Borja and Feschotte, 2015). ERVs also played a major role in the development of placental mammals, including humans. Two of the few functional human ERV (HERV) sequences encode syncytins, proteins that contribute to the formation of the syncytiotrophoblast, a critical tissue during embryo-fetal development, as it secretes pregnancy hormones, facilitates fetal-maternal exchanges, impedes infiltration of the placenta by maternal immune cells, and contributes to immune tolerance and cell-fate determination (Griffiths, 2001, Dopkins and Nixon, 2023). Thus, despite being considered "junk DNA" for a long time, HERVs have now been implicated in critical physiological functions (Dopkins and

Nixon, 2023; Dupressoir et al., 2009; Mi et al., 2000). Various HERV families have been identified based on the specific tRNA amino acid primer needed for retrotranscription (for example, HERV-W is named because it is associated with tryptophan-primed tRNA).

3.2. MS and HERVs: it's going viral

Along with their implications in physiological settings, emerging evidence indicates that HERVs participate in the pathogenesis of several diseases, including cancer (Chen et al., 2019), autoimmunity (de la Hera et al., 2013; Grandi and Tramontano, 2018; Konsta et al., 2014) and various neuropathological conditions (Küry et al., 2018). An interplay between HERVs activation and neuroinflammation has been described (Johnston et al., 2001) in amyotrophic lateral sclerosis (Arru et al., 2018; Li et al., 2015), chronic inflammatory demyelinating polyradiculoneuropathy (Faucard et al., 2016), and schizophrenia (Perron et al., 2012b; Tamouza et al., 2021). These findings provide a rationale for the potential role of HERVs in MS, a neuroinflammatory condition *par excellence*.

Early studies identified an MS-associated retrovirus (MSRV), suggesting an association between MS and retroviruses (Perron et al., 1989). Other independent studies showed elevated levels of HERV-W expression in pwMS (Dolei et al., 2002; Morandi et al., 2017). Further studies correlated MSRV to the HERV-W family, being MSRV a complete virus able to form infectious virions (Dolei, 2005) and HERV-W its endogenous retroviral counterpart. Additional support to the HERV–MS connection is offered by the strong concordance between active MS and the presence of MSRV in liquor and plasma samples (Dolei et al., 2002; Perron et al., 2012a). Since HERVs are physiologically expressed in several tissues, including the brain, a key issue is how to differentiate the role of HERVs in physiological versus MS-related processes. MSRV clones from pwMS are genetically closer to the MSRV reference sequence than HERV-Ws from healthy controls (Perron et al., 2005). This suggests that individual-specific evolution differentiates the HERV subpopulations of pwMS from those of healthy subjects (Magiorkinis et al., 2013).

A recent systematic review and meta-analysis (Morandi et al., 2017) revealed a strong association between MSRV/HERV-W pol and MSRV/HERV-W env RNA in biological tissues obtained from pwMS, including the brain. Specific HERV-W gag protein patterns were also detected in MS lesions (Perron et al., 2005). The significantly higher level of HERV-W RNA expression found in a cohort of pwMS from the Russian Volga region compared to one from the UK supported the hypothesis that HERVs could contribute to MS in individuals descending from Eastern European steppe populations (Tarlinton et al., 2020). Other HERVs implicated in MS include HERV-K and HERV-H (Brütting et al., 2016; Christensen et al., 2007).

Additional evidence for an active role of HERVs in the pathogenesis of MS can be found in the genetic risk factors of the disease. The previously cited TRIM family of proteins co-evolved with ERVs (Gifford, 2012; Stoye, 2012), and some SNPs, like TRIM5 and TRIM22, are associated with MS development (Morris et al., 2019; Nexø et al., 2011; Nexø et al., 2013).

The HERV hypothesis is also consistent with the lack of reliable preclinical models of MS. Rodent MS models, like experimental autoimmune encephalopathy (EAE), have been developed to mimic the human disease. However, EAE is not a primary demyelinating disease and markedly differs from MS in pathology, immunology, and clinical course (Behan and Chaudhuri, 2014). Despite its extensive use in preclinical settings, EAE largely fails to recapitulate the clinical features of MS also with respect to response to therapy (Behan and Chaudhuri, 2014). The focus on myelin antigenicity and demyelination in EAE studies overshadows the role of chronic neurodegeneration, a process encompassing all stages of MS (Giovannoni et al., 2022). Such discrepancy suggests additional pathogenic actors, like HERVs, that, at a patient-specific level, could contribute to the neurodegenerative drive of MS.

4. Exogenous infective agents and HERVs activation

The hypothesis that exogenous infections are involved in the etiology of MS is supported by a correlation of MS with prior exposure to members of the *Herpesviridae* family (Haahr et al., 1992; Khalesi et al., 2023). Notably, different HHV species have been linked to distinct MS phenotypes, including herpes simplex virus type 1 (HSV1) and pediatric MS (Xu et al., 2021), varicella zoster virus (VZV), and relapsing-remitting MS (Rodríguez-Violante et al., 2009; Sotelo et al., 2014, 2008), EBV and MS in HLA-DRB1*1501 carriers (Jacobs et al., 2020), human herpesvirus 6 (HHV-6) and MS in the general population (Grut et al., 2024; Khalesi et al., 2023; Pormohammad et al., 2018).

HHV infections also corroborate the connection of MS with genetic and geographical factors. For instance, VZV exposure shows a strong correlation with MS in Asian countries (Rice et al., 2021). In a recent meta-analysis, the pooled prevalence of VZV positivity in pwMS was higher in Asia (0.84) and lower in North America and Europe (0.62 and 0.36, respectively) (Khalesi et al., 2023). These regional differences support the idea that synergisms between genetic background and environmental (i.e., infectious) factors modulate MS risk. Other HHVs – including CMV, HHV6, and EBV – exhibit similar geographical correlations, suggesting that exposure to a single HHV type may not suffice to trigger MS (Hollsberg et al., 2005; Lucas et al., 2023). Considering putative cooperation between different viruses (Díaz-Muñoz et al., 2017) and the occurrence of quasi-species within each virus type (Shirogane et al., 2019; Yousaf et al., 2023), parallelisms could be drawn between MS and subacute sclerosing panencephalitis manifesting years after latent measles infection (Shirogane et al., 2023). Additionally, modifications of the immune asset during life might modulate MS development via heterologous immunity mediated by cross-reactive T cells (Welsh et al., 2010).

Perron's group has extensively investigated the role of HERV-W in MS and proposed HERV-W trans-activation via HHVs as a central disease mechanism (Perron et al., 2009). The model proposes that neurotropic HHVs crossing the blood-brain barrier are intercepted and captured by resident perivascular macrophages. These cells would control HHVs replication and infectivity but not the HERV-Ws transactivation capacity of the exogenous infection (Perron et al., 2009). *In vitro* evidence and recent preliminary data in humans seem to corroborate a pathogenic EBV-HERV connection (Cossu et al., 2023; Mameli et al., 2012). *In vitro* experiments also showed that EBV transactivates HERV-K (Wieland et al., 2022). Retroviral elements can also modulate HHV expression via the exchange of genetic sequences [for detailed experimental evidence, see (Isfort et al., 1992; Jones et al., 1996; Kost et al., 1993; Niewiadomska and Gifford, 2013; Weiss, 2013)]. Furthermore, amplification of the genomic load of MSRV-type HERVs, probably by reverse transcription, is associated with MS severity, particularly in females (Garcia-Montojo et al., 2013; Mameli et al., 2009). Unlike other HHVs that preferentially target the white matter, cytomegalovirus (CMV, also known as HHV-5) displays a prominent tropism for the grey matter (Perron et al., 2009). A strong influence of genetic background and/or environmental co-factors, along with differences in cell/tissue tropism, may explain why past CMV infection is inversely correlated with MS in Europeans (Grut et al., 2021; Zabalza et al., 2020) but positively correlated in people from the Middle East (Karampoor et al., 2017).

Of note, positive associations with MS were also reported for chronic infection with non-viral agents, such as *Chlamydia pneumoniae* and *Mycobacterium spp.* (Bagos et al., 2006; Cusick et al., 2013; Ekundayo et al., 2022; Hollsberg et al., 2005; Lucas et al., 2023). These associations could be consistent with the hypothesis that HERV reactivation is a component of the chronic inflammatory response, which may derive from infection with HHVs and/or other microbes, based on individual susceptibility (Dopkins and Nixon, 2023). Following this, specific vaccinations might be protective against MS. Large cohort studies are

lacking on this matter, but a protective effect on dementia and neurodegeneration has been demonstrated for vaccination against HHVs (De Francesco, 2024; Schnier et al., 2022).

5. Putative pathogenetic mechanisms of HERVs

5.1. Heparan sulphate proteoglycans as a door to infection-triggered MS

Membrane heparan sulphate proteoglycans (HSPGs) mediate cell-virion adhesion and virion internalization (Koganti et al., 2021). In the adult central nervous system, HSPG is primarily localized along the vascular and glial basal membranes (BMs) surrounding the cerebral vessels and participates in local immune cell recruitment (Sobel, 1998). Glypicans (a family of HSPGs) are highly expressed in acutely and chronically active MS plaques. Conversely, chronic, inactive lesions do not display significant BM changes, suggesting that these alterations transiently characterize highly active lesions (van Horssen et al., 2006). The expression of HSPGs and other sulphated membrane proteins is a *conditio sine qua non* for HERV virion adhesion and internalization into the host cell (Robinson-McCarthy et al., 2018) and is consistent with the detection of HERV-W env in MS lesions. Several SNPs in genes involved in glypicans biosynthesis correlate with MS development and progression (Lorentzen et al., 2010). Altered composition of the BMs of MS plaques, in terms of spatial organization of collagen XVIII, agrin, and perlecan, correlate with HSPGs expression (Van Horssen et al., 2007). Glypican-5 SNPs modulate the interferon-1 beta (IFNβ) response in pwMS and are implicated in neuroinflammatory processes (Baranzini et al., 2009; Byun et al., 2008; Cénit et al., 2009). HSPGs and other extracellular matrix proteins are present in the embryonic nervous system, where they play a central role as guidance molecules for nerve cell processes. After development, HSPGs are down-regulated and can only be detected with some difficulty by immunostaining in certain parts of the brain (Coulson-Thomas, 2016; Reichardt and Tomaselli, 1991). Moreover, HSPGs have been strongly associated with the evolution of neural connectivity (Van Vactor et al., 2006), while their dysregulation has been associated with neurodegenerative diseases and cancer (Cui et al., 2013; Schwartz and Domowicz, 2018). Thus, dysfunctional coordination between HSPGs, exogenous infectious agents, HERVs, and the neuro-immune system may already be present during the embryofetal period.

5.2. HERVs: between immunity and neuroinflammation

Unlike common antigens that require processing by antigen-presenting cells, superantigens – potent immune system activators – bind directly to T cell receptors through a large variety of HLA molecules (Schlievert, 1993). The hypothesis that HERVs act like superantigens (Emmer et al., 2014) is consistent with experimental findings linking EBV infection to HERVs transactivation (Wieland et al., 2022) and with the influence of the host's genetic loci involved in the immune response (Emmer et al., 2018). The HERV-W env protein syncytin-1 is abnormally expressed upon HERV-W transactivation and stimulates, through toll-like receptor 4 (TLR4), an innate immune response (Mameli et al., 2015) (Rolland et al., 2006) that negatively affects oligodendrocyte maturation and myelinization (Madeira et al., 2016). In susceptible individuals, this immune cascade proceeds in parallel with the production of MSRV virions, contributing to the spread of HERV-W nucleic acids and peptides. The diffusion of HERV-W could also be mediated by endogenous reinfection of various cell types, like immune and glial cells, possibly followed by *de novo* integration.

HERV products also promote neural damage by inducing the production of nitric oxide (NO), a free radical implicated in the pathogenesis of MS (Smith and Lassmann, 2002). In addition, overexpression of syncytin-1 triggers endoplasmic reticulum (ER) stress, exacerbating the generation of free radical species (Antony et al., 2011, 2006, 2004; Kremer et al., 2013). The mechanism is therapeutically relevant since pharmacological inhibition of TLR4 and HERV-W rescues env-mediated myelination deficits (Göttle et al., 2021, 2019). Although a gliotoxic effect of HERV-W has been demonstrated from blood and CSF samples of pwMS (Ménard et al., 1998a, 1998b, 1997), the exact mechanisms conferring toxicity to HERV-W are not fully understood.

The pro-inflammatory effects of HERVs are also evidenced by the induction of cytokines like TNF-alpha, IFN-gamma, and IL-10, as observed in *in vitro* studies and in pwMS (Saresella et al., 2009; Wang et al., 2021).

Elevated levels of HERV-Fc1 (a subfamily of HERV located on the X chromosome) were observed in pwMS carrying SNPs that correlate with disease phenotype in Northern and Southern Europe (De la Hera et al., 2014; Hansen et al., 2011; Laska et al., 2012). Genomic analyses have shown the proximity of MS-related SNPs to HERV-K (and other HERVs). Since HERVs are TEs, it could be possible for HERV-W to disrupt the genomic equilibrium of the infected cells, inducing the activation of HERV-K and HERV-H families and expanding the range of associated clinical features.

In conclusion, MS (and possibly other neurodegenerative diseases) could be viewed as the result of the host immune system's response to external infectious agents, such as HHVs (Casanova and Abel, 2022; Samadizadeh et al., 2021). The clinical features of MS could stem from the interplay of HERVs with the immune response to infection, which takes place over several years of host-pathogen interactions (Shirogane et al., 2023; Welsh et al., 2010).

6. Clinical and real-world evidence supporting HERVs activity in multiple sclerosis

Data from real-world settings supports the role of HERVs in MS and their therapeutic exploitability.

IFNβ is the gold standard intervention to manage MS relapses. Notably, the rationale for its initial use stemmed from its antiviral effect (Jacobs and Johnson, 1994). IFNβ treatment markedly decreases anti-HERV-H and HERV-W env reactivity, an effect closely associated with therapeutic efficacy (Petersen et al., 2009). Subsequent studies suggested that HERVs (re)activation and antiviral immune responses play a role in MS development. These processes are modulated by IFNβ (Petersen et al., 2012), which also rapidly reduces MSRV viremia (Mameli et al., 2008). Clinical MS reactivation upon poor response to therapy is associated with MSRV rescue (Mameli et al., 2008). These effects are not limited to IFNβ. Compared to healthy controls, pwMS treated with other disease-modifying therapies (DMT), like fingolimod, azathioprine, or glatiramer acetate, show reduced expression of HERV-W env (Dolei, 2018). While IFNβ may directly act on HERVs due to its antiviral properties, the other compounds exert protective effects by controlling the aberrant immune response in pwMS, with HERV-W reduction as a downstream epiphenomenon.

Autologous hematopoietic stem cell transplantation (AHSCT) has been successfully adopted as a treatment for at least two HIV patients (Gupta et al., 2019). Allogeneic stem cells were obtained from donors lacking CCR5 (CCR5Δ32/Δ32), a co-receptor used by many circulating HIV strains to enter CD4+ T cells. When total chimerism is achieved, HIV is unable to spread to uninfected cells as all the available CD4+ lymphocytes are resistant. Although this procedure has limitations, reprogramming the genetic background leads to durable viral remission (Ndung'u et al., 2019). This effect might explain the therapeutic efficacy of AHSCT in pwMS (Nabizadeh et al., 2022). Total chimerism may reprogram the genetic background of pwMS, impair HERV dynamics, and interfere with chronic degeneration driven by inflammation. However, the underlying mechanism of action is still unclear (Muraro et al., 2017). Recent data indicate that AHSCT decreases cognitive decline, although the timing and modality of the intervention are still debated (Cohen and Cross, 2023).

The link between abortions/miscarriages and MS relapses could also be explained by HERV-W env (syncytin-1) activity, as this protein

significantly contributes to placental homeostasis. In this context, abortions/miscarriages could act as an antigen-presenting mechanism for MS relapses. In pwMS, abortion is associated with clinical and radiological inflammatory rebounds in the first 12 months post-event (Landi et al., 2018). A high relapse rate of neuromyelitis optica spectrum disorders and MS has been reported in the post-partum/post-abortion periods (Tong et al., 2018). On the other hand, childbirth or abortion/miscarriage have not been associated with increased MS risk. One can speculate that HERV-W does not act as a primary independent trigger of MS but instead as a transactivation product of HHV infection. Yet, a clear linear association between abortions and MS relapses has not been established (Hradilek et al., 2022), which may reflect the complex hormonal changes occurring upon pregnancy. Further epidemiological investigations are needed to fully elucidate the role of HERV-W in pregnant pwMS.

Finally, temelimab (previously known as GNbAC1), a humanized IgG4 monoclonal antibody targeting the MSRV env protein, was developed as a treatment option for MS. Pre-clinical and randomized clinical studies showed favorable safety and pharmacokinetic profiles (Curtin et al., 2012; Derfuss et al., 2015). A phase IIb trial indicated no substantial effects on MS symptoms, although radiological signs compatible with neuroprotective activity were noted (Hartung et al., 2022). A possible caveat is represented by the drug's limited spectrum of activity, which targets HERV-W env but no other HERVs. In this respect, it should also be considered that monoclonal antibodies are static therapeutic agents, while HERVs can adapt to evolutionary pressures and change dynamically to evade targeted therapies.

7. A serendipitous trail: putative role for antiretroviral therapy in multiple sclerosis

HIV is an exogenous retrovirus that, with prolonged infection, made possible by pharmacological control of the disease, causes neuropathological alterations associated with neurocognitive dysfunction (Christensen, 2016). Combined anti-retroviral therapy (cART) employed to counteract HIV infection has provided insights that could be translated to MS. Some studies found an inverse correlation between HIV infection and MS (Gold et al., 2015). There is still no solid evidence on whether this inverse association is due to immunosuppression – and thus to the inhibition of autoimmune responses – or cART (Gold et al., 2015; McKay et al., 2023; Nexø et al., 2013; Yen et al., 2017). A recent epidemiological analysis of Swedish and Canadian HIV-positive cohorts showed a significantly lower risk of MS among individuals living with HIV and HIV-positive cART-treated individuals (McKay et al., 2023). Unfortunately, follow-up for individuals not exposed to cART was limited. Evaluating the incidence of MS among people who take cART as pre-exposure prophylaxis (PrEP) could be informative on the impact of cART on MS risk. Reports on cART utilization in pwMS are scarce. Gold et al. conducted a clinical trial testing raltegravir – an HIV integrase inhibitor – on pwMS (Gold et al., 2018). The trial did not result in statistically significant improvements in reducing new or recurrent MS lesions or ameliorating clinical or laboratory parameters. However, as acknowledged by the authors, the trial design had several methodological issues. First, a single anti-retroviral drug can increase the risk of early therapy failure, as retroviruses exhibit exponential mutation rate, and a single drug may not be adequate to achieve rapid and effective clinical benefits. Moreover, integrase inhibitors are suboptimal to counteract HERVs already integrated into the human genome. The implementation of other anti-retroviral drugs directly acting on the viral replication machinery and a more robust pharmaco-pathological rationale could circumvent such limitations.

A systematic review suggested that pharmacological interventions against HIV (i.e., cART) might also be helpful for pwMS (Stefanou et al., 2019). To support this view, we conducted an up-to-date revision of the data, finding and analyzing nine case reports where HIV infections were confirmed after the MS diagnosis (Chalkley and Berger, 2014; Drosu et al., 2024, 2018; Durán et al., 2004; Francesco et al., 2015; Labella et al., 2021; Maruszak et al., 2011; Skarlis et al., 2017; Torkildsen et al., 2020). Follow-up data indicate no major MS relapses up to 3 years after cART initiation, even in patients without specific MS treatment. A paradigmatic case was reported in 2018 by Drosu and colleagues, who described an HIV-negative subject diagnosed with relapsing-remitting MS. The patient, a medical student, independently started combination therapy with zidovudine and lamivudine – two antiretroviral compounds. This therapeutic approach was based on the case report of a pwMS with sustained remission following cART. Symptoms rapidly ameliorated, and follow-up MRI studies failed to detect new MS lesions (Drosu et al., 2018). After discontinuing the first cART regimen, MS relapses occurred. While the patient never used MS-specific DMTs, a new cART regimen was tested. This regimen employed emtricitabine/-tenofovir disoproxil fumarate – two other antiretroviral drugs commonly adopted to restrict HIV. Imaging was stable over the following four years, and no subsequent clinical relapses were reported. The patient still reports occasional fatigue without disease progression (Drosu and Levy, 2024).

It is commonly thought that the clinical efficacy of cART is primarily driven by the anti-EBV effect of tenofovir (Drosu et al., 2024). Although this could explain part of the pharmacological value of cART, not all pwMS show signs of previous EBV infection, and, while few EBV-infected persons will develop MS, some may, in turn, develop cancer or other autoimmune syndromes (Farrell, 2019; Fujiwara and Takei, 2015; Xu et al., 2024). Thus, while EBV may play a role in the pathophysiology of MS (Drosu et al., 2024; Latifi et al., 2022), it may not fully explain the effects of cART. The hypothesis that in pwMS cART acts on retroviral targets independently of EBV infection is supported by evidence that efavirenz – a non-nucleoside reverse transcriptase inhibitor – is effective against MS relapses (Morandi et al., 2019). Additionally, the HIV-naïve patient reported by Drosu et al. (Drosu et al., 2018) showed clinical improvement when tenofovir was not included in the pharmacological regimen. The pwMS reported by Maruszak et al. (Maruszak et al., 2011) experimented several cART regimens which never included tenofovir.

The mechanisms through which cART modulates MS progression are still largely unexplored. One can speculate that cART may interfere with retroviral replication in pwMS. Further investigations on people on PrEP and *in vitro* pharmacological studies are needed to support the hypothesis. Of note, the studies herein reported have significant limitations, including:

- selection bias (only case reports with non-standardized drug regimens and non-controlled cART compliance);
- differences in cART regimens across patients;
- lack of extensive and detailed follow-up to understand the influence of confounding factors;
- HIV-specific cART is not designed to modulate HERVs since HIV and HERVs might interact differently with the tested anti-retroviral drugs;
- individual genetic backgrounds (e.g., TRIM and HPSG SNPs) might modulate the response to cART;
- serological analyses investigating previous HHV exposure and possible reactivation were missing.

Studies investigating anti-HHV drugs in MS therapy produced poor statistical significance for their clinical efficacy against HERVs and HHVs (Bergström, 2000; Lycke, 2017). However, although neurological deterioration did not differ between the anti-HHV drug acyclovir and placebo, exploratory analyses indicate a positive trend in specific subgroups over a 2-year period (Lycke et al., 1996).

8. Towards a pathological framework for HERV involvement in multiple sclerosis

MS and neurodegenerative diseases generally show non-linear progression modulated by interactions between environmental and patient-specific factors. Several groups proposed models by which HERV activation drives MS evolution (Meier et al., 2021; Mentis et al., 2017; Perron et al., 2009). Here, we propose a multilevel model (Fig. 1).

Breaking down disease emergence, the essential part revolves around the activity of gene regulatory networks (GRNs), a model of the causality of biological processes that can also be studied through mathematical formalism (Glass and Kauffman, 1973). GRNs and their protein interactions can be modeled using the Waddington landscape, a mathematical construct adopted to study cell fates in developmental biology (Banerji et al., 2013; Ladewig et al., 2013) and in cancer research (Aranda-Anzaldo and Dent, 2018; Huang et al., 2009). According to these constructs, HERV transactivation by environmental factors triggers a cascade of events that include expression of env and other HERV proteins followed by exosome-based diffusion (mainly, but not exclusively, through HSPGs) and eventually the development of disease manifestations. By binding TLR4, HERV-W env would stimulate the innate and adaptive immune systems.

HERV-W (syncytin-1) alone cannot explain the complex network of interactions underlying MS. MS has also been associated with HERV-K and HERV-H, although there is no firm consensus on this (Brütting et al., 2016; Christensen et al., 2007). In this scenario, HERV-K and HERV-H would be transactivated first, triggering a molecular cascade that recruits HERV-W.

This pathogenic cascade would fit a statistical percolation model rather than a classic cause-effect model. Depending on the permissive genomic background, various possible HHV infections would transactivate specific HERVs, initiating neuroinflammatory pathways linked to different MS phenotypes. Thus, different HERVs would act as hubs, indirectly modifying peripheral GRN dynamics.

Interactions between HERVs and the immune system within the common interindividual genomic landscape could shape the clinical features of prodromal MS or other autoimmune diseases (e.g., fatigue, anemia). Cellular and molecular pathways would eventually diverge due to system-specific interactions, generating distinct clinical features. Symptom modules driven by a particular genetic background could explain overlapping autoimmune syndromes (as in the case of rheumatic and neurological conditions). Therapeutic interventions could result in either "*No evidence of inflammatory disease activity*" (NEIDA) in MS or clinically silent phases in rheumatological diseases. However, relapses would eventually occur if a precarious drug-dependent balance is perturbed with sufficient force.

In this respect, disease progression could be modeled within the framework of phase transition and attractor dynamics. Disease relapses could reflect changes in the configuration of systems deflected from a stable orbit (Creixell et al., 2012; Golberger, 1996). Different HERV families could shape MS development by acting upon heterogeneous genomic landscapes and permissive conditions that ethnic and geographical factors could further modulate (Cárdenas-Robledo et al., 2022; Mirsattari et al., 2001). This complex interplay of genes and the environment could resemble that proposed for the interactions between inborn errors of immunity (IEI) and infectious agents (Casanova and Abel, 2022). In this regard, MS-related SNPs could predispose to MS based on their contribution to HERVs transactivation. Accordingly, interindividual IEI diversity could provide a rationale for the non-linear course of MS development. The ability of HERVs to move inside the genome and interact with other HERVs and HHVs could account for disease-related "genomic metastability".

Our analysis of Hill's criteria combines epidemiological, immunological, and virological information [as previously indicated in the case of EBV in MS (Soldan and Lieberman, 2022)]. Thus, the model bypasses simplistic and linear conceptualization (Table 1).

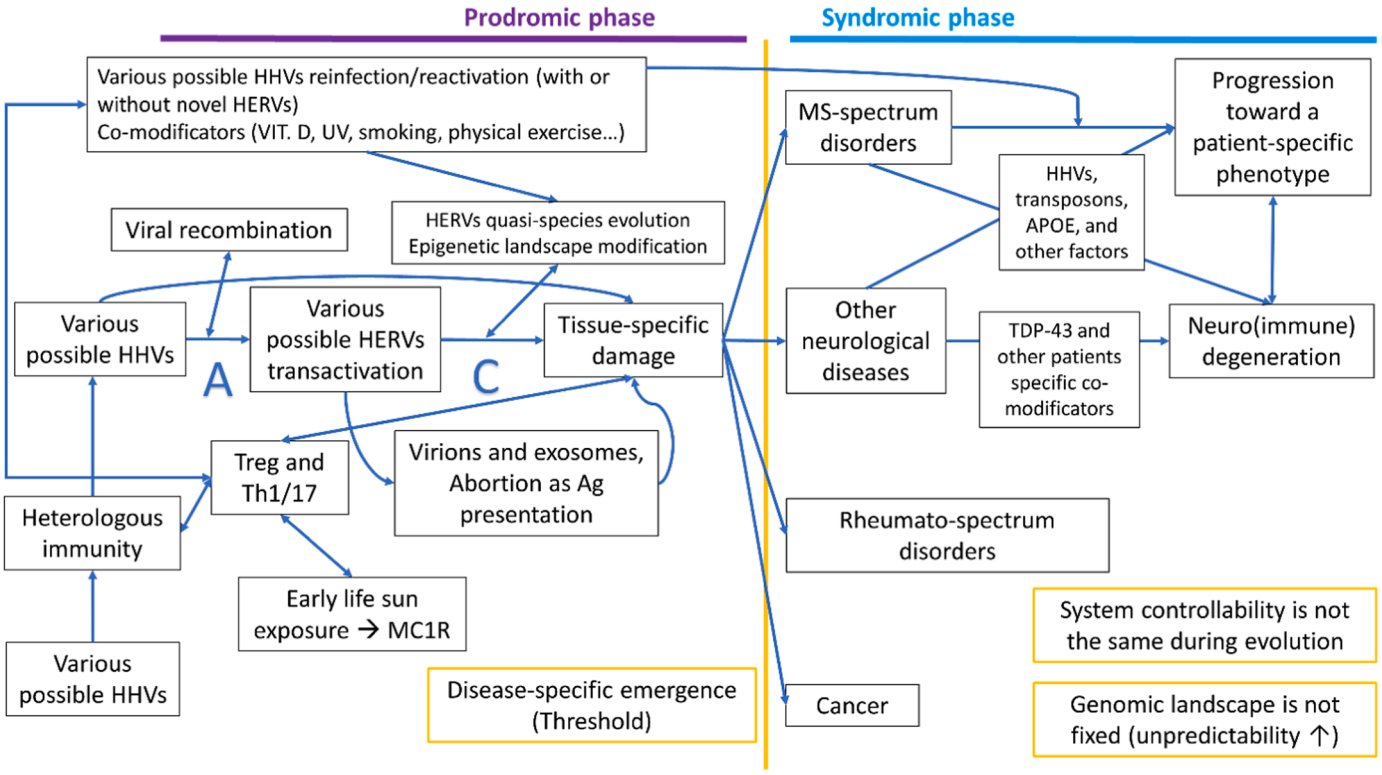

Fig. 1. Proposed model for the role of HERVs in the pathogenesis of neurological diseases, with a focus on multiple sclerosis. HHVs, human herpesviruses; Th, T helper cells; Treg, T regulatory cells; MC1R, melanocortin1 receptor; Ag, antigen; HERVs, human endogenous retroviruses; A, acute phase; C, chronic phase; VIT. D, vitamin D; UV, ultraviolet exposure; MS, multiple sclerosis; APOE, apolipoprotein E; TDP-43, TAR DNA-binding protein 43.

Table 1
Hill's criteria for a possible causal relationship between HERVs activation and multiple sclerosis. The association is summarized from arguments in the main text and references.

Strength of association	What is the relative risk?	(De la Hera et al., 2014; Dolei, 2018; Dolei et al., 2002; Garcia-Montojo et al., 2013; Nexø et al., 2013; Perron et al., 2009; Tarlinton et al., 2020)
Consistency of association	Is there agreement among repeated observations in different places, at various times, using different methodologies, by different researchers, under other circumstances?	(Morandi et al., 2017)
Specificity of association	Is the outcome unique to the exposure?	It cannot be unique since individual genetic background and personal history are always different.
Temporality	Does exposure precede the outcome variable?	HHVs can transactivate HERVs.
Biological gradient	Is there evidence of a dose-response relationship?	Dose dependence does not consider phase transition and other non-linear processes.
Plausibility	Does the causal relationship make biological sense?	See text and also (Perron et al., 2009)
Coherence	Is the causal association compatible with present knowledge of the disease?	See text and also (Perron et al., 2009)
Analogy	Does the causal relationship conform to a previously described relationship?	We tried to unify several theories into one.

Our model also differs from the one proposed by Volkman and Stetson, in which the recognition of retroelements by the immune system is considered a significant contributor to the onset and development of specific autoimmune diseases (Volkman and Stetson, 2014). In our model, HERVs act as reinforcement hubs, and HERVs hyperactivity allows and amplifies chronic neuroinflammation (Fig. 2). The model could be expanded to other neuropathological conditions. Of note, overexpression of TEs (including HERVs) has been found in Alzheimer's disease and is also part of the information theory of aging (ITA) (Liu et al., 2023; Lu et al., 2023; Yang et al., 2023).

In aging, HERVs could act as epigenetic noise, favoring the extension of disorganized cellular subpopulations that accelerate "system-specific aging" (Voisset et al., 2008). Since inflammation and aging are two sides of the same coin (i.e., plastic dis-adaptation to external stimuli with system-specific degrees of freedom), the two conditions might be epiphenomena of increased epigenomic entropy. Inflammation accelerates organ-specific aging, disrupting communication among health-critical body systems and producing symptoms (Tian et al., 2023). A variety of exogenous retroviral infections have been linked to other neurodegenerative diseases [as described by (Manuelidis & Manuelidis, 1989)], and cART can modulate the epigenetic clock in people infected by HIV (Schoepf et al., 2023).

Neurodegeneration is the endpoint of several neurological conditions linked to neuroinflammation, viral infection, and reactivation of TEs /HERVs, including MS, Alzheimer's disease, Parkinson's disease, etc. (Komaroff, 2020; Levine et al., 2023). The human genome encompasses various TE families that, like HERVs, could be transactivated by HHVs and other exogenous infections (Panning and Smiley, 1994). Specific Alu family patterns, for example, have been associated with MS and its clinical variability (Archelos et al., 1998; Correale and de los Milagros Bassani Molinas, 2002; Neven et al., 2016). Partially overlapping neurological syndromes could emerge from shared common molecular networks, as recently suggested by machine learning analyses (Massetti et al., 2022; Mekkes et al., 2024).

MS progression models do not consider the potential role played by viral dynamics (Kuhlmann et al., 2022). We attempted to fill this gap. MS relapses are viewed as triggered by (auto)immune actions exerted by HERVs, while background inflammation is considered the primary drive of neurodegeneration. This is in line with the "smoldering MS" construct proposed by Giovannoni's group (Giovannoni et al., 2022), in which progressive accumulation of disability occurs independently of MS relapse.

9. Conclusions

Back in 1952, in a seminal paper on the neuropathology of demyelinating diseases, Adams and Kubik noted that "neuropathologists pretend to know what a demyelinating disease is, yet they have found it hard to describe in a few simple words. […] There probably is no disease in which myelin destruction is the primary or exclusive pathologic change" (Adams and Kubik, 1952). Today, the etiopathogenesis of MS, the best known among the demyelinating diseases, remains hazy, while its elucidation is a prerequisite for critically needed improvements in MS prevention and treatment (Kuhlmann et al., 2022). MS susceptibility is influenced by ethnicity- and gender-related factors, combined with defined sequence variation in a heterogeneous array of genes, several of which directly impact pathways that modulate immune responses and antimicrobial defenses (Barrie et al., 2024; Brütting et al., 2016; Byun et al., 2008). This genetic substrate is consistent with evidence indicating that the ethnicity-related MS predisposition evolved after exposure to specific infectious pathogens during recent human evolution (Barrie et al., 2024). Thus, the current body of knowledge implies that MS ethiopathogenesis should be investigated and interpreted in the light of the human genetic theory of infectious diseases, where, as in other complex gene-environment interactions, over time, the interplay between pathogen exposure and a dazzling diversity of intrinsic and extrinsic disease mechanisms may account for a spectrum of disease phenotypes that emerge only in the susceptible fraction of the exposed individuals (Casanova, 2015). In this perspective, viral or, more broadly, microbial exposures represent extrinsic triggering factors, per se insufficient for disease development, which instead depends on the extent and duration of the perturbations induced on the intrinsic homeostatic networks, framed into the context of the concurrent environmental variables and of the ethnic-, gender-, and age-related background (Burgner et al., 2006; Chapman and Hill, 2012). The present perspective article incorporates HERVs within this conceptual framework. We propose HERVs activation as a critical hub that modulates the cell/tissue-intrinsic immune-inflammatory cascade responsible for the

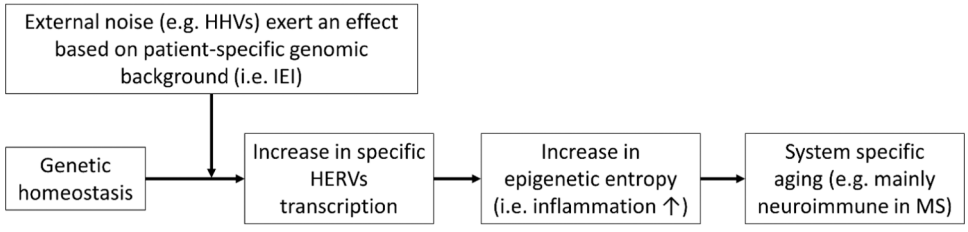

Fig. 2. Proposed model for an informational theory of progressive (neuro)inflammation. HHVs, human herpesviruses; HERVs, human endogenous retroviruses; IEI, inborn errors of immunity;MS, multiple sclerosis.

pathological phenotypes of MS. HERVs, remnants of ancient infectious retroviruses repurposed for key host cell functions, such as regulation of cell-intrinsic immunity and, possibly, direct interference with invading viral pathogens (Srinivasachar Badarinarayan and Sauter, 2021), may explain the link between MS and HHV in the context of the interindividual heterogeneous clinical trajectories of the disease (Khalesi et al., 2023).

The proposed model offers biological and clinical versatility, but several questions remain open. Further optimization, aided by mathematical formalization in analogy with the modulation of brain networks (Gu et al., 2015; Suweis et al., 2019), and experimental proofs of concept are clearly needed. In the meantime, the modeling of HHV-HERV-MS network dynamics might provide clues for new patient-tailored therapeutic approaches (Branigan et al., 2022; Lycke, 2017; Wooliscroft et al., 2023).

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