Human Endogenous Retroviruses

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Human endogenous retroviruses (HERV) have been implicated in the pathogenesis of several nervous system disorders including multiple sclerosis and amyotrophic lateral sclerosis.

Keywords: human endogenous retrovirus ; multiple sclerosis

1. Human Endogenous Retroviruses

Approximately 8% of human genomic DNA has high sequence similarity to retroviruses. These so-called human endogenous retroviral elements (HERV) are derived from exogenous retroviruses that have infected germ-line cells during evolution [1]. Once fixed in the population, these genetic elements were inherited as stable genetic components [1]. Some HERV display very high copy numbers, which might be the result of multiple germ line infections or reverse transcriptase-dependent amplification (retro-transposition) [2][3]. A phenomenon common to most HERV families, and particularly evident in HERV-K (HML-2), is their polymorphic nature, meaning that not all individuals have the same set of retroviruses at the same genomic sites. [4][5][6] Such unfixed proviruses likely arose from divergence of retroviral copies, de novo insertions in the human population, or variable deletion of chromosomes [4][5][6]. As an example, HERV-K113 is present in a maximum of 30% of all individuals, showing a widespread geographic and racial variation [7][8].

Based on their similarity to exogenous viruses, the genomic structures of HERV possess the three viral genes *gag* (group specific antigens, encodes internal structural proteins), *pol* (encodes viral enzymes), and *env* (encodes the envelope protein), which are flanked by regulatory long terminal repeats (LTRs). Additional ERV-derived proteins, which are products of alternative splicing, include the regulatory rec and np9 proteins. However, most of the ERV open reading frames are mutated and cannot produce functional proteins or virions [9]. An earlier genome-wide search revealed only 29 *env*, 17 *gag*, and 13 *pol* open reading frames (ORF) longer than 500 codons, which possibly code for viral proteins, among a total of 38,000 retroviral ORFs examined [10]. The maintenance of ORFs in HERV genomes over many thousands of years of evolution suggests a functional role for these elements. However, an intact ORF alone is not sufficient for protein expression, since HERV are usually epigenetically silenced. Only if HERV become reactivated by intrinsic or extrinsic factors, can viral RNAs and proteins be produced. Their function is largely unknown, even though understanding of their importance has increased in recent years. Both the beneficial and detrimental effects of encoded viral proteins have been reported. Participation in normal physiological processes, such as placental development [11] and modulation of innate immunity [12], shall be mentioned here as examples. Independent of their protein-coding capacity, HERV are able to regulate neighboring genes by providing alternative promoters [13] or by altering the chromatin structure by binding co-repressor proteins like TRIM28 [14][15].

Emerging evidence suggests that members of the HERV-K, HERV-W, and HERV-H families have the potential to regulate immune function [16][17][18][19]. Hence, their aberrant expression has been linked to the development and progression of inflammatory and neurologic diseases, although causal links have yet to be established.

2. Regulation of HERV Expression

To ensure genomic stability and integrity, HERV are usually transcriptionally silent. This is accomplished by DNA methylation and histone modifications [20][21][22][23]. The majority of endogenous retroviral sequences are located in chromosomal regions with repressive, heterochromatic chromatin architecture leading to low transcriptional activity in most cell types [21]. This “epigenetic corset” is established during embryogenesis. However, in early embryonic stages, which are characterized by global hypomethylation, precise regulation of retroviral sequences seems to be involved in physiologic processes such as the induction of viral restriction pathways [24] and the differentiation of stem cells. For instance, neural differentiation involves tight control of HERV-H RNAs via death-associated protein 5 (DAP5, also known

as novel APOBEC-1 target 1, NAT1) and the terminal uridyltransferase TUT7 [25]. Similarly, the down-regulation of highly expressed HERV-K (HML-2) envelope protein in pluripotent stem cells results in dissociation of the stem cell colonies and increased differentiation along neuronal pathways [26].

If the epigenetic control machinery becomes impaired, endogenous retroviral sequences can be activated and become transcriptionally active [27][28]. This is particularly evident in cancer because DNA methylation in cancer cells is often severely impaired. As a consequence, the activity of many HERV, particularly HERV-K, is frequently elevated in tumors like melanoma, breast cancer, and astrocytoma (reviewed in [29]). In contrast, development-specific demethylation in placental tissue leads to the physiologically required expression of HERV during placentogenesis. Syncytin-1, the envelope protein of the HERV-W family member HERVWE1, was shown to contribute to the formation of the syncytiotrophoblast by its membrane fusogenic capacity and seems to also be involved in maternal immune tolerance towards the fetus [30][31].

Additional to epigenetic mechanisms, environmental factors such as caffeine and aspirin are supposed to be regulators of HERV expression [32], although in vivo evidence for this is still lacking. In particular, infections with exogenous viruses represent potent triggers of HERV activation. Thus, transactivation of HERV by human immunodeficiency virus 1 (HIV-1), hepatitis B virus (HBV), human T-lymphotropic virus 1 (HTLV-1), and influenza A virus has been described [33][34][35][36]. For example, the HIV-1 transactivator of transcription (Tat) protein can induce the expression of HERV in lymphocytes and astrocytes through regulation of the nuclear factor kappa B (NFκB) pathway, the nuclear factor of activated T cells (NFAT) pathway, and the toll-like receptor 4 (TLR4) pathway [37][38]. In accordance with that, HIV-1 infected patients show increased antibody titers against the transmembrane unit of HERV-K (HML-2) envelope protein, which decrease with antiviral treatment [39]. The transactivator protein Tax of HTLV-1 increases, similar to HIV-1 Tat, the promoter activity of HERV-K, HERV-W, HERV-H, and HERV-E members in T cells [35]. Herpesviruses including Epstein–Barr virus (EBV) [18][40][41], herpes simplex virus 1 (HSV-1) [42][43][44], and human cytomegalovirus [45] have also been reported to induce HERV transactivation. As a probably important example, the EBV glycoprotein gp350 triggers transcription of the HERV-K18 *env* gene in resting B cells after binding to the EBV receptor CD21 [41]. The same gp350 stimulates HERV-W Env protein expression in astrocytes through the NFκB pathway [46]. Interestingly, since EBV infection is an important risk factor for the development of MS, HERV are discussed as the missing link between EBV infection and disease onset [47]. Additional information on the virus-associated regulation of HERV elements is provided in a recent review by Chen et al. [48]. Infections with other pathogens including *Toxoplasma gondii* were shown to induce a wide range of HERV elements in the Ewing sarcoma cell line SK-N-MC [49]. Inflammatory conditions per se, such as interferon gamma (IFNγ) and other proinflammatory cytokines, were shown to induce HERV expression in vitro [50][51]. It is not yet clear whether HERV occur as a consequence or as a cause of inflammatory processes. For this reason, the interaction of HERV with the immune system is being intensively investigated, especially in the context of diseases such as multiple sclerosis.

3. Multiple Sclerosis

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system resulting in progressive neurodegeneration and neurological disability. The onset usually occurs between the ages of 20 and 40 and is often evidenced by a clinically isolated syndrome (CIS), i.e., a first episode of neurological symptoms caused by inflammation or demyelination [52]. The type of symptomatology is diverse and depends on the affected central nervous system regions; common early signs include vision problems, weakness or fatigue, and balance problems. MS can typically be divided into three clinical types: (i) Relapsing-remitting MS (RRMS), which is characterized by discrete relapses with intermediate periods of remission. Relapses manifest themselves in new or worsening symptoms with underlying active brain lesions with lymphocytic inflammation. (ii) Secondary progressive MS (SPMS) typically develops 10–15 years after RRMS onset, characterized by a slowly progressive disease course with dominant neurodegeneration. (iii) Primary progressive MS (PPMS) is characterized by gradually increasing disability from the onset of the disease involving a dominant neural system, such as lower limb weakness and spasticity; 5–15% of MS patients show a PPMS onset.

White matter lesions incidentally found by magnetic resonance imaging (MRI) in individuals without a clinical history of demyelinating attacks or any other cause of white matter lesions (radiologically isolated syndrome, RIS) indicate that MS begins before the first clinical symptoms become apparent [53][54]. The early clinical course is marked by relapses from which symptomatic recovery is usually complete. Transition from RRMS to SPMS is subtle with relapses occurring on a low background level of progression, before progression becomes dominant. This gradual clinical disease development is consistent with rather continuous pathological changes. At the beginning of the disease, inflammation is suggested as the driving force, while the progressive phase is dominated by neurodegenerative processes. Nevertheless, cognitive impairment and progressive MRI-detectable atrophy occur in early MS, suggesting that neurodegeneration is already present from clinical onset.

The pathological hallmarks of MS are focal inflammatory lesions characterized by primary demyelination in the white and grey matter of the CNS. Oligodendrocyte damage and demyelination originate in the periphery with the activation of self-reactive T cells that infiltrate in the CNS across a disintegrating blood–brain barrier [55]. In active lesions, activated microglia or macrophages, mainly CD8-positive cytotoxic T-lymphocytes, and fewer CD4-positive helper T cells, B cells, and plasma cells can be found [56]. The inflammatory process is accompanied by the activation of astrocytes leading to the formation of astroglial scars [55][57]. Acute axonal damage is most prominent in the early stages of RRMS and SPMS, whereas in PPMS, axon degradation is more constant [58]. Whether axonal damage occurs as a consequence or independently of demyelination is subject to controversial discussion [59].

Extensive remyelination can be frequently observed during the early stages of RRMS [60]. However, recurrent inflammatory attacks and the failure of myelin repair during later progressive phases of the disease ultimately lead to permanent de-myelinization. There is currently no causal therapy for MS. Treatment is designed to reduce inflammatory processes and prevent the progression of symptoms.

Although the cause of MS remains unclear, it is believed that a combination of genetic and environmental factors influences disease susceptibility. Studies with siblings of affected individuals and monozygotic twins indicate a strong genetic component [61][62]. The human major histocompatibility complex (MHC) region on chromosome 6p21 was identified early as the strongest genetic locus for MS [64][63]. More recent genome-wide association studies uncovered more than 200 implicated genetic risk variants, including 110 non-MHC genetic loci [65][66][67], which all confer small increases in disease risk. Moreover, genetic differences between RRMS and PPMS have been identified [68]. The association of different HERV loci and MS risk will be discussed below. The multifactorial character of MS becomes particularly evident in studies showing that the individual risk of disease in genetically predisposed individuals increases when they are additionally exposed to environmental risk factors [69][70][71][72]. Such factors include low vitamin D levels, lack of sun exposure, female sex, EBV infection, obesity during adolescence, and smoking [69]. Among these factors, infection with EBV is considered the strongest risk factor, as the risk of developing MS increases 15-fold with EBV infection in childhood and 30-fold with infection in adolescence compared with uninfected individuals [73]. Moreover, there is a higher frequency of EBV seropositivity in MS patients compared to controls [74] and the beneficial effects of EBV-specific T cell therapy in MS have been demonstrated [75]. Several mechanistic hypotheses addressing the etiologic role of EBV in MS exist and are summarized in a recent review [76].

3.1. HERV-W in MS

In line with a possible virus-associated etiology of MS, the involvement of HERV represents an additional piece of the puzzle in this multifactorial and heterogeneous disease. Over the past 30 years, concurrent studies by several investigators have consistently suggested a relationship between HERV and the development of MS.

The first observation of retroviral particles of presumed endogenous origin in MS patients dates back to the early 1990s [77]. The cDNA sequences derived from particle-associated RNA were then assigned to a “multiple sclerosis-associated retrovirus” (MSRV). Merely a decade later, it was discovered that MSRV belongs to the HERV-W family [78]. HERV-W is a multicopy family with about 650 loci in the human genome [79]. Most of these loci are coding-deficient due to their evolutionary age [80]. However, more than 100 HERV-W loci were found to be transcribed in the human brain [79], although it cannot be excluded that some of these transcripts are caused by recombination events in vitro [81]. Other investigators identified seven transcribed HERV-W env loci in peripheral blood mononuclear cells (PBMC) [82]. Among 13 reported HERV-W loci with full-length env genes, only the HERVWE1 locus on chromosome 7q21.2 codes for a complete HERV-W envelope protein called syncytin-1 [82]. ERVWE2 on chromosome Xq22.3 encodes an incomplete HERV-W env of unknown function [83]. Since there is no counterpart to the initially named MSRV envelope protein (GenBank sequence AF331500) in the human genome, the origin of MSRV env remains open [82][84]. Based on the assumption that reverse transcriptase can switch templates during in vitro PCR amplification [81], recombination of different HERV-W env loci transcripts was proposed [82]. The origin of different published MSRV sequences involving recombination of transcripts from up to six different HERV-W loci is discussed in more detail by Grandi et al. [84]. Other possible explanations for the discrepancy in HERV-W genomic sequences found by various investigators include unfixed copies of HERV-W that are present only in a certain percentage of the population, and the occurrence of somatic recombination events that cannot be detected in unaffected cells [81][85][86].

HERV-W proteins have been found to be physiologically expressed in the normal brain with unknown function [87][88]. Increased amounts of HERV-W RNA, DNA, proteins, virions, and antibodies directed against HERV-W peptides in the blood, cerebrospinal fluid (CSF), and/or brain of MS patients have been associated with disease etiology. HERV-W env has been detected in the brains of MS patients, particularly in macrophages and microglia in lesions, but not in healthy controls [89]. Similarly, active MS lesions show an accumulation of HERV-W gag in axonal structures and endothelial cells

as well as specific expression of HERV-W env in macrophages and microglia cells [87][90][89][91]. Additionally, HERV-W env is elevated on the surface of B cells and monocytes [92][93][94]. Concerning seroreactivity, higher antibody titers against HERV-W env have been identified in patients with active MS compared to patients with stable MS [92], patients with neuromyelitis optica spectrum disorder [95][96], or healthy controls [97][98].

There are several studies that report increased copy numbers of HERV-W pol and env DNA or RNA in the blood (PBMC or serum/plasma) and/or CSF in patients with MS compared to control groups (healthy controls or patients with other neurological diseases) [90][99][100][101][102][103][104]. In this context, the presence of the MRSV in the CSF seems to be associated with disability accumulation and a higher rate of relapses in MS patients in a 10-year follow-up study in a Sardinian cohort [105]. Interestingly, one study found an inverse correlation between MSRV DNA copy numbers and vitamin D concentration in RRMS patients [106]. Although all mentioned studies report increased HERV-W viral loads when comparing MS patients with healthy controls, not all MS patients tested positive for HERV-W/MSRV RNA or anti-HERV-W env antibodies [95][100][107]. Consequently, the detection of HERV-W alone is not sufficient to distinguish MS patients from healthy individuals or patients with other neurological disorders. The variable expression of HERV in MS patients may rather reflect a differential regulation of inherited HERV copies in the genome. Thus, more detailed studies are still needed to determine the applicability of HERV-W as a diagnostic marker in MS.

The hypothesis that HERV-W is a driving factor in the development of MS is further challenged by studies reporting no association between HERV-W yields and the disease. For example, the relative transcript levels of investigated HERV-W elements in PBMC or the brain did not differ significantly between MS patients and controls [79][82] and no HERV-W was detected in the cerebrospinal fluid of MS patients using PCR [108]. Ruprecht and colleagues reported the absence of antibodies and T-cell reactivity against MSRV env and gag proteins in MS patients, respectively [109]. This might be due to self-tolerance to HERV as autoantigens in the investigated subjects. The positive seroreactivity against HERV-W mentioned above [92][95][96][98][97] referred to specific HERV-W peptides being antigenic and leading to a rather low response amplitude, which is consistent with variations in “natural autoantibodies” when corresponding tolerated antigens are released (cell death, tissue damage) or abnormally expressed (HERVs) [110]. Therefore, Ruprecht’s observations do not contradict the other studies. Another study reports syncytin-1 encoding RNA to be increased in MS brains compared to non-MS patients, but not in CSF and plasma [111]. Most of these studies do not consider the treatment effects on HERV formation and persistence. It was shown that interferon-beta (IFN-β) treatment reduces MSRV levels in the plasma of MS patients below detection limits after three months of treatment [112]. Likewise, elevated antibody titers against HERV-W env in MS patients decreased after IFN-β treatment [97]. This may explain in part the absence of HERV-W in other investigations. However, the complex genomic distribution of HERV-W elements leads to limitations in the comparability of studies, since it often remains unclear from which genetic locus the investigated protein or nucleic acid originates. Despite these limitations, a meta-analysis of 12 studies performed by Morandi and colleagues reports a strong association between MSRV/HERV-W pol and env and MS [104].

Although it is not known whether HERV-W has a causal role in the development of MS, there is some evidence that it interacts with the immune system. Thus, MSRV/HERV-W env protein induces the release of inducible nitric oxide synthase and pro-inflammatory cytokines such as tumor necrosis factor alpha, IFNγ, interleukin (IL)-6, and IL-1β from PBMC of MS patients [16][113][114][115]. Moreover, IL-6 and the p40 subunit of IL-12 seem to correlate with disease severity [113]. In addition, the activation of certain cytokines by HERV-W env depends on the clinical course of the patient’s disease. For example, so-called type I cytokines (which favor cellular immune responses) predominate in stimulated PBMC of patients with acute MS, while in patients with stable MS, a type II cytokine profile (which favors humoral immune responses) dominates [116][117]. Interestingly, combined stimulation of PBMC from MS patients with antigens from *Herpesviridae* (herpes zoster virus, human herpesvirus 6A, herpes simplex virus 1) and antigens from HERV-H also leads to an altered Th1/Th2 response [114].

It has been shown for human brain endothelial cells, rat and human oligodendroglial precursor cells, and human PBMC that the HERV-W-induced release of proinflammatory cytokines is mediated by concentration-dependent activation of the pattern recognition receptors CD14 or TLR4 [16][113][115][118][119].

Increased cytokine release after MSRV/HERV-W env stimulation has also been recorded in human brain endothelial cells and rat oligodendrocyte precursor cells (OPCs) [118][119]. In addition to altered cytokine profiles, rat OPCs show a decrease in myelin proteins CNP and MBP as opposed to the unchanged expression of the precursor marker claudin 11 (CLDN11, also known as O4 antigen) following HERV-W env stimulation. This reflects the impairment of myelin sheath formation and cellular differentiation caused by HERV-W env [119]. These negative effects can be successfully neutralized by the anti-HERV-W env antibody GNbAC1 [120][121]. Cytotoxicity on OPCs might also be mediated via HERV-W expression in astrocytes as it induces endoplasmic reticulum stress and the release of redox reactants leading to OPC apoptosis [122]. In accordance, transgenic mice overexpressing HERV-W showed neuroinflammation, decreased levels of

myelin proteins in the corpus callosum, and behavioral deficits compared to wild type littermates [123]. In addition, MSRV/HERV-W env causes axonal injury by altering microglial cells to form a degenerative phenotype and to associate with myelinated axons [91]. The immuno-stimulatory properties of HERV-W env protein were demonstrated using a myelin oligodendrocyte glycoprotein-induced mouse model of experimental autoimmune encephalomyelitis (EAE), in which mice injected with HERV-W instead of mycobacterial lysate developed a disease phenotype [124].

In summary, MSRV/HERV-W env is expressed in chronic active MS lesions. Preclinical models have shown that HERV-W env is a negative regulator of OPC maturation and a TLR4 agonist that activates innate immunity and might be involved in MS etiology.

3.2. Other HERV in MS

In addition to the HERV-W family, an association of other HERV with MS, such as HERV-H/F and HERV-K, has been suggested.

Concerning the HERV-H/F family, increased MS risk in Danish and Norwegian populations was related to the single nucleotide polymorphism (SNP) rs391745 in the vicinity of the *HERVFC1* gene locus [125][126]. The same SNP showed significant association with MS in two Spanish cohorts [127]. Additionally, the amount of HERVFC1 gag RNA in plasma and of HERVFC1 gag protein in T cells and monocytes was increased in active MS patients compared with non-active MS and healthy controls [128]. Whereas HERV-H env and gag RNA was increased in the serum and PBMC of Danish MS patients [129][130], no difference in RNA expression (analyzed in CSF, PBMC, and brain) between MS and patients with other neurological diseases was observed in Spanish and Canadian studies [108][111][122][131]. Expression of HERV-H3 was shown to be significantly increased on the surface of non-classical monocytes in patients with CIS and RRMS compared to healthy controls [132]. However, expression of HERV-H3 seems to be inconsistent and probably depending on pre-treatment of patients [133] as immune-modulating therapy can lead to an increase of nonclassical monocyte populations [134].

Another HERV family implicated in MS is HERV-K (HML-2), which has many human-specific insertions as it contains many of the most recently integrated and “active” retroelements [135][136]. Studies analyzing HERV-K DNA, RNA, and protein levels in MS patients compared with healthy controls report different and sometimes inconsistent results depending on the member of the HERV-K family examined, the part of the virus analyzed (*env*, *pol*, or *gag*), and the investigated tissue. For example, expression of HERV-K *pol* [51], but not of HERV-K *env* [111][122], was elevated in the brain of MS patients compared to control groups. Moreover, an increase in the prevalence of HERV-K113, but not HERV-K115, was reported in patients with MS or Sjögren’s syndrome [7]. However, the same group failed to reproduce these findings in a larger cohort of MS patients [137]. The difference between these studies might be explained by the genetic variability between the populations studied [135][138]. From a genetic point of view, homozygous carriers of the HERV-K18.3 allele have a higher risk of developing MS compared with carriers of the other two alleles K18.1 or K18.2 [139][140]. Moreover, the SNP rs2435031 near the HERV-K113 locus has been shown to be associated with MS [125]. Based on published data, relevance for HERV-K in MS appears to be low. Instead, there is evidence of HERV-K involvement in amyotrophic lateral sclerosis (ALS).

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