Review

Retroviruses and multiple sclerosis – new pieces to the puzzle

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Abstract

The possibility that retroviruses play a role in multiple sclerosis (MS) has long been considered. A genetic test series of fifty endogenous retroviral loci for association with MS in Danes showed markers near a specific endogenous retroviral locus, HERV-Fc1, located on the X-chromosome, to be positive. Recently, a second retrovirus, HERV-K13 on chromosome 19, was found to interact with HERV-Fc1 in the same cohort, also influencing the disease. Also, restriction genes for retroviruses influence the risk of MS, providing further support for a role of such viruses in disease. Finally, HERV-Fc1 gag RNA in plasma was increased 4-fold in patients with recent history of attacks, relative to patients in a stable state and to healthy controls. Bout Onset MS was associated with the HERV-Fc1 locus, while a rarer form of MS, Primary Progressive MS, was not.

Retroviruses may activate the innate immune system in a variety of ways, involving the host proteins, TRIMs, TLRs, TREXs and STING. Results with HIV-positive patients suggest that antiretroviral drugs can curb MS. Thus, we have obtained new data for the etiology and pathogenesis of MS, suggesting useful ways to challenge autoimmune diseases.

Keywords: Multiple Sclerosis; Endogenous Retroviruses; HERV-Fc1; HERV-K13; TRIM; BST2; Genetic Association
Multiple sclerosis (MS) is a chronic inflammatory, demyelinating disease of the central nervous system probably caused by interaction of multiple genes and environmental factors. It is the most common neurological disease causing debilitation in young people in Scandinavia. Disease onset usually occurs in young adults, and it is more common in women [1]. It has a prevalence that ranges between 2 and 150 per 100,000 [2]. The ultimate pathogenic effector appears to be the immune system [3]. Initially, MS in most people is characterized by sudden bouts of disease, called attacks, alternating with periods of remission. Gradually, the disease may become progressive. There is no known cure for multiple sclerosis. Treatments attempt to return function after an attack, prevent new attacks, and prevent disability [1].

The possibility that retroviruses play a role in the pathogenesis of MS has long been considered. In a number of animal models (sheep, mice, and monkeys) demyelinating diseases are well known, and can be caused by horizontally transmitted retroviruses [4-6]. A number of retroviruses have been considered since they have links with similar neurodegenerative disorders, such as HTLV-1, which causes tropical spastic paraparesis in humans, and the Visna-Maedi virus, which causes an MS-like disease in sheep [7]. There is no evidence that MS in humans is contagious, albeit infection with Epstein-Barr virus seems to predispose to MS later in life. This could be one of the environmental factors influencing risk of MS. As will become apparent in the following, we do not see the endogenous retroviruses as alternatives to the immune-mediated damage, but as triggers of it.

MS has a clear genetic component as evidenced by studies of twins [8], and the absence of horizontal transmission has led to a focus on the human endogenous viruses. This could mean that predisposition for disease is inherited in part as proviral loci, which set up an infection-like activity within the
individual. Alternative mechanisms are also possible (see below). Endogenous viruses may well be one or more of the genetic factors in the pathogenesis.

The classical theory for the involvement of endogenous viruses in MS focuses on the HERV-W/MSRV viruses [9,10] or HERV-H viruses [11] and was recently reviewed [12]. More frequent detection of particular antigens of a specific virus has been reported in relation to MS. Enhanced peripheral blood mononuclear cell (PBMC) proliferation and cytokine responses to human HERV peptides in patients with active MS, have also been studied [13]. An intriguing new development has been the report that the number of DNA copies of HERV-W DNA in genomic DNA from peripheral blood mononuclear cells from secondary progressive MS is increased, suggesting that HERV-W replicates in these patients [14].

A potential problem in the implication of HERV-W/MSRVs and HERV-Hs in MS is the inability to distinguish causation and passenger status through expression experiments. Does the virus contribute to disease or does disease activate the virus? This is a problem that cannot be solved within the frame of expression studies. To get around this obstacle, we initially chose to study the genetics of endogenous retroviral loci followed by physiological experiments, only when the identity of an associated locus was established. There is no known mechanism, by which the disease could alter specific polymorphisms in the polyclonal DNA used in these studies, and the direction of causality is thus relatively certain to be from DNA to disease; not the reverse.

By means of an approach based on genetic epidemiology, fifty endogenous retroviral loci were tested for association with MS. The fifty loci were chosen because their sequences indicate that between zero and two mutations would enable encoding at least one full length viral protein. Markers near a specific endogenous retroviral locus, HERV-Fc1, located on the human X-chromosome, were found to be associated with disease in a cohort of 350 MS Danish cases and 500 controls [15]. The association was repeated in one Danish, and in one Norwegian cohort [15,16]. A fourth (Danish) cohort was negative for disease association. Recently, it was found that a second endogenous retroviral locus, HERV-K13
on chromosome 19, interacted statistically with HERV-Fc1 in contributing to MS, possibly because the two viruses complement each other [17]. HERV-Fc1 seems to have open gag and env frames. HERV-K13, in contrast to HERV-Fc1, seems to contain a near-functional pol frame.

Subtypes of MS have also been studied for association with HERV-Fc1. Bout Onset MS, the common forms of MS, encompassing Relapsing/Remitting MS and Secondary Progressive MS, was associated with the locus, while another form of MS, Primary Progressive MS, seemed not to be [16]. Interestingly, an independent study has indicated that Primary Progressive MS may be associated with another endogenous retroviral locus [18]. A search for extra germ line copies of HERV-Fc1 in MS was unfruitful [19].

Two other lines of inquiry also support the involvement of retrovirus in MS. First, in a series of expression studies [20], it was shown that the level of HERV-H/F GAG protein is increased in PBMCs from MS patients relative to healthy controls. It was also found that the level of protein was elevated in the circulating T-cell compartment in MS patients with a recent history of attacks, relative to patients in a stable state and to healthy controls. Finally, in agreement with this it was found that expression of HERV-Fc1 RNA in plasma was increased 4-fold in patients with a recent history of attacks, relative to patients in a stable state and to healthy controls. Combined with the genetic studies this suggests an active role of HERV-Fc1 in the pathogenesis of MS. Secondly, genes known to restrict the replication of viruses, namely TRIM5, TRIM22 and BST2, have been shown to influence the risk of MS. The so-called APOBEC3 genes showed a similar, but statistically insignificant, tendency, while the TREX1 gene seemed inert [21].

Treatment with a demethylating agent 5-aza-dC (5-azadeoxycytidine), resulted in significantly increased levels of HERV-Fc1 mRNA expression in cells previously not expressing HERV-Fc1, or with a very low basic expression level. The extent of expression of HERV-Fc1 RNAs precisely correlated with the apparent extent of demethylation of the related DNA sequences from the HERV-Fc1 5’LTR-gag region [22]. The results are in accordance with recently published data where up to 50
000 fold up-regulation in HERV-Fc1 env mRNA expression was observed upon treatment of RL95-2 cell line with 5-aza-dC [23]. Although we have no data as of yet, one could imagine that other physiological mechanisms might also activate expression of HERV products and could contribute to disease.

Current models of MS pathogenesis implicate the immune system as the ultimate effector, but combine it with neuro-degeneration [3]. How this might be related to the retroviruses is unknown, but several possibilities can be suggested. The endogenous retroviruses in general are defective. However, they may be able to start an infectious process either through complementation or recombination, as we suspect for HERV-Fc1 and HERV-K13. Thus, it might be the entire endogenous retroviral repertoire that determines infectivity and not the individual locus. Once activated, the viruses could trigger the adaptive immune system or, equally likely, the innate immune system.

Several sets of genetic anti-retroviral defense mechanisms exist in the human genome encoding dozens of proteins. One such set includes the TRIM proteins. TRIM5 protein activation is mediated by the incoming viral capsid. Recently, Jeremy Luban’s group reported that TRIM5 protein not only inhibits retroviral replication, but that it also stimulates the innate immune system [24]. As described above, markers in and around the TRIM5 gene are associated with the risk of MS [16, 21]. Thus, there is a distinct possibility that there exists a cascade from HERV-Fc1 (and other HERVs) via the TRIM proteins to the innate immune system.

Alternative mechanisms for the activation of the innate immune system may exist. Un-integrated DNA in the cytosol is known to trigger innate immune signaling [25]. RNA component of internalized viruses activate the innate immune system by stimulating Toll-like receptors in the endosomes [26]. The triggering of TLRs by HERVs in MS has previously been proposed [27]. Moreover, triggering the innate cellular antiviral system by membrane-fusion of virion and cell, may act via the adaptor STING [28]. Finally, an entirely different mechanism was described in a recent paper; Dysregulation of the
heterochromatin factor HP1α binding sites was shown to occur in MS. HP1α was again shown to influence both expression of HERVs and immune factors [29].

Thus, the endogenous viruses are mobile subcellular structures that span the divide between self and foreign. We specifically suggest that the viruses, though now a part of self, have retained the ability to trigger innate immune sensors of foreign patterns. This in turn could lead to stimulation of an adaptive autoimmune response. A combination of the above mechanisms could conceivably lead to a response, initially elicited by the endogenous viruses, but ultimately reacting to a broad range of cellular components.

Noticeably, none of these models require actual productive infection cycles; a steady supply of particles performing the initial parts of an infection would be enough. Therefore, our induction experiments, which show that high levels of viral mRNA expression can be achieved from the endogenous loci, when cells are transformed or exposed to drugs, take on a special significance. However, we sorely miss the identification of normo-physiological mechanisms other than actual replication that can activate endogenous viruses to the necessary extent. Late infection with Epstein Barr Virus (EBV) is associated with MS, and in vitro EBV infection of blood leucocytes and astrocytes lead to activation of HERVs [30]. Maybe, late EBV infection in vivo triggers large scale HERV activation.

Future investigations must substantiate the involvement of HERVs in MS by genetic experiments as well as expression studies. Studies of host factors should serve the same purpose. The activation of the innate immune system by retroviruses and the role of TRIMs, TLRs, TREXs, STING and HP1α should be elucidated in both genetic and expression studies. The potential interaction of HERVs is also of considerable interest.

Importantly, recent data suggest that MS is influenced by highly active anti-retroviral treatment (HAART) [31, 32]. MS is uncommon among HIV-positive, HAART-treated persons (incidence rate ratio = 0.3: 95% confidence interval = 0.04 – 2.2). Although the group-size is small, and the results are
not statistically significant, the effect is fairly strong and in accordance with the expected trend suggesting that antiretroviral medicines can curb MS. If these findings are substantiated, it becomes imperative to investigate in a clinical trial, if anti-retroviral medicine can be effective against MS and possibly other autoimmune diseases.
Author’s contribution

KKN, MJL, BAN: Ideas, drafting. All other authors: Contributory ideas, discussions, review of the manuscript, literature search.

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