

Commentary on Jørgen Clausen's Review – Endogenous Retroviruses in MS

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The possibility that endogenous retroviruses (ERVs) may be involved in multiple sclerosis (MS) and other human autoimmune diseases has been investigated intensively by several groups over the past decade, but as yet no clear consensus view has emerged and the topic remains controversial. The investigations in man were stimulated initially by reports of ERV expression in a number of mouse strains that are genetically predisposed to autoimmune disease.¹

Endogenous retroviral elements in the human genome are stretches of DNA that are related to, and possess significant sequence homology with, infectious exogenous retroviruses such as human T-cell leukaemia virus (HTLV). There are a large number of different endogenous retroviral elements, often present in multiple copies, and altogether they are estimated to constitute as much as 8% of the human genome.² The vast majority of these elements are defective, however, due to the presence of accumulated mutations including deletions and stop codons, and are therefore unable to encode viable infectious retroviral particles. Nevertheless, a small subset does possess intact open reading frames; therefore, these elements have the potential to encode, and even express, certain functional retroviral-like proteins. The origin of endogenous retroviral sequences is uncertain, but it is generally thought that they represent the remnants of ancestral retroviral infections that have become fixed within germline DNA and are therefore inherited in a Mendelian fashion.

Several human endogenous retroviruses (HERVs) have been claimed as potential aetiological agents for a variety of malignancies, autoimmune diseases and neurological disorders.³ In some cases, such as the proposed involvement of a human endogenous retroviral superantigen in type 1 diabetes,⁴ the

findings have not proved reproducible. In many other cases the evidence remains incomplete or has yet to be independently confirmed. Regarding the possible role of ERVs in MS, there has been considerable work on ERV3 and HRES-1, discussed in detail in the accompanying review by Jørgen Clausen (see pages 22–28 of this issue). In addition, Perron and colleagues have published on the association between MS and HERV-W.⁵

An extremely unusual HERV, HERV-W encodes a protein with a known function. The envelope protein of this ERV is thought to mediate fusion of cytotrophoblasts and is therefore likely to play an essential role in the formation of the human placenta.² HERV-W was originally discovered during studies of retroviral particles associated with MS, and was initially designated MS-associated retrovirus, MSRV.⁶ The detection of virion-associated MSRV RNA in the serum of patients with MS⁷ has been independently confirmed in Sardinia, an island with an unusually high incidence of the disease.⁸ Further investigations in Sardinian patients have revealed that MSRV expression may also be associated with other inflammatory neurological diseases⁹ and that, in MS, the detection of MSRV RNA in cerebrospinal fluid may be a prognostic factor correlated with disability progression.¹⁰ HERV-W has also recently been implicated in the development of schizophrenia but this finding has yet to be reproduced by other groups.¹¹

If future studies confirm the association between MS and HERV-W, ERV-3, HRES-1 or any other HERV,¹² the question of potential pathogenic mechanisms will become central. In the case of HERV-W, it has been demonstrated that the envelope protein acts as a superantigen* (referred to as an autoantigen in Clausen's paper**). Researchers have

proposed that this could trigger or contribute to the autoimmune dysregulation seen in MS.¹³ Evidence suggesting that HERV-W might be associated with a novel gliotoxin has also been presented;¹⁴ however, it is important to recognize that for HERVs generally, these potential pathogenic mechanisms are currently in the realm of speculation. It remains possible that HERV expression simply represents an epiphenomenon and that the associations may prove to be casual rather than causal. Although research in this area has revealed many intriguing findings, much more work is needed before any truly coherent picture can be expected to emerge.

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*Antigens occurring in bacterial or viruses which are able to activate T cells non-specifically (according to Dorland's Medical Dictionary, WB Saunders Company).

A normal tissue constituent which is the target of an immune response (according to Dorland's Medical Dictionary, WB Saunders Company). **Please check that you are happy with these definitions.