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Advance in Brief

MSRV/HERV-W/syncytin and its linkage to multiple sclerosis: The usablity and the hazard of a human endogenous retrovirus

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Syncytin is a protein specifically expressed in human placenta during early pregnancy, and found to be responsible for fusion of fetal trophoblast cells into the placental multinucleated syncytiotrophoblast layer, hence allowing embryo implantation (1–2). Syncytin is thought to be encoded by the ERVWE1 locus, the *env* gene of a replication-incompetent human endogenous retrovirus (HERV) belonging to the HERV-W family, located on chromosome 7q21-22 (3–5), in a region of candidate genetic susceptibility for multiple sclerosis (6). As in other HERV families (7), HERV-W is present in the human haploid genome in multiple copies, the majority of them highly defective, but complete proviruses have also been described, for a proposed total of 311 copies (more or less complete proviruses and pseudogenes), plus additional 343 solitary HERV-W long terminal repeats (LTRs, 8). HERV-W components infected our ancestors around 30 millions years ago (4) and have been transmitted along time through integration in the germ line. Placenta is an organ where endogenous retrovirus expression might be expected, since detection of retroviral particles by electron microscopy in normal human placentas is an old finding (9). As for possible HERV functions, apart from syncytiotrophoblast formation and the powerful transcriptional regulatory properties of HERV LTRs, it has been hypothesized that HERV *env* expression in pregnancy might play a role in suppressing the maternal immune response against the fetal allograft (10–11).

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These findings highlight how the host can subvert the usual situation in which viruses use cellular genes to obtain a selective advantage for their own replication or persistence within the host. In the case of syncytin, the host uses the presence of ancestrally transmitted foreign genomes, to serve a pivotal physiological function during pregnancy (12).

The founder member of the HERV-W family is the multiple sclerosis-associated retrovirus (MSRV, 13–14), a presumably complete virus, since it is able to form extracellular, infectious virions. The HERV-W family itself was discovered using MSRV cDNA probes for its identification and characterization (3), and syncytin is highly related to MSRV env (94% homology at the RNA level).

The first evidence on the relationship of MS to MSRV (at that time called LM7, after the leptomeningeal producer cells) was published in 1989 by Perron and colleagues (13), and to date the presence of MSRV virions in MS patients has been detected by several groups, including ourselves, in the blood and the cerebrospinal fluid (CSF, 14–18). On the other hand, extracellular virus is detectable also in body fluids of patients with neuroinflammatory diseases (16–18), and in schizophrenia (a neuropsychiatric disease linked, as MS, to genetic and environmental factors, 19), but in patients without MS the frequency of MSRV detection is much lower. Extracellular MSRV is present also in around 10% of the healthy population (16–17). In a population at high MS risk, such as that of the island of Sardinia, Dolei *et al* detected the extracellular form of MSRV in the plasma of 100% of patients with active MS, and presence of MSRV particles in CSF was found to parallel temporal and clinical progression of the disease (17). Notably, follow up re-examinations of the same patients by Sotgiu *et al* revealed that patients with MSRV-free CSF had a stable MS course, whereas those with MSRV-positive CSF disclosed a more severe, treatment-requiring disease, suggesting

that MSRV presence in CSF could be considered as a negative prognostic marker (20).

Studies carried out with MSRV preparations or with its env protein showed interesting features, that might account for a possible pathogenic role of MSRV in human disease. *In vitro*, MSRV exerted fusogenic properties on cultured cells (21). A gliotoxic (apoptotic) MSRV-associated effect on glial cells, but not on neurones was described by Menard *et al* (22), and virionic MSRV env protein was found by Perron *et al*. to display pro-inflammatory and superantigenic effects on CD4-positive T-cells (23). A positive feedback loop on MSRV expression was observed by Serra *et al* in peripheral blood mononuclear cells (PBMC) from MSRV-positive individuals, that spontaneously release MSRV in culture, which can be upregulated by exposure to the MS detrimental interferonγ and TNFα cytokines, while interferonβ, a therapeutic agent for MS, is a powerful inhibitor of MSRV release (24). Surprisingly, PBMC from MSRV-negative individuals did not express or release MSRV in culture, neither spontaneously nor after treatments; this is unexpected, since, if MSRV were an ubiquitous endogenous virus, one would expect that mitogens and/or cytokines would induce its expression, since the cells would then contain the sequence at the DNA level. These findings suggested the possibility that MSRV might be an exogenous member of the HERV-W family (24), in line with the hypothesis that HERV-W genomes might be copackaged in extracellular particles, produced by replication-competent or transcomplemented HERV-W copies or by an exogenous member of the HERV-W family (25).

The existence of a T-cell-mediated immunopathogenicity was confirmed *in vivo* by Firouzi *et al* (23) with cell-free MSRV virions injected into SCID mice humanized with human lymphoid grafts caused T-lymphocyte-dependent neuropathology (25). A recent paper by Antony *et al* (26) extended these observations by reporting very interesting syncytin-induced activities. Syncytin was found to be upregulated in glial cells within lesions of MS patients, and from *in vitro* and *in vivo* data obtained by using a syncytin-containing viral construct, it was concluded that syncytin is highly suspected to be responsible for at least some MS pathogenic phenomena. Studies from the same group had already shown the expression of several HERVs in inflammatory brain diseases, including MS, and the increase of HERV expression in monocytes with compounds that influence cellular activity; they suggested that increased expression of these viruses is a consequence of increased immune activity rather than causative of distinct diseases (27). Syncytin's proinflammatory properties in the nervous system are strikingly concordant with the previously reported findings on MSRV and MS, and strengthen the possibility of a role in human disease for HERV-W, which may be a target for therapeutic intervention.

In line with these findings, Rolland *et al* (25), recently reported that PBMC stimulation by MSRV env protein induced production of pro-inflammatory cytokines such as TNF-α, IL-6 and interferon-γ, with divergent reactivity between cells from MS patients and controls; in most patients the overproduction of IL-6 and IL-12p40 was found to correlate with disease severity (28). Altogether these findings suggest that MSRV env protein may induce an abnormal cytokine secretion, thus contributing to MS inflammatory processes.

To the above evidences linking MSRV/HERV-W/syncytin to MS, must be added a complex interplay that might occur between the HERV-Ws and other viruses horizontally or vertically transmitted to humans. Interestingly, also the HERV-H family is expressed in cells of MS patients (29), and a HERV-H proviral copy is inserted in chromosome 7q21-22 region, at about 1 kilobase from HERV-W. Another HERV-W provirus is located within a T-cell α–δ receptor (TCR) gene in chromosome 14q11.2 region. These two regions correspond to genetic loci potentially associated with 'multigenic' susceptibility to MS and TCR α chain genetic determinants have been reported to be statistically associated with MS. Perron *et al* (19) hypothesize a role for infectious agents triggering a co-activation of the chromosome 7q HERV tandem, in a pathogenic 'chain-reaction' in MS involving several step-specific pathogenic 'agents' and 'products' somewhat interacting with particular genetic elements (30).

Among other (exogenous) viruses suggested as possible pathogenic factors in MS, are particularly the herpesviruses, since they can be neurotropic, become latent and can be reactivated. The human herpes virus-6 (HHV-6) is one of the most probable candidates, and a elegant meta-analysis by Moore and Wolfson (31) indicates that the available reports provide some support for a relationship between HHV-6 and MS, but none able to show a causative relationship. Nevertheless, herpesviruses might activate HERV expression in patients, since MSRV expression can be transactivated *in vitro* by herpesviruses (32–33), and simultaneous presence of HERV and herpesvirus antigens has pronounced synergistic effects on cell-mediated immune responses (34).

In conclusion, although the role of MSRV/HERV-W/syncytin still remains to be completely understood, there experimental evidence linking the MSRV retrovirus and its HERV-W family to MS disease, and multiple parallelisms exist between the presence and regulation of MSRV production and the presence and behavior of MS disease. In addition, there is the possibility that MSRV might in the future be recognized as an exogenous component of the HERV-W family of human endogenous retroviruses.

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