MSRV, Syncytin and the role of endogenous retroviral proteins in demyelination

Letter to the Editor:

Sir - A major study on the pathogenesis of multiple sclerosis was published in the October issue of Nature Neuroscience accompanied by a flurry of media reports. The study by Antony and colleagues[1] describes the potential role of syncytin, a human endogenous retroviral glycoprotein, in the process of demyelination. We were impressed by the quality of the biochemical, immunohistological and neurobehavioural data presented by Antony et al[1] in support of the 'retroviral hypothesis' but dismayed to see that the authors had omitted to mention or reference the highly relevant and extensive pre-existing literature of at least thirty papers linking multiple sclerosis with this retroviral family.[2-10]

Syncytin (enverin) is the envelope glycoprotein of a defective provirus (ERVWE1) belonging to the human endogenous retrovirus HERV-W family, originally defined by its founder member the multiple sclerosis associated retrovirus, MSRV.[2] By omitting to mention explicitly that syncytin is closely related to the MSRV envelope protein, the authors give the impression that the observed association with multiple sclerosis is a novel finding.

The earliest paper connecting MSRV (referred to as LM7 prior to 1997) and multiple sclerosis was published in 1989[3] and since that time studies from many countries including France[4,5,6], England[7,8], Italy[9] and Poland[10] have confirmed the association. MSRV and extracellular virion-associated MSRV-RNA have been isolated repeatedly from leptomeningeal, choroid plexus and Epstein–Barr virus-immortalized B cells of multiple sclerosis patients and also from their blood and cerebrospinal fluid; in CSF the detection of MSRV was found to parallel clinical progression of the disease.[9] Intriguingly, a gliotoxin which destroys oligodendrocytes but not neurones has been identified in association with MSRV in CSF and monocyte/macrophage culture supernatants from MS patients.[5] This gliotoxic activity may or may not be related to the oligodendrocyte destroying syncytin-induced cytotoxic conditioned medium described by Antony et al.[1]

It is also relevant to note here that the MSRV envelope glycoprotein, either recombinant or virion-derived, displays superantigen properties[4] associated with the production of pro-inflammatory cytokines. Furthermore, the potent pro-inflammatory properties and T cell-mediated immunopathogenic potential of MSRV virions have been dramatically demonstrated *in vivo* using a humanized SCID mouse model.[6]

We believe that the excellent work of Antony and colleagues[1] represents a significant advance in our understanding and confirms the importance of this rapidly developing field in human pathobiology. We trust that this letter provides the essential conceptual background to the work and serves to put the new findings into their appropriate historical context.

References

1. Antony JM, van Marle G, Opii W, et al. Human endogenous retrovirus glycoprotein-mediated induction of redox reactants causes oligodendrocyte death and demyelination. *Nat Neurosci* 2004; **7:** 1088-95.
2. Komurian-Pradel F, Paranhos-Baccala G, Bedin F, et al. Molecular cloning and characterization of MSRV-related sequences associated with retrovirus-like particles. *Virology* 1999; **260:** 1-9.
3. Perron H, Geny C, Laurent A, et al. Leptomeningeal cell line from multiple sclerosis with reverse transcriptase activity and viral particles. *Res Virol* 1989; **140:** 551-61.
4. Perron H, Jouvin-Marche E, Michel M, et al. Multiple sclerosis retrovirus particles and recombinant envelope trigger an abnormal immune response in vitro, by inducing polyclonal Vbeta16 T-lymphocyte activation. *Virology* 2001; **287:** 321-32.
5. Menard A, Amouri R, Michel M, et al. Gliotoxicity, reverse transcriptase activity and retroviral RNA in monocyte/macrophage culture supernatants from patients with multiple sclerosis. *FEBS Lett* 1997; **413:** 477-85.
6. Firouzi R, Rolland A, Michel M, et al. Multiple sclerosis-associated retrovirus particles cause T lymphocyte-dependent death with brain hemorrhage in humanized SCID mice model. *J Neurovirol* 2003; **9:** 79-93.
7. Perron H, Garson JA, Bedin F, et al. Molecular identification of a novel retrovirus repeatedly isolated from patients with multiple sclerosis. The Collaborative Research Group on Multiple Sclerosis. *Proc Natl Acad Sci USA*. 1997; **94:** 7583-8.
8. Garson JA, Tuke PW, Giraud P, Paranhos-Baccala G, Perron H. Detection of virion-associated MSRV-RNA in serum of patients with multiple sclerosis. *Lancet* 1998; **351:** 33.
9. Dolei A, Serra C, Mameli G, et al. Multiple sclerosis-associated retrovirus (MSRV) in Sardinian MS patients. *Neurology* 2002; **58:** 471-3.
10. Nowak J, Januszkiewicz D, Pernak M, et al. Multiple sclerosis-associated virus-related pol sequences found both in multiple sclerosis and healthy donors are more frequently expressed in multiple sclerosis patients. *J Neurovirol* 2003; **9:** 112-7.

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