The possible role of human endogenous retroviruses and herpes viruses in the pathogenesis of multiple sclerosis

Tomasz Brudek, MSc

This PhD dissertation was accepted by the Faculty of Health Sciences, University of Aarhus, and defended June 29, 2007.

Officiels opponents: Klemens Ruprecht, Bent Faber Vestergaard, and Jacob Giehm Mikkelsen.

Tutors: Anné Møller-Larsen, Per Höllsberg, and Finn Skou Pedersen.

Correspondence: Tomasz Brudek, Institute of Medical Microbiology and Immunology, Bartholin Building, Aarhus Universitet, 8000 Aarhus, Denmark.

E-mail: tb@microbiology.au.dk

Dan Med Bull 2007;54:244

ABSTRACT

Multiple sclerosis (MS) is a complex, inflammatory, demyelinating disease of the central nervous system (CNS), occurring mainly in young adults. The leading hypothesis assumes that MS occurs as a result of exposition of genetically susceptible individuals to an unknown environmental agent(s). Several herpes viruses (HSV-1, HHV-6, VZV and EBV) together with human endogenous retroviruses (HERV-H and HERV-W) have been associated with MS for years, but none of the associations are conclusive. Herpes viruses are capable of HERV activation, and both virus groups are known to interact with each other in several ways.

This PhD dissertation presents further evidence of an association of HERVs and herpesviruses with MS. Inactivated (non-infectious) herpesviruses are capable of inducing reverse transcriptase (RT) activity, a hallmark for retrovirus activation. The observed RT activity is significantly higher in MS patients vs. healthy controls, and the reactivation is initiated earlier in the patients. Further, the consequential concomitant presence of HERV and herpesvirus antigens induces synergistic lymphocyte proliferation, resulting in a significantly higher INF-γ production in peripheral lymphocytes from MS patients. Additionally, this production correlates with the synergistic cell proliferations, whereas such correlation cannot be found in controls. The findings suggest that an induced imbalance in Th1/Th2 responses, favoring inflammatory reactions in MS patients, may lead to progression of the disease.

Increased presence of activated HERVs in MS patients has been demonstrated by flow cytometric evaluation of cell membrane expression of HERV-H and HERV-W Env on lymphocytes from patients with active and stable MS in comparison with healthy individuals. Results show significantly increased quantities of HERV-H Env and HERV-W Env together with an increased number of B cells in patients with active MS. B cells and monocytes are the only cell types expressing these envelope proteins. Moreover, active MS patients display high antibody activity towards the two envelope proteins.

These experiments entail additional evidence for the occurrence of activated HERVs in MS patients, especially in those with active MS, and the results further substantiate the theory that herpes viruses and HERVs may play a role in the pathogenesis of MS.