HERV-W/MSRV/Syncytin-1 activation and multiple sclerosis triggers: the EBV/MSRV dual virus hypothesis

Dolei A, Serra C, Mameli G, Poddighe L, Mei A, Uleri E. Department of Biomedical Sciences, University of Sassari, Sassari, Italy

The immunopathogenic phenomena leading to multiple sclerosis (MS) are thought to be triggered by an environmental (viral?) factor operating on a predisposing genetic background. The most consistent studies for a potential virus involvement in MS exist for the Epstein Barr virus (EBV), and for two members of the W family of human endogenous retroviruses (HERV-W): the MSRV element (MS-associated retrovirus), able to form extracellular virions, and Syncytin-1, the env product of the ERVW-1 element, located on human chromosome 7q21-22, that has inactivating mutations in the gag and pol genes and is not able to form virus like particles.

The ascertained links between EBV and MS are history of late primary infection, possibly leading to infectious mononucleosis (IM), and high titers of pre-onset IgG against EBV nuclear antigens (anti-EBNA IgG). During MS, there is no evidence of MS-specific EBV expression, while a continuous expression of HERV-Ws occurs, paralleling disease behaviour.

We found repeatedly extracellular HERV-W/MSRV and MSRV-specific mRNA sequences in MS patients (in blood, spinal fluid, and brain samples), and MRSV presence/load strikingly paralleled MS stages and active/remission phases, as well as therapy outcome. By selective PCR assays, we found that the DNA of MS patients have increased MSRV*env* copies, while unchanged Syncytin-1 copies with respect to controls. Presence of MSRV in the spinal fluid predicted worst MS progression, up to ten years in advance.

In search of EBV/HERV-W/MSRV/syncytin-1 links, we studied *in vitro* the expression of HERV-W/MSRV/syncytin-1, with/without exposure to EBV or to EBV glycoprotein350 (EBVgp350), on PBMC from healthy volunteers and MS patients, and on astrocytes, by discriminatory *env*-specific RT-PCR assays, and by flow cytometry. we verified whether HERV-W might be activated *in vivo*, in hospitalized young adults with IM symptoms, and healthy controls, that were either EBV-negative or latently EBV-infected with/without high titers of anti-EBNA-1 IgG.

The results show that *in vitro* EBV activates the potentially immunopathogenic and neuropathogenic HERV-W/MSRV/syncytin-1, in cells deriving from blood and brain. *In vivo* HERV-W/MSRV activation is higher in blood cells of IM patients, and in healthy controls with high anti-EBNA-1 IgG titers. Thus, the data indicate that the two main links between EBV and MS (IM and high anti-EBNA-1-IgG titers) are paralleled by activation of the potentially neuropathogenic HERV-W/MSRV.

Considering our data and those of the literature on MS pathogenesis, we postulate the possibility for EBV of an initial trigger of future MS, years later, and for MSRV of a direct role of effector of neurotoxicity during MS.