Epstein–Barr virus and multiple sclerosis: causation or association?

"Multiple sclerosis etiology remains elusive; however, both genetic and environmental factors are likely to play important roles in disease pathogenesis"

Kristina Kakalacheva[1] & Manuel Comabella[†]

[1]Institute of Experimental Immunology, Clinical Immunology & Immunotherapy, University of Zurich, Zürich, Switzerland

[†]Author for correspondence: Unitat de Neuroimmunologia Clínica, CEM-Cat. Edif. EUI 2ª planta, Hospital Universitari Vall d'Hebron. Pg. Vall d'Hebron 119–129 08035 Barcelona, Spain ■ Tel.: +34 932 746 834 ■ Fax: +34 932 746 084 ■ mcomabel@ir.vhebron.net

Multiple sclerosis (MS) is a chronic inflammatory demyelinating autoimmune disease of the CNS that leads to significant neurological disability in young adults. From a clinical standpoint, MS patients may follow relapsing-remitting courses, with or without associated progression, or essentially progressive courses. Patients who have had only a single bout of disease, but are not yet diagnosed with MS, are referred to as clinically isolated syndromes (CISs), which is considered the earliest manifestation of the disease. MS etiology remains elusive; however, both genetic and environmental factors are likely to play important roles in disease pathogenesis. One of the leading infectious agents that is being discussed as an etiological factor in MS is the EBV. EBV is a human herpesvirus that persists within memory B cells for the life of the host, modulating its immune system.

The most compelling evidence linking EBV infection to MS comes from epidemiological studies, including evidence that nearly all MS patients are seropositive for EBV, and the risk of MS is two- to three-fold greater among individuals with history of infectious mononucleosis (i.e., infection occurred during adolescence and young adulthood) than in individuals who acquired EBV earlier in life [1]. The MS risk is approximatley 20-fold higher when comparisons are made between individuals with symptomatic primary infection and subjects who are negative for EBV [1]. In addition, individuals who will develop MS present increased IgG humoral responses against the EBV nuclear antigen (EBNA) complex and EBNA1, antigens that are expressed during latent infection, years before the onset of MS [2].

Experimental studies also support a role for EBV in the etiopathogenesis of MS. $CD8^+$ T lymphocytes are important for controlling reactivation of latent herpes virus infections. Altered frequencies of a number of EBV-specific $CD8^+$ T cells have been observed in MS patients compared with healthy donors, while no such differences were detected for human cytomegalovirus, another ubiquitous viral agent [3]. Since the altered frequencies were present only for certain EBV epitopes, it is tempting to speculate that crossreactivity could be a potential mechanism of virus-induced autoimmunity.

$CD4^+$ T cells specific for EBNA1 are known to play a crucial role in EBV immune control in healthy virus carriers. EBNA1-specific $CD4^+$ T-cell responses were found to be significantly elevated in MS patients compared with demographically matched EBV-positive healthy controls who also carried the MS-associated HLA-DR alleles [4]. Moreover, while the healthy-donor T-cell responses preferentially recognized epitopes within the central part of the EBNA1 C-terminus, the MS patients presented more diversified T-cell epitope recognition directed against the entire sequence of the domain. These findings indicate that broadened epitope recognition, rather than a dominant response towards a particular region, contributes to the increased EBNA1-specific cellular activity. Interestingly, a subset of EBNA1-specific T cells was found to preferentially recognize myelin antigens, but not other autoantigens that are not associated with MS [5], suggesting that EBNA1-specific T cells could be actively involved in MS immunopathology by cross-reacting with myelin in a process known as molecular mimicry.

Immune responses to EBV appear to be dysregulated in the early phases of MS. In this context, EBV-specific $CD8^+$ T-cell responses were

Editorial
Future Microbiology

Keywords
■ Epstein-Barr virus ■ molecular mimicry ■ multiple sclerosis ■ virus-induced autoimmunity

future medicine part of fsg

found to be significantly elevated in patients with CIS compared with patients with relapsing-remitting and progressive forms of MS and healthy controls [6]. Interestingly, EBNA1 antibody titers correlated with virus-specific CD8+ T-cell responses; however, the EBNA1-specific antibodies were increased, not only during the early stages of MS, but also in later phases of the disease [6]. In another study, EBNA1 IgG titers correlated with inflammatory disease activity, as measured by brain MRI in CIS patients who later converted to MS based on clinical criteria [7]. A more recent study observed not only increased EBNA1-specific IgG responses in CIS patients compared with healthy controls, but also augmented EBNA1 T-cell responses, while no such difference was observed for other EBV-encoded epitopes or control viruses [8]. Of note, elevated EBNA1-specific IgG responses predicted conversion to MS based on radiological criteria, and correlated with neurological disability during follow-up. Based on these findings, EBNA1-specific IgG titers have been proposed as a prognostic biomarker of the disease [8].

"Despite strong evidence supporting an association between EBV and multiple sclerosis, there are no unequivocal data in favor of a causative role for EBV in the pathogenesis of the disease."

Despite strong evidence supporting an association between EBV and MS, there are no unequivocal data in favor of a causative role for EBV in the pathogenesis of the disease. In this sense, there are several important questions that remain unanswered. Even though EBV is a ubiquitous virus that successfully infects more than 90% of the population worldwide, only a very small proportion of EBV-infected subjects will eventually develop MS. In this context, a synergic interaction between EBV infection and genetic factors, such as the presence of the HLA-DRB1*15:01 allele, has been reported, and may explain an increased risk for MS in a subgroup of EBV-infected individuals [9]. Assuming that a viral agent is implicated in disease etiopathogenesis, and considering that the CNS is the major target of the immune response in MS, one would expect to find the causal virus in the target organ. However, most studies have failed to identify EBV DNA or RNA in cerebrospinal fluid B cells and brain lesions from MS patients. Finally, the intrathecal synthesis of oligoclonal IgG is a characteristic feature of MS that is used in the diagnostic criteria of the disease. However, the specificity of these antibodies remains largely unknown, and studies investigating the intrathecal IgG responses against EBV in MS patients have resulted in divergent results.

The finding of considerable sequence polymorphism in EBV genes, such as *EBNA1*, whose encoded proteins, as discussed previously, are the main targets of the humoral and cellular immune responses observed in MS patients, certainly opens new scenarios in EBV-related MS research [10]. In this setting, high-throughput sequencing of EBV isolates from MS cases and well-matched healthy donors may help to identify EBV strains that are associated with stronger host immune dysregulation and, hence, increased risk for MS. However, studies investigating altered antiviral immune responses in individuals with autoimmune diseases should be interpreted with caution, since the autoimmune background can trigger variations in the way the immune systems responds to pathogens. Thus, altered antiviral immune responses might be the effect rather than the cause of autoimmunity [11].

Based on these observations, the answer to the question of whether EBV is directly involved in the pathophysiology of MS is not trivial, and must be addressed by further studies. In the meantime, the dilemma 'causation or association' in relation to the role of EBV in MS remains open.

Acknowledgements

We thank Jan D Lünemann (Institute of Experimental Immunology, University of Zurich, Switzerland) for critically reviewing this manuscript.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Bibliography

1. Thacker EL, Mirzaei F, Ascherio A: Infectious mononucleosis and risk for multiple sclerosis: a meta-analysis. *Ann. Neurol.* 59(3), 499–503 (2006).
2. Sundström P, Juto P, Wadell G *et al.*: An altered immune response to Epstein–Barr virus in multiple sclerosis: a prospective study. *Neurology* 62(12), 2277–2282 (2004).
3. Höllsberg P, Hansen HJ, Haahr S: Altered CD8+ T cell responses to selected Epstein–Barr virus immunodominant epitopes in patients with multiple sclerosis. *Clin. Exp. Immunol.* 132(1), 137–143 (2003).

4. Lünemann JD, Edwards N, Muraro P *et al.*: Increased frequency and broadened specificity of latent EBV nuclear antigen-1-specific T cells in multiple sclerosis. *Brain* 129(Pt 6), 1493–1506 (2006).
5. Lünemann JD, Jelcić I, Roberts S *et al.*: EBNA1-specific T cells from patients with multiple sclerosis cross react with myelin antigens and co-produce IFN-γ and IL-2. *J. Exp. Med.* 205(8), 1763–1773 (2008).
6. Jilek S, Schluep M, Meylan P *et al.*: Strong EBV-specific $CD8^+$ T-cell response in patients with early multiple sclerosis. *Brain* 131(Pt 7), 1712–1721 (2008).
7. Farrell RA, Antony D, Wall GR *et al.*: Humoral immune response to EBV in multiple sclerosis is associated with disease activity on MRI. *Neurology* 73(1) 32–38 (2009).
8. Lünemann JD, Tintoré M, Messmer B *et al.*: Elevated Epstein–Barr virus-encoded nuclear antigen-1 immune responses predict conversion to multiple sclerosis, *Ann. Neurol.* 67(2), 159–169 (2010).
9. Nielsen TR, Rostgaard K, Askling J *et al.*: Effects of infectious mononucleosis and HLA-DRB1*15 in multiple sclerosis. *Mult. Scler.* 15(4), 431–436 (2009).
10. Brennan RM, Burrows JM, Bell MJ: Strains of Epstein–Barr virus infecting multiple sclerosis patients. *Mult. Scler.* 16(6), 643–651 (2010).
11. Münz C, Lünemann JD, Getts MT, Miller SD: Antiviral immune responses: triggers of or triggered by autoimmunity? *Nat. Rev. Immunol.* 9(4), 246–258 (2009).