EPSTEIN-BARR VIRUS AS A CAUSAL AGENT FOR MULTIPLE SCLEROSIS

Universitat Autònoma de Barcelona
Bibliographic Review

Núria Golf Guerrero
Microbiology Degree
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Objectives & methodology

The main objective is to explore the link between Epstein-Barr virus (EBV) and multiple sclerosis (MS) and how the virus may be contributing to the disease. The search engines used were PubMed and the UAB library catalogue with keywords: “Epstein-Barr virus”, “multiple sclerosis”, “mimicry”, “EBNA1”, “autoreactive B cells”, “miRNA", from 2000-2023.

Introduction

Multiple sclerosis

MS is a chronic inflammatory autoimmune and demyelinating disease, with inflammation, gliosis and neural damage. The etiology is unknown, with many genetic and environmental factors proposed that may be linked.

Epstein-Barr virus

EBV establishes latency in B cells and possesses many immune evasion mechanisms. Immune control is essential to avoid EBV-related diseases, and it has been proposed as a causal agent for the disease.

Treatment

Therapies for MS include B-cell depleting monoclonal antibodies and antiviral drugs (IFN-β), indicating a possible link.

The link between EBV and MS

Bjornevik et al. studied data from 10 million US military personnel over 20 years and determined that **EBV infection increased 32-fold the risk for MS**, but not with other viruses.

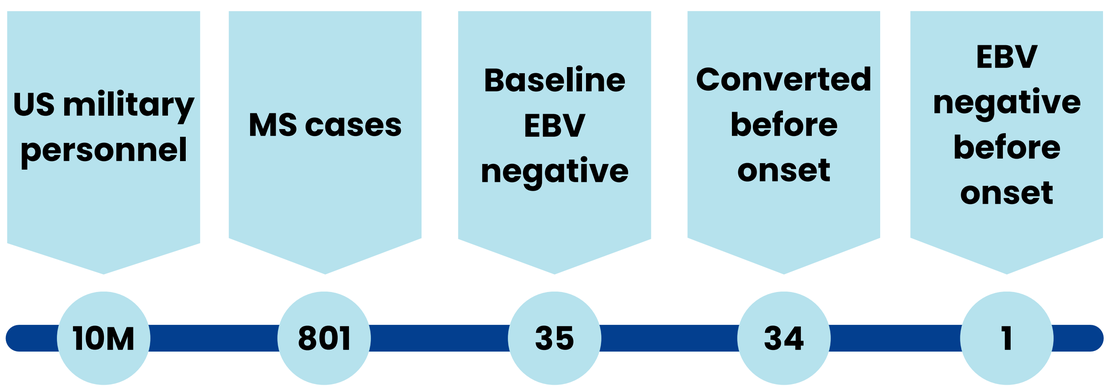

Figure 1. Results from “Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis, Bjornevik et al., 2022” reveal the high seroconversion rate for EBV in PwMS.

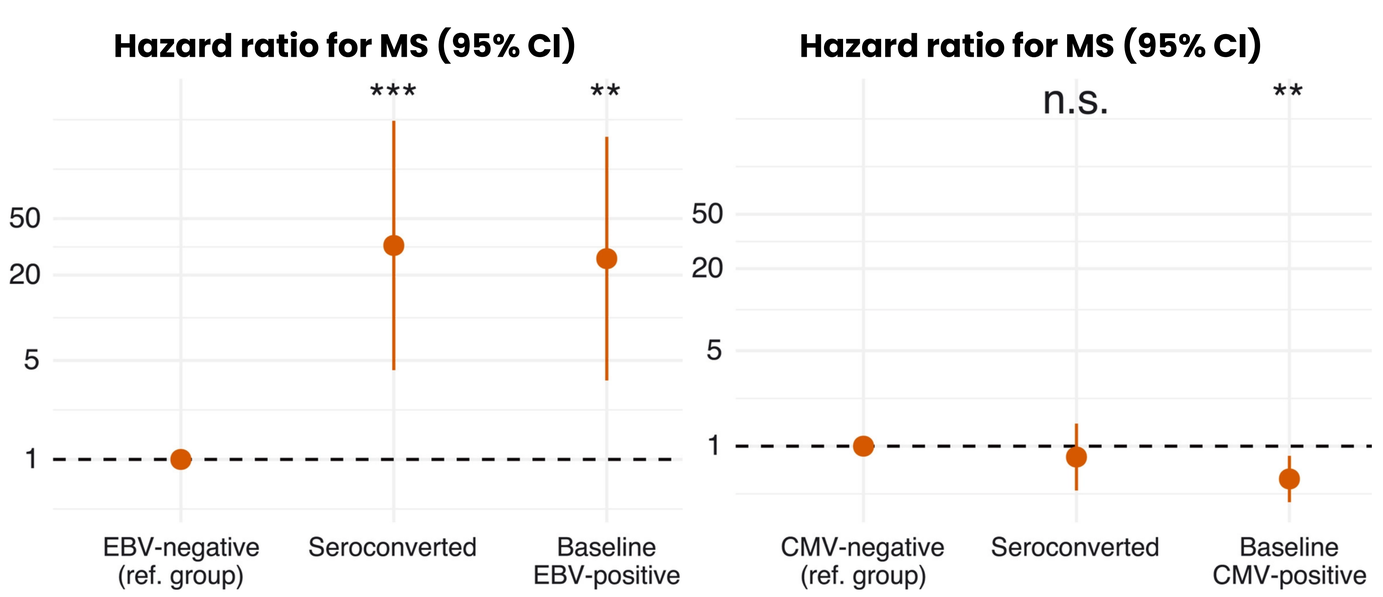

Figure 2. Representation of hazard ratio for MS after EBV and CMV seroconversion. EBV seroconversion greatly increases the risk while CMV seroconversion is slightly protective. Image from “Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis, Bjornevik et al., 2022”

Causative mechanisms

Molecular mimicry

High antibody titers for the short aa385-420 EBNA1 peptide and carriage of DRB1*15:01 increase MS risk 10-fold. This region overlaps many CNS proteins. EBNA1-specific CD4+ cells also cross-react with MBP and GlialCAM.

miRNAs

Exosomes and miRNAs have many proposed roles, like altering antigen presentation, immune evasion, and apoptosis.

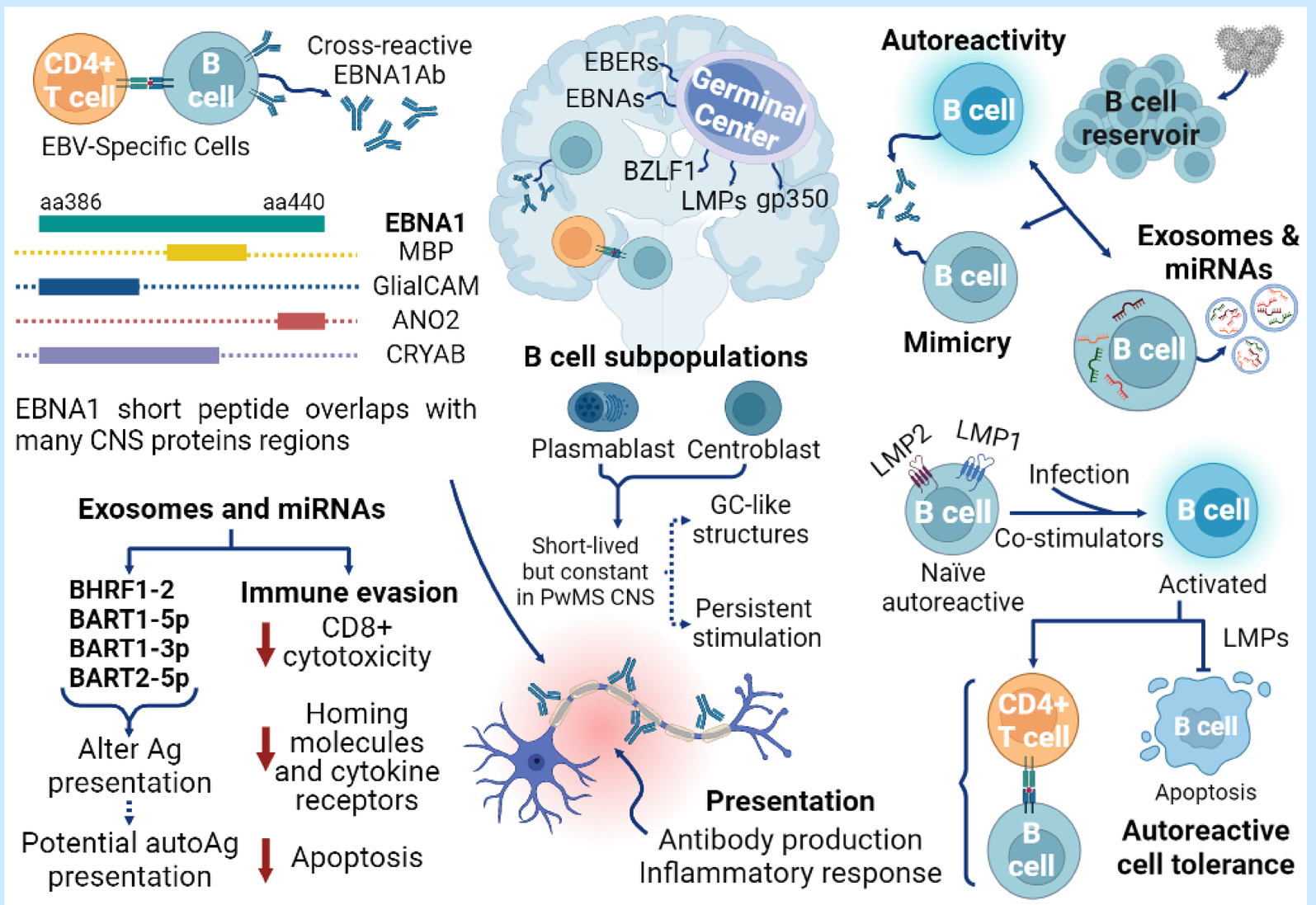

Figure 3. The main causative mechanisms proposed are molecular mimicry, autoreactivity, miRNAs and immune deregulation. Created in BioRender.

Immune deregulation

Mononucleosis creates a B cell reservoir, which may lead to bypassing of elimination in autoreactive B cells and persistence due to molecular mimicry.

Autoreactivity

Latency can lead to B-cell immortalization, promoting autoreactive T-cell survival. LMP1/2 mimic costimulators, bypassing T-cell elimination. EBNA2 also affects MS risk genes. Molecular mimicry could stimulate and sustain these cells.

The main effectors may be plasmablasts and centroblasts, implying CNS germinal centres and migration

The implications for these mechanisms are not yet known

Conclusions

Many advances have been made in the field of multiple sclerosis in recent years, nonetheless, its cause remains elusive. Many studies point to a combination of genetic and environmental factors that greatly increase the risk to develop the disease, and EBV infection is clearly linked, as has been demonstrated in epidemiological studies.

An increasing field of research is that of EBV mechanisms involved in MS pathogenesis, mainly molecular mimicry and immune deregulation in IM, that may sustain autoreactive cells. However, there are newer lines of research such as the implication of miRNAs and the correlation between MS risk genes and EBV. Furthering our knowledge could improve therapies for MS.

Bjornevik K, Cortese M, Healy BC, Kuhle J, Mina MJ, Leng Y, Elledge SJ, Niebuhr DW, Scher AI, Munger KL, et al. Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis. Science (2022) 375:296–301. doi: 10.1126/science.abj8222
Bjornevik K, Münz C, Cohen JI, Ascherio A. Epstein-Barr virus as a leading cause of multiple sclerosis: mechanisms and implications. Nat Rev Neurol (2023) doi: 10.1038/s41582-023-00775-5
Dyer Z, Tscharke D, Sutton I, Massey J. From bedside to bench: how existing therapies inform the relationship between Epstein–Barr virus and multiple sclerosis. Clin Transl Immunology (2023) 12:e1437. doi: 10.1002/cti2.1437
Hassani A, Khan G. Epstein-Barr Virus and miRNAs: Partners in Crime in the Pathogenesis of Multiple Sclerosis? Front Immunol (2019) 10:695. doi: 10.3389/fimmu.2019.00695
Soldan SS, Lieberman PM. Epstein–Barr virus and multiple sclerosis. Nat Rev Microbiol (2022) 21:51–64. doi: 10.1038/s41579-022-00770-5