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Unmasking the Enigma: Epstein-Barr Virus as a Primary Trigger in Multiple Sclerosis

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Abstract

Multiple Sclerosis (MS) is a chronic inflammatory disease, with Epstein-Barr Virus (EBV) infection as a primary cause. MS impacts about 2.8 million people globally, posing significant economic burden due to treatment costs and patient unemployment. The relationship between EBV and MS is substantiated by epidemiological, immunological and virological studies, including higher EBV load in MS patients, presence of EBV proteins in MS lesions and elevation of certain immunological markers post-EBV infection. The precise mechanism by which EBV triggers MS is unclear, but evidence points towards molecular mimicry, wherein the immune response against EBV may also inadvertently target neuronal tissue. Therapies focusing on this relationship are being developed, including EBV-specific cytotoxic T-cell therapy. Despite this, the exact mechanism of EBV-induced MS and the potential for prophylactic vaccines remain areas of ongoing investigation.

Keywords: EBV; MS; Molecular mimicry

Introduction

Multiple Sclerosis (MS) is a chronic inflammatory and demyelinating disease of the Central Nervous System (CNS) and is the leading cause of non-traumatic disability in young adults [1]. The incidence of MS is increasing and approximately 2.8 million people live with MS worldwide [2]. MS causes heavy economic burden due to the high cost of treatment, poor prospect and unemployment of the patients [3]. The symptom of MS is heterogeneous resulting from the various locations of lesions in CNS. The progression of MS is defined as three distinct clinical courses: Relapsing-Remitting MS (RRMS), Secondary Progressive MS (SPMS) and Primary Progressive MS (PPMS) [4]. In addition, Clinical Isolated Syndrome (CIS) also can progress to MS. Various genetic susceptibility and lifestyles and environmental factors contribute to the high risk of developing MS [5]. Pathogens infection is thought to trigger the onset of MS and Epstein-Barr Virus (EBV) infection is the primary cause of the development of MS among the different infectious agents [6].

EBV Infection Promote the Development of MS

EBV belongs to human herpesvirus gamma-subfamily and is also tightly associated with various malignancies [7]. After primary infection, EBV establishes life-long latency in host cells along with repeated reactivation. EBV has a 173 kb double-stranded DNA genome with approximately 100 protein-encoding genes. Lytic genes are classified as immediate early, early and late proteins based on their different expression time in virus life cycle [8]. Latent proteins, EBV nuclear antigens (EBNA-1,-2,-3A,-3B,-3C and -LP) and latent membrane proteins (LMP-1, -2A and -2B) contribute to B cell transformation and tumorigenesis [9].

EBV primary infection in young adults often causes Infectious Mononucleosis (IM), which increases the risk of the development of MS [10]. Increased EBV load was detected in saliva from pediatric MS patients [11]. Expression of EBV latent proteins (EBNA-3A, LMP-2A and LMP) and lytic protein (BZLF-1 and gp350) were detected in inflammatory MS brain lesions [12-16]. Besides, it is reported that the increase of anti-EBNA1 IgG titers in MS patients is correlated with disease progression and CIS patients with elevated EBNA-1 IgG titers are more likely to convert to RRMS [17-20]. Increased EBNA-1-specific T cell response was observed in MS patients and lytic antigen-specific T cell response was also increased in active phase of MS [12,21]. In addition, Oligoclonal Bands (OCBs) specifically binding EBV EBNA-1 and BRRF2 were detected in Cerebrospinal Fluid (CSF) of MS patients [22,23]. Recently, a longitude epidemiological study based on a large cohort of more than 10 million US army personnel confirmed that the risk of MS increased 32-fold after EBV infection [6]. The concentration elevation of Serum Neurofilament Light chain (sNfl), a biomarker of neuroaxonal degeneration, occurred only after EBV infection [6]. The antibody response to other viral peptides except for EBV was similar in MS patients and controls [6]. Overall, EBV infection is required for the development of MS.

The Underlying Mechanism of MS Occurrence Induced by EBV

However, the precise mechanism of EBV infection causing MS remains unclear. EBV infected B cells and plasma cells bypassed with cytotoxic T cells were detected in MS lesions in CNS [13,14,24,25]. EBV could immortalize the naive auto-reactive B cells and bypass the normal elimination process, which leads to the survival of autoreactive B cells [26]. The defective $CD8^+$ and $CD4^+$ T cell surveillance of EBV reactivation in MS patients may lead to the expansion of EBV latently infected B cells and subsequent diseases progress [27]. In addition, EBNA-2 participated the formation of transcription complexes at the MS risk loci [28]. Here, we will focus on the molecular mimicry contributed to the development of MS between EBV and autoantigens.

Multiple EBV proteins are recognized by cross-reactive T cells and antibodies targeting self-antigens. T cells in MS patients autoreactive to self-antigen Myelin Basic Protein (MBP), Anoctamin2 (ANO2), α-crystallin B chain (CRYAB) and Glial Cell Adhesion Molecule (GlialCAM) also cross-reacted with EBNA-1 [21,29-32]. Besides, brain homing $CD4^+$ T cells targeting self-antigen RASGRP2 cross-reacted with EBV lytic protein BHRF1 and BPLF1 [33]. Autoreactive antibodies in MS patients were also cross-reactive with EBNA-1. The epitopes of antibody cross-reactive to ANO2 and EBNA-1 was mapped at aa 140-149 of ANO2 and aa 431-440 of EBNA-1 [29]. Antibodies against peptides of aa 386-405, aa 411-426 and aa 385-420 of EBNA-1 cross-reacted with self-antigens GlialCAM, MBP and CRYAB, respectively [30,34,35]. The cross-reactive antibodies in CSF were evolved from ones only targeted viral proteins and the affinity maturation in brain changed the reactivity of the B cell clones, which led to the cross-reactivity of self-antigens [30]. Additionally, administration of peptides from EBNA-1 aggravated the condition of EAE mice [30].

Potent Viral-Specific Therapeutic for MS Treatment

Considering the key role of EBV infection in MS development, some studies developed viral-specific therapeutic for MS treatment. ATA188, an allogenic EBV CTL therapy, are tested in PPMS, SPMS patients and patients with a first clinical episode highly suggestive of MS (NCT03283826; NCT02912897). Patients received *in vitro* expanded autologous T cells targeting EBNA-1, LMP-1 and LMP-2A with strong reactivity showed clinical improvement [36]. Non-cyclic nucleoside analogue tenofovir alafenamide is tested as an add-on therapy of ocrelizumab in RRMS (NCT04880577). Furthermore, no prophylactic vaccine against EBV infection or MS is available until now. Induction potent and durable humoral and cellular immune response is essential for an ideal vaccine. Vaccines prevented IM in young adults may protect these individuals from development of MS in the future.

Conclusion

In reality, the exact mechanisms through which EBV initiates MS remain uncertain. Two main possibilities are often discussed: The direct action of EBV-infected cells or viral proteins in the Central Nervous System (CNS) and the indirect effects of peripheral inflammation induced by EBV. It's clear from multiple verified studies that EBV, as a precipitating factor, significantly influences MS progression. Consequently, EBV is a promising focus for the development of future treatments or preventative measures for MS.

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Competing Interests

The authors declare no competing interests.

Authors' Contributions

Ling Zhong, Qinjian Zhao and Xiao Zhang wrote the manuscript. All authors read and approved the final manuscript.

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