Epstein–Barr virus and multiple sclerosis: from associations to mechanisms to potential therapies

Jan D Lünemann, Christian Münz

Summary

Background **Epstein–Barr virus, a widespread herpesvirus that establishes lifelong latency after primary infection, has emerged in serological and epidemiological studies as a strong and consistent risk factor for multiple sclerosis.**

Recent developments **Emerging evidence indicates that Epstein–Barr virus can interact with several multiple sclerosis susceptibility loci to modify the transcriptional programmes and differentiation trajectories of B cells. Specifically, Epstein–Barr virus infection has been associated with the expansion of neuroinvasive, atypical B cells, which are enriched in inflamed CNS compartments in people with multiple sclerosis and exhibit a strong capacity to stimulate autoreactive T cells. Dysregulation of Epstein–Barr virus latency by B cells, together with subtle deficiencies in T-cell-mediated control of Epstein–Barr virus, might further amplify the effect of these B cell–T cell interactions and predispose individuals to multiple sclerosis.**

Where next? **These insights support the development of hypothesis-driven therapeutic strategies aimed at attenuating hyperactive autoimmune responses induced by Epstein–Barr virus and the autoimmune responses' access to the CNS. Strategies under investigation include prophylactic and therapeutic vaccines; allogeneic cytotoxic T lymphocytes specific for Epstein–Barr virus and designed to eliminate virus-infected cells; antibody-based and chimeric antigen receptor T-cell-based therapies targeting B-cell subsets induced by Epstein–Barr virus and migrate into the CNS; and conventional antiviral treatments. Together, these approaches might open new perspectives for both prevention and treatment of multiple sclerosis. Furthermore, they might help to clarify whether Epstein–Barr virus infection influences not only susceptibility to multiple sclerosis, but also disease activity and disability accrual after disease onset.**

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Division of Neurology, Department of Medicine, University of British Columbia, Vancouver, BC, Canada (Prof J D Lünemann); **Djavad Mowafaghian Centre for Brain Health, University of British Columbia, Vancouver, BC, Canada** (Prof J D Lünemann); **School of Biomedical Engineering, University of British Columbia, Vancouver, BC, Canada** (Prof J D Lünemann); **Department of Neurology, University Hospital Münster, Albert-Schweitzer-Campus 1, Münster, Germany** (Prof J D Lünemann MD); **Viral Immunobiology, Institute of Experimental Immunology, University of Zürich, Zurich, Switzerland** (Prof C Münz PhD)

Correspondence to:
Prof Jan D Lünemann, Division of Neurology, Department of Medicine, University of British Columbia, Vancouver, BC, V6T 1Z3, Canada
jan.lunemann@ubc.ca

Introduction

Infection with the human γ-herpesvirus Epstein–Barr virus, which persists lifelong in memory B cells, has been identified as a strong and consistent risk factor for the development of multiple sclerosis. This association was initially shown through comprehensive serological and epidemiological studies in which symptomatic primary infection (infectious mononucleosis) and an increase in antibody titres specific for Epstein–Barr virus in previously seronegative individuals were associated with a statistically significantly elevated risk of developing multiple sclerosis. More recently, research has begun to focus less on correlation-based analyses and more on mechanistic investigations, yielding crucial insights into the role of Epstein–Barr virus in multiple sclerosis pathogenesis. These advances are now starting to underpin hypothesis-driven therapeutic strategies aimed at reducing incidence of multiple sclerosis or limiting disability accumulation due to multiple sclerosis. In this Rapid Review, we report recent progress in understanding Epstein–Barr virus biology within the framework of the mechanisms of multiple sclerosis risk, immune function in people with multiple sclerosis, and Epstein–Barr virus as a potential trigger (eg, as a susceptibility factor or factor contributing to disease progression and disability accumulation after onset). We also examine emerging therapeutic approaches that target the virus with the aim of multiple sclerosis prevention and treatment.

Mechanisms linking Epstein–Barr virus infection to multiple sclerosis risk

A consistent major challenge in establishing a causal relationship between Epstein–Barr virus infection and the development—and potentially the progression—of multiple sclerosis has been the temporal gaps between the primary Epstein–Barr virus infection, the biological onset of multiple sclerosis, and the eventual emergence of clinical symptoms or neuroimaging features required for diagnosis. To address this challenge, Bjornevik and colleagues[1] analysed data from over 10 million young adults serving in the US military during a 20-year period. The study found a 32 times greater risk of multiple sclerosis among individuals who underwent Epstein–Barr virus seroconversion—a sensitive indicator of primary Epstein–Barr virus infection—than among people who remained seronegative. Development of multiple sclerosis in seronegative individuals has been described but seems to be rare. These findings strongly support the concept that Epstein–Barr virus infection is, in most cases, necessary for the development of multiple sclerosis and extend earlier serological and epidemiological observations from smaller cohorts. Such a strong association has not been observed for other herpesviruses, and inverse associations between infection with the

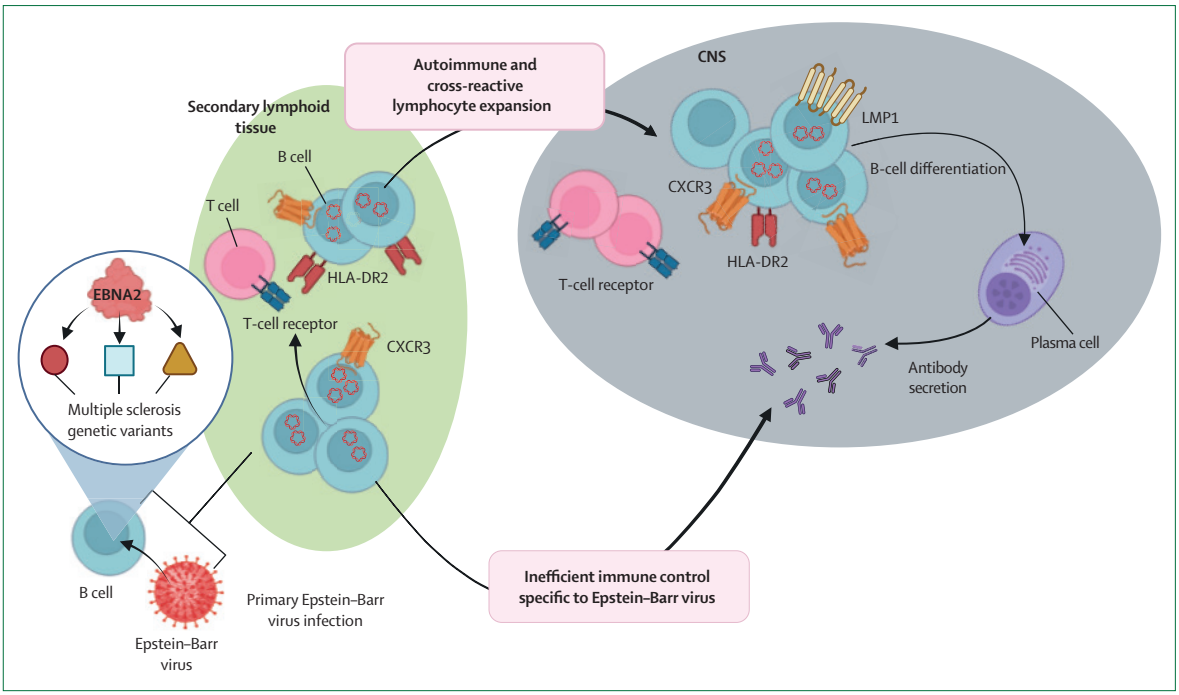

Figure: **Potential mechanisms linking Epstein–Barr virus infection to multiple sclerosis susceptibility and progression**
Epstein–Barr virus infects and persists in B cells, where it interacts via transcription factors such as the Epstein–Barr virus nuclear antigen 2 (EBNA2) with several multiple sclerosis genetic susceptibility loci identified by genome-wide association studies, thereby reprogramming transcriptional profiles and differentiation trajectories of B cells.[3-6] Epstein–Barr virus infection (depicted as a circular viral episome) promotes the expansion of neuroinvasive T-bet$^+$CXCR3$^+$ B cells (shown here as CXCR3$^+$ B cells), which are enriched in the CSF and post-mortem CNS tissue derived from people with multiple sclerosis. These B cells show a potent ability to stimulate autoreactive T cells through B cell–T cell interactions, mediated via B cells expressing HLA-DR2, the haplotype encoding the multiple sclerosis-associated allele *HLA-DRB1*1501*.[6-11] Such B cell–T cell interactions can occur in secondary lymphoid tissue and CNS compartments.[6-11] The CXCR3$^+$ B cells expressing HLADR2 move from one to the other. In the CNS, cross-reactive receptors from CNS-colonising B cells might facilitate the uptake and presentation to inflammatory T cells of antigens derived from Epstein–Barr virus and the CNS. Expression of the Epstein–Barr virus latent membrane protein 1 (LMP1) by B cells might enhance the survival and persistence of pro-inflammatory B cells infected with Epstein–Barr virus, and their differentiation into antibody-secreting plasma cells within the CNS.[12,13] Note that all B cells would express CXCR3, HLA-DR2, and LMP1, but not all these surface proteins are shown on all cells for simplicity. Additionally, dysregulation of Epstein–Barr virus latency within B cells, combined with subtle deficiencies in T-cell-mediated control of Epstein–Barr virus, might further amplify pathological interactions between B cells and T cells (such as release of pathogenic cytokines from the stimulated T cells) that are driven by Epstein–Barr virus in multiple sclerosis.[14-16] Figure created with Biorender.com.

human cytomegalovirus and the risk of developing multiple sclerosis have suggested potential protective effects.[2]

Multiple sclerosis susceptibility genetic variants and risk associated with Epstein–Barr virus

Epstein–Barr virus exposure alone cannot account for multiple sclerosis onset, as only a small fraction of virus carriers—approximately 0·1% of the 90% seropositive adults in mid-latitude regions—go on to develop the disease. This disparity highlights the complexity of the pathobiology of Epstein–Barr virus and multiple sclerosis, and underscores the contribution of additional factors (figure). Accumulating evidence indicates that the relationship between Epstein–Barr virus and multiple sclerosis is modulated by disease-associated genetic risk factors, most notably the MHC class II allele *HLA-DRB1*15:01*, which is encoded in the HLA-DR2 haplotype. Carriers of this allele, as well as individuals with multiple sclerosis, exhibit elevated titres of antibody to Epstein–Barr virus nuclear antigen (EBNA) 1, a consistent and reproducible serological marker of multiple sclerosis risk.[17,18] Importantly, *HLA-DRB1*15:01* and elevated EBNA1 antibody concentrations act synergistically to increase multiple sclerosis susceptibility.[17,18] The combined presence of *HLA-DRB1*15:01*, heightened reactivity to EBNA1 (amino acids 381–452), and autoantibodies directed against antigens associated with multiple sclerosis, such as glial cell adhesion molecule (glialCAM), the chloride channel anoctamin-2 (ANO2), and α-crystallin B (CRYAB), further increases risk for multiple sclerosis.[19] Antibodies against these antigens have been shown to cross-react with EBNA1.[19]

The prominent role of MHC class II alleles in amplifying Epstein–Barr virus associated risk for multiple sclerosis suggests that antiviral CD4$^+$ T cells might contribute to misrecognition of CNS antigens, implying that the effects of molecular mimicry extend beyond humoral immunity. EBNA1 is the Epstein–Barr virus antigen most consistently recognised by CD4$^+$ T cells.[20] EBNA1-specific CD4$^+$ T cells are increased in

frequency in patients with multiple sclerosis[21] and a subset of these cells also recognise CNS myelin antigens.[22] Thomas and colleagues identified cross-reactive CD4+ T cells recognising both EBNA1 and ANO2 in HLA-DR2–positive individuals with multiple sclerosis, and showed that immunisation with ANO2 and adoptive transfer of ANO2-reactive T cells exacerbate experimental autoimmune encephalomyelitis, a mouse model of multiple sclerosis.[23]

Experiments in humanised mice expressing *HLA-DRB1*15:01* in both haematopoietic and stromal compartments have provided mechanistic insight into how Epstein–Barr virus promotes differentiation of neuroinvasive B cells.[7] Epstein–Barr virus infection in these mice induces expansion of T-bet+CXCR3+ B cells that migrate towards leptomeningeal regions of the CNS via a CXCR3-dependent mechanism and recruit activated CD4+ and CD8+ T cells through expression of chemokines induced by Epstein–Barr virus. These T-bet+CXCR3+ B cells resemble atypical B cells—defined by expression of CD19, CD11c, T-bet, and variably CXCR3—which are abundant in people with autoimmune diseases and enriched in inflamed CNS regions in patients with multiple sclerosis.[8–10] Such cells efficiently present antigens to T cells, amplify type 1 helper T-cell responses via release of interferon-gamma, and are epigenetically programmed to interact with self-reactive T cells.[9] EBNA2 functions as a viral transcriptional regulator that binds multiple genetic risk loci associated with multiple sclerosis and modulates expression of risk genes in infected B cells.[3–5] By reprograming B-cell transcriptional and antigen-presentation pathways, Epstein–Barr virus infection also reshapes the repertoire of antigens presented by HLA-DR2 on B cells, supporting expansion of myelin-reactive T cells that are enriched in individuals with multiple sclerosis.[6] Survival of B cells infected with the virus within the CNS might be promoted by expression of the Epstein–Barr virus latent membrane protein 1 (LMP1).[12] Kim and colleagues have shown that murine B cells migrating into the CNS capture antigens directly from the parenchyma but undergo activation-induced cell death unless they receive survival signals from T cells via the CD40 ligand–CD40 receptor axis.[12] LMP1 acts as a constitutively active mimic of CD40, driving survival and proliferative signaling in B cells independently of T-cell help. B cells expressing LMP1 gain a survival advantage and promote formation of inflammatory lesions following CNS transfer. Notably, LMP1-expressing B cells have been detected, albeit at low frequency but at a 100 times greater concentration in lesions than in peripheral blood in people with multiple sclerosis.[12,13]

Together, these findings support the concept that Epstein–Barr virus infection of B cells can enhance the expression and possibly the effect of genetic variants associated with multiple sclerosis, induce migration of infected cells into the CNS, and promote presentation of encephalitogenic antigens via HLA-DR2. Cross-reactive B-cell receptors within the CNS and draining lymphoid tissues[11] might facilitate uptake and presentation to inflammatory T cells of antigens derived from both Epstein–Barr virus and the CNS. Targeting such B cells might hold therapeutic potential in multiple sclerosis.

Epstein–Barr virus-induced dysregulation of B-cell function in multiple sclerosis

Upon primary infection, Epstein–Barr virus establishes lifelong persistence within memory B cells in a state termed viral latency, characterised by highly restricted viral gene expression and actively maintained through host-driven epigenetic silencing mechanisms that keep most viral genes transcriptionally inactive. The host immune system, predominantly mediated by T lymphocytes, exerts stringent control over the virus, thereby preventing uncontrolled viral replication and the development of diseases associated with Epstein–Barr virus.[24,25]

Evidence is growing for both intrinsic dysregulation of B cells and impaired T cell–mediated control of Epstein–Barr virus latency in people with multiple sclerosis, resulting in increased viral transcriptional activity within infected B cells and a heightened propensity for reactivation associated with expression of so called lytic gene products that are required for infectious viral particle production.[14,15] Abnormal B-cell receptor signaling and transcriptional profiles, as observed in B cells infected with Epstein–Barr virus from patients with multiple sclerosis,[15] destabilise viral latency and can also promote plasma cell differentiation, which further facilitates Epstein–Barr virus lytic reactivation. Inefficient T-cell control is reported to be linked to the ability of some Epstein–Barr virus variants to upregulate HLA-E on infected cells, allowing them to evade cytotoxic lymphocyte-mediated elimination,[16] supporting the concept that some viral variants are more relevant to multiple sclerosis than others.[5,16] However, both B-cell-intrinsic dysregulation and Epstein–Barr virus immune evasion result in only marginally increased viral loads in individuals with multiple sclerosis compared with Epstein–Barr virus carriers without multiple sclersosis.[14,21]

Epstein–Barr virus infection is not specifically linked to multiple sclerosis, but is associated with a broad range of conditions, including malignancies and autoimmune disorders such as systemic lupus erythematosus. Its co-evolution and close interaction with the human adaptive immune system and its lifelong persistence might contribute to these multiple associations. However, the biological mechanisms through which Epstein–Barr virus influences risk for multiple sclerosis are possibly governed by pathways that are, at least in part, disease-specific and might involve interactions with genetic risk loci associated with multiple sclerosis, as aforementioned. Notably, elevated immune responses specific to Epstein–Barr virus—particularly against

EBNA1—are seen in both relapsing onset and primary progressive multiple sclerosis,[26] but not in people with related conditions such as aquaporin-4 IgG–positive neuromyelitis optica spectrum disorder or myelin oligodendrocyte glycoprotein antibody-associated disease.[16,27,28] Epstein–Barr virus exposure also correlates with risk for multiple sclerosis in paediatric populations,[29] and children with multiple sclerosis exhibit stronger EBNA1 antibody responses than do those with other demyelinating syndromes.[29,30]

Potential of Epstein–Barr virus vaccines to prevent multiple sclerosis

As understanding of the role of Epstein-Barr virus in multiple sclerosis has progressed beyond correlation-based studies, mechanistic insights have begun to inform the development of therapies targeted to Epstein–Barr virus for both the prevention and treatment of multiple sclerosis. Because a history of infectious mononucleosis—typically acquired during adolescence—is associated with an increased risk of developing multiple sclerosis, prophylactic Epstein–Barr virus vaccination during childhood could, theoretically, reduce multiple sclerosis incidence. Vaccines targeting Epstein–Barr virus envelope glycoproteins are in clinical development to prevent infectious mononucleosis.[31] For example, a recombinant gp350 protein vaccine (targeting the complement receptor 2 [CD21] and 1 [CD35] attachment receptor[32] that Epstein–Barr virus uses to infect B cells[33]) reduced incidence of infectious mononucleosis by 78% in adolescents but did not prevent Epstein–Barr virus infection,[33] probably by lowering viral load sufficiently to permit asymptomatic immune control. Building on this success, some vaccination studies have oligomerised gp350 to induce higher concentrations of neutralising antibodies to Epstein–Barr virus[34] and vaccination approaches have been extended to other glycoproteins to block both B cell and epithelial cell infection.[32,35,36] gH and gL mediate receptor binding and trigger gB-dependent membrane fusion,[37–40] and vaccines incorporating these glycoproteins elicit higher neutralising antibody titres than gp350 vaccines alone, effectively blocking Epstein–Barr virus infection in vitro[37,39] and in mice that carry components of a human immune system.[38,39] Stabilisation in its prefusion conformation, as is found on infectious Epstein–Barr virus particles, might further improve gB-mediated vaccination.[41] Even so, vaccines based on gH and gL elicited higher concentrations of neutralising antibodies than vaccines targeting gp350 and gp42 in mice and non-human primates;[37] vaccines based on a broader set of viral glycoproteins, namely, gp350, gp42, gH, and gL, are now being investigated in clinical trials. The US National Institutes of Health is conducting two early clinical trials with oligomerised gp350 and Matrix-M adjuvant in seropositive and seronegative young healthy adults (NCT04645147 and NCT05683834; table). An mRNA vaccine (mRNA-1189) encoding gH, gL, gp42, and gp220 (an alternatively spliced gp350 mRNA) is currently in phase 1/2 clinical testing (NCT05164094) in healthy individuals, and mRNA-1195 with additional undisclosed antigens is being tested in a phase 1 clinical trial in healthy individuals (NCT05831111). A phase 1 clinical trial in healthy adults with a nanoparticle displaying gH, gL, gp350, and gp42 is also ongoing (NCT06655324). All these trials aim to induce neutralising antibodies, whereas studies in individuals with inborn errors of immunity have revealed that cytotoxic $CD8^+$ T cells, and not antibodies, are crucial for immune control of Epstein–Barr virus.[43]

For prophylactic vaccines to induce protective T-cell responses, antigens other than viral envelope glycoproteins are needed. Expansion of $CD8^+$ T cells specific to latent Epstein–Barr virus antigens coincides with infectious mononucleosis convalescence. Among the latent nuclear proteins and latent membrane proteins, EBNA3A, EBNA3B, EBNA3C, and LMP2 are considered the antigens most frequently recognised by $CD8^+$ T cells, whereas EBNA1 is an antigen consistently recognised by $CD4^+$ T cells that stimulates T cells to maintain protective cytotoxic T-cell function.[24,25] Accordingly, a modified vaccinia virus Ankara (MVA) encoding EBNA1 and LMP2, a recombinant adenovirus 5 (AdV5) encoding EBNA1, and a polyepitope of LMP1 and LMP2 sequences have been explored as vaccine candidates.[44,45] These two vaccine formulations have been used in a heterologous adenovirus prime and MVA boost strategy to induce protective T-cell responses that control EBNA1 transgenic tumour growth in mice.[46] More recently, polyepitopes derived from EBNA1, EBNA3A, and EBNA3C, LMP2 and the lytic EBV antigens BZLF1, BRLF1, and BMLF1 plus gp350 vaccination have also elicited potent neutralising antibody and T-cell responses in mice.[47] Prophylactic vaccination to induce T cells specific to Epstein–Barr virus has, however, not advanced into clinical trials so far. In the clinical development of vaccination strategies for multiple sclerosis, it is important to consider that targeting EBNA1-specific T cells has a risk of activating cross-reactive lymphocytes, which could exacerbate the disease.[22,23]

Exploiting therapies targeting Epstein–Barr virus for the treatment of multiple sclerosis

The oldest pharmacological agent targeting Epstein–Barr virus is aciclovir, which inhibits the viral DNA polymerase.[48] However, this drug targets only the last step of the viral lifecycle in B cells, late lytic replication.[24] Upon primary infection of B cells, latent Epstein–Barr virus gene products (EBNAs and LMPs) drive proliferation, resistance to cell death, and differentiation to memory B cells. This differentiation and the associated epigenetic modification of the viral DNA take about 3 weeks, and only then can lytic replication of Epstein–Barr virus be initiated after plasma cell

	Target	Indication	Clinical trial
Vaccination (prophylactic)*			
Epstein–Barr virus gp350 nanoparticle	Supporting specific immune responses to Epstein–Barr virus	Healthy adults (aged 18–29 years)	Phase 1; NCT04645147
Epstein–Barr virus gp350 nanoparticle	Supporting specific immune responses to Epstein–Barr virus	Healthy adults (aged 18–25 years)	Phase 1/2; NCT05683834
mRNA-1189, encoding Epstein–Barr virus gH, gL, gp42, and -gp220	Supporting specific immune responses to Epstein–Barr virus	Healthy adolescents and adults (aged 10–30 years)	Phase 1/2; NCT05164094
mRNA-1195, encoding undisclosed antigens	Supporting specific immune responses to Epstein–Barr virus	Healthy adults (aged 18–55 years)	Phase 1; NCT05831111
V350A and V350B, nanoparticle displaying gH, gL, gp350, and gp42	Supporting specific immune responses to Epstein–Barr virus	Healthy adolescents and adults (aged 12–30 years)	Phase 1; NCT06655324
Vaccination (therapeutic)			
mRNA-1195, encoding undisclosed antigens	Regulating specific immune responses to Epstein–Barr virus	Adult patients with multiple sclerosis (aged 18–55 years)	Phase 2; NCT06735248
T-cell transfer			
Autologous Epstein–Barr virus-specific cytotoxic T cells	B cells infected with Epstein–Barr virus	Adult patients with multiple sclerosis (aged 18–45 years)	Phase 1; NCT02912897
Antiviral			
Tenofovir–emtricitabine	DNA polymerase	Adult patients with multiple sclerosis (aged ≥18 years)	Phase 2; NCT05957913
Tenofovir, add on to anti-CD20 therapies	DNA polymerase	Adult patients with multiple sclerosis (aged ≥18 years)	Phase 2; NCT04880577
Famciclovir, add on to natalizumab	DNA polymerase	Adult patients with multiple sclerosis (aged ≥18 years)	Phase 2; NCT05283551
VK-2019	EBNA1	Malignancies associated with Epstein–Barr virus in adult patients (aged ≥18 years)†	Phase 2; NCT04925544

*Tested in healthy adults for safety and efficacy but designed to prevent infectious mononucleosis and associated diseases such as multiple sclerosis. †The respective EBNA1 inhibitor showed promise by inhibiting Epstein–Barr virus-transformed B cells from patients with multiple sclerosis.[42] The authors assessed the rationale for conducting a clinical trial with an EBNA1 inhibitor in multiple sclerosis as strong but no clinical trial recruiting individuals diagnosed with multiple sclerosis has been reported so far.

Table: **Ongoing clinical trials of strategies targeting Epstein–Barr virus with potential relevance to prevention and treatment of multiple sclerosis as of May 31, 2026**

differentiation. Only the last step to infectious virus particle generation in plasma cells is inhibited by aciclovir and related compounds such as ganciclovir. Such Lytic replication at mucosal surfaces leads to viral shedding into saliva for transmission. Dissemination of Epstein–Barr virus infection in the human body by latently infected B cells occurs before lytic reactivation,[49] and dissemination in mice with humanised immune systems does not require lytic Epstein–Barr virus replication.[50]

Nevertheless, valganciclovir can reduce shedding of Epstein–Barr virus into saliva.[51] The beneficial effect of the antiretroviral drug tenofovir on multiple sclerosis relapses observed in individual case reports[52] has been attributed to the ability of tenofovir to inhibit Epstein–Barr virus DNA polymerase.[53] Phase 2 clinical trials are currently ongoing to investigate viral DNA inhibition in multiple sclerosis (NCT05957913; table). In contrast to this late targeting of Epstein–Barr virus replication, an EBNA1 inhibitor, targeting viral DNA maintenance in all latent and lytic infection programmes, is being tested in a phase 2 study for malignancies associated with Epstein–Barr virus (NCT04925544). This allosteric EBNA1 inhibitor blocks growth of Epstein–Barr virus transformed B cells that are derived from patients with multiple sclerosis.[54,55]

The second oldest intervention against Epstein–Barr virus associated pathologies is adoptive T-cell transfer, which has been used in clinical practice for patients with malignancies associated with Epstein–Barr virus since the 1990s.[56] T cells expanded with an adenoviral construct encoding EBNA1 and a polyepitope of LMP1 and LMP2 were tested in patients with progressive multiple sclerosis.[42] Three of ten patients showed sustained clinical improvement after 2–3 years, with six initially responding to treatment. However, a terminated phase 1/2 clinical study in patients with progressive multiple sclerosis did not meet its endpoint of confirmed disability improvement at 12 months after adoptive transfer of Epstein–Barr virus-specific T-cells (NCT03283826; Atara Biotherapeutics primary analysis, 2023, according to the company's press release).[57] Another phase 1 trial with expanded T cells specific to Epstein–Barr virus is currently recruiting patients with multiple sclerosis (NCT02912897). Adoptive T-cell treatments are attractive because they should be able to follow B cells infected with Epstein–Barr virus across the blood–brain barrier to eliminate them within the CNS.

However, optimisation of the differentiation stage, efficacy against B cells infected with Epstein–Barr virus, and induction of these T cells by therapeutic vaccination (as currently being tried with the mRNA-1195 vaccine in patients with relapsing–remitting multiple sclerosis in a phase 2 clinical trial; NCT06735248) might be difficult. The transferred or induced T cells might need to be kept at the early differentiated effector memory development stage that is characteristic for $CD8^+$ T cells specific for Epstein–Barr virus in healthy virus carriers[58] and might require their direct isolation from HLA-matched donors.[59] Furthermore, overly ambitious primary endpoints—such as confirmed improvement in the Expanded Disability Status Scale at 12 months after T-cell transfer, as used in the negative phase 1/2 clinical trial of T cell specific to Epstein–Barr virus in multiple sclerosis (NCT03283826)—might lead to underestimation of the biological efficacy and therapeutic potential.

Finally, the most common clinical strategies against lymphoproliferation associated with Epstein–Barr virus are B-cell depleting therapies targeting CD20 or CD19.[60,61] CD20-targeting antibodies are also used therapeutically against multiple sclerosis[62–64] and eliminate CNS-homing B-cell populations that are expanded by Epstein–Barr virus infection in mice with humanised immune systems.[7] Directing B-cell depleting therapies more specifically towards CNS-homing subsets could diminish the infection risk that is associated with such therapies.[65] Moreover, B-cell depleting therapies that might be able to follow CNS-homing B-cell subsets across the blood–brain barrier could be appealing. Along these lines, T cells transgenic for chimeric antigen receptors (CAR) that target the plasmablast and plasma cell marker BCMA were tested in five patients with primary progressive multiple sclerosis.[66] The treatment deleted plasmablasts and plasma cells in the CNS and ameliorated myeloid cell activation; plasmablasts and plasma cells were previously found to readily differentiate from CNS-homing T-bet^+CXCR3^+ memory B-cell populations in patients with multiple sclerosis and in mice with humanised immune systems.[7,67] These studies could be extended to CD19-targeting CAR T cells that are more widely used against B-cell malignancies associated with Epstein–Barr virus.[68] Furthermore, allogeneic T cells specific to Epstein–Barr virus can be equipped with CD19-targeting CARs and have been tested in patients with B-cell malignancies.[69] To increase Epstein–Barr virus specificity, antibodies against the late lytic Epstein–Barr virus antigen gp350 and against LMP2 presented on HLA-A*02:01 have been converted into CARs.[70,71] Respective CAR specificities could also be tested as bispecific T-cell engagers_that crosslink the surface of cells infected with Epstein–Barr virus with CD3 on cytotoxic T cells.[72] Thus, pharmacological inhibition of Epstein–Barr virus, transfer of T-cells specific for Epstein–Barr virus, and depletion of B-lineage cells carrying Epstein–Barr virus are currently being investigated in animal models and are likely to be further developed as potential treatments for multiple sclerosis.

Conclusions and future directions

Recent epidemiological evidence indicates that Epstein–Barr virus infection is an important prerequisite for the initiation of multiple sclerosis, although it is clearly not the only contributing factor. Such infection of B cells alters their transcriptional programmes and differentiation, potentially amplifying the effects of genetic risk variants associated with multiple sclerosis while promoting CNS homing and activation of autoreactive T cells.

To inform multiple sclerosis prevention and treatment strategies, establishing whether Epstein–Barr virus acts solely as a trigger or also drives focal inflammation, disease progression, and disability accrual after disease onset is crucial. Although strong evidence supports its role in the initiation of multiple sclerosis, whether—and by which mechanisms—Epstein–Barr virus contributes to ongoing disease activity remains unclear. Clinical trials of therapies targeting the virus in multiple sclerosis represent a key approach to addressing this question.

Although current high-efficacy therapies for multiple sclerosis effectively suppress focal inflammation and relapses, effective treatments for relapse-independent disease progression remain a major unmet need. Disease progression is incompletely understood but is thought to involve leptomeningeal inflammation, cortical tissue damage, and immunologically active multiple sclerosis lesions.[73] Epstein–Barr virus might contribute to leptomeningeal inflammation, raising the possibility that its therapeutic control could influence progression; however, its direct role in focal inflammation or the core biology of progressive multiple sclerosis is unresolved.

Progress in this area will require rigorously designed clinical studies, from proof-of-concept trials to larger randomised studies, incorporating innovative outcome measures to assess both mechanisms of action and efficacy. Given the complexity of disability accrual, endpoints beyond the EDSS are additionally needed, including advanced imaging and fluid biomarkers capable of detecting subtle progression.[74] These CNS-specific parameters should be combined with in-depth virological and immunological investigations to better understand the biological effects and mechanisms of EBV-targeted therapeutic strategies. Finally, prevention of multiple sclerosis remains a major challenge. Ongoing trials of prophylactic Epstein–Barr virus vaccination to prevent infectious mononucleosis, together with therapies targeting Epstein–Barr virus in people already diagnosed with multiple sclerosis, are expected to provide crucial insights into whether the virus acts exclusively as an initiating factor or continues to drive disease activity and progression after clinical onset of multiple sclerosis.

Search strategy and selection criteria

We searched PubMed, medRxiv, and bioRxiv for articles published in English from Jan 1, 2023, to Feb 10, 2026, using the terms "Epstein–Barr virus and multiple sclerosis", "Epstein–Barr virus and vaccination", "Epstein–Barr virus clinical trials". We reviewed both the articles resulting from these searches and their references, and selected those articles relevant to the scope of this Rapid Review. There were no other exclusion criteria.

Whether changes in host–virus interactions reported in adults with multiple sclerosis also occur with similar characteristics and magnitude in paediatric patients remains incompletely understood. Given the shorter latency between Epstein–Barr virus infection and disease onset in children, studies in paediatric populations offer a unique opportunity to investigate early-life drivers of multiple sclerosis. There is, therefore, a pressing need to better understand the role of Epstein–Barr virus—and consequently, the potential of therapies targeting it—in paediatric patients with multiple sclerosis.

Contributors

Both authors wrote and revised the manuscript. Both authors are also responsible for the decision to submit the manuscript for publication.

Declaration of interests

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