



Epstein-Barr Virus and Multiple Sclerosis

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Multiple sclerosis (MS) is a neurologic disease affecting myelinated nerves in the central nervous system (CNS). The disease often debuts as a clinically isolated syndrome, e.g., optic neuritis (ON), which later develops into relapsing-remitting (RR) MS, with temporal attacks or primary progressive (PP) MS. Characteristic features of MS are inflammatory foci in the CNS and intrathecal synthesis of immunoglobulins (Igs), measured as an IgG index, oligoclonal bands (OCBs), or specific antibody indexes. Major predisposing factors for MS are certain tissue types (e.g., HLA DRB1*15:01), vitamin D deficiency, smoking, obesity, and infection with Epstein-Barr virus (EBV). Many of the clinical signs of MS described above can be explained by chronic/recurrent EBV infection and current models of EBV involvement suggest that RRMS may be caused by repeated entry of EBV-transformed B cells to the CNS in connection with attacks, while PPMS may be caused by more chronic activity of EBV-transformed B cells in the CNS. In line with the model of EBV's role in MS, new treatments based on monoclonal antibodies (MAbs) targeting B cells have shown good efficacy in clinical trials both for RRMS and PPMS, while MAbs inhibiting B cell mobilization and entry to the CNS have shown efficacy in RRMS. Thus, these agents, which are now first line therapy in many patients, may be hypothesized to function by counteracting a chronic EBV infection.

Keywords: Epstein-Barr virus, multiple sclerosis, immune evasion, central nervous system, chronic infection, relapsing-remitting

INTRODUCTION

Multiple sclerosis (MS) is a disease affecting the central nervous system (CNS), with inflammation and demyelination of nerves, eventually resulting in nerve damage and disabilities. MS can take different courses, most often in the form of relapsing-remitting (RR) cycles of disease activity or more rarely as a primary-progressive (PP) disease. RR MS can progress over many years and may eventually develop into a secondary-progressive (SP) disease (1–3).

Initial symptoms of MS are often recorded as solitary symptoms, i.e., a clinically isolated syndrome in the form of optic neuritis (ON) or other neurological disturbances isolated in time and space (1–4). Diagnosis of MS relies on the so-called McDonald criteria, latest updated in 2017 (5). These criteria include detection of active inflammatory foci in the CNS as seen by positron emission tomography (PET) and magnetic resonance imaging (MRI) and intrathecal production of

immunoglobulins (Igs), measured as an elevated cerebrospinal fluid (CSF)/serum IgG index, as a free light chain index or as the occurrence of oligoclonal bands (OCBs) of IgG in CSF (6–10). Each oligoclonal band is a result of intrathecal antibody (Ab) synthesis by single B cell clones and therefore, specific CSF/serum Ab indices (AIs) may also be elevated, e.g., Abs to various viruses, corresponding to the specificity of some of the OCBs (11–15). Accordingly, the OCB Abs show evidence of antigen (Ag) exposure, somatic hypermutation and affinity maturation (16–19).

Differential diagnoses for MS are neuromyelitis optica (NMO) and major oligodendrocyte glycoprotein (MOG) Ab-associated demyelinating disease, but other diseases may also mimic some aspects of MS, including acute disseminated encephalomyelopathy (ADEM), CNS neoplasms and various other diseases with the potential to affect the CNS (20–22).

Therapy of MS was previously mainly empirical and relied on several low molecular weight (LMW) drugs, including glatiramer acetate, teriflunomide, dimethyl fumarate, fingolimod, cladribine and others, however, biological drugs have been introduced for treatment of RRMS, including beta-interferon and several therapeutic monoclonal Abs (MAbs) (23–25). Especially the array of MAbs approved for MS treatment has expanded and currently range from Natalizumab, an integrin $\alpha4\beta1/\alpha4\beta7$ MAb, Alemtuzumab, a CD52 Mab, to MAbs targeting the B cell surface marker CD20 (Rituximab, Ocrelizumab) (25–28). Most interestingly, the latter have been found to have an effect also on PPMS (27, 28).

MS ETIOLOGY AND EPIDEMIOLOGY

No consensus about MS etiology exists at present and theories range from idiopathic loss of self-tolerance, over molecular mimicry to chronic virus infections. However, it is generally accepted that MS involves a combination of genetic predisposing factors and environmental influences (29–34). MS has a female preponderance, which most likely is due to genetic factors and

incidence is highest after puberty, which may be ascribed to either genetic or environmental factors or both.

Genetic factors influencing development of MS are in particular major histocompatibility class II (MHC II) alleles, of which some increase susceptibility (e.g., human leukocyte antigen (HLA) DRB1*15:01), while others decrease susceptibility. Likewise, some MHC I alleles also appear to be protective (e.g., HLA A*02:01), while others increase susceptibility. Overall, more than 100 genes have been found to have an influence on development of MS, of which most are involved in immune system functioning and in particular lymphocyte and Ab functioning (1–3, 29–40).

Environmental factors with an impact on MS incidence include sunlight exposure/vitamin D (vitD) deficiency, dietary and other compounds, smoking and some virus infections [e.g., Epstein-Barr Virus (EBV)] (30).

MS is most prevalent on the Northern hemisphere, a finding which can most likely be related to the intensity of sun light, which may in turn be explained by levels of vitD synthesis. Actually, vitD concentrations have been found to be correlated with MS incidence/prevalence (39, 41–43).

Smoking increases the risk of MS, but some other uses of tobacco may actually reduce the risk of MS (30, 44–46). Other environmental compound exposures have been found to have an effect on MS susceptibility (30) and recently, propionic acid and the composition of the intestinal microbiota has been reported to influence or be influenced by MS (47–49).

Obesity, especially in adolescence has been reported to have an effect on MS susceptibility, but it is unclear whether this may be attributed to genetically determined factors or environmental/socio-economical influences or a combination of different effects, e.g., a low-grade neuro-inflammatory effect or a vitD-sequestering effect (50–53).

Virus infections have for long been suspected to be involved in MS development (29–32, 54–56). Most investigations have focused on EBV, which remains the most likely candidate for a causative virus, but other viruses may also play a role as discussed below.

EPSTEIN-BARR VIRUS (EBV)

EBV is a member of the Human Herpes Virus (HHV) family, which also includes Herpes Simplex Virus (HSV) 1 and 2, Varicella Zoster Virus (VZV), Cytomegalovirus (CMV), HHV 6 and 7, and Kaposi Sarcoma Virus (KSV) (57–59). EBV is an enveloped virus with a 120 kB double-stranded DNA genome, coding for about 85 proteins and a number of non-coding RNAs (60–65).

EBV is transmitted to new victims with saliva and infects pharyngeal epithelial cells. When released from the epithelial cells, EBV infects B cells in the associated underlying tissue, where it may be propagated or enter a state of latency, depending on the B cell environment and the state of the host immune response (66–70). Initially, in the absence of an adaptive immune response, B cells are induced to lytic production of virus. Upon entry to the cell, EBV uncoats in the cytoplasm and transfers its DNA to the nucleus, where an ordered sequence of viral gene

Abbreviations: Ab, antibody; ADEM, acute disseminated encephalomyelitis; Ag, antigen; AI, antibody index; AuAb, autoantibody; AuAg, autoantigen; B, B cell; B', EBV-infected B cell; BBB, blood-brain barrier; BKV, B. K. Virus; CD, cluster of differentiation; CIS, clinically isolated syndrome; CMV, Cytomegalovirus; CNS, central nervous system; CSF, cerebrospinal fluid; D, dendritic cell; Di, Diphtheria; EBV, Epstein-Barr Virus; f, female; FLC, free light chains; HERV, Human Endogenous Retrovirus; Hib, Hemophilus influenzae B; HHV, Human Herpes Virus; HLA, human leukocyte antigen; HPV, Human Papilloma Virus; HSV, Herpes Simplex Virus; Ig, immunoglobulin; IM, infectious mononucleosis; JCV, John Cunningham virus; KSV, Kaposi Sarcoma Virus; L, ligand; LMW, low molecular weight; M, macrophage; m, male; MAb, monoclonal antibody; MIG, microglia cell; MMR, Measles-Mumps-Rubella; MOG, major oligodendrocyte glycoprotein; MRI, magnetic resonance imaging; MS, multiple sclerosis; MuV, Mumps virus; NMO, neuromyelitis optica; OCB, oligoclonal bands; ODC, oligodendrocyte; ON, optic neuritis; PCR, polymerase chain reaction; PD, programmed death; Pe, pertussis; PET, positron emission tomography; Pol, polio; PP, primary-progressive; RR, relapsing-remitting; RuV, Rubella Virus; SP, secondary-progressive; T, T cell; t, time; Te, tetanus; VitD, vitamin D; VZV, Varicella Zoster Virus.

expression then takes place. First, immediate early genes are expressed, coding for transcription factors and other proteins involved in control of the host cell, next early genes are expressed, coding for proteins involved in viral DNA replication, followed by late genes, coding for capsid proteins and other proteins involved in mature virus production [e.g., envelope (glyco)proteins]. Finally, virions are released from the cell by a process resembling the reverse of endocytosis. At later stages, when an adaptive immune response has been established, EBV may enter a latent state, where only few or no viral genes are expressed, but the viral genome may still be replicated along with cellular DNA. This state is called “deep” latency, where from the virus may be reactivated in response to B cell activation (66, 71–80).

As a counter-measure to host immune responses, EBV has evolved a multitude of immune evasion mechanisms, counteracting both host cell intracellular anti-viral processes and host extracellular innate and adaptive immune responses. Cellular anti-viral pathways are many and EBV devotes a large part of its genome to control of cellular anti-viral apoptosis mechanisms and to immune evasion (81–86).

The adaptive immune response to EBV involves both Ab-dependent processes and cytotoxic T cells, and EBV has evolved mechanisms to evade these as described above, e.g., by down-regulating MHC I to avoid recognition by cytotoxic T cells. Therefore, control of EBV relies to a large extent on natural killer cell surveillance of infected cells with too little MHC I on the surface, which is in turn counter-balanced by EBV by upregulation of non-classical MHC molecules (87–102).

Despite the many evasion mechanisms of EBV, the host immune system eventually forces EBV into latency, where a minimal number of EBV genes are expressed as described above. However, T cell immunity eventually wanes with time, allowing EBV to reactivate under certain conditions with lytic production of virions, thus re-invigorating the immune response, again forcing the virus into latency, a cyclic process which may go

on for the rest of a person’s life with smaller or larger intervals, depending on the person’s immune system profile.

Decreased capacity for immune control of EBV may, in some cases manifest itself as a tendency to develop EBV-related diseases, including infectious mononucleosis (IM), various cancers, MS, and other relapsing-remitting autoimmune diseases (e.g., systemic autoimmune diseases) (103–112).

EBV AND MS

In MS, much evidence indicates a role for EBV and specifically that EBV-infected B cells have entered the CNS at some point of disease development (**Table 1**). As described above, some of the major characteristics of MS are the presence of an elevated IgG index and OCBs in the CNS, representing various B cell clones synthesizing Abs in the CNS (6–8). The elevated IgG index and the OCBs cannot reflect simple diffusion of Abs from serum to CSF, since the IgG index is calculated relative to the albumin ratio and the OCBs test is only regarded as positive, when the OCBs are absent from serum. Similarly, intrathecal presence of elevated free light chains represent synthesis of Abs in the CNS (9, 10). Intrathecal synthesis of Abs is also reflected in elevated specific antibody indexes (AIs), representing intrathecal synthesis of Abs to Measles Virus (MeV) antigens (Ags), Mumps Virus (MuV) Ags, HZV Ags, Rubella Virus (RuV) Ags, and other pathogen Ags (11–16). EBV AIs are also elevated, however, not necessarily to the same extent as other AIs, despite the presence of high levels of Abs to EBV in serum of MS patients (15, 124). Interestingly, there is a high degree of correlation between Ab concentrations in serum and in CSF for most or all of the virus Abs described above (15). Since the elevated CSF levels are not caused by diffusion from serum to CSF and since there is a highly significant correlation between serum and CSF Ab levels, the only likely explanation is that there

TABLE 1 | Evidence for Epstein-Barr virus (EBV) involvement in multiple sclerosis (MS).

MS trait/characteristic	EBV relation	References
Elevated IgG index	CNS entry of EBV-infected B cells and differentiation to plasma cells	(6)
OCBs in CSF	CNS entry of EBV-infected B cells and differentiation to plasma cells	(6, 8)
Elevated FLCs	CNS entry of EBV-infected B cells and differentiation to plasma cells	(9, 10)
Elevated specific AIs	CNS entry of EBV-infected B cells and differentiation to plasma cells	(11–19)
CNS inflammatory foci	T cell attack on CNS EBV-infected B cells	(1, 2, 5)
Demyelination in CNS	Inflammatory damage to oligodendrocytes and stimulation of macrophages and microglia cells	(1–3)
AuAbs to myelin AuAgs	Inflammation-induced stimulation of (EBV-infected) B cells and damage to oligodendrocytes	(113–116)
Therapy with CD20 MAbs	Killing of EBV-infected B cells, prevention of CNS entry	(27, 28)
Therapy with integrin MAbs	Prevention of CNS entry of EBV-infected B cells	(117, 118)
Therapy with EBV-specific T cells	Killing of EBV-infected B cells, prevention of CNS entry	(119, 120)
Female preponderance	Reduced EBV control (immune suppression due to menstruation (blood loss, healing, hormonal factors)	(1–3, 30)
Incidence increases after puberty	Increased exposure to EBV, reduced capacity for EBV control due to thymus involution	(3)
HLA DRB1 predisposes	Increased entry and/or decreased immune control of EBV	(1–3, 29–40)
IM predisposes	Increased load of EBV-transformed B cells	(30, 54–56, 121–123)
VitD deficiency predisposes	Reduced EBV control (immune suppression due to vitD deficiency of leukocytes, (e.g., T cells, NK cells)	(39, 41–43)
Smoking predisposes	Reduced EBV control (immune suppression by smoke) and/or increased frequency of EBV reactivation	(30, 44–46)
Obesity predisposes	Reduced EBV control due to immune suppression	(50–53)

Ab, Antibody; Ag, antigen; AI, antibody index; AuAb, autoantibody; AuAg, autoantigen; CD, cluster of differentiation; CNS, central nervous system; EBV, Epstein-Barr virus; FLC, free light chains; HLA, human leukocyte antigen; IM, infectious mononucleosis; MAb, monoclonal antibody; NK, natural killer; VitD, vitamin D.

has been or is a continuous influx of Ab-producing B cells from blood to CSF, most likely in the form of B cell blasts which have differentiated to plasma cells concomitantly in the periphery and in the CNS.

Many studies have revealed increased amounts and increased frequencies of EBV Abs in MS, however, such studies are hampered by the nearly ubiquitous presence of EBV in adults. Moreover, the results seem to depend somewhat on the EBV Ags used and the assay methodology.

Seroconversion from negative to positive for EBV Abs generally increases with age. It has a major incidence peak early in childhood and shows a second peak, especially for females, around puberty, co-incident with the approximate age of IM and co-incident with the female predominance in MS (3, 103, 104, 106, 125–128). EBV infection correlates with pediatric MS and essentially all children with MS are found to be positive for EBV Abs, whereas the positivity rate is considerably lower in healthy children (54, 129–132). When using an array of Ags and methods, all adult MS patients are also found to be positive for EBV Abs and it appears that MS development generally depends on prior EBV infection (54–56, 121, 122, 130, 133–137). Furthermore, prior IM has been found to increase the risk of MS by more than 2-fold by itself and more in combination with other predisposing parameters (30, 54–56, 121–123, 138, 139).

In contrast to the Ab-based studies, polymerase chain reaction (PCR)-based investigations on EBV DNA and RNA in blood, CSF and saliva have generally shown no or only minor differences between MS patients and controls (140–142). These results may depend on the patient cohorts and the methods employed, but they do indicate that the role of EBV in MS reflects a predominantly latent infection (as in most infected persons) with occasional reactivation and transient lytic virus production. However, sequencing-based studies have indicated an association between the presence of EBV variants and MS (143, 144).

In situ hybridization and PCR studies on brain material from MS patients have in some cases indicated the presence of EBV DNA in lesions, but other studies have yielded negative results (145–148). Immuno-histochemical studies are few, but one study has demonstrated the presence of EBV Ags in post-mortem brain tissue of MS patients (149).

Other viruses, including RuV, MuV, MeV, CMV, HHV6, VZV, John Cunningham Virus (JCV), and Human Endogenous Retrovirus W (HERV-W) have also been suggested to play a role in MS, either by themselves or in combination with EBV infection (30, 54, 150–154). This may simply reflect a viral Ag-induced reactivation and stimulation of EBV-infected B cells with specificity for the virus(es) in question (i.e., a secondary role for these viruses), or it may reflect a more active role of the viruses. The virus Ab profile varies much between individual patients, thus favoring a primary role of EBV and a secondary role of other viruses (15). Interestingly, CMV seropositivity appears to afford some protection against MS development (30, 135). CMV is evolutionarily related to EBV, so it may be a likely possibility that CMV may exhibit some cross-reactivity with and protection against EBV (59).

As described above, EBV control relies to a large extent on T cells and NK cells. It could therefore be hypothesized that MS patients have a deficiency in the cellular immune control of EBV and possibly also other viruses. CD8 T cell infiltration of MS brain lesions has been demonstrated in several studies but defective T cell control of EBV has also been reported in MS patients (155–157). This could indicate an imbalance in the T cell control of EBV in MS patients, and one study has actually found increased programmed death (PD) 1 on CD8 T cells with resulting decreased cytolytic activity against EBV-infected B cells (158), while PD1 has also been reported to be increased on regulatory T cells (159).

DISCUSSION

MS has traditionally been regarded as an autoimmune disease. However, the occurrence of autoantibodies (AuAbs) in MS (e.g., myelin basic protein (MBP) and major oligodendrocyte glycoprotein (MOG) Abs) is limited to only some patients and the pathogenic role of AuAbs remains debatable, while the search for autoantigens (AuAgs) in MS continues (113–116, 160–173). For this reason, models of MS etiology have for long revolved around T cells as major contributors. The role of T cells has been suggested to involve idiopathic loss of self tolerance with expansion of self-reactive T cell clones, defective regulatory T cells, infections in combination with (T cell) molecular mimicry and epitope spreading, bystander T cell activation, exhaustion of infection-related T cells, or combinations/imbances of these (1–3, 30, 54, 173–182). Even though EBV-infected B cells appear to play a major role in MS, is an important role for T cells not excluded. EBV-infected memory B cells will be sensitive to stimulation by both their cognate Ags and specific CD4-positive T helper cells and will be a target for CD8-positive cytotoxic T cells. Both stimulation by T helper cells and attack by cytotoxic T cells will contribute to inflammation around EBV-infected B cells. Thus, a major role for T cells in MS is likely, in agreement with the predominance of T cells in MS lesions (1, 2, 173–182).

Thus, exhaustion of cytotoxic T cells and/or NK cells would seem to be highly relevant in relation to EBV involvement in MS as indicated above. This view has gained momentum from the relatively big success of B cell-targeted therapies in MS and CD20 MAbs are now the choice of treatment in many newly diagnosed MS patients (27, 28). These drugs can be hypothesized to work either by elimination of self-reactive B cell clones or elimination of EBV-infected (memory) B cells. As the frequencies of AuAbs in MS are variable and as CD20 is not expressed on differentiated Ab-producing “plasma” B cells, the first possibility can be regarded as more hypothetical (although a contribution of this to therapeutic outcome remains a possibility). Consequently, the second possibility, elimination of EBV-infected memory B cells, appears to be the most likely mechanism for the therapeutic effects of CD20 MAbs. The results described above indicate that EBV-transformed B cells proliferate or have proliferated in the periphery and entered the CNS at some point of disease evolution in connection with

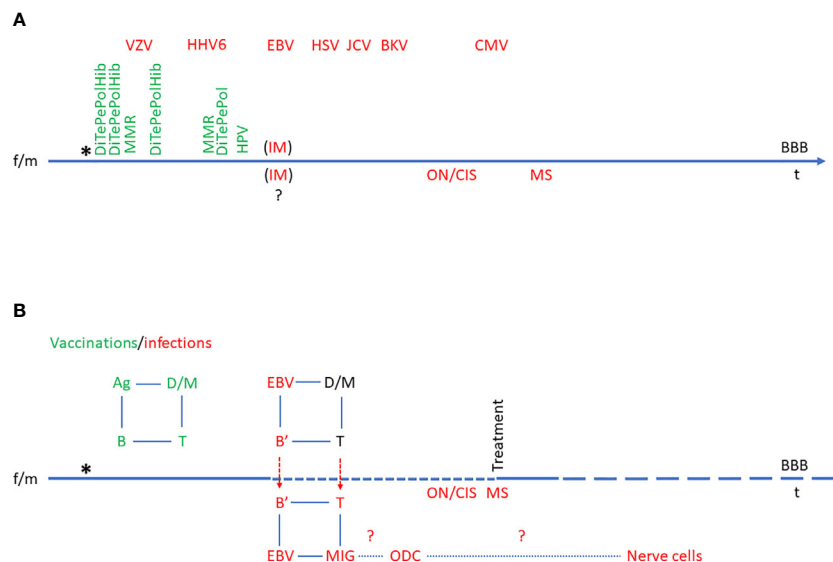


FIGURE 1 | Model of Epstein-Barr virus (EBV)'s role in multiple sclerosis (MS). The time line also represents the blood-brain-barrier (BBB) and events across the BBB. The birth of a child subsequent to the mixing of a female (f) and a male (m) set of genes is indicated by an asterisk (*). **(A)** Time course of normal immune system development with vaccinations (green) and infections (red). The order and time course of vaccinations is defined by vaccination regimens. The order of infections is individual and variable, so the sequence indicated is hypothetical. In some individuals, EBV infection may manifest itself as IM, and it is not known to which extent infectious mononucleosis (IM) affects the CNS at the time of primary infection, but it is known to increase the risk of ON/CIS and eventually MS. **(B)** Schematic presentation of etiological immunological reactions in multiple sclerosis in relation to vaccinations and infections. The normal immunological feed-back loop is indicated in green (e.g., vaccination-induced Ag uptake by dendritic cells (D) and macrophages (M), which interact with T cells, which in turn interact with B cells and vice versa). In the case of EBV infection, the immunological feed-back loop is re-programmed to the advantage of EBV, resulting in chronic infection of B cells (B'). These may enter the CNS (particularly in the case of IM) and be followed by T cells. This results in inflammation in the CNS with the feed-back loop also involving microglia cells (MIG) and at some point also oligodendrocytes (ODC) and eventually, nerve cells. Ag, antigen; B, B cell; B', EBV-infected B cell; BBB, blood-brain barrier; BKV, B. K. Virus infection; CIS, clinically isolated syndrome; CMV, Cytomegalovirus infection; D, dendritic cell; DiTePePolHib, Diphtheria-Tetanus-Pertussis-Polio-Hemophilus influenzae B vaccine; EBV, Epstein-Barr virus infection; f, female; HHV6, Human Herpes Virus 6 infection; HPV, Human Papilloma Virus vaccine; HSV, Herpes Simplex Virus infection; JCV, John Cunningham Virus infection; IM, infectious mononucleosis; m, male; M, macrophage; MIG, microglia cell; MMR, Measles-Mumps-Rubella vaccine; MS, multiple sclerosis; ODC, oligodendrocyte; ON, optic neuritis; t, time; T, T cell; VZV, Varicella Zoster Virus infection.

relapses (RRMS) or have entered the CNS at some point in disease evolution (SPMS and PPMS) (**Figure 1**). CD20-targeted MAbs are administered intravenously and are not expected to enter the CNS to any major degree (in line with the occurrence of CNS OCBs and elevated IgG index not deriving from diffusion from the blood stream). Therefore, the efficacy of these drugs must derive from an effect on CD20-positive B cells in the periphery, both in RRMS and PPMS, indicating that the import of EBV-transformed B cell to the CNS is a continuous process.

Other treatments with an effect in MS can also be related to a role of EBV. Natalizumab inhibits lymphocyte mobilization and entry to the CNS by targeting integrin $\alpha4\beta1/\alpha4\beta7$ (117, 183). Integrins may be used by EBV as entry receptors (118) and Natalizumab might therefore both inhibit entry of EBV to integrin-expressing cells and may also inhibit mobilization and entry of EBV-infected B cells and EBV-directed T cells to the CNS by a general inhibition of lymphocyte trafficking.

Some other low molecular weight MS drugs have also been reported to have an effect on EBV, in particular Teriflunomide, which has been reported to inhibit EBV lytic replication and to influence the immune response to EBV (118, 184). Similarly, the role of vitD in MS can be regarded as a general immune-stimulatory effect

as can other environmental factors (e.g., propionic acid, which has been found to reactivate EBV (thus re-invigorating an EBV-targeted immune response) (119). Smoking can theoretically affect the disease course both by reducing immunity and by reactivating EBV, two effects that may partly oppose each other, thus possibly explaining the apparently protective role of some uses of tobacco (54).

In line with the role of EBV, small trials of MS therapy with autologous *in vitro*-expanded EBV-specific T cells have shown a beneficial effect in some patients (119, 185). The theory of EBV involvement in MS was proposed early by Pender et al. and it has been made likely that MS patients have a deficient T cell control of EBV-infected cells (54, 120, 155, 186–197). The theory of EBV involvement in MS has subsequently been elaborated and substantiated by many studies as described above and summarized in **Table 1**. Several models have been proposed based on the accumulated evidence for the role of EBV in MS (198–201). **Figure 1** represents an attempt to visualize much of this evidence.

In conclusion, the infectious, transforming, anti-apoptotic and immune-evasion properties of EBV makes it a highly likely candidate for an etiologic agent in MS. However, much remains to be investigated in future studies. For example, MS shows characteristics of an indolent neoplastic disease

(metastasis, clonal expansion, overlap with lymphoma, etc.). Thus, the role of the transforming properties of EBV in MS should deserve attention. If the pathogenic role of EBV-specific T cell exhaustion can be confirmed, treatment of MS with immune check point inhibitors (e.g., PD1 and/or PD1 ligand (PD1L) MAbs), known to be effective in several forms of cancer may become a possibility.

AUTHOR CONTRIBUTIONS

GH made the first manuscript draft. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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