Review

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Oligodendrocyte Dysfunction to Immune Pathology in Multiple Sclerosis A Conspiracy of Herpesviruses?

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Abstract

Multiple sclerosis is an immune-driven neurological disease that affect myelinated axons in the central nervous system. However, the trigger of the (dysregulated) immune reactions is not known. According to Wilkin's primary lesion theory, myelin-reactive T cells present in the immune repertoire respond to myelin antigens that are released from idiopathic lesions within the central nervous system. However, neither the cause of the primary lesion, nor the cause of the immune hyper-reactivity are known. We investigated whether these unknown activation signals may be relayed by common herpesviruses. The results highlight **human herpesvirus- 6A** as a potential trigger of primary lesions due to its proven capacity to cause oligodendrogliopathy, **cytomegalovirus** as a trigger for the formation of effector memory cytotoxic T cells with proven capacity to induce multiple sclerosis pathology in a non-human primate MS model and **Epstein Barr Virus** due to its capacity to render B cells capable to effectively present a critical myelin antigen to these effector memory cytotoxic T cells. These results lead us to propose the novel paradigm that the immunopathogenesis of multiple sclerosis results from a conspiracy of common herpesviruses.

Keywords: EBV; CMV; HHV-6; oligodendrogliopathy; autoimmunity

1. Introduction

Multiple sclerosis (MS) is a chronic neurological disorder causing damage to myelinated axons within the central nervous system (CNS) (Noseworthy et al., 2000). Although broad consensus exists that MS is an immune-mediated disease, the trigger of the immunopathogenic process is unknown.

According to a prevalent **outside-in** paradigm exposure to a microbial agent elicits the activation of autoreactive T and B cells present in the peripheral immune repertoire. Activated T cells acquire the capacity to transmigrate the blood-brain-barrier (BBB). By interaction with local antigen presenting cells (APC) pathophysiological reactions are elicited that lead to damage of axon-myelin units (Kawakami and Flugel, 2010). The γ1-herpesvirus Epstein Barr Virus (EBV) is the strongest candidate trigger (Soldan and Lieberman, 2023). A concept connecting virus infection with immunity to tissue proteins is 'molecular mimicry', being the sharing of immunological 'look-alike' motifs between the infectious agent and the target antigen (Libbey et al., 2014a). Examples of mimicry reactions relevant for EBV and MS were published for myelin-specific T cells (Lang et al., 2002) and clonally expanded MS B cells (Lanz et al., 2022).

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A more recently developed **inside-out** paradigm posits that MS is an immunological convolution between primary oligodendrogliopathy and an aberrant immune response of the host (Stys et al., 2012). A mechanistic underpinning is given by Wilkin's primary lesion theory for autoimmune diseases ('t Hart et al., 2021; Wilkin, 1990), which postulates two integrated processes: 1. Presence of lesions within the target organ from which antigens are released; 2. patients developing an autoimmune disease are high immune responders against released antigens.

Here we discuss whether by integrating published functions of MS-related herpesviruses in Wilkin's primary lesion theory a viable concept for the initiation and perpetuation of the CNS directed immune attack in MS can be created.

2. Main Players in the Immune Response and Their Interaction in MS Animal Models

The current understanding of immunopathogenic mechanisms in MS is strongly influenced by the mouse experimental autoimmune encephalomyelitis (EAE) model. This model is created by immunization of genetically susceptible strains of inbred strains of immunologically naïve (SPF-bred) laboratory mice with myelin proteins (e.g. MBP, PLP or MOG) formulated with a strong bacterial adjuvant (CFA). This evokes MS-like symptoms and pathology (Baxter, 2007).

The autoimmune attack on the CNS is led by CD4+ T-cells, which are activated through 3 signals (Krovi and Kuchroo, 2022):

Signal 1: An antigenic peptide bound to an major histocompatibility complex (MHC)-II molecule that is recognized by T cells with their specific antigen receptor.

Signal 2: Cognate interaction of co-stimulatory molecules expressed on the T cell and the APC. The expression of co-stimulatory molecules is induced by conserved molecular structures present in viruses and bacteria that signal through evolutionary conserved innate receptors, such as Toll- or Nod-like receptors (Matzinger, 1994). The relay of signal 1 without signal 2 inactivates the CD4+ T cell and abrogates its pathogenic role in the EAE model. The idea that the trigger of MS must be a microbial infection stems from the dependence of EAE induction from signal 2.

Signal 3: The function of activated T cells is determined by cytokines produced by the APC and tissues cells, which direct activated T cells in pro- or anti-pathogenic direction. The permeabilization of the BBB by CD4+ T-cell-mediated inflammation facilitates secondary infiltration of CD8+ T cells, B cells, macrophages, antibodies and complement factors. Damage to axon-myelin-units (AMU) is mediated by CD8+ T cells attacking oligodendrocytes and/or by antibodies binding to oligodendrocytes and myelin sheaths evoking cytotoxicity of macrophages (ADCC) and /or complement factors (CDC) (Figure 1).

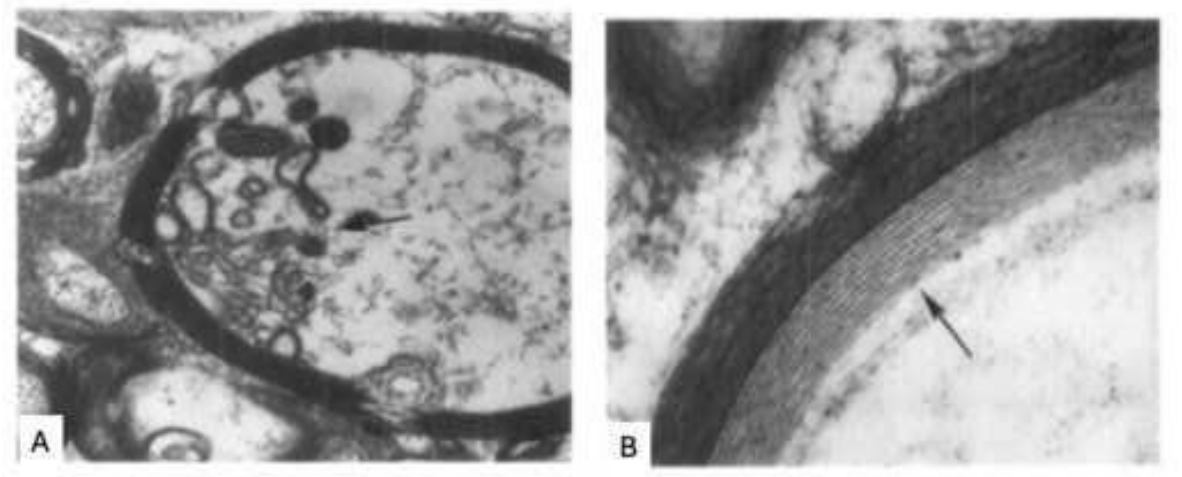

Figure 1.

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The EAE model is frequently criticized for the artificial manner pathology and symptoms are induced, especially the dependence on CFA (Sriram and Steiner, 2005). Virus-induced MS models, such as with Theiler's murine encephalomyelitis (TMEV), corroborate the concept that a CNS targeting immune attack can be elicited by a virus (Libbey and Fujinami, 2021). The TMEV SJL/J mouse model is particularly revealing because of the pathological similarities with MS. Immunostaining combined with electron microscopy detected TMEV viral antigens within the inner and outer myelin loops of myelin, indicating primary infection of oligodendrocytes (Rodriguez et al., 1983). Structural studies showed that axonal damage occurred even when the myelin sheath appears intact - with swollen axons, vacuoles, and abnormal spacing between myelin lamellae. These changes weaken the myelin structure, compromise its insulating function and impair axonal signal conduction (Libbey et al., 2014b; Lipton and Dal Canto, 1976).

Difficulties in the translation of scientific findings in mouse EAE models into effective therapies for MS patients raised doubts about the validity of the mouse EAE-based MS pathogenic concept (t Hart et al., 2021). A major discrepancy is that in the EAE model disease can be eliminated by treatment with anti-CD4 antibody (Biasi et al., 1997), whereas this treatment had no or sometimes detrimental effects in MS (van Oosten et al., 1997). A likely explanation is the fundamental differences between the immune systems of genetically homogeneous populations of 10 weeks old SPF-bred laboratory mice and those of a genetically diverse adult population MS patients living in dirty environments (Brodin and Davis, 2017). The human immunological condition is more closely reproduced in captive-bred colonies of non-human primates ('t Hart et al., 2011). A well-validated EAE model in marmosets revealed a central pathogenic role of MHC-E restricted CD8+ve effector memory cytotoxic T cells (EM- CTL) specific for an epitope (residues 40-48) from the CNS myelin component myelin oligodendrocyte glycoprotein (MOG). These T cells could be directly activated *in vivo* by immunization with a synthetic MOG peptide (residues 34-56) formulated with a mineral oil (incomplete Freund's adjuvant, IFA) that lacks the indispensable alarm signals flagging danger to immune cells in mouse EAE models (Jagessar et al., 2010). The requisite APC for these EM- CTL are B cells infected with the EBV-related γ1-herpesvirus *Callithricine herpesvirus-3* (CalHV3), which process the epitope and present it via MHC-E molecules (Jagessar et al., 2012). An *ex vivo* study in EBV-infected B cells revealed that the virus infection is essential for productive processing of the EM-CTL epitope from the immunizing MOG34-56 peptide (Jagessar et al., 2016; Morandi et al., 2017). Thus activated EM-CTL evoke CNS pathology that strikingly reproduces MS pathology, including inflammatory demyelination in the white and grey matter of brain and spinal cord and the disappearance of oligodendrocytes from lesions ('t Hart et al., 2017).

The MOG34-56 peptide shares a mimicry motif with the major capsid protein of cytomegalovirus (CMV) (Brok et al., 2007). Moreover, a similar population of HLA-E- restricted, CMV-specific EM-CTL has been found in humans (Pietra et al., 2003). We thus hypothesized that the original trigger of the EM-CTL might be a simian CMV. Apparently, the involvement of herpesviruses compensates the lack of signal 2 for pathogenic T cells activation.

3. Herpesviruses Associated with Immune Function

3.1. EBV

EBV (aka human herpesvirus 4; HHV-4), is a γ1-herpesvirus in the genus lymphocryptovirus (LCV) that causes mostly asymptomatic infections in the human population. LCVs are commonly found in both Old and New World primates, where the virus can cause lymphoproliferative disorders, just like EBV does in humans (Muhe and Wang, 2015). Infection occurs mostly by oral transfer of saliva, hence the name kissing disease, and by genital secretions. In Western populations, about half of all five-year-old children and about 90% of adults carry the virus. Infants become susceptible to EBV as soon as maternal antibody protection disappears. Most infected children display no symptoms or symptoms resembling mild childhood illnesses. Infection at adolescent age can cause a more serious clinical condition, infectious mononucleosis. Most infected persons gain

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adaptive immunity. Once EBV's initial lytic infection is brought under control, EBV latency persists lifelong in a person's memory B cells (Thorley-Lawson, 2015).

A strong association of EBV infection with MS, has been suspected for decades but was convincingly proven only in recent years (Bjornevik et al., 2023; Soldan and Lieberman, 2023). The main target of EBV in the immune system is the (memory) B cell (Thorley-Lawson, 2001). The pathogenic role of this cell-type in MS has been underestimated for many years, but gained traction after the discovery that their depletion with a monoclonal antibody against the B- lineage marker CD20 exerts remarkable beneficial effects in relapsing and progressive MS (Hauser et al., 2008; Montalban et al., 2017).

3.2. CMV

CMV (aka human herpesvirus-5, HHV-5) is a β-herpesvirus in the genus Cytomegalovirus that comprises also cytomegaloviruses of non-human primates (Barry and William Chang, 2007). CMV is widely spread throughout the human body. Person to person transmission occurs amongst others via saliva. The infection is usually asymptomatic, but in immunocompromised persons (AIDS, organ transplant recipients) the virus can cause life-threatening clinical problems (Steininger, 2007). Upon infection of healthy persons, the virus remains life-long latent in the body, mainly in myeloid (precursor) cells (Hahn et al., 1998).

CMV engages in complex interactions with the immune system. At increasing age a substantial part of the immune system becomes involved in the maintenance of CMV latency (Sylwester et al., 2005). CMV also exerts a strong influence on the aging of the immune system (immunosenescence) (Goronzy and Weyand, 2013). Immunosenescence implies strong diversity contraction in the naïve and memory T cell compartments contrasting with expansion of CMV-reactive memory T cell clones (Goronzy and Weyand, 2013). Aging diminishes the immune system's ability to control virus latency (Pawelec, 2022) but increases propensity to maintain low burning systemic inflammation and hyperreactivity of T cells (inflammaging) (Muller and Di Benedetto, 2021).

The relation between MS and CMV is controversial. Some studies report beneficial others detrimental effects (Vanheusden et al., 2015). Thus, the jury is still out. It was found that chronic latent infection with CMV creates a repertoire of MHC-E-restricted effector memory cytotoxic T cells (EM-CTL) expressing a marker of natural killer cells (CD56) that play an important role in the defense against the virus (Moretta et al., 2003; Romagnani et al., 2004). Due to their special features these EM-CTL potentially mediate hyper-reactivity against self- antigens ('t Hart et al., 2013) and discussion below.

Similar, albeit not 100% identical, types of NK-related CTL have been found in MS lesions (Saikali et al., 2007; Zaguia et al., 2013) and could be implicated in the marmoset EAE model as main driver of MS-like disease (Kap et al., 2008).

4. The Proverbial Primary Lesion

Information of MS pathology prior to diagnosis is limited. Barnett and Prineas reported on extensive oligodendrocyte apoptosis and small clusters of activated microglia in normal- appearing white matter (NAWM) areas with few or no lymphoid or myeloid immune cells present (Barnett and Prineas, 2004). Others reported that these areas contain besides clusters of activated microglia (nodules) with a degenerating axon in the center (Singh et al., 2013) also myelin blisters (Luchicchi et al., 2021). Blisters are particularly prevalent in NAWM areas with increased citrullination of myelin, aka micro-diffusely abnormal white matter (mDAWM) (Luchicchi et al., 2024). Data suggest that blisters are an early stage in the degeneration of axon- myelin units (AMU), making them a candidate early "primary lesion", from which post- translationally modified (citrullinated) myelin proteins are released.

Rodriguez et al. analyzed the ultrastructure of AMU in MS lesions via electron microscopy of 11 brain biopsies (Rodriguez and Scheithauer, 1994). They observed early degenerative changes preceding myelin destruction and immune cell infiltration, including widening of the inner myelin

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lamellae and disruption of the inner loops while the rest of the sheath remained intact (Figure 2). Different from expectation the first aberration is thus not seen at the surface of myelin sheaths, as in the EAE model, but at the interaction of the myelin sheath's inner lamellae with the enwrapped axon. Similar observations were reported by Huitinga et al.(van den Bosch et al., 2023). Both studies indicate "dying-back oligodendrogliopathy" as primary event in the pre-immune pathology of MS (Rodriguez, 1985).

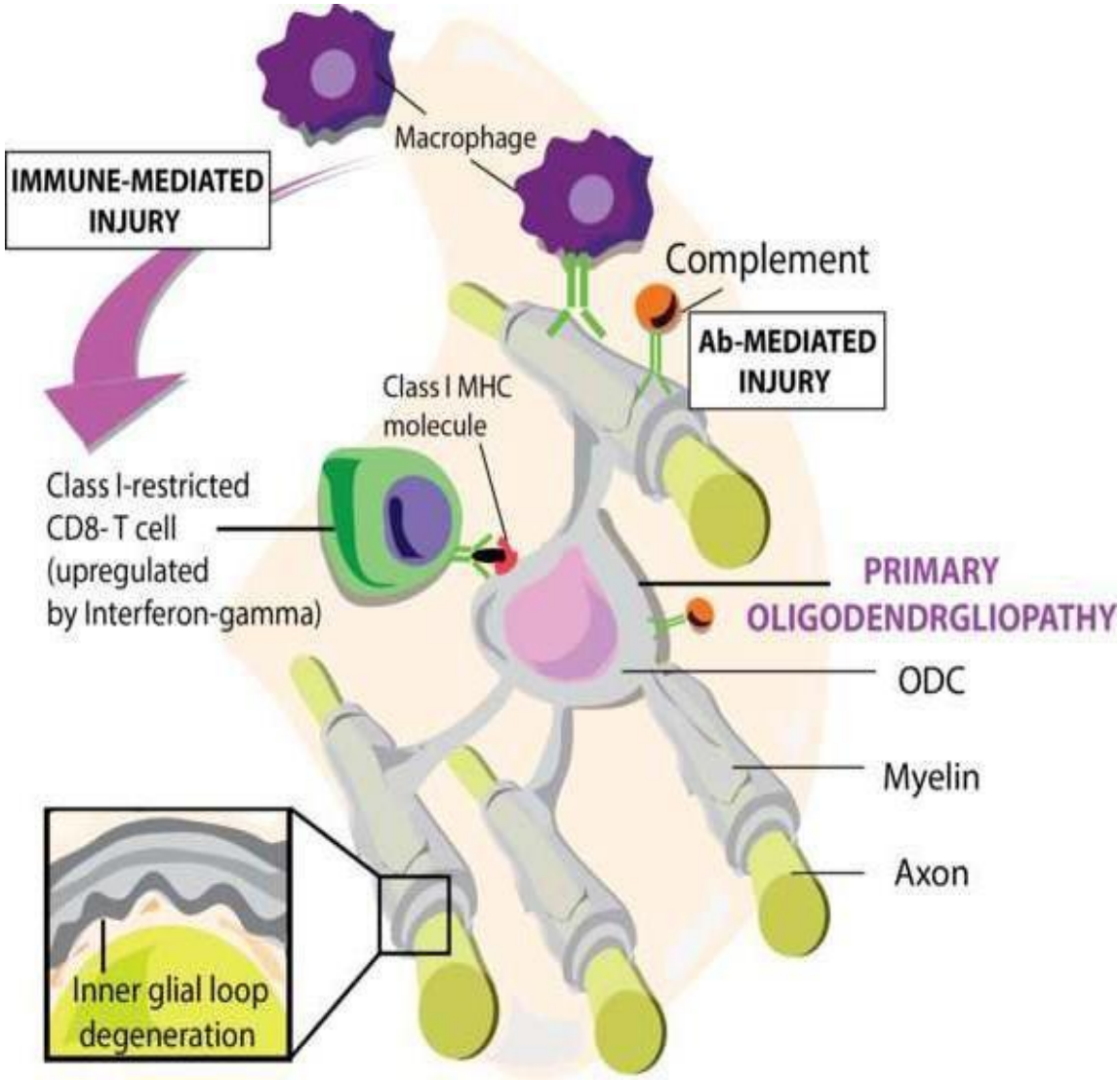

Figure 2.

4.1. A Putative Viral Cause of Primary Lesions: HHV-6

HHV-6 is a β-herpesvirus in the genus *Roseolavirus*. HHV-6 infects > 90% of the adult human population, usually at infant age (between 6 months and 2 years) when protective maternal antibodies have disappeared. Person to person transmission occurs via saliva mostly inducing lifelong mostly asymptomatic infections. HHV-6 infection may cause serious clinical complications, especially in immunocompromised individuals. HHV6 can infect a broad range of human cell types including brain glia cells (microglia, astrocytes and oligodendrocytes) but oligodendrocytes are usually the most severely affected (Skuja et al., 2017).

HHV-6 comprises two subtypes, HHV-6A and HHV-6B. HHV-6A has been described as the more neurovirulent and more frequently associated with MS (Alvarez-Lafuente et al., 2006). HHV-6B has been described as the cause of the common childhood disease *exanthema subitum*. Although in

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immunocompromised patients, such as transplant recipients, CNS inflammation can be observed (Yoshikawa, 2004).

The first report of a relation between HHV-6 and human demyelinating disease concerned an infected case diagnosed with acute disseminated encephalopathy (Kamei et al., 1997). Elevated levels of myelin basic protein(MBP) in cerebrospinal fluid indicated ongoing demyelination. Subsequent studies corroborated the potential linkage of HHV-6A with MS:

Frequent (immunohistochemical) detection of HHV-6 in MS CNS, particularly associated with active demyelinating disease (Knox et al., 2000).

Patients with CSF IgG oligoclonal bands (OCB) binding HHV-6A were younger and had higher overall OCB levels (Pietilainen-Nicklen et al., 2014).

Serum levels of anti-HHV6 IgM and IgG were higher in MS than in healthy controls. Moreover, HHV-6 levels were higher in in mitogen-stimulated leukocyte cultures from MS patients than healthy controls (Ablashi et al., 2000).

A meta-analysis of the literature revealed a correlation between anti-HHV-6 antibody levels in serum and CSF and the MS clinical course (Voumvourakis et al., 2022).

In a subset of MS patients serum HHV-6A IgG levels increased preceding an increase in serum neurofilament light chain (sNfL), a marker of axon destruction (Grut et al., 2024).

Interrogation of MS brains with PCR and immunohistochemistry detected HHV-6A antigens within oligodendrocytes both inside and adjacent to MS lesions (Challoner et al., 1995; Goodman et al., 2003). The virus latent protein HHV-6A u94A alters the ODC cytoskeleton, contributing to ODC dysfunction (Lyman and Enquist, 2009). HHV-6A infection also worsen endoplasmic reticulum (ER) stress and creates abnormalities in UPR pathways in cells of glial and neural origin (Romeo et al., 2020). Finally, infection of oligodendrocytes with HHV-6A induced similar damage to myelin sheaths as found in MS, such as irregularity of membranes and swelling of lamellae (Skuja et al., 2017).

Collectively, these studies support a role of HHV-6 in the etiopathogenesis of MS. Molecular mimicry seems not to provide a mechanistic explanation for the HHV-6/MS association as no significantly different cross-reactivity with HHV-6 or the myelin antigen MBP could be found in T cell lines isolated from 20 MS patients and 16 controls (Cirone et al., 2002).

In an animal model's experimental setting, intravenous inoculation of marmoset monkeys with HHV-6A evoked neurological disease (Leibovitch et al., 2013). Using MRI T2 hyperintense small-sized brain lesions were found in some monkeys suggestive of encephalitis. (Immuno)histology revealed multiple microglia nodules and myelin abnormalities.

5. MS Etiopathogenesis, a Conspiracy of Herpesviruses?

This conceptual question was separated into 6 sub-questions: :

5.1. Where Does the Immune Pathogenic Process Start?

Consistent with Wilkin's primary lesion theory (Wilkin, 1990) we hypothesize that the immune pathogenic process in MS starts with the formation of primary lesions. Studies of the macroscopically nonaffected NAWM of the MS brain revealed oligodendrogliopathy, disturbance of axon-myelin units and microglia nodules as most obvious pathological events. As discussed above, all these pathological features can be associated with HHV-6. There is convincing evidence that serum and CSF levels of neurofilament light (NFL), reporting neuronal damage, are increased in MS patients already in the prodromal phase, i.e. years before clinical diagnosis (Bjornevik et al., 2020). Association of NFL levels with anti-HHV-6 antibody serum levels, reporting virus (re-)activation, has been documented (Grut et al., 2024).

5.2. Where Do EBV-Infected B Cells Pick up Released Myelin Antigens?

In MS patients and MS animal models debris from damaged white matter drain via interstitial and cerebrospinal fluids, ending up in myeloid APC within cervical and lumbar lymph nodes

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(Engelhardt et al., 2016; Laman and Weller, 2013). This drainage route mainly serves to activate immune cells that can dampen (autoimmune) inflammation within the CNS (Kim et al., 2025). According to Engelhard et al. whether immune tolerance or autoimmunity is induced "*is played out at the level of the individual T cell interacting with an individual APC dependent on the reciprocal quantitative and qualitative spectrum of signal 1 (MHC-peptide), signal 2 (panel of costimulatory and co-inhibitory receptors), and signal 3 (spectrum of soluble cytokines)*" (Engelhardt et al., 2016). Based on our studies in the marmoset EAE model we posit that involvement of EBV-infected B cells as APC potentially disrupts the tolerance induction cycle and propagates autoimmunity.

EBV-infected B cells have been found localized within cervical lymph nodes (Sarkkinen et al., 2025). It is therefore a reasonable assumption that EBV-infected B cells can pick up draining myelin antigens there. Myelin debris have been detected within myeloid cells both in EAE models (de Vos et al., 2002) and in MS (Fabriek et al., 2005). Whether EBV-infected B cells can directly capture and digest large myelin fragments or whether these must be preprocessed by myeloid APC remains to be established.

5.3. Which Myelin Antigens Are Selected for Presentation to Pathogenic T Cells?

Marmosets (Jagessar et al., 2008) or mice immunized with MOG-deficient (mouse) myelin do not develop chronic EAE. EAE development could be restored by the addition of recombinant MOG (rMOG) (Smith et al., 2005). The critical peptide for chronic EAE development in marmosets is MOG34-56 (Kap et al., 2008).

5.4. Is the Encephalitogenic MOG34-56 Peptide Differentially Processed in LCV-Infected and Non-Infected B Cells.

Immunotherapy studies showed that the requisite APC in rMOG-induced marmoset EAE models is a B cell infected with the EBV-related lymphocryptovirus CalHV3 ('t Hart and Kap, 2017). The MOG34-56 peptide is instantly destroyed during the processing in B cells but rescued from destructive processing when the B cells are infected with EBV ('t Hart et al., 2017; 't Hart et al., 2016). We propose that this finding provides a mechanistic explanation for the essential role of EBV in the immunopathogenesis of MS.

5.5. Which Pathogenic T Cells Respond to the MOG34-56 Peptide?

Injection of marmosets with synthetic MOG34-56 peptide in IFA, activating mainly memory cells (Croft et al., 1994), induced a neurological disease with MS-like symptoms and pathology (Jagessar et al., 2010). Consistent with the memory status of the marmoset T cell response, immunization of immunologically naïve C57Bl/6 and Biozzi ABH mice with MOG34-56/IFA proved completely inert (Jagessar et al., 2010). Profiling of the T cell response revealed activation of CD3+CD4/8+CD56+ T cells producing IL-17A and TNF-α and displaying cytotoxic activity towards MOG34-56 peptide pulsed autologous EBV-infected B cells. In an earlier study the specific epitope was defined at residues 40 to 48 and the MHC restriction element was defined at *Caja-E*, being the marmoset equivalent of *HLA-E* (Jagessar et al., 2012). Based on the sharing of a mimicry motif between the MOG peptide and the UL86 ORF encoded major capsid protein of CMV (Brok et al., 2007) we assume that this virus may be the original inducer of the memory status.

5.6. where Does T Cell Activation by EBV-Infected B Cells Occur?

One possible site of pathogenic T cell activation is inside the CLN (Walsh et al., 2014). Another potential site is inside the CNS, more specific in the meningeal compartment *(Magliozzi et al., 2013)*. A recent study in humanized mice revealed that by EBV-infection human B cells acquire the capacity to infiltrate the CNS parenchyma and to recruit co-infiltration of activated human CD4+ and CD8+ effector memory T cells (Laderach et al., 2025). Predictably, depletion of B cells with rituximab abrogates T cell infiltration into the CNS.

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6. Concluding Remarks

We asked whether the two principal aspects of Wilkin's primary lesion theory might be attributable to herpesviruses:

Formation of a primary lesion from which excess antigen is released. We discussed that HHV-6A is a potential inducer of oligodendrogliopathy that may underlie instability of axon-myelin units. Virus-stressed oligodendrocytes release citrullinated myelin antigens, which render them more immunogenic (Yang et al., 2016).

Hyper-reactivity of the immune system against myelin antigens. We discussed that chronic latent infection with **CMV** creates a repertoire of potentially auto-aggressive HLA-E-restricted EM-CTL. HLA-E is a non-classical MHC class I^b molecule that is upregulated on cells with reduced or absent expression of classical MHC class I^a molecules to ward off an attack by natural killer cells (Pietra et al., 2009). HLA-E is loaded with processed antigenic peptides in the endoplasmatic reticulum as MHC class Ia molecules, but in autophagosomes (Camilli et al., 2016). The autophagy pathway is virtually inactive in naïve B cells but is strongly upregulated in B cells infected with **EBV**(Jagessar et al., 2016). Through the association with autophagosomes the pathogenic MOG peptide is not only protected against fast degradation (Morandi et al., 2017) but can also associate with HLA-E.

The concept that the immune attack on axon-myelin units in MS might be caused by the conspiracy of three ubiquitous herpesviruses raises the question why MS is a relatively rare disease. The answer might be found in the specificity of the EBV-infected B cell. B cells are highly efficient APC because they can capture antigens using their highly specific antigen receptors. The clonal organization of the B cell compartment implies that only a small fraction of the B cells (< 1%) bears receptors for the myelin antigen MOG (Elong Ngono et al., 2015). The frequency of B cells that contains EBV is also very low (<0,01%) (Khan et al., 1996). It can thus be envisaged that the chance that a myelin-reactive B cell contains EBV is very low. In *mononucleosis infectiosa* patients the frequency of EBV-infected B cells can initially increase dramatically, up to 1 per 10^4 circulating B cells, lowering to 1 per 10^5 -10^6 circulating B cells (Kurth et al., 2000). This may explain why the MS risk is about 3-fold higher in people diagnosed with infectious mononucleosis than in the general population (Goldacre, 2024).

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Declaration of interests: The authors have no interests to declare.

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