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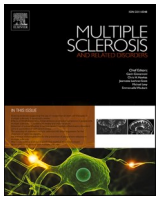

Editorial

Probing the association between Multiple Sclerosis and Epstein Barr Virus from a therapeutic perspective

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Epstein-Barr virus (EBV) is a ubiquitous human γ-herpesvirus, that infects 90-95% of adults worldwide (Cohen, 2000). EBV infection is also one of the most well-established environmental risk factors for the subsequent development of multiple sclerosis (MS). A causal role for EBV in MS is supported by several key immunological and epidemiological studies (Warner and RI, 1981, Thacker et al., 2006, Levin et al., 2010, Munger et al., 2011, Dobson et al., 2017) that arguably fulfill the Bradford-Hill criteria for causality except for one – experiment. This criterion could be met by demonstrating that an anti-EBV agent or an EBV vaccine reduces the incidence of MS, or modifies the progression of disease in established MS. Several promising EBV vaccines are currently in the early phases of preclinical development; however, it will likely take several years of clinical development before these vaccines are widely available (Cohen, 2018, van Zyl et al., 2019). A sterilizing anti-EBV vaccine has the potential to eliminate not just MS but also Burkitt lymphoma, Hodgkin and non-Hodgkin lymphoma and nasopharyngeal cancer – as well as infectious mononucleosis (Rolls et al., 2010). In the meantime, it may be possible to answer mechanistic questions concerning the role of EBV in MS by focusing on antiviral drugs. If an anti-EBV therapy were to be clinically effective in MS in the absence of immunosuppression, this would not only cement the causal relationship between EBV and MS, but would also clarify the mechanistic underpinnings of MS pathogenesis and suggest novel therapeutic avenues for future drug development.

Early evidence supporting an association between EBV and risk of MS came from observations that the epidemiology of infectious mononucleosis (IM) is strikingly similar to that of MS (Warner and RI, 1981), and that a history of infectious mononucleosis (IM) confers a 2-3 fold increased risk of MS compared to those who have not had IM (Thacker et al., 2006). Further studies demonstrated that the risk of MS is extremely low, if any, in individuals who are seronegative for EBV and increases dramatically after EBV infection in the same individuals (Levin et al., 2010). The risk of developing MS among healthy young adults is also proportional to the serum titers of anti-EBV nuclear antigen (EBNA) antibodies (Munger et al., 2011). Among individuals who are EBV seropositive, the relative risk of MS over a 5-year follow-up period is >30 times higher among those with high anti-EBNA titers compared to low anti-EBNA titers (Munger et al., 2011). Despite the strength of the association between EBV infection and risk of MS, the mechanism to explain this link – and whether EBV continues to play a role throughout the course of MS – remains unknown and speculative.

Several hypotheses have been proposed to explain how EBV infection may contribute to MS risk and disease progression (Bar-Or et al., 2020). These include molecular mimicry or cross-reactivity between EBV proteins and autoantigens, direct infection of autoreactive B-cells, EBV-induced inflammatory gene expression, activation of endogenous retroviral elements, and bystander damage due to an aberrant immune response primarily directed against EBV (Bar-Or et al., 2020). It has been difficult to interrogate these hypotheses at the bench due to a lack of appropriate animal models since most animals lack the receptors required for entry of EBV. A spontaneous inflammatory demyelinating disease in a colony of Japanese macaques has been described (Axthelm et al., 2011). Intriguingly, a novel B-cell tropic γ-herpesvirus similar to EBV was cultured from acute white matter lesions (Axthelm et al., 2011). With respect to non-primate models, EBV can infect humanized mice but does not directly cause MS-like disease, suggesting that the context in which EBV infection occurs may be outcome determinant. A recent study in mice humanized with the HLA-DRB1*1501 allele, the strongest genetic risk factor for MS, hints at this possibility as these animals have impaired immune control of lytic EBV infection with higher viral loads and increased reactivity towards MS autoantigens (Zdimerova et al., 2020).

In the past few years, anti-CD20 therapies have emerged as some of the most effective disease-modifying therapies (DMTs) for MS. It has been suggested that the dramatic efficacy of anti-CD20 therapies for MS may be due to a direct effect on EBV; however, this is speculative. Interestingly, rituximab is the only licensed anti-EBV therapy; in EBV-associated post-transplantation lymphoproliferative disorders, peripheral EBV viral loads plummet after rituximab therapy. After anti-CD20 treatment, EBV is undetectable or extremely low in peripheral blood

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mononuclear cells (Hoover et al., 2008), which is consistent with the sharp reduction in relapses and MRI activity observed in trials for MS (Hauser et al., 2017). If anti-CD20 therapies are acting as nonspecific antiviral agents, it may be possible to target EBV directly and avoid side effects due to systemic immunosuppression. Early trials using adoptive transfer of autologous EBV-specific cytotoxic T-cells to treat advanced progressive MS have reported promising preliminary results that support targeting EBV (Pender et al., 2018). However, all these trials are open-label and blinded controlled trials are needed to verify these results.

A paradigmatic approach would be to trial an antiviral agent for EBV in MS. Classically, anti-herpes viral drugs target the viral-encoded DNA polymerase and act as chain-terminating agents to block viral DNA synthesis (Li et al., 2018). Inhibiting DNA replication may be beneficial in suppressing an aberrant immune response to EBV because blocking continuous DNA synthesis dynamically suppresses viral gene expression (Li et al., 2018). Furthermore, EBV DNA produced during lytic replication is recognized by toll-like receptors and can activate immune cells even in the absence of direct infection (Fiola et al., 2010). While no antivirals for EBV have been developed for clinical use, a recent study identified tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF) as safe drugs with highly potent anti-EBV activity (Drosu et al., 2020), suggesting options for antiviral agents that could be trialed for MS in the immediate term. Preliminary anecdotal evidence to support a future study with these antivirals for EBV comes from several case reports of patients with MS treated with TDF or TAF in the absence of DMTs, which have reported improvement or remission of MS coinciding with antiviral treatment (Stefanou et al., 2019, Labella et al., 2021, Torkildsen et al., 2020).

Efforts have been made in the past to trial anti-herpes viral drugs for MS, although these experiments were not done purposefully to treat EBV. Three phase-2 randomized placebo-controlled trials have been published – one using acyclovir and two using the prodrug form valacyclovir (Lycke, 2017). In patients treated with acyclovir or placebo (n=60), the mean annualized relapse rate (ARR) was 34% lower in the acyclovir group than the placebo group (ARR 1.03 vs. 1.57, p=0.083). When patients were grouped in low (0-2), medium (Thacker et al., 2006, Levin et al., 2010, Munger et al., 2011) and high (>6) relapse rates, the difference was significant (p=0.017). Similar results were obtained with valacyclovir in a subgroup of patients (n=17) with high MRI activity at baseline, where treated patients had significantly fewer lesions per scan compared to placebo (Lycke, 2017). These modest results must be interpreted in the context of acyclovir/valacyclovir as drugs with low potency against EBV. To this point, acyclovir shows no benefit in animal models of γ-herpesvirus infection, where more potent drugs demonstrate the ability to achieve a dramatic benefit (Neyts and De Clercq, 1998). The development of novel antiviral drugs will likely be required to definitively answer key questions concerning the role of EBV in MS.

Demonstrating that an EBV antiviral drug is effective in the treatment of MS would have dramatic ramifications. First, it would establish EBV as a definitive contributor to the pathogenesis of MS. Second, it would provide an entirely novel class of DMTs by removing the need for continuous immunosuppression. Finally, it would clarify the mechanism by which EBV contributes to the pathogenesis of MS, which could open new avenues to understand and treat autoimmune diseases in a broader context. While awaiting a vaccine for EBV, well-designed controlled trials of antivirals in MS are warranted in the near term.

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