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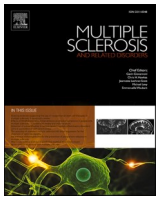

Editorial

EBV as the "gluten of MS" hypothesis provides a rationale for trialing antiviral therapies

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Infection with the Epstein-Barr virus (EBV) has long been established as an environmental factor associated with multiple sclerosis (MS) risk (Thacker et al., 2006, Munger et al., 2011, Levin et al., 2010, Ascherio and Munger, 2007). More recent epidemiological evidence has cemented its role as the likely causal agent for the development of MS (Bjornevik et al., 2022). However, the current evidence linking EBV to MS does not distinguish between EBV as merely a trigger for development of disease vs. an actual contributor to disease pathogenesis after diagnosis. The mechanisms by which EBV infection leads to MS remain elusive, and an extensive list of hypotheses has been proposed to date (Bar-Or et al., 2020). A non-exhaustive summary of suggested models includes (1) the hit-and-run hypothesis, where the initial EBV infection created a milieu for autoimmunity but EBV itself is no longer driving the disease, (2) the two-hit hypothesis which requires a second exposure to an unknown environmental factor timed synchronously to interact with EBV, (3) the direct infection of central nervous system (CNS) antigen-specific B cells where EBV latent proteins modify B cells to become autoreactive, (4) cross-reactivity where EBV antigens associated with MS (e.g. EBNA-1) are erroneously mistaken by the immune system as self and (5) bystander damage where a vigorous response to EBV creates toxic mediators which preferentially cause oligodendrocyte cell death. To date, no single hypothesis has been sufficient to explain MS.

An intriguing new idea was put forth by Iversen and Sollid in 2020, which we will call the EBV as the "gluten of MS" hypothesis (Iversen and Sollid, 2020). In this model, one or more antigens encoded by EBV is the driver of MS by similar mechanisms as gluten is the driver of Celiac disease (CD) (Iversen and Sollid, 2020, Sollid, 2022). There are several features shared between these two diseases. Both MS and CD are caused by exposure to a ubiquitous antigen that triggers autoimmunity only in a small percentage of the population. Exposure to dietary gluten, the known driver of CD, is nearly universal – as is infection with EBV, where >90% of people are exposed by adulthood (Cohen, 2000). Since the causal agent is precisely defined in CD, it has been possible to pinpoint the immune response to CD4 T cells that specifically recognize deamidated gliadin peptides presented on HLA-class II molecules by antigen-presenting cells (APCs) (Sollid, 2000). In accordance with the pathogenesis, the major genetic risk factors for CD are in the HLA-class II locus, and more than 90% of patients with CD carry a variant of DQ2 (DQA1*05/DQB*02) or DQ8 (DQA1*03/DQB1*0302) (Sollid, 2000, Sollid and Lie, 2005). Similarly, the major genetic risk factor for MS is also found in the HLA-class II locus, specifically HLA-DRB1*15:01, which has been associated with MS in nearly every population tested (The International Multiple Sclerosis Genetics Consortium & The Wellcome Trust Case Control Consortium 2, 2011). Additionally, in both CD and MS there exists a gene dosage effect for homozygous compared to heterozygous individuals (Ploski et al., 1993, Barcellos et al., 2003). Despite prevalent exposures and common genetic risk factors, only a small minority of people develop CD or MS. Given these shared features, it is intriguing to consider that autoimmunity may arise from an inappropriate response to foreign antigens in two seemingly unrelated diseases.

If EBV acts as the "gluten of MS", the implications are far-reaching. First, this provides a path forward for experimental approaches that evaluate the interplay between EBV infection and subsequent development of MS using CD as a model system for T cell biology. This hypothesis would predict that the HLA genetic locus driving MS risk is directly related to the presentation of EBV to the immune system. EBV-specific CD4 T cells would then be predicted to generate abnormal immune responses in the presence of EBV-infected B cells. As previously proposed, these T cells would be expected to be present in the CSF of patients with MS in the same way that CD4 T cells specific to gluten peptides are enriched in the gut of patients with CD (Sollid, 2022). Demyelination could occur as bystander damage when an EBV-infected B cell dares to traffic into the CNS whereupon EBV-reactive T cells are primed to attack and destroy it, inducing a broader inflammatory reaction that also injures the surrounding vulnerable myelin. Alternatively, EBV-reactive CD4 T cells may be activating peripheral CD8 T cells against an EBV epitope that bears resemblance to a myelin protein that they later encounter while surveilling the CNS; for example, molecular mimicry between an EBV epitope to EBNA1 and the myelin protein, GlialCAM, has been recently demonstrated in patients with MS (Lanz et al., January 24, 2022).

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This hypothesis also supports clinical testing of antiviral treatments for MS. While antivirals targeting EBV have been contemplated in MS for many years, no mechanistic rationale has been offered for why they should be trialed in patients with established disease. To date, there is minimal evidence for increased viral load in patients with MS – at best, viral load is only two-fold increased in peripheral blood in comparison to healthy individuals, but not in saliva (Agostini et al., 2018, Torring et al., 2014, Holden et al., 2018). However, if CD4 T cells reactive to EBV are driving MS pathogenesis, this would provide a reason for trialing antiviral therapies in established MS. Removing the presentation of the causal antigen to CD4 T cells by treatment with antivirals would in essence mimic a gluten-free diet. More specifically, blocking lytic replication would be an optimal strategy because the immunodominant CD4 T cell response to EBV is directed towards structural virion proteins (Adhikary et al., 2007). The expression of these proteins is directly downregulated by using agents that block lytic DNA replication and would therefore be strategically eliminated from immunosurveillance (Drosu et al., 2020).

We must also note that it is difficult to overlook the dramatic clinical efficacy of B-cell depleting therapies which also deplete EBV-infected B cells (Hoover et al., 2008). These drugs may be acting fortituously as antiviral agents – this provides indirect evidence that EBV may continue to play a role in established disease. It is tempting to speculate that the reason why B-cell depleting therapies do not significantly affect the progressive stage of the disease is that they do not eliminate EBV (Hoover et al., 2008). Several novel BTK inhibitors, which are the subject of multiple current phase III drug trials in MS, are highly potent inhibitors of EBV lytic DNA replication (Kosowicz et al., 2017). If these drugs are proven to be effective, decoupling the effects of therapeutics on EBV from their effects as immunosuppressants would provide answers to critical questions in MS. If the therapeutic effect results from inhibition of EBV replication, future MS treatments could reasonably move away from immunosuppression.

In summary, EBV as the "gluten of MS" hypothesis provides a framework for investigating mechanisms of autoimmunity in MS. This hypothesis would pinpoint the cause of MS not to any aspect of EBV infection itself, but to the inappropriate immune response to one or more EBV antigens in susceptible individuals. It also suggests that antiviral treatments targeting EBV may be an effective treatment for MS by eliminating the causal foreign antigen(s) driving the disease.

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