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EBV infection drives MS pathology: No

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Opinion

The seminal Science publication by Ascherio and coworkers[1] leaves little room for doubts about the essential contribution of Epstein–Barr virus (EBV) to the pathogenic process in multiple sclerosis (MS). However, via which mechanisms EBV enhances the risk of an individual to develop MS is debated. EBV could drive the disease by serving as antigen to which immune cells and antibodies react. Cross-reactivity between viral and central nervous system (CNS) antigens has been demonstrated (molecular mimicry), but current evidence that this phenomenon directly drives MS pathology is inconclusive. A less explored alternative mechanism is that EBV alters peripheral immune cells in such a way that subsets cross the blood–brain barrier (BBB) and interact with antigens released from a primary lesion inside the CNS.[2] Conceptually, the subsequent accumulation of pathogenic immune subsets drives low-grade smoldering MS pathology. In this controversy, we argue that EBV rather amplifies the contribution of pathogenic lymphocyte subsets to MS, than directly drives MS pathology.

Argumentation

Several aspects of EBV tropism and anti-EBV responses are difficult to align with epidemiological and experimental observations in MS. First, EBV infection is common, while MS is relatively rare. It remains incompletely understood how a virus that is almost ubiquitous in the human population (>90% infection prevalence) triggers a disease with a prevalence in global high-risk areas of around 0.1%. A presumed explanation is involvement of a genetic susceptibility factor, but studies are needed for better understanding why, nevertheless, MS concordance in genetically identical monozygotic twins is only 30%.

Classical mechanisms explaining the connection between virus infection and autoimmune disease (such as MS) are molecular mimicry, bystander activation, and epitope spreading. The relevance of each phenomenon for the initiation and/or perpetuation of CNS pathology is particularly clear in murine MS models (e.g. EAE), but still needs to be firmly proven for the human disease. It has also been proposed that EBV-infected B cells form ectopic lymphoid structures inside the CNS, in which EBV-specific pro-inflammatory T cells can be reactivated to cause damage. However, others could not detect EBV in MS brain or cerebrospinal fluid (CSF)[3] and anti-EBV antibodies have rarely been reported to be present in MS CSF, in contrast to blood. The recently revealed genetic architecture of MS disability progression does not point to anti-viral responses as an underlying mechanism, nor shows an association with Human Leukocyte Antigen (HLA) polymorphisms as seen in

MS susceptibility. In our view, these observations argue against EBV as dominant driver of MS pathology, but rather suggest a more complex interplay between virus, immune system, and target organ.

Alternative view

A well-documented orchestrating role of B cells in MS pathogenesis is that of an antigen-presenting cell (APC). B cells are exquisitely capable of capturing low amounts of antigens through highly specific surface-expressed immunoglobulins. After internalization and processing, naive B cells present antigenic peptides to $CD4^+$ T cells via polymorphic HLA class II molecules to get help for differentiation into memory or antibody-secreting cells. Since peripheral selection of autoreactive naïve B cells is impaired in people with MS,[4] the presence of the major MS risk allele *HLA-DRB1*1501* may already be an important determinant of this process due to the presentation of different types of viral and/or self-peptides. In addition, after primary infection EBV can hijack the activation program of naïve B cells, which could trigger alternative processing of antigens for presentation[5] and further empower their APC potential due to direct interaction of EBV antigen with genetic risk variants. Probably as a consequence, memory B cells promote $CD4^+$ T cells to infiltrate the MS brain, especially in individuals carrying *HLA-DRB1*1501*. Notably, such $CD4^+$ T cells are highly responsive to EBV,[6] suggesting that certain subsets indeed preferentially interact with EBV-infected memory B cells. Together with their possible escape from peripheral control by $CD8^+$ T cells in HLA class I risk carriers, B cells instruct Th17.1 cells that can activate and migrate through the BBB as a possible first pathogenic event leading to MS.[7] This way of BBB activation enables other pathogenic immune subsets such as (non-EBV-specific) B cells and $CD8^+$ T cells to immigrate the CNS and cause pathology. Results obtained in a valid MS animal model in marmoset monkeys revealed that EBV-infected B cells directly activate autoaggressive $CD8^+$ effector memory cytotoxic T cells. Upon entry into the CNS these were found to induce widespread MS-like pathology in white and cortical gray matter.[5]

B cells also receive signals such as IFN-γ from interacting $CD4^+$ T cells to induce expression of transcription factor T-bet and chemokine receptor CXCR3, which can be potentiated by EBV and guides their entry into the CNS. To drive MS pathology, the accumulation of EBV-infected $CXCR3^+$ B cells in the perivascular space of people with MS may also give rise to clones that produce autoantibodies or post-translationally modified (myelin) peptides that can form toxic amyloid-like aggregates,[8,9] yet this hypothesis needs to be further tested. Although $CD8^+$ T cells are enriched in the MS brain, their exhausted features in risk HLA (and their cytotoxic capacity in protective HLA) carriers could further promote local B-cell maturation and persistence.[10]

As the frequency of B cells containing EBV is very low during the latency phase (between 1 and 50 per 10^6 B cells), it is tempting to speculate that the wide prevalence gap between EBV infection and MS (a factor ~700) may be explained by the low chance that a B cell with relevant specificity and function in MS (as explained above) contains the virus. Alternatively, and maybe also more likely, it is not the latency but the primary infection phase when occurring at adolescent age (infectious mononucleosis) in which EBV-infected B cells are shaped to drive pathology with an MS diagnosis in later years.

Summary and concluding remarks

The central pathogenic role of EBV infection in the initiation and perpetuation of MS is undeniable, but incompletely understood. We posit here that the pathogenic process within the CNS is not driven by EBV itself or by immune reactions against the virus, but by CNS-homing T cells that have acquired pathogenic functionality from EBV-infected B cells in the periphery. We posit that probably during and shortly after the primary infection phase, EBV-infected B cells escape from peripheral control and serve as overly potent memory APCs to promote $CD4^+$ T cells to interrupt the BBB. After this first event, pathogenic B and T cells gradually enter and accumulate in the CNS to, irrespective of relapse occurrence and EBV reactivity, instigate MS pathology.

Data Availability Statement

Data sharing not applicable to this article as no data sets were generated or analyzed during the current study.

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EBV infection drives MS pathology: Commentary

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The discovery that infection with the Epstein–Barr virus (EBV) is the leading cause of MS calls into question the optimality of current treatments, which target EBV only indirectly, have broad immunosuppressive effects, and, while markedly reducing relapses and onset of demyelinating lesions, do not halt disability progression, nor eliminate fatigue and other disabling symptoms.[1,2] Could therapeutics directly and selectively targeting EBV be safer and more effective? Resolving the controversy in the current journal issue on whether and how EBV drives MS pathology is key to answering this question and has transcending implications for millions of people with MS. In the scenario proposed by Aloisi and Salvetti, in which EBV-specific cytotoxic T-cells targeting lytic antigens are the primary effector, prevention of EBV lytic reactivation—a lower hanging fruit than the complete elimination of EBV infection—could be effective in MS. Such interventions, however, would be ineffective if latently EBV-infected B-cells, acting primarily as antigen-presenting cells, activate non-EBV-specific cytotoxic T-cells that cause tissue damage without further viral stimulation, as proposed by t'Hart and van Luijn. There is support for both sets of mechanisms, which are not mutually exclusive, but evidence remains inconclusive because of the difficulty of discerning critical effects from epiphenomena in observational human studies, or of extrapolating from animal models to human disease. Considering that EBV infection is active and persistent throughout the lifetime of the host, and that an increased MS risk is observed for 20 or more years after primary EBV infection,[3] it may seem unlikely that the presence of the virus, which periodically reactivates and is a continuous source of antigenic stimulation, becomes irrelevant to MS progression, but it is nevertheless possible considering the complex genetic and epigenetic effects of EBV in infected cells.[4,5]

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