Epstein-Barr virus infection, B-cell dysfunction, and other risk factors combine in gut-associated lymphoid tissue to cause multiple sclerosis.

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Abstract

Epstein-Barr virus (EBV) infection, B-cell dysfunction, gut dysbiosis, and environmental and genetic risk factors, including female sex, are linked to multiple sclerosis. There is still no disease model that takes into account all of these variables. Here, we postulate that memory B cells (MBCs) infected with EBV migrate to gut-associated lymphoid tissue (GALT) through EBV-induced expression of LPAM-1, where they are subsequently activated by gut microbes and/or their products, causing EBV Marginal zone (MZ) B cells that activate CD4+ T cells through the HLA-DRB1 promote downstream B cell differentiation towards CD11c+/Tbet+ MBCs as well as traditional MBCs in these responses. EBV proteins, such as EBNA-1, that cross-react with central nervous system (CNS) autoantigens are made more susceptible to polyreactive BCR/antibody responses when MZ B cells and CD11c+/Tbet+ MBCs express low-affinity B-cell receptors (BCRs) intrinsically (e.g. GlialCAM). Because they express CXCR3, EBV protein/autoantigen-specific CD11c+/Tbet+ MBCs are more likely to migrate to the CNS and meningeal immune system, where they trigger cytotoxic CD8+ T-cell responses against CNS autoantigens amplified by BAFF and released by EBV-infected MBCs.

Keywords: CD11c+/T-bet+ memory B-cells, Epstein–Barr virus, Gut associated lymphoid tissue, Marginal zone B cells.

Introduction

The central nervous system (CNS) inflammatory disease known as multiple sclerosis (MS) causes demyelination of neurons and neurological impairment. Female sex; genetic variations affecting immune system function, particularly three alleles of genes encoding human leucocyte antigens (HLAs), of which HLA-DRB1*1501 is the strongest genetic risk factor and other factors have all been linked to an increased risk of developing multiple sclerosis (MS). 4; persistent Epstein-Barr virus (EBV) infection; 5; variation in the gut microbiome; low exposure to ultraviolet radiation (UVR); low vitamin D levels; and cigarette smoking. While CD4+ T cells have been the focus of previous research on the immunopathology of MS, knowledge of CD8+ T cells. The observed increased abundance of circulating IgA+ MBCs in MS patients may also be a result of GALT-derived immune responses, such as disease-promoting IgA antibody responses against EBV and regulatory IgA+ plasma cells that are specific to the gut microbiota [1].

Female sex boosts CD11c+/Tbet+ MBC and MZ B cell activity, while environmental risk factors influence gut dysbiosis. Therefore, EBV infection, B-cell dysfunction, and other risk factors combine in GALT to produce aberrant B-cell responses, which in turn trigger pathogenic T-cell responses in the CNS are key components of the immunopathology that underlies MS. 6 The hypothesis put forth here is that EBV infection, B-cell dysfunction, and other risk factors congregate in gut-associated lymphoid tissue (GALT) to produce aberrant B-cell responses that lead to pathogenic T-cell responses in the CNS. We have examined various aspects of B-cell dysfunction and the relationship of gut microbiome-derived short-chain fatty acids (SCFAs) with immune dysfunction in patients with early MS. In the brains of MS patients, the perivascular and parenchymal inflammatory infiltrates linked to demyelination are characterised by an abundance of CD8+. While uncertainty remains about interactions between CD8+ T cells and B cells, 6 B cells clearly play a fundamental role in the inflammatory process [2,3].

Oligodendrocytes have been found in the CNS of some patients. In addition, three separate groups of MS patients had significantly higher plasma levels of IgG antibodies to GlialCAM than did controls. 12 These results offer a mechanistic explanation for the many reports linking MS and EBV infection, culminating in recent reports that 100% of MS patients have serological evidence of EBV infection, 18 and that EBV infection acquired in late adolescence or early adulthood is linked to a 32-fold increased risk of developing MS. 13 Furthermore, According to reports, high serum levels of anti-EBNA1 IgG antibodies are not only linked to an increased risk of developing MS but also work in concert

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with other risk factors to increase that risk and predict the progression from clinically isolated syndrome suggestive of MS (CIS) to MS, in contrast to antibodies to other EBV proteins [4].

Our hypothesis proposes mechanisms to explain altered B-cell phenotypes, the production of B-cell and antibody responses against EBV proteins that cross-react with CNS autoantigens, the contribution of CD4+ T cells, and the coexistence of CD8+ T cells and B cells in CNS inflammatory lesions. It combines the major genetic and environmental risk factors for developing MS into a single disease model. Additionally, it opens up new directions for MS immunopathogenesis and treatment research. As demonstrated in, each of the three types of MBCs probably plays a role in the immunopathogenesis of MS, albeit in a unique way. All subpopulations express CD20, so all would be eliminated by monoclonal anti-CD20. Such research may uncover new therapeutic targets to control EBV-associated immunopathology in the CNS as well as new biomarkers to evaluate how EBV interacts with B cells [5].

Conclusion

We propose that studies of gut microbiota-specific immune responses, particularly those involving MZ B cells, CD11c+/ Tbet+ IgG+ MBCs, and IgA+ MBCs, may be as instructive as studies of EBV-specific immune responses arising in GALT. In addition, it should be taken into account that all GALT-associated B cells might contribute to the gut-meningeal immune axis 69 in both health and disease. Such research could result in more specialised treatments to control B-cell dysfunction. Adenosine receptor 2a on CD11c+/Tbet+ MBCs 159, for instance, may be therapeutically inhibited to reduce pathogenic B-cell responses without compromising overall B-cell function. Continuing research on the gut microbiota analysis of the connection between EBV reactivation and the activation of circulating MBCs, particularly MZ B cells, should be part of any study of MS pathogenesis.

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