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Discoveries beyond molecular mimicry describe how EBV drives multiple sclerosis

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https://doi.org/10.1016/j.cell.2025.12.047

In the current issue of *Cell*, three papers describe new mechanistic information about how EBV transforms B cells to become antigen-presenting cells in the brain that drive demyelinating disease.[1–3]

In 2022, Bjornevik and colleagues studied ten million individuals in the US military and demonstrated that infection with Epstein-Barr virus (EBV) increased the risk of multiple sclerosis (MS) 32-fold, and they proclaimed that EBV is the cause of MS.[4] Within days, Lanz and colleagues published that the Epstein-Barr nuclear antigen 1 (EBNA1) had molecular mimicry with a myelin molecule, the glial cell adhesion molecule (GlialCAM).[5] A clonal antibody in the cerebrospinal fluid of MS binds to GlialCAM and EBNA1.

A series of papers focusing on molecular mimicry within EBNA1 followed, showing that there were molecular mimics within a stretch of 50 amino acids on EBNA1, not only to GlialCAM but also to other proteins in brain, including a chloride channel anoctamin-2 (ANO2)[6] and myelin basic protein (MBP).[7] A fourth molecular mimic within this 50-amino acid linear stretch of EBNA1 contained a molecular mimic to aB crystallin (CRYAB), a small heat-shock protein that acts as a checkpoint on neuroinflammation.[6,8] A recent collaboration between scientists at Stanford and the Karolinska studied 1,311 patients. Approximately 80 percent of individuals with MS have antibodies to the molecular mimics in EBNA1. Having HLA-DRB1*15:01, plus anti-EBNA1 antibody, together with antibody to one of these molecular mimics increased the chance of developing MS approximately 10-fold.[6] Three papers in this issue of *Cell*[1–3] reflect a pivot in emphasis in molecular research on how EBV induces MS, from a focus on molecular mimicry to a new emphasis on mechanistic studies of how infection of B cells with EBV transforms the B cell's ability to present self-antigen to the T cell (Figure 1).

In Kim et al.,[1] the investigators emphasize how one of the critical genes in EBV infection, known as latent membrane protein 1 (LMP1), reprograms the B cell that it infects, providing a co-stimulatory signal akin to CD40. Expression of LMP1 is seen in B cells that have been infected with EBV in the brains of those with MS.[9] Kim and colleagues demonstrate that B cells migrate to the brain. When they encounter myelin antigens, self-antigens, they are deleted in a process called activation-induced cell death (AICD). However, if B cells are infected with EBV and thus express LMP1, they survive and capture antigens, including myelin proteins and EBV proteins.

We know that some EBV antigens like EBNA1 can cross-react to myelin antigens like GlialCAM and MBP, as well as to channel proteins like ANO2.[3–5,7] Even guardian proteins like CRYAB, another molecular mimic of EBNA1, are recognized by B cells that migrate to the brain in MS. CRYAB is a guardian molecule protecting against neuroinflammation.[8] LMP1-infected B cells are not deleted, and thus unwanted autoimmunity to myelin proteins, to channel proteins, and even to guardian proteins ensues inside the MS brain.

Kim and colleagues show that this leads to inflammation and demyelination within the central nervous system, a hallmark of MS. The authors acknowledge that LMP1-expressing B cells ought to be detected in MS lesions in the brain. Recent work cited by the authors[1] shows that this requirement has been validated: LMP1-expressing B cells have been detected in MS lesions.[10]

The second paper discussed here that appears in this issue of *Cell*[2] analyzes how antigens are processed in EBV-infected B cells and how this alters what is presented to the immune system, including $CD4^+$ helper T cells. The authors of this paper[2] studied $CD4^+$ T cell responses to MBP in the cerebrospinal fluid (CSF) and brain tissue in individuals carrying the major HLA class II protein HLA DR15 that confers susceptibility to MS. As mentioned, having the HLA-DR15 gene, as well as antibodies to EBNA1 and either GlialCAM, CRYAB, or ANO2, increases the odds ratio of getting MS to approximately 10.[6] The main region of MBP recognized by $CD4^+$ T cells in HLA DR15+ individuals is the region from peptides 83–99. In the B cells of individuals who are HLA DR15+ and who are infected with EBV, the antigen presentation process is transformed and the B cells present peptides ending at position 90, not position 99, to $CD4^+$ T cells. Thus, EBV infection of B cells transforms the transcriptome of myelin peptides presented to the immune system. This illuminated another critical piece of the pathophysiology that ensues following infection of EBV in B cells that migrate to the brain and the CSF. These B cells have been reprogrammed and present critical changes contributing to the mechanisms of pathophysiology in MS.

In the third paper,[3] Thomas and colleagues continue their brilliant work on ANO2, a chloride channel protein and a molecular mimic in the constellation of molecules that are "mimics" within a 50-amino-acid stretch of the EBNA1 protein. It is noteworthy that GlialCAM is both a myelin molecule and a chaperone of a water channel, whereas ANO2 is a chloride channel. The investigators

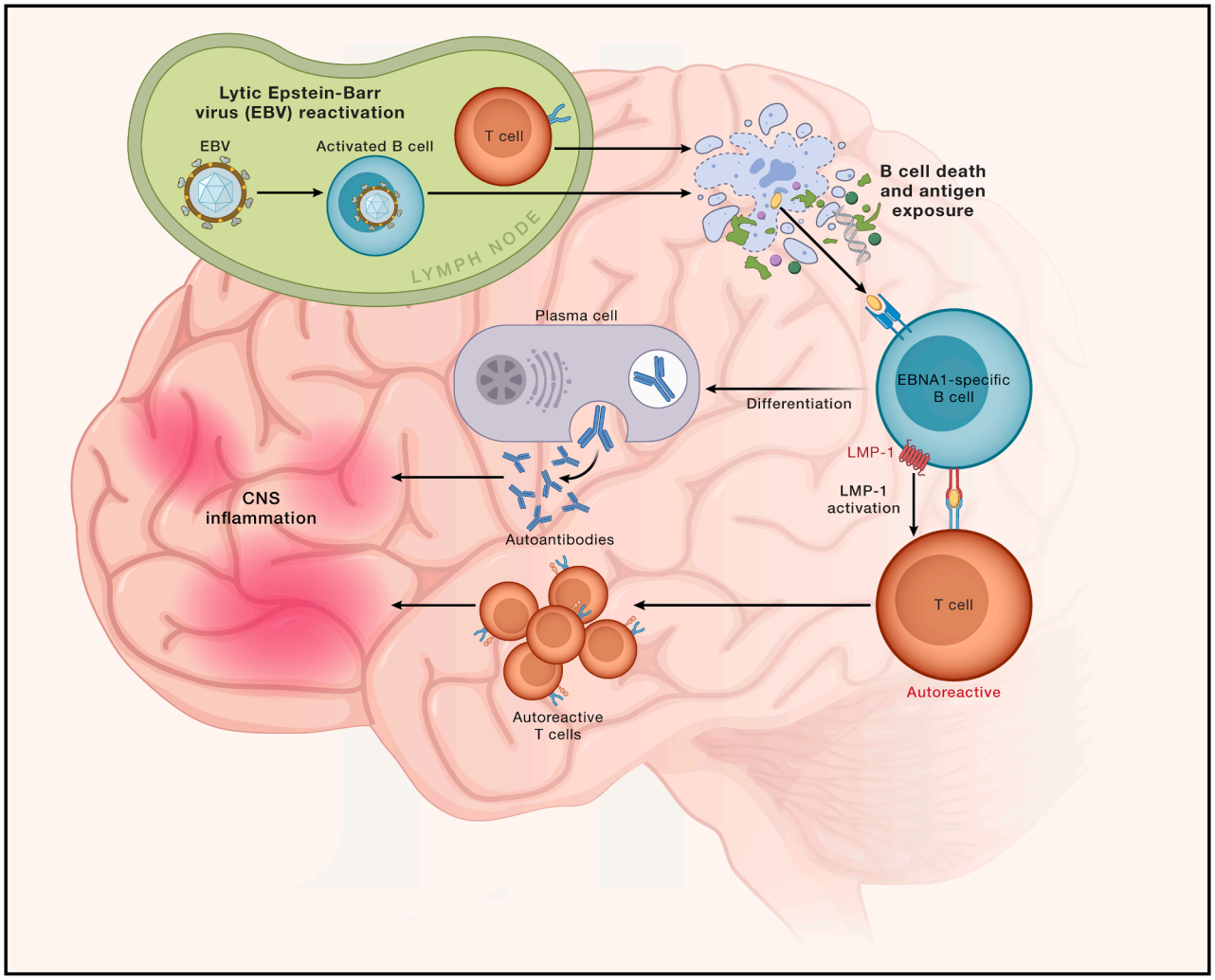

Figure 1. EBV transforms B cells to become antigen-presenting cells in the brain

Inset: In the lymph nodes, EBV infects B cells in the periphery, eliciting LMP1. In the brain, T cells and B cells home to the central nervous system via alpha4 integrin (ITGA4) on their surface. Within the central nervous system, B cells, via their B cell receptor, encounter antigens including GlialCAM, CRYAB, MBP, and ANO2. LMP1 prevents antigen-induced cell death, and the B cells are able to present these EBNA1 mimics to T cells, inducing a pathologic loop where autoantigen triggers both antibody production via plasma cells and expansion of antigen-specific T cells.[12]

demonstrate that immunization with ANO2, as well as adoptive transfer of ANO2-reactive T cells, can worsen experimental autoimmune encephalomyelitis. The presence of ANO2 antibodies, as well as carrying the HLA DRB1*15:01 gene and having the anti-EBNA1 antibody, increases the odds ratio of getting MS approximately 5-fold.

Here, Thomas and co-workers[3] discuss how an autoimmune attack against ANO2 in MS could arise through secondary uptake of cell debris from ANO2-bearing target cells. Subsequent uptake by B cells infected with EBV and transformed by its LMP1 protein could then lead to presentation of ANO2 to specific T cells. This raises the potential and plausible scenario whereby an attack against myelin within the central nervous system could create a debris field. Thomas and colleagues performed experiments that successfully show how debris from an inflammatory attack against myelin can activate a T cell reactive to ANO2.

There are multiple pathophysiologic mechanisms in play after EBV infection of B cells in MS. Molecular mimicry that exists within a stretch of 50 consecutive amino acids of EBNA1 and myelin proteins is one mechanism.[5–10] Now scientists are focusing on how EBV transforms antigen presentation of the immunopeptidome in B cells as they collaborate with T cells in the complex pathophysiology of MS.

Recently, we learned that other diseases where EBV infection is prominent, like systemic lupus erythematosus, also illustrate how the EBV hijacks the process of antigen presentation.[11] Research on the pathophysiology that may emerge in susceptible individuals after infection with EBV has evolved from studies on molecular mimicry to detailed studies on the transformed capacity of B cells to present antigens in the central nervous

system in MS and other autoimmune conditions.[10,11]

DECLARATION OF INTERESTS

The authors declare no competing interests.

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