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EBV and MS: The evidence is growing stronger

Autoimmune cross-reaction of specific antibodies to Epstein-Barr virus (EBV) has been associated with development of multiple sclerosis (MS). In this issue of *Cell*, Vietzen et al. identify additional immunological regulatory mechanisms that protect against autoimmunity in healthy people but are reduced in MS cases. The results confirm the link between EBV and MS.

Multiple sclerosis (MS) affects the brain and various nerves, including the peripheral nerve system, with localized damage to the myelin sheath around neurons reducing nerve function. MS is an autoimmune disease that has long been suspected to be associated with Epstein-Barr virus (EBV) infection. In this issue of *Cell*, Vietzen et al.[1] identify mechanisms that normally control the degree of EBV autoimmunity but are reduced in MS cases. The results confirm that autoimmune cross-reaction of some antibodies to the EBV EBNA1 protein with a protein in glial cells triggers nerve damage in MS.

Most people become infected by EBV and then carry the virus for life as a latent infection in long-lived memory B lymphocytes, occasionally reactivating virus production and shedding infectious virus in their saliva. Typically, people become infected by EBV in early childhood with no apparent symptoms. If EBV infection is delayed until late teenage years or adulthood, some people are still asymptomatically infected, but others experience infectious mononucleosis caused by an excessive immune response to the EBV infection. Usually, the exaggerated immune reaction subsides after a while, after which individuals carry the virus for life, as do individuals who were infected as young children. Such symptom-free carriers of EBV have antibodies in their blood to various epitopes in EBNA1 and some other EBV proteins.

Long-term control of EBV in infected individuals is mainly mediated by cytotoxic T cells, which recognize epitopes from EBV proteins. In contrast, the pathogenic MS autoimmune response to EBV EBNA1 protein is thought to be mainly due to certain cross-reacting antibodies to EBNA1. The importance of antibodies in the MS mechanism is supported by the efficacy of some treatments for MS, which either deplete B lymphocytes (Ocrelizumab) or prevent B lymphocytes from crossing the blood-brain barrier (Nataluzimab).

Two important recent papers[2,3] set the scene for the new results reported by Vietzen et al.[1] First, a remarkable epidemiological study using the medical records and stored serum samples of 10 million US military service personnel showed a clear link between delayed EBV infection and subsequent development of MS.[2] The risk factor for MS after delayed EBV infection was increased 32-fold compared to EBV infection in early childhood. Experiencing the symptoms of infectious mononucleosis only accounted for a small part of that 32-fold increased risk, so it is mainly the immune response to delayed EBV infection that gives the MS risk.[2]

The second big advance was identification of a specific antibody response to an epitope in the EBV EBNA1 protein that seems to mediate the disease. These antibodies to amino acids 386–405 of EBNA1 do not react with myelin but recognize amino acids 370–389 of the GlialCAM protein in nerve tissue.[3] This protein is expressed in glial cells and helps to maintain the myelin sheath on neurons. A monoclonal antibody corresponding to this cross-reacting specificity was shown to cause MS-like symptoms in a mouse model for the disease, and the presence of these antibodies in people correlates with MS.[3] Antibodies cross-reacting with αβ-crystallin have also been described.[4]

So far, so good, but there were still some clear examples of people who could potentially make such autoreactive antibodies without developing MS. Additional variables regulating the basic mechanism have now been identified by Vietzen et al.[1] Their new data reveal that autoreactive cells may be eliminated by certain cytotoxic natural killer cells and by some EBV-specific T cells that can target the autoreactive GlialCAM-specific B cells. Immune evasion of the auto-reactive cells was found to depend on induction of HLA-E expression, which can occur in response to IL27 or the LMP1 protein of EBV. Natural sequence variation in LMP1 and in the HLA-E alleles affected the magnitude of the HLA-E dependent effects. Taking into account the complex interplay of all these variables resulted in a huge risk factor of up to 260-fold that links delayed EBV infection in those who carry the appropriate risk alleles to future development of MS.[1] Such a high risk factor validates this as the mechanism.

Could novel forms of intervention such as EBV vaccines prevent MS? Antibodies to some of the surface glycoproteins on EBV (gp350, gp42, etc.) can neutralize EBV infection of B lymphocytes in cell culture, and an early clinical trial showed that immunization of EBV-negative adults with a soluble form of EBV glycoprotein gp350 partly reduces the incidence of infectious mononucleosis, but it did not prevent EBV infection.[5] A more immunogenic version of the gp350 vaccine[6] is now being trialed by the NIH NIAID with Novavax, while Moderna is testing an EBV mRNA vaccine. Those vaccines might also be tested for prevention of EBV transplant lymphomas and infectious mononucleosis, but no vaccine to EBV or any of the other herpes viruses has yet given sterilizing immunity to infection. It is not known whether the EBV vaccines will result in an immunological state similar to childhood EBV infection or more like the asymptomatic adult infection. Notably, there are differences in the consequences of EBV infection depending on whether it occurs in infancy or adulthood. The hematology and immunology of infants are well known to differ in various ways from adults. It has also become clear that EBV infects a wider range of cell types in infants than in adults. B lymphocytes are the main blood cell type that EBV infects, but in infants, some T cells[7,8] and probably some NK cells[9] also become infected. At present, what determines the long-term differences between being infected by EBV as an infant or an adult is not known, and it will be important to consider these factors in any potential future testing of EBV vaccines in relation to MS.

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