Epstein-Barr Virus and Multiple Sclerosis

ALTHOUGH THE CAUSE OF MULTIPLE SCLEROSIS (MS) is unknown, clinical and pathologic evidence strongly suggest a link between an infectious agent and an autoimmune response directed against myelin.[1-3] Epidemiologic studies also have implicated an environmental factor, most likely an infectious agent, as a necessary element in the development of MS.[2] One possibility is that antigens from infectious pathogens may activate autoreactive T cells, causing them to expand and leading to clinical autoimmune disease.[4,5] However, molecular mimicry (as this process is termed) has found limited empirical support as a general mechanism to explain the origin and course of a broad range of autoimmune diseases. Another possibility is that rather than there being a specific pathogen causing MS, infections in and of themselves may be able to aggravate autoimmune processes. For example, infectious processes such as *Chlamydia pneumoniae* can activate antigen-presenting cells and consequently activate autoreactive T cells that do not cross-react with chlamydial antigens.[6] The diversity of infectious agents associated with

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onset or exacerbation of clinical MS, the difficulty in identifying pathogen-associated antigens that activate autoreactive T cells, and the demonstration that antigen-presenting cell activation by infection can trigger an autoimmune response all suggest that the role of infection in autoimmunity may not be specific to a particular pathogen.

Epstein-Barr virus (EBV) is a pathogen that has been associated with the pathogenesis of MS. The titer of antibodies directed against EBV are higher in patients with MS than in control subjects.[7] While almost all patients with MS are seropositive for EBV, about 10% of the general population is seronegative for the virus. Patients with MS are more likely to have had a history of mononucleosis than people who do not develop the disease. In addition, children who develop MS can be distinguished from control subjects by higher immunoreactivity to EBV but not to other common viral pathogens.[8] A similar observation was made in donors who later went on to develop MS.[9] Another possible indicator of EBV in the pathogenesis of MS is the observation that there is an increase in EBV DNA levels in the blood of patients with MS during relapse.[10]

Recent studies have used sophisticated molecular techniques to implicate EBV in the pathogenesis of MS. One common observation in MS is the development of oligoclonal antibodies in the cerebrospinal fluid. One such study screened the oligoclonal antibodies from patients with MS on protein expression arrays and demonstrated that the most frequent MS-specific reactivities were identified as EBV proteins, including the Epstein-Barr nuclear antigen (EBNA-1).[11] Interestingly, $CD8^+$ T cell responses were also examined to the latent EBV proteins and were found to be higher in patients with MS than in controls.

In this issue of the ARCHIVES, DeLorenze and colleagues[12] studied the levels of anti-EBV antibodies in blood specimens collected up to 30 years prior to the onset of MS. The antibody titers to both the Epstein-Barr nuclear antigen complex and EBNA-1 were significantly higher in patients with MS compared with matched controls. A 4-fold increase in antibody titers for the EBNA complex increased the relative risk for MS by 2.1 and for EBNA-1 by 1.8. This prospective study with a 30-year follow-up period suggests that elevation of EBV antibody titer could be a very early event in MS.

Keeping the previously mentioned results in mind, how can EBV participate in MS pathogenesis? One possibility is that the virus could persist in the central nervous system and become reactivated at times of disease activity. Glia cells can express the EBV entry receptor and can be infected with the virus; however, EBV messenger RNA has not been detected in MS lesions.[13] Another possibility is that infected B cells could spread the virus to the central nervous system and that a local antiviral immune response could contribute to establishing inflammation in the central nervous system.

Another potential scenario hypothesizes that EBV-infected peripheral B cells may trigger an immune response against the virus that may trigger a cross-reactive autoimmune response against central nervous system antigens (molecular mimicry). Reactivation of the virus could expand both the T-cell and antibody response against the virus. Because of the life-long persistence of EBV in infected individuals and its potential for several rounds of reactivation, we can envision a scenario where this cross-reactive autoimmune response can be stimulated for decades before eventually eliciting the clinical signs of MS. The present study gives credence to this hypothesis by demonstrating the presence of high anti-EBV titers decades before the clinical appearance of MS. Interestingly, decades are not always required as noted by the observation that even pediatric patients with MS can have elevated titers of EBV.[8]

As researchers solidify the link between EBV and MS, important questions still remain. If many individuals can harbor EBV and make an immune response against the

virus, what are the mechanisms that result in disease initiation and progression? Furthermore, would patients with MS who make an immune response against EBV that cross-reacts with myelin antigens benefit from strategies that alter the latency of EBV or the immune response against the virus? These are questions that remain to be answered and could address the fundamental role of infections in autoimmunity. Until that time, the current data suggest that EBV is one of many pathogens that has the potential to increase an individual's susceptibility to developing MS.

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Announcement

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