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MINIREVIEW

Epstein-Barr Virus: Environmental Trigger of Multiple Sclerosis?▽

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Autoimmune diseases affect approximately 5% of the population in the United States and are the third most common disease category after cancer and heart disease. At least 15 diseases are known to be the direct result of an autoimmune response, while circumstantial evidence implicates autoimmunity in more than 80 conditions. Multiple sclerosis (MS), autoimmune skin and thyroid diseases, systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA) are among the most prevalent disorders in this category.

Diseases of autoimmune origin are generally believed to arise from unfortunate combinations of genetic susceptibility and environmental insults. HLA-DR and -DQ alleles within the HLA class II region on chromosome 6 are by far the strongest risk-conferring genes for most of the aforementioned entities. Viral and bacterial infections are logical candidates as environmental triggers. However, for the numerous agents that have been linked with specific autoimmune diseases based on serology, pathology, or virus isolation, none of the postulated associations has been conclusive. The difficulty in identifying a causative single microorganism might indicate that Koch's paradigm, "one organism, one disease," does not apply to such complex diseases and suggests that several different agents can induce or exacerbate autoimmune diseases and that these are most likely ubiquitous pathogens of a high prevalence in the population (37, 69).

Epstein-Barr virus (EBV) has been a leading candidate trigger for several autoimmune diseases since the initial description of raised EBV-specific antibody titers in patients with SLE in 1971 (23). EBV is a biologically plausible candidate since it is ubiquitous in nature, establishes a lifelong dormant infection with continuous virus production due to reactivation, and modulates the human immune system. In its immune-modifying function, EBV rescues infected B cells via latent antigen expression and assists their differentiation into memory B cells, in which it persists. In addition, the virus continuously stimulates strong T-cell responses via chronic antigen presence, and this immune control is crucial to prevent EBV-associated malignancies.

Recent studies indicate that EBV-specific cellular and humoral immune responses and the regulation of viral persistence in EBV-infected memory B cells are altered in patients with autoimmune diseases (3, 29, 38, 52, 54, 79, 80). In MS patients, longitudinal analyses of serum samples collected more than 10 years before the onset of clinical symptoms consistently showed that the risk of developing the disease increased significantly with the level of EBV antibody titers, and the strongest association was found for immunoglobulin G (IgG) antibodies binding to a EBV latent antigen, nuclear antigen 1 (EBNA1) (3, 21, 46). The mechanisms responsible for the association of EBV infection and the evolution of MS have so far not been clarified. In this review, we will discuss new evidence and hypotheses for a potential linkage between host-EBV interactions and the initiation as well as maintenance of autoimmune diseases. Since the existing literature suggests that different mechanisms lead to EBV association with the various autoimmune diseases, we will focus our discussion primarily on MS and refer to SLE and RA only when similarities or differences between these diseases and MS have been clearly defined.

MULTIPLE SCLEROSIS

MS is a chronic inflammatory disease of the central nervous system (CNS) which usually begins in early adulthood and is characterized by demyelination and gliosis, with various degrees of axonal pathology and episodic or progressive neurological disability. More than 1 million people worldwide and at least 350,000 individuals in the United States alone are affected by MS, which is second only to trauma as a cause of acquired disability in young adults in most Caucasian populations (69). Numerous studies on the genetic epidemiology of MS provide compelling evidence that the susceptibility to the disease is inherited, although additional environmental factors might be necessary to trigger the disease. The disease prevalence of MS varies between 60 and 200 per 100,000 people in North America and Northern Europe and generally follows a north-to-south gradient in the northern hemisphere and the opposite in the southern hemisphere, with very low rates or a virtual absence of the disease near the equator.

The heterogeneous nature of MS is reflected by its variable clinical phenotype, its nonuniform neuropathology, and its het-

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erogenous molecular pathogenesis. Autoreactive T cells are considered to play a key role in mediating the disease process. Evidence for the latter stems from the composition of inflammatory infiltrates, which consist mainly of lymphocytes and monocytes, in the CNS and from data from its animal model, experimental allergic (autoimmune) encephalomyelitis. In this model, the injection of myelin components into susceptible animals leads to a $CD4^+$ T-cell-mediated autoimmune disease resembling MS, which can be adoptively transferred from sick to naïve animals via encephalitogenic $CD4^+$ T cells. A role for autoaggressive T cells in MS pathology is further supported by the fact that certain major histocompatibility complex (MHC) class II alleles, in particular the HLA-DR2 haplotype, represent the strongest genetic risk factor, presumably as restriction elements of pathogenic $CD4^+$ T cells and by the therapeutic, though limited, efficacy of immunosuppressive and immunomodulatory agents.

A persistent synthesis of IgG antibodies in the cerebrospinal fluid (CSF) is an immunological hallmark in MS. In the steady state, only a very low number of B cells are trafficking through the human brain (2). Once inflammation has started, however, B cells, antibodies, and complement can enter the CNS compartment and B cells, plasma cells, and myelin-specific antibodies are detected in late chronic MS plaques as well as in areas of active demyelination in MS patients (59). Autoreactive antibodies can cause demyelination by opsonization of myelin for phagocytosis and via complement activation, leading to membrane attack complex deposition and complement-mediated cytolysis (70). In contrast to the phenotypic composition of B cells in the blood, most of the B cells in the CSF of patients with MS display a memory phenotype ($CD27^+$) (16). A receptor analysis of T cells and B cells in the CSF and brain tissue of patients with MS showed clonal expansions in both populations, indicating clonal reactivity to just a few disease-relevant antigens that are yet incompletely defined (30).

In addition to genetic predisposition for MS via distinct MHC class II alleles, inflammatory events are considered to initiate and drive the disease process during early stages. The myelin damage and axonal injury that accounts for the permanent neurological deficit seen during later phases of MS likely result from a complex sequence of events, including processes intrinsic to the CNS, such as increased vulnerability to tissue injury and/or poor repair, which might progress independently of immune pathology. MS is therefore not solely a disease of the immune system; rather, CNS-specific components, though largely overlooked in their potential disease-promoting role during the past decades, are presumably equally important for its pathogenesis (26, 69).

For many years, an infectious etiology of MS has been suspected, as it fits with a number of epidemiological observations about, and immunopathological characteristics of, the disease. Migration studies showed that individuals who migrate from high-risk to low-risk areas after the age of 15 tend to take their risk of MS with them, whereas individuals who migrate from high-risk to low-risk areas before the age of 15 acquire a lower risk, indicating that childhood exposure to an environmental factor increases disease susceptibility. These observations suggest that an environmental factor is relevant for the initiation of the disease process (41). In addition, viral infections are closely associated with clinical disease exacerbation (67).

As for the other major autoimmune diseases, no specific transmissible agent has so far been linked convincingly to MS. The most consistent data for a potential role in the disease exist for EBV and neurotropic human herpesvirus 6 (HHV-6) based on the detection of viral DNA in some brain specimens derived from MS lesions (in the case of HHV-6) and on consistent seroepidemiological studies (46, 68). Both are ubiquitous viruses that act at the population level and produce latent, recurrent infections. The mechanisms by which these viruses and other potential candidates might initiate, exacerbate, and perpetuate the disease are, however, far from understood. However, the immunobiology of EBV might suggest mechanisms by which this persistent oncogenic virus might be involved in the initiation and exacerbation of the autoimmune disease MS.

EPSTEIN-BARR VIRUS: HOST-PATHOGEN INTERACTIONS

EBV manipulates the human B-cell compartment to achieve persistence in memory B cells (4). The virus preferentially infects B lymphocytes through binding to the CD21 receptor and MHC class II as its coreceptor (24, 49). EBV-infected B cells in vivo can express four different programs of gene usage, depending on the location and the differentiation state of the infected B cell (5, 42). The lytic program is used to produce infectious virus. The other three programs are all associated with latent infection, in which no infectious virus is produced, and are known as follows: the growth program, in which all eight known latent proteins are expressed and stimulate proliferation of the infected host cell; the default program, in which a restricted set of three latent proteins are expressed and help infected B cells to survive the germinal center reaction by mimicking B-cell receptor signaling and T-cell help; and the latency program, in which the virus persists in memory B cells without EBV protein expression. All of these confer resistance to apoptosis induction to various degrees, increasing with the number of expressed latent EBV antigens, as suggested by a recent study of Burkitt's lymphoma variants (39). This result suggests that EBV might be able to sustain autoreactive B cells, as discussed in more detail below.

In healthy virus carriers, EBV persists in a lifelong manner in a transcriptionally quiescent state within the resting memory B-cell compartment (4). Lytic EBV infection can be activated from the memory B-cell pool, presumably after an encounter with the cognate B-cell receptor antigen (42). Among more than 80 lytic and 8 latent EBV gene products, the latency-associated EBNA1 is the only protein consistently expressed in infected proliferating memory B cells in healthy virus carriers (33). During homeostatic B-cell division, EBNA1 initiates viral replication by binding to the EBV circular DNA or episome with its C-terminal domain and cross-links the episome to mitotic chromosomes as a protein anchor, thereby accomplishing the transmission of the episome into progeny cells (36). Persistent infection is characterized by stable numbers of latently infected B cells in the blood (0.5 to 50 per million) and the steady shedding of infectious virus into saliva (40). EBNA1, the crucial EBV antigen for persistence of the virus, constitutes a dominant antigen for both humoral and cell-mediated immune responses to the virus, and the deregulation

of EBV-specific immunity in MS has been characterized primarily for this antigen.

In humoral immunity to EBV, most antibody responses, such as the IgM, IgA, and IgG responses to virus-encoded nucleocapsid antigens (VCA) and the IgG responses to the EBV latent antigen EBNA2 peak during acute infection, are against latent and lytic antigens (18, 64). The expansion of these antibody responses probably follows the availability of their respective antigens. In contrast, antibody responses against EBNA1 and the most abundant viral envelope protein, gp350, do not follow this pattern. Both reach their highest titer during convalescence from infectious mononucleosis (IM) (31, 77). IgG responses against gp350 have proven to be neutralizing (34, 76) and might contribute to the resolution of IM. EBNA1-specific antibodies are, however, most probably useless for protective humoral immunity to EBV, since the EBNA antigens are expressed only intracellularly. Nevertheless, most healthy virus carriers maintain anti-EBNA1 as well as anti-gp350 and anti-VCA IgG responses during persistent EBV infection (64), and these responses are used diagnostically to assess if individuals have been infected with EBV. Deregulation of these EBV-specific antibodies was found to be associated with autoimmune diseases, including MS, and has spurred investigations into a possible contribution of this virus for disease progression.

The initiation of EBV-specific immune control is probably mediated by dendritic cells cross-presenting EBV antigens from infected B cells, and then it centers around strong memory $CD4^+$ and $CD8^+$ T-cell responses, whereby the $CD4^+$ T cells maintain EBV-specific Th1 immunity, and both $CD4^+$ and $CD8^+$ T cells target EBV-infected cells directly. $CD8^+$ T cells expand dramatically during acute infection, with up to 25 to 50% of all $CD8^+$ T cells being directed against individual EBV lytic antigens in certain patients with the symptomatic primary EBV infection IM (13, 14). During persistent EBV infection, both lytic and latent EBV antigen-specific $CD8^+$ T cells can be maintained at frequencies of up to 1 to 5% of peripheral blood $CD8^+$ T cells (73). $CD4^+$ T cells are thought to orchestrate virus-specific immune responses and are crucial for the priming and maintenance of $CD8^+$ T cells (7, 15, 65, 66, 87). The functional differentiation of virus-specific $CD4^+$ T cells is crucial for efficient humoral or cell-mediated immune responses. Th1 responses, which are characterized by the secretion of the antiviral cytokine gamma interferon, are more protective against viral infections and support the generation of virus-specific $CD8^+$ T cells, which are the effectors of cell-mediated adaptive immunity (53) (63). Even during primary infection in IM patients, EBV-specific $CD4^+$ T cells never reach the high frequencies of EBV-specific $CD8^+$ T cells in peripheral blood. Virus-specific $CD4^+$ T cells reach only one-tenth of the frequency of their EBV-specific $CD8^+$ T-cell counterparts during primary and persistent infection, and it has become evident that $CD4^+$ T cells target a different set of latent EBV antigens than $CD8^+$ T cells.

EBNA1 was shown to be consistently recognized by $CD4^+$ T cells of healthy EBV carriers and evoked responses more frequently than any other latent EBV antigen. EBNA1-specifc $CD4^+$ T cells are Th1 in function (45, 55) (8), recognize autologous EBV-transformed B-cell lines (B-LCL) (51, 82), and have the capacity to kill EBNA1-expressing targets via CD95/CD95L (60) as well as the ability to inhibit the outgrowth of B-LCL in vitro (57) and of EBNA1-positive Burkitt's lymphoma cells in vivo (27). Thus, T cells specific for EBNA1 are considered to be a crucial component of EBV-specific immune control. The characteristic glycine-alanine repeat of the protein inhibits its proteasomal degradation (9, 44, 47, 48) but does allow MHC class II loading via autophagy-mediated pathways and the recognition of EBNA1-expressing targets (61). EBNA1 is therefore the only EBV antigen consistently expressed in proliferating cells with latent EBV infection in healthy virus carriers and represents a key target antigen for $CD4^+$ T cell-mediated immune control mechanisms of EBV infection in healthy individuals.

ALTERED IMMUNE RESPONSES TO EBV IN MULTIPLE SCLEROSIS

Epidemiological studies first reported a positive association between a history of IM and the occurrence of MS (50, 56, 58). A recent cohort study consisting of more than 25,000 Scandinavian patients with IM who were followed up for the occurrence of MS (56) and a meta-analysis of smaller previous studies on the association of IM and MS pointed out that individuals with a history of IM have a more-than-twofold-increased risk of developing MS compared to subjects who acquired the virus without symptoms (74). By comparison, a history of IM is associated with a not-higher-than-fourfold-increased risk for EBV-associated Hodgkin's lymphoma (32). Large prospective seroepidemiological studies analyzing antibody responses to standard diagnostic enzyme-linked immunosorbent assay antigens consistently demonstrated that MS patients are universally, i.e., close to 100%, seropositive for EBV, supporting the argument that infection with EBV was a possible requirement for the development of MS (3, 10, 46, 71, 81, 83). The differences in EBV seroprevalence between subjects with MS and age-matched, healthy individuals became even more evident in a pediatric MS cohort (83% versus 42%, respectively) (1). Similar results were also reported for pediatric lupus patients (54). A recent German study even found near-complete seropositivity for EBV antibodies in children with MS (98.6% versus 72.1% for age-matched healthy controls tested for VCA-IgG) (62).

Further indicating an association between EBV infection and the development of MS, several independent longitudinal investigations of serum samples collected before the onset of disease in an healthy adult population showed that the risk of developing the disease increased significantly with elevated EBV-antibody titers more than 10 years before occurrence of the first symptoms, and the strongest association was found for EBNA1-specific IgG (3, 21, 46). Findings of increased antibody titers in patients with MS have to be interpreted with some caution, since elevated levels of various infectious agents have been reported in patients with autoimmune diseases and only a small number of studies included the appropriate controls, such as immune responses to other and closely related viruses. The quality of these studies has been substantially improved over the last years, and all of the above-mentioned investigations were prospective and well-controlled investigations. However, another prospective European study also reported increased titers to HHV-6 and measles virus to be associated

with the development of MS (71). Therefore, although current data consistently show that symptomatic primary EBV infection predisposes individuals for MS, it is less clear whether and to what degree the increase in virus-specific antibody responses prior to the onset of clinical symptoms is specific for EBV or whether it is merely a sign of a less specific immune dysregulation.

The CSF of patients with MS is enriched with clonally expanded memory B cells (16, 19, 20), and the presence of oligoclonal IgG is a long-known hallmark immunological finding with MS. Despite this fact, memory B-cell and oligoclonal IgG specificities are largely unknown. By using a cDNA library derived from fetal brain tissue and epitope-mapping techniques to analyze the specificities of oligoclonal IgG antibodies in the patients' CSF compared to that for other neuroinflammatory diseases, the two most frequent MS-specific and high-affinity epitopes were identified. Both of them, EBNA1 and another, less-characterized structural EBV protein (BRRF2) (17), derived from EBV. This study is in accordance with previous reports on a higher frequency of CSF-derived EBNA1-specific IgG antibodies in patients with MS (11), suggesting that EBV-specific antibodies not only are systemically elevated in MS but also are enriched in the CSF of affected patients, possibly contributing to MS pathology.

Other, albeit indirect evidence for a putative role of EBV in MS came from studies of individual receptors of pathogenic T-cell clones. In an attempt to characterize molecular mimics to immunodominant myelin-derived T-cell epitopes, Wucherpfennig and Strominger identified several virus-derived peptide sequences that were stimulatory for a myelin basic protein (MBP) (peptides 83 to 99)-specific $CD4^+$ T-cell clones (85). One of the mimics with strong agonistic activity was derived from the DNA-polymerase protein of EBV, and Lang and coworkers showed that one of the cross-reactive T-cell clones recognized the MBP peptide with DR2b (DRB1*1501) and the EBV peptide in the context of DR2a (DRB5*0101), notably the two HLA-class II molecules with the strongest genetic association with MS (43). While these elegant experiments demonstrated molecular mimicry between EBV- and CNS-derived epitopes in the context of the most important genetic risk factors for MS, the relevance of these studies for MS is, however, less clear since it is not known whether EBV DNA polymerase-specific immune responses are part of EBV-specific immune control in humans and whether they qualitatively or quantitatively differ in patients with MS.

At the level of EBV-specific T-cell responses, we recently could determine that patients with MS showed enhanced Th1-polarized responses to EBNA1, which could be attributed primarily to $CD4^+$ memory T cells. In addition, patients with MS showed a substantially broadened epitope recognition by EBNA1-specifc $CD4^+$ T cells compared to healthy virus carriers matched for age and gender and, notably, also for the expression of MS-associated MHC class II alleles (52). In healthy individuals, the vast majority of positive responses were directed toward the central part of the immunogenic C-terminal domain of EBNA1 (amino acids 452 to 548). Interestingly, no clear immunodominance was detected in patients with MS. The frequency of EBV-specific $CD8^+$ T cells targeting selected lytic and latent EBV antigens did not differ between patients and controls (28, 52). Quantification of EBV viral loads in peripheral blood mononuclear cells by real-time PCR showed higher levels of EBV copy numbers in some patients with MS, although the overall difference in viral loads was not statistically significant compared with that for healthy virus carriers (52). Viral loads increased up to 40-fold have been described for patients with SLE (38), and viral loads increased up to 10-fold have been described for patients with RA (6). These findings suggested that, although the virus is efficiently controlled, the EBNA1-specific $CD4^+$ T-cell response is selectively deregulated in MS, and T-cell specificities, which were preferentially detected in MS patients, might promote disease progression.

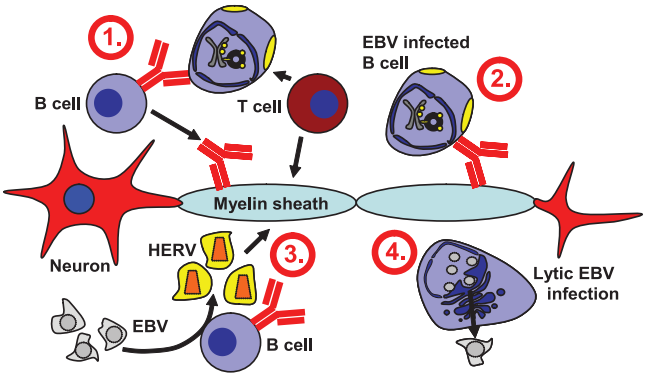

FIG. 1. Potential mechanisms responsible for the association of EBV infection with MS. (1) EBV-specific T cells or antibodies could cross-react with autoantigens expressed in the CNS and attack the myelin sheath of axons. (2) Latent EBV antigens could sustain the survival of autoreactive B cells. (3) EBV infection transactivates retroviral elements such as HERVs, which in turn mediate cell death of oligodendrocytes. (4) Autoreactive B-cell activation could initiate EBV replication and in turn augment EBV-specific T- and B-cell responses.

Altogether, the volume of data linking EBV with MS is substantial. However, most studies demonstrate only descriptive epidemiological and serological evidence that EBV is a critical factor for the development and progression of the disease and lack mechanistic insights. Despite an increasing knowledge of cell-mediated EBV-specific immune control mechanisms in healthy virus carriers and their failure in patients with EBV-associated malignancies, our understanding of the mechanism responsible for the altered immune recognition of EBV in patient with MS and for the impact on the immunopathogenesis of MS is still sparse.

POTENTIAL MECHANISMS FOR EBV INFECTION IN MS PATHOGENESIS

We propose four main possible scenarios that could explain the altered humoral and cell-mediated immune responses to EBV in patients with MS and the potential contribution of EBV to the pathogenesis of the disease (Fig. 1). The scenarios are based on the assumption that host factors predisposing for MS, such as allelic variants of susceptibility genes, influence the immune response to EBV, and all scenarios could apply to other autoimmune diseases.

(i) Protective T-cell responses to EBV initiate and sustain autoimmunity in MS. EBV continuously stimulates strong T-cell responses during persistent infection. In regression assays,

the in vitro outgrowth and Ig production of EBV-infected B cells is usually suppressed by cocultured autologous, in vivo-primed EBV-specific T cells. Patients with SLE and RA were reported to have defective EBV-specific immune control in such assays (78, 80). More recently, Kang et al. found that lupus patients have a tenfold-increased frequency of EBV lysate-stimulated gamma interferon-producing $CD4^+$ T cells (38). The up-to-40-fold EBV viral load increases in SLE patients were positively correlated with the frequency of $CD4^+$ and inversely correlated with the frequencies of $CD8^+$ T cells, indicating a role for $CD4^+$ T cells in controlling, and a possible defect in $CD8^+$ T cells in regulating, increased viral loads in lupus patients. Patients with MS show increased frequencies of EBNA1-specific $CD4^+$ T cells (52). It is currently, however, not clear whether the increased EBV-specific $CD4^+$ T-cell responses reflect enhanced stimulation via cross-recognition of myelin specific autoantigens ("molecular mimicry"). EBV viral loads are not substantially elevated in MS, and EBV-specific $CD8^+$ T-cell responses do not seem to differ from those of healthy virus carriers. This result supports the argument against enhanced EBV-specific $CD4^+$ T-cell reactivity being a result of increased EBV reactivation from auto-aggressive B cells, compensation for diminished EBV-specific $CD8^+$ T-cell responses, or of "bystander activation" due to the inflammatory environment of MS. However, until cross-reactive specificities of EBV-specific $CD4^+$ T-cell responses have been identified, the involvement of "molecular mimicry" in the pathogenesis of MS remains hypothetical.

(ii) EBV assists in the maintenance of autoreactive B cells. EBV gene products might stimulate cross-reactive autoimmune B cells directly or increase their survival after infection. Autoreactive B-cell species are normally neutralized or controlled by several tolerance checkpoints during B-cell development and differentiation. EBV-transformed B cells could be less susceptible to mechanisms of peripheral B-cell tolerance. Indeed, in mice transgenic for the EBV latent membrane protein 2 (LMP2) with targeted expression in their B-cell compartment, B cells which had escaped deletion in germinal centers despite faulty B-cell receptor expression could be found in the periphery (12). In addition to providing constitutive B-cell receptor signaling via LMP2, EBV mimics T-cell help for B-cell differentiation via LMP1 (75), possibly sustaining autoreactive B cells in the absence of autoreactive T cells. This might add to the already reported defects in B-cell tolerance checkpoints in patients with SLE (84, 86). Chronic stimulation of autoreactive B cells by autoantigens could, in turn, drive the replication of the virus and trigger enhanced EBV-specific T-cell immunity.

In addition, other viruses associated with MS, such as HHV-6, were reported to be capable of transactivating EBV in latently infected cell lines (25). Superinfection with and reciprocal effects between different pathogens could, hypothetically, stimulate autoreactive B cells in MS patients.

(iii) EBV transactivates the expression of HERV elements, which are cytotoxic for oligodendrocytes. Human endogenous retroviruses (HERVs) constitute 8% of the human genome and have been implicated in various disease states. Increased HERV gene activity occurs in immunologically activated glia and also in MS brain lesions. Oligodendrocytes which produce the insulating myelin sheath in the CNS were shown to be sensitive for HERV type W-encoded glycoprotein syncytin-mediated release of redox reactants from astrocytes in a mouse model of MS (2). EBV and other herpesviruses are capable of transactivating the expression of HERV elements in various in vitro models. It has been documented that EBV transactivates HERV-K18 from B cells after binding to CD21 (35, 72). Therefore, EBV-mediated transactivation of endogenous retroviruses, which can establish lytic replication or toxic defense mechanisms in oligodendrocytes, might potentially contribute to MS pathogenesis. However, EBV has never been documented in MS lesions or anywhere within the CNS compartment in patients with MS.

(iv) Altered immune responses to EBV as a nonpathogenic epiphenomenon. Altered EBV responses might be the result of certain host factors predisposing for autoimmune diseases, but they might not be directly involved in MS pathogenesis. The immune system is intimately involved in the regulation of EBV. The virus usurps the biology of mature B cells for its persistence in vivo and requires a strong cell-mediated immunity in order to limit its replication. A dysfunctional B-cell compartment, such as that in patients with SLE, likely affects the biology of EBV persistence with subsequent consequences for virus-specific cellular and humoral immune responses. Gross et al. showed that lupus patients have abnormally high frequencies of EBV-infected B cells in their blood with aberrant expression of viral lytic (BZLF1) and latent (latency membrane proteins 1 and 2a) genes (29). As suggested by the authors, these observations can be attributed simply to defects in the immune functions in SLE patients without the need to invoke or deny a causative role of EBV in the pathogenesis of SLE. Increased stimulation of the B-cell compartment by autoantigens could, for example, stimulate enhanced EBV replication, thereby increasing the viral load and antiviral immune responses. Alternatively, autoimmunity resulting from dysregulated regulatory T cells might also lead to enhanced EBV-specific immune responses, without them being responsible for MS pathogenesis. The sensitivity of the virus to perturbations of the immune system causes a dilemma in defining an experimental paradigm to test a causative role of EBV in human autoimmune diseases. Until now, although the concepts outlined above are highly intriguing, no data unequivocally support a direct etiologic role of the virus in the evolution of MS and other autoaggressive diseases.

CONCLUDING REMARKS

EBV has been a leading candidate trigger for several autoimmune diseases since the initial description of raised EBV-specific antibody titers in patients with SLE in 1971 (22). Although numerous studies have found increased seroprevalence rates, antibody titers, and T-cell reactivity to EBV in patients with major autoimmune diseases, unequivocal evidence for a causative role of the virus in the evolution of MS, SLE, or RA is still lacking.

In principle, the long coevolution and the intertwined relationship of EBV with the human immune system, in particular the virus's influence on B-cell biology and the requirement for a strong protective T-cell response, are compatible with both a pathogenic and an epiphenomenal function of EBV in autoimmune diseases. At the same time, the intimate involvement

of the immune system in the regulation of EBV makes it extremely difficult to constitute or to exclude a causative role for the virus in promoting autoimmunity.

The lack of seronegativity to EBV in adult patients and the substantially increased seroprevalence in children with MS, together with the consistent observation that the risk for developing the disease years before occurrence of the first symptoms increases significantly with the level of EBV antibody titers, suggest a possible involvement of EBV early in the pathogenesis. An interdisciplinary approach will be necessary to better understand the pathways by which EBV might trigger and sustain autoimmunity in a complex and heterogeneous disease like MS. Experimental mechanistic studies of immune functions in relation to the biology of EBV and in comparison to other infectious agents need to be combined with careful and detailed phenotypic patient characterizations. Since the absence of seronegativity and the increase in EBV-specifc IgG responses are universally present across patients with various and phenotypically different autoimmune diseases, it will be interesting to directly compare findings on the regulation of EBV infection in patients with MS, RA, and SLE, since the mechanisms responsible for aberrant humoral and cellular responses to EBV might be disease specific. The integration of these data might eventually allow us to better define the role of EBV in the etiology and pathogenesis of MS and other autoimmune diseases and might also generate exciting insights into the immunobiology of host-EBV interactions.

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REFERENCES

1. **Alotaibi, S., J. Kennedy, R. Tellier, D. Stephens, and B. Banwell.** 2004. Epstein-Barr virus in pediatric multiple sclerosis. JAMA **291:**1875–1879.
2. **Antony, J. M., G. van Marle, W. Opii, D. A. Butterfield, F. Mallet, V. W. Yong, J. L. Wallace, R. M. Deacon, K. Warren, and C. Power.** 2004. Human endogenous retrovirus glycoprotein-mediated induction of redox reactants causes oligodendrocyte death and demyelination. Nat. Neurosci. **7:**1088–1095.
3. **Ascherio, A., K. L. Munger, E. T. Lennette, D. Spiegelman, M. A. Hernan, M. J. Olek, S. E. Hankinson, and D. J. Hunter.** 2001. Epstein-Barr virus antibodies and risk of multiple sclerosis: a prospective study. JAMA **286:**3083–3088.
4. **Babcock, G. J., L. L. Decker, M. Volk, and D. A. Thorley-Lawson.** 1998. EBV persistence in memory B cells in vivo. Immunity **9:**395–404.
5. **Babcock, G. J., D. Hochberg, and A. D. Thorley-Lawson.** 2000. The expression pattern of Epstein-Barr virus latent genes in vivo is dependent upon the differentiation stage of the infected B cell. Immunity **13:**497–506.
6. **Balandraud, N., J. B. Meynard, I. Auger, H. Sovran, B. Mugnier, D. Reviron, J. Roudier, and C. Roudier.** 2003. Epstein-Barr virus load in the peripheral blood of patients with rheumatoid arthritis: accurate quantification using real-time polymerase chain reaction. Arthritis Rheum. **48:**1223–1228.
7. **Bennett, S. R., F. R. Carbone, F. Karamalis, R. A. Flavell, J. F. Miller, and W. R. Heath.** 1998. Help for cytotoxic-T-cell responses is mediated by CD40 signalling. Nature **393:**478–480.
8. **Bickham, K., C. Münz, M. L. Tsang, M. Larsson, J. F. Fonteneau, N. Bhardwaj, and R. Steinman.** 2001. EBNA1-specific $CD4^+$ T cells in healthy carriers of Epstein-Barr virus are primarily Th1 in function. J. Clin. Investig. **107:**121–130.
9. **Blake, N., S. Lee, I. Redchenko, W. Thomas, N. Steven, A. Leese, P. Steigerwald-Mullen, M. G. Kurilla, L. Frappier, and A. Rickinson.** 1997. Human $CD8^+$ T cell responses to EBV EBNA1: HLA class I presentation of the (Gly-Ala)-containing protein requires exogenous processing. Immunity **7:**791–802.
10. **Bray, P. F., L. C. Bloomer, V. C. Salmon, M. H. Bagley, and P. D. Larsen.** 1983. Epstein-Barr virus infection and antibody synthesis in patients with multiple sclerosis. Arch. Neurol. **40:**406–408.
11. **Bray, P. F., J. Luka, K. W. Culp, and J. P. Schlight.** 1992. Antibodies against Epstein-Barr nuclear antigen (EBNA) in multiple sclerosis CSF, and two pentapeptide sequence identities between EBNA and myelin basic protein. Neurology **42:**1798–1804.
12. **Caldwell, R. G., J. B. Wilson, S. J. Anderson, and R. Longnecker.** 1998. Epstein-Barr virus LMP2A drives B cell development and survival in the absence of normal B cell receptor signals. Immunity **9:**405–411.
13. **Callan, M. F., N. Annels, N. Steven, L. Tan, J. Wilson, A. J. McMichael, and A. B. Rickinson.** 1998. T cell selection during the evolution of $CD8^+$ T cell memory in vivo. Eur. J. Immunol. **28:**4382–4390.
14. **Callan, M. F., L. Tan, N. Annels, G. S. Ogg, J. D. Wilson, C. A. O'Callaghan, N. Steven, A. J. McMichael, and A. B. Rickinson.** 1998. Direct visualization of antigen-specific $CD8^+$ T cells during the primary immune response to Epstein-Barr virus in vivo. J. Exp. Med. **187:**1395–1402.
15. **Cardin, R. D., J. W. Brooks, S. R. Sarawar, and P. C. Doherty.** 1996. Progressive loss of $CD8^+$ T cell-mediated control of a gamma-herpesvirus in the absence of $CD4^+$ T cells. J. Exp. Med. **184:**863–871.
16. **Cepok, S., B. Rosche, V. Grummel, F. Vogel, D. Zhou, J. Sayn, N. Sommer, H. P. Hartung, and B. Hemmer.** 2005. Short-lived plasma blasts are the main B cell effector subset during the course of multiple sclerosis. Brain **128:**1667–1676.
17. **Cepok, S., D. Zhou, R. Srivastava, S. Nessler, S. Stei, K. Bussow, N. Sommer, and B. Hemmer.** 2005. Identification of Epstein-Barr virus proteins as putative targets of the immune response in multiple sclerosis. J. Clin. Investig. **115:**1352–1360.
18. **Cohen, J. I.** 2000. Epstein-Barr virus infection. N. Engl. J. Med. **343:**481–492.
19. **Colombo, M., M. Dono, P. Gazzola, N. Chiorazzi, G. Mancardi, and M. Ferrarini.** 2003. Maintenance of B lymphocyte-related clones in the cerebrospinal fluid of multiple sclerosis patients. Eur. J. Immunol. **33:**3433–3438.
20. **Colombo, M., M. Dono, P. Gazzola, S. Roncella, A. Valetto, N. Chiorazzi, G. L. Mancardi, and M. Ferrarini.** 2000. Accumulation of clonally related B lymphocytes in the cerebrospinal fluid of multiple sclerosis patients. J. Immunol. **164:**2782–2789.
21. **DeLorenze, G. N., K. L. Munger, E. T. Lennette, N. Orentreich, J. H. Vogelman, and A. Ascherio.** 2006. Epstein-Barr virus and multiple sclerosis: evidence of association from a prospective study with long-term follow-up. Arch. Neurol. **63:**839–844.
22. **Evans, A. S.** 1971. The spectrum of infections with Epstein-Barr virus: a hypothesis. J. Infect. Dis. **124:**330–337.
23. **Evans, A. S., N. F. Rothfield, and J. C. Niederman.** 1971. Raised antibody titres to E.B. virus in systemic lupus erythematosus. Lancet **i:**167–168.
24. **Fingeroth, J. D., J. J. Weis, T. F. Tedder, J. L. Strominger, P. A. Biro, and D. T. Fearon.** 1984. Epstein-Barr virus receptor of human B lymphocytes is the C3d receptor CR2. Proc. Natl. Acad. Sci. USA **81:**4510–4514.
25. **Flamand, L., and J. Menezes.** 1996. Cyclic AMP-responsive element-dependent activation of Epstein-Barr virus zebra promoter by human herpesvirus 6. J. Virol. **70:**1784–1791.
26. **Frohman, E. M., M. K. Racke, and C. S. Raine.** 2006. Multiple sclerosis—the plaque and its pathogenesis. N. Engl. J. Med. **354:**942–955.
27. **Fu, T., K. S. Voo, and R. F. Wang.** 2004. Critical role of EBNA1-specific $CD4^+$ T cells in the control of mouse Burkitt lymphoma in vivo. J. Clin. Investig. **114:**542–550.
28. **Gronen, F., K. Ruprecht, B. Weissbrich, E. Klinker, A. Kroner, H. H. Hofstetter, and P. Rieckmann.** 2006. Frequency analysis of HLA-B7-restricted Epstein-Barr virus-specific cytotoxic T lymphocytes in patients with multiple sclerosis and healthy controls. J. Neuroimmunol. **180:**185–192.
29. **Gross, A. J., D. Hochberg, W. M. Rand, and D. A. Thorley-Lawson.** 2005. EBV and systemic lupus erythematosus: a new perspective. J. Immunol. **174:**6599–6607.
30. **Hafler, D. A.** 2004. Multiple sclerosis. J. Clin. Investig. **113:**788–794.
31. **Henle, W., G. Henle, J. Andersson, I. Ernberg, G. Klein, C. A. Horwitz, G. Marklund, L. Rymo, C. Wellinder, and S. E. Straus.** 1987. Antibody responses to Epstein-Barr virus-determined nuclear antigen (EBNA)-1 and EBNA-2 in acute and chronic Epstein-Barr virus infection. Proc. Natl. Acad. Sci. USA **84:**570–574.
32. **Hjalgrim, H., J. Askling, K. Rostgaard, S. Hamilton-Dutoit, M. Frisch, J. S. Zhang, M. Madsen, N. Rosdahl, H. B. Konradsen, H. H. Storm, and M.**

Melbye. 2003. Characteristics of Hodgkin's lymphoma after infectious mononucleosis. N. Engl. J. Med. **349:**1324–1332.
33. **Hochberg, D., J. M. Middeldorp, M. Catalina, J. L. Sullivan, K. Luzuriaga, and D. A. Thorley-Lawson.** 2004. Demonstration of the Burkitt's lymphoma Epstein-Barr virus phenotype in dividing latently infected memory cells in vivo. Proc. Natl. Acad. Sci. USA **101:**239–244.
34. **Hoffman, G. J., S. G. Lazarowitz, and S. D. Hayward.** 1980. Monoclonal antibody against a 250,000-dalton glycoprotein of Epstein-Barr virus identifies a membrane antigen and a neutralizing antigen. Proc. Natl. Acad. Sci. USA **77:**2979–2983.
35. **Hsiao, F. C., M. Lin, A. Tai, G. Chen, and B. T. Huber.** 2006. Cutting edge: Epstein-Barr virus transactivates the HERV-K18 superantigen by docking to the human complement receptor 2 (CD21) on primary B cells. J. Immunol. **177:**2056–2060.
36. **Humme, S., G. Reisbach, R. Feederle, H. J. Delecluse, K. Bousset, W. Hammerschmidt, and A. Schepers.** 2003. The EBV nuclear antigen 1 (EBNA1) enhances B cell immortalization several thousandfold. Proc. Natl. Acad. Sci. USA **100:**10989–10994.
37. **Kamradt, T., and N. A. Mitchison.** 2001. Tolerance and autoimmunity. N. Engl. J. Med. **344:**655–664.
38. **Kang, I., T. Quan, H. Nolasco, S. H. Park, M. S. Hong, J. Crouch, E. G. Pamer, J. G. Howe, and J. Craft.** 2004. Defective control of latent Epstein-Barr virus infection in systemic lupus erythematosus. J. Immunol. **172:**1287–1294.
39. **Kelly, G. L., A. E. Milner, G. S. Baldwin, A. I. Bell, and A. B. Rickinson.** 2006. Three restricted forms of Epstein-Barr virus latency counteracting apoptosis in c-myc-expressing Burkitt lymphoma cells. Proc. Natl. Acad. Sci. USA **103:**14935–14940.
40. **Khan, G., E. M. Miyashita, B. Yang, G. J. Babcock, and D. A. Thorley-Lawson.** 1996. Is EBV persistence in vivo a model for B cell homeostasis? Immunity **5:**173–179.
41. **Kurtzke, J. F.** 2005. Epidemiology and etiology of multiple sclerosis. Phys. Med. Rehabil. Clin. N. Am. **16:**327–349.
42. **Laichalk, L. L., and D. A. Thorley-Lawson.** 2005. Terminal differentiation into plasma cells initiates the replicative cycle of Epstein-Barr virus in vivo. J. Virol. **79:**1296–1307.
43. **Lang, H. L., H. Jacobsen, S. Ikemizu, C. Andersson, K. Harlos, L. Madsen, P. Hjorth, L. Sondergaard, A. Svejgaard, K. Wucherpfennig, D. I. Stuart, J. I. Bell, E. Y. Jones, and L. Fugger.** 2002. A functional and structural basis for TCR cross-reactivity in multiple sclerosis. Nat. Immunol. **3:**940–943.
44. **Lee, S. P., J. M. Brooks, H. Al-Jarrah, W. A. Thomas, T. A. Haigh, G. S. Taylor, S. Humme, A. Schepers, W. Hammerschmidt, J. L. Yates, A. B. Rickinson, and N. W. Blake.** 2004. CD8 T cell recognition of endogenously expressed Epstein-Barr virus nuclear antigen 1. J. Exp. Med. **199:**1409–1420.
45. **Leen, A., P. Meij, I. Redchenko, J. Middeldorp, E. Bloemena, A. Rickinson, and N. Blake.** 2001. Differential immunogenicity of Epstein-Barr virus latent-cycle proteins for human $CD4^+$ T-helper 1 responses. J. Virol. **75:**8649–8659.
46. **Levin, L. I., K. L. Munger, M. V. Rubertone, C. A. Peck, E. T. Lennette, D. Spiegelman, and A. Ascherio.** 2005. Temporal relationship between elevation of Epstein-Barr virus antibody titers and initial onset of neurological symptoms in multiple sclerosis. JAMA **293:**2496–2500.
47. **Levitskaya, J., M. Coram, V. Levitsky, S. Imreh, P. M. Steigerwald-Mullen, G. Klein, M. G. Kurilla, and M. G. Masucci.** 1995. Inhibition of antigen processing by the internal repeat region of the Epstein-Barr virus nuclear antigen-1. Nature **375:**685–688.
48. **Levitskaya, J., A. Sharipo, A. Leonchiks, A. Ciechanover, and M. G. Masucci.** 1997. Inhibition of ubiquitin/proteasome-dependent protein degradation by the Gly-Ala repeat domain of the Epstein-Barr virus nuclear antigen 1. Proc. Natl. Acad. Sci. USA **94:**12616–12621.
49. **Li, Q., M. K. Spriggs, S. Kovats, S. M. Turk, M. R. Comeau, B. Nepom, and L. M. Hutt-Fletcher.** 1997. Epstein-Barr virus uses HLA class II as a cofactor for infection of B lymphocytes. J. Virol. **71:**4657–4662.
50. **Lindberg, C., O. Andersen, A. Vahlne, M. Dalton, and B. Runmarker.** 1991. Epidemiological investigation of the association between infectious mononucleosis and multiple sclerosis. Neuroepidemiology **10:**62–65.
51. **Long, H. M., T. A. Haigh, N. H. Gudgeon, A. M. Leen, C. W. Tsang, J. Brooks, E. Landais, E. Houssaint, S. P. Lee, A. B. Rickinson, and G. S. Taylor.** 2005. $CD4^+$ T-cell responses to Epstein-Barr virus (EBV) latent-cycle antigens and the recognition of EBV-transformed lymphoblastoid cell lines. J. Virol. **79:**4896–4907.
52. **Lünemann, J. D., N. Edwards, P. A. Muraro, S. Hayashi, J. I. Cohen, C. Münz, and R. Martin.** 2006. Increased frequency and broadened specificity of latent EBV nuclear antigen-1-specific T cells in multiple sclerosis. Brain **129:**1493–1506.
53. **Maloy, K. J., C. Burkhart, T. M. Junt, B. Odermatt, A. Oxenius, L. Piali, R. M. Zinkernagel, and H. Hengartner.** 2000. $CD4^+$ T cell subsets during virus infection. Protective capacity depends on effector cytokine secretion and on migratory capability. J. Exp. Med. **191:**2159–2170.
54. **McClain, M. T., B. D. Poole, B. F. Bruner, K. M. Kaufman, J. B. Harley, and J. A. James.** 2006. An altered immune response to Epstein-Barr nuclear antigen 1 in pediatric systemic lupus erythematosus. Arthritis Rheum. **54:**360–368.
55. **Münz, C., K. L. Bickham, M. Subklewe, M. L. Tsang, A. Chahroudi, M. G. Kurilla, D. Zhang, M. O'Donnell, and R. M. Steinman.** 2000. Human $CD4^+$ T lymphocytes consistently respond to the latent Epstein-Barr virus nuclear antigen EBNA1. J. Exp. Med. **191:**1649–1660.
56. **Nielsen, T. R., K. Rostgaard, N. M. Nielsen, N. Koch-Henriksen, S. Haahr, P. S. Sorensen, and H. Hjalgrim.** 2007. Multiple sclerosis after infectious mononucleosis. Arch. Neurol. **64:**72–75.
57. **Nikiforow, S., K. Bottomly, G. Miller, and C. Münz.** 2003. Cytolytic $CD4^+$-T-cell clones reactive to EBNA1 inhibit Epstein-Barr virus-induced B-cell proliferation. J. Virol. **77:**12088–12104.
58. **Operskalski, E. A., B. R. Visscher, R. M. Malmgren, and R. Detels.** 1989. A case-control study of multiple sclerosis. Neurology **39:**825–829.
59. **Ozawa, K., G. Suchanek, H. Breitschopf, W. Bruck, H. Budka, K. Jellinger, and H. Lassmann.** 1994. Patterns of oligodendroglia pathology in multiple sclerosis. Brain **117:**1311–1322.
60. **Paludan, C., K. Bickham, S. Nikiforow, M. L. Tsang, K. Goodman, W. A. Hanekom, J. F. Fonteneau, S. Stevanovic, and C. Münz.** 2002. Epstein-Barr nuclear antigen 1-specific $CD4^+$ Th1 cells kill Burkitt's lymphoma cells. J. Immunol. **169:**1593–1603.
61. **Paludan, C., D. Schmid, M. Landthaler, M. Vockerodt, D. Kube, T. Tuschl, and C. Münz.** 2005. Endogenous MHC class II processing of a viral nuclear antigen after autophagy. Science **307:**593–596.
62. **Pohl, D., B. Krone, K. Rostasy, E. Kahler, E. Brunner, M. Lehnert, H. J. Wagner, J. Gartner, and F. Hanefeld.** 2006. High seroprevalence of Epstein-Barr virus in children with multiple sclerosis. Neurology **67:**2063–2065.
63. **Rentenaar, R. J., L. E. Gamadia, N. van DerHoek, F. N. van Diepen, R. Boom, J. F. Weel, P. M. Wertheim-van Dillen, R. A. van Lier, and I. J. ten Berge.** 2000. Development of virus-specific $CD4^+$ T cells during primary cytomegalovirus infection. J. Clin. Investig. **105:**541–548.
64. **Rickinson, A. B., and E. Kieff.** 2007. Epstein-Barr virus, p. 2655–2700. *In* D. M. Knipe and P. M. Howley (ed.), Fields Virology, 5th ed. Wolters Kluwer/Lippincott, Williams & Wilkins, Philadelphia, PA.
65. **Ridge, J. P., F. Di Rosa, and P. Matzinger.** 1998. A conditioned dendritic cell can be a temporal bridge between a $CD4^+$ T-helper and a T-killer cell. Nature **393:**474–478.
66. **Schoenberger, S. P., R. E. Toes, E. I. van der Voort, R. Offringa, and C. J. Melief.** 1998. T-cell help for cytotoxic T lymphocytes is mediated by CD40-CD40L interactions. Nature **393:**480–483.
67. **Sibley, W. A., C. R. Bamford, and K. Clark.** 1985. Clinical viral infections and multiple sclerosis. Lancet **i:**1313–1315.
68. **Soldan, S. S., R. Berti, N. Salem, P. Secchiero, L. Flamand, P. A. Calabresi, M. B. Brennan, H. W. Maloni, H. F. McFarland, H. C. Lin, M. Patnaik, and S. Jacobson.** 1997. Association of human herpes virus 6 (HHV-6) with multiple sclerosis: increased IgM response to HHV-6 early antigen and detection of serum HHV-6 DNA. Nat. Med. **3:**1394–1397.
69. **Sospedra, M., and R. Martin.** 2005. Immunology of multiple sclerosis. Annu. Rev. Immunol. **23:**683–747.
70. **Storch, M. K., S. Piddlesden, M. Haltia, M. Iivanainen, P. Morgan, and H. Lassmann.** 1998. Multiple sclerosis: in situ evidence for antibody- and complement-mediated demyelination. Ann. Neurol. **43:**465–471.
71. **Sundstrom, P., P. Juto, G. Wadell, G. Hallmans, A. Svenningsson, L. Nystrom, J. Dillner, and L. Forsgren.** 2004. An altered immune response to Epstein-Barr virus in multiple sclerosis: a prospective study. Neurology **62:**2277–2282.
72. **Sutkowski, N., B. Conrad, D. A. Thorley-Lawson, and B. T. Huber.** 2001. Epstein-Barr virus transactivates the human endogenous retrovirus HERV-K18 that encodes a superantigen. Immunity **15:**579–589.
73. **Tan, L. C., N. Gudgeon, N. E. Annels, P. Hansasuta, C. A. O'Callaghan, S. Rowland-Jones, A. J. McMichael, A. B. Rickinson, and M. F. Callan.** 1999. A re-evaluation of the frequency of $CD8^+$ T cells specific for EBV in healthy virus carriers. J. Immunol. **162:**1827–1835.
74. **Thacker, E. L., F. Mirzaei, and A. Ascherio.** 2006. Infectious mononucleosis and risk for multiple sclerosis: a meta-analysis. Ann. Neurol. **59:**499–503.
75. **Thorley-Lawson, D. A.** 2001. Epstein-Barr virus: exploiting the immune system. Nat. Rev. Immunol. **1:**75–82.
76. **Thorley-Lawson, D. A., and K. Geilinger.** 1980. Monoclonal antibodies against the major glycoprotein (gp350/220) of Epstein-Barr virus neutralize infectivity. Proc. Natl. Acad. Sci. USA **77:**5307–5311.
77. **Thorley-Lawson, D. A., and C. A. Poodry.** 1982. Identification and isolation of the main component (gp350-gp220) of Epstein-Barr virus responsible for generating neutralizing antibodies in vivo. J. Virol. **43:**730–736.
78. **Tosato, G., A. D. Steinberg, and R. M. Blaese.** 1981. Defective EBV-specific suppressor T-cell function in rheumatoid arthritis. N. Engl. J. Med. **305:**1238–1243.
79. **Tosato, G., A. D. Steinberg, R. Yarchoan, C. A. Heilman, S. E. Pike, V. De Seau, and R. M. Blaese.** 1984. Abnormally elevated frequency of Epstein-Barr virus-infected B cells in the blood of patients with rheumatoid arthritis. J. Clin. Investig. **73:**1789–1795.
80. **Tsokos, G. C., I. T. Magrath, and J. E. Balow.** 1983. Epstein-Barr virus

induces normal B cell responses but defective suppressor T cell responses in patients with systemic lupus erythematosus. J. Immunol. **131:**1797–1801.
81. **Villoslada, P., C. Juste, M. Tintore, V. Llorenc, G. Codina, P. Pozo-Rosich, and X. Montalban.** 2003. The immune response against herpesvirus is more prominent in the early stages of MS. Neurology **60:**1944–1948.
82. **Voo, K. S., T. Fu, H. E. Heslop, M. K. Brenner, C. M. Rooney, and R. F. Wang.** 2002. Identification of HLA-DP3-restricted peptides from EBNA1 recognized by $CD4^+$ T cells. Cancer Res. **62:**7195–7199.
83. **Wandinger, K., W. Jabs, A. Siekhaus, S. Bubel, P. Trillenberg, H. Wagner, K. Wessel, H. Kirchner, and H. Hennig.** 2000. Association between clinical disease activity and Epstein-Barr virus reactivation in MS. Neurology **55:** 178–184.
84. **Wardemann, H., S. Yurasov, A. Schaefer, J. W. Young, E. Meffre, and M. C. Nussenzweig.** 2003. Predominant autoantibody production by early human B cell precursors. Science **301:**1374–1377.
85. **Wucherpfennig, K. W., and J. L. Strominger.** 1995. Molecular mimicry in T cell-mediated autoimmunity: viral peptides activate human T cell clones specific for myelin basic protein. Cell **80:**695–705.
86. **Yurasov, S., H. Wardemann, J. Hammersen, M. Tsuiji, E. Meffre, V. Pascual, and M. C. Nussenzweig.** 2005. Defective B cell tolerance checkpoints in systemic lupus erythematosus. J. Exp. Med. **201:**703–711.
87. **Zajac, A. J., J. N. Blattman, K. Murali-Krishna, D. J. Sourdive, M. Suresh, J. D. Altman, and R. Ahmed.** 1998. Viral immune evasion due to persistence of activated T cells without effector function. J. Exp. Med. **188:**2205–2213.