



# Infection of autoreactive B lymphocytes with EBV, causing chronic autoimmune diseases

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**I hypothesize that human chronic autoimmune diseases are based on infection of autoreactive B lymphocytes by Epstein–Barr virus (EBV), in the following proposed scenario. During primary infection, autoreactive B cells are infected by EBV, proliferate and become latently infected memory B cells, which are resistant to the apoptosis that occurs during normal B-cell homeostasis because they express virus-encoded anti-apoptotic molecules. Genetic susceptibility to the effects of B-cell infection by EBV leads to an increased number of latently infected autoreactive memory B cells, which lodge in organs where their target antigen is expressed, and act there as antigen-presenting cells. When CD4<sup>+</sup> T cells that recognize antigens within the target organ are activated in lymphoid organs by cross-reactivity with infectious agents, they migrate to the target organ but fail to undergo activation-induced apoptosis because they receive a co-stimulatory survival signal from the infected B cells. The autoreactive T cells proliferate and produce cytokines, which recruit other inflammatory cells, with resultant target organ damage and chronic autoimmune disease.**

Epstein–Barr virus (EBV) has been suspected of involvement in the aetiology of various human chronic autoimmune diseases since the finding of elevated levels of antibodies to the virus in systemic lupus erythematosus (SLE) in 1971 [1]. There is now a large body of evidence implicating the virus in several different autoimmune diseases, including SLE [1–3], multiple sclerosis (MS) [4–8], Sjögren's syndrome [9–11], rheumatoid arthritis [12], autoimmune thyroiditis [13], autoimmune hepatitis [14], cryptogenic fibrosing alveolitis [15] and pure red cell aplasia [16,17]. Published hypotheses generally focus on individual autoimmune diseases and are based primarily on cross-reactivity between EBV and self-antigens or on EBV-targeted immune-mediated organ damage. Here, I propose a novel hypothesis that is based primarily on the unique ability of EBV to infect, activate and latently persist in B lymphocytes, including autoreactive B cells, and that incorporates the known association of different autoimmune diseases in individuals and among family members. The advantage of this hypothesis over previous

hypotheses for a unique role of EBV in chronic autoimmune disease is that it is based on what is unique about the relationship between EBV and the immune system, namely its ability to immortalize B cells, rather than what is common to all viruses, which is the potential for molecular mimicry and cross-reactivity between viral and self-antigens. The hypothesis also incorporates a role for CD4<sup>+</sup> T-cell cross-reactivity between viral (including EBV) antigens and self-antigens to explain why people with different MHC class II genes develop chronic autoimmune disease in different target organs following EBV infection of B cells. My hypothesis differs from that of Haahr and Munch [18], in that it provides a rationale for the importance of B-cell infection by EBV, it implicates genetic susceptibility and all chronic autoimmune diseases (not just MS) and it does not involve a retrovirus.

## Universally high prevalence of EBV seropositivity in MS and SLE

Elevated levels of antibodies to various viruses are present in people with different chronic autoimmune diseases. What is unique and striking about the serology for EBV is that it is almost universally (>99%) positive in those autoimmune diseases in which it has been thoroughly studied, namely SLE [3] and MS [7], compared to a positivity rate of 90% in the general adult population. The positivity rate of 99% in SLE is maintained even in young subjects where the general rate is only 70% [3]. These findings do not apply to other herpes viruses. Further studies are required to determine whether other human chronic autoimmune diseases are also associated with such a high seropositivity rate for EBV.

The fact that virtually all individuals with SLE or MS are EBV-seropositive suggests that prior infection with EBV is essential for the development of these autoimmune diseases. However, infection itself is clearly not sufficient for disease development. The timing and severity of primary infection also have a role. Chronic autoimmune diseases are uncommon in the developing world where primary infection with EBV occurs much earlier and probably with a lower dose of virus than in the developed world [19]. Furthermore, a definite clinical history of infectious mononucleosis, which indicates primary infection with a high frequency of infected B cells [19], further increases the risk of MS in EBV-seropositive subjects

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(eightfold, if infection occurs before the age of 18 years) [6]. Recently, Levin *et al.* [8], in a study of blood samples from US military personnel collected before the onset of MS, have shown that the presence of high titres of antibodies to EBV increases the risk 34-fold for developing MS. However, differences in environmental exposure to EBV are not sufficient to explain why only a minority of infected individuals develops autoimmune disease. There must also be another determinant. Is genetic susceptibility to the effects of B-cell infection by EBV the determinant?

### Genetic susceptibility to 'autoimmunity-in-general' in individuals with different chronic autoimmune diseases

Genetic factors clearly contribute to the development of chronic autoimmune diseases. MHC class II genes account for part of the genetic susceptibility but other genes must also be involved. The fact that individual autoimmune diseases, such as MS, are associated with other autoimmune diseases in affected individuals and family members [20,21], suggests a genetic predisposition to 'autoimmunity-in-general'. Indeed, studies on autoimmune family pedigrees have led to the proposal that autoimmunity is an autosomal dominant trait with penetrance (disease expression) in ~92% of females and 49% of males carrying the abnormal gene [22]. Is the autoimmune trait a result of a genetic susceptibility to the effects of B-cell infection by EBV? There are several possible general mechanisms for such genetic susceptibility, namely: increased uptake of virus by B cells (e.g. increased expression of CD21, the receptor for the virus), decreased elimination of virus-infected B cells by EBV-specific cytotoxic CD8<sup>+</sup> T cells (e.g. due to decreased processing of EBV antigens or decreased expression of MHC class I molecules), and indirect mechanisms superimposed on B-cell infection (e.g. a genetic defect in the immunoregulation of autoreactive B cells).

### Infection of B cells of normal individuals with EBV results in the production of monoclonal autoantibodies

When EBV infects resting B cells *in vitro*, it drives them into activation and proliferation independently of T-cell help. Infection of B cells from normal individuals *in vitro* results in the production of monoclonal autoantibodies reacting with antigens in multiple organs [23]. This accounts for the transient appearance of autoantibodies during the course of infectious mononucleosis [19]. Usually, the proliferating infected B cells are eventually eliminated by EBV-specific cytotoxic CD8<sup>+</sup> T cells (Figure 1) but latently infected non-proliferating memory B cells persist in the individual for life [24]. Antigen-driven differentiation of latently infected memory B cells into plasma cells might trigger entry into the lytic cycle with the production of infectious virus [24].

### Defective T-cell control of EBV-infected B cells in different chronic autoimmune diseases

Patients with rheumatoid arthritis (RA) have an abnormally increased frequency of circulating EBV-infected B cells [12]. This is not due to an increased uptake of virus by B cells but could be explained by the defective control of infected B cells by EBV-specific T cells [12]. A similar defect

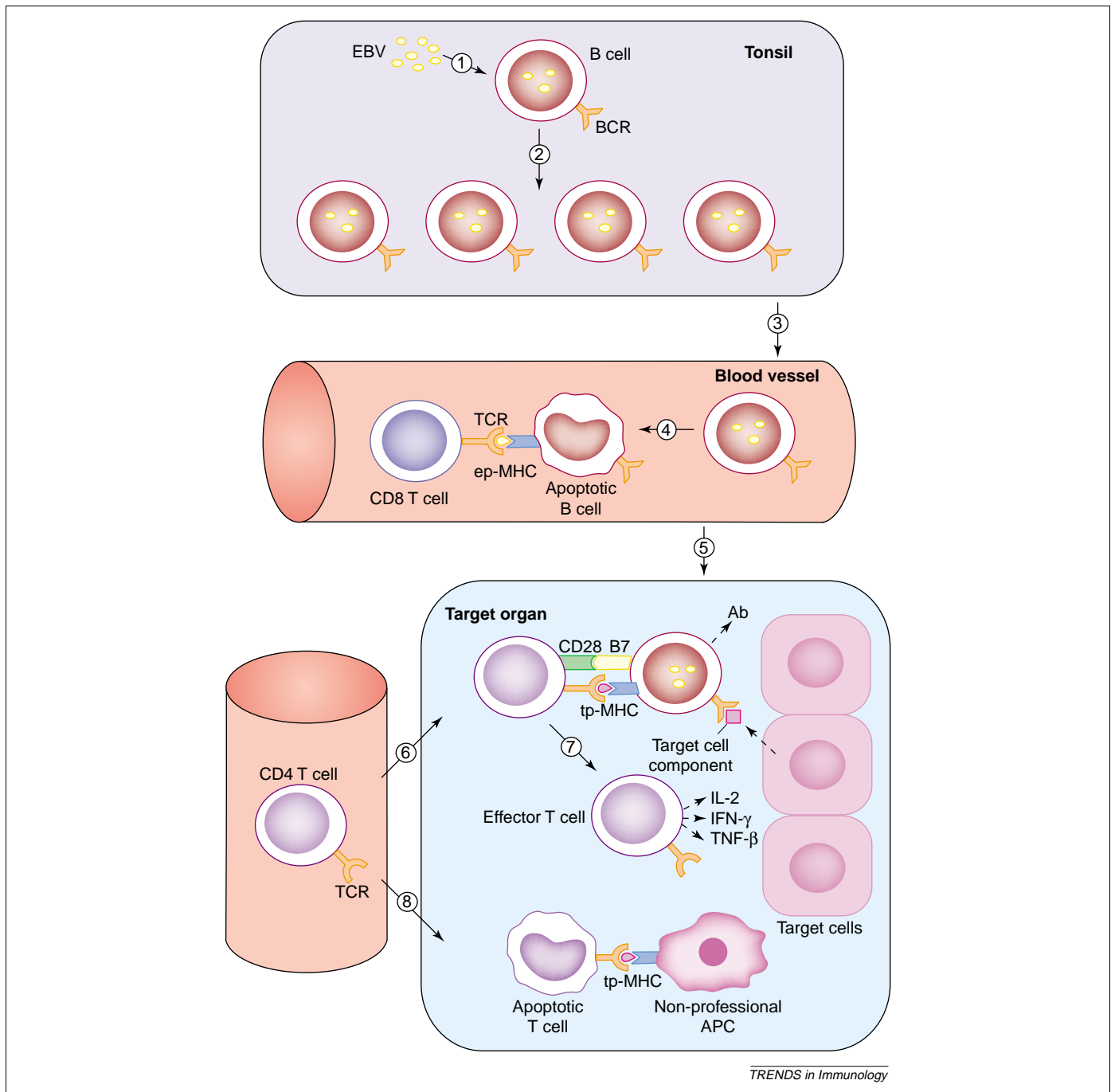
is also present in MS [5], SLE [2] and Sjögren's syndrome [9,10]. In SLE, T cells from normal EBV-seropositive subjects can control the numbers of infected B cells from SLE patients but T cells from patients cannot control infected B cells from normal subjects or patients [2]; this indicates impaired viral control by T cells. In Sjögren's syndrome, the defective viral control is due to decreased EBV-specific T-cell cytotoxicity [9]. However, all these studies on T-cell control of EBV in chronic autoimmune disease were performed before the identification of CD8<sup>+</sup> T-cell EBV epitopes and have not been subsequently studied in the light of this knowledge. Nevertheless, these early studies raise the possibility that a genetically determined defect in the generation of EBV-specific cytotoxic CD8<sup>+</sup> T cells might lead to the impaired elimination of EBV-infected B cells in chronic autoimmune disease.

One possible genetic mechanism for decreased EBV-specific cytotoxic CD8<sup>+</sup> T cells is deficient MHC class I expression on B cells, which has been reported to occur in chronic autoimmune diseases, including insulin-dependent diabetes mellitus, Hashimoto's thyroiditis, Graves' disease, SLE, RA, Sjögren's syndrome and MS [25,26], although it remains unclear whether the reported decrease is sufficient to account for decreased T-cell cytotoxicity. Alternatively, it could be argued that the above T- and B-cell changes in chronic autoimmune disease might be secondary to immune dysfunction associated with autoimmune disease, and that a genetic defect in the immunoregulation of B cells could enable the persistence and proliferation of memory autoreactive B cells infected with EBV.

### Do EBV-infected autoreactive B cells persist in the target organs and promote autoimmune disease?

I propose that, following primary EBV infection in individuals with a genetic predisposition to autoimmunity, virus-infected activated autoreactive B cells circulate in the blood and accumulate in organs containing the target antigen. Activated antigen-specific B cells can traffic across even the intact blood-brain barrier and can lodge in the brain if the antigen is present [27]. Thus, it appears that activated B cells traffic in the same way as activated T cells, which preferentially migrate from the blood into non-lymphoid organs, as opposed to resting T cells, which exit through lymph node high-endothelial venules [28]. The EBV-infected autoreactive B cells might persist in the target organ independently of T-cell help because latently-infected B cells express viral latent membrane proteins that protect them from the apoptosis that occurs during normal B-cell homeostasis [24] and in the target organ in self-limited autoimmune disease [29]. Latently infected B cells could be the source of the monoclonally expanded B cells in the salivary glands in Sjögren's syndrome [30], the thyroid gland in autoimmune thyroiditis [31] and the brain in MS [32]. These B cells could act as antigen-presenting cells (APCs), which present their cognate antigen and other physically linked self-antigens to activated autoreactive T cells trafficking through the target organ (Figure 1).

Healthy subjects experience surges of circulating autoreactive T cells, presumably activated by cross-reacting



**Figure 1.** Role of B cells latently infected by EBV in chronic autoimmune disease. During primary infection with EBV, EBV infects B cells, including autoreactive B cells, in the tonsil (Step 1), causing them to undergo T-cell-independent clonal expansion (Step 2). The activated infected B cells circulate in the blood (Step 3). The number of infected B cells is normally controlled by EBV-specific cytotoxic CD8<sup>+</sup> T cells, which kill the infected B cells (Step 4) but not if there is a genetically determined defect in this mechanism, for example, decreased MHC class I expression on B cells. Surviving EBV-infected autoreactive B cells lodge and persist in organs containing the self-antigen they recognize (Step 5). When CD4<sup>+</sup> T cells are activated in peripheral lymphoid organs following viral (including EBV) infections, they circulate in the peripheral blood, traffic through non-lymphoid organs and lodge in the target organ containing the self-antigen with which they cross-react (Step 6 or 8). Normally, these T cells are eliminated in the target organ by activation-induced T-cell apoptosis following interaction with class II MHC-expressing non-professional APCs (Step 8). However, if instead they interact with EBV-infected autoreactive B cells lodged in the organ, they receive a co-stimulatory survival signal that inhibits activation-induced T-cell apoptosis (Step 6). The CD4<sup>+</sup> T cells survive, activate the B cells to produce Ab, which reacts with the target organ, and act as effector T cells leading to autoimmune target organ damage (Step 7). Abbreviations: Ab, antibody; APCs, antigen-presenting cells; BCR, B-cell receptor; EBV, Epstein-Barr virus; ep-MHC, EBV peptide complexed to MHC class I; IFN- $\gamma$ , interferon- $\gamma$ ; IL-2, interleukin-2; TCR, T-cell receptor; TNF- $\beta$ , tumour necrosis factor- $\beta$ ; tp-MHC, target antigen peptide complexed to MHC class II. B7 represents co-stimulatory molecules and CD28 represents their receptors on the T cell.

infectious agents [33]. I have proposed that these T cells would normally be eliminated in the target organ by activation-induced apoptosis (Figure 1) but could survive if they received co-stimulatory signals from professional APCs, such as B cells [34,35]. Autoreactive B cells latently infected by EBV might provide this co-stimulatory survival

signal to T cells in the target organ. The autoreactive T cells could then proliferate and produce cytokines, which recruit and activate macrophages and other B and T cells, with resultant target organ damage. In turn, target organ damage would lead to the release of autoantigens and further T-cell and B-cell activation, with spreading of the

immune response to other antigens and perpetuation of the immune attack. Latently infected B cells might also produce B-cell-attracting chemokine-1, enabling the development of germinal centres in the target organ [36]. This model would not depend on latently infected B cells becoming lytically infected and releasing infectious virus in the target organ, but if this occurred after differentiation into plasma cells, it could lead to infection and proliferation of other autoreactive B cells and to recruitment of T cells specific for lytic-cycle viral antigens with further immune attack. The presence of EBV-infected B cells in the target organ could also result in the development of B-cell lymphoma, which has been reported to occur within the salivary glands in Sjögren's syndrome [37], within the thyroid gland in autoimmune thyroiditis [38] and within the central nervous system in MS [39].

### Role of MHC

Specific alleles of MHC class II have an important role in determining the risk of developing particular autoimmune diseases. The mechanism for this is unclear but one possibility is that these specific alleles determine which self-antigens (and therefore which organs) are recognized by cross-reacting CD4<sup>+</sup> T cells that have been activated by foreign antigens. This situation might be analogous to that proposed for the shaping of the CD8<sup>+</sup> T-cell repertoire against alloantigens by MHC class I-restricted antiviral T-cell responses [40]. Acute viral infections, including EBV, can lead to dramatic clonal expansion of T cells [24,40], which could cross-react with other antigens. For example, CD8<sup>+</sup> T-cell clones specific for a HLA-B8-restricted EBV epitope cross-react with several common HLA-B alleles as alloantigens [40]; EBV-specific T cells cross-react with self-HLA alleles in oligoarticular juvenile idiopathic arthritis [41]; and a CD4<sup>+</sup> T-cell clone reacts with both a DRB5\*0101-restricted EBV peptide and a DRB1\*1501-restricted myelin basic protein peptide in MS [42]. During acute EBV and other viral infections, MHC class II genes will determine the fine specificities of the virus-reactive CD4<sup>+</sup> T-cell populations and thus determine which self-antigens are targeted by cross-reacting virus-specific CD4<sup>+</sup> T cells, and therefore in which organs autoimmune disease develops after interaction between the circulating activated T cells and resident autoreactive B cells. Thus, CD4<sup>+</sup> T-cell cross-reactivity between viral antigens and self-antigens could explain why people with different class II MHC genes develop chronic autoimmune disease in different target organs following EBV infection of B cells. This model does not depend on recognition of B-cell EBV antigens by EBV-specific T cells in the target organ but if this occurred it would contribute to the immune attack.

### Testing the hypothesis

To test the hypothesis, first, monoclonal B-cell populations could be isolated from target organs (e.g. cerebrospinal fluid, thyroid gland, synovium) and examined to determine whether they express EBV-encoded small nuclear RNAs (EBERs), virus-encoded anti-apoptotic latent membrane proteins, co-stimulatory molecules and B-cell-attracting chemokine-1, and also to determine whether they are autoreactive against the organ from which they have been

isolated. These studies will be technically demanding, will require the use of appropriate controls and will need care in analysis and interpretation. For example, in a study using a highly sensitive *in situ* hybridization technique to detect EBERs in synovial membrane biopsy samples of patients with RA, it was concluded that there was a lack of evidence for involvement of EBV [43]. Yet, the study actually found EBERs in seven (19%) of 37 patients with RA and in zero of 51 patients with other joint diseases; cells expressing EBERs were B cells and plasma cells. These results could also be interpreted as supporting a role for EBV infection of B cells in the pathogenesis of RA if the negative results in the other patients with RA were due to the limitations imposed by sampling.

Second, it could be determined whether autologous EBV-specific cytotoxic CD8<sup>+</sup> T cells from the peripheral blood fail to kill EBV-infected autoreactive B cells from the target organ, for example, because of defective MHC class I expression by B cells. Third, it could be analyzed whether EBV-specific CD4<sup>+</sup> T-cell lines react with self-antigens from the target organ presented by autologous APCs. Unlike the other tests proposed here, this test does not depend on B-cell infection by EBV but rather is a test for cross-reactivity between EBV and self-antigens. Fourth, monozygotic twins discordant for autoimmune disease should be tested for differences in frequencies of EBV-infected B cells, T-cell cytotoxicity against infected B cells and MHC class I expression. Finally and most importantly, if the hypothesis is correct, control of EBV-infected B cells should inhibit the progression of chronic autoimmune diseases. Such control might be achieved by: general B-cell depletion (e.g. by rituximab); transferring EBV-specific cytotoxic CD8<sup>+</sup> T cells; antiviral agents or agents that interfere with the anti-apoptotic effects of viral latent membrane proteins.

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