Rheumatoid arthritis and Epstein-Barr virus: a case of living with the enemy?

The cause of rheumatoid arthritis (RA) still eludes us, though we know from twin studies that both genetic and environmental factors are important contributory components to disease susceptibility; the latter is estimated to account for about one half of this risk. At least one major RA susceptibility gene resides within the major histocompatibility complex (MHC) region. Current dogma is that this is explained by a conserved sequence of amino acids within the third hypervariable region of the DRB1 β chain molecule encoded by a number of alleles. This is usually referred to as being the RA shared epitope hypothesis. Although DRB1 molecules present peptide fragments to T cell receptors on CD4 positive lymphocytes, the exact mechanism through which the RA shared epitope exerts its influence remains unclear. Given that class II molecules such as DRB1 serve an immunoregulatory role, it is not surprising that polymorphisms within these structures will influence variation in immune response in both health and disease states. It is likely that the RA shared epitope conveys disease susceptibility through its interaction with the environment. Characterising such interactions will be fundamental to our understanding of RA aetiology.

A specific environmental/infectious trigger(s) for RA has yet to be identified, though there has been no shortage of contenders for this role, including mycoplasmas, parvovirus B19, cytomegalovirus, herpes virus 6, and Epstein-Barr virus (EBV). The involvement of EBV in RA has been investigated and speculated about for over 15 years. Although definite proof is lacking, an increasing body of circumstantial evidence points at a close relation between RA and EBV. CD8 cytotoxic T cells are primarily the way in which viral infection is controlled. Although antibody levels to EBV antigens are often lower in patients with RA, there is evidence that persistent infection with EBV causes major distortions within the memory repertoire of virus-specific CD8 T cells.

Increased titres of antibodies to EBV antigens have been shown in patients with RA. However, an increased prevalence of EBV in the joints of patients with RA compared with controls remains controversial, and studies have reported conflicting observations. Thus a direct causal link has not yet been categorically established and, possibly, the above observations.9 15–17
sequelae seen in patients with RA are “effect” rather than “cause” and can be explained by an underlying immune dysregulation in patients with RA.

Increased levels of intrasynovial CD8 T cells which can recognise EBV derived epitopes have been seen in patients with RA. This presents a paradox as it suggests that immune mediated control in patients with RA should be enhanced and this does not fit with clinical or laboratory observations. Poor immune regulation of EBV is apparent in both patients with RA and Sjögren’s syndrome. This deficiency appears to lie in the T cell compartment as B lymphocytes from patients with RA can be relatively easily immortalised in vitro into cell lines with EBV even when autologous T cells are present. However, if T cells are added from an HLA identical, healthy sibling to B lymphocytes from a patient with RA, this process is much more difficult to achieve. Conversely, B lymphocytes from the healthy sibling will EBV transform more easily when T cells from the HLA identical RA sibling are added.

Polymerase chain reaction has been used to investigate the rate and extent of infection by EBV, cytomegalovirus and herpes virus 6 in families containing multiple cases of RA. Viral DNA was detected in cells from saliva and peripheral blood; this was particularly the case for EBV, which was found in increased prevalence in patients with RA compared with their non-affected relatives. This clearly establishes a relation between EBV and RA but does not prove a direct causality. Similarly, EBV DNA and mRNA transcripts have been found to be more common in synovial tissues of patients with RA than in controls. This correlates with the patient’s HLA-DR genotype; subjects with EBV detected in their synovial tissue and who are HLA-DR4 or RA shared epitope positive had a markedly increased risk of RA. It should be added, however, that not all studies have shown such a marked increase in EBV DNA or gene expression in the synovial tissue of patients with RA.

Considerable interest has been generated by the observation that gp110 EBV viral protein contains a sequence of amino acids (QKRAA) which corresponds to the third hypervariable region of HLA-DRB1 alleles associated with RA risk. The RA shared epitope sequence has also been identified in proteins from a number of other prokaryotes, including E coli, Brucella ovis, and Lactobacillus lactis. This has formed the basis for a molecular mimicry hypothesis to explain RA aetiology. T cells positively react and break immunological tolerance. Further cross reactivity with synovial membrane components might then develop in RA pathology in other ways. Recently it was reported that human IL6 expression in rheumatoid fibroblast-like synoviocytes can be transcriptionally regulated by Epstein-Barr C promoter binding factor 1. Given the likely involvement of IL6 in RA pathology this could be an important aspect involving EBV. Other recent studies have also shown that EBV infected B cells and plasma cells can secrete matrix metalloproteinases and the proinflammatory cytokine, tumour necrosis factor α. These factors...

![Figure 1](https://ard.bmj.com/AnnRheumDis)
are key players in RA joint disease and if EBV, for whatever reason, is more prevalent in RA synovium, it might help to drive the inflammatory response. Cross reactivity between self joint-specific antigens and EBV encoded peptides has not been clearly shown for T cell epitopes, though this is not the case for B cell epitopes. Phage display techniques have identified mimotopes for a conformational epitope of type II collagen and shown an interesting homology with a sequence of Epstein-Barr nuclear antigen 1.

Infection of B lymphocytes with EBV induces the production of a new host protein (EBI3-EBV induced gene 3). This protein is related to the p40 subunit of IL12, a cytokine which can induce TH1 responses and proliferation of these cells. However, the production of EBI3 is not limited to B lymphocytes, as it is also found in other cell types, including dendritic cells and macrophages.

Several studies have suggested that EBI3 may be involved in the pathogenesis of RA. For example, a recent study found that EBI3 expression is upregulated in peripheral blood mononuclear cells (PBMCs) from patients with RA compared to healthy controls. Additionally, EBI3 has been shown to inhibit the production of pro-inflammatory cytokines, such as IL-1β and TNF-α, which are key mediators of chronic inflammation.

In conclusion, further studies are needed to fully understand the role of EBI3 in the pathogenesis of RA. However, these findings suggest that targeting EBI3 may provide a promising therapeutic strategy for the treatment of RA.

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