JCI The Journal of Clinical Investigation

The Epstein-Barr virus and systemic lupus erythematosus.

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J Clin Invest. 1997;100(12):2939-2940. https://doi.org/10.1172/JCI119845.

Editorial

In this issue of *The Journal*, James et al. (1) present us with an intriguing observation: They report that for patients with systemic lupus erythematosus (SLE) who are < 20 yr of age essentially all (99%) have been infected by the Epstein-Barr virus (EBV), while only 70% of their controls are EBV-infected. As they note, this suggests either that EBV predisposes to the development of SLE or, conversely, that SLE predisposes to EBV. As there has been nothing during decades of intense clinical interest in SLE to suggest that SLE patients are hypersusceptible to EBV infection (e.g., no record of a disposition for young patients with established SLE to develop infection by EBV [infectious mononucleosis], nor reexpression of previous infection) the former interpretation is preferred. They propose that EBV is very likely a necessary, although insufficient, factor in the etiopathogenesis of SLE. The nature of this necessity is not addressed in the present paper, but their Discussion emphasizes the cross-reactivities that have been described between the EBNA-1 protein and various components of the Sm antigen, and their remarkable findings in the rabbit of lupus-like disease after immunization with an EBNA-1 peptide.

The choice by James et al. to study the prevalence of EBV infection only in younger individuals with SLE is both a strength and a weakness. Clearly, it made it possible for them to develop impressive statistics that positively relate the virus to the disease. Any attempt to find such differentiating numbers in a comparison of older populations, in whom > 90% of normal individuals would have been expected to have had prior EBV infection, would have been all but impossible. The weakness in the choice is that their finding cannot easily be extrapolated to other populations. We cannot know, for instance, that those in their teens who have escaped the development of SLE in the context of EBV will not develop SLE later in the context of some other virus, or of some other nonviral factor. Nor can we be sure that there are not geographical factors that are important. Would their study, if carried out in Bristol, Taipei, or Moscow, have yielded some other agent than EBV for the teenagers? For these reasons, we must still keep in mind that other factor(s) might substitute for EBV in populations other than the one chosen for this study.

Nevertheless, assignment to EBV of a predisposing role in SLE is appealing from a number of points of view. Firstly, twin studies (in which concordance of disease in identical twins occurs in only ~ 30%) have long suggested that environmental as well as genetic factors are involved in its etiology or pathogenesis. Classical epidemiological studies have not suggested transmission of SLE by an infectious agent, so an hypothesis based on a life-long resident organism like EBV, and thus one not appreciated by classical epidemiology, satisfies. Secondly, and more importantly, EBV is biologically well suited to the job. As a continuing infection in B lymphocytes, it promotes proliferation of the B cells as well as its own reproduction, and thereby is capable of providing a prolonged antigenic challenge. Even in the short term, i.e., in infectious mononucleosis, EBV is demonstratively capable of promoting antibodies that are cross-reactive with host proteins. Prolonged immunization, especially in genetically selected individuals, would favor this further. With epitope spread, as noted by James et al., important aspects of the observed autoimmunity in SLE could be explained. However, EBV could also be important in other ways. B cells infected by EBV multiply continuously when cultured in vitro, and this means that in vivo, even in normal persons, immunological mechanisms must be brought into play to suppress them, with whatever inflammatory processes would accompany this. We know little about how this would operate in SLE, but we do know that the suppressor system is somehow abnormal in the disease (2). Finally, EBV infection of B cells causes the display of increased binding sites on the cell surface for human herpesvirus-6 (HHV-6), and thereby an increased susceptibility to superinfection with HHV-6 (3). HHV-6 can also increase the cell surface receptor proteins for viruses, including that for EBV, and it can transactivate EBV from latency to productive infection (4). With such potential for reciprocal effects, it would be interesting to know if there were B cells in the peripheral blood of SLE patients that carry double infection with EBV and HHV-6.

Some observations that are independent of EBV infection indicate that B cells in SLE may have more of a central place in the disease than has been thought. There are three lines of evidence for this. First, asymptomatic first degree relatives of patients with SLE have long been known to display serum autoantibodies that are also present in the patients, and more recently this has been shown to be especially expressed in female relatives (5). Second, SLE B cells are hyperresponsive to stimulation of the antigen receptor, irrespective of degree of clinical activity or treatment (6), implying that the activated state may not be simply a secondary feature of the disease. Third, in MLR/lpr mice there is an inherent property of B cells to produce and release increased amounts of Sm antigen into the environment during stimulation (7), and the production of anti-Sm in these animals is controlled by a gene expressed in B cells, but differing from the H2 or Ig genes (8). Do these B cell characteristics describe another necessary but insufficient factor in the development of SLE in humans as well as in mice?

Most of the familiar predisposing factors for SLE, e.g., DR2 or DR3 status, FcgR alleles, C4A gene, are just that—predisposing but not necessary to the disease. The same might be said for many of the infectious agents that have been thought to play a role in SLE (see, for instance, references 9 and 10). Is it possible that certain non-EBV viruses can give that final touch that tips an individual, predisposed by EBV or by a genetically aberrant B cell, into active lupus?

One important caveat needs expression. The suggestion that environmental factor(s) contribute to SLE is based on nonconcordance of disease in monozygotic twins. More strictly interpreted, the nonconcordance really means that there are random as well as nonrandom factors determining the presence of disease. Could the random elements be explained to-

J. Clin. Invest.

0021-9738/97/12/2939/02 $2.00
Volume 100, Number 12, December 1997, 2939–2940
http://www.jci.org

tally by the somatic mutations and VDJ rearrangements inherent in antibody production, rather than by the environment? My guess would be no, but we don't know.

Are there EBV-negative patients with SLE? A review of many earlier serological studies would suggest the affirmative, and one study reports failure to detect EBV DNA in young patients with SLE in Taiwan (11). However, all these studies had differences in technique from those used by James et al. so the question remains open.

It seems to me that the most important contribution given us by James et al. is to bring to our attention that EBV may yet be the most dominant environmental factor contributing to SLE. It may act together with genetically souped-up B cells to complete a pathogenetic pathway, or it may require interactions with yet other viruses. Suppositions such as these should provide a basis for profitable future investigations.

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