Workshop report

International workshop: EB virus and rheumatoid arthritis

A workshop sponsored by the Arthritis and Rheumatism Council was held at The London Hospital Medical College on 30 September and 1 October 1982, and attended by 77 participants.

Programme


Workshop B. HLA, virus infection and family studies. Introductory speaker: J. S. H. Gaston.

Workshop C. Biochemical and molecular characterisation of nuclear protein antigens. Introductory speakers: Interactions of viral products and host proteins (D. Lane). Biochemical and molecular characterisation of EBV antigens (J. Luka).


Summing-up. N. J. Zvaifler.

Summary

The discussions during the workshop addressed 3 main questions arising out of recent work:

1. Are there grounds for considering an aetiological role for EB virus in rheumatoid arthritis (RA)?
2. Does the incidence or level of EB virus antibodies have diagnostic significance in RA?
3. What may in-vitro experiments with rheumatoid lymphoid cells and EB virus tell us about immunoregulatory disturbances in RA?

For the purposes of this report the gist of discussions of the first 2 questions may be combined. Although the ubiquity of EBV, its close relationship with lymphocytes, and its persistence after initial infection made it an ‘ideal’ aetiological candidate in RA, it had to be agreed that the occurrence of RA in patients without serological evidence of previous EBV infection (eg anti-VCA antibody) ruled out a direct causal role. The frequencies of anti-VCA and anti-EBNA antibodies being unequivocally similar in RA and in normals, was there evidence of increased viral exposure in RA? Again, the strength of the case in favour was limited, since although anti-EBV antibody titres are on the whole somewhat higher in RA than normals, similarly raised titres are not unusual in other lymphoproliferative diseases. Discussion centering around anti-RANA, the antibody reactive with an EBV related antigen present in lymphoblastoid cells transformed by the virus, confirmed the conclusion that, while anti-RANA levels and incidence are rather higher in RA, normals may be positive also. Possession of the tissue antigen HLA-DR4 apparently affects neither EBV antibody responses nor the incidence of anti-RANA. In early cases of RA higher RANA titres were reported than at later stages of the diseases, and unexpectedly antibodies also to the early antigen of CMV.

A newer contour of the RANA puzzle took shape with an interesting exchange of observations noting the ability of SV40 virus to induce antibodies against host protein, and of evidence of a similar interaction of EBNA with the latter. Also, a non-EBV related protein was identified in the RANA complex. Is host protein thus rendered more immunogenic as a result of virus infection?

Little evidence was forthcoming of an increased burden of EB virus in RA, at least with regard to frequency of EBV presence in throat secretions.

Cellular Basis

Much of the workshop’s time was devoted to reports attempting to use in-vitro experiments with EBV infection to define the cellular basis of the immunoregulatory defect in RA.

In normal individuals T lymphocyte mediated mechanisms appear to be of central importance in regulating the control of EBV induced transformation of B cells. On the basis of in-vitro observations T cell regulation can be divided into ‘early’ and ‘late’ events. The important early effects are mediated by α-interferon produced by T cells which, in addition to its antiviral effect, may itself activate ‘natural killer’ mediated cytolysis of EBV infected
cells. This control mechanism may act as a temporary brake on virus B cell interactions in vivo. Proliferation of EBNA positive cells in a preimmunised host is later controlled by EBV specific cytotoxic T cells between 14–28 days of culture in vitro. This is observed as a regression of the outgrowth of B cells. A T cell mediated suppression of immunoglobulin synthesis induced by EBV is also observed as a ‘late’ effect and appears to be dependent on a cytotoxic or suppressor T cell population.

Many studies were presented which suggested a number of rheumatoid T cell abnormalities in the regulation of EBV induced changes in vitro. Thus, lymphoblastoid cell lines are established more readily in RA lymphocytes than in normals. The outcome resembles that seen in normal cultures depleted of T cells or treated with cyclosporin A. In one set of experiments reported, this abnormality was attributed to a defective production of α-interferon, which in turn was dependent on enhanced sensitivity of RA lymphocytes to prostaglandins. Specific T cell cytotoxicity was also reported to be impaired in RA, but appeared to normalise with diminution of disease activity consequent upon antirheumatoid therapy. Finally, T cell mediated regulation of antibody synthesis induced by EBV is also impaired in RA. The dissection of regulatory responses indicated the development of T cell clones that recognise a biochemically characterised antigen on B blasts, which may be the target for recognition by T cells.

HYPOTHESIS

The polyclonal activation in vitro of B cells by EBV results in immunoglobulin synthesis, especially of IgM class. The antibodies induce include rheumatoid factors, and other autoantibodies also seen in patients with EBV infection. These observations have led to speculation that RA may itself result from polyclonal activation. A selective induction of rheumatoid factor in immature B lymphocytes by EBV was reported, as was an over-representation in the circulation of a subpopulation of B cells which carry the hallmarks of immaturity. Thus there is indirect support for speculation that EBV or a related virus may induce autoimmunity, especially in individuals in whom T cell regulation is compromised, and result in RA. However, in view of a lack of evidence of an increased load of infection by EBV in RA, it has to be admitted that this tempting hypothesis has no substantive proof at present.

Recent studies of the biological and immunological properties of EBV have provided research workers with some interesting hypotheses and conceptual models of the nature of the immune disturbance in rheumatoid arthritis. It is likely that in the long term such investment would prove rewarding in elucidating the aetiology of RA.

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List of participants