EXPERIMENTAL ARTHRITIS EBV INDUCES ARTHRITIS IN MICE

Epstein–Barr virus (EBV) has been implicated in the pathogenesis of rheumatoid arthritis (RA) on the basis of a range of observations, such as the increased circulating EBV load and the frequent presence of activated EBV-specific CD8⁺ T cells in patients with this disease. However, no direct evidence of EBV involvement in RA has been demonstrated in experimental animals, because no appropriate animal model has been devised. Kuwana and colleagues, who had previously developed a humanized mouse model of EBV infection, studied joint histopathology in these animals following inoculation with the virus, and found erosive arthritis with several features reminiscent of human RA.

The mouse model was created by transplanting human CD34⁺ stem cells (obtained from cord blood) into the NOG (NOD/Shi-*scid*/IL-2R γ^{null}) mouse strain, resulting in reconstitution of human immune components. Subsequent infection with EBV in these humanized NOG (hNOG) mice leads to the appearance of key features of human EBV, including lymphoproliferative disorder and asymptomatic persistent infection.

The current experiment included 23 hNOG mice infected with EBV, and 9 control animals that were not infected. Histologic analysis of major joints revealed evidence of synovial proliferation and inflammatory cell infiltration in 15 (65%) of 23 EBV-infected mice; none of the control mice showed these features. The viral dose received at inoculation did not affect the development of erosive arthritis features. Other signs characteristic of human RA were observed in some EBV-infected animals, such as overgrowth of granulation tissue on the load-bearing surface of the joint containing multinucleated giant cells (similar to pannus formation) and infiltration of mononuclear cells to the bone marrow near affected joints (resembling bone marrow edema). Rheumatoid factor and antibodies against cyclic citrullinated peptide were not found.

These results strongly implicate EBV as a causative agent in RA, and demonstrate the potential of EBV-infected hNOG mice in the future study of RA pathogenesis.

Nick Warde

Original article Kuwana, Y. *et al.* Epstein–Barr virus induces erosive arthritis in humanized mice. *PLoS ONE* 6, e26630 (2011)