

CONNECTIVE TISSUE DISEASES

Epstein–Barr virus in Sjögren’s syndrome salivary glands drives local autoimmunity

An aetiological link has been proposed between the B-cell-trophic Epstein–Barr virus (EBV) and Sjögren’s syndrome, but evidence of preferential expression of EBV in the salivary glands of patients with Sjögren’s syndrome is conflicting. A new study published in *Arthritis & Rheumatology* suggests the answer might lie in ectopic lymphoid structures (ELS) within the salivary glands of patients with Sjögren’s syndrome, which serve as niches for latency and reactivation of EBV and contribute to the activation and differentiation of plasma cells.

Comparing the salivary glands of 28 patients with Sjögren’s syndrome and 38 individuals with nonspecific chronic sialoadenitis (NSCS), Croia *et al.* showed that EBV is aberrantly expressed in the salivary glands of the former, specifically in those glands that displayed ELS, as revealed by the presence of EBV-encoded small RNA (EBER) transcripts and EBER⁺ cells within infiltrating cells.

Furthermore, B cells within ectopic follicles expressed the EBV latency protein LMP2A, and perifollicular plasma cells expressed the EBV lytic antigen BFRF1; by contrast, virtually none of the salivary glands without ELS or from patients with NSCS displayed latent or lytic EBV.

Cytotoxic CD8⁺ T-cells were found to accumulate outside B-cell follicles, in areas rich in BFRF1⁺ cells. Notably, staining for both BFRF1 and the major Sjögren’s syndrome antigen Ro52 revealed that EBV reactivation occurs in a substantial proportion of perifollicular plasma cells that produce anti-Ro52 antibodies.

Further investigations suggested the autoreactive profile of EBV-infected B cells is disease-specific: perifollicular plasma cells from Sjögren’s syndrome salivary glands reacted with Ro52 but not citrullinated fibrinogen and, conversely, autoreactive plasma cells from ELS-containing synovial tissue from patients with rheumatoid arthritis (RA)

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reacted with citrullinated fibrinogen but not Ro52. Confirming these findings *in vivo*, engraftment of ELS-containing salivary glands or RA synovia into SCID mice supported the local production of antibodies against EBV and disease-specific autoantigens.

The results suggest that EBV infection is closely associated with an ectopic germinal-centre-like reaction, although a causal link between the virus and Sjögren’s syndrome remains to be determined.

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Original article Croia, C. *et al.* Implication of Epstein-Barr virus infection in disease-specific autoreactive B cell activation in ectopic lymphoid structures of Sjögren’s syndrome. *Arthritis Rheum.* doi:10.1002/art.38726