Cytotoxic CD8 T cells (the effectors) against EBV-infected B cells (the targets): clues for virus-driven immunopathology in multiple sclerosis

Short title: EBV-B cell-T cell interactions in the MS brain

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Epstein-Barr virus (EBV) is strongly associated with MS but the mechanisms linking EBV infection to MS pathology remain unclear. Taken together with increased anti-EBV immune reactivity in MS patients, the B-cell tropism of EBV and the high therapeutic efficacy of B-cell depletion in MS raise the suspicion that EBV-infected B cells and anti-EBV immunity are instrumental in boosting the immunopathological response that harms the central nervous system (CNS). Consistent with this hypothesis are the following findings: predominance of cytotoxic CD8 T cells, which have an essential role in the control of viral infections, in the MS brain; selective enrichment of EBV-specific CD8 T cells in patient CSF; alterations in frequency and function of EBV-specific CD8 T cells in patient peripheral blood. Furthermore, our studies in postmortem MS brain samples suggest presence of an active EBV infection in CNS-infiltrating B-lineage cells, CD8 T cell-mediated cytotoxicity toward EBV-infected cells and an association between EBV reactivation and CNS inflammation. Here, we present the results of a study evaluating the frequency, cytotoxic phenotype and interaction with virus-infected B cells of EBV-specific CD8 T cells and NK cells in the MS brain. The results obtained suggest that MS shows analogies with human T-lymphotropic virus type 1-associated myelopathy/HAM, an infrequent neurological complication of HTLV-1 infection. In HAM, circulating HTLV-1-infected T cells invade the CNS and trigger a cytotoxic immune response against the virus which inadvertently damages neural cells. Likewise, in MS CD8 T cells could mediate an immunopathological response toward an EBV infection brought inside the CNS by B lymphocytes. B-cell depletion would lower EBV load and, hence, the burden of T-cell mediated immunopathology. The tripartite relationship between EBV, B cells and CD8 T cells in MS offers a rationale for current and future treatments and for MS prevention.