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ROLE OF EBV IN NEUROINFLAMMATION:
IMPLICATIONS FOR MULTIPLE SCLEROSIS PATHOGENESIS

by

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Abstract

Multiple sclerosis (MS) is a demyelinating disease of the CNS with unknown cause. Individuals who are genetically predisposed and exposed to specific environmental factors have an increased risk of developing MS. Epstein-Barr virus (EBV) infection is linked to MS development, according to a large body of seroepidemiological and pathological evidence. EBV is a ubiquitous human herpesvirus that typically produces silent infection but can also cause a wide range of illnesses. We have previously examined a large cohort of MS and non-MS control cases and demonstrated the prevalent presence of EBV in MS. However, the role of the virus in the disease is unclear. The main objective of this research was to understand the viral dynamics in vivo and the consequences of peripheral infection on the CNS. To this end, a novel rabbit model of EBV, which produces latent infection comparable to the persistent infection in human carriers, was used in this study. The present dissertation contains (1) human study and (2) animal study for correlation of the results. In the human study, EBV-positive MS cases were examined for histopathological changes. In the animal study, EBV was injected intravenously in one group of animals, and PBS was injected in the control group, with and without immunosuppression. Histopathological changes and viral dynamics were evaluated in the peripheral blood, spleen, brain, and spinal cord, using molecular and histopathology techniques. A number of important aspects of EBV infection were revealed. Peripheral EBV infection led to CNS infection and promoted neuroinflammation in the form of immune aggregates. EBV infected B cells were most likely the source of CNS infection. The immune aggregates were more prevalent in immunosuppressed animals and consisted of focal accumulation of macrophages surrounded by reactive astrocytes and dispersed B and T lymphocytes. The center of aggregates exhibited signs of myelin destruction. Moreover, studying EBV infection over time revealed that the peak in viral load in the periphery and CNS corresponded to an increase in the occurrence of cellular aggregates in the brain. Additionally, altered expression of viral latent transcripts correlated with upregulation of several proinflammatory cytokines in the periphery and the CNS. Increased expression of IL-6 at the mRNA and protein level in the brain was associated with neuroinflammation. Finally, several similarities and differences were observed between the pathology in EBV positive MS cases and EBV infected rabbit CNS. This work establishes the first direct in vivo evidence for the role of peripheral EBV infection in CNS pathology, and demonstrates the utility of a novel model for dissecting viral mechanisms involved in the development of EBV- associated diseases including MS.

Keywords: Epstein-Barr virus, peripheral infection, neuroinflammation, demyelination, CNS infection, multiple sclerosis, rabbit model.