Applying OCCAMS molecular razor to study the relationship between EBV and MS

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REPORT

MULTIPLE SCLEROSIS

Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis

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Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system of unknown etiology. We tested the hypothesis that MS is caused by Epstein-Barr virus (EBV) in a cohort comprising more than 10 million young adults on active duty in the US military, 955 of whom were diagnosed with MS during their period of service. Risk of MS increased 32-fold after infection with EBV but was not increased after infection with other viruses, including the similarly transmitted cytomegalovirus. Serum levels of neurofilament light chain, a biomarker of neuroaxonal degeneration, increased only after EBV seroconversion. These findings cannot be explained by any known risk factor for MS and suggest EBV as the leading cause of MS.

Article

Clonally expanded B cells in multiple sclerosis bind EBV EBNA1 and GlialCAM

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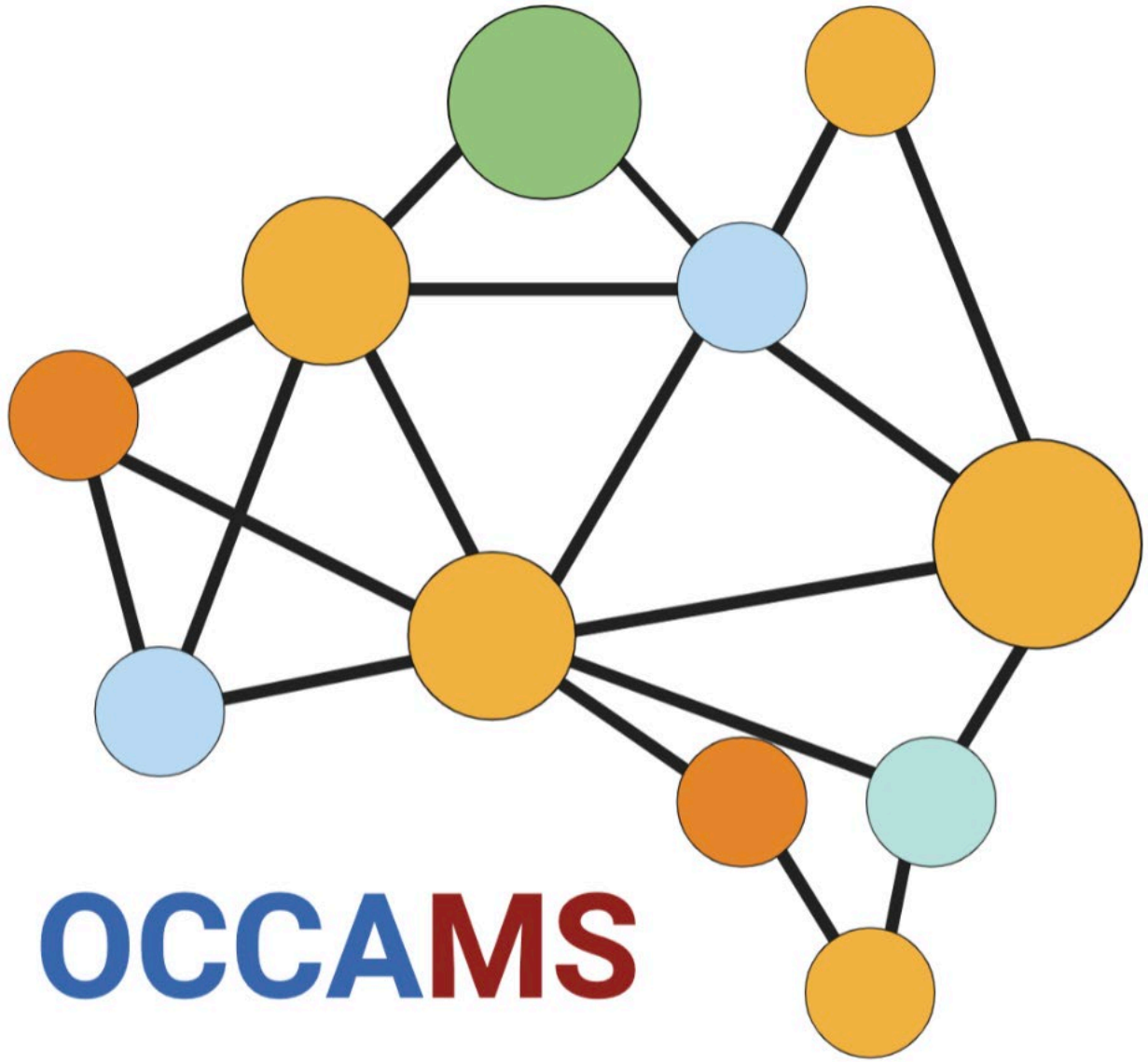
Multiple sclerosis (MS) is a heterogenous autoimmune disease in which autoreactive lymphocytes attack the myelin sheath of the central nervous system. B lymphocytes in the cerebrospinal fluid (CSF) of patients with MS contribute to inflammation and secrete oligoclonal immunoglobulins[1,2]. Epstein–Barr virus (EBV) infection has been epidemiologically linked to MS, but its pathological role remains unclear[3]. Here we demonstrate high-affinity molecular mimicry between the EBV transcription factor EBV nuclear antigen 1 (EBNA1) and the central nervous system protein glial cell adhesion molecule (GlialCAM) and provide structural and in vivo functional evidence for its relevance. A cross-reactive CSF-derived antibody was initially identified by single-cell sequencing of the paired-chain B cell repertoire of MS blood and CSF, followed by protein microarray-based testing of recombinantly expressed CSF-derived antibodies against MS-associated viruses. Sequence analysis, affinity measurements and the crystal structure of the EBNA1–peptide epitope in complex with the autoreactive Fab fragment enabled tracking of the development of the naive EBNA1-restricted antibody to a mature EBNA1–GlialCAM cross-reactive antibody. Molecular mimicry is facilitated by a post-translational modification of GlialCAM. EBNA1 immunization exacerbates disease in a mouse model of MS, and anti-EBNA1 and anti-GlialCAM antibodies are prevalent in patients with MS. Our results provide a mechanistic link for the association between MS and EBV and could guide the development of new MS therapies.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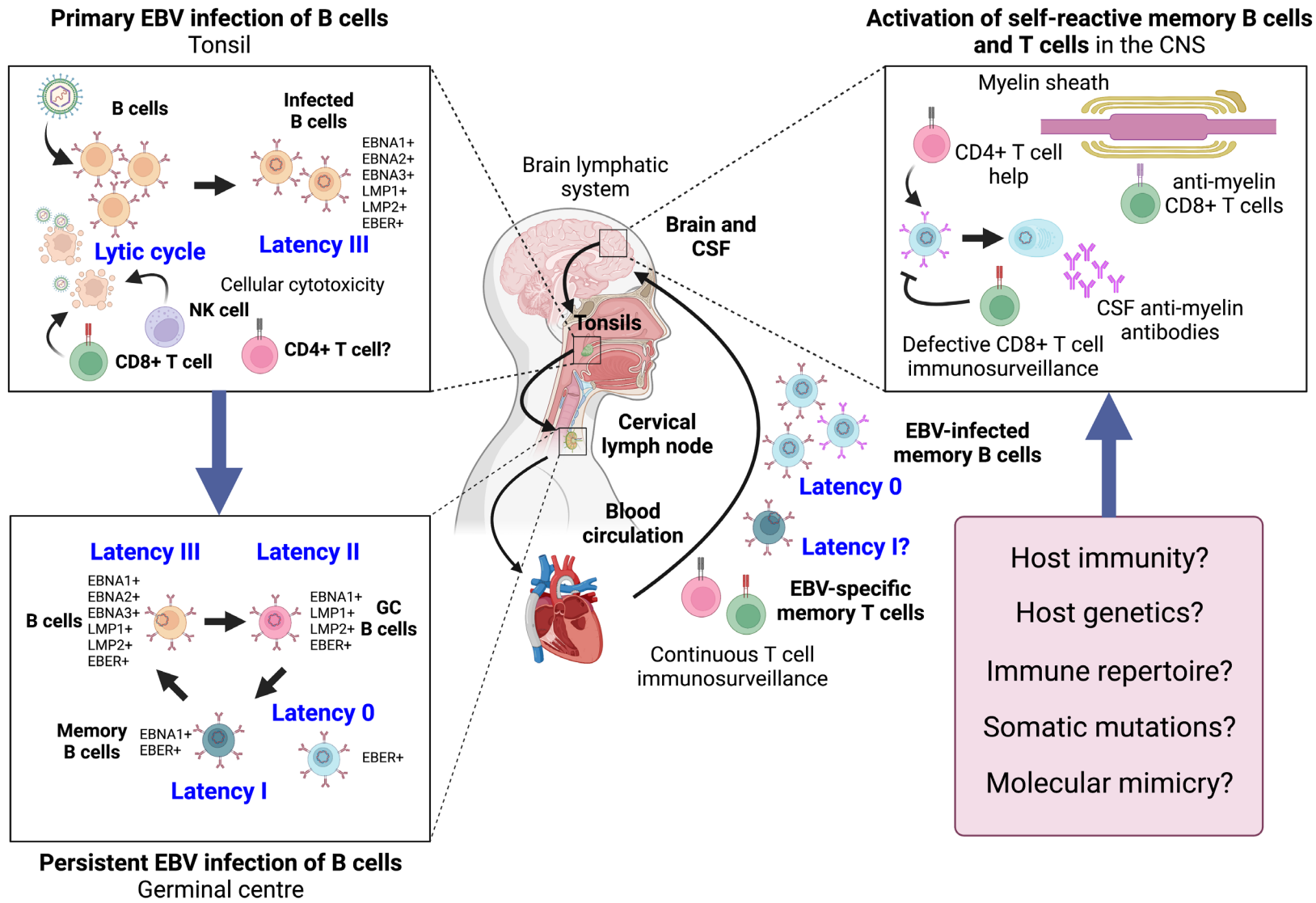
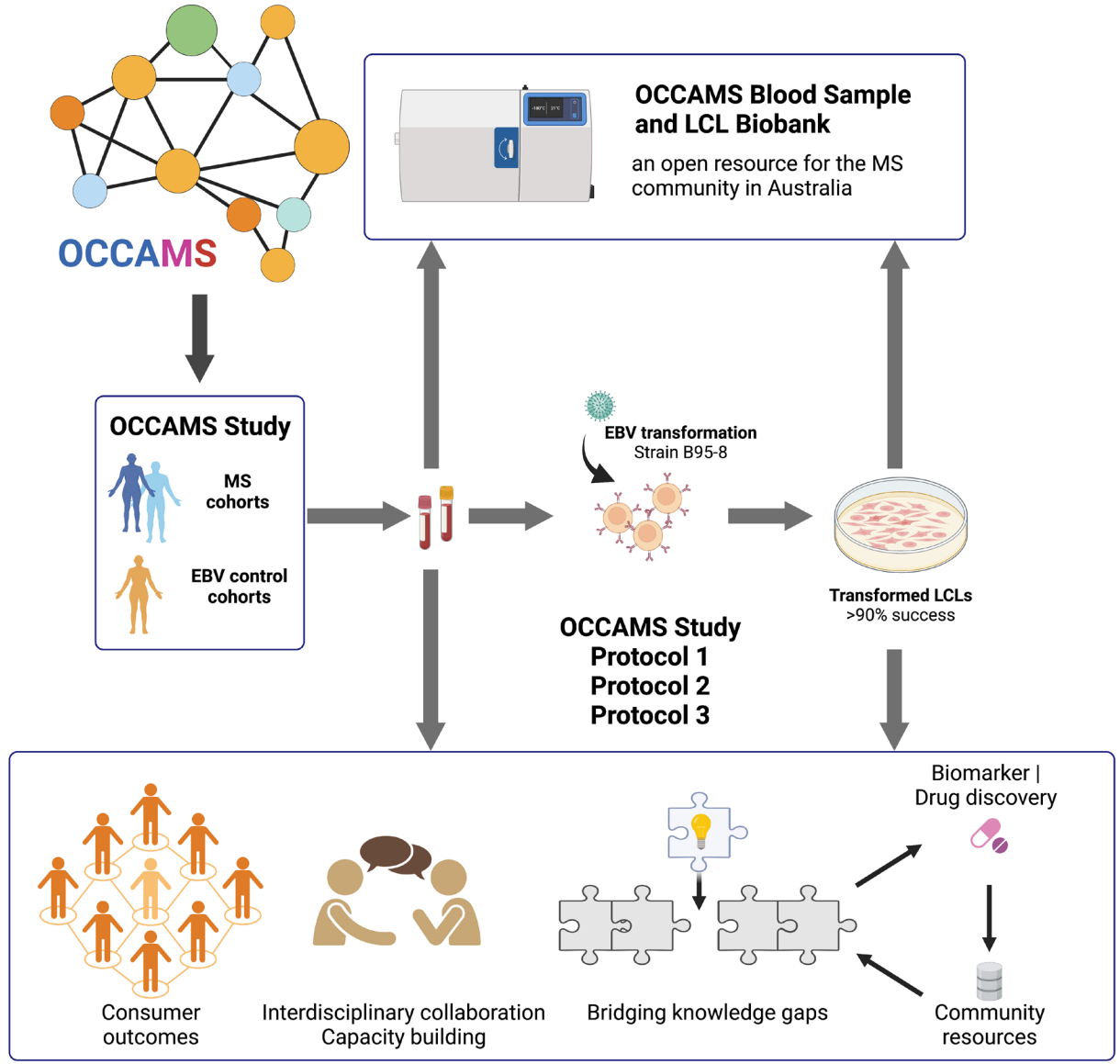

Primary EBV infection of B cells
Tonsil
B cells
Infected B cells
EBNA1+
EBNA2+
EBNA3+
LMP1+
LMP2+
EBER+
Lytic cycle
Latency III
Cellular cytotoxicity
NK cell
CD8+ T cell
CD4+ T cell?
Latency III
Latency II
B cells
EBNA1+
EBNA2+
EBNA3+
LMP1+
LMP2+
EBER+
EBNA1+
LMP1+
LMP2+
EBER+
GC B cells
Latency 0
Memory B cells
EBNA1+
EBER+
EBER+
Latency I
Persistent EBV infection of B cells
Germinal centre
Brain lymphatic system
Brain and CSF
Tonsils
Cervical lymph node
Blood circulation
EBV-infected memory B cells
Latency 0
Latency I?
EBV-specific memory T cells
Continuous T cell immunosurveillance
Activation of self-reactive memory B cells and T cells in the CNS
Myelin sheath
CD4+ T cell help
anti-myelin CD8+ T cells
CSF anti-myelin antibodies
Defective CD8+ T cell immunosurveillance
Host immunity?
Host genetics?
Immune repertoire?
Somatic mutations?
Molecular mimicry?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