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Exposure to the Epstein-Barr viral antigen latent membrane protein 1 induces myelin-reactive antibodies in vivo

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Abstract

© 2017 Lomakin, Arapidi, Chernov, Ziganshin, Tcyganov, Lyadova, Butenko, Osetrova, Ponomarenko, Telegin, Govorun, Gabibov and Belogurov. Multiple sclerosis (MS) is an autoimmune chronic inflammatory disease of the central nervous system (CNS). Cross-reactivity of neuronal proteins with exogenous antigens is considered one of the possible mechanisms of MS triggering. Previously, we showed that monoclonal myelin basic protein (MBP)-specific antibodies from MS patients cross-react with Epstein-Barr virus (EBV) latent membrane protein 1 (LMP1). In this study, we report that exposure of mice to LMP1 results in induction of myelin-reactive autoantibodies in vivo. We posit that chronic exposure or multiple acute exposures to viral antigen may redirect B cells from production of antiviral antibodies to antibodies, specific to myelin antigen. However, even in inbred animals, which are almost identical in terms of their genomes, such an effect is only observed in 20-50% of animals, indicating that this change occurs by chance, rather than systematically. Cross-immunoprecipitation analysis showed that only part of anti-MBP antibodies from LMP1-immunized mice might simultaneously bind LMP1. In contrast, the majority of anti-LMP1 antibodies from MBP-immunized mice bind MBP. De novo sequencing of anti-LMP1 and anti-MBP antibodies by mass spectrometry demonstrated enhanced clonal diversity in LMP1-immunized mice in comparison with MBP-immunized mice. We suggest that induction of MBP-reactive antibodies in LMP1-immunized mice may be caused by either Follicular dendritic cells (FDCs) or by T cells that are primed by myelin antigens directly in CNS. Our findings help to elucidate the still enigmatic link between EBV infection and MS development, suggesting that myelin-reactive antibodies raised as a response toward EBV protein LMP1 are not truly cross-reactive but are primarily caused by epitope spreading.

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Keywords

Autoantibodies, Cross-reactivity, Epitope spreading, Epstein-Barr virus, Latent membrane protein 1, Multiple sclerosis, Myelin basic protein

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