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Ineffective Immune Control of Epstein-Barr Virus-Induced Autoreactive Responses is an Important Cause of Multiple Sclerosis

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Introduction:

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system (CNS). Epstein-Barr virus (EBV) contributes to the MS pathogenesis, as high-levels of EBV EBNA386-405-specific antibodies cross-react with the CNS-derived glial cell adhesion molecule (GlialCAM370-389). However, it is unclear why only some individuals with such high autoreactive antibody titers develop MS. However, it is unclear why only some individuals with such high autoreactive antibody titers develop MS.

Objectives/Aims:

The aim of this study was to investigate, which factors determine whether individuals, who develop high-level EBNA386-405-specific autoimmune responses against the GlialCAM370-389, further evolve into MS.

Methods:

For this study a total of 12,708 EBV-seropositive MS patients and healthy controls were initially recruited with retrospective follow-up serum samples (with maximal intervals of 12 months) until EBV seroconversion of the patients serologically proven by EBV-specific IgG antibodies. EBV-strain needed to be available for sequence analysis, obtained at the time of infectious mononucleosis or in asymptomatic patients during a reactivation episode at another time point before MS diagnosis. Infecting human Cytomegalovirus (HCMV)-strain needed to be available from HCMV seropositive patients obtained between EBV seroconversion and MS diagnosis. From 20 MS patients (7.4%) and 80 controls (29.6%), additional peripheral blood mononuclear cells (PBMC) were available, which were collected from MS patients immediately (0-6 days) after MS diagnosis, or at a matched time point after EBV seroconversion for the controls.

Results:

Autoreactive cells are eliminated by distinct immune responses, which are determined by genetic variations of the host as well as the infecting EBV- and HCMV strains. We demonstrate that potent cytotoxic NKG2C+ and NKG2D+ NK cells and distinct EBV-specific T-cell responses kill autoreactive GlialCAM370-389-specific cells. Furthermore, immune evasion of these autoreactive cells was induced by EBV-strain-specific upregulation of the immunomodulatory HLA-E. These defined virus and host genetic pre-dispositions are associated with an up to 260-fold increased risk of MS.

Conclusion:

Our findings thus allow the early identification of patients at risk for MS and suggest new therapeutic options against MS.

Disclosures:
All authors have nothing to disclose