Epstein-Barr Virus: Review

- Epstein-Barr virus infects 90% of adults worldwide
- Young children – asymptomatic
- Adolescents and adults – infectious mononucleosis
  - Generally self-limiting
  - Rare cases
    - Fulminant infectious mononucleosis – leads to death in days or weeks
    - Chronic active infectious mononucleosis – persistent symptoms

Veroni C et al. *Front Immunol*. 2021;12:665718.

Epstein-Barr Virus (EBV): Immunology of Latency

- Remains in infected cells for the life of the host
- EBV unique among viruses infecting humans in that it infects and remains latent in B cells
- In healthy individuals, EBV-specific cytotoxic $CD8^+$ T cells and NK cells kill any cells with proliferating and destructive EBV
- Immunologic balance can be disrupted by certain genetic or environmental factors leading to immunosuppression

NK, natural killer.

Pender MP et al. *JCI Insight*. 2018;3:e124714; Veroni C et al. *Front Immunol*. 2021;12:665718.

Epstein-Barr Virus (EBV) and MS

- All MS patients tested have been positive for EBV
- EBV is one of the greater environmental risk factors for developing MS

Potential Mechanisms Linking EBV and MS Pathophysiology

Autoantibodies: Autoreactive B-cells infected by EBV produce antibodies to CNS proteins that migrate into CNS and stimulate central autoreactive CD4 T-cells. No MS-related autoantibodies have been identified.

Mistaken self: EBV triggers expression of specific protein in B cells (alpha-B-crystallin). B cells then activate pathologic CD4 T-cells which recognize this protein in glial cells within the CNS. No direct evidence for T-cell recognition of alpha-B-crystallin in MS

EBV-driven immunopathology: Cytotoxic T-cells respond to reactivated EBV in the CNS. There is some supportive evidence; $CD8^+$ T-cells are active in brains of MS patients, and there is an increased level of EBV-specific $CD8^+$ T-cells in the CSF and brain tissue in MS. The reactivation of latent EBV-infected cells in MS is not established.

Molecular mimicry: Antibodies and CD4 T-cells cross react with peptides from EBV proteins and from myelin or other CNS proteins. The pathogenic nature of this cross-recognition has not been confirmed.

CNS, central nervous system; CSF, cerebral spinal fluid.

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