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Abstract Title: Latent EBV-specific CD8⁺ T cells Exhibit Disease-specific Transcriptional Programming in Multiple Sclerosis

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Background

Multiple sclerosis (MS) is a chronic central nervous system disease characterised by immune cell infiltration, with Epstein-Barr virus (EBV) infection strongly linked to its development. Although T cells control EBV latency and lytic reactivation, the viral lifecycle stage dysregulated in MS remains unclear.

Objectives/Aims

To determine whether MS is associated with stage-specific dysregulation of EBV-specific CD8⁺ T cell immunity by resolving transcriptional and T cell receptor (TCR) features across latent and lytic programs.

Methods

Peripheral blood mononuclear cells from 21 treatment-naïve pwMS and 19 matched controls were analysed using HLA-matched peptide-MHC multimer enrichment with single-cell transcriptomic and paired TCR profiling to define the epitope-resolved transcriptional and clonal landscape of EBV-specific CD8⁺ T cells. A subset of 10 pwMS and 10 controls underwent autologous EBV lymphoblastoid cell line (LCL) stimulation to assess antigen-driven responses.

Results

We identified stage-specific dysregulation of EBV immunity in pwMS, with selective expansion of latency III-specific CD8⁺ T cells ($P_{FDR} = 0.04$), predominantly driven by EBNA1- and EBNA3A-specific responses. These cells showed enhanced cytotoxic programming ($P_{FDR} = 0.03$) that correlated with clonal expansion, consistent with persistent antigen exposure, while other stages were unchanged. Following autologous LCL stimulation, pwMS displayed selective amplification of a *GZMK*⁺ interferon-associated program within late effector memory cells ($P_{FDR} < 0.05$), including genes linked to interferon signalling (*IFI6*, *HERC5*), antigen presentation (*HLA-B*, *HLA-C*), and immune

signalling and trafficking (*IL7R*, *JAK1*, *CXCR4*). Integration with MS GWAS highlighted overlap with a core module including *IL7R*, *JAK1*, and *HLA-B*.

Conclusion

These findings define a distinct, antigen-resolved EBV-specific CD8⁺ T cell program in MS linking latent viral recognition to pathogenic immune activation. By identifying latent EBV infection as a key stage of dysregulation and connecting EBV persistence with genetically anchored pathways, this work provides a mechanistic framework for MS and highlights latent antigen-specific T cell responses as therapeutic targets.

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