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Host Genetics Dictate Whether Chronic Herpesvirus Infection Triggers Brain T-Cell Infiltration

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More than 90% of adults worldwide carry latent human gammaherpesviruses such as Epstein-Barr virus (EBV), typically without severe neurological consequences. Yet epidemiological and longitudinal cohort studies -- including landmark work by Bjornevik and colleagues -- have established EBV as a leading environmental trigger for multiple sclerosis (MS), an autoimmune demyelinating disorder of the central nervous system . A central paradox has long puzzled neuroimmunologists: if almost everyone is infected with these persistent herpesviruses, why do only a small fraction of hosts develop destructive brain inflammation ?

New research from the University of Vermont (UVM) , reported in November 2026, points directly to host genetic background as a decisive gatekeeper. Using genetically diverse mouse strains engineered to mirror human genetic variation, researchers infected hosts with a chronic murine gammaherpesvirus and tracked immune trafficking in the central nervous system. Strains genetically predisposed to weak viral containment exhibited a pronounced accumulation of virus-specific T cells inside the brain -- even before any overt clinical signs of autoimmunity appeared -- whereas genetically distinct strains that suppressed the virus effectively showed minimal brain T-cell infiltration.

Modeling Human Genetic Diversity in Chronic Herpesvirus Control

Classical laboratory immunology relies heavily on a single inbred mouse strain (such as C57BL/6), which flattens the natural genetic variation seen across human populations. In the UVM investigation, researchers leveraged genetically diverse mouse cohorts to capture how polymorphisms across immune-regulatory loci alter host-pathogen equilibrium during lifelong viral latency.

Following acute gammaherpesvirus exposure, the virus establishes a persistent latent reservoir in B lymphocytes and peripheral lymphoid tissues, periodically reactivating at low levels. In genetically "high-controller" hosts, peripheral cytotoxic CD8 + T cells and innate interferon pathways rapidly contain viral reactivation without needing to mobilize large effector waves into protected organs. In contrast, genetically "low-controller" hosts fail to lock down peripheral viral replication cleanly, permitting sustained antigenic stimulation that drives virus-specific T lymphocytes across the blood-brain barrier .

| Host Genetic Phenotype | | Peripheral Viral Containment | | Central Nervous System Immune State | | Downstream Neuroinflammatory Risk |

| Effective Viral Controller | | Strong innate & peripheral CD8 + suppression of reactivation | | Minimal virus-specific T-cell infiltration into brain parenchyma | | Low baseline neuroinflammation; preserved immune privilege |

| Poor Viral Controller | | Incomplete containment; elevated chronic viral antigen

load | | Early accumulation of virus-specific T cells inside the brain | | Microglial priming, blood-brain barrier stress, autoimmune susceptibility |

Pre-Autoimmune T-Cell Seeding and the Multiple Sclerosis Link

One of the most striking observations from the study is the timing of central nervous system entry. Virus-specific T cells accumulated inside the brain parenchyma of poorly controlled hosts prior to any clinical or histological evidence of autoimmune demyelination . Rather than autoimmunity opening the door for stray lymphocytes, genetic failure to contain a chronic herpesvirus appears to seed the brain with activated effector T cells first, establishing a primed inflammatory microenvironment.

Once stationed in perivascular spaces and brain tissue, infiltrating T cells release pro-inflammatory cytokines -- such as interferon-gamma (IFN-gamma) and tumor necrosis factor (TNF) -- that shift resident brain microglia out of their homeostatic maintenance state. In humans carrying MS susceptibility alleles (particularly within the Major Histocompatibility Complex / HLA class II region), this viral-triggered inflammatory priming can intersect with molecular mimicry , in which antibodies or T-cell receptors directed against viral proteins such as EBNA1 cross-react with central nervous system myelin or glial antigens like GlialCAM.

Complementary Innate Defenses in Neurotropic Herpesviruses

The UVM gammaherpesvirus findings complement parallel discoveries across alphaherpesviruses such as herpes simplex virus type 1 (HSV-1). While over 60% of humans harbor latent HSV-1 in sensory ganglia, rare inborn errors of immunity affecting Toll-like receptor 3 (TLR3), type I interferon signaling (UNC93B1 , STAT1 , IFNAR1), or neuron -intrinsic restriction factors like TMEFF1 can allow unchecked viral spread into the brain, causing life-threatening herpes simplex encephalitis.

Even without fulminant encephalitis, experimental HSV-1 brain exposure reprograms resident microglia into sustained interferon-driven defense states accompanied by chromatin remodeling , transiently downregulating normal synaptic pruning and debris clearance. Across both alpha- and gammaherpesviruses, host genetics determines whether the central nervous system remains an unperturbed sanctuary or becomes a chronic immunological battleground.

Implications for Targeted Prevention and Stratification

Identifying host genetic control of viral latency as an upstream driver of brain T-cell infiltration carries important translational implications. Instead of treating neuroinflammatory diseases solely with broad systemic immunosuppression after myelin damage has occurred, clinicians may eventually stratify high-risk individuals using polygenic susceptibility scores combined with viral-load or T-cell-exhaustion biomarkers.

Preventive strategies -- including next-generation Epstein-Barr virus vaccines, targeted antiviral suppressors, or therapies that bolster peripheral cytotoxic containment -- could prove especially impactful for genetically vulnerable individuals, intercepting the cascade before virus-specific T cells ever take up

residence inside the brain.

References & Primary Sources

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