Viral infection activates myelin-specific T cells, triggering MS-like CNS inflammatory demyelination

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Abstract

Background: Multiple sclerosis (MS) has been suggested to be triggered by microbial infections in genetically susceptible hosts harboring anti-myelin autoimmune T cells. Myelin oligodendrocyte glycoprotein (MOG)-specific T cell receptor (TCR) transgenic (tg) 2D2 mice develop experimental autoimmune encephalomyelitis (EAE) following MOG sensitization. In contrast, only 4% of 2D2-tg mice develop spontaneous EAE with mild inflammation in the central nervous system (CNS) after 3 months of age.

Objective: To determine whether viral infection can activate MOG-specific T cells as an adjuvant and confer susceptibility to EAE in 2D2-tg mice.

Materials and Methods: We injected 6-week-old 2D2-tg or wild-type C57BL/6 mice intraperitoneally with the following microbes and microbe mimics: Theiler’s murine encephalomyelitis virus (TMEV), RNA virus, poly(I:C) (RNA virus mimic), murine cytomegalovirus (MCMV, DNA virus), and curdlan (bacterial/fungal component, Chitin Inhibitor).

Results: During the 2-months observation period, intraperitoneal TMEV injection induced hind limb paralysis in 43% of 2D2-tg mice (mean onset 36.7 ± 5.6 days) with severe inflammatory demyelination and axial demyelination. In contrast, only a few 2D2-tg mice injected with MCMV or curdlan had mild CNS signs. Intracerebral injection of TMEV was more effective for inducing CNS inflammatory demyelination than the intraperitoneal injection, the mean disease onset was earlier (13.1 ± 1.7 days).

Conclusions: Viral infection may activate anti-myelin T cells as an adjuvant, triggering CNS inflammatory demyelination.

Materials and Methods

Wild-type C57BL/6 and 2D2-tg mice (6 weeks old)

Intraperitoneal injection of Theiler’s virus causes severe demyelination in 2D2-tg mice

Naïve or MCMV-infected 2D2-tg mice

Thelier’s virus-infected 2D2-tg mice

Curdlan-injected 2D2-tg mice

Disease sign – Inflammation – Paralysis ++ Demyelination +++ Disease sign – Inflammation +

Luxol fast blue staining showed no demyelination in naïve or MCMV-infected 2D2-tg mice (left). In contrast, Thelier’s virus-infected 2D2-tg mice with EAE developed severe inflammatory demyelination (middle). Although curdlan-treated 2D2-tg mice did not exhibit EAE signs, a few mice from the group had mild inflammation in the CNS (right).

Experimental autoimmune encephalomyelitis (EAE)

- Animal model of MS
- Similar to MS clinically and histologically
- Sensitizing mice with myelin antigen with complete Freund’s adjuvant and pertussis toxin injection for inducing myelin-specific immune responses
- Complicated data interpretation due to the artificial sensitization protocol

Spontaneous EAE: 2D2-transgenic (tg) mice

- Have myelin oligodendrocyte glycoprotein (MOG)-specific T cell receptors (TCR) in the majority of CD4+ T cells
- No disease in the first 3 months after birth
- Accelerate EAE with a higher incidence by injecting pertussis toxin alone
- Useful for investigating interactions between autoimmune responses and microbial infections

Gaps in knowledge and “hypothesis”

How certain microbial infections trigger MS?

“Microbes or microbial components could activate MOG-specific T cells as an adjuvant, causing EAE?”

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