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. However, oligoglectinyl- and glycycolipid-specific T cell receptors (TCR) are not well characterized in MS. Method: We injected 6-week-old 2D2-tg or wild-type C57BL/6 mice intracerebrally with the following microbes or microbe mimics: Theiler’s murine encephalomyelitis virus (TMEV, RNA virus), poly(C) (RNA virus mimics), murine cytomegalovirus (MCMV, DNA virus), and curdlan (bacteria/fungus component, TLR3 agonist). Results: The TMEV infected-2D2-tg mice exhibited EAE signs, while wild-type C57BL/6 mice intraperitoneally injected with TMEV did not. Medium daytime observation period, intraperitoneal TMEV injection induced hind-limb paralysis in 43% of 2D2-tg mice (mean onset 36.7 ± 1.7 days) with severe inflammatory demyelination and axonal degeneration in the CNS. Among other groups, only a few 2D2-tg mice injected with MCMV or the bacteria/fungus component, TLR3 agonist poly(C) had mild CNS involvement. Intracerebral injection of TMEV was more effective for inducing CNS disease: 83% of 2D2-tg mice developed severe inflammatory demyelination with earlier onset time (13.1 ± 1.7 days). No wild-type mice developed CNS demyelination from poly(C) treatment (mean onset 36.7 ± 1.7 days). Conclusion: Viral infection may activate anti-myelin T cells as an adjuvant, triggering CNS inflammatory demyelination.

Materials & Methods

Experimental design

Wild-type C57BL/6 and 2D2-tg mice were intraperitoneally injected with the following microbes or microbe mimics: TMEV, poly(C), murine cytomegalovirus, or curdlan. EAE signs and CNS pathology were evaluated.

Thaller’s murine encephalomyelitis virus (Thaller’s virus)

- Non-enveloped, positive-sense, single-stranded RNA virus that belongs to the family Picornaviridae
- Recognized by toll-like receptor (TLR) 3 and TLR7
- Induces immune-mediated demyelination 1 month after infection by only intracerebral injection
- Causes demyelination depending on mouse strains, MHC, susceptible SJL/J vs. resistant C57BL/6 mice

Murine cytomegalovirus (MCMV)

- Enveloped, double-stranded DNA virus that belongs to the family Herpesviridae
- Recognized by TLR9 and cyclic GMP-AMP synthase (cGAS)

Curdlan

- Synthetic analog of double-stranded RNA
- Mimics RNA virus infections
- Activates the anti-viral pattern recognition receptor, TLR3

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

Hind-limb paralysis

Inflammatory demyelination

Antigen

Myelin-specific T cell

Autoimmunity

Myelin-specific T cell Anti-myelin antibody

Microbial infection

Genetic factors

MHC (major histocompatibility complex)

EAE incidence

0

10

20

30

40

50

60

Days post injection

Disease sign

No disease

Before 1 month

By peripheral injection

In C57BL6 mice


Sato et al., J. Neuroimm., in press


Results

Intracerebral injection of Thaller’s virus causes severe demyelination in 2D2-tg mice

- Naive or MCMV-infected 2D2-tg mice
- Thaller’s virus-infected 2D2-tg mice
- Curdlan-infected 2D2-tg mice

Disease sign

Paralysis ↔

Demyelination ↔

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

Spontaneous EAE

- Intracerebral injection of Thaller’s virus

- No disease

- Spontaneous EAE

- Intracerebral injection

- No disease

Acknowledgements

How certain microbial infections trigger MS?

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

Gaps in knowledge and “hypothesis”

- How certain microbial infections trigger MS?
- Other microbes and microbe mimics also act as adjuvants, inducing subclinical EAE
- Which PRRs and what factors are critical for inducing bystander activation?

Conclusions

- Thaller’s virus infection accelerates spontaneous EAE
- Other microbes and microbe mimics also act as adjuvants, inducing subclinical EAE
- Thaller’s virus may act as an effective adjuvant, triggering demyelination by bystander activation?

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