

## Theiler's murine encephalomyelitis virus with

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### What is known about TMEV?

**Byung S. Kim:** Theiler's murine encephalomyelitis virus (TMEV) is a common enteric virus in mice and belongs to Cardiovirus genus in the Picornavirus family. TMEV is divided into two groups based on neurovirulence and antigenicity. The less virulent Theiler's original viruses (TO) such as BeAn8386 and DA strains result in a biphasic neurological disease leading to flaccid limb paralysis and degeneration of neurons after intracerebral inoculation in susceptible mouse strains. TMEV-infected susceptible mice develop

a chronic immune-mediated demyelinating disease similar to human MS involving strong autoimmunity to myelin antigens. Furthermore, the genetic association between susceptibility and the MHC and/or TCR  $\beta$ -chain, as well as the gender bias susceptibility are parallel to MS (1). Although the cause of MS is not yet known, epidemiological studies suggest a viral etiology for this disease. Thus, the TMEV-induced demyelination system has been extensively studied as a relevant model.

### Which immune parameters influence on susceptibility to TMEV-induced disease?

**Byung S. Kim:** *Immune responses to viral and self antigens:* T cell responses to viral antigens and self antigens have previously been detected in the CNS of mice with demyelinating disease (1). However, the relative contributions and protective/pathogenic immune components are not yet entirely clear. Our recent studies indicate that resistant C57BL/6 mice display stronger early CD4<sup>+</sup> and CD8<sup>+</sup> T cell responses to viral determinants in the CNS compared to susceptible mice ((2) and unpublished data). However, such immune responses are higher in susceptible SJL/J mice later during the course of viral infection. Clonal expansion of infiltrating T cells at the site of viral persistence, CNS, is apparent during the course of viral persistence (3), suggesting that infiltrating T cells are preferentially expanded and/or retained. These T cell clones in the CNS

appear to be significantly different from those in the periphery and these populations may be critical for pathogenesis of demyelination.

*MHC and T-cell receptor:* It has previously shown that the MHC is closely associated with the frequency of many different autoimmune diseases including human multiple sclerosis. In addition, TCR  $\beta$ -chain polymorphism appears to influence susceptibility. Similarly, both MHC and TCR  $\beta$ -chain genes (the J $\beta$ 1 region in particular) are associated with susceptibility to TMEV-induced demyelinating disease (4). The association between TCR  $\alpha$ -chain polymorphism and MS is not consistent. We found that this polymorphism can influence the susceptibility to TMEV-induced demyelinating disease only in conjunction with TCR  $\beta$ -chain genes and/or MHC, demonstrating the pres-

ence of many similarities between these two diseases. The expression of susceptible H-2<sup>s</sup> overrides the resistant effect of the BALB/c TCR  $\beta$ -chain gene in CXJ recombinant-inbred and BALB.S congenic mice. These results strongly suggest that the genes involved in shaping TCR repertoire affect susceptibility to demyelinating disease. Our recent studies with susceptible SJL/J (H-2K<sup>s</sup>A<sup>s</sup>D<sup>s</sup>), BALB.S (H-2K<sup>s</sup>A<sup>s</sup>D<sup>s</sup>), and resistant BALB.S3R (H-2K<sup>s</sup>A<sup>s</sup>D<sup>d</sup>/L<sup>d</sup>) mice

indicate that no preferential use of V $\beta$  families is associated with either the differences in the MHC components or susceptibility to disease (5). CD8<sup>+</sup> T cells restricted with a MHC class I locus (H-2D<sup>d</sup>/L<sup>d</sup>) exert the resistance in BALB.S3R mice. Therefore, TCR V $\beta$  family as well as MHC class II genes may be secondary to a particular MHC class I gene-associated CD8<sup>+</sup> T cell response. Such an association with MHC class I is also found in human MS.

### Why is susceptibility to demyelinating disease between males and females different?

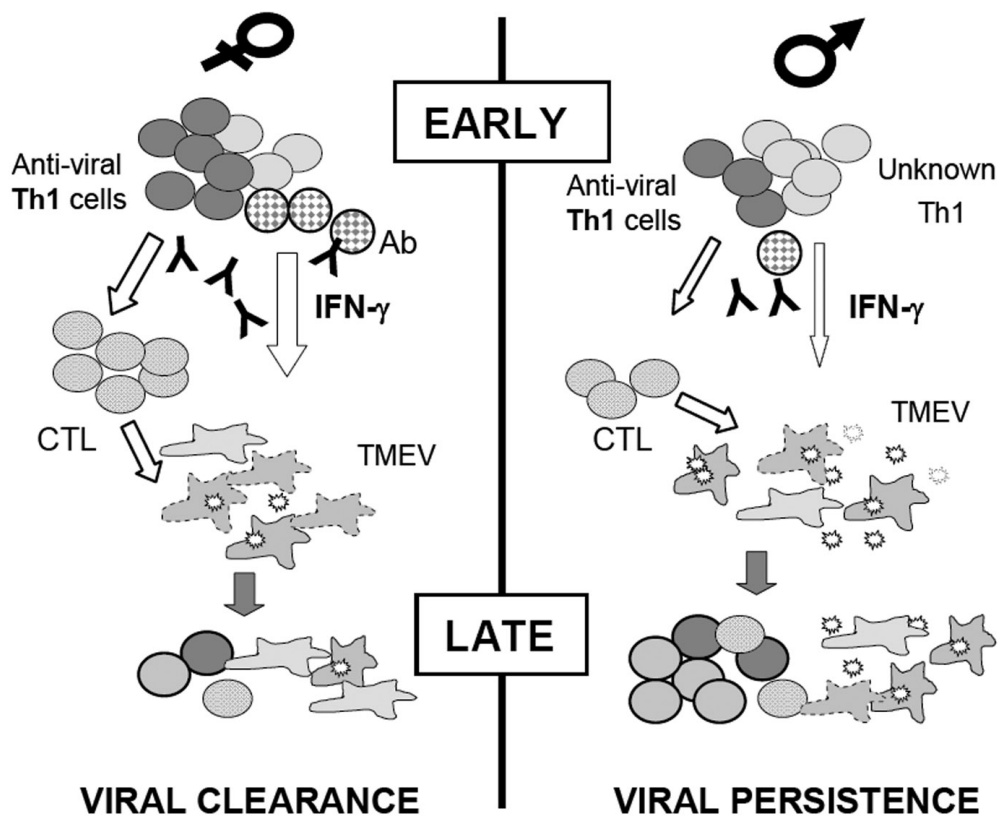
**Byung S. Kim:** It has long been recognized that females display significantly higher incidence of many different types of autoimmune diseases including multiple sclerosis (MS) in which 60-75% of all cases are female. TMEV-induced demyelinating disease also displays a gender bias, but males are susceptible to disease while females are completely resistant in the C57L/J strain of mice. Female C57L/J mice induce significantly higher levels of TMEV-specific neutralizing antibody as well as a stronger peripheral T cell response throughout the course of viral infection. In contrast, male mice have higher infiltration levels of virus-specific CD4<sup>+</sup> and CD8<sup>+</sup> T cells into the CNS as well as viral persistence. Thus, a higher level of the initial anti-viral immune response in female mice appears to

effectively clear virus from the periphery as well as CNS and consequently prevent further disease manifestations (6). Preliminary results show that treatment of male mice with estradiol renders the mice resistant to the clinical symptoms, suggesting a role for female sex hormone as an immune modulator. It appears that females with a higher level of estrogen are able to mount enhanced levels of immune responses to infectious agents for protection. However, such an enhancement of immunity may also result in increased immunity to self antigens leading to chronic immune mediated autoimmune diseases. At this point, however, the underlying mechanisms and factors that contribute to this difference in the immune responses are not yet known.

### What can be learned from this model for potential therapy?

**Byung S. Kim:** Epidemiologic studies have suggest that MS is likely associated with certain viral infections coupled with the genetic disposition associated with T cell responses. The TMEV system parallels these clinical, histological, genetic, as well as immunological

parameters of human MS (7). We believe that this system will provide the basic immunological mechanisms involved in the pathogenesis of chronic demyelinating disease, such as type and properties of pathogenic T cells accumulated in the CNS. In addition, it will elucidate



potential role of infectious agents in developing chronic immune mediated diseases to persistent foreign and self antigens. Understanding the pathogenesis of this viral system will lead to the means to intervene in the harmful immune responses, ultimately applicable to human MS as well as other chronic immune mediated inflammatory diseases.

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