

***Domino*, a dominant mutation that causes exaggerated susceptibility to MCMV infection in mice.**

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Natural Killer (NK) cells play a crucial role in the innate immune response to viral infections. NK cell depletion in mice enhances susceptibility to mouse cytomegalovirus (MCMV). Activation of dendritic cells (DC) upon MCMV infection leads to cytokine-mediated

NK cell activation, involving the production of interleukin-12 (IL-12), interferon- γ (IFN- γ) and type I IFN (IFN- β/γ). This early immune response occurs within

5 days after MCMV infection. C57BL/6J mice are naturally resistant to MCMV, and in part, this resistance is due to NK cell expression of Ly49H, an activating receptor that recognizes the virally encoded *m157* protein on the surface of infected cells.

Ly49H deficiency

renders BALB/cByJ mice susceptible to MCMV. To find other loci encoding functionally non-redundant MCMV resistance proteins in C57BL/6J mice, we developed an *in vivo* screen in *N*-ethyl-*N*-Nitrosourea (ENU)-induced germline mutants. So far, 8036 ENU mutant mice, representing 1581 micropedigrees, have been analyzed and 26 mutations that confer susceptibility to MCMV have been identified. One such mutation, *Domino* (*Dmo*), causes a dominant susceptibility to MCMV. *Dmo*/+ mice are viable and fertile. Three days post-infection, they begin to sicken while wild-type mice are free of symptoms, and 50% lethality is observed on the fourth day. Sickness in the susceptible BALB/cByJ strain appears after 4 to 5 days and 50% of these mice die 7 days after MCMV infection. Spleens of *Dmo* mutants have an enhanced viral burden and show severe, widespread necrosis following infection with MCMV. 36 hours after infection, *Dmo* mutant mice show no difference in serum IFN- γ concentration as compared with BALB/cByJ mice, whereas production of IL-12 and IFN- γ are enhanced in comparison with both BALB/cByJ and C57BL/6J controls. To our knowledge, *Dmo* is the first dominant mutation known to enhance MCMV susceptibility in mice. This may suggest that genes relevant to MCMV resistance remain to be identified.