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Elimination of Friend Retrovirus in the Absence of CD8$^+$ T Cells

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Friend retrovirus complex (FV) induces acute erythroid cell hyperplasia and massive splenomegaly followed by the emergence of fatal erythroleukemia upon inoculation into adult mice of susceptible strains (1–3). Because the disease can progress in the presence of host immune responses, FV has served as a useful model to study how retroviruses evade immune control (1, 3, 4). Depending on genotypes at several host loci, some strains of mice can eliminate virus-producing cells and recover from splenomegaly, while others progress rapidly to fatal pathology (1, 3, 5). Results from several research groups largely agree on the role of virus-neutralizing antibodies and CD4$^+$ T cells in immune control of FV infection (6–15). Natural killer cells also contribute to FV elimination and are essential for vaccine-induced protection of highly susceptible mice (8, 16). However, there are conflicting views on the role of CD8$^+$ T cells in FV control.

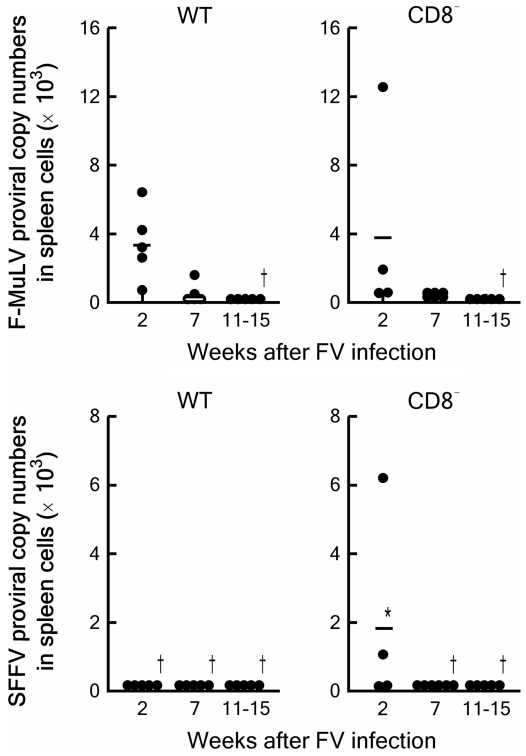

FIG 1 Changes in proviral copy numbers in the spleens of wild-type (WT) or CD8$^+$ T cell-deficient (CD8$^-$) B6 mice after inoculation of 5,000 spleen focus-forming units of FV. Wild-type B6 and CD8$^+$ T cell-deficient B6.129P2-β_2 m^{tm1Unc}/J mice carrying homozygous disruption of the β_2 microglobulin gene are those described in reference 24. Genomic DNA extraction and real-time PCR quantification of F-MuLV and SFFV proviruses were performed as described previously (24). Each closed circle represents an absolute copy number of F-MuLV or SFFV provirus in 100 ng of genomic DNA (equal to about 1.7×10^4 cells) detected from an individual mouse. Bars indicate averages for each genetic group and time point. *, significantly higher copy numbers than those in the WT animals [$P = 0.0159 < \alpha_3(0.05) = 0.0170$ by Mann-Whitney test for non-Gaussian distributions with Bonferroni's *post hoc* test for multiple comparisons]. †, undetectable in all animals examined.

Earlier studies associated major histocompatibility complex class I (MHC-I) alleles with spontaneous recovery from FV-induced splenomegaly, and FV-specific, CD8$^+$ cytotoxic T cells were detected (1, 5). Further, the recovery in *H2*^{b} mice was abrogated when CD8$^+$ T cells were depleted (6). On the other hand, by using FV-encoded epitopes recognized by CD4$^+$ T cells as peptide vaccines, we have shown that highly susceptible (BALB/c × C57BL/6)F_1 mice can still be protected from FV challenge and eliminate virus-producing cells in the absence of CD8$^+$ T cells (9). Interestingly, MHC-I genotypes influenced cytokine production from CD4$^+$ T cells upon FV infection (17, 18), indicating the possible indirect role of CD8$^+$ T cells.

C57BL/6 (B6) mice lack the expression of a short form of hematopoietic cell-specific receptor tyrosine kinase, Stk, and do not develop FV-induced erythroid cell proliferation (19). Some reports have indicated that CD8$^+$ T cells are essential in controlling FV infection in B6 mice, as infectious centers at an early time point after FV infection increased upon depletion of CD8$^+$ T cells (20–22). However, infectious centers were detected in the above-described reports with monoclonal antibody 720 (23) that reacts only with the helper component of FV, Friend murine leukemia virus (F-MuLV), but not with the pathogenic component, the spleen focus-forming virus (SFFV). In our recent work (24), SFFV was eliminated from B6 mice by 2 weeks after infection, and CD8$^+$ T cell-deficient B6 mice remained resistant to FV-induced disease development. Thus, the increase of F-MuLV infectious centers after CD8$^+$ T cell depletion, albeit statistically significant, may not reflect pathologically significant changes in SFFV load.

Here, we examined changes in SFFV copy numbers in CD8$^+$ T cell-deficient B6 mice after FV infection. CD8$^+$ T cell-deficient B6 mice nevertheless eliminated both F-MuLV and SFFV proviruses, though more slowly than the wild-type B6 mice did, as shown in Fig. 1. Thus, while CD8$^+$ T cells do contribute to control FV infection, they are not essential for the elimination of FV in B6 mice.

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