Murine gammaherpesvirus 68 infection protects lupus-prone mice from the development of autoimmunity

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AUTHOR SUMMARY

Systemic lupus erythematosus is a chronic autoimmune disease characterized by proliferation and activation of white blood cells, production of autoantibodies, and end-organ damage (heart, kidney, brain, or skin). It has been suggested that infections can trigger or exacerbate lupus, and EBV is a prime suspect (1). In this study, we investigated the role of infection by a gammaherpesvirus like EBV on lupus development in a mouse model. We found that infection neither triggers nor exacerbates lupus disease in healthy or lupus-prone mice. Instead, it strongly suppresses the development and progression of the disease. Our findings have important implications for understanding the etiology of lupus.

Although 95% of the adult human population is infected with EBV, less than 2% develop the autoimmune diseases that are correlated with it. This suggests that EBV infection does not inevitably lead to autoimmunity. Because EBV does not infect mice, studying the mechanisms behind these specific immune effects has been difficult. Previous studies have circumvented this problem by using gammaherpesvirus 68 (γHV68), which resembles EBV and infects mice (2). A previous study indicated that γHV68 infection of normal, healthy mice promotes autoantibody formation and suggested that it might lead to the development of autoimmunity, potentially mimicking EBV in humans (3).

In this study, we investigated whether γHV68 infection can promote autoimmunity in healthy or lupus-prone mice. More specifically, we explored the effects of infection on autoimmune characteristics associated with antibodies, B and T immune cells (lymphocytes), and kidney damage. We began our study by exploring whether γHV68 infection in healthy mice could sustain the long-term production of autoantibodies and induce other symptoms of autoimmunity. These experiments generated results similar to those previously reported, namely, that mice produce autoantibodies after acute infection. However, we show that this autoantibody production simply reflects the increase in total serum antibodies produced in response to the infection and is likely driven by the general, nonspecific stimulation of all B lymphocytes. In fact, by measuring autoantibody titers in the serum of infected nonautoimmune mice over time, we show that these autoantibodies are produced for only about 8 wk postinfection and are not detectable afterward. This again suggests that the antibodies are a byproduct of the acute viral infection. In accordance, healthy mice infected with γHV68 for almost a year have normal, if not reduced, numbers of lymphocytes, as well as intact kidney function. Therefore, these mice do not exhibit any autoimmune symptoms.

The disparity between the frequency of EBV infection in humans and the occurrence of associated autoimmunity suggests that EBV may promote lupus only in individuals who bear lupus-promoting genes. To investigate this possibility, we infected mice from a strain that carries three distinct genetic loci known to contribute to the development of lupus in mice, and that have some correspondence to the lupus-susceptibility loci in humans (4, 5). We first infected these lupus-prone mice at a young age, before any symptoms of disease had developed, and followed the presence of autoantibodies in their serum for almost 1 y (Fig. P1). Surprisingly, we found that infected, lupus-prone mice displayed much lower autoantibody titers than noninfected controls past the acute infection, leading to the development of autoantibodies.
although this effect was only present in females. Moreover, at 1 y of age, all infected, lupus-prone mice failed to display the expanded lymphocyte populations or high frequency of activated lymphocytes that characterized the autoimmune mice in the noninfected, control group. Finally, although the kidneys of every noninfected, lupus-prone mouse were compromised in morphology and function at 1 y of age, those of infected mice were normal and similar to those of healthy mice (Fig. P1). This point is particularly significant because lupus-prone mice eventually succumb to kidney failure.

In additional experiments, we found that γHV68 infection can also inhibit the exacerbation of autoimmunity in lupus-prone mice that are infected at an older age, after lupus symptoms have already manifested. Furthermore, γHV68 infection also inhibits the production of autoantibodies in another autoimmune-prone mouse strain that manifests a much more aggressive form of the disease. This indicates that the ability of γHV68 infection to inhibit autoimmunity may be a general property of this infection.

Our study demonstrated that γHV68 infection neither triggers nor exacerbates lupus disease in healthy or lupus-prone mice. Instead, γHV68 infection inhibits the development and progression of murine lupus at the humoral (antibody), cellular (lymphocyte), and organ levels.

Gammaherpesviruses coevolved with vertebrate immune systems, developing mechanisms to establish lifelong infections (2). The long-term effects of these viruses on the immune system are mostly unclear; however, our research sheds some light on this topic. Specifically, our finding that γHV68 infection prevents rather than exacerbates autoimmunity suggests that such infection with gammaherpesviruses may be mostly protective. Furthermore, EBV infection may lead to autoimmunity only in association with certain and rare genetic dispositions. Future studies could explain the disparity between the incidence of EBV infection and the frequency of autoimmunity, and could reveal new preventative and therapeutic targets for lupus treatment.