

Exacerbation of Autoantibody-Mediated Hemolytic Anemia by Viral Infection

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Strong enhancement of the pathogenicity of an antierythrocyte monoclonal antibody was observed after infection of mice with lactate dehydrogenase-elevating virus. While injection of the antierythrocyte antibody alone induced only moderate anemia, concomitant infection with this virus, which is harmless in most normal mice, led to a dramatic drop in the hematocrit and to death of infected animals. In vitro and in vivo analyses showed a dramatic increase in the ability of macrophages from infected mice to phagocytose antibody-coated erythrocytes. These results indicate that viruses can trigger the onset of autoimmune disease by enhancing the pathogenicity of autoantibodies. They may explain how unrelated viruses could be implicated in the etiology of autoantibody-mediated autoimmune diseases.

A causal connection between viral infection and the development of clinical pathology has long been suspected for a number of autoimmune diseases mediated by autoantibodies (reviewed in reference 36). Interestingly, in most cases, several different viruses have been proposed as etiologic agents of the same disease. Experimental data have suggested that viruses trigger an autoimmune humoral response by distinct mechanisms, including polyclonal B-lymphocyte activation, antigenic mimicry, modification of self-antigen, production of anti-idiotypic antibodies, or enhancement of major histocompatibility complex molecule expression on potential antigen-presenting cells (4, 9, 11, 15, 20, 25, 31, 37). However, although it has been conclusively shown in several models that autoantibody secretion was triggered by infection, the actual pathogenicity of these antibodies has not always been demonstrated. Similarly, other stimuli, like immunization of mice with rat red blood cells, may lead to autoantibody production without development of the corresponding disease, in this case, hemolytic anemia (8, 24, 34). Therefore, it may be that mere autoantibody secretion is not sufficient to trigger an autoimmune disease and that the immune environment of the host plays an important role in the pathogenicity of such autoantibodies.

Viruses have also been shown to variably affect macrophage functions, including cytokine production and the ability to present antigens (6, 16). Since it is known that some autoantibody-mediated diseases involve phagocytosis by macrophages, we postulated that modulation of this cellular function may explain the induction of such clinical diseases observed in the course of viral infections. To test this hypothesis, we used an experimental model of anemia induced by administration of antierythrocyte monoclonal antibodies (29). Our results indi-

cate that a viral infection with lactate dehydrogenase-elevating virus (LDV) may trigger a dramatic hemolytic disease by enhancing the pathogenicity of autoantibodies. If confirmed with other models, this observation may indicate how different viruses can trigger similar clinical autoimmune diseases and open the way to novel therapeutic approaches.

MATERIALS AND METHODS

Mice. Female BALB/c mice were bred at the Ludwig Institute for Cancer Research by G. Warnier and used when 6 to 8 weeks old.

Antibody. Immunoglobulin G1 (IgG1) 31-9D and IgG2a 34-3C anti-mouse erythrocyte monoclonal antibodies have been derived from NZB mice (29) and were purified from cell supernatants by two successive precipitations with ammonium sulfate.

Viruses. The Riley strain of LDV, from the American Type Culture Collection, was grown in NMRI mice and titrated by injection of serial dilutions into groups of mice (7). Approximately 2×10^7 50% infective doses were injected intraperitoneally in 0.5 ml of saline into recipient animals.

Hematocrit. Mice were bled by retro-orbital puncture after appropriate anesthesia. Hematocrit was measured after centrifugation of heparinized blood in a Hettich-Haematokrit centrifuge (Hettich, Tuttingen, Germany).

In vitro erythrophagocytosis. The ability of macrophages to phagocytose sensitized red cells was measured as described previously (28). Briefly, normal mouse red cells were sensitized by incubation of 500 μ l of packed erythrocytes with 50 μ g of monoclonal antibody in 10 ml of phosphate-buffered saline with 2% bovine serum albumin for 2 h at room temperature. Macrophages were derived from total peritoneal cells by adhesion on a tissue culture petri dish for 3 h. They were then incubated for 3 h with 20 μ l of washed sensitized red cells in 2 ml of supplemented Dulbecco's medium containing 10% fetal calf serum, washed with phosphate-buffered saline, and stained with *o*-toluidine. Phagocytosis was expressed as the percentage of cells having internalized at least five erythrocytes.

Analysis of liver sections. Liver sections fixed in Bouin solution and embedded in paraffin were analyzed after staining with hematoxylin.

RESULTS

Effect of LDV infection on in vivo autoantibody-induced anemia. BALB/c mice were infected with LDV after inoculation of antierythrocyte monoclonal antibody. Two different antierythrocyte antibodies were used, both derived from NZB mice (29). Injection of both antibodies leads to in vivo anemia in normal uninfected mice, although by distinct pathways. Whereas IgG2a 34-3C triggers erythrophagocytosis (28, 29), erythrocyte destruction induced by IgG1 31-9D is mediated by cell sequestration in the spleen and liver (29). As shown in Fig. 1 for a typical experiment of six performed, the 34-3C mono-

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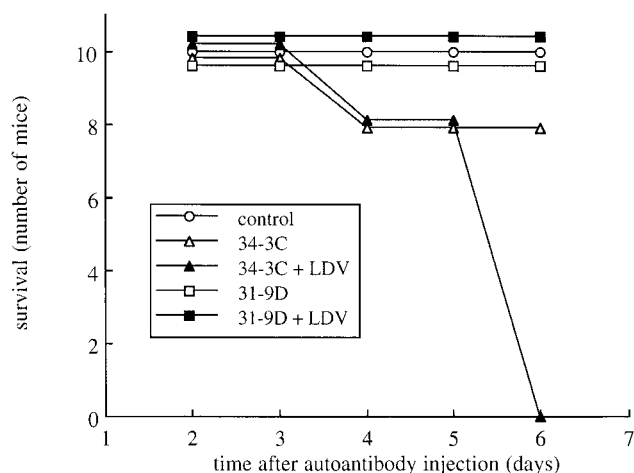


FIG. 1. Effect of LDV infection on survival after antierythrocyte autoantibody inoculation. Survival was determined every day in groups of 10 BALB/c mice that received 4 mg of antierythrocyte autoantibody 34-3C or 31-9D, followed 1 day later by LDV infection. Control animals were untreated or received autoantibody 34-3C or 31-9D only.

clonal autoantibody alone induced only moderate lethality (2 out of 10 mice in this experiment died, while in other experiments, all of the mice in this experimental group survived). No further modifications of survival were observed at later times (not shown). In sharp contrast, all animals died when they were infected with LDV after receiving the 34-3C antibody. This effect of LDV infection on autoantibody pathogenicity was not observed with the 31-9D antibody, since all mice, infected or uninfected, survived the administration of this antierythrocyte monoclonal antibody. This indicated also that LDV by itself did not induce the death of infected mice.

To determine whether this increase of lethality in LDV-infected mice was related to an enhancement of antierythrocyte autoantibody pathogenicity, we measured hematocrit at different times after 34-3C antibody administration (Fig. 2

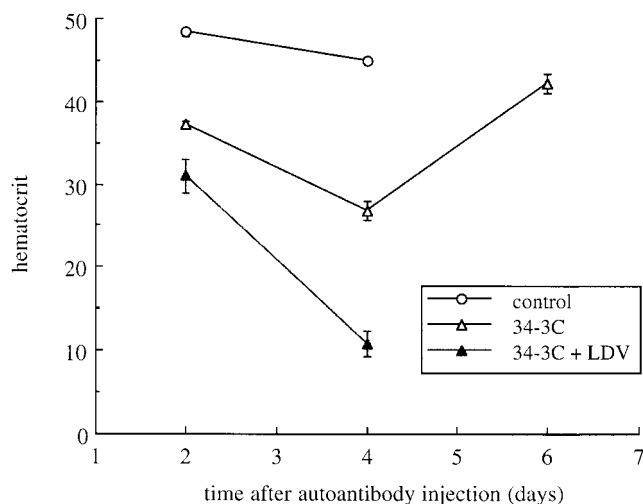


FIG. 2. Enhancement of 34-3C antierythrocyte autoantibody-induced anemia by LDV infection. Hematocrit was measured at different times after injection of 2 mg of antierythrocyte autoantibody in groups of four or five uninfected BALB/c mice or in animals also infected with LDV. Controls were uninfected animals that received no antibody. Results are expressed as mean $\pm$ standard errors.

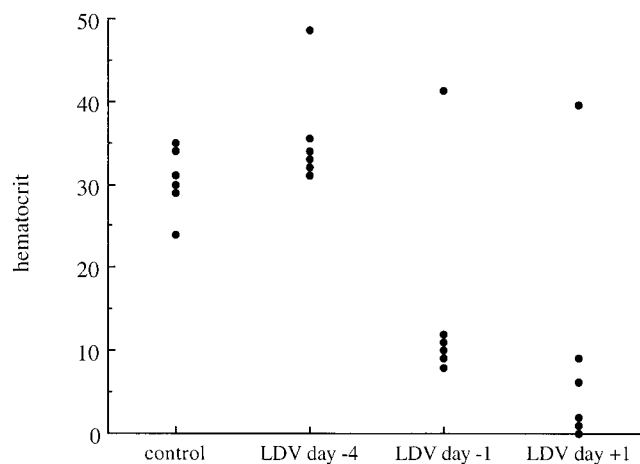


FIG. 3. Kinetics of LDV-induced enhancement of anemia. Hematocrit was determined 4 days after injection of 2 mg of the 34-3C antibody into BALB/c mice. LDV infection was performed at different times before or after 34-3C inoculation, as shown. Control mice were uninfected. Mice with a hematocrit of 0 were dead.

shows typical results of five experiments performed). In uninfected mice, 34-3C triggered a moderate anemia that reached a maximum 4 days after autoantibody administration and resolved 2 days later. In contrast, infected mice that received the 34-3C antibody developed a dramatic anemia 4 days later, with hematocrits dropping to about 20 to 25% of normal values (Fig. 2). Although other causes may be considered as well, this almost complete destruction of red blood cells is likely to have contributed to the death at day 6 after autoantibody injection of all of the animals that simultaneously received the 34-3C antierythrocyte autoantibody and the virus. Whereas LDV-induced lethality required the administration of at least 1 mg of antierythrocyte antibody, enhancement of autoantibody pathogenicity by viral infection was observed with as little as 100 μ g of 34-3C. Indeed, while in a typical experiment, the latter dose of antibody triggered only a minimal hematocrit drop, from 49.8 ± 0.4 to 43.1 ± 1.3 , in uninfected animals in 4 days, it induced a much more important decrease in LDV-infected mice, from 49.9 ± 0.5 to 34.3 ± 2.3 .

This effect of LDV infection on autoantibody pathogenicity was transient, as shown in Fig. 3. Five out of six animals that received LDV 1 day before or 1 day after antierythrocyte autoantibody administration either had a hematocrit below 10.5 at day 4 after this antibody injection or were dead. In contrast, animals that had been infected 4 days before 34-3C inoculation developed a moderate anemia, similar to that of uninfected mice.

The pattern of anemia triggered by the administration of the 31-9D autoantibody in uninfected mice was not different from that following 34-3C inoculation, although variations were observed from one experiment to another. However, in contrast to what had been observed with the 34-3C antibody, the 31-9D-mediated anemia was only slightly modified by LDV infection (data not shown).

Enhancement of *in vitro* and *in vivo* erythrophagocytosis by macrophages after LDV infection. Because it has been previously demonstrated that 34-3C-mediated anemia, but not 31-9D-mediated anemia, involves phagocytosis of autoantibody-sensitized red cells by macrophages (29), it was postulated that the effect of LDV on the disease triggered by the 34-3C antibody could be related to an increase in the ability of macro-

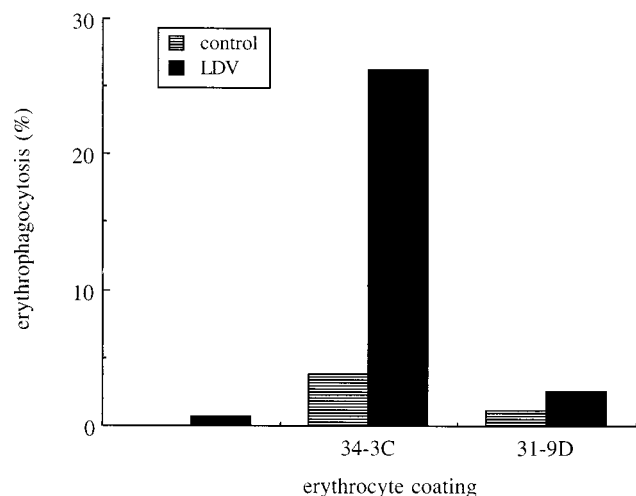


FIG. 4. In vitro erythrophagocytosis by macrophages from LDV-infected mice. Macrophages from groups of four control BALB/c mice or from four animals infected for 4 days with LDV were pooled, and their ability to phagocytose either normal red cells or erythrocytes sensitized with the 34-3C or 31-9D monoclonal antibody was measured in vitro as described in Materials and Methods.

phages from infected animals to ingest autoantibody-coated cells. To test this hypothesis, peritoneal macrophages were derived from normal and infected BALB/c mice and their ability to ingest normal red cells or erythrocytes sensitized with

either the 34-3C or the 31-9D autoantibody was measured in vitro. As shown in Fig. 4 (results of a typical experiment of six performed), no significant erythrophagocytosis was observed with normal red cells, neither with macrophages from control mice nor with cells from LDV-infected animals. In contrast, LDV infection strongly increased the ability of macrophages to ingest 34-3C-coated red cells, which were already significantly phagocytosed by macrophages from normal animals. Internalization of 31-9D-sensitized erythrocytes by macrophages from uninfected mice was marginal and only moderately increased after LDV infection.

That LDV could enhance erythrophagocytosis was confirmed by ex vivo analysis of liver sections. As shown in Fig. 5 for typical mice, 4 days after concomitant administration of 34-3C autoantibody and infection with LDV, numerous macrophages that had ingested large numbers of erythrocytes could be detected. In contrast, only a few phagocytosed red cells were observed in liver sections from mice that received the autoantibody alone and none were seen in control infected or uninfected animals.

DISCUSSION

Using an experimental model of autoimmune hemolytic anemia induced by the administration of monoclonal autoantibodies reacting with erythrocyte antigens, we have shown in this work that a virus could enhance the pathogenicity of these autoantibodies, leading to the development of overt disease

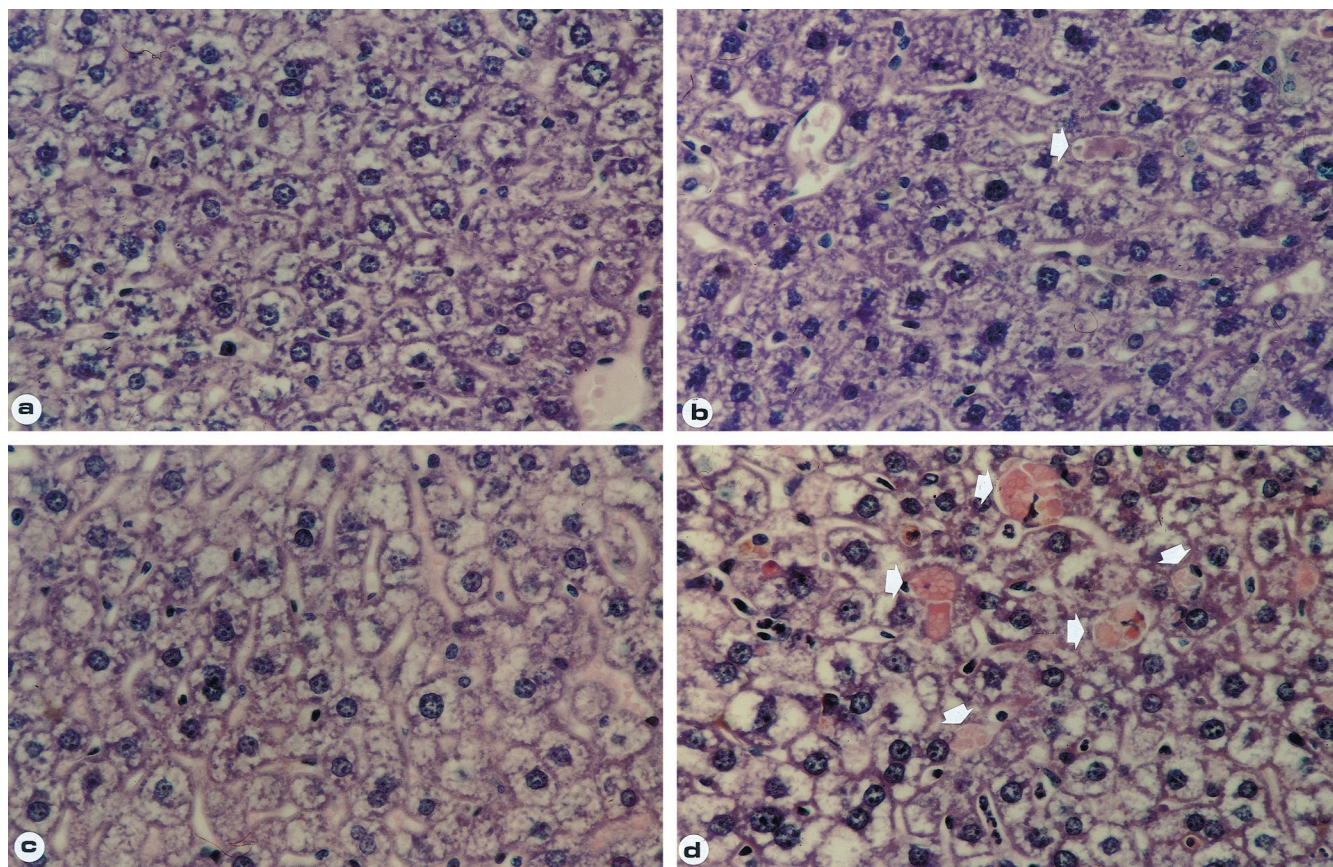


FIG. 5. In vivo erythrophagocytosis in LDV-infected mice. Liver sections were prepared from control mice (a) and from mice 4 days after administration of 2 mg of the 34-3C antibody alone (b), LDV alone (c), or the 34-3C antibody and LDV (d). Cells that have phagocytosed large numbers of erythrocytes are shown by white arrows. The experiment was performed twice with three mice per group. Original magnification, $\times 460$.

and even death of the infected animals. In contrast to most mechanisms that have been proposed so far to explain how a virus can trigger an autoimmune disease, in this case, the virus does not induce the autoimmune response itself—e.g., autoantibody production—but modifies the immune environment of the infected host, which results in increased pathogenicity of pre-existing autoantibodies. Therefore, disease development requires at least two distinct steps: first, initiation of the anti-self reaction, mimicked here by passive autoantibody administration, and then enhancement of the pathogenicity of this autoimmune response. This could correspond to the actual progression of some human autoimmune diseases which may often be enhanced by viral infections. Such a mechanism may also explain why different viruses can be involved in the development of a particular disease, since, contrary to the production of autoantibodies, the modulation of the host environment is not antigen specific but can most probably be explained by responses elicited similarly by different infectious agents, like cytokine secretion. Indeed, we observed a similar enhancement of antierythrocyte autoantibody pathogenicity after infection with mouse hepatitis virus (not shown), which supports this hypothesis.

The mechanism by which LDV increases antierythrocyte autoantibody pathogenicity appears to be, at least mainly, enhancement of macrophage phagocytic function. Indeed, LDV could increase the anemia induced by the 34-3C antibody, which has been shown to trigger erythrophagocytosis (29), but only slightly modified the disease initiated by the 31-9D antibody, which involves a different pathogenic pathway. In addition, *in vitro* analysis of macrophage phagocytic function indicated that the ability to ingest 34-3C-coated, but not uncoated or 31-9D-coated, red cells was strongly enhanced in mice infected with the virus (Fig. 4). Finally, *ex vivo* analysis of liver sections showed the phagocytosis of numerous red cells in mice that had received both the 34-3C antibody and the virus but not in control animals (Fig. 5). Although many viral infections result in a decrease in macrophage functions, including phagocytosis, some viruses, such as herpes simplex virus (2), Coxsackie virus (22), or Newcastle disease virus (19), have been shown to enhance the ability of these cells to incorporate various targets. Whereas contradictory results have been reported after LDV infection (17, 18, 32), another nidovirus, mouse hepatitis virus, can also increase macrophage-mediated phagocytosis (33).

Enhancement of the phagocytic activity of a particular macrophage most probably does not require infection of this cell, although this remains to be demonstrated. Our results (Fig. 4) suggest that after LDV infection, the frequency of macrophages with increased phagocytic activity (more than 25%) is higher than the frequency of macrophages from adult mice reported to be infected by this virus (5 to 15%; 26). In addition, whereas the phagocytic activity is fully increased 4 days after LDV inoculation (Fig. 4), it has been previously shown that as soon as 3 days postinfection, most infected cells have been killed by the virus (1). Quite possibly, production of cytokines, such as gamma interferon or granulocyte-macrophage colony-stimulating factor, in the course of infection can activate macrophages enough to enhance their ability to ingest antibody-coated targets. Indeed, the latter cytokine has been reported to dramatically enhance *in vivo* 34-3C antierythrocyte pathogenicity (3). On the other hand, gamma interferon which is secreted after infection with many viruses, including both LDV and mouse hepatitis virus (27, 30, and unpublished results), has been shown to promote phagocytosis by macrophages (10). Interestingly, this effect of gamma interferon has been proposed to explain enhanced phagocytic activity after Newcastle

disease virus or vesicular stomatitis virus infection (13, 14). The possibility that the virus-mediated increase in autoantibody pathogenicity reported here is linked to an enhancement of macrophage expression of Fc γ receptors, molecules that are involved in 34-3C-induced anemia (5, 21) and are upregulated by interferons and granulocyte-macrophage colony-stimulating factor (12, 23, 35), is currently under investigation.

This observation that the pathogenicity of autoantibodies depends on their microenvironment, including the microbiological status of the host, may open the way to new therapeutic approaches to autoimmune diseases. For example, targeting of macrophage activation in addition to the autoimmune response itself may prove valuable for patients with autoantibody-mediated diseases. A more complete elucidation of the mechanisms leading to macrophage activation may therefore provide interesting information on the pathogenesis of autoimmune diseases and on possible alternative ways to treat them.

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