Effective Clearance of a Persistent Viral Infection Requires Cooperation between Virus-Specific Lyt2\(^{+}\) T Cells and Nonspecific Bone Marrow-Derived Cells

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The lifelong chronic lymphocytic choriomeningitis virus (LCMV) infection established in neonatally or congenitally infected mice can be eliminated by adoptive transfer of lymphoid cells from LCMV-immune mice. In this study, we have identified the effector cells mediating the clearance of persistent and disseminated LCMV infection. Using mice that are recombinant in the H-2 region and by selective depletion of lymphocyte subpopulations, we show that viral clearance was mediated by LCMV-specific Lyt2\(^{+}\) L3T4\(^{-}\) T cells that are restricted to the class I genes of the major histocompatibility complex. In addition, our results show a requirement for host-derived bone marrow cells for the effective elimination of virus from the liver. These studies emphasize the importance of virus-specific T cells and an intact bone marrow function in viral clearance.

The effector mechanisms responsible for eliminating a persistent and disseminated viral infection are not fully understood. To study the basic principles of immune clearance, we have selected the mouse model of persistent infection with lymphocytic choriomeningitis virus (LCMV). In the accompanying paper (1), we described the kinetics of viral clearance from various tissues after adoptive immune therapy of LCMV carrier mice and have shown that distinct patterns of viral clearance and histopathology are observed in different organs. In the present study, we identified the effector cells mediating the clearance of persistent LCMV infection.

MATERIALS AND METHODS

Viruses. The LCMV strains used in this study were described in the accompanying paper (1). The An 3739 strain of Pichinde virus was used. All virus strains were triple plaque purified on Vero cells, and stocks were then grown in BHK-21 cells. Virus stocks at the passage 1 or passage 2 level were used in all experiments.

Mice. The BALB/c ByJ and C57BL/6 LCMV carrier and immune mice have been described previously (1). The B.10.D2 (K\(^{b}\)/D\(^{b}\)) and B.10.D2 (R107) (K\(^{b}\)/D\(^{b}\)) mice were purchased from the Jackson Laboratory, Bar Harbor, Maine. The B.10.D2 (R107) carrier mice were 1-day-old mice injected intracerebrally with 10\(^{4}\) PFU of LCMV (Arm-13). The B.10.D2 and B.10.D2 (R107) immune mice were 6- to 8-week-old mice injected intraperitoneally (i.p.) with 10\(^{4}\) PFU of LCMV (Arm-7).

Immune therapy of persistently infected mice, virus titrations, immunofluorescence, and histology. The methods for immune therapy, virus titration, immunofluorescence assay, and histology were as described in the accompanying paper (1).

Antibodies. The following monoclonal antibodies (MAbs) were used to deplete the various lymphocyte subpopulations. AD4(15) and CG16 were used to deplete Lyt2.2\(^{+}\) and Lyt1.2\(^{+}\) cells, respectively. Both MAbs were purchased in the form of ascites fluid from Cedarlane Laboratories Limited, Hornby, Ontario, Canada, and used at concentrations specified by the supplier. The MAb designated HO-13-4 (12) was used to kill Thy1.2\(^{+}\) cells, the antibody J11d (5) was used to deplete B cells, and GK1.5 (8) and RL172.4 (7) were used to remove L3T4\(^{-}\) cells. Hybridomas producing these MAbs were grown in our laboratories at the University of California at Los Angeles and Lilly Research. Supernatants at a 1:2 dilution were used for the antibody-plus-complement (C\(^{+}\))-mediated depletions, except for GK1.5, which was used as purified antibody.

Depletion of lymphocyte subpopulations. The following protocol was used for the antibody-plus-complement-mediated cell depletions. Spleen and/or lymph node (LN) cells (2 \times 10\(^{6}\) to 3 \times 10\(^{6}\)) at a concentration of 10\(^{6}\)/ml were treated with antibody at an appropriate concentration for 1 h at 4°C. The cells were then washed and suspended at a concentration of 5 \times 10\(^{6}\)/ml in a 1:8 dilution of rabbit complement (low tox M) purchased from Cedarlane. After 1 h of incubation at 37°C, the cells were centrifuged and suspended in medium. The dead cells formed a clump and were allowed to settle to the bottom of the tube, and the suspended cells were transferred to a new tube. To ensure effective depletion of the appropriate lymphocyte subset, the entire cytotoxicity procedure was repeated. After the two cycles of treatment with antibody and complement, a portion of the cell sample was stained with trypan blue and counted in a hemacytometer to determine the cytotoxic index (CI). CI was calculated as follows: CI = 100 \times \% cytotoxicity of MAb + C\(^{+}\) depletion – \% cytotoxicity with C\(^{+}\) alone)/(100 – \% cytotoxicity with C\(^{+}\) alone). The various lymphocyte subsets were depleted as follows. (i) Lyt2.2\(^{+}\) cells were removed by two cycles of treatment with the MAb AD4(15) plus complement. This treatment killed between 8.5 and 11.0% of the spleen cells. (ii) A protocol using both in vivo and in vitro treatments was used to deplete L3T4\(^{-}\) cells. LCMV-immune mice were injected

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i.p. with a total of 1.5 mg of purified GK1.5 antibody. This was given in three doses of 500 μg each on days −7, −4, and −2. The immune mice treated in vivo with GK1.5 antibody were sacrificed on day 0, and the spleens and LN were removed. Single cell suspensions were prepared and then treated in vitro with RL172.4 antibody plus C' as described above. After this combined in vivo and in vitro treatment, the immune lymphocytes contained ≤5% L3T4+ cells. (iii) Lyt1,2+ cells were depleted by two cycles of treatment with CG16 plus C'. The CI after this treatment was 24.6. (iv) B cells were removed by a protocol using both panning and antibody-plus-C'-mediated lysis. The spleen and LN cells from immune mice were first treated twice with J11d plus C' to kill the B cells. The dead cells were removed, and the viable cells were then subjected to panning on anti-kappa antibody-coated plates to deplete any remaining B cells. The nonadherent fraction, consisting predominantly of T cells, was collected by washing several times with medium. This cell population was used for immune therapy of carrier mice and contained <5% B cells as determined by immunofluorescence with rhodamine-conjugated goat anti-mouse immunoglobulin G (Cooper Biomedical, Inc., West Chester, Pa.).

**Antibody titrations.** LCMV-specific antibody in the serum was measured by a solid-phase enzyme-linked immunosorbent assay with purified virus as the antigen. The details of this assay have been described by Ahmed et al. (2).

## RESULTS

**Virus specificity of effector cells.** BALB/c ByJ LCMV carrier mice were injected with 5 × 10^7 spleen and LN cells from either normal BALB/c ByJ mice or mice previously immunized with LCMV or Pichinde virus (another member of the Arenavirus genus). Only carrier mice receiving LCMV-specific immune cells showed clearance of virus from the serum. Neither unprimed spleen cells nor Pichinde virus immune cells had any effect on the level of LCMV in carrier mice (Table 1). These results show that clearance is mediated by virus-specific cells.

**Requirement for Lyt2+ T cells for clearance of virus from persistently infected mice.** To identify the type of cell(s) responsible for viral clearance, specific subpopulations of lymphocytes were depleted from the immune spleen and LN cells prior to transfer into carrier mice. MAb's directed against the L3T4 cell surface molecule were used to deplete T cells of the helper subset (7, 8). T cells of the cytotoxic subset were eliminated with anti-Lyt2 MAb, and B cells were removed with MAb against the J11D surface antigen found on mature B cells (5). Treatment with these reagents removed 90 to 95% of the appropriate subset of lymphocytes as determined by immunofluorescence staining. In addition, functional tests confirmed the specificity of the depletion protocols. Treatment with anti-L3T4 decreased the ability of T cells to provide help for LCMV-specific antibody production. Anti-J11D also diminished the amount of viral antibody produced. Removal of Lyt2+ T cells eliminated LCMV-specific cytotoxic T lymphocyte (CTL) activity. In one such experiment, spleen cells from mice infected with LCMV 8 days previously showed 78% specific killing of H-2-matched LCMV-infected targets in a 6-h ⁵¹Cr-release assay. Treatment of this same population of lymphocytes with anti-Lyt2 MAb plus C' decreased CTL activity (11% killing).

Immune cells treated with Lyt2+ C' or Lyt1 plus C' were unable to clear virus from persistently infected mice (Fig. 1 and Table 2). The Lyt1 antigen is present on the cell surface of most T cells, whereas the Lyt2 molecule is a marker for CTL (6, 11). Although Lyt2+ T cells constituted only 8.5 to 11.0% of the total spleen cells, removal of this subpopulation abrogated the ability of immune spleen cells to clear virus from chronically infected mice. In a few instances, carrier mice receiving Lyt2-depleted immune spleen cells showed virus reduction in the spleen (two of seven mice) and LN (one of seven mice) (Table 2). Since it is unlikely that the MAb treatment killed all the Lyt2+ T cells, the partial reduction seen in these two mice is probably due to the few remaining Lyt2+ T cells. It should be pointed out that clearance was not observed from any of the other organs tested, and there was minimal or no reduction in the level of viremia (Fig. 1 and Table 2). In contrast to the results seen upon removal of Lyt2+ T cells, depletion of L3T4+ cells or B cells had no effect on the ability of immune cells to eliminate virus from carrier mice. Taken together, these results (Fig. 1 and Table 2) show that LCMV-specific Lyt2+ L3T4+ T cells were essential for effective immune therapy of persistently infected mice.

**MHC restriction of effector cells.** Adoptive transfer experiments were done between unmatched (allogeneic) mice and between mice recombinant in the H-2 region to study the major histocompatibility complex (MHC) restriction of the effector cells mediating clearance of persistent LCMV infection. Immune lymphocytes from B.10.D2 (KkIhDd) mice had no effect on virus levels in C57BL/6 (KkIpDd) carrier mice but were effective in reducing virus titers in B.10.D2 (R107) (KkIpDd) carrier mice. The reduction of virus levels in the spleens of B.10.D2 (R107) carrier mice was the same whether the immune cells were derived from B.10.D2 mice (matched only at the D end) or from completely matched B.10.D2 (R107) mice (Fig. 2). These results show that homology at the D end of the H-2 locus is sufficient for viral clearance and that the effector cells mediating clearance are restricted to the MHC class I genes.

**LCMV-specific antibody in carrier mice receiving immune therapy.** We checked the level of virus-specific antibody in the sera of carrier mice receiving (i) unfractionated immune cells, (ii) Lyt2-depleted immune cells, or (iii) B-cell-depleted immune cells. At various times after cell transfer, the amount of LCMV-specific antibody was quantitated by an enzyme-linked immunosorbent assay and the virus titer in the serum was determined by a plaque assay on Vero cells. The results are shown in Fig. 3. Carrier mice receiving untreated immune cells showed a >10,000-fold increase in the level of virus-specific antibody and, as documented...
above (Fig. 1 and Table 2), a decrease in the level of viremia. Mice receiving Lyt2-depleted immune cells showed minimal or no clearance of virus but contained nearly as much virus-specific antibody (10,000-fold increase) as did mice receiving untreated immune cells. In contrast, carrier mice adoptively transferred with B-cell-depleted immune cells eliminated the virus but contained considerably lower (1,000-fold) antibody levels than did mice receiving Lyt2-depleted immune cells. Taken together, these results show that there was no correlation between the amount of LCMV-specific antibody produced and viral clearance; virus was not eliminated even when high levels of antibody were present (Lyt2-depleted immune cells), whereas viral clearance occurred when there was considerably less antiviral antibody (B-cell-depleted immune cells).

**Requirement for host bone marrow-derived cells for successful immune therapy.** In the results presented so far, we have identified the effector cell(s) in the spleens of immune mice that are responsible for eliminating virus from persistently infected mice after adoptive immune therapy. As summarized in Table 3, this clearance is mediated by donor-derived virus-specific MHC class I-restricted Lyt2+ T cells. We next investigated whether any host-derived functions are also required for viral clearance. This was tested by irradiating carrier mice prior to immune cell transfer. The elimination of virus was monitored in C57BL/6 LCMV carrier

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**FIG. 1.** Surface phenotypes of effector cells mediating viral clearance. C57BL/6 mice, 4 to 8 weeks old, persistently infected with LCMV received $2 \times 10^7$ lymphocytes from syngeneic LCMV-immune mice. Prior to transfer, the immune spleen and LN cells were treated to remove specific subpopulations of lymphocytes. At 30 days after cell transfer, the serum was tested for the level of infectious LCMV. Each point represents the titer of an individual mouse, and the horizontal bar is the average titer of the indicated group. All mice contained between $10^4$ and $10^5$ PFU/ml of LCMV in serum at the start of the experiment as determined by titration of samples collected before cell transfer.
I-COMPLEMENT

The procedures were described. For example, mice were sacrificed, and the various organs were harvested, homogenized, and titrated on Vero cell monolayers. ND, Not done.

**TABLE 2. Lyt2+ T cells mediate clearance of infectious virus from tissues of persistently infected mice**

<table>
<thead>
<tr>
<th>Group†</th>
<th>Treatment of immune cells before transfer‡</th>
<th>LCMV titer (log10 PFU/g or ml) at 54 days post-cell transfer*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Serum</td>
<td>Liver</td>
</tr>
<tr>
<td>I → C</td>
<td>Complement only</td>
<td>&lt;1.6</td>
</tr>
<tr>
<td></td>
<td>C57BL/6</td>
<td>B10.D2</td>
</tr>
<tr>
<td>Ø → C</td>
<td>None</td>
<td>4.9</td>
</tr>
<tr>
<td></td>
<td>C57BL/6</td>
<td>B10.D2</td>
</tr>
</tbody>
</table>

mice that were irradiated (650 to 700 R) 3 days before the cell transfer. These irradiated carrier mice receiving immune therapy showed only minimal viral clearance from the liver. In contrast, unirradiated carrier mice receiving the same pool of immune cells showed effective clearance of both infectious virus and viral antigen from the liver within 2 weeks. Bone marrow reconstitution of the irradiated carrier mice restored the ability to clear virus from the liver. The bone marrow cells were obtained from syngeneic carrier mice and were given 1 day after the irradiation and 2 days before the transfer of immune cells (day -3, irradiation; day -2, bone marrow cells; day 0, immune cells). The results of three such experiments are summarized in Fig. 4, and an example of immunofluorescence staining is shown in Fig. 5. These results show that effective clearance of virus from the liver of persistently infected mice required not only donor-derived virus-specific Lyt2+ T cells but also host-derived bone marrow cells.

**DISCUSSION**

We have studied the mechanism(s) by which a persistent viral infection is eliminated. In the accompanying paper (1), we showed that distinct patterns of viral clearance and histopathology were observed in different organs after adoptive immune therapy of LCMV carrier mice. In the present study, we characterized the effector cells mediating the

**FIG. 2.** MHC restriction of effector cells. Spleen and LN cells (5 x 10^7) from B10.D2 or B10.D2 (RI07) immune mice were injected i.p. into C57BL/6 or B10.D2 (RI07) carrier mice. The amount of infectious virus in the spleen was determined 8 days after cell transfer. The data are presented as percent residual infectious virus in carrier mice receiving immune therapy by using the amount of virus in the spleens of untreated carrier mice (average of six mice) as 100%. In these experiments, all LCMV carrier mice were irradiated (500 R) 1 day prior to adoptive transfer to prevent rejection of the transferred cells.
clearance of this disseminated and lifelong chronic infection. Our results (Table 3) show that clearance was mediated by virus-specific MHC class I-restricted Lyt2+ T cells. In addition, we found that the effective elimination of virus from persistently infected mice required cooperation between donor-derived virus-specific Lyt2+ T cells and non-specific bone marrow-derived cells from the carrier host.

In contrast to the results seen upon depletion of Lyt2+ cells, the removal of L3T4+ T cells had no effect on the ability of immune cells to clear virus from carrier mice. A protocol using both in vivo and in vitro treatments was used to deplete L3T4+ cells. This is a fairly rigorous procedure, and after the combined treatments, the immune lymphocytes contained ≤5% L3T4+ cells. These results suggest that T helper cells from the immune donors are not essential for effective immune therapy. However, our conclusions have to be somewhat tempered, since the transfer of some L3T4+ cells into carrier mice cannot be ruled out. Nevertheless, it is clear that the removal of the majority of L3T4+ cells had minimal or no effect on the ability of Lyt2+ T cells to eliminate virus from persistently infected mice. Similar results have been reported by Oldstone et al. (15). We are currently studying the role of T helper cells in the generation of primary and secondary LCMV-specific immune responses.

As first shown by Volkert and associates (17) and subsequently confirmed by others (9, 10), extremely high levels of virus-specific antibody in carrier mice were found after the transfer of immune cells. However, there was no correlation between the amount of antibody produced and viral clearance (Fig. 3). There was no elimination of virus after the transfer of Lyt2-depleted immune cells despite high levels of virus-specific antibody. On the other hand, virus was cleared after the transfer of B-cell-depleted immune cells when there was 1,000-fold less antiviral antibody. Taken together, these results suggest that antiviral antibody plays a minimal role in the clearance of persistent LCMV infection. Although high levels of anti-LCMV antibody are made after immune ther-

FIG. 3. LCMV-specific antibody levels in mice receiving immune therapy. C57BL/6 LCMV carrier mice were injected i.p. with the indicated cell population (2 × 10^6 cells). At various times after cell transfer, the level of LCMV-specific antibody and the virus titer in the serum were determined. Each line represents the titer of virus-specific antibody in an individual mouse, and the numbers on the graph show the amount of infectious virus in serum (log_{10} PFU/ml). ELISA, Enzyme-linked immunosorbent assay.
apy, LCMV-neutralizing antibody titers remain low or undetectable (17; B. D. Jamieson and R. Ahmed, unpublished data).

MHC restriction of the effector cells responsible for eliminating virus from carrier mice was determined by using mice recombinant in the H-2 region. We found that the T cells mediating clearance were restricted to the D end of the MHC class I genes and homology at the I region was not necessary for effective immune therapy. These studies show the importance of MHC class I genes in the clearance of persistent LCMV infection. Other studies have shown a role for MHC class I genes in the lethal LCM disease and in controlling acute LCMV infection (20, 21).

We have shown that virus-specific Lyt2+ MHC class I-restricted T cells were essential for effective immune therapy of persistently infected mice. What are the functions mediated by these T cells? As can be predicted from their surface phenotype and MHC class I restriction, these cells are capable of killing virus-infected cells, i.e., they are virus-specific CTL (18). However, in the LCMV system, Lyt2+ MHC class I-restricted T cells also mediate delayed-type hypersensitivity (DTH) responses (20; R. Ahmed and L. D. Butler, unpublished data). This is in contrast to most other systems in which DTH reactions are mediated by L3T4+ T cells that are restricted to the MHC class II genes (8). It is not known whether the same LCMV-specific T cell carries out both functions or whether there are two different populations of Lyt2+ T cells, one mediating cytotoxicity and the other mediating DTH responses. T-cell clones that can kill virus-infected cells and also release macrophage-activating factor, a lymphokine involved in DTH reactions, have been described in other viral systems (13). In a recent study, Baenziger et al. (4) described an LCMV-specific CTL line that could also mediate a DTH reaction but only if injected directly into the footpad. These studies with T-cell clones have shown that virus-specific T cells can carry out multiple functions, and it is possible that both LCMV-specific CTL and DTH responses are mediated by the same T cells.

What are the relative contributions of the DTH response and direct killing of virus-infected cells in the elimination of chronic LCMV infection? The studies of Thomsen et al. (16) have suggested a role for the DTH response in controlling acute LCMV infection. We have shown that host bone marrow-derived mononuclear cells as well as virus-specific

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**TABLE 3. Virus-specific MHC class I-restricted Lyt2+ L3T4+ T cells mediate LCMV clearance of persistent LCMV infection**

<table>
<thead>
<tr>
<th>Characteristic measured</th>
<th>Immune donor</th>
<th>LCMV carrier recipient</th>
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<tr>
<td></td>
<td>Virus</td>
<td>H-2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>K</td>
</tr>
<tr>
<td>Virus specificitya</td>
<td>Mock</td>
<td>d</td>
</tr>
<tr>
<td></td>
<td>LCMV</td>
<td>d</td>
</tr>
<tr>
<td></td>
<td>Pichinde</td>
<td>d</td>
</tr>
<tr>
<td>MHC restrictionb</td>
<td>LCMV</td>
<td>d</td>
</tr>
<tr>
<td></td>
<td>LCMV</td>
<td>d</td>
</tr>
<tr>
<td></td>
<td>LCMV</td>
<td>b</td>
</tr>
<tr>
<td>Surface phenotypec</td>
<td>LCMV</td>
<td>b</td>
</tr>
<tr>
<td></td>
<td>LCMV</td>
<td>b</td>
</tr>
<tr>
<td></td>
<td>LCMV</td>
<td>b</td>
</tr>
<tr>
<td></td>
<td>LCMV</td>
<td>b</td>
</tr>
</tbody>
</table>

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*See data in Table 1.
*See data in Fig. 2.
*See data Fig. 1 and Table 2.
FIG. 5. Cooperation between LCMV-specific T cells and nonspecific bone marrow cells for viral clearance. Immunofluorescence staining of liver sections for LCMV antigen is shown at 8 days post-cell transfer. (A) Irradiated (650 R) C57BL/6 LCMV carrier mouse receiving immune LN cells only. (B) Irradiated carrier mouse receiving both carrier bone marrow cells and immune LN cells. Magnification, ×100.

T cells from immune donors were required for the effective immune therapy of carrier mice. These results show that virus-specific CTL by themselves were unable to effectively clear a persistent LCMV infection from the liver. However, the results do not necessarily rule out a contribution of cytolysis in vivo by CTL in controlling the infection. In fact, the histological studies of the liver described in the accompanying paper (1) revealed extensive lymphocyte infiltrates and necrosis of hepatocytes, suggesting killing of infected hepatocytes by CTL. A recent study by Zinkernagel et al. (19) also supports the view that antiviral CTL are directly cytolytic in vivo. What then is the contribution of the bone marrow-derived mononuclear cells? This is a heterogeneous cell population, and several different functions are possible, but we would like to propose that one of the critical functions of these bone marrow-derived mononuclear cells is to help the virus-specific T cells invade the tissue parenchyma and gain access to the sites of infection within the
organ. A possible sequence of events is as follows. LCMV-
specific Lyt2+ T cells bind viral antigen on infected endo-
thelial cells in a blood vessel, and this recognition leads to
the release of lymphokines, such as migration-inhibitory
factor and gamma interferon. These factors will recruit and
activate monocytes. The activated monocytes release cy-
tokines (e.g., tumor necrosis factor, alpha interferon, etc.)
and enzymes (e.g., proteases, lysosomal hydrolyases, etc.)
which affect the permeability of the vessels and the move-
ment of lymphoid and nonlymphoid cells to the inflamma-
tory site. This cascade may facilitate the entry of virus-specific T
cells to the sites of infection within the tissue where the cells
(or their products) can kill virus-infected cells and restrict
viral replication.

In conclusion, our studies have shown the importance of
virus-specific T cells, MHC class I antigens, and nonspecific
bone marrow-derived mononuclear cells in the elimination of
a persistent and disseminated viral infection. Similar im-
une surveillance mechanisms have been shown to operate
in the control of malignant tumors (3, 14). Taken together,
these studies emphasize the need to consider the importance
of antigen-specific T cells and an intact bone marrow func-
tion when designing protocols for the treatment of chronic
viral infections and tumors.

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