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Complement-Mediated Anti-HIV-1 Effect Induced by Human IgM Monoclonal Antibody Against Ganglioside GM2

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HIV-infected cells aberrantly express a high level of antigenic glycosidic structures such as GM2 and Gg4. Some normal sera containing natural IgM Abs to GM2 and/or Gg4 cause C-mediated cytolysis of HIV-infected cells. In the present study we demonstrated that a human IgM anti-GM2 mAb (L55 Ab) can induce cytolysis of HIV-infected cells. Increased GM2 expression by HIV-1 infection of a human T cell line (MOLT4), a human monocyte cell line (U937), and human lymphoblastoid cells was confirmed by immunofluorescence staining with L55 Ab. These infected cells were readily lysed by L55 Ab in the presence of fresh human serum as a C source that alone did not cause cytolysis. L55 Ab also had the ability to destroy HIV-1 particles via C-mediated lysis. By adding L55 Ab together with human C to mixed culture of HIV-infected cells and naive cells, HIV-1 replication was significantly suppressed, and this effect was synergistic when L55 Ab was combined with a reverse transcriptase inhibitor and a protease inhibitor. Therefore, a human IgM anti-GM2 mAb may be effective in treating HIV-infected patients, especially when used together with chemotherapeutic agents. The Journal of Immunology, 1999, 162: 533–539.

Materials and Methods

mAbs and polyclonal serum Abs

A human IgM mAb to GM2 (L55 Ab) (7, 8) was secreted from EBV-transformed human B cells that were grown in a serum-free medium (AIM-V, Life Technologies, Gaithersburg, MD). The Ab was highly purified using four different sequential column chromatographies. A human IgM mAb to GM3 (L612 Ab) (9, 10) was prepared by similar procedures and used as a control Ab. Normal fresh human serum (FHS), which did not induce cytolysis, was used as the human C source in all experiments. A normal fresh human serum found to contain IgM Ab to GM2 that caused cytolysis of HIV-1-infected cells (4) was designated lytic FHS (L-FHS) and used as a positive control. The serum was prepared by refrigerated centrifugation, aliquoted, and frozen at −80°C until used. 0.5β (11) and NM-01 (12) are mouse IgM Abs against HIV gp120 Ag that were donated by Dr. T. Matsushita (Kumamoto University, Kumamoto, Japan) and Dr. T. Ohno (Jikei Medical University, Tokyo, Japan), respectively. UCHT1 (13), a mAb against CD3, was donated by Dr. P. C. Beverley (University of Cambridge, Cambridge, U.K.).

HIV strains and human cell lines

The HIV-1-susceptible cell lines, MOLT4 (a human T cell line) and U937 (a human monocyte cell line), were grown in RPMI 1640 supplemented with 10% FCS, 2 μM glutamine, 100 IU/ml penicillin, and 100 μg/ml streptomycin. The cell lines were kept free of mycoplasma. These cells were infected with 10 × TCID50 of HIV-IIIB (14) or HIV-MN (15)/cell and cultured for 4 wk or more before use as a source of persistently HIV-infected cells. More than 95% of the cells were HIV env Ag (gp120) positive as detected by 0.5β and NM-01 using flow cytometry.

Clinical isolates of an HIV strain were obtained from PBMC of an HIV-infected patient as follows. Ten milliliters of whole blood was collected into sterile heparinized tubes and centrifuged at 1800 rpm for 5 min. The pellets were resuspended in twice the original blood volume of PBS and subjected to a Ficoll-Hypaque gradient centrifugation to isolate PBMC. After CD8+ and CD4+ cells were depleted by a MiniMACS separation column (Miltenyi Biotech, Auburn, CA), PBMC (1 × 106 cells/ml/well) were stimulated by UCHT1 (0.5 μg/ml) in a 24-well plate. On day 3 the cells were washed and suspended in RPMI 1640 medium containing 50 U/ml IL-2 (Shionogi, Osaka, Japan). On day 10 the culture supernatants were collected as a source of virus.

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3 Abbreviations used in this paper: FHS, fresh human serum; L-FHS, lytic fresh human serum; PE, phycoerythrin; AZT, azidothymidine; HHS, heat-inactivated human serum; DAF, decay-accelerating factor; MCP, membrane cofactor protein; HRF20, 20-kDa homologous restriction factor.
Detection of gangliosides on cells by flow cytometry

One million HIV-infected or noninfected cell pellets were added to 20 µl of L55 Ab or L612 Ab (100 µg/ml) and were incubated for 30 min at room temperature. Cells were washed with PBS and were incubated for 30 min at 4°C with 20 µl of FITC-conjugated goat anti-human IgM (10 µg/ml). After washing, the cells were subjected to flow cytometric analysis on FACS calibur (Becon Dickinson, Mountain View, CA).

PBMC fractionated by Ficoll-Hypaque gradient centrifugation of heparinized blood from healthy adult donors were depleted of CD8+ cells and stimulated with 0.01% PHA (PHA-P, Difco, Detroit, MI) for 3 days to generate PHA blasts. The PHA-blasts were infected with HIV-IIIB or mock infected and were cultivated in the presence of 50 U/ml of IL-2. One week after the infection cells were stained with FITC-labeled human mAb against GM2 (FITC-L55) and PE-labeled mouse mAb against gp120 (PE-0.5B).

C-mediated cytolytic assay

Target cells were labeled with 51Cr, and 2 × 10^4 labeled cells were incubated with L55 Ab in the presence of FHS, which was used as a C source. FHS alone had no lytic activity against HIV-infected cells. A total volume of 100 µl consisting of target cells, L55 Ab, and FHS in a U-bottomed 96-well plate was incubated at 37°C for 90 min in a CO2 incubator. As a positive control, wells containing target cells and L-FHS (25%, v/v) were prepared for each experiment. 51Cr release by cells treated with 5% Triton X-100 was used as a 100% release value. All assays were performed in triplicate.

Absorption of anti-GM2 Abs with GM2-containing liposomes

L-FHS was subjected to Sephadex G-200 gel filtration, and the protein concentration of the IgM fraction was adjusted to 250 µg/ml. Anti-GM2 Abs in the IgM fraction was absorbed using GM2-containing liposomes (GM2-liposomes). Liposomes were prepared with cholesterol, phosphatidylinoline, and GM2 at a molar ratio of 1:1:0.1 as described previously.[16] Two hundred microliters of the IgM fraction was mixed with a 5 mmol phospholipid equivalent of GM2-liposomes. After incubation for 60 min at room temperature, the mixture was centrifuged at 5000 g for 30 min, and the supernatant was collected. Liposomes without GM2 were used as a control in the absorption test.

HIV preparation and virology assay

HIV particles were prepared from culture supernatants of HIV-1-infected cell lines and lymphoblasts of an HIV-infected patient. The supernatant (2 ml) was centrifuged at 100,000 × g for 30 min, and 1.8 ml of supernatant was removed. The remaining 0.2 ml, including the viral pellet, was suspended in 4 ml of RPMI 1640 medium and used as HIV-1 preparations. Virology was determined by the method of Sullivan et al. (17) with a slight modification. Briefly, 100 µl of virus preparation was incubated at 37°C for 1 h with 25% FHS in the presence or the absence of L55 or L612 Ab. Five and twenty-five percent L-FHS was used as positive controls. The virus preparation was treated with RPMI 1640 medium to determine the background release of p24 or with Triton X-100 (final concentration of 1%) to determine 100% lysis. After incubation, the degree of p24 release from virions was determined by a HIV p24 ELISA kit (DuPont, Boston, MA). All assays were performed in triplicate.

Anti-HIV infectivity assay

Naive U937 cells (2 × 10^5) were mixed with 2 × 10^3 HIV-IIIB-infected U937 cells in 24-well plates with 1 ml of medium containing one or more of the following reagents: 20% FHS, L55 Ab (35 µg/ml), azidohydrazine (AZT; 1 µM), a reverse transcriptase inhibitor (18), and KNI-272 (1 µM; a protease inhibitor) (19), or their combinations. The mixtures were incubated at 37°C in a CO2 incubator. After 48 and 72 h, the number of HIV-infected cells was assessed by a Coulter Colon KC57-FITC anti-p24 mAb (Coulter, Hialeah, FL) following the manufacturer’s protocol (20), and the amount of HIV in the supernatant fluids was assessed by determining the amount of p24 as described above.

In another experiment, 2 × 10^5 naive U937 cells were mixed with 2 × 10^5 HIV-IIIB-infected U937 cells or HIV-MN-infected U937 cells in 24-well plates with 1 ml of medium containing one or more of the following reagents: 20% FHS, AZT (1 µM), and L55 Ab (50 µg/ml). Every fourth day, 0.9 ml of the cultures was collected, and the percentage of infected cells was assessed by the KC57-FITC anti-p24 mAb as described above. The remaining cells were adjusted to 2 × 10^7/ml with RPMI 1640 medium containing 20% FHS with or without L55 Ab and/or AZT.

To measure the anti-HIV activity of L55 Ab in primary culture of human lymphocytes, PBMC from healthy adult donors were depleted of CD8+ and were stimulated with 0.01% PHA for 3 days to generate PHA blasts. The PHA-blasts were infected with 1 × 10^6 cells/ml/well) were cultured in a 24-well plate in the presence of 1) 20% FHS, 2) 20% FHS plus 50 µg/ml L612, 3) 20% FHS plus 1 µM AZT, 4) 20% FHS plus 50 µg/ml L55 Ab, or 5) 20% FHS, 1 µM AZT, and 50 µg/ml L55 Ab. On day 5 the cells were washed and suspended in fresh medium containing the above reagents (no. 1–5). To determine the HIV propagation in these cultures, the culture supernatants on days 5 and 10 were tested for HIV p24.

Results

Ganglioside expression on the cell surface of HIV-infected and noninfected cells

Cell surface expression of GM2 and GM3 was assessed before and after HIV infection of MOLT4 and U937 cells by flow cytometry using L55 and L612 Ab. On both types of cells, GM2 expression increased significantly after HIV-IIIB infection (Fig. 1A). In contrast, GM3 became undetectable after the infection. This observation is concordant with the suggestion that HIV-1 infection may transactivate GalNAc transferase (1, 2), which is the enzyme responsible for converting ganglioside GM3 to GM2.

After CD8+ cells were depleted, normal lymphoblast cells were treated with HIV-IIIB for 1 wk to detect gp120 and GM2 using two-color stained flow cytometry. As shown in Fig. 1B, a much higher GM2 expression was observed on the gp120-positive cells compared with the gp120-negative cells or uninfected lymphoblasts.

Cytolysis of HIV-1-infected MOLT4 and U937 cell lines by L55 Ab

The cytolytic activity of L55 Ab (20 and 100 µg/ml) was tested using five target cell lines, MOLT4, HIV-IIIB-infected MOLT4 (MOLT4-IIIB), U937, HIV-IIIB-infected U937 (U937-IIIB), and HIV-MN-infected U937 cells (U937-MN), in the presence of 25% FHS or heat-inactivated human serum (HHS). As shown in Fig. 2, specific cytolysis of HIV-1-infected cells was induced in a dose-dependent manner against all the cell lines. U937-MN cells exhibited the greatest lysis among all the cell lines tested; 77% cell lysis was obtained with 100 µg/ml L55 Ab plus FHS. None of the cell lines was lysed significantly by L55 Ab plus HHS, L612 Ab plus FHS, or FHS alone. Twenty-five percent L-FHS, which contained both natural IgM anti-GM2 Abs and C, showed >90% lysis against both HIV-IIIB-infected and HIV-MN-infected U937 cells.

Cytolysis of HIV-infected cells was due solely to IgM anti-GM2 Ab

To determine whether the cytolytic activity of the L-FHS was due solely to IgM anti-GM2 Ab, the IgM fraction of the L-FHS was isolated and tested after absorption with GM2-containing liposomes or with control liposomes. We then assessed whether an IgM fraction devoid of anti-GM2 Ab prepared from L-FHS could mimic the cytolytic activity of L55 Ab. 31Cr-labeled U937-IIIB cells were mixed with absorbed IgM fraction and various concentrations (0.6–60 µg/ml) of L55 Ab in the presence of FHS as a C source. As shown in Fig. 3, the lytic activity of the IgM fraction absorbed with control liposomes was 45%, whereas there was no such lytic activity after absorption with GM2-liposomes. Furthermore, the GM2-liposome-absorbed IgM fraction was not able to enhance the cytolytic activity of L55 Ab in the presence of FHS. These results indicate that the IgM fraction of L-FHS does not inherently contain some other IgM Ab that could synergize with anti-GM2 Ab to induce C-mediated cytolysis of HIV-infected cells.
Lysis of HIV-1 particles recovered from MOLT4 cells, U937 cells, or HIV-infected patient’s lymphoblasts

We tested the effects of L55 Ab and C against HIV-1 particles isolated from four sources; MOLT4-IIIB cells, U937-IIIB cells, U937-MN cells, and lymphoblasts from an HIV-infected patient. The virion lysis was determined by p24 release as described in Materials and Methods. As shown in Fig. 4, HIV virions from all four sources were lysed by L55 Ab in the presence of FHS. HIV-MN showed the greatest lysis among all the HIV tested. No such HIV lysis was observed with L55 Ab (data not shown) alone, L55 Ab plus HHS (data not shown), or L612 Ab in the presence of FHS.

Inhibition of HIV spread to U937 cells

To mimic an in vivo model of IgM Ab protection against HIV infection and spread, 2 × 10^5 naive U937 cells and 2 × 10^4 HIV-IIIB-infected U937 cells were cocultivated in the presence of L55 Ab and other reagents. In the presence of FHS only, the numbers of infected cells (Fig. 5A) was 8.8 × 10^5 after cultivation for 48 h and 12.6 × 10^5 after 72 h. The amounts of p24 produced (Fig. 5B) were 37.1 and 118.0 ng/ml after cultivation for 48 and 72 h, respectively. Addition of L55 Ab, AZT, or KNI-272 reduced the number of infected cells to 2.5 × 10^5 and 4.5 × 10^5, 5.0 × 10^5 and 7.3 × 10^5, 6.0 × 10^5 and 6.3 × 10^5 after 48- and 72-h cultivations, respectively. The amounts of p24 were reduced to 14.2 and 39.4, 18.1 and 27.4, and 9.3 and 17.5 ng/ml after 48- and 72-h cultivations, respectively. Combined addition of L55 Ab, AZT, and KNI-272 resulted in the greatest reduction in both the number of infected cells and the amount of p24 by >80% as shown in Fig. 5.

In the long term cocultivation experiment, the percentage of cells infected by HIV-IIIB on days 8 and 12 were 45 and 75%, respectively, in the presence of FHS alone, whereas in the presence of L55 Ab or AZT, these values were only 10 and 35%, respectively (Fig. 6A). As shown in Fig. 6B, the infectivity of HIV-MN was much lower than that of HIV-IIIB. However, with HIV-MN, by day 28 the percentage of infected cells in the FHS alone group was 71%, whereas that in the L55 Ab plus FHS group was only 8%. We also assessed the synergistic effect of L55 Ab and AZT in U937-IIIB and U937-MN cells. We were not able to obtain accountable results when U937-MN cells were tested in these studies, as the HIV-suppressive activity of L55 Ab or AZT was almost 100% during the observation period of 28 days (Fig. 6B). When U937-IIIB cells were used in the same experimental system, significant differences among AZT only, L55 Ab only, and AZT plus L55 Ab were observed by day 12 (Fig. 6A). On day 16, 20% of the cells were infected in the AZT plus L55 Ab group, while >50% of the cells were infected in both AZT only and L55 Ab only groups. On day 24, the percentage of infected cells in the former group was 40%, and the percentage was >95% in the later groups.

Effect of L55 Ab on HIV-1 propagation in PBMC

An experiment was designed to mimic the in vivo model of HIV infection using normal human PBMC as described in Materials and Methods. As indexes for HIV propagation, the p24 presence in culture supernatants on days 5 and 10 was measured. As shown in Fig. 7, strong inhibition was demonstrated by L55 Ab plus FHS in all HIV-IIIB, HIV-MN, and HIV-1 isolated from an infected patient’s lymphoblasts. The combination of L55 Ab and AZT suppressed HIV-1 replication in lymphoblasts by 90%. The suppressive effect of L55 Ab was stronger than that of AZT in this experiment, and this discrepancy between the results of the U937 culture cell experiments and the PBMC experiments may have been due to differences in AZT susceptibility of these two cells.
cell types. L612 Ab plus FHS had no inhibitory effect on HIV replication.

Discussion

We previously reported that some normal human sera harboring natural IgM Ab against Gg4 or GM2 can induce C-mediated cytolysis of HIV-1-infected cells (3, 4). Since cells are normally protected from homologous C by species-specific membrane inhibitors of C (21), such as DAF (22), MCP (23), and HRF20/CD59 (24), C activation by natural IgM Ab on HIV-infected cells may negate the restriction by these membrane inhibitors. Decreased expressions of DAF and HRF20/CD59 have been observed to some extent on HIV-infected cells (3) and lymphocytes of AIDS patients (25, 26). However, HIV-infected cells acted upon by IgG Abs are resistant to C-mediated cytolysis (3). Therefore, some other reasons must be involved in the cytolysis of HIV-infected cells by IgM Ab and homologous human C. In addition to the high efficiency of IgM Ab in C activation, its large molecular size may allow for C activation relatively far away from the membrane inhibitors, thus overcoming restriction by these inhibitors.
Although the cytolytic capacity of the lytic sera harboring IgM Ab against Gg4 or GM2 was removed by absorption with liposomes containing Gg4 or GM2, respectively, it was possible that some other Abs had been contributing to the lytic function. In other words, the presence of an unknown factor in addition to the IgM Ab against Gg4 or GM2 might be required for the lytic function. To investigate this point, we used a human mAb against GM2 (L55 Ab). We studied whether the mAb alone has the capacity to cause cytolysis of HIV-infected cells in the presence of FHS as a source of homologous C. Although we had to use a relatively high concentration of the Ab, L55 Ab effectively killed HIV-infected cells and prevented HIV infection of naive cells in the presence of C. High doses of the mAb may be required to activate complement to overcome the restriction by HRF20 (CD59) of membrane attack complex formation. In addition, the inhibition of HIV spreading was significantly enhanced by addition of AZT or KNI-272 (Figs. 5 and 6).

**FIGURE 5.** Effect of L55 Ab on HIV-1 propagation in U937 cells. Naive U937 cells (2 × 10⁵) were mixed with 2 × 10⁴ HIV-1-IIIb cells in 24-well plates in 1 ml of RPMI 1640 medium containing 20% FHS and L55 Ab (35 μg/ml), AZT (1 μM), or KNI-272 (1 μM), or their combinations. After 48-h (□) and 72-h (■) incubations, the number of HIV-infected cells was assessed by flow cytometry using a Coulter Colon KC57-FITC anti-p24 Ab, and the amount of HIV in the supernatants was assessed by determining the amount of p24. The total number of cells after incubation was essentially the same among the groups. The values shown represent the mean of two independent experiments.

**FIGURE 6.** Effect of L55 Ab on HIV-1 propagation in U937 cells in long term cocultivation. Naive U937 cells (2 × 10⁴) were mixed with 2 × 10³ U937-IIIb (A) or U937-MN (B) cells in 24-well plates with 1 ml of RPMI 1640 medium containing 20% FHS (□), 20% FHS and 50 μg/ml L55 Ab (■), 20% FHS and 1 μM AZT (●), or 20% FHS, AZT, and L55 Ab (○). The mixtures were incubated at 37°C in a CO₂ incubator for 28 days, and media were exchanged every 4 days. The number of HIV-infected cells was assessed as described in Materials and Methods. The values shown represent the mean of assays performed in triplicate (SD shown).
Cultured in RPMI 1640 medium containing 20% FHS only, 20% FHS and infected with HIV-IIIB, HIV-MN, and HIV-1 from an HIV-infected patient tested for HIV p24 by ELISA performed in triplicate (SD shown). Culture supernatants of lymphoblasts on day 5 (Ab, or 20% FHS, AZT, and L55 Ab. Media were exchanged on day 5. The infected patients contained IgM Ab against GM2 as determined by (27). Recently, we found that most of the lytic sera from HIV-infected patients contained IgM Ab against GM2 as determined by

5–7) (26). We previously reported that seropositive populations who had survived >10 yr had IgM lytic Abs to HIV-infected cells in higher numbers than patients who had not survived for this long (27). Recently, we found that most of the lytic sera from HIV-infected patients contained IgM Ab against GM2 as determined by ELISA (our manuscript in preparation). Therefore, anti-GM2 Ab may be a key factor in prolonged protection against AIDS.

The mechanisms of action for elimination of HIV-infected cells by C-mediated cytolysis are different from those for RT inhibitors or protease inhibitors. Agents that inhibit RT or protease cannot eliminate infected cells that have already incorporated the HIV-1 genome as proviral DNA. The role of RT inhibitor or protease inhibitor is to prevent the establishment of infection in those cells newly invaded by HIV-1 or the production of infective virus in HIV-infected cells. However, C-mediated cytolysis as well as T cell-mediated cellular cytolysis can directly eliminate the cells containing HIV-1 genome.

Since lytic serum harboring anti-GM2 natural Ab has been found to destroy HIV particles and HIV-infected cells (4), we anticipated and confirmed that the L55 Ab can also destroy HIV-infected cells as well as HIV-1 particles in the presence of human C (Fig. 3). These results lead us to expect that such an IgM mAb can destroy HIV-1 particles as well as HIV-1-infected cells in vivo, and the resulting beneficial effect may be synergized by treatment with RT inhibitors and protease inhibitors as suggested by these experiments (Figs. 5–7). The amount of L55 Ab required to induce cytolysis was as high as 50 μg/ml. However, this concentration could be achieved in vivo by i.v. administration with 500 mg of the Ab. Since neuronal cells express GM2, L55 Ab may react with these cells. However, the concentration of GM2 on neuronal cells may not be sufficiently high to induce C-mediated damage, because individuals harboring anti-GM2 IgM Ab, including HIV-infected patients, do not show neuropathological symptoms.

Although combination chemotherapy with three RT and protease inhibitors is significantly effective in the early stages of HIV-1 infection, it is difficult to eradicate HIV-1 in highly progressed patients by this method (28). Reduction of HIV-1 particles and HIV-1-infected cells by an anti-GM2 mAb could enhance the therapeutic effect of combination therapy in these patients.

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