Molecular Mimicry between the Human Immunodeficiency Virus Type 1 gp120 V3 Loop and Human Brain Proteins

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Immunologically cross-reactive proteins in the human brain that resemble the V3 loop of human immunodeficiency virus type 1 (HIV-1) gp120 have been identified. When several homogenized tissues from normal brains were used, a monoclonal antibody raised against amino acids 308 to 320 of the V3 loop reacted with three prominent human brain proteins (HBP) of 35, 55, and 110 kDa. Among the three, the 55-kDa HBP appears to be specific to the central nervous system. These results indicate that the V3 loop of HIV-1 gp120 shares an epitope with HBP. An immune response to the V3 loop that generates cross-reactive antibodies to cellular proteins may be an autoimmune mechanism by which HIV-1 can damage the central nervous system.

Viruses share antigenic sites with normal host cell components, a phenomenon known as molecular mimicry. Viral infections can induce autoimmune responses by several mechanisms, including molecular mimicry (8). Monoclonal antibodies (MAbs) to viral proteins can bind to host components (4, 9, 36). In one study, more than 600 antiviral MAbs generated against 11 different viruses reacted with 3.5% of cells specific for uninfected mouse organs (36). In another study, a hepatitis B virus polymerase peptide that shares six consecutive amino acids with the encephalitogenic site of rabbit myelin basic protein was able to initiate autoimmune disease (7).

Endogenous retrovirus-related sequences exist within the normal genomic DNA of all eukaryotes. These sequences appear to be important to the nature and biology of related exogenous retroviruses and may also play a role in cellular function. Horwitz et al. (14) found endogenous human sequences that were similar to sequences in the envelope cellular protease cleavage site of human immunodeficiency virus type 1 (HIV-1) and the overlapping reading frame for Rev and gp41. In addition, retroviruses were found to encode proteins related to neurotoxins (10, 11, 39, 43). For example, the Nef protein of primate lentiviruses (43) and HIV-1 envelope proteins SU and TM (39) were found to contain sequences related to potent scorpion neurotoxins. The Tat protein of several primate lentiviruses contains sequences similar to a neurotoxin produced by venomous snakes (10).

Autoimmune mechanisms are suggested to play a role in the pathogenesis of AIDS (13, 19, 24) and AIDS-related neurological diseases (20, 29, 33, 44). MAbs against a synthetic peptide of HIV-1 gp41 cross-reacted with human and rodent astrocytes. In the same study, antibodies from AIDS patients with neurological complications also reacted with astrocytes (44). Since most patients with AIDS dementia complex (ADC) have anti-HIV-1 gp120 antibodies (41), in the present study we sought to determine whether antibodies to HIV-1 gp120 could cross-react with normal human brains and contribute to the neuropathology observed in ADC through molecular mimicry.

Brain tissues were obtained from HIV-1-seronegative individuals 3 to 5 h postmortem. Brain samples were homogenized and fractionated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (21). Proteins were transferred either electrophoretically (38) or passively (1) to a nitrocellulose membrane

(0.22-mm pore size; Bio-Rad). Western blot (immunoblot) analysis of the brain proteins was performed with several monoclonal and polyclonal anti-HIV-1 antibodies including polyclonal rabbit anti-HIV-1 gp120 (American Bio-Technologies, Inc., Cambridge, Mass.); monoclonal anti-gp120 V3 loop (NEA-9205), anti-gp41 (NEA-9303), and anti-p24 (NEA-9306) (NEN, Boston, Mass.); anti-p17 and polyclonal sheep anti-HIV-1 gp120 sera (AIDS Research & Reference Reagent Program, Rockville, Md.); anti-Vpu antibody (kindly provided by Z. Matsuda [25]); and anti-Vpr antibody (kindly provided by X. Yuan [45]). One of the anti-gp120 V3 MAbs that corresponded to amino acids 308 to 322 (RIQRGPGRFVTIGK) (NEA-9205) specifically reacted with three prominent human brain proteins (HBP) of approximately 35, 55, and 110 kDa (data not shown). In addition to the three HBP, other less prominent proteins reacted with the V3 MAb, including one of 23 and one of 65 kDa.

These experiments were repeated with a second homogenized brain and were probed with two anti-HIV-1 gp120 mouse MAbs: the previous V3 MAb (NEA-9205) and a second MAb that was raised against amino acids 475 to 486 (MRDNWRSELYKY) (NEA-9201). Western blot analysis showed that only the V3 MAb (NEA-9205) reacted with the same HBP (Fig. 1). To determine whether reactivity for these HBP was specific to the V3 region, a different V3 MAb (NEA-9284) raised against amino acids 307 to 330 (QRIQRGPGRFVTIGKIGNMRQA) was used to probe two different brain samples. It also recognized proteins of 35, 55, and 110 kDa, confirming V3 MAb reactivity (data not shown). The three HBP appear to be specific to the V3 loop of HIV-1 gp120. Five additional normal brains were probed with V3 MAb (NEA-9205) by Western blot analysis and yielded identical results. In addition, a second mouse MAb that was upstream from the V3 loop (amino acids 476 to 486) did not recognize any HBP, suggesting V3 loop specificity. Determining whether this reactivity is exclusive to the V3 loop will require more extensive analysis of gp120 MAbs.

The anti-HIV-1 polyclonal antibodies raised against the entire gp120 molecule did not react with HBP. It appears that these sera do not react with the linear epitope that was recognized by the V3 MAbs. It is possible that this difference is related to the animal species in which these antibodies were raised. The V3 MAbs were produced in mice, while the polyclonal antibodies were made in sheep and/or rabbits.

To determine whether this reactivity was specific to the

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FIG. 1. Western blot analysis (as described in reference 1) of a homogenized normal brain with specific anti-HIV-1 envelope antibodies at a dilution of 1:500. Lane 1, anti-V3 MAb (NEA-9205); lane 2, anti-gp120 MAb (475-486); lanes 3 and 4, anti-gp120 polyclonal antibodies from rabbits and sheep, respectively; lane 5, anti-gp41 MAb; and lane 6, negative control without the first antibody. Arrows indicate proteins of 35, 55, and 110 kDa.

central nervous system, brain tissues from the cerebral cortex, cerebellum, and spinal cord, as well as other tissues including the kidney, liver, lung, and spleen, were examined. An HIV-1 cell lysate from the MoltIIIb cell line was used as a positive control. The tissues and the HIV-1 cell lysate were probed with V3 MAb (NEA-9205). As shown in Fig. 2A, three prominent HBP were expressed from brain-derived tissues, with a higher expression from the cerebral cortex and cerebellum than the spinal cord, particularly for a 110-kDa protein. V3 MAb (NEA-9205) also reacted with kidney and liver proteins of 35 and 110 kDa. Proteins from the lung or spleen did not react

with the V3 MAb. To exclude the possibility of a lack of protein from these organs, the same homogenized organs were probed with serum from an HIV-1-seropositive individual. Notice in Fig. 2B the presence of proteins from lung and spleen tissues. It appears that the 55-kDa HBP is specific to the central nervous system. The 35- and 110-kDa HBP were both detected in kidney and liver tissues, suggesting a common epitope that is homologous to the V3 loop sequence.

To further determine the distribution of proteins that reacted with V3 MAb (NEA-9205), several cell lines from the central nervous system, kidney, and liver were studied by Western blot analysis, including human neuroblastoma SK-N-MC, human retinoblastoma Y-79, astrocytoma U937-MG, human rhabdomyosarcoma RD, human hepatoblastoma HepG2, African green monkey kidney CV-1, promonocyte THP1, and lymphocyte SupT1 (American Type Culture Collection, Rockville, Md.). A normal HBP was included as a reference (Fig. 3). The V3 MAb (NEA-9205) reacted with proteins of 35 and 110 kDa from cell lines derived from the nervous system (SK-N-MC, Y79, U937-MG) and from non-neuronal cell lines, except for the kidney cell line CV-1, which presented only a 35-kDa protein. The 55-kDa HBP was observed only in normal brain tissues.

Interestingly, the V3 MAb reacted strongly with proteins of 35 and 110 kDa from THP1 and SupT1, a promonocytic and a lymphocytic cell line, respectively. The V3 MAb did not react with proteins from homogenized spleen even when 10 times more spleen protein was included (data not shown). The lack of reactivity in the spleen was surprising since T lymphocytes and macrophages are the predominant cell types in the spleen. The most likely explanation for this finding is that epitopes of the tumor cell lines THP1 and SupT1 that reacted with the V3 MAb are not present in normal spleen cells.

To determine whether the HBP are specific to the V3 loop, a blocking experiment using recombinant HIV-1 gp120 (rgp120) from a baculovirus expression system was performed (Fig. 4A). Seven dilutions of rgp120 (10, 7.5, 5.0, 2.5, 0.5, and 0.1 μ g/ml) were incubated with V3 MAb (NEA-9205) at a 1:500 dilution for 1 h at 37°C. As an internal control, 10 μ g of bovine albumin per ml was tested for nonspecific inhibition. V3

FIG. 2. (A) Western blot analysis of approximately 1 mg each of several homogenized tissues from an HIV-1-negative patient including the cerebral cortex (CC), cerebellum (Ce), spinal cord (SC), kidney (K), liver (Li), lung (Lu), spleen (S), and an HIV-1 cell lysate (HIV-1). These were each probed with V3 MAb at a dilution of 1:500. The arrows indicate proteins of 35, 55, and 110 kDa. The arrow to the left indicates HIV-1 gp120. (B) The same Western blot as above probed with serum from an HIV-1-positive patient. Arrows indicate HIV-1 gp120 and gp41 proteins. Notice the presence of nonspecific reactivity in the spleen and lung.

FIG. 3. Western blot analysis of several cell lines including human neuroblastoma (SK-N-MC), retinoblastoma (Y-79), astrocytoma (U937-MG), rhabdomyosarcoma (RD), African green monkey kidney (CV-1), hepatoblastoma (HepG2), promonocyte (THP1), and lymphocyte (SupT1) that were probed with V3 MAb (NEA-9205) at a dilution of 1:500. A normal human brain (NB) was simultaneously analyzed as a reference for protein size. Arrows indicate proteins of 35, 55, and 110 kDa.

MAb was not blocked by this protein. Serum from an HIV-1-seropositive individual with ADC was also used as a negative control. The patient's serum was previously evaluated by Western blot and consistently recognized a 50-kDa brain protein (40). Since it was not blocked or absorbed by rgp120 or MoltIIb, respectively, it was used as a negative control for the V3 MAb. Western blot was performed with the conditions mentioned above. Binding between the V3 MAb and HBP was significantly blocked with 2.5 μ g of rgp120, with a complete effect at 10 μ g (Fig. 4). The serum from the HIV-1 positive patient was not blocked by rgp120. Similarly, 10 μ g of rgp120

inhibited the binding of V3 MAb to gp120 in viral lysate (data not shown).

In this study we showed that the V3 loop of HIV-1 gp120 shares an epitope with three prominent HBP of approximately 35, 55, and 110 kDa. The three HBP appear to be specific to the V3 loop sequence of HIV-1 gp120. These observations may have several implications. First, several studies have demonstrated that the principal neutralizing domain of HIV-1 lies within the V3 loop region (16, 22). This loop is formed by a disulfide bridge between Cys residues 303 and 338. Although most of the amino acids of the V3 loop are highly variable between different strains of HIV-1, a Gly-Pro-Gly-Arg sequence at the tip of the loop is highly conserved among isolates derived from Europe and North America (22). This highly conserved tip is part of an epitope for antibodies that can inhibit fusion of HIV-1-infected cells and block HIV-1 infection (17, 26, 34, 35).

In addition to being a major epitope for the cytotoxic T-lymphocyte response (37), the V3 loop appears to be critical for modulating HIV-1 tropism for macrophages, T-lymphoid cells, and microglial cells (15, 28, 30, 32). Furthermore, the V3 loop has been identified as a fusion domain (3, 6). Antibodies to the V3 loop cannot prevent interaction between gp120 and CD4 but can neutralize the virus at stages following CD4 binding (23, 35). The V3 loop has therefore been suggested to bind cell surface molecules distinct from CD4 during fusion to the cell membrane.

MAbs have been employed to probe for viral and cellular receptors (31). Anti-idiotypic antibodies against specific viral MAbs have been used as molecular probes to determine virus-receptor interaction (42). These techniques utilize the structure complementarity of the antigen binding domain (paratope) of the antibody to the antigen it recognizes. An antibody (Ab1) can be used as an immunogen to elicit anti-idiotypic antibodies (Ab2). Some of these Ab2 molecules will possess paratopes complementary to the paratope of Ab1. Thus, some of the Ab2 antibodies will present paratopes which resemble the antigenic determinant recognized by Ab1 (42).

FIG. 4. Blocking experiment using recombinant HIV-1 gp120 from a baculovirus expression. Seven dilutions of rgp120 (10, 7.5, 5.0, 2.5, 0.5, and 0.1 μ g) were incubated with V3 MAb at a 1:500 dilution for 1 h at 37°C. Ten micrograms of bovine albumin was used as an internal control and did not have an inhibitory effect on the V3 MAb. Serum from a patient with ADC that consistently reacted with a 50-kDa protein was used as a negative control. Arrows indicate the competitive blocking of the 35-, 55-, and 110-kDa proteins. No competitive blocking of the 50-kDa HBP was observed with the HIV-positive control serum.

The methods used in our study may represent a model to identify V3 loop-cell receptor interaction. In this case, if a V3 MAb (Ab1) contains the receptor attachment site, some of the paratopes of anti-anti-V3 (Ab2) antibodies may resemble the receptor attachment site. Therefore, the identification of proteins which share an epitope with the V3 loop will allow us to explore V3 loop interaction with other cellular proteins and V3 loop binding to the target cell.

Antibody cross-reactivity with cellular proteins may suggest a possible mechanism for autoimmunity in AIDS. Cross-reactivity between antibodies to the V3 loop and HBP may suggest a potential means by which HIV-1 can cause damage to the central nervous system and other organs. Anti-HIV-1 gp120 antibodies have been detected in the majority of individuals infected with HIV-1, including those with ADC (27, 41). Therefore, it will be interesting to determine whether antibodies generated against the V3 loop in ADC patients cross-react with HBP. In addition to neurological diseases, kidney disease is one of the first manifestations of HIV-1 infection before AIDS develops (2). Recently, Kimmel et al. (18) reported an idiopathic immunoglobulin A nephropathy in patients with HIV-1 infection. They attributed this nephropathy to the deposition of circulating immunoglobulin A-anti-HIV-1 antibody complexes rather than to HIV-1 infection. Our finding raises the possibility that antibodies directed to the HIV-1 envelope protein may trigger an autoimmune response with resultant kidney disease in HIV-infected individuals.

In vitro characteristics of an anti-V3 antibody domain suggest that this type of antibody can by itself prevent infection in vivo (23, 35). Furthermore, an anti-V3 antibody was able to convey protection pre- and postexposure in two chimpanzees infected with HIV-1 (5). These findings suggest that V3 MAbs may be used as potential prophylactic agents. However, our finding of cross-reactivity between V3 MAbs and normal HBP and other tissues suggests that V3 MAbs may induce autoimmune diseases. Although the presence of autoimmune side effects was not evaluated in the studies mentioned above, further analysis is warranted. Passive immunotherapy with V3 MAbs may generate autoimmune side effects (12).

These results suggest that the V3 loop of HIV-1 gp120 shares an epitope with cellular proteins. Further identification of V3-related brain proteins and their interaction with other cellular proteins can also give insight into how the V3 loop binds with target cells as well as into a potential mechanism for the pathogenesis of AIDS.

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