IDENTIFICATION OF HOMOLOGOUS REGIONS IN HUMAN IMMUNODEFICIENCY VIRUS I gp41 AND HUMAN MHC CLASS II β 1 DOMAIN

I. Monoclonal Antibodies Against the gp41-derived Peptide and Patients' Sera React with Native HLA Class II Antigens, Suggesting a Role for Autoimmunity in the Pathogenesis of Acquired Immune Deficiency Syndrome

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The CD4 molecule, which is expressed by a subset of mature human T cells, has been identified as the cellular receptor for the human immunodeficiency virus type I (HIV I)[1] (1, 2). In searching for the putative region in the HIV I envelope protein that interacts with the CD4 receptor, we postulated that this virus had evolved to mimic the natural ligand of CD4. It was previously established that CD4 plays an auxiliary role during T cell activation, probably by interacting with MHC class II molecules on APCs that also serve as restriction elements for presentation of foreign antigens to the T cell receptors (3–5). Furthermore, results from a study in which chimeric class I/class II molecules bearing L cells were used led us to suspect that the NH_2-terminal domain of the MHC class II β chain (β 1 domain) is involved in CD4 binding (5).

In this report we describe a computer search comparing the conserved amino acid regions of HLA class II α and β chains with the amino acid sequences of HIV I proteins. This search identified an homology between two highly conserved sequences in the β 1 domain of HLA class II molecules and in the gp41 region of HIV I envelope protein.

To assess the biological relevance of this homology, peptides from the conserved regions of HIV gp41 and HLA class II were synthesized and tested for their ability to generate antibodies that would recognize the native protein molecules. This report describes the generation of murine mAbs against the gp41-derived peptide and their crossreactivity on native HIV I env as well as on human class II antigens. Moreover, in screening of HIV I–infected individuals,

[1] *Abbreviations used in this paper:* AA, amino acids; CSA, chicken serum album; HIV I, human immunodeficiency virus type I.

35% of AIDS patients were found to have circulating antibodies that bind to the monomorphic class II–derived peptide. Such autoantibodies could conceivably contribute to the immune abnormalities in AIDS patients.

Materials and Methods

Computer Search. The amino acid sequences of human class II antigens were deduced from the DNA sequences of cloned α and β genes of DR, DQ, and DP subregions from several alleles that were recently published (6). For our computer search, we first identified the most conserved regions in the extracellular domains of human Class II α and β chains. These conserved regions were then compared with the published sequences of HIV I proteins (env, gag, pol, and 3′orf) using the SFASTP program (devised by W. Pearson), which is based on a modification of an algorithm by Wilbur and Lipman (7). A high degree of homology was found between a conserved region located in the β 1 domain of DR and DQ (amino acids [AA] 19–25) and the COOH terminus of HIV I gp41 (the transmembrane segment of the gp160 env, AA 838–844). This region is also highly conserved among different isolates of HIV I. This high order of sequence homology was not equaled in the entire available protein data base (Protein Identification Resource No. 6, 1986) except for two DNA-directed polymerases.

Synthesis of Peptides. The peptides used in this study were synthesized according to a previously described protocol (8). Briefly, peptides were synthesized using an automated synthesizer (model 430A; Applied Biosystems Inc., Foster City, CA). The peptides were released from the solid-phase resin by treating the protected peptides with anhydrous hydrofluoric acid containing 10% thioanisole or 10% anisole. The peptides were then extracted with ethyl acetate, dissolved in 20 ml 10% acetic acid, filtered to remove the resin, and lyophilized. Purity was verified by HPLC and amino acid analysis. The peptides were conjugated to chicken serum albumin (CSA) as previously described (8).

Generation of Murine mAbs. BALB/c mice (Jackson Laboratories, Cold Spring Harbor, ME) were immunized with 1 mg CSA peptide in CFA followed by three additional injections in IFA at 2-wk intervals. Spleen cells from mice with high antibody titers were fused to the NS-1 nonsecreting plasmacytoma and hybridomas were selected in HAT-containing medium. The hybridomas secreting antipeptide antibody were cloned by limiting dilution (0.3 cells/well).

Antibody Assays. ELISAs were performed by coating plates (Immunolon I; Dynatech Laboratories, Inc., Alexandria, VA) with peptides at 10 μg/ml in bicarbonate buffer at pH 9.6. BSA, 1 mg/ml in PBS, was added to block unbound sites. Mouse monoclonal IgM antibodies or patients' sera were incubated at various dilutions for 2 h at room temperature. This was followed by incubation with either goat anti–mouse μ chain–specific or goat anti–human γ chain–specific alkaline phosphatase–linked antibody (Sigma Chemical Co., St. Louis, MO) for 2 h at room temperature. Between each step extensive washing was performed with PBS containing 0.1% Tween 20. Color was developed by addition of the substrate, *p*-nitrophenyl phosphate (Sigma Chemical Co.) for 1–3 h at room temperature. The optical densities were read at 405 nm using a Multiscan MC (Titertek, Helsinki, Finland). In the inhibition experiments, the mouse mAb against the gp41 peptide was preincubated with CSA-peptide or CSA overnight at 4°C and then added to the peptide-coated or HIV I–coated (Genetic Systems, Seattle, WA) plates.

FACS Analysis. Human EBV-transformed B cell lines (9) or mouse L cells transfected with the structural genes of HLA class II antigens DR, DQ, and DP (Sekaly, R., and E. Long [10]) were stained with the following reagents: (*a*) class II–specific mAb that recognizes monomorphic determinant present on all HLA class II antigens (Becton Dickinson & Co., Mountain View, CA); (*b*) the newly generated murine mAb against HIV I gp41 peptide (see above); or (*c*) a control TNP-specific murine mAb. All cells were incubated with the mAb at 4°C for 30 min in the presence of 0.1% sodium azide. The developing reagent, FITC goat anti–mouse Ig (H and L chain) antiserum (Cappel Laboratories; CooperBiomedical, Inc., Malvern, PA) was added for 30 min at 4°C, and the samples were analyzed in a FACS (model II; Becton Dickinson & Co.). Data are presented on a logarithmic scale.

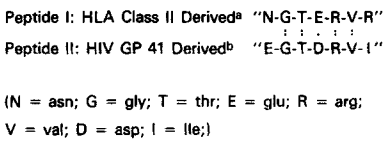

FIGURE 1. HLA class II and HIV I gp41 contain regions with high homology to each other. Peptide I represents AA 19–25 in the β 1 domain of HLA class II β chain. Peptide II represents AA 837–844 in the gp160 envelope protein of HIV I. Two dots indicates amino acids that are identical in the two peptides. One dot indicates a conservative change of glutamic to aspartic acid.

Screening of AIDS Sera. All the patients' sera used in the study were obtained from AIDS patients with active disease. All sera reacted with multiple HIV I proteins on Western blots (Biotech Research Labs Inc., Rockville, MD). The control group consisted of normal volunteers (lab personnel) as well as five seronegative homosexuals (high risk group).

Results and Discussion

HLA Class II and HIV I gp41 Share a Region of High Homology. Many viruses gain access into the cytoplasm of new host cells by direct fusion with the plasma membrane (11), while other viruses, such as EBV (12) and HIV I (2), use special cellular receptors that are found on a more restricted number of cell types. The normal function of these receptors usually involves their interaction with biological ligands that could either be soluble compounds (12) or cell-bound molecules expressed on the same or other cell types (3–5). It was intriguing to test the possibility that during evolution, the latter type of viruses had developed attachment sites that mimic the natural ligands of their cellular receptor. In the case of HIV I, it was assumed that the primary sequence of these attachment sites might bear homology to one of the natural ligands for CD4, namely, MHC class II molecules, as was previously suggested (3–5). Our computer search, therefore, compared 12 conserved regions in α and β chains of human class II molecules to HIV I proteins from 13 different isolates (see Materials and Methods). This analysis revealed homology between a region in the β 1 domain of HLA DR and DQ and the gp41 part of HIV I envelope glycoprotein. The homologous sequences are shown in Fig. 1. As can be seen, they share a core of five amino acids that are identical except for a single conservative change of glutamic to aspartic acid, which does not change the overall charge of these two regions.

To assess the functional importance of the homologous regions found in HIV I gp41 (peptide II) and class II antigens (peptide I), the septamers were synthesized, coupled to CSA, and used to immunize BALB/c mice. The spleen cells of mice with high serum antibodies against the gp41-derived peptide were used for the generation of hybridomas. Five hybridomas were identified that bound strongly to the gp41-derived peptide in an ELISA. All were found to be of the IgM isotype and κ light chain.

Specificity of Anti-gp41 mAbs. The specificity of the mAbs that were generated from mice immunized with the gp41 peptide conjugates was examined using ELISA plates coated with either the gp41- or HLA class II–derived peptides. As depicted in Fig. 2, the mAbs were found to bind equally well to plates coated with either peptide (Fig. 2*A*), and this binding could be blocked by CSA-gp41 peptide but not by CSA alone (Fig. 2*C*). In contrast, a control mAb of the same isotype but of different specificity (anti-TNP) did not bind to either peptide (Fig. 2*A*). The gp41 peptide-specific mAb also bound to plates that are coated with

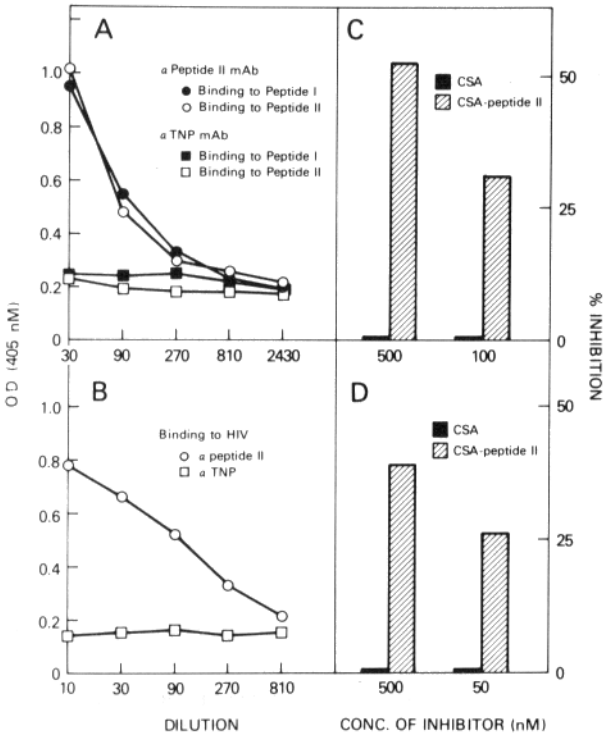

FIGURE 2. Specificity of murine mAb raised against the HIV I gp41-derived peptide. mAbs were produced from spleens of mice immunized with the gp41 peptide conjugated to CSA. (*A*) The binding of anti-gp41 peptide (●, ○) or anti-TNP (■, □) mAb at the indicated dilutions of ascites, to an ELISA plate coated with the gp41-derived peptide (●, ■), or HLA class II–derived peptide (○, □). (*B*) Binding of anti-gp41 peptide (○) or anti-TNP (□) mAb to a "Genetic Systems" plate coated with cell-free, HIV I virus–containing supernatant. (*C*) Percent inhibition of anti-gp41 mAb binding to a plate coated with the gp41-derived peptide by preincubation with CSA (■) or CSA peptide II (▨) at the indicated concentrations. (*D*) Percent inhibition of anti-gp41 peptide mAb binding to "Genetic Systems" plate by preincubation with CSA (■) or CSA peptide II (▨).

inactivated HIV I virus from HIV I–infected CEM cells, which do not express MHC class II. This binding could also be blocked by CSA-gp41 peptide (Fig. 2, *B* and *D*). No reactivity was seen on control plates coated with CSA or irrelevant peptides. In addition, these mAb also react with the gp160 band on HIV I immunoblots (not shown). Thus, the mAb against the gp41-derived peptide can recognize this sequence both in a peptide form (peptides I and II) and in the context of the entire envelope protein.

Anti-gp41 Peptide mAbs React with Native Class II Antigens. It was of interest to determine whether the mAb that we raised against the HIV I septamer would also recognize native MHC class II molecules. For this purpose a panel of EBV-transformed B cell lines were stained in parallel with one of the following: (*a*) a monomorphic anti–class II antibody (Becton Dickinson & Co.); (*b*) the gp41 peptide–specific mAb; or (*c*) control anti-TNP mAbs. As can be seen in Fig. 3, the human B cell lines were not only stained with the class II–specific mAbs (Fig. 3*A*), but also with the gp41 peptide–specific mAbs (Fig. 3, *C* and *D*). In contrast, no staining of the B cells was obtained with control TNP-specific mAbs. A panel of class II^- human cell lines, including CEM (T cell) and a fibroblast line, were not stained by either mAb (not shown).

To confirm that the mAbs against gp41 peptide did indeed bind to native MHC class II molecules on the surface of B cells, we tested their ability to stain murine fibroblast L cells that were transfected with the structural genes of human DR α and β chains (kindly provided to us by Sekaly and Long [10]). As depicted in Fig. 4, the DR4-transfected L cells stained brightly with the DR-

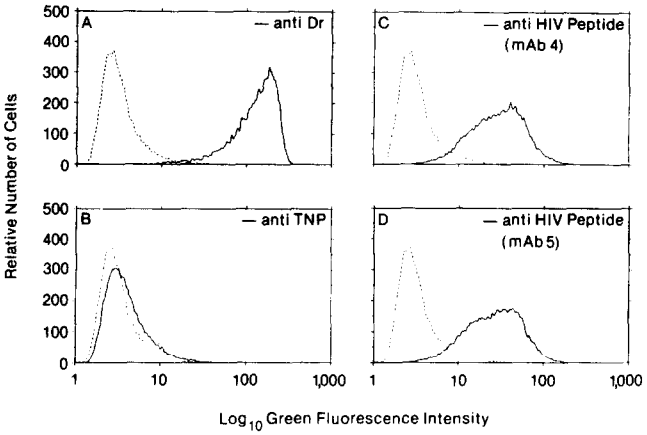

FIGURE 3. Murine mAb specific for HIV I gp41 peptide bind to human EBV-transformed B cell lines. The B cell line (1:13; reference 9) was stained with anti-DR mAb (*A*), anti-TNP mAb (*B*), or anti-gp41 peptide mAb No. 4 (*C*) and No. 5 (*D*), followed by FITC goat anti-mouse mAb (——). Control cells were stained with the developing reagent alone (– – –).

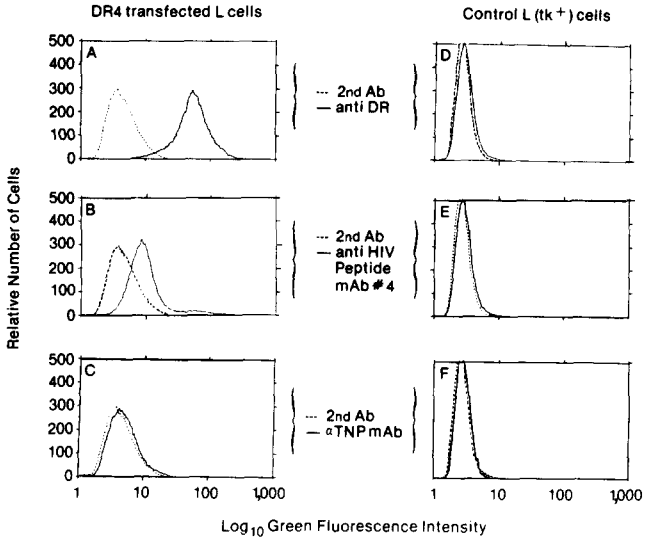

FIGURE 4. Murine mAb specific for HIV I gp41 peptide binds to L cells transfected with human DR genes. L cells transfected with DR4 α and β structural genes (*A–C*) or with the herpes simplex thymidine kinase (tk) gene (*D–F*) were stained with anti-DR mAb (*A* and *D*), anti-gp41 mAb No. 4 (*B* and *E*), or anti-TNP mAb (*C* and *F*).

specific reagent (Becton Dickinson & Co.) (Fig. 4*A*), demonstrating that the transfected α and β gene products were coexpressed on the surface of these murine L cells that normally do not express any MHC class II antigens (Fig. 4*D*). More importantly, these DR-expressing L cells also stained positively (albeit to a lesser degree) with the gp41 peptide–specific mAbs (Fig. 4 *B*). The control L(tk$^+$) cell line was only transfected with a selection marker (Herpes Simplex tk gene), and thus expresses only mouse MHC class I but not class II antigens. It was not stained by any of our gp41 peptide–specific mAbs (Fig. 4*E*). Similar results were obtained with murine L cells that were transfected with other class II structural genes namely, DP and DQ (not shown).

These data demonstrate that the mAbs raised against a conserved region in the COOH terminus of HIV I envelope protein crossreacts with native class II molecules that express the homologous region. Therefore, although the class II α and β chains possess two extracellular domains that interact with each other noncovalently to form a complex tertiary structure, mAb against a β chain

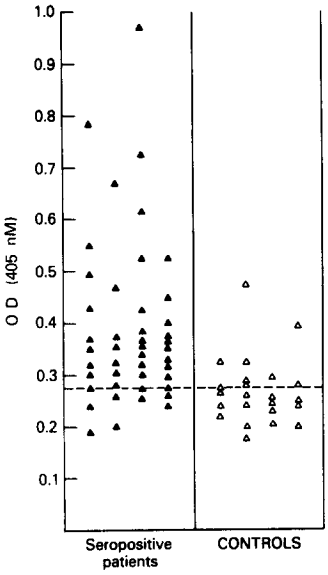

FIGURE 5. Reactivity of AIDS sera against human HLA class II–derived peptide I. Sera from 43 AIDS patients and 23 controls (18 seronegative normal volunteers and 5 healthy male homosexuals) were tested by ELISA for reactivity to the HLA class II–derived peptide I (shown in Fig. 1). The broken line represents the mean absorbance value (405 nm) of the control group.

peptide could recognize the native molecules. This was of interest since most antibodies against short peptides derived from class II molecules do not react with the native two-chain structure. The reactivity found with our mAb indicates that the conserved region, which maps to the NH_2 terminus of the class II β chain, is not buried inside the native class II molecules and is therefore accessible for recognition by the murine mAb.

Screening of AIDS Patients for Anti–class II Peptide Reactivity. The findings described above led us to consider the possibility that HIV I–infected individuals may generate antibodies against the gp41 COOH-terminal region which could crossreact with self class II antigens and thus behave as autoantibodies. To test this possibility, we screened sera from 45 seropositive AIDS patients as well as 23 controls. The AIDS patients' sera all tested positive against HIV I and contained antibodies against different viral products including gp41 as detected on immunoblots. The control group consisted of either normal volunteers (n = 18) or healthy seronegative homosexuals (5 high risk controls). The sera were tested for binding to ELISA plates coated with the HLA class II–derived peptide. As can be seen in Fig. 5, 15 sera from the seropositive patient group (36%) contained antibodies that reacted with the class II–derived peptide with absorbance (405 nm) >3 SD above the mean control value. Two of the control sera were also positive, but interestingly, they were obtained from seronegative homosexuals (high risk individuals). It is possible, therefore, that the reactivity found against a class II–derived peptide, which bears a high degree of homology to a region in the gp41 protein, resulted from exposure of these individuals to HIV I that was not yet detectable by standard HIV I serological assays.

AIDS Patients' Antibodies That Bind to Peptide I Crossreact on Whole Class II Molecules. It was important to determine whether the reactivity against the class II–derived peptide found in the AIDS patients' sera was specifically against this region of the class II molecules (AA 19–25), and more importantly, whether the

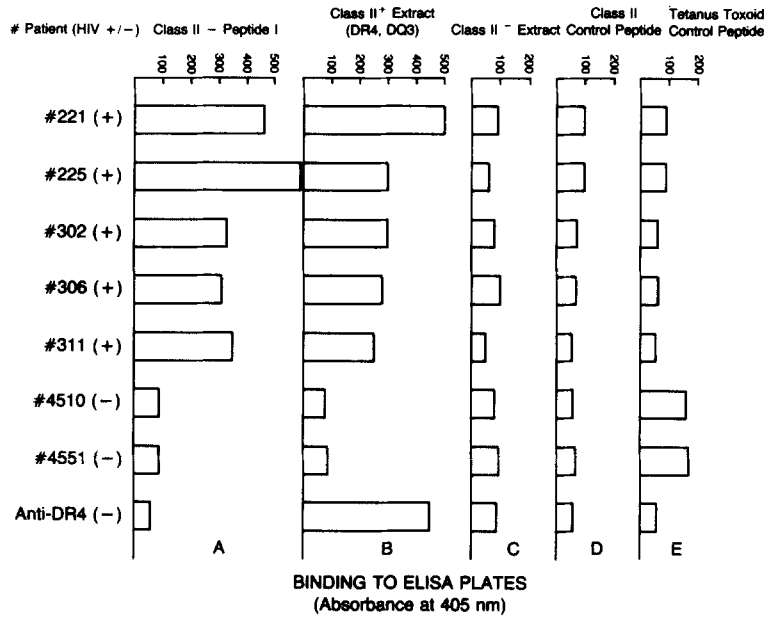

FIGURE 6. AIDS sera that bind to class II–derived peptide I bind also to intact class II molecules. Sera from five AIDS patients (+), two seronegative individuals (−), and DR4-specific alloantiserum were diluted 1:50 and tested for binding to ELISA plates coated with (*A*) the class II–derived peptide I (β 1 domain, AA 19–25); (*B*) class II–rich cell extract from the H9 (DR4,DQ3) human T cell line; (*C*) class II–negative cell extract from the CEM cell line; (*D*) a control, conserved class II–derived peptide (β 1 domain, AA 38–45); and (*E*) a control peptide derived from tetanus toxoid. All plates were coated with the indicated preparations at 10 μg/ml protein concentration.

same antibodies crossreact on intact class II molecules (as was the case with the murine antipeptide mAb).

Five of the AIDS sera that reacted with the class II–derived peptide I were tested in parallel for reactivity against (*a*) class II–derived peptide I; (*b*) human class II–enriched cell extract preparation from uninfected H9 (DR4,DQ3) cells (prepared by Dr. M. Phelan, Division of Virology, FDA; this extract contains intact class II heterodimers that are recognized on Western blots by DR4-specific human alloantiserum and by murine mAb against human class II monomorphic determinant, but not by alloantisera specific for DR2, 3, 5, and 7); (*c*) identically prepared extract from the class II negative cell line CEM; (*d*) a control, highly conserved, class II–derived peptide (AA 39–45 in β 1 domain); and (*e*) control peptide derived from Tetanus toxoid, not related to either HIV I or to class II molecules. The data depicted in Fig. 6 clearly show that the patients' sera, which reacted with the class II–derived peptide I, also bound to plates coated with the intact class II molecule–containing extracts, but not with similar extracts obtained from the class II$^-$ cell line. Furthermore, no reactivity was seen with control peptides derived from another class II β 1 domain conserved region (AA 39–45) or from tetanus toxoid. The seronegative control sera (from uninfected individuals) did not react with either the class II–derived peptide I or with the class II–enriched extract, but did bind somewhat to the tetanus toxoid–derived peptide

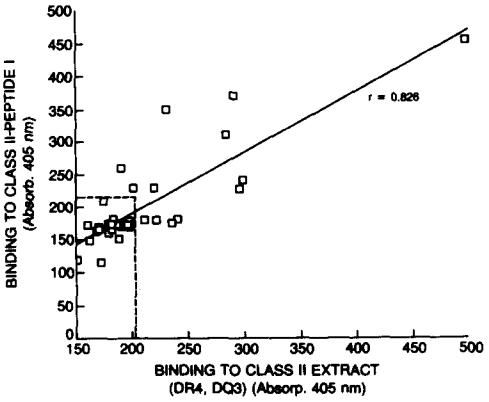

FIGURE 7. Correlation of AIDS sera-binding to class II-derived peptide I and to class II–rich cell extract. Linear regression analysis was used to establish the correlation between binding to class II–derived peptide I (y axis) and binding to intact class II molecules from H9 cell extract (x axis) for 35 AIDS patients. The broken lines represent the mean + 2 SD values of the control sera tested in parallel for binding to the same ELISA plates.

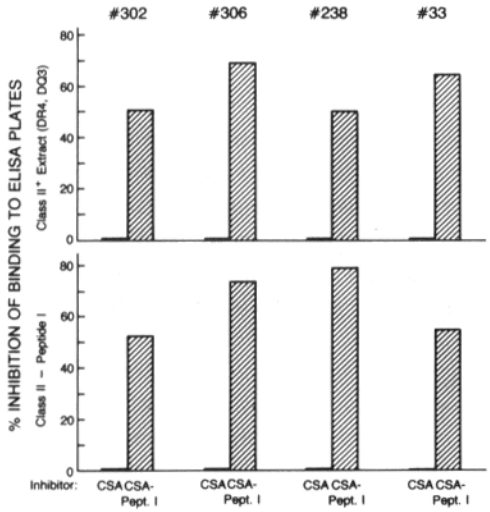

FIGURE 8. Soluble CSA peptide I blocks binding of AIDS sera to class II–derived peptide I and to class II–rich cell extract. Patient sera (1:50 dilutions) were preincubated with CSA (■) or CSA peptide I (▨) (4 mg/ml) overnight at 4°C and were then added to ELISA plates coated with class II–rich cell extract (DR4, DQ3) (*upper panel*) or class II–derived peptide I (*lower panel*). The data is expressed as percent inhibition of absorbance (405 nM) compared to the binding of sera preincubated with PBS.

(probably reflecting their immune memory against tetanus toxoid, which is a commonly used vaccine). The human anti-DR4 alloantiserum was also tested. As expected, it reacted with the DR4-containing extract but not with the Ia^- extract, or with the nonpolymorphic class II–derived peptides.

Three of the patients whose sera were tested in this experiment were HLA typed and were found to express at least one of the class II antigens that are present in the class II–rich extract. Patients 302 and 311 are $DQ3^+$, and patient 306 is $DR4^+$. Thus, it seems that irrespective of their HLA haplotype, AIDS patients may produce antibodies that recognize a nonpolymorphic region on their class II molecules. A similar screen was performed on sera from 38 patients, and a good correlation ($r = 0.8260$) was found between their reactivity with the class II–derived peptide I and with the class II heterodimer–containing extract (Fig. 7).

To further establish the specificity of the binding observed in the ELISAs (Figs. 5–7), patients' sera were preincubated with soluble CSA peptide I or with CSA, and then added to the ELISA plates. As can be seen in Fig. 8, soluble CSA

peptide I could efficiently block binding of AIDS sera not only to the peptide I–coated plates (*lower panel*), but also to the intact class II molecules (*upper panel*).

Our study suggests that about a third of AIDS patients contain circulating antibodies that react with a nonpolymorphic region of class II molecules. This ratio, as well as the level of anti–class II antibodies detected, is probably underestimated because such anti-self antibodies are most likely bound to class II–bearing cells such as B cells, macrophages, and some T cells in vivo, and are therefore not available for detection in the ELISAs. This possibility can be tested by examination of lymphoid cells from AIDS patients for the presence of cytophilic antibodies specific for the gp41/class II homologous regions described in our study.

The fact that infection with HIV I may lead to the generation of crossreactive antibodies against nonpolymorphic region of self class II molecules in infected individuals could be of major consequence. Such antibodies may interfere with the normal cellular interactions between $CD4^+$ T cells and MHC class II–bearing APCs. Alternatively, they could be involved in cytopathic mechanisms; e.g., ADCC or complement-mediated killing of class II–expressing cells such as B cells, macrophages, and even activated $CD4^+$ T cells. These possibilities are currently being examined in our laboratory and preliminary results demonstrate the ability of the mAb to block proliferative responses of human CD4-bearing cell lines. Our findings could also have important implications for HIV I vaccine development. One of the potential vaccines currently being tested contains the entire gp160 envelope protein that has been cloned into a Vaccinia vector. This preparation thus contains in its COOH terminal the sequence described in this study, and may inadvertently lead to the generation of class II–reacting autoantibodies in vaccinated individuals. To avoid this outcome, it would be advisable to remove this region from the gp160 or to replace it with an inert sequence.

Summary

Homologous regions of five amino acids each, were identified in the NH_2-terminal domain of human class II β chains and the COOH terminus of HIV I envelope protein. The homologous regions are highly conserved among different DR and DQ alleles and also among different isolates of HIV. Septamers containing these sequences were synthesized and used for the generation of murine mAbs. The mAbs selected for this study were raised against the HIV I–derived peptide and reacted strongly not only with the immunizing peptide, but also with the homologous class II–derived peptide. These mAbs also reacted with native MHC class II antigens expressed on human B cell lines and on murine fibroblast L cell lines transfected with the genes coding for the α and β chains of human class II antigens. Furthermore, sera from 36% of AIDS patients tested contained antibodies that reacted with the class II–derived peptide, as well as with intact class II molecule-rich cell extracts. Such antibodies in HIV I–infected individuals may recognize self class II antigens, triggering autoimmune mechanisms that could contribute to the development of immunodeficiency in AIDS patients.

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