Identification of a Human CD4-CDR3-like Surface Involved in CD4+ T Cell Function*

The CD4 molecule is expressed on the surface of helper T cells. This molecule contains four tandem external immunoglobulin-like domains (D1–D4), a transmembrane domain, and a cytoplasmic tail. Through the use of molecular modeling techniques, peptide analogs of the CDR3-like region of the human CD4 molecule, analog hPGP, a cyclized peptide 13 amino acids long, was synthesized and tested for its ability to inhibit proliferation in human mixed lymphocyte reactions. A conservative amino acid substitution was made at position 5 (D → N) to increase its activity and designated hPGP(N). A series of alanine substitution peptides were synthesized based on the sequence of hPGP(N) to determine the importance of each residue to the peptide’s function. The substitutions of amino acids in positions 3, 7, and 8 had essentially no effect on the inhibitory activity of hPGP(N), while substitutions of amino acids in positions 4 and 6 increased its inhibitory effect. Alanine substitutions of amino acids in positions 2, 5, and 9 dramatically decreased the inhibitory effect of analog hPGP(N). Molecular modeling of the native CD4-CDR3-like domain suggested that the residues corresponding to positions 2, 5, and 9 of the peptide formed a contiguous surface representing the active site.

The CD4 molecule is a 60-kDa transmembrane glycoprotein expressed on the surface of helper T cells (1). The molecule contains four tandem external immunoglobulin-like domains (D1–D4), a transmembrane domain, and a cytoplasmic tail (2–4). Transfection studies and adhesion assays have indicated that the CD4 molecule binds to nonpolymorphic sites of class II MHC molecules (5, 6), and mutagenesis studies have implicated regions of the D1 domain as being responsible for this interaction (7). In addition to its role as an adhesion molecule, co-precipitation experiments have suggested that CD4 also interacts with components of the T cell receptor (TCR) complex on the T cell surface (8–12). The association of src-family tyrosine kinase p56lck with the cytoplasmic tail of the CD4 molecule supports the notion that CD4 is closely involved in the delivery of intracellular signals required for antigen-MHC activation of T cells (13–15). The critical role of CD4 in signal transduction was based initially on cross-linking studies of CD4 with anti-CD4 monoclonal antibodies (mAb), which causes an increase in p56lck kinase activity (16, 17). In addition, the use of CD4 cytoplasmic tail mutants which compromises the p56lck binding site resulted in significantly diminished antigen-specific T cell activation (18), although this may not be true for all antigen-driven situations (19). Overall, it is clear that CD4 is involved in both adhesion and co-receptor activity important for helper T cell activation.

Similar to immunoglobulin structure, the amino-terminal membrane distal (D1) domain of the CD4 molecule contains three complementarity-determining-like regions, i.e. CDR1, CDR2, and CDR3, that are likely to be involved in protein-protein interactions (20–22). The CDR2 site has been identified as essential for HIV envelope glycoprotein gp120 binding to the CD4 molecule (6, 23–25). Interaction with MHC class II molecules is likely to be more complicated and seems to involve several sites on both the D1 and D2 domains (26), while the sites responsible for co-receptor interaction on the T cell surface are completely obscure. In this regard, recent studies utilized molecular modeling techniques to design a family of stable peptide analogs that mimicked the surface of the CDR3-like region of the murine CD4-D1 molecule (27). These analogs were shown to be potent inhibitors of both in vitro (28) and in vivo (29) murine CD4+ T cell-mediated responses. Through the use of computer-assisted structure-based design, we have generated peptide analogs modeled from the human CD4-CDR3-like region of the D1 domain. These analogs were tested in one-way human mixed lymphocyte reactions (MLR) for their ability to inhibit T cell proliferation. In addition, to determine the importance of each residue to the peptide’s function, a series of alanine substitution peptides were similarly tested. The results demonstrated that these analogs could specifically inhibit human CD4+ T cell-mediated function, while having no toxic effect on dividing cell lines. Furthermore, the inhibitory effects of alanine substitution peptides suggested a structure-function relationship between the surface of the CDR3-like domain and T cell function.

EXPERIMENTAL PROCEDURES

Reagents—Ficoll 1077, bovine serum albumin, and human serum (catalog nos. 4522 or 2520) were purchased from Sigma. RPMI, l-glutamine, penicillin/streptomycin, fetal calf serum, and phosphate-buffered saline were purchased from BioWhitaker (Walkersville, MD). (3H)Tdr was purchased from Amersham Corp. Purified mouse anti-human CD8 mAb, mouse anti-human CD4, or anti-CD8 fluorescein isothiocyanate-conjugated mAb were purchased from Pharmingen (San Diego, CA). Goat anti-mouse IgG antibody was purchased from Cappel (Durham, NC).

Cell Lines—The J32.10 human T cell leukemia (30) and the Daudi Burkitt lymphoma lines were kindly provided by Dr. Bice Perussia, Kimmel Cancer Institute. These lines were maintained in RPMI supplemented with 7.5% heat-inactivated (56 °C, 30 min) fetal calf serum, 50 IU/ml penicillin/streptomycin, and 2 mM l-glutamine. Cultures were...
maintained at 37 °C in a humidified 5% CO₂ atmosphere.

Preparation of Peripheral Blood Lymphocytes—Whole blood (50–60 ml) was collected into anticoagulant (acid citrate dextrose)-containing tubes. In 50-ml conical tubes, 20 ml of blood were layered over 20 ml of Ficoll 1077 and centrifuged at 2000 rpm for 35–40 min at 15–20 °C. Buffy coats and serum were collected in three times the volume of phosphate-buffered saline and centrifuged at 1500 rpm for 15 min at 15–20 °C. Supernatants were discarded, cells were washed twice in 50 ml of phosphate-buffered saline, and resuspended in RPMI supplemented with 10% heat-inactivated (56°C, 30 min) human serum, 50 IU/ml penicillin/streptomycin, and 2 mM L-glutamine.

Enrichment for CD4⁺ T Cells—Peripheral blood lymphocytes (10⁶ cells/ml) were incubated with mouse anti-human CD8 mAb at a concentration of 5 μg/ml for 45 min at 4 °C. Cells were washed three times with phosphate-buffered saline containing 0.1% bovine serum albumin. CD8⁺ cells were then removed by panning with the use of plates coated with goat anti-mouse IgG antibody at a concentration of 10 μg/ml. The nonadherent cells were collected, washed three times with phosphate-buffered saline containing 0.1% bovine serum albumin, analyzed by flow cytometry, and cultured in a MLR assay.

Flow Cytometry—In a 96-well round-bottom microtiter plate, cells were distributed in phosphate-buffered saline containing 1% bovine serum albumin and 0.3% sodium azide, incubated with the appropriate mAb at a concentration of 10 μg/ml for 45 min at 4 °C, washed three times, and analyzed using a Coulter II analyzer (Coulter, Miami, FL).

Molecular Modeling—Studies were performed on a SG Onyx computer system (Silicon Graphics, Palo Alto, CA) using the software package supplied by Tripos (St. Louis, MO). The peptide analogs were originally designed using the high resolution crystal structure of CD4 as a template (31). The alanine-containing peptides were modeled in a TABLE I

| Peptide analogs | Peptide sequence | Inhibition (range) | n |
|-----------------|------------------|--------------------|---|
| 84–100C-C       | CEVEDQKEVQGLVFGCLC | 34 ± 5 (13–58)     | 9 |
| hPGP            | CEVEDQKEEFPGC    | 12 ± 4 (9–16)      | 3 |
| hPGP(N)         | CEVENQKEEFPGC    | 28 ± 8 (12–53)     | 5 |
| hPGP(N)A2       | CAVENQKEEFPGC    | 7 ± 4 (0–15)       | 4 |
| hPGP(N)A3       | CEAVENQKEEFPGC   | 18 ± 2 (12–22)     | 4 |
| hPGP(N)A4       | CEVANQKEEFPGC    | 52 ± 7 (23–93)     | 11|
| hPGP(N)A5       | CEVEAQKEEFPGC    | 9 ± 7 (6–22)       | 4 |
| hPGP(N)A6       | CEVENQKEEFPGC    | 49 ± 4 (34–68)     | 10|
| hPGP(N)A7       | CEVENQKEEFPGC    | 20 ± 4 (7–58)      | 5 |
| hPGP(N)A8       | CEVENQKEEFPGC    | 26 ± 15 (0–58)     | 4 |
| hPGP(N)A9       | CEVENQKEEFPGC    | 3 ± 3 (0–8)        | 4 |
bulk aqueous environment. Dynamic trajectory runs (100 ps) were
saved and analyzed for low energy conformers.

Peptide Synthesis—Peptides were synthesized on a 430A fully auto-
mated peptidesynthesizer(AppliedBiosystems,FosterCity,CA),using
standard Fmoc (N-(9-fluorenyl)methoxycarbonyl) chemistry, as de-
scribed previously (29). Intramolecular disulfide bonds were enriched
by a standard air oxidation protocol (29), after which the peptides
exhibited 95% intramolecular bonding, as monitored by Ellman’s
reagent. Peptides were purified by reversed-phase high performance
liquid chromatography (Waters 600E system controller, Waters 490E
programmable multiwavelength detector, Millipore Corp., Bedford,
MA) using a Vydak 2.2 cm × 25-cm C18 column (Rainin, Emeryville,
CA), before use in biological assays. The sequences of the synthesized
peptides are as follows: h84–100C-C, CEVEDQKEEVQLLVFGLC; hPGP,
CEVEDQKEEPGPC; hPGP(N), CEVENQKEEPGPC; hPGP(N)A2, CAVENQKEEPGPC; hPG-
PGP(N)A3, CEAENQKEEPGPC; hPGP(N)A4, CEVENQKEEPGPC; hPGP
PGP(N)A7 (n = 5), hPGP(N)A6
(n = 10), and hPGP(N)A4 (n = 11). Peptides were added at a final
concentration of 100 μM.

FIG. 3. Effect of alanine substitution peptide analogs on T cell
proliferation in MLR assays. Peripheral blood lymphocytes (10^5
cells/well) were plated with irradiated stimulators (2 × 10^5 cells/well) in
a 96-well plate, with or without alanine substitution hPGP(N) analogs,
A2-A9. After seven days in culture, [3H]Tdr incorporation was mea-
sured, and the inhibitory effects of peptide analogs was calculated. Data
were pooled from multiple experiments and presented as percent inhi-
bition of control T cell proliferation ± S.E. assaying analogs hPGP-
PGP(N)A2, A3, A5, A8, and A9 (n = 4), hPGP(N)A7 (n = 5), hPGP(N)A6
(n = 10), and hPGP(N)A4 (n = 11). Peptides were added at a final
concentration of 100 μM.

FIG. 4. Titration of hPGP(N)A4 in MLR assays. Peripheral blood
lymphocytes (10^5 cells/well) were plated with irradiated stimulators
(2 × 10^5 cells/well) in a 96-well plate with or without hPGP(N)A4, at a
final concentration of either 100, 10, 1, 0.1, or 0.01 μM. After 7 days in
culture, [3H]Tdr incorporation was measured, and the concentration
dependent inhibitory effects of the hPGP(N)A4 analog was calculated as
percent inhibition of control T cell proliferation. The data are from a
single representative of three similar experiments.

FIG. 5. Toxicity test of hPGP(N)A4 on growth of B and T cell
cell lines. The immortalized T (J32.10) and B (Daudi) cell lines were plated
in 96-well plates (2.5 × 10^4 cells/well), with (●) or without (□) the
hPGP(N)A4 analog. After 24 and 48 h in culture, [3H]Tdr incorporation
was measured and compared between peptide treated and untreated
cultures. Peptide was added at a final concentration 100 μM. The data
are from a single representative of two similar experiments.

FIG. 6. Effect of the hPGP(N)A4 peptide analog on CD4

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T cell

proliferation in a MLR assay. CD4+ T cells were enriched from
peripheral blood lymphocytes (10^5 cells/well), as described under Ex-
perimental Procedures, and plated with irradiated stimulators (2 ×
10^5 cells/well) in a 96-well plate, with or without the hPGP(N)A4 ana-
log. The effect of hPGP(N)A4 on CD4+ T cells was assayed on days 6–8
of culture by [3H]Tdr incorporation, and measured as percent inhibi-
tion of control T cell proliferation. The data are from a single repre-
sentative of two similar experiments.
MLR Assay—In a 96-well flat-bottom microtiter plate (Nunc, Denmark) 3 \times 10^5 responder peripheral blood lymphocytes were cultured with 2 \times 10^5 irradiated (30 Gy) stimulator peripheral blood lymphocytes/well in a final volume of 200 \mu l and incubated for 6–8 days at 37°C in a humidified 7% CO2 atmosphere. Unless otherwise specified, peptide analogs were added at a final concentration of 100 \mu M immediately after the cells were plated. For radiolabeling, the cells were incubated with 1 \mu Ci of [\textsuperscript{3}H]TdR/well (25 \mu l volume) for the final 6 h of the assay day. Cells were harvested onto glass fiber filters (Wallac Oy, Turku, Finland) with a Harvester 96 (TomTec, Orange, CN) and counted in a 1205 Beta-Plate reader (Wallac, Gaithersburg, MD). The mean [\textsuperscript{3}H]TdR incorporation from quadruplicate wells was calculated.

RESULTS

Design and Biological Testing of the Human CD4-CDR3 Peptide Analogs—Using the crystal structure of the human CD4 molecule’s most distal Ig domain (D1) as a modeling template, the human CD4 peptide analog h84–100C-C was synthesized as a potential inhibitor of human helper T cell responses. Based on our previous findings utilizing a CD4-CDR3-like peptide analog in a murine model for CD4-(L3T4)-dependent T cell activation (28), we reasoned that the similar CDR3-like region of the human CD4 protein would be involved in helper T cell activation. As in the case of the murine CD4-CDR3 peptide analogs (28, 29), in order to mimic the native CD4 structure, a cysteine-cysteine disulfide bridge was used to restrain the conformation of the h84–100 and stabilize the putative active surface. The h84–100 peptide was then shortened to h84–92 and a proline-glycine-proline (PGP) turn introduced, leading to a stable 13-amino acid long structure, designated analog hPGP (Fig. 1). Both h84–100C-C and hPGP peptides were tested for biological activity in one-way human MLR assays. The results shown in Fig. 2 indicated that while both analogs could inhibit CD4 T cell-dependent proliferation as measured by [\textsuperscript{3}H]TdR incorporation, the shorter hPGP analog was much less effective (12% inhibition versus 34% for h84–100C-C).

Molecular modeling of hPGP suggested a high probability of a salt bridge forming between the aspartic acid (D) in position 5 and the lysine (K) in position 7. The formation of a salt bridge between the functional groups of these two amino acids could alter the conformation of the peptide and thereby interfere with the binding of the peptide to its ligand. A conservative substitution was introduced in analog hPGP, replacing the aspartic acid (D) in position 5 with asparagine (N), removing a reactive functional group and thus eliminating the possibility of salt bridge formation. This new peptide, hPGP(N) (Fig. 1), was synthesized and tested for activity in an MLR assay. As shown in Fig. 2, the hPGP(N) analog was more inhibitory than hPGP (28 versus 12% inhibition, respectively). This result supported the hypothesis that salt bridge formation had led to reduced inhibitory activity of the hPGP analog. Although hPGP(N) is not as inhibitory as h84–100C-C, it has the practical advantage of being seven amino acids shorter, in addition to potentially reducing its immunogenicity and increasing its stability.

Alanine Substitution Analogs—A series of alanine (A) substitution analogs were synthesized based on the sequence of hPGP(N) to determine which amino acids in this peptide were most important for its inhibitory activity. These peptides designated hPGP(N)A2-A9 (Fig. 1, Table I) were tested for activity in MLR assays. The results (Fig. 3, Table I) indicated that alanine substitutions in positions 2, 5, and 9 had greatly decreased activity from that of hPGP(N) (7, 9, and 3%, inhibition, respectively). Substitutions of alanine for amino acids in positions 4 (hPGP(N)A4, Fig. 1) and 6 (hPGP(N)A6,
Fig. 1) exhibited increased inhibitory effects over that of hPGP(N) (52 and 49% inhibition, respectively). These increased inhibitory activities were observed at concentrations as low as 1 μM for both substitution peptides; as shown in Fig. 4, the concentration dependence for the hPGP(N)A4 analog was evident.

To determine that the inhibitory effects of the analogs were not due to generalized cytotoxicity, two human cell lines, J52 and Daudi, were grown for 24 or 48 h either in the presence or absence of the hPGP(N)A4 analog. The cells were allowed to incorporate [1H]TdR during the last 6 h of incubation and uptake of [1H]TdR was compared to that of untreated cell cultures (Fig. 5). Cell proliferation at either time point was not inhibited by the peptide.

Specificity of Analog Effect on CD4+ T Cells—Both CD8+ and CD4+ cells are capable of proliferating in a MLR assay. In order to establish that the hPGP(N)A4 analog was specifically inhibiting proliferation of CD4+ T cells, the sample of peripheral blood lymphocytes was depleted of CD8+ and CD4+ T cells by mAb and panning procedures, as described under “Experimental Procedures,” determined to be >80% CD4+ by flow cytometric analysis (data not shown), and cultured in a MLR assay. The cells were incubated in the presence or absence of the hPGP(N)A4 analog and radiolabeled on days 6–8 of culture. As shown in Fig. 6, hPGP(N)A4 inhibited CD4+ T cell proliferation by 50, 37, and 18%, respectively, during these days of culture.

DISCUSSION

The structure-function relationship study of the human CD4-CDR3 region has led us to the design of the hPGP(N) peptide analog, which exhibited inhibition of CD4+ T cell proliferation in MLR. Alanine substitutions of the specific amino acids valine (position 3), lysine (position 7), and glutamic acid (position 8) yielded a series of peptide analogs whose inhibitory effects in the MLR assay were similar to that of hPGP(N), suggesting that these specific residues were not required for peptide function. Conversely, alanine substitutions of the specific amino acids glutamic acid (position 2), asparagine (position 5), and glutamic acid (position 9) yielded a series of peptide analogs with greatly diminished inhibitory effect in the MLR assay as compared to that of hPGP(N), suggesting that these residues were critical for peptide function. Molecular modeling of the surface of the CDR3-like region of the native CD4 protein indicated that the functional groups of amino acid residues glutamic acid (position 82), aspartic acid (position 85), and glutamic acid (position 92) form a contiguous surface on the protein molecule (Fig. 7). Alanine substitutions of the corresponding residues in the hPGP(N) analog diminished the peptide function. These results strongly suggest a direct structure-function relationship between this surface of the CDR3-like region of the CD4 molecule and its involvement in T cell function.

Alanine substitutions of glutamic acid (position 4) and glutamine (position 6) yielded peptide analogs whose inhibitory effects in MLR were greater than that of hPGP(N). These effects were exhibited in a concentration dependent manner and indicated that these amino acid residues are not involved in the activity of the peptide. However, one or the other of these amino acids is absolutely necessary to retain the increased inhibitory activity of hPGP(N)A4 and hPGP(N)A6, as a peptide analog (hPGP(N)A4,6) with alanine substitutions in both positions 4 and 6 abolished the inhibitory effect (data not shown). Molecular modeling of hPGP(N), hPGP(N)A4, and hPGP(N)A6 suggested that the side chains of the glutamic acid and glutamine might be interacting with the backbone of the peptide molecule, thereby limiting the peptide’s interaction with its ligand. Substitution of one, but not both of these residues, could eliminate this hindrance while maintaining the conformational requirements for inhibitory activity. Thus, the enhancement of activity seen with either the hPGP(N)A4 or hPGP(N)A6 analogs seems to involve stabilizing a more efficient conformational state of the hPGP(N) analog.

Although the mechanism of action of these peptide analogs is still not known, one possibility could be the induction of apoptosis. Exclusion of the CD4 molecule from the activation complex formed upon T cell recognition of class II-presented antigen results in the induction of apoptosis of the T cell (32). The CD4 molecule has been found to co-precipitate with at least two cell surface proteins that are involved in T cell activation, i.e. the TCR-CD3 complex (8, 33, 34) and CD45 (12, 35). Interference with these interactions by small peptides mimicking the CDR3-like region of the CD4 molecule may disrupt proper activation signals. It has been postulated that the CD4-D1 domain docks to the membrane-proximal second domain of the β subunit (β2) of MHC class II (26). Moreover, there is also evidence suggesting the formation of a stable class II binding site requires the dimerization of CD4 (36). The peptide analogs may function by binding to one or both of the CD4 molecules and interfering with the dimerization process.

We have shown that a series of peptide analogs designed to mimic part of the active surface of the CDR3-like region of the human CD4 molecule can exhibit biological activity. This study demonstrates that peptide analogs can be used for identifying biologically active substructures as well as biological probes for characterizing receptor-ligand interactions.

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