Bioactive Peptide Design Based on Protein Surface Epitopes
A CYCLIC HEPTEPEPTIDE MIMICS CD4 DOMAIN 1 CC’ LOOP AND INHIBITS CD4 BIOLOGICAL FUNCTION*  

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The interaction between CD4 and major histocompatibility complex class II proteins provides a critical co-receptor function for the activation of CD4+ T cells implicated in the pathogenesis of a number of autoimmune diseases and transplant rejection responses. A small synthetic cyclic heptapeptide was designed and shown by high resolution NMR spectroscopy to closely mimic the CD4 domain 1 CC’ surface loop. This peptide effectively blocked stable CD4-major histocompatibility complex class II interaction, possessed significant immunosuppressive activity in vitro and in vivo, and strongly resisited proteolytic degradation. These results demonstrate the therapeutic potential of this peptide as a novel immunosuppressive agent and suggest a general strategy of drug design by using small conformationally constrained peptide mimics of protein surface epitopes to inhibit protein interactions and biological functions.

Protein-protein interactions play an important role in a wide range of physiological and pathological processes. The interactions between proteins generally involve large interfaces with many intermolecular contacts (1). As such, the rational design of small molecular inhibitors of these surfaces has long been considered a formidable challenge. Despite this commonly held view, recent studies indicate that proteins may actually interact through small surface binding epitopes, as in the human growth hormone-receptor complex (2) and the erythropoietin-receptor complex (3). These findings raise an intriguing possibility that mimics of such small binding epitopes may be sufficient for blockade of a large protein-protein interface. However, the general applicability of this hypothesis and its implications for rational drug design remain to be tested and demonstrated in different biological systems. Undoubtedly, the development of a general approach to inhibit protein-protein interactions will have a tremendous impact on understanding the structural basis of these interactions and in developing new therapeutic strategies for many human diseases.

CD4 is a glycoprotein consisting of four Ig-like extracellular domains (D1–D4) and is expressed on the surface of helper T cells (4). Major histocompatibility complex (MHC) class II is a heterodimeric glycoprotein expressed on the surface of antigen-presenting cells and binds antigenic peptides for recognition by the T cell receptor. The interaction between CD4 and non-polymorphic regions of the MHC class II molecule is critical for optimal CD4+ T cell activation, with CD4 serving as a co-receptor for T cell receptor-antigen engagement (5). Numerous mutation studies have been performed to determine the regions of CD4 involved in MHC class II binding, and like many protein-protein complexes, the interface is generally believed to involve a large surface area of both D1 and D2, with many contact sites (6–9).

CD4+ T cells participate in the pathogenesis of a number of immune-based human conditions, including autoimmune diseases, allogenic organ transplant rejection, and graft versus host disease (GVHD) following allogenic bone marrow transplantation. Small molecular inhibitors of the CD4-MHC class II interaction could potentially block the undesirable activation of CD4+ T cells and could thus serve as effective immunosuppressive agents.

EXPERIMENTAL PROCEDURES

Peptide Synthesis—As described previously (10), the peptides were prepared by solid-phase synthesis using Fmoc strategy on a Model 430A peptide synthesizer (Applied Biosystems, Inc., Foster City, CA) and a Model 9060 Pepsysynthesizer Plus (Perceptive Biosystems, Cambridge, MA). A 4-fold excess of N-Fmoc-amino acid, 2-(1H-benzoazol-1-yl)-1,1,3,3-tetramethylyuronium hexafluorophosphate, and 1-hydroxybenzotriazole and a 10-fold excess of diisopropylethylamine were used in every coupling reaction step. Removal of the N-terminal Fmoc group was accomplished by 20% piperidine in dimethylformamide. The cleavage of a peptide from the resin was carried out with reagent K (11) for 2 h at room temperature with gentle stirring. The crude peptide was then precipitated in ice-cold methyl-t-butyl ether, centrifuged, and lyophilized. The cyclization of disulfide cyclic peptides was achieved by using a modified procedure of Misicka et al. (12). The crude peptide was then purified by preparative reverse-phase HPLC using a Dynamax®-300A C18 column (25 cm × 21.4 mm, inner diameter) with a flow rate of 9 ml/min and two solvent systems of 0.1% trifluoroacetic acid/H2O and 0.1% trifluoroacetic acid/acetonitrile. The fractions containing the peptide were pooled together and lyophilized. The purity of the final products was assessed by analytical reverse-phase HPLC, capillary electrophoresis, and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry.

NMR Structure Determination—All NMR experiments were performed on a Bruker AMX 600 spectrometer equipped with a 5-mm broad-band inverse probe or a 5-mm triple resonance 1H,13C,N z-gradient probe, at a proton frequency of 600.13 MHz, using the XWIN-NMR Version 1.0 software package run on a Silicon Graphics INDY workstation. The NMR sample of peptide IV (final concentration ~ 5 mM) was prepared by dissolving the lyophilized powder in 0.4 ml of 9H,13C,N z-gradient probe, at a proton frequency of 600.13 MHz, using the XWIN-NMR Version 1.0 software package run on a Silicon Graphics INDY workstation. The NMR sample of peptide IV (final concentration ~ 5 mM) was prepared by dissolving the lyophilized powder in 0.4 ml of
NOE contacts, NH-aaH coupling constants (J_{\text{aaH}}), and NH temperature coefficients (\Delta d_{\text{aaH}}/\Delta T) of the cyclic heptapeptide IV in MeSO-d_6.

TABLE I

|          | Cys1 | Asn2 | Ser3 | Asn4 | Gln5 | Ile6 | Cys7 |
|----------|------|------|------|------|------|------|------|
| d_{\text{fe}} (i, i+1) |      |      |      |      |      |      |      |
| d_{\text{fo}} (i, i+1) |      |      |      |      |      |      |      |
| d_{\text{io}} (i, i+1) |      |      |      |      |      |      |      |
| d_{\text{no}} (i, i+1) |      |      |      |      |      |      |      |
| d_{\text{on}} (i, i+1) |      |      |      |      |      |      |      |
| d_{\text{nn}} (i, i+1) |      |      |      |      |      |      |      |
| d_{\text{nn}} (i, i+2) |      |      |      |      |      |      |      |
| d_{\text{nn}} (i, i+3) |      |      |      |      |      |      |      |
| J_{\text{aaH}}  | 8.2  | 4.2  | 7.8  | 7.4  | 8.0  | 8.6  |      |
| \Delta d_{\text{aaH}}/\Delta T (ppm/K) | 3.9  | 6.9  | 2.7  | -2.8 | 6.9  | 5.2  |      |

MeSO-d_6 (Wilmad). Spectra were acquired locked and at 305 K, unless otherwise specified. Intraresidue connectivities and spin systems were deduced by means of double quantum filtered COSY and total correlation spectroscopy (\tau_m = 55 and 110 ms) (13) experiments. Gradient-assisted 13C-1H heteronuclear single quantum correlation spectroscopy (coherence pathway rejection) (14) was employed to verify the proton resonance assignments obtained as described above. All two-dimensional experiments were acquired phase-sensitive via time proportional phase increments (15) and processed with shifted (45–90°) sine-bell functions, followed by automatic base-line correction in both dimensions. NOE intensities classified as strong, medium, and weak were obtained from a NOE correlation spectroscopy experiment with a \tau_z of 200 ms; the NOE build-up was found to be linear up to this value, translating into minimal spin diffusion for mixing times up to \sim 200 ms.

\textsuperscript{1}H chemical shifts reported here are referenced to the residual MeSO signal (\delta = 2.525 ppm at 305 K). The observation of a single set of resonances in the \textsuperscript{1}H and \textsuperscript{13}C-\textsuperscript{1}H spectra is consistent with the presence of one major form of the peptide and the absence of impurities as well as multiple conformations in slow exchange with each other on the NMR time scale. The absence of such exchange is also corroborated by rotating frame nuclear Overhauser effect spectroscopy experiments (data not shown).

NMR-based structure determination of peptide IV was carried out within the QUANTA\textsuperscript{\textregistered} Version 4.1 molecular modeling program (Molecular Simulations Inc.) using the XPLOR Version 3.1 package and the CHARMM (Version 23.0) force field in tandem with the NMRCompass\textsuperscript{\textregistered} Version 2.5 package used for the complete analysis and bookkeeping of NOE correlation spectroscopy data. A set of 61 NOE-based distance restraints (29 intraresidues, 25 sequential, and 7 long-range) involving the amide, \alpha- and \beta-protons within the molecule was used in the conformational search according to the following protocol. First, a set of 75 initial structures was generated from a covalent template of the cyclic peptide by a round of distance geometry, followed by simulated annealing (10-ps time steps at 1000 K, with subsequent 2-ps cooling to a final temperature of 300 K) and finally 5 ps of refinement dynamics (0.001-ps steps, 100 K final temperature). After this stage of the protocol, it was apparent that the \phi angle for Ser-3 in a majority of the structures generated fell in the vicinity of one of the allowed solutions based on the spin-spin coupling data (\textit{i.e.} \sim 60°). Hence, this angle was restrained initially to the range \sim 80 to 40° and subsequently to \sim 60 ± 20°. Using this augmented set of restraints, two rounds of refinement dynamics (10 ps) followed by Powell energy minimization (500 steps) were conducted. In the fourth and final stage of structure calculations, the distance between the carbonyl oxygen of Asn-2 and the amide hydrogen of Gln-5 was constrained to the range 1.9–2.5 Å, consistent with a \beta-turn in the region of the sequence encompassing these residues, and in accordance with the spin-spin coupling and amide temperature coefficient data (see Table I). Using this final set of restraints, another 10 ps of refinement dynamics plus 5000 energy minimization steps were performed. Of the 75 structures refined in this fashion, the best 10, which satisfied all dihedral angle restraints (\pm an additional 10°) and exhibited no upper bound distance violations in excess of 0.3 Å, were selected.

Cell Adhesion Assay—Following a modified procedure of Moebius et al. (16), 5 × 10\textsuperscript{5} COS-7 cells/well of a six-well plate were transfected with 2 \mu g of T4-cDNA3 (Invitrogen) and 6 \mu g of DOSPER (Boehringer Mannheim) according to the supplier’s protocol for the DOSPER liposomal transfection reagent. Normally 30–60% of transfected COS-7 cells express human CD4 as determined by immunofluorescence. MHC class II-expressing Raji Burkitt’s lymphoma cells (10\textsuperscript{5}) were added to CD4-transfected COS-7 cells (48 h post-transfection) for 1 h at 37 °C (in 1 ml of RPMI 1640 medium containing 10% fetal calf serum and 200 mm glutamine) in the presence of peptides at appropriate concentrations. The inhibition of rosette formation by peptides was determined by the
number of rosettes obtained in the presence of the peptides relative to the number of rosettes in the positive control. COS-7 cells transfected with pcDNA3 vector alone served as negative controls, which showed no rosette formation. Other studies have demonstrated that the enumeration of rosetting as performed here correlates well with quantitative cell binding assays employing radiolabeled Raji cells (16).

**Mixed-lymphocyte Reaction (MLR) Assay**—As described previously (17), MLR assays were established by co-culturing 1 × 10^5 responder peripheral blood lymphocytes with 2 × 10^5 irradiated (30 Gy) stimulator peripheral blood lymphocytes in quadruplicate wells of a 96-well microtiter plate. Peptide analogs were added at a final concentration of 100 μM immediately after the cells were plated. For measuring proliferation, 1 μCi of [3H]dThd was added to the wells for the final 6 h of day 6. Cells were harvested onto glass-fiber filters and counted in a Model 1205 Beta-Plate reader (Wallac, Gaithersburg, MD). The mean thymidine incorporation was calculated, and results are expressed as mean percent inhibition by peptide analogs relative to control (untreated) T cell proliferation.

**RESULTS AND DISCUSSION**

To search for potential CD4 functional epitopes that could be targeted for the design of new inhibitors, a computer analysis was conducted for CD4 D1 in conjunction with synthetic peptide mapping using a procedure published previously (10). This led to the identification of a surface pocket potentially involved in the CD4-MHC class II interaction (Fig. 1) (18). This CD4 surface pocket is formed by the FG loop (also known as the...
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A series of linear peptides based upon the CC' loop region were synthesized to test whether this site was involved in CD4-MHC class II interaction (6) and recent studies with peptide mimics have confirmed their involvement (17, 19, 20), our analysis suggested that the highly protruded CC' loop may also serve as a surface epitope critical for CD4 function.

A series of linear peptides based upon the CC' loop region were synthesized to test whether this site was involved in CD4-MHC class II interaction. Peptide I (KNSNQIK) was derived from the entire CC' loop (amino acids 29–35) of human CD4 D1. Peptides II (KNSNQ) and III (SNQIK) were truncated analogs of peptide I corresponding to the C and N termini, respectively. In assays for T cell proliferation as measured by MLRs, peptide I exhibited an inhibitory effect of 21% at 100 μM, and the N- and C-terminal truncated analogs II and III exhibited reduced activities of 11% and 15%, respectively, at the same concentration. This finding indicates that the bioactive region of the CD4 D1 CC' loop lies on the sequence of NSNQ, which adopts a type I β-turn, as observed in the crystal structure of CD4 D1 and D2 (9). These results led to the design of the cyclic peptide IV (cyclo(CNSNQIC)), incorporating a disulfide bridge to enhance the structural stability of the β-turn around NSNQ. Molecular modeling studies predicted that the cyclic heptapeptide IV closely mimics the conformational feature of the β-turn of the native CC' loop (data not shown).

To confirm our design principle, the structure of the cyclic peptide IV was determined by high resolution two-dimensional NMR spectroscopy. Table I summarizes the data from NMR experiments. Several lines of evidence are consistent with the existence of a type I β-turn spanning NSNQ and closely resembling the native CC' loop. (i) There are a number of weak NOE contacts between Asn-2 and Gln-5 (the residue numbering follows the sequence of the peptide) as well as between Ser-3 and Gln-5. (ii) There is a strong dNN interaction between Asn-4 and Gln-5. (iii) The coupling constant data conform closest to those expected for a type I β-turn (i.e. JHNH-N values of 9 and 4 Hz are expected for the i+1 and i+2 turn residues, respectively (21)). (iv) The low amide temperature coefficients for Gln-5 and, to a lesser extent, Asn-4 are highly diagnostic of their participation in intramolecular hydrogen bonding, whereas the remaining amides are largely solvent-exposed. This finding is consistent with the expected hydrogen bond between the carboxyl of residue i and the NH of residue i+3 in the β-turn (22).

Structure determination based on the obtained NMR data was carried out for the cyclic peptide IV. Ten structures of the peptide that best fit the NOE and dihedral angle data were selected from the extensive conformational search (Fig. 2). The conformational search of the peptide was performed without restricting its structure to a specific type of turn (i.e. type I) a priori. As shown in Fig. 2, the cyclic peptide IV adopted well defined conformation around the sequence NSNQ, which approximately resembled the type I β-turn structure of the CC' loop in the native CD4 protein. The ψ(i+1) and ϕ(i+2) angles deviate from idealness and push the backbone amide of Asn-4 in toward the carboxyl of Asn-2. This results in an appreciably shorter interatomic distance than that observed for the i+i+3 putative hydrogen bond (≈2.1 versus 2.5 Å) in these structures. As such, the structure of the peptide deviated slightly from the ideal type I β-turn; nevertheless, the overall backbone and side donor bone marrow cells alone or in combination with 3 × 10^6 CD4⁺ T cells. Peptide (0.5 mg in 0.2 ml of buffered saline solution) was administered intravenously on days 0, 3, and 6. Statistical significance was determined by Wilcoxin rank analysis. ATBM, anti-T cell antibody-treated bone marrow cells.
chain topologies of the functionally important region of the peptide closely mimic those of the native CD4 CC’ loop. In contrast to the bioactive region, the disulfide bridge region was somewhat ill defined, probably due to the low number of observed NOE restraints in this region.

If the CC’ loop of CD4 D1 is a critical epitope for MHC class II binding, as predicted by theoretical analysis, the structural mimicry of the native CD4 D1 CC’ loop region by peptide IV suggests that the peptide might block CD4-MHC class II interaction. CD4-MHC class II binding studies, using a cell rosetting assay (5, 16), were performed to test this hypothesis. Peptide IV inhibited rosette formation by as much as 50% in a concentration-dependent manner (Fig. 3A). The linear peptide I exhibited flexible conformations as suggested by modeling studies and consequently displayed decreased potency in comparison with the constrained cyclic peptide IV. This result strongly suggests that the stable β-turn conformation mimicking the native protein surface region is important for inhibitory activity of the peptide. The inhibitory effect of peptide IV was sequence-specific, as demonstrated by the lack of activity of a scrambled peptide (peptide IV-scr; identical amino acid composition, but a fixed randomized sequence). The selective effect of peptide IV on CD4-MHC class II interaction was also indicated by its inability to inhibit cell rosetting mediated by CD8-MHC class I interaction (data not shown). These results strongly support the notion that the CC’ loop of CD4 D1 is a critical functional epitope for MHC class II binding and that small peptide mimics such as peptide IV are sufficient to block this interaction.

The ability of peptide IV to inhibit CD4-MHC class II interaction suggested that it could interrupt the activation of CD4+ T cells. In this regard, the peptide was tested in MLRs and found to inhibit proliferation by at least 40% of the control response at 100 μM (Fig. 3B). In addition, peptide IV exhibited significantly higher activity than the other linear peptides derived from the same region, again supporting the conformational dependence of the peptide inhibition.

Since a major limitation of peptide-based therapeutics is their susceptibility to proteolytic degradation, the synthetic CD4 peptides were tested for their proteolytic stability by incubation in 90% human serum. The linear peptide I was highly susceptible to serum proteases and was completely degraded after 24 h, whereas peptide IV exhibited significant proteolytic resistance, with nearly 75% of the peptide remaining intact after 72 h. This resistance is likely due to the small size and cyclic nature of peptide IV, so the molecule is constrained into conformations that are not favorable for proteolytic recognition.

The in vivo immunosuppressive activity of peptide IV was tested in three different CD4+ T cell-dependent murine models: EAE, skin allograft rejection across a MHC class II antigen difference, and GVHD across a haplomismatch MHC difference. Following induction of EAE in SJL mice, the maximum mean disease severity level reached by the untreated control group was 1.8 (Fig. 4A), whereas mice treated with a single dose of peptide IV on day 12 (0.5 mg intravenously) attained a significantly lower maximum of 0.4 (p < 0.01 on days 18–22). In the skin allograft model, a single dose of peptide IV (0.5 mg; intravenous) 3 h before transplantation significantly (p < 0.04), not significantly different from those transplanted with only anti-T cell antibody-treated bone marrow cells (p > 0.60). The effectiveness of the peptide in these different animal models for autoimmune disease and transplantation reactions demonstrated the in vivo immunosuppressive activity of this small constrained peptide and its potential as a novel therapeutic agent.

Current immunotherapeutic strategies include the use of monoclonal antibodies, such as monoclonal anti-CD4 antibody, to block T cell activation (23). However, these broad-based monoclonal antibody approaches can result in pan-T cell depletion, and in addition, their value as an effective treatment have been reduced by their inherent immunogenicity. In comparison, small peptide-based therapeutics are less immunogenic and can therefore be used over longer periods of time. In regard to pan-T cell depletion, spleen and lymph nodes from mice treated 48 h earlier with peptide IV have normal cellularity and T and B cell subset composition (data not shown). The combined results of the above studies clearly indicate the potential of synthetic chemically modified peptides as an alternative therapeutic approach.

The present study of small peptide mimics of the CD4 surface may suggest a starting point for developing a general approach to inhibit other Ig-related protein structures and interactions. As members of the Ig superfamily have a conserved backbone-folding pattern, it is likely that this generic structure provides some common scaffolds for efficient protein-protein interactions. For example, a surface pocket consisting of the FG and CC’ loops, analogous to that seen here in CD4, is found in the following: CD8, which mediates dimerization (24); the IgE high affinity receptor, which binds IgE (25); CD2, which binds LFA-3 (26); and CD28, which binds CD80/86 (27).

In summary, we have proposed that the CC’ loop is an important functional epitope on the CD4 surface for intermolecular binding and found that small peptide mimics of this epitope are sufficient to interrupt a larger protein-protein interface. In particular, a synthetic cyclic heptapeptide (peptide IV) has been shown to closely mimic the CC’ surface epitope, to effectively block CD4-MHC class II-dependent cell rosetting, to possess significant immunosuppressive activity in vitro and in vivo, and to strongly resist proteolytic degradation. These findings have demonstrated a general approach of bioactive peptide design by the functional mimicry of protein surface epitopes to generate potential novel therapeutic agents.

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