T Cell Antigen Receptor Peptide-Lipid Membrane Interactions Using Surface Plasmon Resonance*

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This study examines the binding properties of a new class of immunomodulating peptides derived from the transmembrane region of the T cell antigen receptor, on model membranes using surface plasmon resonance. The di-basic “core” peptide was found to bind to both zwitterionic and anionic model membranes as well as to a T cell membrane preparation. By contrast, switching one or both of the basic residues to acidic residues led to a complete loss of binding to model membranes. In addition, the position of the charged amino acids in the sequence, the number of hydrophobic amino acids between the charged residues, and substitution of one or both basic to neutral amino acids were found to effect binding. These results when compared with in vitro T cell stimulation assays and in vivo adjuvant-induced arthritis models, showed very close correlation and confirmed the findings that amino acid charge and location may have a role in peptide activity. These initial biological peptide-membrane interactions are critically important and correlate well with the subsequent cellular expression and biological effect of these hydrophobic peptides. Targeting and understanding the biological interactions between peptides and membranes at their site of action is paramount to the description of cell function and drug design.

T cells constitute an important component of our immune system and are concerned with immune surveillance and antigen recognition. Whereas this is normally a beneficial, protective effect, recognition of “self-antigens” under altered pathological states leads to autoimmune disease with deleterious consequences. The T cell antigen receptor (TCR)1 is a cell surface multisubunit protein complex present only on T cells and involved with antigen recognition and subsequent T cell activation. The TCR consists of two clonotypic chains (TCR-α and -β) that are noncovalently linked to CD3-ε, -γ, -δ, and -ζη invariant proteins. Two important structural features common to these chains is the presence of a single transmembrane spanning domain and the presence of charged amino acid(s) within their predicted transmembrane region. The invariant chains have a single negative charge and TCR-α and -β have two and one positive charges, respectively. These charged amino acids influence the intracellular fate of these proteins and are critical for TCR assembly (1, 2). Following TCR cell surface expression a key event in initiating antigen-induced signal transduction is the formation of higher order oligomerization complexes between TCR, co-receptors, and accessory molecules at the cell membrane. This protein-protein-lipid interface allows a number of biochemical events to proceed rapidly commencing with tyrosine or serine/threonine phosphorylation of the TCR chains (3) that subsequently translates into T cell activation and cytokine production. The ability to inhibit pathogenic T cells by blocking the TCR by hydrophobic transmembrane-derived peptides has been the focus of our research for a number of years (4–8).

We have previously identified and subsequently shown in vitro that a nonapeptide derived from the TCR-α transmembrane region was able to inhibit IL-2 production in T cells following antigen recognition (9). This hydrophobic transmembrane peptide (core peptide, CP) contains two positively charged amino acids that are critical for receptor assembly. When examining pairwise interactions we noted that these transmembrane charges have an important role in TCR-α/CD3-δ and TCR-α/CD3-ε interactions, which constitute important partial subunit complexes, leading to the formation of a complete TCR (10). Extending these studies, in vivo CP given subcutaneously or intraperitoneally significantly reduced the induction of T cell-mediated inflammation in animal models with adjuvant-induced arthritis, allergic encephalomyelitis, and delayed type contact hypersensitivity (4, 5). More recently we have shown that CP and its lipid conjugates have a comparable effect to cyclosporine in reducing inflammation in the adjuvant-induced rat arthritis model.2 Gollner et al. (11) have used CP in humans and in their few cases examined noted that it was effective in the treatment of autoimmune skin conditions. More recently Mahnke et al. (12) have genetically engineered dendritic cells to secrete the peptide and reduce inflammation in a T cell-dependent animal disease model, experimental allergic encephalomyelitis. Interestingly, the therapeutic effect was antigen specific.

Antigen recognition by TCR induces receptor aggregation and recruitment of accessory molecules CD2, CD4, and CD8 leading to phosphorylation of CD3 subunits and subsequent T cell activation (3). We hypothesize that CP associates with the TCR at the transmembrane level and that during T cell activation colocalizes with the TCR within lipid rafts blocking the oligomerization of co-accessory and co-stimulatory molecules required for T cell activation. Experimental support for this view is provided from studies by Wang et al. (6, 7) using confocal microscopy and T cell activation studies with cross-

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§ The abbreviations used are: TCR, T cell antigen receptor; CP, core peptide; DMPC, dimyristoyl phosphatidylcholine; DMPG, dimyristoyl phosphatidylglycerol; SPR, surface plasmon resonance; HBS, HEPES-buffered saline; IL-2, interleukin-2; RU, response units.

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linking antibodies to the CD3 complex or with phorbol 12-myristate 13-acetate or ionomycin.

To understand the mechanism of action, $^{31}\text{P}$ and $^3\text{H}$ solid-state NMR spectroscopy and CD were used to study the effect of CP on model membranes. Ali et al. (8) reported that the structure of model membranes was not significantly perturbed by CP and only at higher lipid/peptide ratios were significant effects observed. The present investigation expands on previous studies and describes the interaction of CP and its analogues with immobilized model membranes using surface plasmon resonance technology. The biophysical findings are then correlated with the biological effects of these peptides on T cell IL-2 production reflecting T cell activation.

**EXPERIMENTAL PROCEDURES**

Materials—Dimyristoyl-t-a-phosphatidylcholine (DMPC), dimyristoyl-t-a-phosphatidyl-i-glycerol (DMPG), and N-actetyl-t-p-glucopyranoside were purchased from Sigma. Anti-mouse CD3 polyclonal antibody (M20) was from Santa Cruz (Santa Cruz, CA) and anti-goat IgG H&L chain-specific (rabbit) peroxidase conjugate was purchased from Calbiochem (Sydney, Australia). Pioneer Chips L1 were purchased from Biacore (Uppsala, Sweden). A2B4 antibody was affinity purified from hybridoma supernatant using the protein A column. This antibody has specificity against 2B4 TCR-a chain (13).

Peptides—Peptides were either purchased from Auspep (Melbourne, Australia) or synthesized in our laboratories (Table I). Syntheses were by the manual solid-phase method using the Fmoc (N-(9-fluorenyl)methoxy carbonyl) chemistry. Peptides were shown to be of high purity by high performance liquid chromatography and by electrospray mass spectrometry. They were dissolved in dimethyl sulfoxide as 20 and 10 mM stock solutions and diluted with the HEPES-buffered saline (HBS-N) running buffer prior to the surface plasmon resonance (SPR) studies or with culture media for the bioassays to give final concentrations of 10–100 nM as required.

Preparation of Small Unilamellar Vesicles—Model membranes composed of zwitterionic and anionic phospholipids and their mixtures in proportion similar to that found in vertebrate cell membranes were produced. Briefly, DMPC and DMPG were dissolved in dry chloroform and chloroform/methanol (2:1), respectively, to give 10 mg/ml solutions. These were evaporated under reduced pressure and the resulting lipid films dried overnight in vacuo. Lipids were hydrated by resuspending in HEPES buffer for 60 min at 34 °C to give 0.5 mM concentration in respect of phospholipids. The solution was sonicated in an ultrasonic bath for 20 min. Eight cycles of freeze/thawing was followed by extrusion through polycarbonate filters, first 100 mM (21 times), then 50-nm pore diameters (21 times), using a Lipofast apparatus (Avestin, Ottawa, Canada). Small unilamellar vesicles were used immediately.

T Cell Membrane Preparation—The method of May et al. (14) was used. Briefly 8 × 10$^7$ 2B4.11 cells were washed and resuspended in cationic peptide injection the dissociation stage was 1200 s. Regeneration of the sensor chip was achieved with 40 mM octyl glycoside (30 l/min) followed by running buffer (100 μl, 10 μl/min) (15). Liposomes (small unilamellar vesicles) were injected (100 μl, 5 μl/min) giving a response of ~8000 RU. 10 mM NaOH (40 μl, 10 μl/min) removed any multilamellars vesicles from the surface that was followed by 10 mM glycine, pH 2.2 (10 μl, 10 μl/min) before injecting the peptide of interest (100 μl, 5 μl/min). After peptide injection the dissociation stage was 1200 s. Regeneration of the sensor chip was achieved with 40 mM octyl glycoside (30 μl, 10 μl/min). All SPR experiments were run at 25 °C and all analyses were performed using BIACore evaluation software (Biacore). Binding of CP on T cell membrane preparation was carried out as above except that the volume of membrane preparation injected was 70 μl giving a response of ~1150 RU. After a buffer wash the peptide solution was applied to the chip (100 μl, 2 μl/min). Dissociation was 1200 s. Peptide binding was expressed as the difference in signal between points before sample injection and after dissociation.

For the comparative binding of peptide analogues determination of percentage binding was expressed as a percentage of CP binding. The values are representative of three injections under identical conditions for each peptide.

To study the effect of interaction time on CP binding the “variable contact times” injection command was utilized on the Biacore 2000 instrument. This was achieved by switching additional flow cells into contact times” injection command was utilized on the Biacore 2000 instrument. This was achieved by switching additional flow cells into the flow path as the injection proceeds; thus the injections end at the same time.

**Antigen Activation Assay**—This is an established assay (4) used to assess T cell activation by measuring IL-2 produced in response to antigen. Briefly, 2B4.11 hybridoma (5 × 10$^4$ cells) and LK35.2 (5 × 10$^4$ cells) were incubated with pigeon cytochrome c (50 μM) in 96-well microtiter plates for 24 h in the presence and absence of peptides (25 μM). An aliquot of each supernatant (100 μl) was removed and serial 2-fold dilutions were prepared using RPMI medium. Diluted supernatant was then incubated with CTL cells (2 × 10$^4$) for 18 h in microtiter plates. [H]Thymidine (0.5 μCi) was then added for 6 h and the CTL cells collected on glass fiber filter paper using a cell harvester (TiterTek™, Packard Bioscience). [H]Thymidine uptake was measured by scintillation counting (Packard Bioscience) and compared with standard curves to determine the amount of IL-2 produced.

**RESULTS**

**Binding of CP**—Membrane binding behavior of CP with immobilized DMPC, DMPG, and a mixture of DMPG:DMPC (70:30) is shown in Fig. 1. CP showed association to, and dissociation from, both zwitterionic and anionic liposomes. The sensorsgrams reveal that CP, like several other cationic hydrophobic peptide sequences reported (15–18) binds to liposomes with a rapid initial association. The dissociation was slower and the signal did not return to baseline even after extensive washing with buffer, indicating that some of the peptide bound irreversibly to both membranes. The binding to the anionic DMPG, however, was twice as high (2480 RU) as that of the zwitterionic DMPC (1460 RU). This sensorsgram also shows the binding of CP to membranes in which the ratio of zwitterionic to anionic lipids is 70:30.
Effect of Variable Contact Times on CP Binding—Interaction time of the peptide with the model membranes may effect the level of bound peptide and indicate a step in the mechanism of binding, where the initially bound CP may undergo a change in conformation.

Fig. 2, a and b, shows the effect of variable contact times of CP with DMPC and DMPG liposomes. Diminished binding was revealed with reduced contact times with both zwitterionic and anionic liposomes. CP binding to DMPC membranes was 437, 406, 242, and 221 RU for 1200-, 960-, 720-, and 480-s interaction times, respectively. CP binding to the DMPG membrane was 1135, 1020, 600, and 600 RU for 1200-, 960-, 720-, and 480-s interaction times. It appears that reducing the contact time by 50% resulted in a 45% decrease in the binding of CP.

Peptide Analogue Binding—To examine the biophysical requisites for peptide binding, a number of CP analogues varying in length, electrostatic charge, and hydrophobicity were examined (Table I). Peptide E, in which the basic residues (Arg and Lys) are substituted with acidic ones (Asp and Glu), gave a “box-like” sensorgram when compared with CP (Fig. 3) representing a change in refractive index during peptide injection. The sensorgram returned to baseline indicating no binding of peptide E to the membrane. When the two basic amino acids (Arg and Lys) were substituted with the neutral amino acid glycine (Peptide C) there was no binding to the anionic liposomes. No binding was observed with peptide M, which contains a single charge of an aspartic acid residue, to either DMPC or DMPG model membranes. Peptides A, B, and M also contain only a single basic amino acid, arginine and lysine, respectively, but their position has been moved in the sequence. Interestingly, the sensorgrams of these peptides showed diminished binding to zwitterionic, and limited binding to anionic membranes. The shape of the sensorgram exhibited by these peptides, however, was similar to CP. Peptides A and B also contain only a single basic amino acid, arginine and lysine, respectively, but their position has been moved in the sequence. Interestingly, the sensorgrams of these peptides showed no binding either to zwitterionic or to anionic liposomes. No binding was observed with peptide M, which contains a single charge of an aspartic acid residue, to either DMPG or DMPC model membranes. Peptides A, B, and M exhibited a box-like shape similar to peptide E shown in Fig. 3, a and b. An additional isoleucine inserted in the sequence increasing the stretch of hydrophobic amino acids was tested in peptide F. Fig. 4 revealed that compared with CP the peptide binding was somewhat diminished.

When these peptides were tested for their ability to inhibit T cell activation there was a close correlation between binding and IL-2 inhibition (Fig. 5). When compared with CP peptide E did not inhibit IL-2 production, whereas, peptide C reduced IL-2 production much less compared with CP (28% versus 63% inhibition, respectively). In the biological assay there was no difference in IL-2 effect between peptides D and CP. The SPR
The behavior of these peptides correlated well with inhibition of T cell activation (IL-2 assays) carried out simultaneously (Fig. 5).

**Binding of Core Peptide to T Cell Membrane Preparation**—To correlate the findings noted using model membranes with real-time events on the T cell surface we prepared T cell surface membranes and examined CP binding using SPR. Cell membrane preparations of mouse T cell 2B4.11 hybridoma cells were purified and tested for the presence of TCR content by immunoprecipitation. Fig. 6 shows the presence of the CD3ε chain as co-precipitated by the TCR-α-speciﬁc AβB1 antibody. The ability to co-precipitate CD3ε with an antibody to TCR-α implies some degree of receptor integrity between the membrane and the TCR complex.

The binding of CP to the cell membrane preparation is shown in Fig. 7. The plasma membrane preparation was applied to the sensor chip followed by a solution of CP. The sensorgram showed a response typical for CP on model membranes.

**DISCUSSION**

SPR is a new and sensitive technique useful for studying the interaction of peptides with phospholipid model membranes. It has been used to demonstrate the mode of action of peptides such as melittin, its analogues, and magainin and to understand the mode of action of membrane-active peptides using anionic and zwitterionic lipids (15–17). The technique of SPR offers the ability to study structure/function relationships (19) while overcoming the need to use labeled peptides as well as cumbersome separation procedures. It allows real-time monitoring of peptide binding to, and dissociation from, these model membranes.

In the present study we examined binding of CP and its analogues to model membranes using SPR. We demonstrated that CP binds to both zwitterionic and anionic phospholipids with a 2-fold increase in irreversible binding to DMPG when compared with DMPC. This value is small in comparison with other cationic peptides such as magainin and melittin, which demonstrated a much higher irreversible binding to the anionic DMPG than to the zwitterionic DMPC liposomes leading to the conclusion that these peptides translocate to the cytosolic side of the plasma membrane (15, 17). Our conclusions inferred from these previous studies is that it is unlikely for CP to translocate across the T cell membrane and localize solely in the inner cytoplasmic leaflet. It is possible that the peptide translocates only into the inner membrane via an initial interaction with the charged lipid head groups (8). Mozsolits et al. (16) recently reported the membrane binding characteristics of a peptide corresponding to the C terminus of the angiotensin II receptor. They reported an ∼10-fold increase in irreversible binding to DMPG liposomes compared with zwitterionic DMPC. A peptide analogue where lysines were substituted with norleucines showed very little binding to either lipid, demonstrating that the charged amino acids were crucial to the interaction. Because the binding of this peptide to the anionic membrane was so much stronger, it was proposed that it associates with the cytoplasmic face of the cell membrane, supposedly rich in negatively charged phospholipids, to modulate local receptor attachment and function. In contrast, the irreversible binding of CP was only moderately stronger to DMPG than to DMPC, which largely excludes the interaction of the peptide with the inner leaflet of the T cell plasma membrane.

A percentage of the peptide, however, irreversibly bound to the membranes. Increasing the ionic strength of the buffer or washing with sodium hydroxide after the dissociation step did not succeed in removing the bound peptide from either the DMPC or DMPG membranes (data not shown). This lends support to the suggestion that there are hydrophobic interactions occurring at this stage of binding. Similar findings have been shown with other membrane active cationic peptides (17, 20).

Earlier studies (8) in our laboratories demonstrated that in the presence of DMPC membranes the CD spectrum of CP was similar to that revealed by an aqueous solution of the peptide, containing some α-helical and some random coil structures. CP exhibited a spectrum typical for a peptide with secondary structure of about 25% α-helix and 75% random coil in aqueous solution, whereas in trifluoroethanol the level of α-helical structure was 40%. It was suggested that when CP came in contact with the zwitterionic membrane the peptide may be associated with the “water surrounded” lipid head groups but not with the hydrophobic lipid acyl chains. The peptide probably resides on the membrane interface and may not therefore deeply insert into the membrane. The spectrum in the presence of the DMPC/DMPG membrane (70:30 ratio) was found to be characteristic for peptides primarily in the β-conformation at lower concentration, and at higher CP concentration the spectrum was typical for an exclusively β-structure, attributed to aggregated peptides associated with the negatively charged DMPG components. A conformational change was also reflected in our studies on the effect of variable contact times indicating that a secondary reorganization step may be taking place.

Analysis of the kinetic data (not shown) of CP fitted neither parallel or conformational models well. This raised concern about the accuracy and robustness of the methodology used and introduced issues such as bulk contribution, liposome stability, and other factors that may account for the poor fits. However, the effect of bulk contribution was excluded, as the data were analyzed and fitted taking this into consideration. Liposome stability was further ruled out by starting each sensorgram only after a stable baseline was achieved, representing a stable initial liposome layer. After peptide injection, dissociation was extended to view the liposome surface following peptide bind-
associates with the membranes, most likely with the lipid head groups (8). In negatively charged model membranes, the peptide at the lower concentration (2%) aggregated on the surface without disrupting the membrane structure. However, at the higher peptide concentration (10%), most of the lipids were no longer in a planar lamellar phase and NMR spectra indicated that peptides and lipids were part of amorphous aggregate structures. These observations indicate that at higher peptide concentrations the mechanism of peptide/membrane interaction may be somewhat different and seem to support our finding with the binding of CP to model membranes.

Sequence variation had major effects on peptide model membrane interactions. Peptides E and M, which are negatively charged, did not associate with either DMPC or DMPG liposomes. Immunosuppressive effects of peptide E and biotinylated peptide E on T cells, measured by antigen-induced IL-2 production assay, were indistinguishable from control (6). Peptide E in vivo showed no protective effects on the development of adjuvant-induced arthritis (4). The presence of the positively charged amino acids were also essential for localization of the peptide with the plasma membrane of TCR, but no membrane localization was observed when the acidic or neutral peptides were tested (6).

These results support our hypothesis that the cationic nature of the peptides may lead to initial electrostatic membrane binding followed by hydrophobic peptide-lipid interactions (21, 22). Peptides D, G, and F contain positive charges located toward the N- and C-terminal of the peptides. This feature may be an important requirement for interaction with acidic head groups of phospholipid vesicles. Shortening the distance by one amino acid, peptide G, had very little effect on binding but lengthening it with only one amino acid, in the sequence of peptide F, showed a decrease in the ability of the peptide to bind. In the peptide D sequence the positions of arginine and lysine have been exchanged, leaving the overall charge and hydrophobicity of the peptide unchanged. The binding of this peptide was similar to that of CP (Fig. 4). This corroborated well with the results of inhibition of IL-2 production by this peptide and inhibition of adjuvant-induced arthritis in rats (4).

Peptides A, B, H, and I all carry a single positively charged amino acid, either lysine or arginine. In peptides A and B these are located at the center of the peptide sequence and it was found that neither peptide A nor peptide B bound to zwitterionic and anionic membranes. The sensorgrams reveal that the abrogation of binding occurs early in the association phase displaying a box-like shape similar to that given by the negatively charged peptides. Both peptides H and I showed diminished binding to both zwitterionic and anionic membranes, hence emphasizing the requirement for two positively charged amino acids for optimal binding.

Peptide C with no charged amino acid in the sequence did not bind to the anionic liposome but did show some (although

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diminished) binding to zwitterionic membranes. It is likely that the binding of peptide C to the zwitterionic model membranes is effected by hydrophobic interaction because purely hydrophobic interactions do not require acidic head groups on lipids (23). The shape of the curve on the sensogram depicting peptide C was more reminiscent of that obtained from binding of CP (Fig. 3). IL-2 inhibition (Fig. 5) reflected this result in the vicinity of 30% inhibition compared with the 63% shown by CP, whereas no inhibition of IL-2 and no binding of this peptide was observed with peptide E, where the arginine and lysine are substituted with acidic amino acids. It appears that the extent of binding reflects the degree of inhibition. The results of binding studies on negatively charged and neutral peptides corroborate well with our earlier findings examining the in vitro and in vivo effects of CP on T cells. CP, but not the charge modified peptides inhibit antigen-induced IL-2 production (see Fig. 5).

Decreasing the number of hydrophobic amino acids in the peptide sequence linking the two basic amino acids (peptide G) had only a slight effect on peptide binding to model membranes but lengthening the linker with one hydrophobic amino acid (peptide F) decreased the binding to approximately 60% of CP. This is consistent with previous findings that peptide G showed a similar immunosuppressive effect in animals with T cell-mediated adjuvant-induced arthritis (4) but peptide F showed a decreased protective effect. Thus there is also good agreement found between the binding of peptides E and C, and CP to the model membranes and the biological function of the association of CP with the plasma membrane of human T cells.

From the above results we conclude that CP and peptide D show optimal binding and inhibitory activity and that the two basic amino acids in the sequence are essential for activity. Even the substitution of one basic amino acid showed a considerable effect on binding, as did the position of the charged amino acid. However, apart from electrostatic and hydrophobic effects discussed above there are other theoretical possibilities such as helix forming propensities and oligomerization, which may influence the peptides biological and biophysical properties (24).

Binding of CP analogues as shown in Fig. 4, a and b, demonstrate the effect of sequence modification in the interaction with model membranes. The results of some of our IL-2 assays compiled in Fig. 5 reveal a remarkable agreement with the data showing the binding of these analogues to model membranes in the SPR experiments. Binding of CP to a preparation of T cell membrane attached to the sensor chips confirmed our earlier findings that CP associated with the T cell membranes. Although biosensor technology is very useful in providing information on the binding of peptides to membranes it is unable to determine the degree of insertion of the peptides into the membrane. Current work in our laboratory using alternate biophysical tools is focusing on this question.

In summary, we propose that the efficacy of CP to express its inhibition is dependent on its ability to bind to the plasma membrane. The technique of SPR has proved to be an excellent tool for the study of CP and its analogues interacting with model and T cell membranes. This study together with earlier observations (6) show specific association of CP with TCR and give support to the proposed theory of inhibition of T cell function occurring by the disruption of the TCR complexes in the plasma membrane.

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