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Individuals infected with HIV possess antibodies against IL-2

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SUMMARY

Studies are presented here which demonstrate that antibodies reacting with human interleukin-2 (IL-2) are present in the sera of patients infected with the human immunodeficiency virus (HIV). It is likely that these antibodies are present due to a homology between the HIV envelope protein and IL-2. The homologues are six amino acids in length corresponding to the carboxy teminus of gp41, Leu-Glu-Arg-Ile-Leu-Leu (LERILL), and residues 14–19 of secreted IL-2, Leu-Glu-His-Leu-Leu-Leu (LEHLLL). Thus, we questioned whether antibodies made against this HIV envelope peptide would cross-react with IL-2. Not only do a high percentage of the HIV-infected individuals tested here have antibodies against LERILL, but these antibodies cross-react with the IL-2 sequence, LEHLLL. Additional antigenic processing of IL-2 is suggested by the finding that epitopes other than this sixmer are also recognized by antibodies in patients' sera. Thus, these studies suggest a mechanism by which infection with HIV can induce a potentially suppressive autoimmune response. Specifically, antibodies against an HIV envelope peptide cross-react with an epitope in IL-2.

INTRODUCTION

The observation that the genome of human immunodeficiency virus (HIV) encodes a protein which has sequence homology with human interleukin-2 (IL-2) (Weigent *et al.*, 1986; Reiher, Blalock & Brunck, 1986) suggested a possible mechanism by which viral infection could induce an autoimmune response. Antibody against the carboxyl terminal six amino acids of the HIV envelope protein gp41, Leu-Glu-Arg-Ile-Leu-Leu (LERILL), which cross-reacts with the IL-2 sequence (Taniguchi *et al.*, 1983), Leu-Glu-His-Leu-Leu-Leu (LEHLLL), might contribute to the immunosuppression, which is a hallmark of HIV infection. The possibility that cross-reactive antibodies would be immunosuppressive seemed likely since this IL-2 sequence has been shown to be a binding site for IL-2 to its receptor (Weigent *et al.*, 1986; Bost, Smith & Blalock, 1985; Ju *et al.*, 1987; Brandhuber *et al.*, 1987). We show that the majority of HIV-infected patients tested here have antibody titres against this envelope peptide, as would be expected since this sequence is conserved among virus strains isolated to date (Reiher *et al.*, 1986; Ratner *et al.*, 1985; Hahn *et al.*, 1986; Starcich *et al.*, 1986). More importantly, these antibodies cross-react with IL-2, suggesting a mechanism by which infection may suppress immune responses.

Abbreviations: HIV, human immunodeficiency virus; IL-2, interleukin-2; LEHLLL, Leu-Glu-His-Leu-Leu-Leu; LERILL, Leu-Glu-Arg-Ile-Leu-Leu.

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MATERIALS AND METHODS

Patients' sera

Sera were collected from individuals sero-positive for HIV, filtered (0·2 μm) and stored in aliquots at −80° until used. While all were clearly sero-positive, extensive clinical data were not available on every patient. Therefore, for this study a correlation between antibody titres and clinical disease was not attempted and was not critical for the points to be made here. For patients whose clinical characteristics were known, two were stage I, three were stage II, two were stage III, two were stage IV, and three were stage V using the Walter Reed Staging Classification (Redfield, Wright & Tramont, 1986).

Preparation of peptides

Each peptide was synthesized on a 9500 Solid-Phase Peptide Synthesizer (Biosearch, San Rafel, CA) using t-boc chemistry. Peptides were cleaved from the resin using a hydrogen fluoride cleavage apparatus (Peninsula Laboratories, Belmont, CA) at 0° in the presence of 10% anisole. After ethyl acetate precipitation, peptides were dissolved in 0·5 M acetic acid, lyophilized and then subjected to high-pressure liquid chromatography (HPLC) purification using a C-18 150A Dynamax HPLC column (Rainin, Woburn, MA). Purity of peptides was assessed by the appearance of a single symmetrical peak on HPLC and amino acid compositional analysis. Peptides were greater than 95% pure using these criteria and were stored under nitrogen at 4° until used.

Enzyme-linked immunosorbent assay (ELISA)

In order to test reactivity of patients' sera against the HIV envelope peptide, Leu-Glu-Arg-Ile-Leu-Leu (LERILL), an ELISA assay was used. One milligram of peptide was coupled to 5 mg bovine serum albumin (BSA) using 10 mM glutaraldehyde for 4 hr at room temperature. After dialysis against 0·05 M phosphate-buffered saline (PBS, pH 7·2), BSA-LERILL was stored in aliquots at −20°. The coupling efficiency for this reaction was 71% as determined using an ^{125}I-tyrosine-containing analogue of LERILL. The reason for coupling the peptide to a carrier protein was to increase the coating efficiency in the ELISA assay (Bost & Blalock, 1988).

LERILL conjugated to BSA was coated onto Nunc immuno-plates (Nunc, Thousand Oaks, CA) in 0·05 M carbonate buffer (pH 9·2) at 10 μg of peptide per well. After 18 hr at 4°, non-adsorbed peptide was removed using buffer (PBS-0·5% BSA-0·05% Tween 20) and plates were blocked with PBS-2% BSA for 2 hr at room temperature. Sera were diluted in buffer and 0·1 ml incubated on peptide-coated plates for 90 min. After washing three times, an alkaline phosphatase-conjugated anti-human γ chain- or μ chain-specific antibody (Boehringer Mannheim, Indianapolis, IN) was diluted 1:1000 in buffer and incubated on plates for 60 min. Unbound antibody was washed off and bound antibody detected by the addition of nitrophenyl phosphate (1 mg/ml) in carbonate buffer. Absorbances were read at 405 nM using a 2550 EIA reader (Bio-Rad, Richmond, CA), and antibody titres determined as being the last dilution of sera giving an absorbance twice that of background.

To test reactivity against IL-2, 400 ng/well of recombinant IL-2 (AMGEN, Thousand Oaks, CA) was adsorbed onto Nunc high protein-binding microwell modules (Nunc) in carbonate buffer (pH 9·2) for 18 hr. At this point, the same ELISA procedure described above was followed. For IL-2-coated plates, 0·1 nM of an anti-human IL-2 polyclonal antisera (Genzyme, Boston, MA) was able to produce an absorbance reaction at 405 nm of approximately 1·0 10 min after addition of substrate. Greater than 90% of this reactivity was blockable with 1 μg/well of recombinant IL-2.

To assure specificity of the ELISA reactions, several controls were used. First, sera from normal donors negative for HIV were obtained from the American Red Cross (Birmingham, AL). Normal sera was treated identically to HIV-positive sera, and used as a control of non-specific immunoglobulin binding to ELISA wells. Second, to demonstrate specificity of binding, excess soluble antigen was added to parallel wells to demonstrate blockability of the reaction. For ELISA assays detecting LERILL, sera were diluted with PBS-0·05% Tween 20 containing 1 mM LERILL or 1 mM LEHLLL (conjugated to BSA) plus the appropriate amount of BSA to make the total BSA concentration 0·5%. For ELISA assays detecting IL-2, sera were diluted in PBS-0·5% BSA-0·05% Tween 20 containing 10 μg/ml recombinant IL-2 (AMGEN). This represented approximately a 50-fold excess of soluble IL-2 relative to the amount adsorbed to the well as detected using ^{125}I-IL-2. As a final set of controls, irrelevant peptides conjugated to BSA (i.e. BSA-MAYKE, BSA-YRMQ, BSA-SATCTI) were used to detect non-specific antibody binding. Binding to these control peptides was always less than 10% of experimental values.

Affinity purification of antibodies

Sera were pooled from several patients and diluted 1:2 with 0·05 M HEPES (pH 8·0). Immunoglobulin was isolated by passage over a protein A affinity column (Du Pont, Wilmington, DE), and adherent material was eluted with 0·1 M glycine-0·1 M NaCl (pH 3·0). Immunoglobulin was then neutralized, concentrated (Centriprep, Amicon, Danvers, MA) and dialysed versus PBS.

Antibodies against LERILL were purified from total immunoglobulin using affinity chromatography. Fifty milligrams of LERILL were dissolved in 0·05 M HEPES buffer (pH 8·0) and reacted with 10 ml of Affigel-10 (Bio-Rad) for 18 hr at 4°. Untreated groups were blocked with excess glycine. Protein A-purified immunoglobulin was passed over the peptide column, and bound antibodies were eluted, dialysed, and concentrated as described above. Both bound and pass-through immunoglobulin preparations were then used in assays. Antibody concentration was determined by absorbance at 280 nm (Shimadzu UV-160, Koyoto, Japan). Greater than 95% of protein binding to the affinity column was immunoglobulin, as determined by densitometric scans of SDS–PAGE gels.

^{125}I-IL-2 binding assay

Protein A-adherent immunoglobulin from patient's sera depleted of anti-LERILL antibodies by affinity chromatography was coated onto Nunc high protein-binding microwell modules (Nunc) at 5 mg/ml for 18 hr at 4°. Unadsorbed immunoglobulin was washed out with buffer (PBS-0·5% BSA-0·01% bacitracin 0·05% Tween 20) and wells blocked with PBS-2% BSA for 2 hr. ^{125}I-IL-2 (New England Nuclear, Boston, MA) was diluted in buffer and varying dilutions incubated on triplicate wells for 90 min. After washing three times with buffer, wells were separated and counted (TM Analytical, Elk Grove, IL). Non-specific binding was determined using microtitre plates coated with protein A-purified immunoglobulin from normal, sero-negative donors. Non-specific counts were subtracted from experimental values prior to analysis of the data. Non-specific binding was never greater than 20% of experimental values. Specific binding was determined in the presence of 20 ng per well soluble recombinant IL-2 (AMGEN).

RESULTS

Sera reactivity against the envelope peptide LERILL

The carboxy terminal six amino acids of gp41 are quite conserved between most of the strains of HIV sequenced thus far (Reiher *et al.*, 1986; Ratner *et al.*, 1985; Hahn *et al.*, 1986; Starcich *et al.*, 1986). If during the course of HIV infection this particular sequence is immunogenic, then a high percentage of infected individuals would be expected to have antibodies reacting with this peptide. To address this possibility, sera from 25 individuals sero-positive for HIV were assayed using an ELISA procedure for the presence of anti-LERILL antibodies. Table 1 shows that 20 of these patients had IgG titres of 1:100 or greater. In fact, only two of 25 individuals had negligible titres (i.e. 24 and 25). The antibody response was predominately of the IgG class since a smaller percentage (20%) had IgM titres of this magnitude. The specificity of the ELISA was demonstrated by the inability of sera from normal individuals to react with LERILL. Furthermore, for the patients with a titre of 1:50 or greater, a mean of 77% (±11%) of the reactivity was blocked in

Table 1. Sera from patients positive for HIV react with the envelope peptide, LERILL

Patient*	IgG titre^{-1} against LERILL†	% blockable with 1 mM LERILL‡	IgM titre^{-1} against LERILL†	% blockable with 1 mM LERILL‡
1	>1000	62	>1000	85
2	800	85	50	74
3	800	57	25	75
4	800	77	50	79
5	400	69	50	84
6	400	89	ND	ND
7	400	77	50	96
8	400	86	100	91
9	400	62	200	84
10	200	91	100	88
11	200	85	25	64
12	200	69	50	77
13	200	74	50	68
14	200	92	25	61
15	100	58	25	54
16	100	78	100	91
17	100	83	25	72
18	100	76	50	63
19	100	84	ND	ND
20	100	83	ND	ND
21	50	91	10	7
22	50	69	10	5
23	50	87	10	8
24	25	49	25	35
25	10	6	10	10
Normal ($n=6$)	17±8	11±10	16±6	10±9

* Sera from 25 different patients were positive for HIV antigens.

† An ELISA procedure was used to detect reactivity against LERILL-coated microtitre wells. An alkaline phosphatase anti-human γ or μ chain-specific antibody was used. Titres were defined as the last dilution of sera giving at least two times above the absorbance at 405 nM over background.

‡ To determine specificity of the ELISA, 1 mM soluble LERILL was added to parallel wells. Results are presented as an average of duplicate wells.

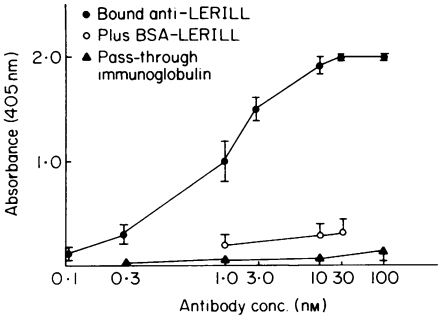

Figure 1. ELISA reactivity of affinity-purified anti-LERILL antibodies. Protein A-purified immunoglobulin from the sera of patients positive for HIV was passed over an agarose affinity column conjugated with the peptide LERILL. Bound antibody and pass-through immunoglobulin fractions were collected and assayed for reactivity to LERILL using an ELISA. Antibody bound to the LERILL column was reacted in the presence (O—O) or absence (●—●) of 1 mM soluble peptide (LERILL or LEHLLL) conjugated to BSA. Immunoglobulin passing through the LERILL affinity column (▲—▲) was used as a negative control. Results are expressed as means of triplicate determinations ± SD.

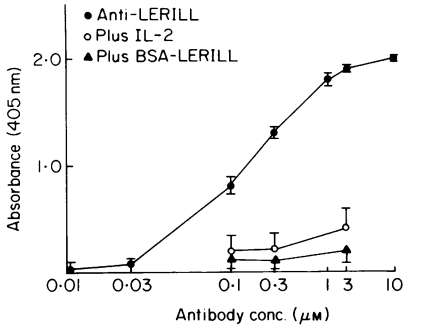

Figure 2. ELISA reactivity of anti-LERILL antibodies with IL-2. Affinity-purified anti-LERILL antibodies isolated from the sera of patients positive for HIV were tested for reactivity against IL-2 using an ELISA. Anti-LERILL antibodies were reacted on IL-2-coated plates in the absence (●—●) or presence of 1 mM soluble LERILL or LEHLLL conjugated to BSA (▲—▲) or 1 μg/well soluble, recombinant IL-2 (O—O). Results are expressed as the mean of triplicate determinations ± SD.

the presence of 1 mM soluble peptide. Thus, as was anticipated, the majority of infected individuals have antibodies against this particular envelope peptide.

Anti-LERILL antibodies react with IL-2

The ability of a large percentage of patients to have such high titres against such a small peptide contained within gp41 following viral infection is by itself an interesting observation. However, the ability of these antibodies to cross-react with a host protein sequence would suggest a possible mechanism by which viral infection could induce an autoimmune response. To critically examine whether anti-LERILL antibodies could also bind the IL-2 sequence LEHLLL, it was necessary to use affinity chromatography to purify the antibodies. Immunoglobulin was first isolated from pooled sera using a protein A affinity column and then passed over a second affinity column conjugated with LERILL. Both pass-through and bound immunoglobulin fractions were collected, and Fig. 1 demonstrates the efficiency of this chromatographic procedure. Antibodies binding to the LERILL affinity column reacted with the peptide at concentrations as low as 0·3 nM, whereas immunoglobulin passing through the column did not react at more than 100 times this concentration. Furthermore, the same pass through immunoglobulin had no reactivity with BSA-LEHLLL-coated plates (data not shown) and 1 mM soluble LEHLLL was as effective as LERILL in blocking anti-LERILL binding (Fig. 1). Thus, the affinity chromatographic procedure was able to deplete the presence of anti-LERILL antibodies from immunoglobulin preparations.

Varying dilutions of the affinity-purified anti-LERILL antibodies were then screened by ELISA on plates coated with IL-2. As shown in Fig. 2, only approximately 50 nM of antibody were needed to detect IL-2 in this assay. What may be even more

Table 2. Sera from patients positive for HIV react with human IL-2

Patient*	Absorbance at 405 nm† IgG reactivity	Absorbance at 405 nm† IgM reactivity	% blocked with 1 mM LERILL‡	% blocked IL-2§
1	605	344	35	69
2	438	104	39	74
3	337	15	22	51
4	431	185	51	67
5	530	267	39	71
6	463	101	42	81
7	984	381	12	74
8	1013	426	15	52
9	481	341	29	63
10	369	640	38	74
11	286	47	19	79
12	360	64	27	84
13	107	86	39	68
14	201	71	42	77
Normal ($n=6$)	43 ($\pm$22)	19$\pm$(18)	4 ($\pm$2)	6 ($\pm$8)

* Patient sera is numbered the same as Table 1.

† A 1:50 dilution of sera was assayed for the ability to bind IL-2 using an ELISA procedure. Absorbances at 405 nM were taken 60 min after substrate addition.

‡ Percentage of absorbance blocked with 1 mM soluble LERILL.

§ Percentage of absorbance blocked with 1 μg per well soluble, recombinant IL-2.

significant is the ability to block reactivity with either excess LERILL or IL-2. Clearly, the HIV envelope peptide, LERILL, and the IL-2 sequence, LEHLLL, must be cross-reactive epitopes. This finding is supported by: (i) the ability of affinity-pure anti-LERILL antibodies to bind IL-2; (ii) the ability of either soluble LERILL or LEHLLL to block anti-LERILL binding to IL-2; (iii) the ability of soluble IL-2 to block anti-LERILL binding to IL-2.

Sera reactivity against IL-2

Since antibodies against LERILL also reacted with IL-2, patients with high anti-LERILL titres would be expected to have high anti-IL-2 titres. To determine if this correlation existed, individual patients' sera were assayed using the same IL-2 ELISA. All 14 patients in Table 2 had significant IgG reactivity and 10 had significant IgM reactivity against IL-2 compared with sera from normal individuals. In general, there was a positive correlation between anti-LERILL titres from Table 1 and anti-IL-2 reactivity in Table 2. That is, patients with high anti-LERILL titres also reacted well with IL-2. If the reactivity against IL-2 was the result of cross-reactive anti-LERILL antibodies, then an excess of either IL-2 or LERILL should block the reactivity. Surprisingly, IL-2 was able to block anti-IL-2 reactivity much better than the peptide. A 50-fold excess of IL-2 blocked a mean of 70% ($\pm$10%), whereas 1 mM LERILL blocked a mean of 32% ($\pm$11%) of the anti-IL-2 reactivity. While the percentage of inhibition using excess peptide was significant, IL-2 was always a better inhibitor of the reaction. There are several possible explanations for this

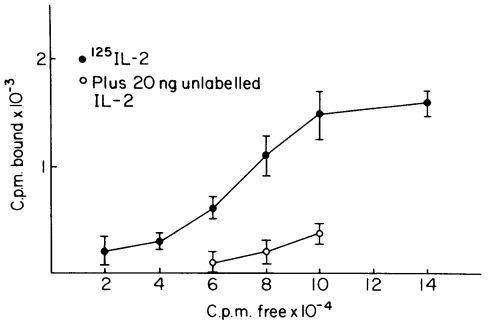

Figure 3. Binding of ^{125}I-IL-2 by immunoglobulin from HIV-infected patients. Protein A-purified immunoglobulin from sera of patients infected with HIV were depleted of anti-LERILL reactivity by passage over a LERILL affinity column (Fig. 1). Pass-through immunoglobulin was coated onto microtitre plates and the ability to bind ^{125}I-IL-2 was determined in the presence (o—o) or absence (•—•) of 20 ng of unlabelled IL-2. Results are expressed as the mean triplicate determinations $\pm$ SD. Non-specific binding of ^{125}I-IL-2 binding to normal immunoglobulin coated plates was subtracted from experimental values. Non-specific binding was never greater than 20% of experimental values.

observation, but the one which seemed most likely was that the antibodies to IL-2 were recognizing determinants on IL-2 in addition to the cross-reactive epitope, LEHLLL.

Anti-IL-2 reactivity to epitopes other than LEHLLL

If sera could be depleted of antibodies against LERILL and still react with IL-2, this would strongly argue that determinants other than LEHLLL on IL-2 were being recognized. To test this possibility, protein A-purified immunoglobulin from pooled sera was depleted of anti-LERILL antibody by passage over a peptide-conjugated affinity column. As shown in Fig. 1, this pass-through immunoglobulin had no reactivity with LERILL or LEHLLL. Thus, any IL-2 binding to immunoglobulin must certainly be through different epitopes. Figure 3 shows that immunoglobulin depleted of LERILL reactivity could bind ^{125}I-IL-2 and this binding was blockable with 50 ng unlabelled IL-2. These data are consistent with the possibility that antibodies to IL-2 present in sera of HIV-infected individuals recognize antigenic determinants in addition to LEHLLL.

DISCUSSION

In the present report, we have demonstrated that a high percentage of individuals infected by HIV possess significant antibody titres against an envelope peptide sequence, LERILL. This sequence corresponds to the predicted carboxyterminal six amino acids of the HIV envelope protein, gp41, and in addition is a homologue of a sequence within IL-2 (LEHLLL) that has been identified as a binding site for IL-2 to its receptor (Weigent *et al.*, 1986; Bost *et al.*, 1985; Ju *et al.*, 1987; Branhuber *et al.*, 1987). As predicted, anti-LERILL antibodies were shown to bind IL-2 and this reactivity was completely blockable with excess LERILL or IL-2. However, anti-LERILL antibodies were not the only anti-IL-2 antibodies in patients' sera. The ability of anti-LERILL-depleted immunoglobulin to bind IL-2 suggested that other IL-2 determinants were also being recognized.

It is not difficult to conceptualize the formation of anti-LERILL antibodies. Hypothetically, during the course of an immune response against HIV, antibodies are formed against this antigen, which cross-react with IL-2. The mechanism of formation of antibodies against other IL-2 epitopes is not so straightforward. Since there do not appear to be any other homologies between HIV proteins and IL-2, the formation of antibodies against different epitopes on IL-2 seems to be an indirect one. While there are several possibilities, the one we consider most likely is that formation of antibodies against multiple determinants on IL-2 occurs subsequent to the formation of anti-LERILL antibodies. Anti-LERILL antibodies which bind IL-2 may permit antigenic processing of IL-2. Subsequent to processing, multiple determinants would then be available to stimulate additional antibody responses.

In this study, no attempt was made to correlate clinical presentation of HIV infection with the levels of anti-LERILL antibodies. The limited amount of information gathered on some of the patients made this type of analysis difficult. The only observation which can be made from this study is that high titres of anti-LERILL antibodies can be seen very early after seroconversion. For example, patient no. 6 (Tables 1 and 2) was tested soon after seroconversion (WR1, Walter Reed Staging; Redfield *et al.*, 1986) and had high anti-LERILL and anti-IL-2 antibody titres. Presently, serial serum samples are being collected from a variety of patients so that the level of antibodies can be followed.

The presence of significant levels of circulating anti-IL-2 antibodies in patients infected by HIV could conceivably play a role in the pathophysiology of AIDS and related conditions. Presently, the major contributing factor to HIV-induced immunosuppression appears to be a deficiency, both in number and functionality, of the helper/inducer subset of T lymphocytes which express the T4 antigen (Gluckman, Klatzmann & Montagnier, 1986). While many of the immunologic defects can be attributed to infection and cytopathicity of T4+ lymphocytes, it has been suggested that this may not explain completely the immunodeficiencies observed in AIDS (Klatzmann & Montagnier, 1986). Since IL-2 is essential for normal immune function (Smith, 1984), it is possible that the presence of antibodies to IL-2 may contribute to the immunosuppression seen in AIDS patients. When antibodies to IL-2 have been applied to *in vitro* and *in vivo* model systems (Piperno, Andrus & Reich, 1984), immunological abnormalities have resulted. Furthermore, rabbit antisera directed against an IL-2 peptide 7-21 (which includes LEHLLL) neutralized IL-2 biological activity (Jenson *et al.*, 1986). Thus, it would seem likely that the presence of antibodies against LEHLLL, which is involved in binding of IL-2 to its receptor (Weigent *et al.*, 1986; Bost *et al.*, 1985; Ju *et al.*, 1987; Brandhuber *et al.*, 1987) or against other IL-2 epitopes would be deleterious. Ongoing investigations in our laboratory are directed at addressing this possibility.

As a final consideration, perhaps, caution should be exercised during the development of a HIV vaccine. Specifically, these findings suggest that the terminal 6 amino acids should be deleted from gp41 to preclude any antibody response to IL-2.

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