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Research Article

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ABSTRACT Antileukocyte antibodies in sera from patients with systemic lupus erythematosus (SLE) were characterized by determining cross-reacting specificies with the antigens defined by OKT3, OKT4, OKT8, OKM1 and anti-Ia hybridoma antibodies (Abs). T cells were prepared by sheep erythrocyte (E) rosetting after removal of adherent cells. T cells, or non-T cells, were preincubated with SLE sera at 4°C and then with monoclonal Abs. Binding by specific monoclonal Abs was assessed by two methods: rosetting with ox erythrocytes conjugated with goat anti-mouse IgG and also in the fluorescence-activated cell sorter using fluorescein isothiocyanate-conjugated goat anti-mouse IgG. Using the rosetting method, we found that sera from SLE can block the binding of monoclonal mouse hybridoma anti-Ia Abs to T cells; the blocking of other monoclonal Abs was not consistent. Using fluorescence-activated cell sorter analysis, preincubation with SLE sera lowered the intensity of staining and total percentage of either T or non-T cells stained by monoclonal anti-Ia Abs. Blocking of anti-Ia Abs binding by SLE sera was not histocompatibility leukocyte antigen (HLA)-DR restricted and was not due to Fc receptor binding. These results indicated that antibodies in SLE sera react with structures contiguous to or identical with Ia determinants. Anti-Ia activities in SLE sera correlate with SLE disease activity. In addition, there was a significant negative correlation between anti-Ia blocking activity in the sera and the percentage of Ia-positive T cells in the blood of SLE patients. Antibodies in SLE sera with anti-Ia blocking activity may play an important role in immune dysregulation in SLE patients.

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INTRODUCTION

Systemic lupus erythematosus (SLE)[1] is an autoimmune disease characterized by multiple immunologic dysregulations such as B cell hyperreactivity (1–2) and altered cell-mediated immune function (3–5). It has been postulated that B cell hyperreactivity in SLE results from a defect in suppressor T cell function. Loss of suppressor T cell function associated with SLE has been described by many investigators using various in vitro systems (6–8).

Patients with SLE are known to produce antileukocyte antibodies (9–12). These antibodies are heterogeneous, with multiple specificities, including normal T and B lymphocyte surface antigens (9–11) and T cell subsets (12), and monocytes (13). Antileukocyte antibodies have been shown to react directly with suppressor cell populations and to block the generation of suppressor cells in vitro (14, 15).

Recently, there has been great interest in the role of Ia antigens in the regulation of the immune response. These antigens are expressed on B lymphocytes, macrophages, Langerhans cells (16), and some malignant cells (17, 18). In addition, Ia antigens have also been found on a small proportion of normal T cells (19–21). The percentage of T cells bearing Ia increases after stimulation by mitogens or alloantigens (22). Functionally, Ia-positive T cells activated by alloantigens have been shown to participate as suppressor cells in vitro (23). In the present investigation we have found that sera from patients with SLE contain antibodies that block the binding of monoclonal mouse anti-Ia antibodies to T and B cells. These results sug-

[1] *Abbreviations used in this paper*: FACS, fluorescence-activated cell sorter; NHS, normal human serum; PBS, phosphate-buffered saline; SLE, systemic lupus erythematosus.

gest that the anti-Ia blocking activity in SLE sera may play a role in the loss of suppressor cell function in this disease.

METHODS

SLE patients. Serum samples were collected from 27 patients with SLE. All patients met the American Rheumatism Association criteria for the diagnosis of SLE (24). Disease activity was assessed at the time blood was collected on the basis of clinical signs of active disease including arthritis, serositis, skin rash, central nervous system involvement, active renal disease, and fever. This assessment was made by the clinician caring for the patient before the results of our laboratory studies were known. After collection, sera were frozen at −20°C in small aliquots. Before use, sera were heated at 56°C for 30 min. In some experiments sera were pepsin-digested at pH 4.0, 37°C, using 2 mg pepsin/ml of whole serum. After 14 h of pepsin digestion, the precipitate was pelleted in the ultracentrifuge (Sorvall RC2-B, Sorvall Biomedical Div., DuPont Co., Newtown, Conn.) at 20,000 *g* for 30 min. The supernate containing $F(ab)'_2$ fragments was then dialyzed overnight against 0.005 M phosphate buffer pH 7.5. Such pepsin-digested sera showed no residual IgG Fc fragment antigens by micro-Ouchterlony analysis.

In some experiments, heparinized blood was obtained from SLE patients simultaneous with serum samples, for percentage analysis of Ia(+) T cells (described below).

Isolation of lymphocyte populations. Peripheral blood mononuclear cells were separated from heparinized blood of normal donors by differential centrifugation over Ficoll-Hypaque. Purified T cells were obtained by incubation of peripheral blood mononuclear cells with neuraminidase-treated sheep erythrocytes at 4°C for 1 h and subsequent Ficoll-Hypaque gradient centrifugation. The sheep erythrocytes contained in the rosetting fraction were lysed with ammonium chloride-tris buffer. After washing, adherent cells were removed by incubation at 37°C for 45 min on glass petri dishes. Such T cell preparations were assayed for purity using immunofluorescence and mouse hybridomas OKT11 and 9.6 reacting with sheep erythrocyte (E)-rosette receptors (25). Reactivity with these two anti-T cell reagents was ≥97%. In addition, T cell preparations showed <1% cells with surface Ig, and <2% peroxidase-positive cells.

In some experiments activated T cells were prepared by incubating E rosette-positive cells for 7 d with phytohemagglutinin (2.0 μg/ml; Difco Laboratory, Detroit, Mich.). Blast cells were then partially enriched by density centrifugation. After washing, cell viabilities of these preparations were >98% by trypan blue exclusion.

Monoclonal antibodies. Mouse hybridoma monoclonal antibodies of the OK series were kindly provided by Dr. Rhodes, Ortho Pharmaceuticals, Raritan, N. J. The antibodies used were OKT_6, reacting with common thymocytes and used as a negative control on peripheral T cells (26); OKT_3, reacting with all peripheral blood T cells (27); OKT_4, helper-inducer T cells (27); OKT_8, cytotoxic-suppressor T cells (28) and OKM_1, against cells of myelomonocytic origin (29). In addition, anti-Ia monoclonal antibody (Clone L 243, Becton, Dickinson & Co., Mountain View, Calif.) was used. This reagent reacts with the common or core determinant of human Ia antigen and precipitates 28,000- and 34,000- dalton chains from ^{125}I-labeled NP-40 extracts of human B cell lines (30). A separate anti-Ia monoclonal antibody was generously provided by Dr. S. Ferrone of Scripps Research Institute. This reagent (Q-5/13) recognizes an antigenic determinant on the majority of human Ia-like molecules, and does not react with non-Ia-bearing cell lines (31).

Monoclonal antibody rosetting technique. Bovine erythrocytes were coupled to immunoabsorbent purified goat anti-mouse IgG (Tago, Inc., Burlingame, Calif.) with the chromic chloride method (32) and resuspended as a 1% suspension in RPMI 1640 with 10% fetal calf serum. Coating of bovine erythrocytes was checked using Coombs reactivity with rabbit anti-goat IgG antiserum. T lymphocytes were incubated with monoclonal antibodies for 30 min at 4°C, were then washed twice with cold phosphate-buffered saline (PBS) in a refrigerated centrifuge (Damon DPR-6000, Damon Corp., Needham Heights, Mass.) resuspended to a concentration of 4×10^6 cells/ml in RPMI + 10% fetal calf serum, and were then mixed with an equal volume of the treated ox erythrocytes. The mixture was centrifuged for 10 min at 200 *g*, incubated for 30 min on ice, gently resuspended, and the percentage of rosetting cells counted. When antibody-coated ox erythrocytes were incubated with untreated T cells, the percentage of nonspecific rosetting was always <2%.

Immunofluorescence analysis. A cell pellet containing 10^6 cells was incubated for 30 min on ice with 50 μl of an appropriate dilution of mouse hybridoma monoclonal antibody (2.5–5 μg/ml) or mouse IgG_2 (10 μg/ml) purified on Sepharose protein A (Pharmacia Fine Chemicals, Div. of Pharmacia Inc., Piscataway, N. J.). The cells were washed twice in the refrigerated centrifuge with PBS containing 0.01% azide. The pellet was further incubated with 50 μl of a 1/10 dilution of fluorescein-conjugated goat anti-mouse IgG (Meloy Laboratories, Inc., Springfield, Va.) for 30 min on ice. This second antibody had previously been absorbed with human Cohn fraction II insolubilized on Sepharose 4B. The cell pellet was washed twice, resuspended in 1 ml PBS-azide and analyzed using the fluorescent-activated cell sorter (FACS) III (Becton, Dickinson & Co.). The percent positive cells were calculated by comparing cells stained with mouse IgG_2 and anti-mouse fluorescein isothiocyanate-conjugated IgG to cells stained with the monoclonal antibody and anti-mouse fluorescein isothiocyanate-conjugated IgG. 10^4 cells were counted. The limit of negativity was set so that the vast majority of the cells in the control sample (with mouse IgG_2) were negative. The percent positive cells was calculated from the absolute number of cells above this limit after correction for the positive cells in the control sample: (absolute number of positive cells − nonspecific positive cells)/10,000 − nonspecific positive cells.

Blocking of monoclonal antibody binding by SLE sera. To test the capacity of SLE sera to block the binding of monoclonal antibodies, lymphocyte preparations containing 10^6 cells were incubated with 100 μl of SLE serum or normal human serum (NHS) for 1 h at 4°C, followed by incubation with the appropriate dilution of the monoclonal antibody in the presence of the serum sample. In some experiments the cells were washed between exposure to SLE sera and incubation with monoclonal antibody. Washing of test cells between SLE serum addition and application of mouse monoclonal antibodies did not produce results significantly different from experiments in which no washing in between SLE and hybridoma antibody addition was performed. After sensitization, cells were washed and the percentage of positive cells analyzed using the rosette technique or the FACS.

Microcytotoxicity assay. The microcytotoxicity test for antileukocyte antibodies was performed according to the method of Terasaki et al. (33), in order to correlate monoclonal antibody blocking experiments with serum-mediated lymphocyte killing in individual SLE sera. T lymphocytes

TABLE I

Blocking of Binding of Monoclonal Anti-Ia Antibody to Normal Resting or Activated T Cells by Sera from Patients with SLE

Sera	Percent Ia(+) cells*						Mean percent inhibition‡ by SLE sera‡
	Resting T cells			Activated T cells			
	A	B	C	D	E	F	%
NHS 1	11.5	8.5	14.5	22.0	20.0	18.0	
NHS 2	11.0	9.0	13.5	19.0	19.0	17.0	
NHS 3	10.0	7.5	15.0				
SLE 1	8.0	5.0	7.0				39
SLE 2	8.0	5.5	7.0				37
SLE 3	5.5	2.5	6.5				58
SLE 4	6.5	6.0	10.5				32
SLE 5	7.5	5.5	11.0				29
SLE 6	9.5	6.5	13.0	12.0	11.5	12.0	25
SLE 7	5.5	5.0	8.5	9.5	9.0	11.5	45
SLE 8	5.0	4.5	8.5	14.5	11.0	9.0	43
SLE 9				17.5	12.0	14.5	23
SLE 10				6.0	8.5	5.5	64
SLE 11				4.0	7.0	5.0	71

* The target T cells, either resting or activated, were preincubated with SLE sera or NHS and then sensitized with monoclonal anti-Ia antibody. Binding by anti-Ia antibody was assessed by rosetting with ox erythrocytes conjugated with goat anti-mouse IgG. Target cells A through F come from different individuals.

‡ The last column gives the mean for each SLE serum of the percent inhibition of binding of anti-Ia antibody against the different T cell targets.

and test serum were first incubated for 30 min at 15°C followed by an additional 3-h incubation with undiluted rabbit complement at 15°C. Test cells were stained with 5% eosin and fixed with neutral formaldehyde. The percent cytotoxicity was determined under phase-contrast microscopy. More than 30% killing was recorded as positive.

RESULTS

The capacity of SLE sera to block the binding of monoclonal anti-Ia antibody to a panel of normal resting or activated T cells was assessed by percent rosette inhibition (Table I). T cells prepared from normal donors by E rosetting techniques were incubated serially with SLE sera at 4°C, followed by addition of monoclonal anti-Ia antibody. The binding of anti-Ia antibody was assessed by rosetting with ox erythrocytes conjugated with goat anti-mouse IgG. In preliminary experiments, we could detect Ia antigens on 11.7±4.0% of unstimulated T cells from 22 normal donors using the rosette method; background percentage of rosetting cells in the presence of SLE sera alone was <1.0% and was not different from NHS (data not shown). As seen in Table I, preincubation with SLE sera caused a substantial decrease in the amount of anti-Ia antibody subsequently bound to the target T cells. This occurred whether resting or activated T cells were used as targets. The degree of inhibition caused by a given SLE sera was similar across several different targets. Table II shows that SLE sera caused the same degree of inhibition of binding of two different monoclonal anti-Ia antibodies.

We also assessed the relation between the inhibition of anti-Ia binding and disease activity. As shown in Fig. 1, sera from patients with active disease showed a significant anti-Ia blocking effect compared with

TABLE II

Blocking by SLE Sera of the Binding of Two Different Monoclonal Anti-Ia Antibodies to Resting T Cells

Sera	Percent T cells stained by monoclonal anti-Ia*	
	L243	Q 5/13
	%	
NHS 1	13.5	13.0
NHS 2	14.0	12.0
SLE 1	9.5 (30.9)	9.0 (28.0)
SLE 2	5.5 (60.0)	5.0 (60.0)
SLE 3	8.0 (41.8)	9.5 (24.0)
SLE 4	5.5 (60.0)	6.5 (48.0)
SLE 5	10.0 (27.3)	11.0 (12.0)
SLE 6	9.0 (34.5)	9.5 (24.0)

* See Table I for experimental procedure. The numbers of the SLE patients do not correspond to those in Table I. Percent inhibition of anti-Ia binding is given in parentheses.

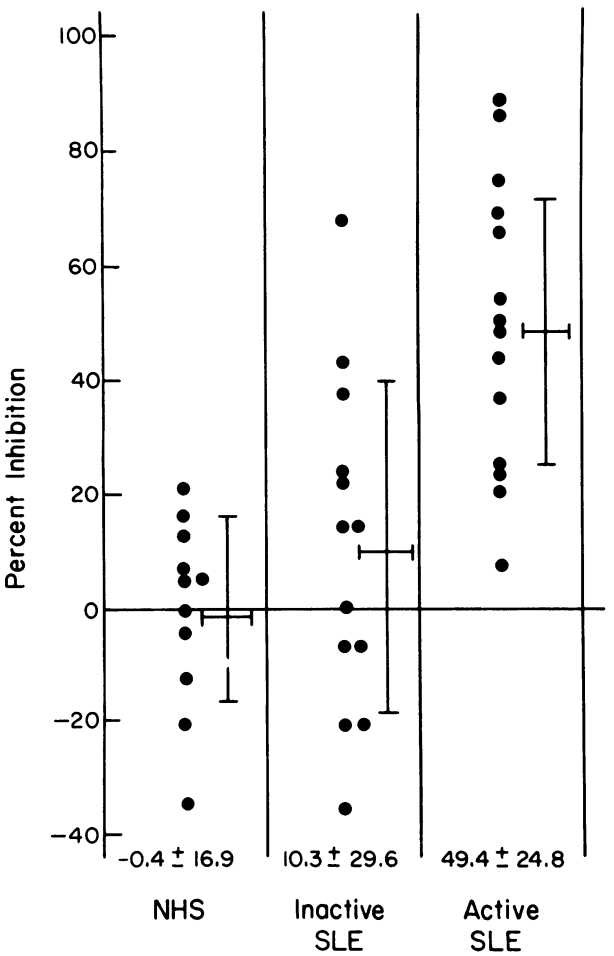

FIGURE 1 Anti-Ia blocking effects of SLE sera were compared according to the disease activity. Sera from the active SLE patients showed significantly more blocking effect compared to sera from inactive SLE patients and NHS ($P < 0.0005$). Sera from the inactive stage SLE patients showed no significant difference from NHS ($P = 0.15$). Percent inhibition was calculated as 1 − number of positive cells preincubated with SLE serum divided by the number of positive cells preincubated with NHS × 100. Vertical bars indicate ±1-SD from the mean.

NHS or sera from patients with inactive disease ($P < 0.0005$). Sera from the inactive SLE patients showed no significant difference from NHS ($P = 0.15$). In addition, different serum samples from an SLE patient taken at various stages of disease activity were examined for the blocking effect of anti-Ia antibody. Only serum obtained during the active stage of disease could block anti-Ia antibody effectively, (active stage: 88.5%, inactive stage: 0%) in spite of the fact that there was no difference in anti-T cell cytotoxicity. The relation between anti-Ia inhibition and anti-T cell cytotoxicity in SLE sera was assessed; no significant correlation was obtained ($n = 19$, $r = 0.21$, $P > 0.05$).

In contrast to blocking of anti-Ia antibody, the SLE sera caused no significant blocking of the binding of the monoclonal antibodies directed against other specific lymphocyte subsets defined by hybridoma OKT3, OKT4, OKT8, and OKM1 (Table III). In addition we found that NHS showed no blocking effect against any of the monoclonal antibodies.

Ia antigen may be closely related to Fc receptors on lymphocyte surface membranes (34); therefore it seemed possible that the blocking of anti-Ia binding by SLE sera might be due to immune complexes in the sera binding to Fc receptors. To evaluate this question, three types of experiments were conducted. First, preincubation of T cells with NHS plus aggregated IgG (500 μg/ml) did not block binding of the monoclonal anti-Ia antibody. Second, pepsin digestion of three SLE sera with high anti-Ia blocking effects did not result in a decrease in the blocking of binding of anti-Ia antigens (59±14% inhibition by three untreated SLE sera vs. 59±10% after pepsin digestion). Third, SLE sera showed identical blocking effect on anti-Ia antibodies before and after clearing by ultracentrifugation at 100,000 *g* for 30 min. In these studies after ultracentrifugation only the upper half of the centrifuged serum sample was tested to insure complete absence of aggregates or complexes. These three sets of experiments suggest that the rosette inhibition effect was not due to Fc binding of immune complexes in SLE sera.

The anti-Ia antibody blocking effect of SLE sera was tested using T cells from three donors of different HLA-DR type. As shown in Table IV, although a slight variation was seen between individuals, the general tendency of blocking was almost the same in each serum. These results indicate that blocking effect found in SLE sera was not HLA-DR restricted. We also compared the sensitivity of the rosette inhibition method to a FACS analysis (Table V). FACS analysis demonstrated a similar degree of inhibition of binding of anti-Ia by SLE sera as did the rosette technique.

Since Ia antigens are most prominent in B cells and monocytes, the blocking effect of SLE sera was also tested using non-T cells as targets. These experiments were done using FACS analysis because the rosette inhibition technique could not be applied due to nonspecific rosetting of B cell fractions. A representative blocking pattern of one SLE serum is presented in Fig. 2. After preincubation with SLE serum, the percentage of cells staining with anti-Ia antibody decreased from 63.7% to 43.0%. In addition, Fig. 1 illustrates a striking downward shift in intensity of staining by the anti-Ia antibody. Not shown in this figure, the percentage of

TABLE III
*Inhibition of the Binding of Monoclonal Antibodies by SLE Sera**

Monoclonal antibody	OKT3	OKT4	OKT8	OKM1	Anti-Ia‡
No. sera tested	(16)	(16)	(16)	(15)	(27)
Percent inhibition§	3.6±5.4	8.6±10.5	6.7±13.6	4.5±15.8	30.6±33.3

* Capacity of SLE sera to block the binding of monoclonal antibodies was assessed by percent rosette inhibition. Purified T cells were preincubated with SLE sera and then sensitized with monoclonal antibodies. Binding by monoclonal antibodies was assessed by rosetting with ox erythrocytes conjugated with goat anti-mouse IgG.

‡ The inhibition of anti-Ia binding by SLE sera was significantly greater than inhibition of binding of other monoclonal reagents, $P < .0001$, by Student's t test.

§ Data given as mean±SD. Percent inhibition was calculated as 1 − number of positive cells preincubated with SLE serum divided by number of positive cells preincubated with NHS × 100.

the most intensely staining cells in the last channel of the FACS decreased from 10.5% with NHS to 1% with SLE sera. Therefore it appeared that the anti-Ia blocking activity in SLE sera is not restricted to Ia antigens on T cells only.

Yu et al. (35) have reported an increase in Ia(+) T cells in the peripheral blood of patients with SLE. Therefore we examined the relationship between anti-Ia blocking activity in the sera and Ia(+) T cells in the blood of 10 patients with SLE. The results, shown in Fig. 3, demonstrate a significant inverse relationship between anti-Ia blocking activity in sera and the percentage of Ia(+) T cells in blood. In addition, the SLE patients with active disease (open circles) had a significantly lower percentage of Ia(+) T cells (6.1±0.8, mean±SEM) than did inactive patients (13.7±1.0, $P < 0.02$) or 22 normal controls (11.7±0.8, $P < 0.02$).

TABLE IV
Anti-Ia Blocking by SLE Sera Using T Cells from Three Different Donors

	Percent inhibition of anti-Ia binding Donors*			
Sera	G(DR3, 7)	H(DR4, 6)	I(DR1, 5)	Mean percent inhibition
SLE 1	54.7	47.7	42.1	(48.2)
SLE 2	52.4	31.8	31.1	(38.4)
SLE 3	50.0	34.1	28.4	(37.5)
SLE 4	69.0	61.4	57.9	(62.8)
SLE 5	28.6	31.8	42.1	(34.2)
SLE 6	66.7	47.7	50.0	(54.8)
SLE 7	31.0	20.5	26.3	(25.9)
SLE 8	47.6	40.9	36.8	(41.8)

* Using three different HLA-DR type donors, the capacities of SLE sera to block the binding of anti-Ia monoclonal antibody against activated T cells were examined by the rosette inhibition method. Results are expressed as percent inhibition. The numbers of SLE patients do not correspond to those in the other tables.

DISCUSSION

The results presented here indicate that antibodies found in sera from patients with SLE have cross-reactive specificities with antigens defined by two anti-Ia hybridoma antibodies. This cross-reactivity is apparent when either resting T cells, activated T cells, or non-T cells are used as targets. The blocking effect of SLE sera is not due to Fc receptor binding by immune complexes, nor is the blocking effect HLA-DR restricted. Blocking of anti-Ia reactivity by SLE sera may be due to direct interaction of antibodies with Ia determinants, or alternatively, it could be due to steric hindrance through reaction with closely approximated structures.

Comparison of disease activity and anti-Ia blocking effect clearly demonstrated that most sera from active SLE patients contain anti-Ia cross-reactivity, and suggested that these anti-Ia cross-reactive antibodies may play a role in SLE disease activity. Recently, Yu et al.

TABLE V
Comparison of Anti-Ia Antibody Blocking Activity in SLE Sera Using Rosette Method and FACS Assay

	Percent inhibition*	
Sera/Donors	FACS	Rosette method (Mean of three experiments)
SLE 1	30.3	24.1
SLE 2	33.3	38.6
SLE 3	50.0	64.5
SLE 4	64.8	62.2

* Purified T cells preincubated with SLE sera and then sensitized with anti-Ia antibody. Binding of anti-Ia antibody was assessed using FACS assay and the rosette method. Capacity of SLE sera was assessed as percent inhibition. Percent inhibition was calculated as 1 − number of positive cells preincubated with SLE serum divided by number of positive cells preincubated with NHS × 100.

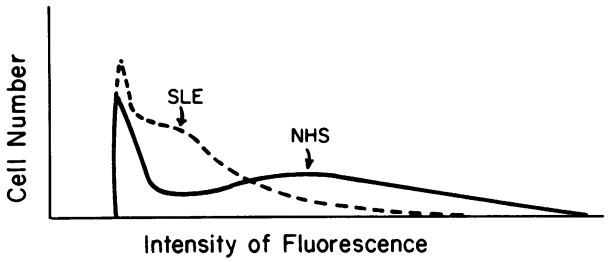

FIGURE 2 Non-T cells were prepared from a normal donor and preincubated with SLE serum or NHS and then anti-Ia antibody. Sensitized non-T cells were stained with fluorescein isothiocyanate-conjugated anti-mouse IgG and assessed by FACS. Total percentage of Ia-positive cells was 63.7% after preincubation with NHS and 43.0% after preincubation with SLE serum. The percentage of off scale high intensity staining cells (not shown in the figure) was 10.5% in NHS and 1.0% in SLE serum. The scale for both cell number and fluorescence intensity was linear.

(35) have reported that T cells expressing Ia antigens in the peripheral blood of SLE patients are increased, but the disease activity of these patients was not recorded. We found an inverse correlation between anti-Ia reactivity in sera and percent Ia(+) T cells in blood of 10 SLE patients tested. The active patients with high anti-Ia blocking activity had a significantly lower percentage of Ia-positive T cells than did inactive patients or controls. The anti-Ia activity in SLE sera could be blocking the Ia antigen on SLE T cells or it could have caused elimination of Ia(+) T cells in vivo. Partial evidence for this second possibility is the fact that overnight incubation of T cells from an active SLE patient did not result in an increased percentage of Ia(+) cells.

Morimoto et al. (36) have recently reported a selective reactivity of anti-T cell antibodies in SLE sera for the cytotoxic/suppressor subset defined by OKT8. Moreover, during active SLE, OKT8(+) T cells show significant depression (37). In the present report we found no blocking of OKT8 antibody binding to T cells by SLE sera. Therefore if SLE sera react selectively with OKT8(+) T cells, it would appear that such reactivity may be related to additional antigens on OKT8(+) cells. Recent work in our laboratory indicates that Ia antigen is relatively enriched on OKT8(+) T cells (38). Thus selective reactivity of SLE sera for OKT8(+) T cells may be directly related to anti-Ia specificity. This specificity may also be related to anti-Tγ cell reactivity noted in some SLE sera (39) since Ia(+) T cells appear to be largely Tγ cells (21, 40).

Messner et al. (41) reported that lymphocytotoxic activity of sera from SLE patients and their families was inhibited by preincubation of the target peripheral blood mononuclear cells with F(ab)$'_2$ fragments of xenoantisera against β_2-microglobulin or the heavy chains of the HLA-A, B, C antigenic molecular complex. On the other hand, anti-HLA-DR xenoantiserum did not block cytotoxicity by SLE sera against peripheral blood mononuclear cells. The discrepancy between our data and theirs may be due to the differential sensitivity of the assay systems used. We used two different systems, a rosette method and FACS assay. Both methods showed substantial blocking by SLE sera of the binding of anti-Ia antibody to T cells or to non-T cells. This was shown most strikingly in Fig. 2, illustrating a FACS analysis using non-T cells.

Activated T cells in allogenic culture have been reported to inhibit a subsequent mixed lymphocyte response (42, 43) and Ia(+) T cells mainly participate in this suppression (23). Considering that Ia-positive T cells are mostly contained in the Tγ cell fraction (21, 40), these anti-Ia SLE reactive antibodies may cause the decrease of Tγ cells found in active SLE patients. This conclusion is consistent with our previous findings that IgG anti Tγ cell antibody in SLE sera can block the induction of suppressor cells (44).

Furthermore, the autologous mixed lymphocyte response in which T cells respond to autologous non-T

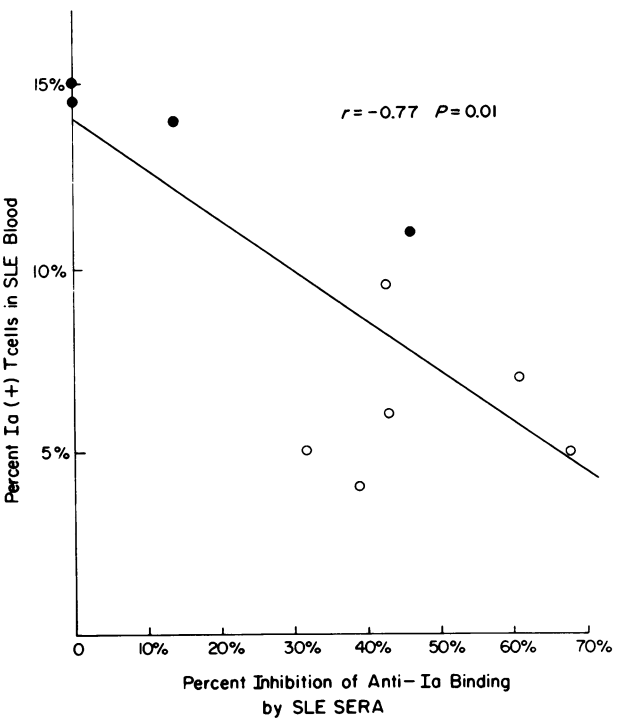

FIGURE 3 Correlation between the percent inhibition of anti-Ia binding to normal T cells by sera from SLE patients and the percent of Ia-positive T cells in the peripheral blood of those same SLE patients. The SLE patients with active disease are noted by the open circles and those with inactive disease by filled circles.

cell surface membrane antigens that are closely linked to the HLA-DR locus has been reported to induce suppressor T cells in vitro (45). This reaction, which is decreased in SLE (46, 47), has been proposed as a mechanism by which T cells regulate lymphocyte function. We are presently studying the possibility that the decreased autologous mixed lymphocyte response in these autoimmune diseases might be caused by anti-Ia reactivity in patients' sera.

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