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Increased IgE-dependent cytotoxicity by blood mononuclear cells of allergic patients

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SUMMARY

Peripheral blood mononuclear cells from 14 healthy donors and 22 allergic patients were incubated with ^{51}Cr-labelled chicken erythrocytes coated with an IgE myeloma protein or rabbit IgG antibodies. Mononuclear cells from patients with severe atopic disorders released a significantly greater percentage of ^{51}Cr ($P<0{\cdot}001$) from IgE-coated target cells than mononuclear cells from healthy controls, patients with mild atopic disease, or patients with severe atopic disease taking oral prednisone. Specific ^{51}Cr-release from IgE-coated target cells was directly correlated to the percentage of monocytes (latex-ingesting cells) with Fc receptors for IgE ($r=0{\cdot}87$, $P<0{\cdot}01$) as detected by a rosette assay employing ox erythrocytes coated with IgE. Mononuclear cells from patients and normals released similar amounts of ^{51}Cr from IgG-sensitized target cells. Depletion of monocytes from mononuclear cell preparations from two severe atopic patients decreased ^{51}Cr-release from IgE-coated target cells to levels seen in healthy donors or patients with mild allergic disease. These results demonstrate that mononuclear cells from severely allergic patients have a significantly increased cytotoxicity toward IgE-coated target cells and that this cytotoxicity correlates highly with the percentage of monocytes with Fc receptors for IgE in these mononuclear cell preparations.

INTRODUCTION

Fc receptors for IgE (Fcε) are present on the surface of mast cells and basophils (Ishizaka, 1970). A subpopulation of human peripheral blood monocytes (Melewicz & Spiegelberg, 1980) and lymphocytes (Gonzalez-Molina & Spiegelberg, 1977) have also been shown to have Fcε receptors. Approximately 1 to 2% of normal peripheral blood lymphocytes and 20% of monocytes have Fcε receptors as demonstrated by rosette assays employing indicator cells coated with IgE myeloma proteins (Spiegelberg & Melewicz, 1980). Purified monocytes but not lymphocytes display specific *in vitro* cytotoxicity for IgE-coated target cells and this cytotoxicity is highly correlated to the percentage of monocytes bearing Fcε receptors (Melewicz & Spiegelberg, 1980). It is dependent upon an intact, native Fc portion of IgE because target cells coated with reduced and alkylated or 56°C heated IgE are not specifically lysed by monocytes (Melewicz & Spiegelberg, 1980).

Since monocytes with Fcε receptors may be involved in the pathogenesis of allergic disease, we determined the percentage of monocytes with Fcε receptors in mononuclear cell preparations from

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allergic patients and incubated these mononuclear cells with radiolabelled IgE-coated target cells to determine levels of IgE-dependent cytotoxicity.

MATERIALS AND METHODS

Allergic patients and normal controls. Fourteen healthy laboratory and clerical workers (aged 21 to 43) who had no history of allergic disorders served as controls. Twenty-two out-patients with atopic disease were selected from the allergy clinics of the Kaiser Permanente Medical Center, San Diego, and University Hospital, University of California at San Diego. The clinical diagnoses of allergic rhinitis and asthma were confirmed by skin tests and/or radioallergosorbent tests against historically relevant allergens. At the time of study none of the patients had a clinically apparent bacterial or viral infection. Peripheral blood was obtained by venipuncture. Patients had taken no medication for at least 12 hr prior to obtaining their blood. Control individuals were not taking any medication.

The patients' age, sex, diagnoses, serum IgE levels, WBC counts and treatment are shown in Table 1. The patients were divided into three groups according to severity of their disease and systemic corticosteroid treatment. Most patients of Group I had only mild allergic rhinitis. Two had localized atopic dermatitis and asthma, and their symptoms were well controlled by medication at the time of testing. All patients of Groups II and III, except patient 19, had severe generalized atopic dermatitis which involved 75% or more of their body surface from early childhood. Four of six patients in Group II were using topical corticosteroids. The patients of Group III required alternate-day oral prednisone to control their asthmatic symptoms. Their atopic dermatitis was stable at the time of testing.

Mononuclear cell isolation. Mononuclear cells were isolated from heparinized venous blood by density-gradient centrifugation (Böyum, 1976). Briefly, the blood was diluted 1:1 with sterile phosphate-buffered 0·15 M NaCl, pH 7·4 (PBS), and centrifuged over Ficoll–Paque (Pharmacia Fine Chemicals, Piscataway, New Jersey). The cells at the interface were washed once with PBS and resuspended at 5×10^6 cells/ml in RPMI 1640 media. Viability was greater than 95% as determined by trypan blue exclusion. Contamination with polymorphonuclear cells was less than 1%.

Monocyte depletion of mononuclear cells. Mononuclear cells at a concentration of 1×10^7/ml in RPMI 1640–50% FCS were incubated with 40 mg/ml carbonyl iron powder (GAF Corp., New York) at 37°C for 30 min with intermittent mixing. The iron particles and phagocytic cells were then removed with a magnet. The remaining cells were washed and resuspended in RPMI 1640. Cell recovery after this procedure was approximately 60% and viability was greater than 95%.

Rosette assay for monocytes with Fcε receptors. Monocytes with Fcε receptors (Fcε$^+$) were detected by a rosette assay employing pyruvic aldehyde- and formaldehye-fixed ox erythrocytes (E_o') coated with a human IgE myeloma protein (E_o'-IgE) (Gonzalez-Molina & Spiegelberg, 1977). For latex ingestion, 1·0 ml of mononuclear cells at 5×10^6/ml in medium containing 20% heat-inactivated fetal calf serum (FCS) (Flow Laboratories, McLean, Virginia) were first incubated for 1 hr at 37°C with 20 μl of a 5% latex bead suspension in PBS (2·0-μm uniform latex particles, Dow Diagnostics, Dow Chemical Co., Indianapolis, Indiana). The cells were then washed and resuspended in RPMI 1640 media to 5×10^6 cells/ml for use in the rosette assay. Cells which had ingested five or more latex beads were scored as latex$^+$ and cells binding three or more E_o'-IgE indicator cells were scored as Fcε$^+$. Five hundred or more cells were counted to obtain the percentage of positive cells. The IgE specificity of rosette formation was tested by incubation of mononuclear cells with and without soluble IgE (final concentration 6·0 mg/ml) for 15 min at 20°C prior to the addition of E_o'-IgE indicator cells. The percentage of rosettes not inhibited by IgE (non-specific rosettes) were subtracted from the percentage of rosettes formed in the absence of IgE. Non-specific rosette formation was usually less than 0·4%.

Cytotoxicity assay. Preparations of chicken erythrocyte target cells were coated with an IgE myeloma protein (E_c-IgE) or rabbit IgG antibodies (E_cA) and the cytotoxicity assay was carried out as previously described (Melewicz & Spiegelberg, 1980). Specific ^{51}Cr-release from IgE-coated target cells (E_c-IgE) was determined by subtracting the percentage of ^{51}Cr released into the

Table 1. Clinical data of atopic patients

Patient no.	Age/sex	Diagnosis	iu IgE/ml	WBC × 10^3/mm^3	Treatment: Corticosteroids Systemic*	Treatment: Corticosteroids Topical	Treatment: Antihist.	Treatment: β-adrenergic agonists	Treatment: Theophylline
I. Mild to moderate atopic patients									
1	36/F	AR	200	6·5	–	–	–	–	–
2	32/M	AR	900	8·5	–	–	+	–	–
3	28/M	AR	1,200	3·6	–	–	+	–	–
4	22/F	AR	1,700	6·2	–	–	+	–	–
5	37/F	AR	250	5·8	–	–	+	–	–
6	38/F	AD, AR	2,300	7·8	–	+	–	–	–
7	14/M	AR, A	2,150	5·3	–	–	–	+	+
8	13/F	AD, AR, A	600	6·2	–	–	–	+	+
9	22/M	AR, A	2,250	7·5	–	+	–	–	–
10	47/F	AR	900	4·5	–	–	+	–	–
11	33/M	AR	850	7·0	–	–	–	–	–
12	9/M	AR, A	1,650	6·5	–	–	+	+	–
Total				6·2 ± 1·4					
II. Severe atopic patients									
13	13/M	AD, AR, A	77,500	9·0	–	–	–	–	–
14	27/M	AD, AR, A	12,500	10·1	–	+	+	–	–
15	32/M	AD, AR, A	8,000	6·5	–	+	+	–	–
16	28/M	AD, AR, A	14,500	7·2	–	+	+	–	–
17	39/F	AD, AR, A	3,350	4·8	–	+	–	–	–
18	10/M	AD, AR, A	11,500	5·5	–	–	+	–	–
Total				7·2 ± 2·1					
III. Severe atopic patients on oral corticosteroid treatment									
19	9/M	AR, A	12,000	4·7	10	–	–	+	+
20	63/M	AD, A	23,500	7·5	15	+	+	–	+
21	19/F	AD, A	95,000	8·0	25	+	+	–	+
22	34/F	AD, AR, A	10,500	7·3	15	+	+	–	–
Total				6·9 ± 1·5					

AD = atopic dermatitis, AR = allergic rhinitis, A = asthma.

* Milligrams oral prednisone, alternate days.

supernatant from target cells coated with 56°C heated IgE, non-specific ^{51}Cr-release from the percentage of ^{51}Cr released from E_c-IgE. Heating of IgE at 56°C for 3 hr causes conformational changes in the Fc portion of the molecule (Dorrington & Bennich, 1973) and destroys its ability to bind to Fcε receptors (Ishizaka, Ishizaka & Menzel, 1967). The percentage of ^{51}Cr-release from target cells coated with heated IgE was usually less than 5%. All assays were performed in duplicate at a mononuclear cell to target cell ratio of 2:1 in the presence of 10% heat-inactivated autologous serum. In several experiments, mononuclear cells from normals were incubated with target cells in the presence of serum from patients with severe atopic disease (Group II).

Measurement of serum IgE. Serum IgE concentrations were determined by a solid-phase radioimmunoassay (Phadebas IgE Prist®, Pharmacia Diagnostics, Piscataway, New Jersey).

Statistical analysis. The mean values and standard deviations were calculated and analysed by Student's *t*-test. *P* values greater than 0·05 were not considered significant. The correlation coefficient was calculated from means, standard deviations and covariance.

RESULTS

Percentage of ^{51}Cr-release from IgE-coated target cells (E_o-IgE) and IgG-sensitized target cells (E_cA). The percentage (mean ± s.d.) of specific ^{51}Cr-release from E_c-IgE and E_cA by mononuclear cells of patients and normals is shown in Table 2. There was a significantly increased ($P<0·001$) ^{51}Cr-release from E_c-IgE for mononuclear cells from patients of Group II when compared to normals or other patients. The percentage of ^{51}Cr-release obtained with each normal donor and patient's mononuclear cells is shown in Fig. 1. There was a decreased ^{51}Cr-release from E_c-IgE and E_cA when mononuclear cells from patients on oral corticosteroids were used but this decrease was not statistically significant ($P>0·3$). No correlation was noted between the percentage of specific ^{51}Cr-release and the age or sex of patients, treatment with topical or systemic steroids, antihistamine, β agonists or theophylline.

The percentage of ^{51}Cr-release from E_cA target cells was similar in all patient groups and normals. The percentage of ^{51}Cr-release from E_c-IgE and E_cA was not increased when mononuclear cells from normals were incubated with target cells in the presence of serum from either patients 17 or 18 of Group II.

Percentage of monocytes and Fcε$^+$ monocytes in mononuclear cell preparations. Since we have previously demonstrated that the major effector cell which mediates ^{51}Cr-release from E_c-IgE target cells is a monocyte (Melewicz & Spiegelberg, 1980), we determined the percentage of monocytes (defined as latex bead-ingesting cells) and monocytes with Fc receptors for IgE (Fcε$^+$) in the

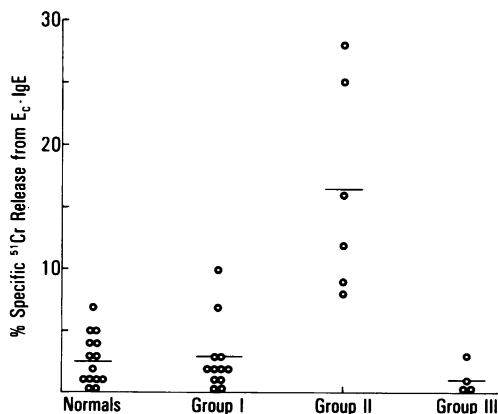

Fig. 1. Percentage of specific ^{51}Cr-release from IgE-coated target cells by mononuclear cells from 14 normals, 12 patients with mild (Group I) disease, six patients with severe disease (Group II) and four patients with severe disease treated with oral prednisone. The geometric mean of each group is indicated by a horizontal line.

Table 2. Percentage of specific ^{51}Cr-release from E_c-IgE and E_cA target cells by mononuclear cells from atopic patients and normals

	Number	Per cent ^{51}Cr-release*	
		E_c-IgE	E_cA
Normals	14	2·6±2·2	51·8±11·1
Mild atopics (Group I)	12	2·9±2·9	48·8±18·6
Severe atopics (Group II)	6	16·3±8·4†	48·7±17·6
Severe atopics on oral corticosteroids (Group III)	4	1·0±1·4	41·0±9·1

* Mean±s.d.
† $P<0·001$.

Table 3. Percentage of monocytes and $Fc\varepsilon^+$ monocytes in mononuclear cell preparations from normal donors and atopic patients

	Number	Per cent latex$^+$	Per cent latex$^+$ and $Fc\varepsilon^+$
Normals	14	7·4±2·1*	1·2±0·6
Mild atopics (Group I)	12	6·6±1·5	1·3±0·8
Severe atopics (Group II)	6	6·7±0·6	3·6±0·9†
Severe atopics on oral corticosteroids (Group III)	4	6·5±1·3	0·4±0·5

* Mean±s.d.
† $P<0·01$.

Table 4. Effect of depletion of monocytes by carbonyl iron treatment of mononuclear cells from two atopic patients on the percentage of ^{51}Cr-release from E_c-IgE and E_cA target cells

Mn cell	Per cent latex$^+$	Per cent latex$^+$ and $Fc\varepsilon^+$	Per cent latex$^-$ and $Fc\varepsilon^+$	Per cent ^{51}Cr-release	
				E_c-IgE	E_cA
Unfractionated	6·0	4·2	1·3	16	43
Monocyte-depleted	0·5	0·3	1·2	3	54
Unfractionated	5·0	2·5	0·9	12	33
Monocyte-depleted	0·5	0·4	1·3	4	31

mononuclear cell preparations used in the cytotoxicity assay. There was no significant difference in the percentage of monocytes in patients or normals. A significant increase ($P<0{\cdot}01$) in the percentage of $Fc\varepsilon^+$ monocytes was seen in the severe atopic patients (Group II) when compared to normals or other patient groups (Table 3). A highly significant correlation ($r=0{\cdot}87$, $P<0{\cdot}01$) was noted between the percentage of $Fc\varepsilon^+$ monocytes in mononuclear cell preparations from patients and specific ^{51}Cr-release from E_c-IgE. There was no significant correlation between the percentage of total monocytes and specific ^{51}Cr-release from E_c-IgE or E_cA.

Depletion of monocytes from mononuclear cells of atopic patients. Mononuclear cells from two severe atopic patients were depleted of monocytes by incubation with carbonyl iron particles. A marked decrease in ^{51}Cr-release from E_c-IgE and the percentage of total monocytes and $Fc\varepsilon^+$ monocytes was seen after the carbonyl iron treatment (Table 4). There was no change in the percentage of $Fc\varepsilon^+$ lymphocytes (cells not ingesting latex beads) or the percentage of ^{51}Cr-release from E_cA target cells. Viability of the monocyte-depleted cells was greater than 95%.

DISCUSSION

These studies demonstrate that mononuclear cells from patients with severe atopic disorders have significantly increased IgE-dependent cytotoxic activity as measured by ^{51}Cr-release from target cells coated with IgE. This cytotoxicity is highly correlated ($P<0{\cdot}01$) to the percentage of $Fc\varepsilon^+$ monocytes present in these mononuclear cell preparations and is decreased to background levels by removal of monocytes, indicating that monocytes bearing $Fc\varepsilon$ receptors were responsible for the increase in ^{51}Cr-release. In contrast to severely atopic patients, mononuclear cells from patients with mild disease did not show a significant increase in either the percentage of $Fc\varepsilon^+$ monocytes or IgE-dependent cytotoxicity as compared to the normal donors.

Monocytes with $Fc\varepsilon$ receptors may play a role in the pathogenesis of allergic disorders. Fc receptors for IgG on monocytes are involved in the lysis of IgG-coated target cells (Shaw, Levy & LoBuglio, 1979). It is likely that $Fc\varepsilon$ receptors function in a similar manner since IgE-coated target cells can be lysed by monocytes (Melewicz & Spiegelberg, 1980). The reason for the increase in $Fc\varepsilon^+$ monocytes in mononuclear cells of severe atopic patients is unknown. $Fc\varepsilon^+$ lymphocytes are also increased in severe atopic patients (Spiegelberg *et al.*, 1979). Circulating IgE complexes have been detected in the serum of severely atopic patients (Brostoff, Johns & Stanworth, 1977). These complexes may activate monocytes with $Fc\varepsilon$ receptors to release monokines or enzymes, since binding of aggregated rat IgE to $Fc\varepsilon$ receptors on rat macrophages causes cell activation as measured by increases in intracellular cyclic GMP and release of β-glucuronidase (Dessaint *et al.*, 1979, 1980). After incubation with IgE and anti-IgE, human alveolar macrophages release lysosomal enzymes and produce superoxide anion (Joseph *et al.*, 1980). This provides additional evidence that complexed IgE can activate macrophages.

An intriguing possibility is that monocytes, after interaction with IgE, release mediators of immediate hypersensitivity such as slow-reacting substance of anaphylaxis (SRS-A) since after a phagocytic stimulus, mouse peritoneal macrophages release leukotriene-C, a prostaglandin derivative with potent slow-reacting substance activity (Rouzer *et al.*, 1980). In this regard it is of interest that among human peripheral blood mononuclear cells, monocytes are the major source of prostaglandins and related lipids (Kennedy, Stobo & Goldyne, 1980). Release of such substances could be a mechanism of monocyte- and macrophage-mediated immediate hypersensitivity in man.

The serum IgE level may modulate the number of $Fc\varepsilon$ receptors on monocytes as has been shown for basophils (Malveaux *et al.*, 1978). This is unlikely since *in vitro* culturing of human lymphocytes (Spiegelberg & Melewicz, 1980) or monocytes with IgE does not increase the percentage of cells with $Fc\varepsilon$ receptors (manuscript in preparation).

The possibility that autologous serum factors may have contributed to the increased IgE-dependent cytotoxicity observed with mononuclear cells from severely atopic patients is unlikely, since release of ^{51}Cr from IgG-sensitive target cells was similar in patients and normal donors. Furthermore, cytotoxicity for both IgE- and IgG-coated target cells was not increased when mononuclear cells from normal donors were used as effector cells in the presence of serum with markedly elevated

IgE levels from severely atopic patients. The amount of IgE in the serum does not directly influence the level of cytotoxicity because the patients on oral prednisone had IgE levels greater than 10,000 iu and their mononuclear cells demonstrated decreased IgE-dependent cytotoxic activity. Corticosteroids are known to decrease the Fcγ and C3 receptor activity of human monocytes *in vitro* (Schreiber *et al.*, 1975). A similar effect could occur with respect to Fcε receptors since atopic patients on oral prednisone have a decreased percentage of $Fc\varepsilon^+$ monocytes and $Fc\varepsilon^+$ lymphocytes (Spiegelberg & Melewicz, 1980). Additional studies will be needed to define the effect of corticosteroids on the activity of Fcε receptors.

A previously reported abnormality of monocyte function in severe atopic patients is a decrease in monocyte-mediated antibody-dependent cellular cytotoxicity (ADCC) against IgG-coated target cells (Kragballe, 1979). In the present study employing unfractionated mononuclear cells, we found no significant difference in IgG-dependent ADCC between such patients and normals although there was some decrease noted in the severe atopic patients on oral prednisone. This difference may be explained by IgG-dependent ADCC activity mediated by lymphocytes in the unfractionated mononuclear cell preparations, whereas in the other study, mononuclear cells containing 10 to 20% lymphocytes were used.

We conclude that monocytes with Fcε receptors are increased in severe atopic patients and that these cells demonstrate increased IgE-dependent cytotoxicity toward IgE-coated target cells. The increased cytotoxicity may reflect activation of $Fc\varepsilon^+$ monocytes and this increase in Fcε receptor activity may be important in the clearance of circulating allergen–IgE immune complexes and release of mediators of immediate hypersensitivity. The relationship between IgE-dependent cytotoxicity and the clinical course of patients with severe allergic disease will require sequential studies of patients. Further investigation will be necessary to define the role of $Fc\varepsilon^+$ monocytes in the pathogenesis of atopic disorders.

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