

INCREASED PERIPHERAL BLOOD MONOCYTES WITH Fc RECEPTORS FOR IgE IN PATIENTS WITH SEVERE ALLERGIC DISORDERS¹

F. MICHAEL MELEWICZ, ROBERT S. ZEIGER, MICHAEL H. MELLON, RICHARD D. O'CONNOR, AND HANS L. SPIEGELBERG

From the Department of Immunopathology, Scripps Clinic and Research Foundation, La Jolla, California, Kaiser Permanente Medical Center, Division of Allergy and Clinical Immunology, San Diego, and Allergy and Immunology Division, Department of Pediatrics, University of California, San Diego

Peripheral blood monocytes, defined as latex bead-ingesting mononuclear cells, from 15 healthy nonallergic donors and 22 patients with allergic disorders were analyzed for Fc receptors for IgE (Fc_ε) by a rosette assay employing ox erythrocytes coated with IgE. The patients were divided into 3 groups. Group I: 12 patients with mild to moderate atopic disease and serum IgE levels up to 2300 IU/ml. Group II: 6 patients with severe generalized atopic dermatitis, allergic rhinitis, and asthma, of which 5 had IgE serum levels of 8000 to 77,500 IU/ml. Group III: 4 severely atopic patients with IgE levels greater than 10,000 IU/ml and receiving oral corticosteroids. The numbers of monocytes were similar in healthy donors and patients. In contrast, severely atopic patients (Group II) had significantly more ($p < 0.01$) Fc_ε⁺ monocytes ($107 \pm 42/\text{mm}^3$) than healthy donors ($29 \pm 14/\text{mm}^3$) or patients of Group I ($31 \pm 14/\text{mm}^3$). Patients of Group III had significantly fewer ($p < 0.05$) Fc_ε⁺ monocytes ($12 \pm 16/\text{mm}^3$) than controls and patients of Groups I and II. We conclude that patients with severe allergic disorders have a significant increase of peripheral blood monocytes with Fc receptors for IgE, which suggests that these cells may participate in the pathophysiology of atopic disease.

Antigen-specific IgE antibodies are an important component of atopic disorders. The Fc portion of IgE antibodies binds to specific cell surface receptors (Fc_ε receptors)² on mast cells and basophilic granulocytes, and subsequent to reaction with antigen, histamine and other vasoactive substances are released from these cells (1). Until recently, only mast cells and basophils were known to have Fc_ε receptors. However, human peripheral B (2) and T (3) lymphocytes and monocytes (4, 5) were also shown to bind IgE. The Fc_ε receptors on lymphocytes and monocytes most likely differ from those on mast cells because they bind IgE with a much lower affinity (4). As shown by rosette assays, approximately 1 to 2% of normal peripheral blood lymphocytes and 20% of monocytes have Fc_ε receptors (4, 5). Patients with severe atopic disorders have a significant increase of lymphocytes with Fc_ε receptors, which suggests that these cells may be involved in the regulation of IgE antibody formation (3, 6). In this study, we determined whether

peripheral blood monocytes with Fc_ε receptors are also increased in patients with allergic disease.

MATERIALS AND METHODS

Allergic patients and normal controls. Fifteen healthy laboratory and clerical workers (age 21 to 43) who had no history of allergic disorders served as controls. Twenty-two outpatients 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. None of the patients had a clinically apparent bacterial or viral infection at that time of study. 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 I. The patients were divided into 3 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 No. 19, had severe generalized atopic dermatitis that had involved 75% or more of their body surface since early childhood. Patients of Group II had severe atopic dermatitis, and 4 of 6 were using topical corticosteroids. The patients of Group III required alternate-day oral prednisone to control their symptoms. They did not have asthmatic symptoms but still had atopic dermatitis at the time of testing.

Mononuclear cell isolation. Mononuclear cells were isolated from heparinized venous blood by density gradient centrifugation (7). Briefly, the blood was diluted 1:1 with sterile phosphate buffered 0.15 M NaCl, pH 7.4 (PBS), and centrifuged over Ficoll-Hypaque (Pharmacia Fine Chemicals, Piscataway, NJ). The cells at the interface were washed once with PBS and resuspended at 5×10^6 cells/ml in RPMI 1640 media. The mononuclear cells of 4 patients of Group II were enriched for monocytes by depletion of T lymphocytes forming spontaneous rosettes with sheep erythrocytes (E) as previously described (8).

Rosette assay for monocytes with Fc_ε receptors. Monocytes with Fc_ε receptors (Fc_ε⁺) were detected by a rosette assay employing pyruvic aldehyde and formaldehyde fixed ox erythrocytes (E_o) coated with a human IgE myeloma protein (E_o-IgE) (2, 4). For latex ingestion, 1.0 ml of mononuclear cells at 5×10^6 /ml in medium containing 20% heat inactivated fetal calf serum (Flow Laboratories, McLean, VA) were first incubated for 1 hr at 37°C with 20 μ l of a 5% latex bead suspension in PBS (2.0 μ uniform latex particles, Dow Diagnostics, Dow Chemical Co., Indianapolis, IN). The cells were then washed and resuspended in RPMI 1640 media to 5×10^6 cells/ml for use in the rosette assay (4). Mononuclear cells that had ingested 5 or more latex beads were scored as latex⁺, and mononuclear cells binding 3 or more E_o-IgE indicator cells were scored as Fc_ε⁺. Five hundred or more cells were counted to obtain the percentage of positive cells. The absolute number of monocytes/mm³ of blood was calculated by multiplying the percentage of monocytes (latex-ingesting cells) in the mononuclear cell preparations by the absolute number of mononuclear cells/mm³ determined from the WBC/mm³ and differential of the Wright's stained peripheral blood smear. To test the specificity of rosette formation, mononuclear cells were incubated with and without soluble IgE (final concentration 8.0 mg/ml) for 15 min at 20°C prior to the addition of E_o-IgE indicator cells. Incubation of mononuclear cells with the same concentration of normal human IgG did not inhibit rosette formation with E_o-IgE indicator cells. The percentage of rosettes not inhibited by IgE (nonspecific rosettes) was subtracted from the percentage of rosettes formed in the absence of IgE. Nonspecific rosette formation was usually less than 0.4%.

Rosette assay for monocytes with Fc_γ receptors. Freshly washed ox erythrocytes (E_o) were sensitized with a subagglutinating dose of rabbit IgG

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² Abbreviations used in this paper: Fc_ε, Fc_γ, Fc receptors for IgE and IgG; E, sheep erythrocytes; E_o, ox erythrocytes; E_o⁺, ox erythrocytes fixed with pyruvic aldehyde and formaldehyde; E_o-A, E_o sensitized with rabbit IgG anti-E_o antibodies; E_o-IgE, E_o coated with a human IgE myeloma protein.

TABLE I
Clinical data of atopic patients

Patient	Age	Sex	Diagnoses	I.U. IgE/ml	WBC × 10 ³ /mm ³	Treatment				
						Corticosteroids		Antihist.	β-adrenergic agonists	Theophylline
						Systemic ^a	Topical			
I. Mild to moderate atopic patients										
Patient #										
1	11	M	AR	1,650	6.0	—	—	—	—	—
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	—	—	+	+	—
					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	—	—	+	—	—
					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	+	+	—	—
					6.9 ± 1.5					

AD, atopic dermatitis

AR, allergic rhinitis

A, asthma

^a mg oral Prednisone q.o.d.

anti E_o antibodies. These indicator cells (E_oA) were used in a rosette assay as described (4). Mononuclear cells bind 3 or more indicator cells and were scored as Fc_ε⁺.

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

Statistical analysis. The mean values and standard deviations were calculated and analyzed by Student's *t*-test. Values of *p* greater than 0.05 were not considered significant. The correlation coefficient was calculated from means, standard deviations, and covariance.

RESULTS

Monocytes with Fc_ε receptors in normals and allergic patients. The isolated mononuclear cells were analyzed for percentages of all latex-ingesting cells (total monocytes) and those latex-ingesting cells that formed E_o-IgE rosettes (Fc_ε⁺ monocytes). The number of monocytes/mm³ of blood was determined from these percentages as described in *Materials and Methods*. Latex ingestion was used to distinguish Fc_ε⁺ monocytes from Fc_ε⁺ lymphocytes. In normals and patients approximately 65% of all Fc_ε⁺ mononuclear cells were monocytes.

There was no significant difference between patients and normals with respect to numbers of total monocytes/mm³. The number (mean $\pm$ SD) of total monocytes/mm³ was: normals 189 ± 79 , patient Group I 176 ± 37 , Group II 191 ± 23 , and Group III 172 ± 25 . The number of Fc_ε⁺ monocytes/mm³ of each normal donor and patient are shown in Figure 1. Patients with mild atopic disease (Group I) had numbers (mean $\pm$ SD) of Fc_ε⁺ monocytes/mm³ (31 ± 14) similar to the normal donors (29 ± 14). In contrast, the severely atopic patients (Group II) had significantly more ($p < 0.01$) Fc_ε⁺ monocytes/mm³ (107 ± 42) than the normals or mild atopic patients. The 4 patients with severe atopic disease who were

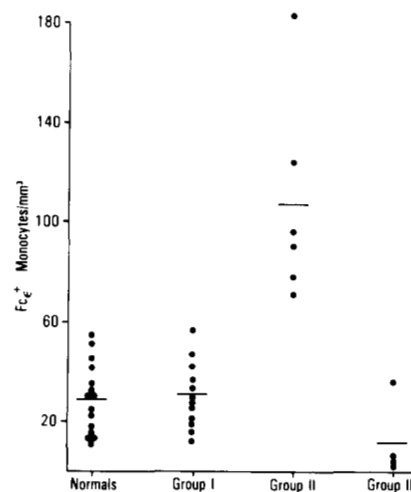


Figure 1. Number of Fc_ε⁺ monocytes/mm³ of blood in 15 normal donors, 12 allergic patients with mild disease (Group I), 6 patients with severe disease (Group II), and 4 patients with severe disease treated with prednisone (Group III). The geometric mean of each group is indicated by a horizontal line.

taking oral corticosteroids (Group III) had significantly fewer ($p < 0.05$) Fc_ε⁺ monocytes/mm³ (12 ± 16) than normals or patients of Groups I and II. There was no significant correlation between the number of Fc_ε⁺ monocytes/mm³ and treatment with topical steroids, antihistamine, β -agonists, or theophylline. The age and sex of patients and controls also did not correlate significantly with the number of Fc_ε⁺ monocytes.

The percentage of total monocytes and Fc_ϵ monocytes in mononuclear cell preparations of normal donors and patient groups is shown in Table II. The mononuclear cells of Group II patients had a significant increase ($p < 0.01$) in the percentage of Fc_ϵ monocytes when compared to the other patient groups or normals. The percentage of total monocytes was similar in patients and normals. Thus, the differences observed among the patient groups and normals with respect to the number of Fc_ϵ monocytes/mm³ of blood were the result of differences in the proportion of total monocytes that were Fc_ϵ and not of differences in the number of total monocytes. The mean percentage of total monocytes forming E_0 -IgE rosettes (Fc_ϵ) was 16% in normal donors, 18% in Group I, 56% in Group II, and 7% in Group III.

Two patients of Group II were studied when their disease activity was minimal. One patient (No. 17) with severe atopic dermatitis was studied 4 mo later when her disease was in spontaneous remission. At that time she was asymptomatic and receiving no medication. Her isolated mononuclear cells contained 4% Fc_ϵ monocytes during active disease and decreased to 1.7% at the time of remission. The serum IgE level during remission decreased only slightly from 3300 IU/ml to 2500 IU/ml. The other patient (No. 18) was initially studied at a time when his atopic dermatitis was minimal and then several months later, when he had a severe exacerbation of eczema. The Fc_ϵ monocytes in his mononuclear cells increased from 1.0% at the time of minimal disease to 3.8% when his dermatitis was severe.

The correlation coefficient (r) between the serum IgE level and the number of Fc_ϵ monocytes/mm³ was calculated for patients of Groups I and II. No significant correlation was found in Group I ($r = 0.33$). In contrast, there was a significant correlation ($p < 0.01$) between the serum IgE level and the number of Fc_ϵ monocytes for Groups I and II combined ($r = 0.81$) and Group II alone ($r = 0.85$).

Monocytes with Fc_ϵ receptors in normals and allergic patients. The percentage of monocytes with Fc_ϵ receptors in mononuclear cell preparations was not significantly different among patient groups and normals. The percentage of mononuclear cells that were latex positive and formed rosettes with E_0A was: Normals $5.6 \pm 2.1\%$, Group I $5.3 \pm 2.4\%$, Group II $5.2 \pm 2.3\%$, and Group III $4.5 \pm 1.6\%$. Approximately 80% of total monocytes in patients and normals had Fc_ϵ receptors. There was no significant difference in the absolute number of Fc_ϵ monocytes/mm³ of blood among the normals and patient groups.

Monocytes with Fc_ϵ receptors in monocyte-enriched cell fractions. Isolated mononuclear cells of 4 patients of Group II were enriched for monocytes by depletion of E rosetting cells to determine if this enrichment would result in a change in the percentage of monocytes with Fc_ϵ receptors. After E rosette depletion, the percentage of Fc_ϵ monocytes increased proportionally to the increase in percentage of total monocytes (Table III). There was no significant change in the percentage of total monocytes that had Fc_ϵ receptors. Similar results were obtained with E rosette depleted monocyte-enriched cell fractions from normal and mild atopic patients.

DISCUSSION

These data demonstrate that patients with severe atopic disorders have increased numbers of peripheral blood monocytes with Fc_ϵ receptors when compared to normals or patients with mild disease. This increase is due to a greater percentage of monocytes bearing Fc_ϵ receptors, as patients and normal donors had similar numbers of monocytes. Two patients with severe atopic dermatitis were studied when their disease activity was minimal, and during

this period their mononuclear cells contained a normal percentage of Fc_ϵ monocytes. The level of Fc_ϵ monocytes seems to correlate with disease severity and activity. However, additional studies of patients with severe atopic disease in remission will be required to confirm this finding.

The role of the Fc_ϵ monocytes in atopic disease is presently unknown. Circulating IgE-antigen complexes may activate monocytes to release various monokines and mediators of immediate hypersensitivity. Rat macrophages have recently been shown to increase intracellular cyclic GMP and release β -glucuronidase after interaction with aggregated rat IgE (9, 10). In contrast, interaction with monomeric IgE did not induce these changes. Furthermore, a phagocytic stimulus causes mouse peritoneal macrophages to release leukotrienes (11, 12), prostaglandin derivatives that have been shown to be the major component of slow reacting substances of anaphylaxis (SRS-A) isolated from human, rat, and mouse sources (13, 14). Among human peripheral blood mononuclear cells, monocytes are the major producers of prostaglandins and related lipids (15). After *in vitro* incubation with Fc fragments of IgG or aggregated IgG, human monocytes release increased amounts of prostaglandins (16). This release does not occur after incubation with monomeric IgG. It is possible that release of prostaglandins and substances with SRS-A activity from human monocytes after interaction with IgE containing immune complexes may be an important mechanism by which monocytes participate in atopic disease. From the evidence cited above, it is likely that IgE must be in a complexed form in order to activate monocytes to release such substances. IgE complexes have been detected in the serum of atopic patients (17), so activation of Fc_ϵ monocytes may be regulated by the level of circulating IgE-allergen immune complexes.

Fc receptors of IgG on monocytes have been shown to promote phagocytosis of IgG antigen-antibody complexes and to mediate antibody-dependent lysis of IgG coated target cells (18). The Fc_ϵ receptors on monocytes appear to function in a similar manner. We have shown that human monocytes are able to specifically lyse IgE-coated target cells (5). Recent studies in our laboratory showed that monocyte cytotoxicity against IgE-coated target cells is markedly elevated in severe atopic patients and is highly correlated with the level of Fc_ϵ monocytes in the blood of these patients (manuscript in preparation).

The reason for the increase of Fc_ϵ monocytes in severely atopic patients is not understood. A nonspecific enhancement of receptor activity is improbable because there was no increase in Fc_γ monocytes in these patients. The serum level of IgE could modulate the expression of Fc_ϵ receptors on monocytes. This is unlikely because a low correlation was found between the number of Fc_ϵ monocytes and the serum IgE levels in patients with mild disease. Also, patients with severe atopic disease on oral prednisone had low numbers of Fc_ϵ monocytes and serum IgE levels greater than 10,000 IU/ml. Furthermore, incubation of human monocytes *in vitro* with various concentrations of IgE did not result in an increase in the percentage of Fc_ϵ cells (manuscript in preparation). For *in vitro* induction of Fc_ϵ lymphocytes, both IgE and antigen-activated lymphocytes are required (19). Rather than correlating directly with the serum IgE level, Fc_ϵ receptor expression on monocytes may relate to the binding and phagocytosis of circulating IgE-allergen immune complexes.

TABLE III

Fc_ϵ monocytes in mononuclear cells enriched for monocytes by depletion of E rosetting cells in severely atopic patients

Patient Number	Mononuclear Cells	% Total Latex ⁺	% Latex ⁺ /Fc _ε ⁺	% Latex ⁺ /Fc _ε ⁺ of Total Latex ⁺
13	Unfractionated	6.0	5.1	85
	E depleted	20.0	16.8	84
14	Unfractionated	7.5	3.5	46
	E depleted	30.0	11.4	38
15	Unfractionated	7.0	3.0	43
	E depleted	26.0	9.4	36
16	Unfractionated	6.5	2.5	38
	E depleted	23.0	8.3	36

TABLE II

Percentage of monocytes and Fc_ϵ monocytes in mononuclear cell preparations from normal donors and atopic patients

	Number	% Latex ⁺	% Latex ⁺ and Fc _ε ⁺
Normals	15	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 (Group III) (oral corticosteroids)	4	6.5 ± 1.3	0.4 ± 0.5

*Mean ± SD.

† $p < 0.01$.

Four severely atopic patients treated with oral corticosteroids (Group III) had significantly fewer Fc_ϵ monocytes than normals. The number of Fc_ϵ lymphocytes was also found to be significantly lower than normal in these patients (6). In addition 3 patients with mild atopic disease and taking oral corticosteroids were studied, and all 3 had lower than normal levels of Fc_ϵ monocytes. The patients of Group III were studied at least 24 hr after their last dose of prednisone, as studies of patients on alternate-day oral prednisone reveal a transient lymphopenia and monocytopenia occurring on the day of medication (20). Corticosteroids may directly suppress the formation of Fc receptors or cause a shift of Fc_ϵ cells from the circulation into lymphoid tissues. *In vitro* studies of Fc_γ and C3 receptor function of human monocytes demonstrate a decrease in receptor activity after incubation with pharmacologic concentrations of corticosteroids (21). Additional *in vivo* and *in vitro* studies will be necessary to define the effect of corticosteroids on Fc_ϵ receptors.

In this study a high concentration of IgE (8.0 mg/ml) was used to inhibit E'_{ϕ} -IgE rosette formation to ensure that if the monocytes of atopic patients had increased numbers of Fc_ϵ receptors, E'_{ϕ} -IgE rosette formation would be inhibited. Recent experiments in our laboratory demonstrate that lower concentrations of IgE (1.0 mg/ml), which completely inhibit E'_{ϕ} -IgE rosette formation of normal lymphocytes, can also completely inhibit E'_{ϕ} -IgE rosette formation of highly purified normal monocytes and of an Fc_ϵ monocyte-like human cell line (U-937). Furthermore, the binding affinity of ^{125}I radiolabeled monomeric IgE to lymphocytes, monocytes, and Fc_ϵ lymphoblastoid and monocyte-like human cell lines is similar (manuscript in preparation).

In conclusion, the significant increase of blood monocytes with Fc_ϵ receptors in severely atopic patients suggests that these cells are important in the regulation and expression of allergic disease. Further investigations will be needed to determine their role in the pathogenesis and maintenance of atopic disorders.

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