

Human Neutrophils Express Immunoglobulin E (IgE)-binding Proteins (Mac-2/εBP) of the S-Type Lectin Family: Role in IgE-dependent Activation

By Marie-José Truong, Valérie Gruart, Jean-Pierre Kusnierz, Jean-Paul Papin, Sylvie Loiseau, André Capron, and Monique Capron

From the Centre d'Immunologie et de Biologie Parasitaire (CIBP), Unité Mixte Institut National de la Santé et de la Recherche Médicale (INSERM) U167-Centre National de la Recherche Scientifique (CNRS) 624, Institut Pasteur, 59019 Lille, France

Summary

It has been suggested that neutrophils may be involved in the late-phase reaction of immunoglobulin E (IgE)-dependent hypersensitivity states. However, the identity of neutrophil-associated molecules inducing the release of mediators remains unclear. In this report, we demonstrate that human neutrophils from normal donors or from patients with inflammatory disorders could bind myeloma IgE proteins, especially after desialylation. Northern blot, immunoprecipitation, and flow cytometry analyses revealed that neutrophils did not express FcεRII/CD23, but rather Mac-2/ε binding protein (BP), belonging to the S-type lectin family. Similarly to IgA used as positive control, myeloma IgE proteins, as well as polyclonal IgE antibodies with or without antibody specificity, were both capable of inducing a neutrophil respiratory burst. Anti-Mac-2 but not anti-CD23 mAb strongly decreased the IgE-dependent activation of neutrophils, induced either by the specific antigen or by anti-IgE antibodies. These findings open new perspectives on the functional role of neutrophils in IgE-associated diseases including allergic states or parasitic infections.

Inflammatory reactions generally involve a vast array of mediators and a variety of effector cells such as mast cells, macrophages, eosinophils, platelets, and neutrophils. Among them, neutrophils have been rather neglected in studies concerning allergic diseases, although an increase in neutrophil numbers and activity was found to be correlated to airway hyperresponsiveness in asthmatic patients (1). These findings have suggested that neutrophils might play a role in allergic diseases characterized by a marked elevation of serum IgE, such as asthma, especially during the late-phase reaction. However, neutrophils represent the only blood cell population that does not seem to express conventional Fc receptors for IgE, neither FcεRI, like basophils or mast cells (2), nor FcεRII, like macrophages, eosinophils, or platelets (3). Besides these IgE Fc receptors, a new family of IgE-binding molecules has been recently described. They belong to S-type lectins with the ability to bind IgE through carbohydrate recognition domain (4). Members of the family include Mac-2/εBP, which are endogenous soluble lectins and can be expressed by various cell types (5, 6). One feature of εBP molecules is their restricted recognition by specific glycoforms of IgE. It is interesting that the majority of myeloma IgE proteins and polyclonal IgE from some patients are able to bind to εBP only after desialylation (5, 7). In this respect, it has to be mentioned that the few IgE binding assays previously reported

on human neutrophils (8, 9) have been performed with myeloma IgE proteins, and therefore did not allow us to investigate the existence of functional interactions between neutrophils and IgE antibodies from patients. The wide cell distribution of Mac-2/εBP molecules and their recent demonstration in eosinophils from hypereosinophilic patients (10) led us to investigate their possible existence in human neutrophils.

Materials and Methods

Neutrophil Preparations. Patient neutrophils were obtained from the venous blood of patients with various diseases (allergic diseases, parasitic infections, and eosinophilic disorders) by centrifugation through metrizamide discontinuous gradients, according to previously described techniques (11), and collected in the lower density layer (layer II) corresponding to 20–22% metrizamide solutions. Neutrophils from normal blood donors were isolated by the same technique or by dextran sedimentation, followed by centrifugation through a cushion of Ficoll-Hypaque (Pharmacia Fine Chemicals, Piscataway, NJ) and hypotonic lysis to remove remaining erythrocytes (12). The degree of purity (up to 97.5%) and the morphologic integrity of cell populations were estimated after staining of cytocentrifuged preparations with Giemsa. Contamination by eosinophils in neutrophil preparations was <10%. As control, human alveolar macrophages were obtained by bronchoalveolar lavage of

asthmatic patients (Truong, M. J., V. Gruart, F.-T. Liu, L. Prin, A. Capron, and M. Capron, manuscript submitted for publication).

Immunoglobulins, Antibodies, and Antigens. Human myeloma IgE-PS was kindly donated by Dr. H. L. Spiegelberg (School of Medicine, University of California, San Diego, CA) and IgE-BL was purchased from Bennett Laboratories (Buena Park, CA). Human sera from patients with hyper-IgE syndrome (25,000 IU/ml) were obtained from Dr. F.-T. Liu (The Scripps Research Institute, La Jolla, CA). Human sera from patients infected with the parasite *Schistosoma mansoni* were provided by Dr. P. Desreumaux (Centre Hospitalier St. Louis, St. Louis, Sénégal). Serum IgA was obtained from Sigma Chemical Co. (St. Louis, MO). The anti-Mac-2 hybridoma supernatant, previously described (13), a kind gift of Dr. B. Cherayil (MGH Cancer Research, Boston, MA) and irrelevant anti-*S. mansoni* hybridoma supernatant have been used at different dilutions in the various assays. Anti-CD23 mAb (8-30) directed against the IgE binding domain of CD23 (14) was donated by Dr. Suemura (Osaka University Hospital, Osaka, Japan). FITC-labeled anti-human IgE, anti-human IgA, anti-rat IgG, or anti-mouse IgM antibodies (Fab 2') were purchased from Cappel Laboratories (Cochranville, PA). Unlabeled anti-human IgE and anti-human IgA antibodies were obtained from Immunotech (Marseille, France). The recombinant antigen Sm28GST from *S. mansoni* (15) was kindly given by F. Trottein (CIBP, Institut Pasteur).

Northern Blot Analysis. Total RNA was isolated from neutrophil populations and was subjected to electrophoresis in a formaldehyde/1.2% agarose gel, blotted onto a nylon filter, and successively hybridized overnight at 42°C with ³²P-labeled CD23 (16), Mac-2 cDNA (6), and β-actin probes. Probes were removed by boiling the blot on a 0.1% SDS solution, and washes were carried out in 1× SSC, 0.05% SDS at 55°C.

Labeling of Leukocytes and Immunoprecipitations. The cells were lysed with a nonionic/detergent mixture and cell extracts were iodinated with ¹²⁵I as previously described (Truong et al., manuscript submitted for publication). Aliquots of 2 × 10⁶ cpm radioiodinated cell extracts were precleared for 2 h with normal rat serum and 50 μl of protein G-Sepharose (Pharmacia Fine Chemicals) in TNSTEN (50 mM Tris-HCl pH 8.2, 500 mM NaCl, 0.1% SDS, 0.5% Triton-X 100, 5 mM EDTA, 0.02% NaN₃) with 0.1% aprotinin. Immunoprecipitation was carried out by adding anti-Mac-2 hybridoma supernatant (1:10 final dilution) followed by 50 μl of protein G-Sepharose. After overnight incubation at 4°C, the Sepharose beads were washed 10 times with TNSTEN, 0.1% aprotinin, and then resuspended and boiled for 3 min in 40 μl of 1× SDS-PAGE sample buffer. Aliquots of released material were analyzed by SDS-PAGE.

Flow Cytometry. For the detection of surface Mac-2, 10⁶ neutrophils were incubated with anti-Mac-2 or control anti-*S. mansoni* supernatants at a final dilution of 1:10 in PBS for 1 h at 4°C. For IgE and IgA binding analysis, neutrophils were incubated with 50 μg/ml of myeloma IgE (IgE-PS or IgE-BL) or serum IgA for 1 h at 4°C. In some experiments, myeloma IgE proteins or IgA have been incubated with untreated or heat-inactivated neuraminidase (*Clostridium perfringens* type, 0.5 U/mg of protein, Sigma Chemical Co.) for 90 min at 37°C before binding to neutrophils. For the detection of CD23, neutrophils were incubated with 50 μg/ml mAb 8-30 or control IgM mAb for 1 h at 4°C. In all experiments, after washing with PBS, cells were incubated with the corresponding FITC-conjugated anti-Ig antibodies (1:40 final dilution) for 30 min at 4°C. After washing, cells were fixed with 1% paraformaldehyde and analyzed with an Orthocytofluorograph (model 50H; Ortho Diagnostics Systems, Westwood, MA) using a logarithmic fluores-

cence intensity scale. Results are expressed as a percentage of labeled neutrophils after subtraction of the background fluorescence obtained with isotype controls, similarly to techniques reported for eosinophils (17).

Neutrophil Activation. Neutrophils (2.5 × 10⁶/ml) were incubated with 10 μg/ml myeloma IgE proteins, serum IgA, or with medium for 30 min at 4°C. Anti-IgE or anti-IgA antibodies (25 μg/ml) were then added, respectively. Experiments also have been performed with polyclonal IgE present in serum from *S. mansoni*-infected patients, and further stimulation with the specific antigen (recombinant Sm28GST) (15) or with anti-IgE. Sera from patients with hyper-IgE syndrome also have been used to activate neutrophils. The respiratory burst after activation was evaluated by a chemiluminescence (CL) procedure in the presence of luminol (250 μg/ml). Light emission was monitored after 15-30 min of incubation at 37°C using a photometer (Nucleotimetre 107; Interbio CLV, Villeurbanne, France) and was expressed in mV (100 CL U = 1 mV). For inhibition experiments, anti-Mac-2 or control hybridoma supernatants and anti-CD23 or control mAb were added at various concentrations together with IgE or serum before addition of anti-IgE antibodies or antigen.

Statistical Analysis. Student's *t* test for unpaired and paired experiments, and correlation analysis have been used.

Results and Discussion

Detection of mRNA Encoding Mac-2/εBP. The existence of IgE-binding molecules such as FcεRII/CD23 or Mac-2/εBP in purified human neutrophils was first investigated by Northern blot (Fig. 1). Neutrophil RNA extracted from different donors was first probed with the cDNA encoding CD23. No apparent mRNA band was detected at the expected 1.7-kb size. The same Northern blot was then hybridized with the Mac-2 cDNA probe. Neutrophils from both normal donors (Fig. 1, lanes 1 and 2) or patients (Fig. 1, lanes 3-5) expressed the 1.2-kb mRNA corresponding to Mac-2/εBP. Neutrophils purified from some patients (Fig. 1, lanes 4 and 5) appeared to express higher amounts of Mac-2/εBP mRNA than neutrophils purified from other patients or from normal donors. These findings seem in agreement with the variable levels of S-type lectin expression during cell differen-

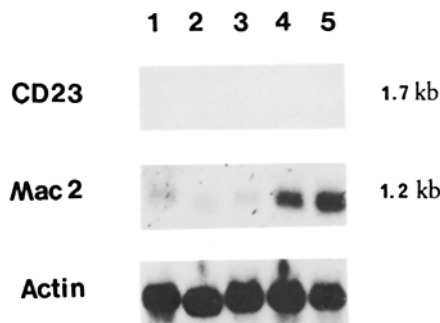


Figure 1. Northern blot analysis of neutrophil RNA prepared from normal donors (lanes 1 and 2) and from three patients with allergic diseases (lanes 3-5). The blot was successively hybridized with CD23, hMac-2, and β-actin probes.

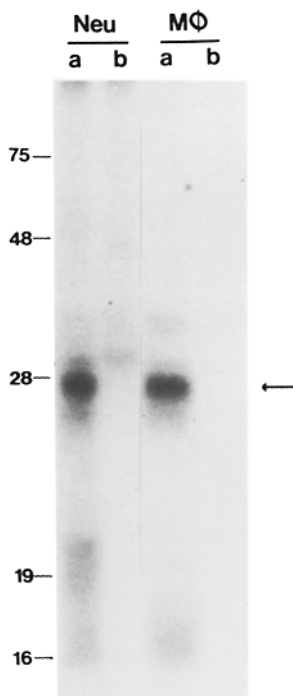


Figure 2. Immunoprecipitation of ^{125}I -labeled lysates of neutrophils from one patient with hypereosinophilic syndrome (*Neu*), and of alveolar macrophages (*MΦ*) as control. Results were obtained with anti-Mac-2 hybridoma supernatant (lanes *a*) and with normal rat serum control (lanes *b*). The M_r is indicated in kD. (\leftarrow) 28-kD molecule.

tiation and maturation, such as in HL60 differentiated to macrophages (6) or in different mast cell lines (18). The variations in Mac-2 mRNA denoted in patients suggest that, in some diseases, neutrophils could be in different stages of maturation, leading therefore to higher expression of Mac-2 mRNA. Our results indicate that neutrophils did not seem to express CD23 mRNA, but have the capacity to synthesize Mac-2/ ϵ BP mRNA, although in lower amounts than eosinophils (Truong, M. J., et al., manuscript submitted for publication).

Characterization of Mac-2/ ϵ BP Molecules by Immunoprecipitation. To characterize the translation products of Mac-2/ ϵ BP mRNA detected above, immunoprecipitation by anti-Mac-2 hybridoma supernatant (Fig. 2, lanes *a*) or control (Fig. 2, lanes *b*) was performed with neutrophil extract from one representative patient (*Neu*) and with alveolar macrophage ex-

tract (*MΦ*). Similarly to results obtained with macrophages, the 28-kD molecule could be detected in human neutrophils. Based upon these results, it was concluded that human neutrophils have the capacity to express Mac-2/ ϵ BP, previously detected in a variety of cell types such as macrophages, mast cell lines, and eosinophils (6, 7, 10, 18).

Flow Cytometry Analysis of Mac-2 Surface Expression and IgE-binding Capacity. The detection of Mac-2/ ϵ BP by Northern blot and by immunoprecipitation led us to investigate their surface expression on neutrophils, by flow cytometry (Table 1). In comparison to Fc ϵ R2/CD23, which was not detected on neutrophils, a finding in agreement with Northern blot results, surface Mac-2 molecules were expressed on a significant percentage of neutrophils purified from patients as well as from normal donors. Since Mac-2/ ϵ BP lectins have the capacity to bind to carbohydrate determinants of IgE (5, 7), we have evaluated the binding of IgE to neutrophils by flow cytometry (Table 1). When myeloma IgE-PS was used, a significant correlation was obtained between the expression of Mac-2 and the binding of IgE-PS, both for patients ($r = 0.57$; $p < 0.01$) and for normal donors ($r = 0.56$; $p < 0.05$), suggesting that IgE-PS could bind to Mac-2 expressed on neutrophil surface. Increased IgE binding was observed in the case of neutrophils from patients, which also showed similar increased binding of IgA, known to bind to neutrophils (19). These findings, already described for eosinophils (8) could be related to the state of activation of neutrophils from patients. It is interesting that the IgE-binding capacity of neutrophils from all donors varied according to the myeloma IgE tested (Table 1). A significantly lower percentage of neutrophils bound to IgE-BL in comparison to IgE-PS ($p < 0.001$). This result was surprising since it has been previously reported that myeloma IgE-PS was poorly recognized by Mac-2/ ϵ BP (7). A comparative analysis between the two IgE-PS preparations (one provided by Dr. Ishizaka, La Jolla Institute Allergy and Immunology, La Jolla, CA) and the other by Dr. Spiegelberg) has been performed, and results indicate that the IgE-PS used in the present work was better recognized by ϵ BP, a finding probably reflecting different glycosylation between the two IgE preparations (Dr. F.-T. Liu, personal communication).

Table 1. Flow Cytometry Analysis of Membrane Expression of CD23, Mac-2, IgE- and IgA-binding Molecules

Source of neutrophils*	Percent positive cells [†]				
	CD23	Mac-2	IgE-PS	IgE-BL	IgA
Patients	2.1 \pm 0.8	40.1 \pm 4.7	40.1 \pm 5.9	9.7 \pm 3.6	52.9 \pm 13.6
Normal donors	2.3 \pm 1.2	54.6 \pm 5.6	27.9 \pm 8.0	13.8 \pm 4.2	33.3 \pm 5.9

* Neutrophils were purified from patients ($n = 16$) or from normal donors ($n = 10$).

[†] Neutrophils were incubated with 50 $\mu\text{g}/\text{ml}$ anti-CD23 8-30 mAb, myeloma IgE (PS or BL), serum IgA, or anti-Mac-2 hybridoma supernatant (dilution 1:10), before staining with the corresponding FITC-conjugated anti-Ig antibodies. The percentage of positive cells was obtained after subtraction of the nonspecific binding with the control antibody or medium (mean \pm SEM).

Table 2. Binding of Neuraminidase-treated Ig to Neutrophils

Treatment of Ig	Percent positive cells*		
	IgE-PS	IgE-BL	IgA
None	58.7 ± 8.1	16.8 ± 2.1	47.3 ± 7.9
Neuraminidase [†]	79.5 ± 4.4	55.7 ± 5.1	50.1 ± 8.5
Heat-inactivated neuraminidase [‡]	60.7 ± 5.9	22.5 ± 4.0	52.7 ± 11.6

* Neutrophils were incubated with 50 µg/ml IgE-PS, IgE-BL, or serum IgA and stained with the corresponding FITC-labeled anti-Ig (mean of 4–11 experiments ± SEM).

[†] The various Ig have been treated with neuraminidase (0.03 U/ml) for 90 min at 37°C before incubation with neutrophils.

[‡] Neuraminidase was heat-inactivated for 1 h at 56°C before incubation with Ig.

In relation to the fact that Mac-2/εBP could bind to restricted IgE glycoforms, experiments were performed with the same myeloma IgE proteins previously treated with neuraminidase (Table 2). A significant increase in IgE binding was observed both for IgE-PS and for IgE-BL, but more pronounced for the latter. In contrast, neuraminidase treatment did not affect the binding of serum IgA to neutrophils, which occurs through the myeloid FcαR (19). It has to be noticed that the effect of neuraminidase on IgE-BL binding was abolished after heat inactivation. It was concluded that neutrophils can bind some IgE glycoforms likely through surface Mac-2/εBP and not through transmembrane CD23. In contrast to eosinophils which express both CD23 epitopes (17) and Mac-2/εBP (10) and which therefore can bind myeloma IgE independently of their degree of glycosylation, neutrophils seem to express only molecules of the S-type lectin family with IgE recognition modulated by sialylation of IgE oligosaccharides.

Neutrophil Activation by Myeloma or Polyclonal IgE. The function of IgE-binding molecules expressed on neutrophil

surface has been investigated in an experimental assay measuring the respiratory burst by CL. After preliminary dose-dependence studies, we could show that incubation of neutrophils with 10 µg/ml of IgE or IgA and then with the corresponding anti-Ig antibodies, induced a luminol-dependent CL reaction. As shown in Fig. 3 A, only myeloma IgE-PS, but not IgE-BL, induced a CL level close to that induced by serum IgA, as positive control (19). In addition, the magnitude order of IgE-PS- and IgA-dependent respiratory burst was significantly higher for neutrophils from patients than from normal donors. These results were in agreement with IgE-PS- and IgA-binding observed by flow cytometry (Table 1). Unfortunately, CL experiments with neuraminidase-treated Ig could not be performed since neuraminidase by itself nonspecifically inhibited the CL production.

To know whether, in addition to myeloma IgE, polyclonal IgE with or without antibody specificity could also induce neutrophil activation, neutrophils were incubated either with the serum from patients with hyper-IgE syndrome or from schistosomiasis-infected patients (Fig. 3 B). The former sera,

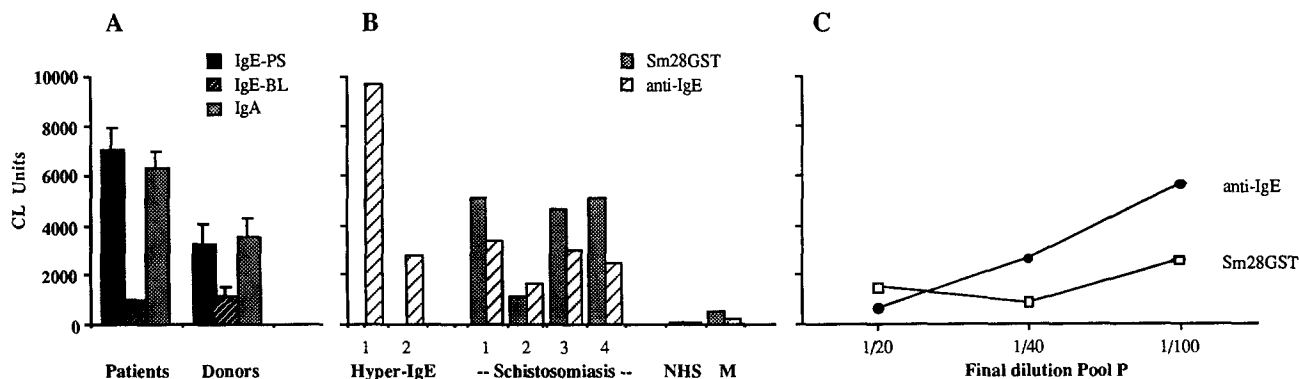


Figure 3. IgE-dependent activation of neutrophils from individual donors measured by CL. (A). CL of neutrophils purified from hyper-eosinophilic patients (associated or not with parasitic infections or allergic disease) and from normal donors by incubation with 10 µg/ml myeloma IgE (IgE-PS and IgE-BL) or serum IgA, and 25 µg/ml anti-IgE or anti-IgA antibodies. (B). Normal donors' neutrophil CL induced by anti-IgE (▨) or Sm28GST Ag (▩) with: sera from two patients with hyper-IgE syndrome (1 and 2) which contained 8,000 IU/ml IgE; and sera from four different patients with schistosomiasis (1–4). Normal human serum (NHS), Sm28GST, and anti-IgE alone (M) represented the controls. (C) Normal donors' neutrophil CL induced by different concentrations of pooled sera from schistosomiasis patients (P = 1, 3, and 4). The evaluation of CL was calculated as described in Materials and Methods.

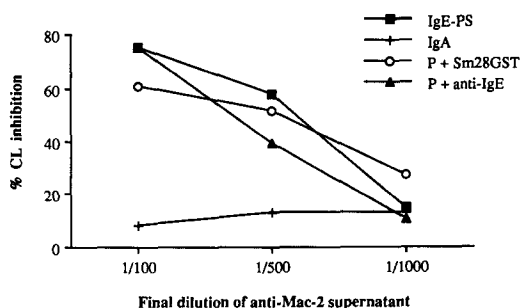


Figure 4. Dose-effect of anti-Mac-2 supernatant on myeloma IgE-PS (—■—) and IgA (+) dependent CL, on pool P (polyclonal IgE)-dependent activation induced by Sm28GST (—○—) or anti-IgE (—▲—) on normal donors' neutrophils. The percent CL inhibition was calculated by comparison to results obtained with control used at the same concentrations, as described in Materials and Methods.

previously shown to bind to Sepharose-linked hεBP (7), induced a variable respiratory burst in the presence of anti-IgE varying with neutrophil donors and with patient sera. In the case of schistosomiasis patient sera, the incubation with specific antigen Sm28GST as well as with anti-IgE antibodies induced a respiratory burst (Fig. 3 B). No CL was produced when only serum, antigen Sm28GST, or anti-IgE alone was added to neutrophils. These results indicate that after cross-linking with antigen or anti-IgE, specific IgE antibodies can induce a respiratory burst in neutrophils. Sera from three schistosomiasis patients were pooled (P, sera 1, 3, and 4) and the pool was shown to induce a dose-dependent CL reaction, in the presence of either specific antigen Sm28GST or anti-IgE (Fig. 3 C). The 1:100 dilution was selected for further experiments.

Role of Mac-2/εBP in IgE-dependent Neutrophil Activation. To identify the nature of the molecules involved in IgE-dependent activation of neutrophils, inhibition procedures with various antibodies were performed (Fig. 4). In the case of activation with myeloma IgE and anti-IgE antibodies, a dose-dependent inhibition of CL was observed with anti-Mac-2 hybridoma supernatant, in comparison to control supernatant. In contrast, anti-Mac-2 antibodies showed no significant effect on IgA-dependent activation.

The involvement of Mac-2 was also investigated in neutrophil activation induced by polyclonal IgE antibodies. According to the stimulus (Sm28GST or anti-IgE), a significant dose-dependent inhibition of neutrophil respiratory burst was obtained with anti-Mac-2 mAb (Fig. 4). No significant inhibition was induced by anti-CD23 mAb for a concentration

of 50 μg/ml in the case of Sm28GST antigen or anti-IgE stimulations (14.8 and 0% inhibition, respectively). It has to be noticed that no CL was produced after incubation of neutrophils with anti-Mac-2 or anti-CD23 mAb either alone or after cross-linking with antiisotype antibodies. Based upon these results, Mac-2 molecules but not CD23, appeared involved in IgE-dependent activation of human neutrophils.

Taken together, the present results suggest that human neutrophils from patients with various diseases, but also from normal donors, could express functional IgE-binding molecules. Interactions between mouse neutrophils and IgE antibodies in cytotoxicity assays have been previously reported. However, no attempt at characterization of IgE-binding molecules potentially expressed by neutrophils was made at this time (20). The more interesting question in relation to the *in vivo* relevance was certainly to know whether neutrophils could bind to and be activated by polyclonal IgE from patients. Our results indicate that not only restricted glycoforms of myeloma IgE proteins but also polyclonal IgE antibodies could induce neutrophil activation in an antigen-specific manner. These findings suggest that in addition to FcεR-bearing cell populations, neutrophils might participate in IgE-dependent reactions. It remains to be determined whether, as for other cell populations, the IgE-dependent activation of neutrophils may induce the generation of mediators potentially involved in inflammatory reactions. Along the same line, further experiments are needed to demonstrate the possible implication of neutrophils in the IgE-dependent protective immunity against schistosomiasis (21). When compared with eosinophils, Mac-2 molecules seemed to be expressed on the surface of a larger majority of neutrophil donors (2 negative out of 16 patients and 3 negative out of 10 normal donors), whereas Mac-2 was expressed on the surface of only half of HE patients (Truong, M. J. et al., manuscript submitted for publication). This might indicate a difference in the regulatory process of surface expression of these endogenous lectins on the two cell populations. Another interesting difference between neutrophils and eosinophils is that only Mac-2, but not CD23, seemed to be expressed and was functional on neutrophils, whereas eosinophils possessed both types of molecules. This finding probably explains why all myeloma IgE proteins could bind to eosinophils (8), irrespective of their degree of glycosylation, whereas their binding to neutrophils was increased after sialidase treatment. Thus, it was concluded that neutrophils, similarly to other cell populations, might participate in the IgE-dependent effector phase of various diseases.

The authors wish to thank Drs. J. P. Dessaint and M. Joseph for critically reading the manuscript; C. Drolez for technical assistance; and M. F. Massard for secretarial assistance.

This work was supported by Unité Mixte INSERM U 167 - CNRS 624.

Address correspondence to Marie-José Truong, CIBP, Institut Pasteur, BP 245, 59019 Lille Cédex, France.

Received for publication 1 September 1992.

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