

IL-1 receptor-type expression in relation to atopy

Kirtibala Gupta, MSc, and Agandra Bewtra, MD Omaha, Neb

Background: IL-1 has 2 receptors, type I (IL-1RI) and type II (IL-1RII), which have 2 forms each, membrane (m) and soluble (s). When IL-1 binds to mIL-1RI, the *active* receptor, an inflammatory response is initiated, which does not occur when IL-1 binds to mIL-1RII, the *decoy* receptor. Both sIL-1RI and sIL-1RII function as IL-1-mopping mechanisms. We hypothesized that the ratio of active (mIL-1RI) to inactive (mIL-1RII, sIL-1RI, and sIL-1RII) receptors is important in determining the amount of inflammation produced in allergic reactions.

Objective: Our aim was to compare the concentrations of mIL-1RI and mIL-1RII on cultured PBLs and sIL-1RI, sIL-1RII, and IL-1 β in sera and supernatants of cultured PBMCs from atopic and nonatopic subjects.

Methods: The membrane receptors, soluble receptors, and IL-1 β concentrations were measured by ELISA with specific mAbs.

Results: Although there was no difference in the level of serum IL-1 β between the 2 groups, PBMCs from atopic persons spontaneously secreted higher levels of IL-1 β than those from nonatopic donors ($P < .05$). PBLs from atopic subjects compared with those from nonatopic individuals expressed higher mIL-1RI ($P < .0001$) and mIL-1RII ($P < .05$). Levels of both the soluble receptors from both serum ($P < .0001$) and PBMCs ($P < .05$) of nonatopic donors were higher than those found in atopic donors.

Conclusion: This augmentation of mIL-1RI concomitant with a reduction in soluble receptors may be an important contributory factor to the inflammation that occurs with allergen exposure. (*J Allergy Clin Immunol* 1999;103:1100-7.)

Key words: IL-1 β , IL-1R, lymphocytes, atopy

IL-1 mediates a broad array of both local and systemic events integral to the allergic response, as illustrated in Fig 1 and reviewed extensively by Rosenwasser.¹ After the first association of IL-1 with allergic reactions by Bochner et al,² IL-1 was detected in the upper airways of allergic subjects³ and shown to rise during early- and late-phase responses in the nasal fluid of patients with allergic rhinitis.⁴ This IL-1 may be secreted by airway monocytes that synthesize it after stimulation with antigen in asthmatic subjects.⁵ IL-1 has 2 isoforms, α and β , which share considerable homology and bind to recep-

Abbreviations used

mIL-1R: Membrane IL-1 receptor
sIL-1R: Soluble IL-1 receptor

tors with similar affinity. Culture supernates and various human body fluids have been shown to contain more IL-1 β than IL-1 α , as reviewed by Vannier and Dinarello.⁶

IL-1 has 2 kinds of receptors, type I (IL-1RI) and type II (IL-1RII),⁷⁻⁹ both of which have membrane (m) and soluble (s) forms that bind with similar affinity to IL-1 α and IL-1 β . mIL-1RI, an 80-kd protein, is thought to be present only on the surface of T lymphocytes, keratinocytes, fibroblasts, endothelial cells, and hepatocytes.^{7,9} Shirakawa et al¹⁰ have shown that healthy human peripheral T cells express only 40 and 350 IL-1 receptors per cell before and after mitogen stimulation, respectively. Although this group did not differentiate between IL-1RI and IL-1RII, one can postulate that these numbers represent only IL-1RI because T cells have been shown to express only the type I receptor. mIL-1RII is a 68-kd protein expressed on B lymphocytes, monocytes, neutrophils, and bone marrow cells.^{8,9}

Membrane IL-1 receptors belong to the immunoglobulin receptor superfamily and are made up of an extracellular, a single transmembrane, and an intracellular domain. As shown in Fig 2, the 2 mIL-1Rs differ mainly in the intracellular region, which transduces signals on IL-1 binding to only mIL-1RI¹¹ and not to mIL-1RII. Hence mIL-1RI is categorized as the *active* receptor, whereas mIL-1RII is termed the *decoy* receptor.¹² Both sIL-1RI and sIL-1RII have been found in circulation,^{13,14} and they bind IL-1 with the same affinity as the membrane forms. However, because they lack the intracellular region, they are not associated with signal transduction and function only as IL-1-mopping mechanisms.

Thus the ratio of active (mIL-1RI) to inactive (mIL-1RI, sIL-1RI, and sIL-1RII) receptors may determine the amount of inflammation induced. In this study we determined the concentrations of IL-1 β and its soluble receptors in the sera and supernatants of cultured PBMCs isolated from atopic and nonatopic individuals. We also measured levels of mIL-1R on the surface of PBLs of atopic and nonatopic subjects.

METHODS

Materials

Culture materials. Ficoll-Hypaque, used in PBMC separation, was purchased from Sigma (St Louis, Mo). Cell culture media

From Creighton University Department of Medicine/Division of Allergy, Omaha.

Supported by Creighton University.

Received for publication July 30, 1998; revised Feb 8, 1999; accepted for publication Feb 8, 1999.

Reprint requests: Agandra Bewtra, MD, Allergic Disease Center, Creighton University, 2500 California Plaza, Omaha, NE 68178.

Copyright © 1999 by Mosby, Inc.

0091-6749/99 \$8.00 + 0 1/1/97839

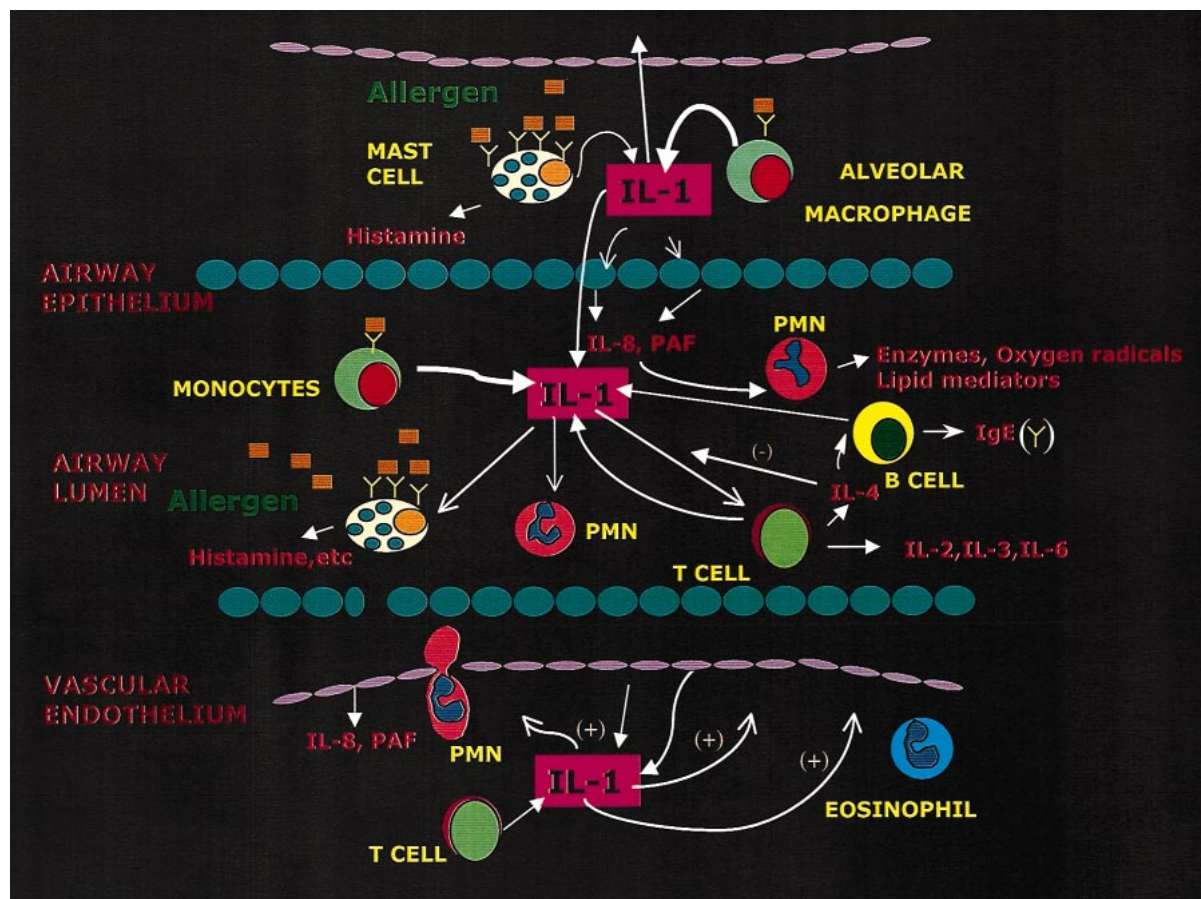


FIG 1. Role of IL-1. *Thick arrows*, Synthesis and secretion; *thin arrows*, action; (+), upregulation; (-), down-regulation. PAF, Platelet-activating factor.

RPMI-1640 was supplemented with 1.7 mmol/L L-glutamine, 0.087 mmol/L nonessential amino acids, 0.87 mmol/L sodium pyruvate, penicillin (100 U/mL), streptomycin (100 mg/mL) (all of the above items were purchased from Gibco Laboratories, Grand Island, NY), and 10% FCS (purchased from Atlanta Biologicals, Atlanta, Ga). Cell culture plates were obtained from Fisher Scientific (Fairlawn, NJ). PHA was purchased from Gibco Laboratories.

ELISA materials. Cell surface IL-1 receptor type I (M1) and type II (M22), soluble IL-1 receptor type I (huIL1R-M8) and type II (huIL1RII-M2) mAbs, and sheep anti-sIL-1RI (huIL1R-P3) and rabbit anti-sIL-1RII (huIL1RII-P4) polyclonal antiserum were kindly provided by Immunex Corporation (Seattle, Wash). The Immunex Corporation also donated recombinant human IL-1RI and IL-1RII. Biotinylated anti-rat and anti-mouse secondary antibodies were purchased from Pharmingen (San Diego, Calif). Biotinylated anti-sheep and anti-rabbit secondary antibodies were obtained from Jackson Laboratories (Bar Harbor, Me). High-binding ELISA plates were purchased from Fisher Scientific. Purified anti-IL-1 β mAbs, recombinant human IL-1 β , and biotinylated anti-IL-1 β secondary antibodies were purchased from R&D systems (Minneapolis, Minn). The chemicals used in these immunoassays and paraformaldehyde were purchased from Sigma Laboratories. The substrate (ABTS) for ELISA assays was made by adding 150 mg of 2,2-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid), purchased from Sigma Laboratories, to 500 mL of 0.1 mol/L citric acid in distilled water (pH 4.35). Aliquots (11 mL) of the substrate were frozen (-5°C) until immediately before use, when 10 μ L of 30% hydrogen peroxide was added.

Experimental subjects

Nonatopic volunteers, aged 19 to 40 years (IL-1 β : n = 6 [3 women and 3 men]; IL-1 receptors: n = 12 [6 women and 6 men]), and atopic patients, aged 19 to 40 years (IL-1 β : n = 6 [3 women and 3 men]; IL-1 receptors: n = 8 [4 women and 4 men]) had 60 mL of blood drawn in 0.2% EDTA after overnight avoidance of caffeine. Atopic status was determined on the basis of a complete detailed history. The subjects were all skin tested to house dust mites, Midwestern grass mix, weed mix, tree mix, ragweed, indoor and outdoor molds, and histamine and saline. The skin test responses were positive for more than one antigen in all instances and correlated with the history for atopic subjects. All the atopic patients had allergic rhinitis, 2 of them also had asthma, and only 1 had atopic eczema. The asthmatic subjects had mild disease and were taking no medication at the time of study. The study was conducted out of season, and all the subjects were asymptomatic at the time of study. The study was approved by the Institutional Review Board of Creighton University School of Medicine, and all the subjects provided informed consent.

Cell culture

PBMCs were isolated by using a Ficoll-Hypaque density gradient, washed with saline, and suspended in RPMI-1640. Serum obtained from these volunteers was immediately frozen (-20°C) until assayed with ELISA. After viability was checked by trypan blue exclusion (>98%), PBMCs were incubated in 12-well culture

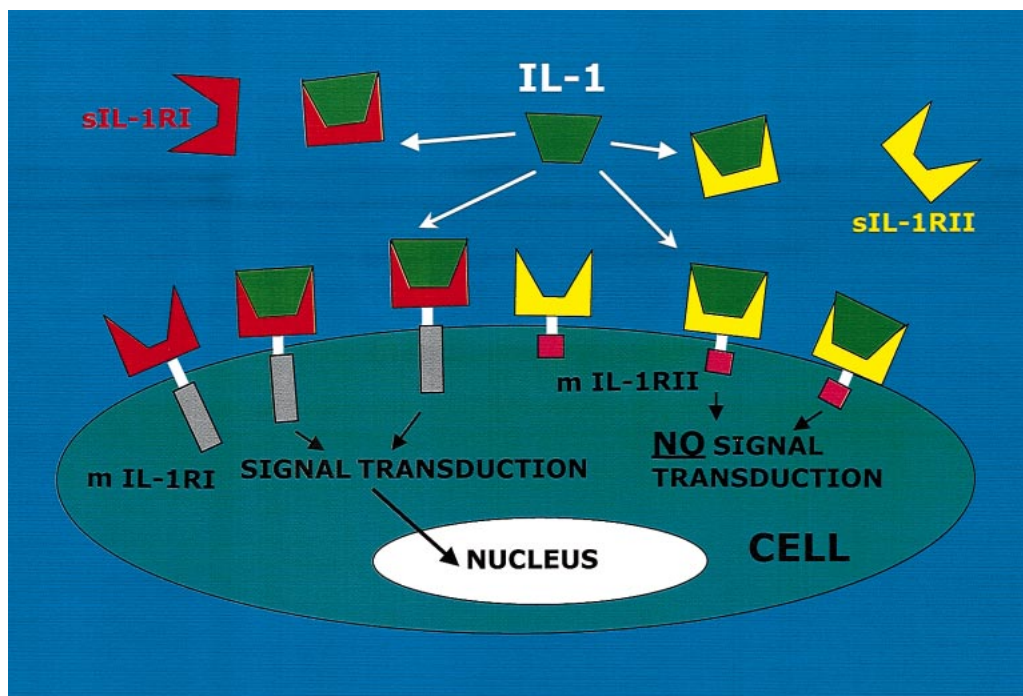


FIG 2. IL-1 has 2 receptors, IL-1RI and IL-1RII. Both types have membrane (mIL-1R) and soluble (sIL-1R) forms. mIL-1RI is the active receptor because it has a signal transduction mechanism associated with it. mIL-1RII is the decoy receptor because it has no signal transducing capability. sIL-1RI and sIL-1RII are soluble receptors with no signal transduction mechanisms, and thus they act as mops for IL-1.

plates at 37°C in a humidified atmosphere of 5% CO₂ at 5×10^6 cells/mL. PHA was used as a stimulus (25 µg/mL).

Assay

mIL-1R ELISA. A standard curve was obtained for each receptor type (IL-1RI and IL-1RII) with specific mAbs. The range for both IL-1RI and IL-1RII was 3.9 pg/mL to 2000 pg/mL. The protocol for mIL-1R measurement was modified from that of Posner et al.¹⁵ PBLs, consisting of only T and B lymphocytes (monocytes were removed by adherence to plastic for 24 hours), were centrifuged (1000 rpm for 15 minutes), and pellets were resuspended in 400 µL of 4% paraformaldehyde. The cells were transferred to an ELISA high-binding plate with constant vortexing and incubated overnight (4°C). After removal of the supernatant, the plates were blocked with PBS/10% FCS for 2 hours at room temperature and washed with PBS/Tween. IL-1 receptor-specific antibody (M1 or M22) was added (10 µg/mL), and the plates were incubated overnight at 4°C. Subsequent to washing the plates, 100 µL/well biotinylated anti-mouse IgG or anti-rat IgG (2 µg/mL) in PBS/10% FCS was added and incubated at room temperature for 45 minutes. After washing, the plates were incubated at room temperature for 30 minutes with 100 µL of 2.5 µL/mL avidin peroxidase in PBS/10% FCS. Immediately after washing, 100 µL of the ABTS substrate was added to each well, and the color reaction was developed for 40 minutes. Optical density was read at 405 nm with a Biorad 3550 microplate reader.

IL-1β and sIL-1R ELISA. A standard curve for IL-1β in the range of 3.9 pg/mL to 1000 pg/mL and for sIL-1R in the range of 3.9 pg/mL to 2000 pg/mL was obtained for every plate. To measure sIL-1RI, sIL-1RII, and IL-1β secreted by cells in culture, supernatants from cultured PBMCs were harvested after 24 hours of culture, and ELISA was performed by using a protocol based on the principles

outlined by Davies.¹⁶ Capture mAb (M8 for sIL-1RI, M2 for sIL-1RII, or anti-IL-1β) was used at a concentration of 2 µg/mL. For sIL-1RI and sIL-1RII, detection was accomplished with sheep anti-sIL-1RI and rabbit anti-sIL-1RII polyclonal antiserum (2 µL/mL). Further detection was done with biotinylated detection antibodies (biotinylated anti-sheep, biotinylated anti-rabbit, or biotinylated anti-IL-1β) at a concentration of 2 µg/mL. ABTS substrate color reaction was measured after 40 minutes at 405 nm.

Data analysis

Patients were classified into 2 groups according to their atopic status. Data are reported as means of triplicates ± SD. A trendline equation was generated for every sample ELISA by using EXCEL software (MS Office 95). With the help of this equation, sample concentrations were calculated, and differences between the 2 groups were analyzed with the EXCEL program by using Student's nonpaired *t* test. Probability (*P*) values of less than .05 were considered significant.

RESULTS

IL-1β

A serum IL-1β level of 60 ± 1.7 pg/mL for nonatopic subjects (*n* = 6) and 67 ± 2.5 pg/mL for atopic individuals (*n* = 8) was obtained, with no statistical difference in the values (*P* > .05). Unstimulated PBMCs from atopic subjects secreted 330 ± 104.7 pg/mL IL-1β, whereas cells from nonatopic subjects produced only 49.6 ± 0.5 pg/mL (*P* < .05; Fig 3). On stimulation with PHA, there was an increase in secretion of IL-1β by PBMCs from atopic subjects (691.7 ± 93.6 pg/mL) and nonatopic sub-

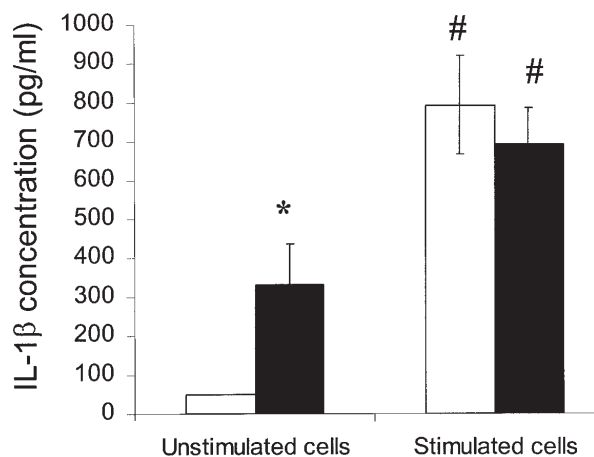


FIG 3. IL-1 β secreted by cultured PBMCs from 6 nonatopic (open bars) and 8 atopic donors (filled bars) into the supernatant was measured in triplicate with ELISA and is represented as means $\pm$ SD. PBMCs were cultured for 24 hours with PHA (stimulated cells) or without PHA (unstimulated cells). *, Statistical significance between atopic and nonatopic individuals (unstimulated state, $P < .05$); #, statistical significance between unstimulated and stimulated states (atopic donors, $P < .005$; nonatopic donors, $P < .005$).

jects (791.6 ± 126.7 pg/mL; Fig 3). Although the increase caused by stimulus was statistically significant in cells from both types of subjects ($P < .005$), the difference between the groups was not statistically significant ($P > .05$).

mIL-1R

PHA-stimulated PBLs isolated from both atopic ($n = 8$) and nonatopic ($n = 12$) donors were used for determining mIL-1RI and mIL-1RII concentrations. We found a 5-fold higher concentration of mIL-1RI expression on PBLs from atopic subjects (56.9 ± 6.9 pg/mL) than on those from nonatopic subjects (11.7 ± 8.4 pg/mL, $P < .0001$; Fig 4, A). A similar trend was observed with mIL-1RII expression. PBLs from atopic subjects ($n = 8$) expressed a higher concentration (3.12 ± 1.9 pg/mL) than PBLs from nonatopic donors ($n = 12$), which expressed 1.6 ± 0.6 pg/mL mIL-1RII ($P < 0.05$; Fig 4, B). However, comparing the concentrations of both receptors on PBLs from atopic subjects, we found 18-fold higher levels of mIL-1RI than mIL-1RII. In comparison, mIL-1RI expression was only 10-fold higher than mIL-1RII expression on PBLs from nonatopic subjects.

sIL-1R

We measured serum concentrations of both soluble receptors in atopic ($n = 8$) and nonatopic ($n = 12$) donors. Serum from atopic subjects (46.88 ± 0.02 pg/mL) had a 2-fold lower concentration of sIL-1RI than that from nonatopic individuals (107.02 ± 0.1 pg/mL, $P < .0001$; Fig 5). Similar results were obtained with serum sIL-1RII, but the difference was 160-fold. Serum from nonatopic subjects had 324.7 ± 10.9 pg/mL, and that

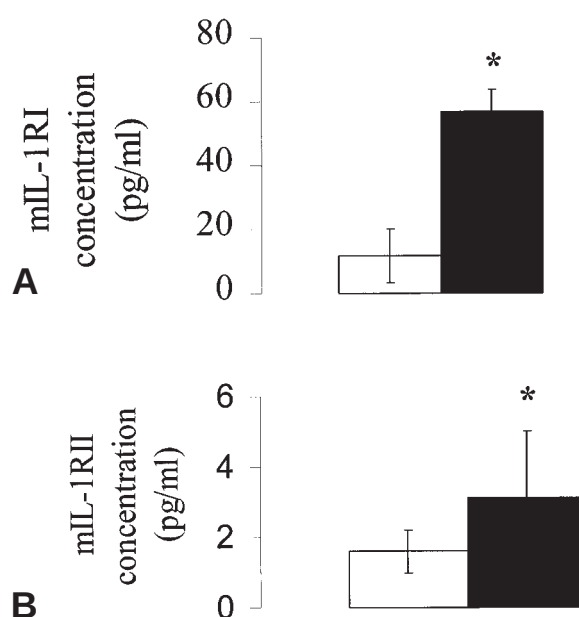


FIG 4. Membrane IL-1 receptors type I (A) and type II (B) PBLs were measured in triplicate with ELISA, and concentrations were determined as detailed in the Methods section. PBLs isolated from 12 nonatopic and 8 atopic donors were stimulated with PHA and cultured for 24 hours. Open bars represent receptors expressed on PBLs from atopic donors, and filled bars represent mIL-1Rs expressed on PBLs from atopic donors. Data are represented as means $\pm$ SD. *, Statistical significance of mIL-1R expression by PBLs from atopic and nonatopic persons (mIL-1RI, $P < .0001$; mIL-1RII, $P < .05$).

from atopic subjects had only 2.18 ± 0.08 pg/mL sIL-1RII ($P < .0001$; Fig 5). On comparing the levels of both soluble receptors in serum from atopic persons, we found sIL-1RI to be 23 times greater than levels of sIL-1RII. There was only a 3-fold difference in the concentration of both soluble receptors in nonatopic serum, with sIL-1RII levels being much higher than sIL-1RI.

Only PBMCs from atopic individuals ($n = 8$) secreted sIL-1RI in the unstimulated state (4.53 ± 2.5 pg/mL), but PBMCs from nonatopic subjects ($n = 12$) did not ($P < .001$; Fig 6, A). On stimulation of PBMCs from atopic subjects, secretion of sIL-1RI was reduced to below measurable limits, whereas that from nonatopic subjects was increased to 18.59 ± 1.1 pg/mL ($P < .001$). Thus there was a statistically significant decrease in sIL-1RI levels after stimulation in cells from atopic subjects ($P < .005$) and a significant increase in nonatopic subjects ($P < .05$).

PBMCs from nonatopic donors secreted higher amounts of sIL-1RII in both unstimulated and stimulated states than PBMCs from atopic donors (Fig 6, B). Concentration of sIL-1RII secreted by unstimulated PBMCs from atopic subjects was lower than the range limit both before and after stimulation. In the case of cells from nonatopic subjects, secretion increased from 12.24 ± 2.5 pg/mL before stimulation to 44.48 ± 18.2 pg/mL after stimulation ($P < .01$).

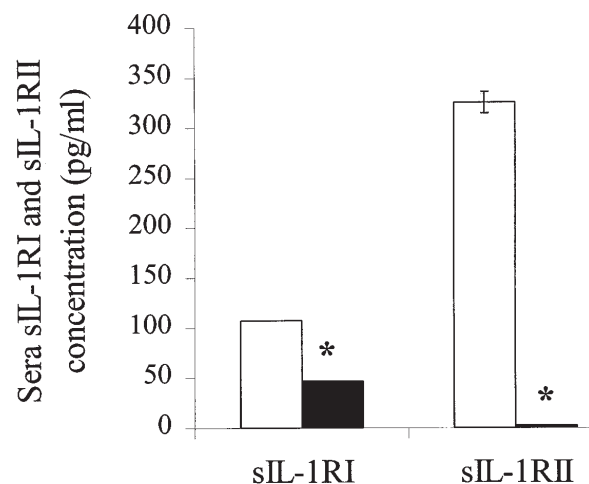


FIG 5. Sera sIL-1RI and sIL-1RII obtained from 12 nonatopic (open bars) and 8 atopic donors (filled bars) were measured with ELISA in triplicate. Values denoted are mean concentrations $\pm$ SD. *, Statistical significance between atopic and nonatopic persons (sIL-1RI, $P < .0001$; sIL-1RII, $P < .0001$).

DISCUSSION

Our results, as depicted in Fig 7, show that we found no difference in serum IL-1 β levels between atopic and nonatopic subjects. As shown in Fig 7, both mIL-1RI and mIL-1RII were expressed at a higher concentration on PBLs from atopic than nonatopic subjects. On the other hand, both soluble receptor secretions by PBMCs and in sera were elevated in nonatopic, rather than atopic, persons. As shown in Fig 7, this results in an increased tendency of IL-1 binding to mIL-1 receptors in atopic subjects and to soluble IL-1 receptors in nonatopic subjects. This higher ratio of active receptors to inactive receptors may be crucial in developing or amplifying an inflammatory response.

It has been postulated that IL-1 can only be found in disease states,¹⁷ but we found 60 pg/mL IL-1 β in the serum of nonatopic donors, as did Cannon et al¹⁸ who also showed the presence of 60 pg/mL IL-1 β in the circulation of healthy individuals. We had expected to find higher concentrations of IL-1 β in atopic serum on the basis of the report by Pellegrino et al¹⁹ because they had shown an increase in plasma level of IL-1 β in symptomatic asthmatic subjects, although their subjects had active allergies. However, we found no statistically significant difference between atopic and nonatopic individuals, perhaps because our atopic subjects were asymptomatic. Urushibata et al²⁰ confirmed our findings because they too did not detect higher serum IL-1 β levels in persons with allergic inflammation as opposed to normal subjects. It has been reported that IL-1 is increased in nasal fluids of patients with allergic rhinitis and in the BAL fluid of symptomatic asthmatic subjects.^{4,21} In view of our findings of normal serum concentrations of IL-1 β in atopic donors, it seems plausible that IL-1 β is released locally, has a potent local effect, and is immediately

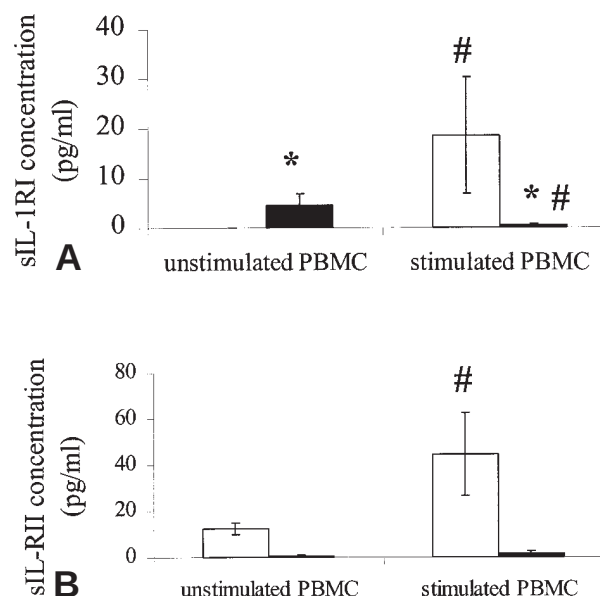


FIG 6. Soluble IL-1 receptor type I (A) and type II (B) levels in supernatants of cultured PBMCs from atopic ($n = 8$; filled bars) and nonatopic ($n = 12$; open bars) subjects were determined in triplicate. PBMCs were cultured for 24 hours with PHA (stimulated PBMC) and without PHA (unstimulated PBMC), and values are represented as means $\pm$ SD. *, Statistical significance between atopic and nonatopic individuals (sIL-1RI levels in unstimulated and stimulated state, $P < .001$); #, statistical significance between unstimulated and stimulated states (sIL-1RI in atopic donors, $P < .005$; nonatopic donors, $P < .05$; sIL-1RII in nonatopic donors, $P < .01$).

either degraded or mopped up, thus preventing it from entering the systemic circulation. However, because we used neutralizing antibodies for the detection of IL-1 β , it is also possible that soluble receptor-bound IL-1 β may not have been detected by our ELISA technique.

To measure locally released IL-1 β from lymphocytes and monocytes, we cultured them for 24 hours with or without stimulus, having previously determined that this was the optimal time for IL-1 β production. Unstimulated PBMCs from atopic donors secreted significantly more IL-1 β than PBMCs from nonatopic donors. This finding was similar to that observed by Poulsen et al²² who observed higher spontaneous production of IL-1 α by PBMCs from patients with atopic dermatitis than from nonallergic individuals after 24 hours of culture. The spontaneous release of IL-1 observed by us can be explained by one or more of the following reasons. First, previous exposure of the cells to allergens in vivo may have lead to the cells being already primed. Atopic subjects were asymptomatic at the time of phlebotomy, but they may have had some subclinical exposure to an allergen, leading to the initiation of IL-1 β synthesis. Second, only the cells from atopic individuals may be hyperresponsive or hypersensitive to the small amount of endotoxin present in the media (below the detectable limit of 6 Eu/mL). Endotoxin (especially LPS) is a potent stimulator of IL-1 synthesis, and therefore there may have

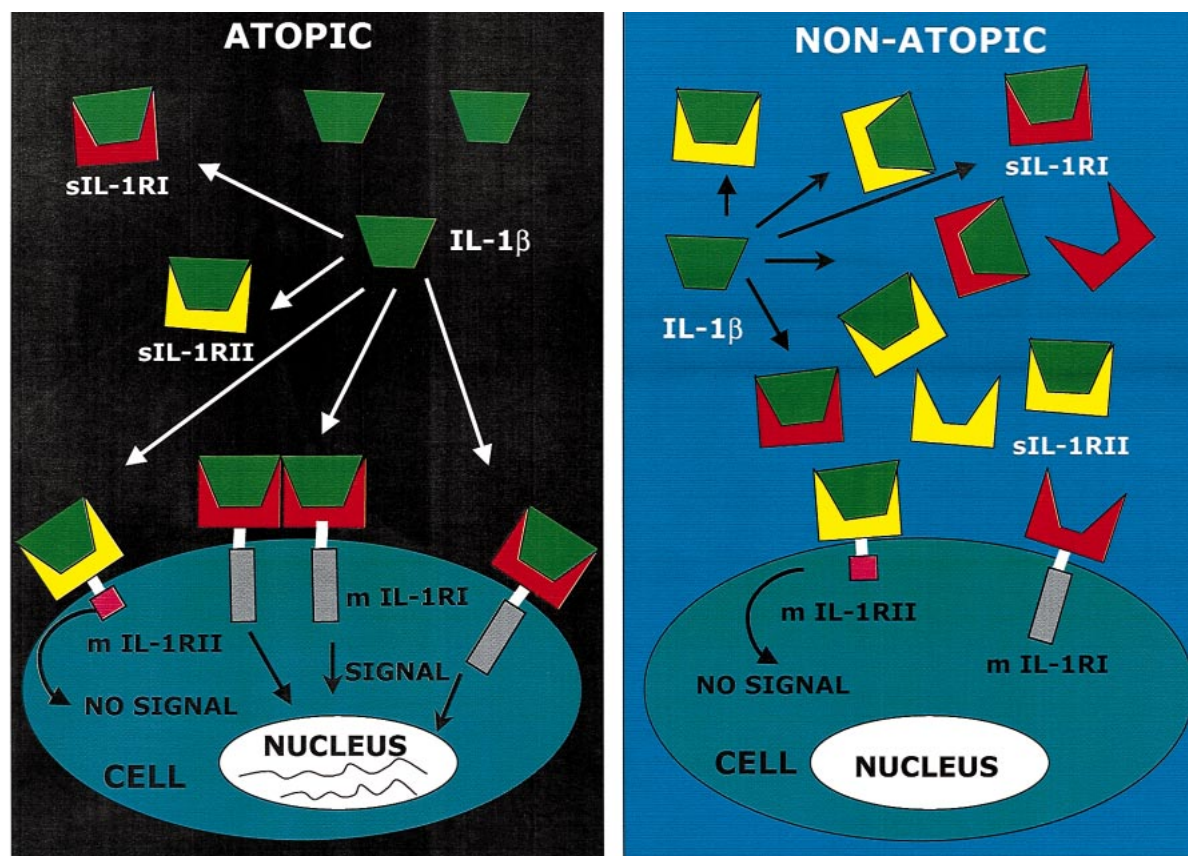


FIG 7. The 2 panels illustrate our results of atopic and nonatopic individuals. We found similar concentrations of IL-1 β in both donors but higher numbers of mIL-1Rs on PBLs of atopic donors. We also found higher concentrations of both soluble receptors in the circulation and cultured PBL supernatants of nonatopic donors. Thus there is an increased tendency of IL-1 β binding to mIL-1Rs in an atopic individual, leading to signal transduction and an inflammatory response. In nonatopic subjects there is a higher tendency of IL-1 β binding to sIL-1Rs, which therefore results in no inflammatory response.

been enough to trigger the release of IL-1 β by PBMCs from atopic individuals.¹⁷ Third, PBMCs from atopic patients may have an increased capacity to synthesize IL-1 β . However, this explanation is unlikely because on stimulation cells from both groups secreted similar amounts of IL-1 β .

For IL-1 to have an effect, it has to bind specifically to mIL-1RI. To the best of our knowledge, this is the first report of a difference between IL-1 receptor expression in cells from atopic versus nonatopic subjects. However, some researchers have noted the association of other pathologic conditions with IL-1 receptors. For example, IL-1RI and IL-1RII are upregulated on human synovial fibroblasts in osteoarthritis.²³ Although the receptor subtype was not identified, Donati et al²⁴ also demonstrated that the numbers of monocyte IL-1 receptors increased in patients undergoing hemodialysis over that of healthy volunteers. The higher expression of membrane receptors on PBLs from atopic individuals may be due to a number of factors. First, the membrane receptors may be differentially synthesized because of a dysregulation in receptor gene transcription. In human osteoclasts present

in areas of cartilage and bone destruction, Xu et al²⁵ found increased IL-1RI mRNA. Hepatocytes also show upregulation of IL-1RI mRNA after stimulation with LPS.²⁶ Alternatively, it is tempting to speculate that there may be a reduced degradation or turnover rate of the receptors in cells from atopic donors.

Serum concentrations of both soluble receptors were lower in atopic than in nonatopic individuals. To the best of our knowledge, this is the first report of lower concentrations of sIL-1RI associated with a pathologic condition. On the other hand, Giri et al²⁷ had reported an increase in serum concentrations of sIL-1RII in patients with sepsis syndrome. We suggest the following reasons for our finding of decreased sIL-1R in the serum of atopic persons. First, there may be an impairment of synthesis of soluble receptors in atopic persons. This is supported by our data showing that stimulated PBMCs from atopic subjects secrete less of both soluble receptors than PBMCs from nonatopic donors. Alternatively, nonatopic individuals could be preferentially synthesizing soluble receptors. We observed that when nonatopic PBMCs are maximally stimulated, they secrete high levels of sIL-1R.

Indeed, it may be that in atopic patients the membrane receptors are preferentially synthesized, as we have also shown. Soluble receptors may also be degraded at an increased rate in the serum of atopic persons. This was not confirmed by our study. Finally, the antibody used to detect sIL-1RII has been shown by others to detect sIL-1RII, even when it is bound to IL-1,²⁸ but this is not the case with sIL-1RI, and therefore we may be measuring only unbound sIL-1RI.

Our results suggest that in atopic individuals there may be an upregulation of IL-1RI synthesis, but the predominant form is mIL-1RI, which is active, rather than sIL-1RI, which mops up IL-1. This reasoning is supported by our finding that cultured stimulated PBMCs of atopic subjects secrete less sIL-1RI than unstimulated PBMCs. Hence we propose that there is a selective upregulation of the active receptor in atopic individuals. When PBMCs from nonatopic subjects were cultured, they secreted high amounts of sIL-1RII in both the unstimulated and stimulated state, but high amounts of sIL-1RI in only the stimulated state. Thus there is selective synthesis of sIL-1RII in nonatopic subjects.

We found higher expression of the mIL-1RI on PBLs from atopic patients and a concomitant reduction in synthesis or reduced expression of the sIL-1R (Fig 7). Hence there is a selective synthesis or secretion of receptors in atopic individuals that may relate to their disease state. There are various reports on the clinical relevance of these receptor types in different disease states. Mullarkey et al²⁹ performed a prospective, randomized, double-blind, placebo-controlled study of 15 allergic patients to determine the effect of sIL-1R on the cutaneous late-phase reaction. They found that microgram quantities of sIL-1R inhibited the clinical signs and symptoms of the late-phase reaction, although they did not determine its effect on the inflammatory infiltrate. In graft-versus-host disease there is release of inflammatory cytokines, including IL-1. McCarthy et al³⁰ treated patients with progressive or persistent graft-versus-host disease with recombinant human IL-1 receptor and found an improvement after the therapy.

Atopy and asthma are disease states in which inflammation is a predominant factor. Any agent that would help reduce or inhibit the inflammation may be of value in therapy. On the basis of our findings of differences in the level of receptors to IL-1, there is a potential to develop therapies by using sIL-1Rs for treatment of allergic rhinitis and asthma. We propose that more experiments be conducted to evaluate this potential role of sIL-1Rs.

We thank Caroline Crocker for her help in writing the manuscript.

REFERENCES

1. Rosenwasser L. Biologic activities of IL-1 and its role in human disease. *J Allergy Clin Immunol* 1998;102:344-50.
2. Bochner BS, Charlesworth EN, Lichtenstein LM, Derse CP, Gillis S, Dinarello CA, et al. Interleukin-1 is released at sites of human cutaneous allergic reactions. *J Allergy Clin Immunol* 1990;86:830-9.
3. Sim TC, Grant JA, Hilsmeier KA, Fukuda Y, Alam R. Proinflammatory cytokines in nasal secretions of allergic subjects after allergen challenge. *Am J Respir Crit Care Med* 1994;149:3394-4.
4. Gosset P, Malaquin F, Delneste Y, Wallaert B, Capron A, Joseph M, et al. Interleukin-6 and interleukin-1 α production is associated with antigen-induced late nasal response. *J Allergy Clin Immunol* 1993;92:878-90.
5. Borish L, Mascali JJ, Rosenwasser LJ. IgE-dependent cytokine production by human peripheral blood mononuclear phagocytes. *J Immunol* 1991;146:63-7.
6. Vannier E, Dinarello CA. Interleukin-1 and tumor necrosis factor in allergic reactions. In: Townley RG, Agrawal DK, editors. *Immunopharmacology of allergic diseases*. 1st ed. New York: Marcel Dekker, Inc; 1996. p. 309-34.
7. Sims JE, Acres RB, Grubin CE, McMahan CJ, Wignall JM, March CJ, et al. Cloning the interleukin 1 receptor from human T cells. *Proc Natl Acad Sci USA* 1989;86:46-50.
8. McMahan CJ, Slack JL, Mosley B, Cosman D, Lupton SD, Brunton LL, et al. A novel IL-1 receptor, cloned from B cells by mammalian expression, is expressed in many cell types. *EMBO J* 1991;10:2821-32.
9. Bomsztyk K, Sims JE, Stanton TH, Slack J, McMahan CJ, Valentine MA, et al. Evidence for different interleukin 1 receptors in murine B- and T-cell lines. *Proc Natl Acad Sci USA* 1989;86:8034-8.
10. Shirakawa F, Tanaka Y, Ota T, Suzuki H, Eto S, Yamashita U. Expression of interleukin 1 receptors on human peripheral T cells. *J Immunol* 1987;138:4243-8.
11. Sims JE, Gayle MA, Slack JL, Alderson MR, Bird TA, Giri JG, et al. Interleukin 1 signaling occurs exclusively via the type I receptor. *Proc Natl Acad Sci USA* 1993;90:6155-9.
12. Colotta F, Re F, Muzio M, Bertini R, Polentarutti N, Sironi M, et al. Interleukin-1 type II receptor: a decoy target for IL-1 that is regulated by IL-4. *Science* 1993;261:472-5.
13. Giri JG, Newton RC, Horuk R. Identification of soluble interleukin-1 binding protein in cell-free supernatants. Evidence for soluble interleukin-1 receptor. *J Biol Chem* 1990;265:17416-9.
14. Svenson M, Hansen MB, Heegard P, Abell K, Bendtzen K. Specific binding of interleukin 1 (IL-1) beta and IL-1 receptor antagonist (IL-1ra) to human serum. High affinity binding of IL-1ra to soluble IL-1 receptor type I. *Cytokine* 1993;5:427-35.
15. Posner MR, Antoniou D, Griffin J, Schlossman SF, Lazarus H. An enzyme-linked immunosorbent assay (ELISA) for the detection of monoclonal antibodies to cell surface antigens on viable cells. *J Immunol Methods* 1982;48:23-31.
16. Davies C. Principles. In: Wild D, editor. *The immunoassay handbook*. 1st ed. New York: Stockton Press; 1994. p. 3-47.
17. Dinarello CA. Interleukin-1 and interleukin-1 antagonism. *Blood* 1991;77:1627-52.
18. Cannon JG, van der Meer JW, Kwiatkowski D, Endres S, Lonnemann G, Burke JF, et al. Interleukin-1 beta in human plasma: Optimization of blood collection, plasma extraction and immunoassay methods. *Lymphokine Res* 1988;7:457-63.
19. Pellegrino M, Minervini B, Musto P, Matera R, Greco A, Checchia de Ambrosio C. Tumor necrosis factor alpha and interleukin-1 beta. Two possible mediators of allergic inflammation. *Minerva Pediatr* 1996;48:309-12.
20. Urushibata T, Uesugi K, Yoshino K, Kubota N, Takeyama I. Pollinosis etiologic relationship between excessive IL-4 production and down-regulation of the inflammation-suppressive system. *Acta Otolaryngol Suppl Stockh* 1996;522:68-73.
21. Broide DH, Lotz M, Cuomo AJ, Coburn DA, Federman EC, Wasserman SI. Cytokines in symptomatic asthma airways. *J Allergy Clin Immunol* 1992;89:958-67.
22. Poulsen LK, Bindslev Jensen C, Diamant M, Hansen MB, Jepsen KF, Reimer CM, et al. Biomolecular regulation of the IgE immune response III. Cytokine profiles in atopic dermatitis, inhalant allergy and non-allergic donors. *Cytokine* 1996;8:651-7.
23. Sadouk MB, Pelletier JP, Tardif G, Kiansa K, Cloutier JM, Martel Pelletier J. Human synovial fibroblasts coexpress IL-1 receptor type I and type II mRNA. The increased level of the IL-1 receptor in osteoarthritic cells is related to an increased level of the type I receptor. *Lab Invest* 1995;73:347-55.
24. Donati D, Degiannis D, Mazzola E, Gastaldi L, Raskova J, Raska K Jr, et al. Interleukin-1 receptors and receptor antagonist in hemodialysis. *Nephrol Dial Transplant* 1997;12:111-8.

25. Xu LX, Kukita T, Nakano Y, Yu H, Hotokebuchi T, Kuratani T, et al. Osteoclasts in normal and adjuvant arthritis bone tissues express the mRNA for both type I and type II interleukin-1 receptors. *Lab Invest* 1996;75:677-87.
26. Ito A, Takii T, Soji T, Onozaki K. Endotoxin-induced upregulation of type I receptor mRNA expression in hepatocytes of mice: role of cytokines. *J Interferon Cytokine Res* 1997;17:55-61.
27. Giri JG, Wells J, Dower SK, McCall CE, Guzman RN, Slack J, et al. Elevated levels of shed type II IL-1 receptor in sepsis. Potential role for type II receptor in regulation of IL-1 responses. *J Immunol* 1994;153:5802-9.
28. Altenberger EA, Pope HA, Wewers MD. Detection of soluble type II receptor in the presence of its natural ligand IL-1 beta. Quantification by sandwich ELISA. *J Immunol Methods* 1995;185:115-22.
29. Mullarkey MF, Leiferman KM, Peters MS, Caro I, Roux ER, Hanna RK, et al. Human cutaneous allergic late-phase response is inhibited by soluble IL-1 receptor. *J Immunol* 1994;152:2033-41.
30. McCarthy PL Jr, Williams L, Harris-Bacile M, Yen J, Przepiorka D, Ippoliti C, et al. A clinical phase I/II study of recombinant human interleukin-1 receptor in glucocorticoid-resistant graft-versus-host disease. *Transplantation* 1996;62:626-31.