Interleukin 5 Modifies Histamine Release and Leukotriene Generation by Human Basophils in Response to Diverse Agonists

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Summary

Human interleukin 5 (IL-5), known as a selective colony-stimulating factor of the eosinophil lineage and activator of mature eosinophils, also profoundly influences the mediator release profile of human basophils. IL-5 by itself triggers neither granule release nor de novo synthesis of lipid mediators. However, at low concentrations (0.1–10 ng/ml), IL-5 rapidly primes basophils for enhanced histamine release and leukotriene C4 (LTC4) generation in response to all established basophil agonists. LTC4 generation is more strongly affected by IL-5 than histamine release. In particular, IL-5 renders basophils capable of producing large quantities of LTC4 in response to C5a, which, without the cytokine, induces histamine release only. Finally, IL-5 renders basophils responsive to agonists (neutrophil-activating peptide 1 and C3a), which are otherwise inefficient triggers for basophil mediator release. The effects are similar to the recently established bioactivity of IL-3 on basophils, with the exception of its influence on IgE-dependent basophil activation, which is less pronounced. Thus, IL-5 strongly modulates the function not only of eosinophils but also of basophils, the two major effector leukocyte types involved in allergic inflammatory processes, e.g., in asthma.

In contrast to most cytokines, which have a pleiotropic action on a variety of cell types, the biological activity of human IL-5 has been assumed to be restricted to the eosinophil cell lineage (1–3). IL-5 stimulates the growth and differentiation of human eosinophil progenitors without influencing cells committed to neutrophils, basophils, or monocytes (1). Moreover, IL-5 selectively enhances the responsiveness of mature eosinophils, inducing polarization, shape change, and chemotaxis, enhancing cytotoxicity and oxygen radical release, as well as prolonging their survival, particularly in the presence of fibroblasts (2, 3). However, effects on other mature inflammatory effector cells have not yet been described. Murine IL-5 (T cell replacing factor, B cell growth factor II) has been originally isolated and cloned according to its activity on B cells (4). The human IL-5 has never been purified to homogeneity from stimulated leukocytes, but was recently cloned using the murine IL-5 cDNA as a hybridization probe (5). In contrast to the mouse system, however, IL-5 seems to be inactive on human B cells (6).

Beside eosinophils, human basophils presumably play an important role in the late phase of allergic reactions, as well as in certain types of delayed-type hypersensitivity (7, 8). The extent of mediator release by basophils may therefore be of particular relevance to the severity of symptoms in allergic diseases (8). Recent studies showed that the multipotent hematopoietic growth factor IL-3 enhances the release of inflammatory mediators not only from eosinophils (9) but also from basophils (10–12). Furthermore, granulocyte/macrophage CSF (GM-CSF)[1] enhances the responsiveness of all mature myeloid cells including basophils (13, 14, and unpublished results). Here, we demonstrate that the biological activity of IL-5 is not restricted to eosinophils, since this cytokine profoundly modifies the basophil response to diverse cell agonists. In particular, IL-5 most strongly affects de novo synthesis of leukotriene C4 (LTC4), further supporting the concept of a major regulatory role of hematopoietic growth factors in lipid mediator generation by inflammatory effector cells (9–14). Our results also show that IL-5 together with IL-3 and GM-CSF belongs to a particular set of cytokines, able to modify the function of eosinophils as well as basophils, the two predominant effector cell types infiltrating allergic inflammatory sites.

Materials and Methods

Reagents. Dextran, Ficoll Hypaque, and Percoll were obtained from Pharmacia Fine Chemicals (Uppsala, Sweden); Hepes was from Calbiochem-Behring Corp. (La Jolla, CA); BSA, fatty acid free,

[1] *Abbreviations used in this paper:* GM-CSF, granulocyte/macrophage CSF; LTC4, leukotriene C4; NAP-1, neutrophil-activating peptide 1.

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was from Boehringer Mannheim, Inc. (Mannheim, FRG); EDTA was from Fluka AG (Buchs, Switzerland); and Dynabeads M-450 Pan T was from Dynal A.S. (Skoyen, Norway).

Cell Preparation. Basophils were prepared from venous blood of unselected human volunteers exactly as described in detail previously (10). For most experiments, PBMC depleted of neutrophils and eosinophils by Ficoll-Hypaque density centrifugations containing 1–8% (mean, 3%) basophils were used (10). In some experiments, whole leukocytes were fractionated by Percoll density centrifugation as described (10), resulting in different fractions containing variable proportions of leukocyte types, including one fraction consisting of 15–40% basophils and contaminated exclusively with small lymphocytes. In two experiments, the basophil-enriched Percoll fraction was depleted of T lymphocytes using immunomagnetic beads coated with mouse anti-CD2 mAb. This procedure increased basophil purity from 32 and 38% to 88 and 94%, respectively, decreasing the lymphocyte contamination to 12 and 6%.

Cell Stimuli. Human rIL-5, expressed in *Escherichia coli* and purified to at least 95%, as assessed by SDS-PAGE, was obtained from Amgen Biologicals (Thousand Oaks, CA). Its biological activity (10^6 U/mg) has been determined in a bone marrow progenitor cell assay of cell proliferation and differentiation into eosinophils. Human rIL-3 (bioactivity, 0.7×10^6 U/mg in a proliferation assay with cultures of leukocytes from patients with chronic myeloic leukemia), human rGM-CSF (bioactivity, 3.7×10^6 U/mg in the same assay as for IL-3), and human recombinant neutrophil-activating peptide 1 (rNAP-1) (11) were from Sandoz (Basel, Switzerland and Vienna, Austria, respectively). rIL-1β (bioactivity, 10^7 U/mg, determined in a LAF inhibition assay) was obtained from Biogen-Glaxo S.A. (Genève, Switzerland). The complement cleavage products C3a and C5a were purified from yeast-activated human serum as described (10, 12). FMLP (Bachem AG, Bubendorf, Switzerland) and mouse anti-IgE mAb LE27 (12) were dissolved in PBS. All agents were stored in small aliquots at −70°C and thawed just before use.

Mediator Release Assay. Cells were suspended in HACM buffer (20 mM hepes, 125 mM NaCl, 5 mM KCl, 0.5 mM glucose, 0.025% BSA, 1 mM $CaCl_2$, 1 mM $MgCl_2$) at a cell density of $3–5 \times 10^6$ cells/ml, except for pure basophils ($0.2–0.5 \times 10^6$ cells/ml). The release experiments were performed in a shaking water bath at 37°C. After a warming-up period of 10 min, the cells were preincubated with cytokines (IL-5, IL-3, IL-1β, GM-CSF) or in buffer for 10 min, followed by addition of the triggering agent (C5a, anti-IgE, FMLP, NAP-1, C3a). The reaction was stopped 20 min after addition of the second stimulus, a time determined to be sufficient for a complete mediator release reaction for all the agonists studied. Histamine and LTC4 release were measured as described (10–12).

Data Presentation. Histamine release is expressed as percent of total histamine content per tube after cell lysis. Leukotriene data are presented as picograms LTC4 per nanograms total cellular histamine content in order to correct for different basophil numbers; except for experiments with highly purified basophils, where leukotriene data are expressed as nanograms LTC4 per 10^6 basophils.

Results

IL-5 Modifies Basophil Mediator Release Triggered by IgE-dependent and IgE-independent Agonists. Table 1 shows that histamine release from basophils triggered with maximally effective concentrations of C5a, anti-IgE, or FMLP is considerably augmented when cells have been preincubated for 10 min with 10 ng/ml human rIL-5. De novo synthesis of lipid mediators is even more strongly enhanced (Table 2). In particular, IL-5-primed basophils produce large quantities of LTC4 in response to C5a, which by itself is unable to promote lipid mediator synthesis (10). For comparison, the effects of the three other cytokines known to affect basophil mediator release (10–12, 14) have been examined within the same experiments. These results show that IL-5, IL-3, and GM-CSF modulate basophil mediator release in response to all agonists in a qualitatively identical manner. IL-5, by itself, neither induces histamine release above that of the buffer control nor causes LTC4 generation above the detection limit (Tables 1 and 2 and see Figure 2).

Table 1. *Effect of IL-5 Preincubation upon Basophil Histamine Release Induced by Various Agonists and Comparison with other Cytokines*

	Histamine release (percent of total histamine content)					
	O	C5a	aIgE	FMLP	C3a	NAP-1
O	5.1	43.4	35.6	39.8	5.3	5.1
IL-5	5.8	74.5	57.1	62.0	15.9	17.3
IL-3	8.6	76.3	73.0	61.3	16.9	17.4
GM-CSF	5.7	71.8	70.1	58.3	16.1	18.8
IL-1β	5.4	43.7	36.2	38.9	6.6	8.1

Cells were preincubated in buffer (O) or with cytokines (IL-5, IL-3, GM-CSF: 10 ng/ml; IL-1β: 100 ng/ml) for 10 min and further incubated in buffer (O), or stimulated for 20 min by C5a (10^{-8} M), anti-IgE (aIgE; 100 μg/ml), FMLP (2.5×10^{-6} M), C3a (10^{-6} M), or NAP-1 (10^{-7} M) as second signals. The mean of histamine release from three separate experiments, each performed in triplicate, with cells from a representative donor is shown. The SD of triplicates was <5% of the mean, and that of the three experiments was <15% of the mean.

In some experiments, the different hematopoietic growth factors have been added simultaneously in various combinations, all at maximally effective concentrations of 10 ng/ml (IL-3 + GM-CSF, IL-3 + IL-5, IL-5 + GM-CSF, IL-3 + IL-5 + GM-CSF), 10 min before stimulating the basophils with C5a. No further increase of histamine release and leukotriene generation over that observed in cells primed by the different cytokines alone can be measured (data not shown). By contrast, the effects of IL-1β, which has been reported to enhance IgE-mediated histamine release (15), are only marginal, even at the maximally effective concentration of 100 ng/ml. Additionally, IL-1β is unable to render basophils capable of producing LTC4 in response to C5a (Table 2).

IL-5 Renders Basophils Responsive to NAP-1 and C3a. In previous studies, we have shown that, in contrast to other chemotactic factors such as C5a and FMLP, the cell-derived NAP-1, by itself, neither induces histamine release nor LTC4 generation, at least at physiologically relevant concentrations

Table 2. *Effect of IL-5 Preincubation upon Leukotriene C4 Generation by Basophils in Response to Various Agonists and Comparison with other Cytokines*

	Leukotriene generation (LTC4/total histamine content)					
	O	C5a	aIgE	FMLP	C3a	NAP-1
			pg/ng			
O	<1	<1	4.8	11.9	<1	<1
IL-5	<1	29.9	23.1	28.8	6.4	6.4
IL-3	<1	29.6	33.4	29.8	6.6	7.3
GM-CSF	<1	30.8	30.5	32.2	6.3	7.9
IL-1β	<1	<1	7.3	13.2	<1	<1

Cells were preincubated in buffer (O) or with cytokines (IL-5, IL-3, GM-CSF: 10 ng/ml; IL-1β: 100 ng/ml) for 10 min and further incubated in buffer (O), or stimulated for 20 min by C5a (10^{-8} M), anti-IgE (aIgE; 100 μg/ml), FMLP (2.5×10^{-6} M), C3a (10^{-6} M), or NAP-1 (10^{-7} M) as second signals. The mean of leukotriene generation from three separate experiments, each performed in triplicate, with cells from a representative donor is shown. The SD of triplicates was <5% of the mean, and that of the three experiments was <15% of the mean.

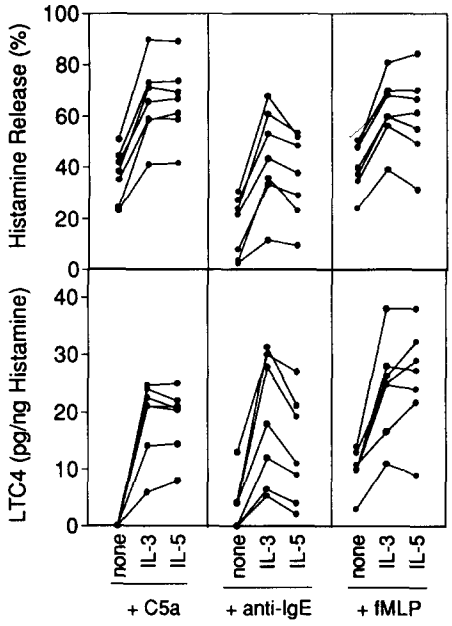

Figure 1. IL-5- and IL-3-induced modulation of basophil mediator release: comparison of different donors. Basophils were stimulated with C5a (10^{-8} M; *left*), anti-IgE (100 ng/ml; *middle*), or FMLP (2.5×10^{-6} M; *right*) after preincubating the cells during 10 min in buffer or with IL-3 or IL-5 (10 ng/ml). Histamine release (three upper panels) and leukotriene generation (three lower panels) from seven experiments performed with seven different donors are shown. Each point represents the mean of triplicates. The data of each experiment were connected by lines in order to allow comparison of mediator release by cells of different donors. Statistical analysis (paired *t* test): IL-3 + anti-IgE vs. IL-5 + anti-IgE, $p < 0.01$ (histamine) and $p < 0.001$ (leukotriene); IL-3 + C5a vs. IL-5 + C5a or IL-3 + FMLP vs. IL-5 + FMLP; $p > 0.05$ (histamine, leukotriene).

of up to 10^{-7} M. In IL-3-primed basophils, however, NAP-1 becomes an efficient trigger for basophil mediator release (11). Similarly, the complement component C3a is an inefficient basophil agonist, even at a concentration of 10^{-6} M, but in the presence of IL-3 or GM-CSF, it triggers basophil mediator release even at a 1,000-fold lower concentration of C3a (12). The present study demonstrates that IL-5 renders basophils responsive to NAP-1 as well as to C3a in a manner identically to IL-3 and GM-CSF (Tables 1 and 2).

Highly Purified Basophils. To determine the cellular source of LTC4 and to exclude an indirect action of IL-5, we purified basophils up to 94%. The pattern of mediator release and the modulatory effect of IL-5 is found to be independent of the basophil purity. Using 94% pure basophils at 0.5×10^6 cell/ml, it can be confirmed at a much lower detection limit that C5a is unable to induce LTC4 synthesis (<0.05 ng LTC4/10^6 basophils), but efficiently stimulates histamine release (65% vs. 2% in controls). In the presence of IL-5, this cell preparation produces 15.7 ± 1.2 ng LTC4/10^6 basophils in response to C5a (mean ± SD, $n = 4$). FMLP-induced LTC4 synthesis is enhanced from 8.2 ± 0.7 to 21.4 ± 1.5 ng LTC4/10^6 basophils by IL-5 preincubation. Furthermore, PBMC and PMN (93% neutrophils, 7% eosinophils) depleted of basophils by Percoll gradients do not produce detectable amounts of LTC4 in response to the different agonists with or without IL-5 priming (<0.01 ng LTC4/10^6 cells).

Variability of Basophil Mediator Release. Triggering the cells of different unselected donors with anti-IgE, C5a, or FMLP results in considerable differences in releaseability (Fig. 1), which have been reported repeatedly. In agreement with previous studies, no correlation was found between the extent of mediator release induced by the three different agonists alone in cells from different donors (regression analysis: C5a vs. anti-IgE, C5a vs. FMLP, anti-IgE vs. FMLP; all $p > 0.05$). In all cases, however, IL-5 strongly enhances histamine release and leukotriene generation, regardless of the different responsiveness of the cell preparations to a certain agonist. Even cells from individuals, that do not respond to anti-IgE alone, so-called "non-responders," release mediators after cell priming with IL-5. In addition, all donors generate LTC4 in response to C5a after IL-5-preincubation, while LTC4 has never been detected in supernatants of cells exposed to C5a alone. An interindividual difference of the total amount of mediators released, however, is observed with or without priming with IL-5. This difference cannot be explained by day-to-day variability of mediator release, since the SD of experiments performed with different cell preparations of the same individual repeated up to five times never exceeded 15% of the mean. In parallel experiments, the effect of IL-3 preincubation upon basophil mediator release has been examined using the cells from the same donors (Fig. 1). IL-3 and IL-5 modify the basophil response towards IgE-independent agonists in an identical manner, whereas IL-5 is slightly but reproducibly less efficient in enhancing anti-IgE-induced mediator release (paired *t* test, $p < 0.001$). Also worth mentioning,

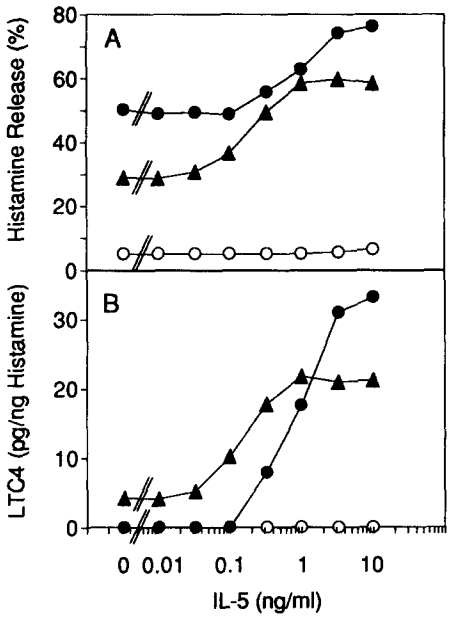

Figure 2. IL-5 dose response. Basophils were preincubated in buffer or with IL-5 at the concentrations indicated. After 10 min, C5a (10^{-8} M; ●), anti-IgE (100 ng/ml; ▲), or buffer control (○) was added for 20 min. (*A*) Histamine release; (*B*) leukotriene generation. The mean of triplicates of a representative experiment is shown. Parallel dose-response curves were obtained with cells from three different donors. The enhancement by IL-5 of FMLP-induced mediator release occurred over the same concentration range as that of C5a (not shown).

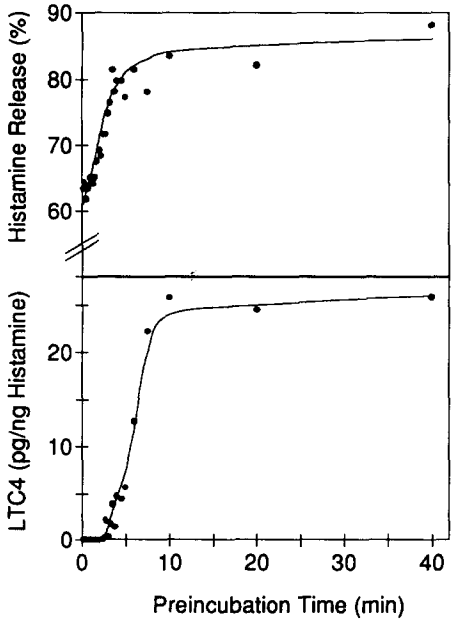

Figure 3. Kinetic of the IL-5 priming process. Basophils were preincubated with 10 ng/ml of IL-5 for variable times and then stimulated by C5a (10^{-8} M). The time interval between IL-5 and C5a addition is indicated in the *x*-axis. The upper panel shows histamine release, the lower panel shows LTC4 generation. Each point represents a single determination. Data from a typical experiment are shown.

there are no interindividual differences in the extent of priming by these two cytokines.

Dose Response of IL-5. IL-5 enhances histamine release and primes for leukotriene synthesis over a similar concentration range, regardless of which trigger is used as a second signal. The effect increases dose dependently from 0.1–3 ng/ml IL-5, and becomes maximal at 3–10 ng/ml (Fig. 2). The modulation of the IgE-dependent basophil response tends to reach a maximal effect at slightly lower concentrations (1–3 ng/ml). These data exclude that the somewhat weaker effect of IL-5, as compared with IL-3, upon the IgE-dependent basophil response (Fig. 1) is due to a suboptimal IL-5 concentration.

Kinetic of IL-5 Priming. When IL-5 is added simultaneously with the agonist, no enhancement of mediator release is observed (data not shown). Experiments, in which the time interval between IL-5 and C5a addition has been varied, show that the enhancement of histamine release occurs almost immediately after IL-5 addition and becomes maximal after 5 min. Priming for C5a-induced LTC4 formation starts after a lag period of 3–4 min, with optimal effects after 9–10 min. This altered responsiveness remains unchanged up to an observation period of 40 min (Fig. 3).

Discussion

The present study demonstrates that the biological activity of human IL-5 is not restricted to cells of the eosinophil lineage but strongly enhances mediator release by mature human basophils. The data support our concept that a major function of hematopoietic growth factors is their ability to allow the synthesis of lipid mediators by inflammatory effector cells in response to agonists that are otherwise inactive in this respect (10–13). The fact that two cellular signals are generally necessary for lipid mediator synthesis has also been observed in neutrophils (13), and in monocytes (16). The similarity of the biological activities between IL-5, IL-3, and GM-CSF upon basophil function suggests a similarity also in their mechanism of action. This hypothesis is further supported by the fact that the effect of optimal concentrations of a single growth factor cannot be enhanced by the combination of these cytokines. In this respect, it is interesting that the receptors of most leukocyte growth factors, including IL-3 and GM-CSF, belong to a large family of structurally related proteins (erythropoietin receptor family) (see reference 17), and it is likely that the IL-5R also belongs to this class of receptors. Recent studies have shown that the IL-6 ligand-receptor complex, by its extracellular domain, interacts with another membrane protein (GP 130), which seems to mediate signal transduction (18). It is tempting to speculate that IL-5, IL-3, and GM-CSF ligand-receptor complexes interact with a similar protein, which may even be shared among these three cytokine receptors.

There are, however, discrete differences between the priming effects of IL-5, GM-CSF, and IL-3 upon basophil function. While IL-5 and IL-3 modulate the basophil response to all IgE-independent agonists examined (FMLP, C5a, C3a, NAP-1) in an identical manner, IL-5 enhances the anti-IgE-induced mediator release somewhat less efficiently as compared with

IL-3. Whereas IL-5 alone does not induce any mediator release, IL-3 occasionally causes a small histamine release above controls (10). Histamine release induced by IL-3 alone is more readily observed in cell buffers containing D_2O (19). IL-5 also induces marginal degranulation when using D_2O-containing buffer, but clearly less strongly than that caused by IL-3 (own unpublished results). The priming process for enhancement of histamine release and generation of LTC4 in response to C5a proceeds slightly more rapidly by IL-3 (10) as compared to IL-5. Finally, the altered state of basophil responsiveness induced by GM-CSF is more transient (unpublished observation) than that induced by IL-5 or IL-3.

The fact that low concentrations of IL-5 rapidly, within minutes, modulate mediator release suggests a direct action of this cytokine on basophils, presumably through a specific receptor. The probable lack of effects of IL-5 on other human PBMC (1, 2, 5), and our observation that basophils purified up to 94% respond identically to IL-5 as basophils in PBMC, further argue against the involvement of other leukocytes in the IL-5 effect on basophils. Under the stimulation protocols used in this study, the basophil is the only relevant source of LTC4, since: (*a*) LTC4 production strongly correlates with the basophil number and was not affected by the presence of variable proportions of other leukocyte types in different cell fractions of Percoll gradients (10, and unpublished results); and (*b*) no LTC4 is produced with or without cytokine priming by other leukocyte types (e.g., monocytes or neutrophils) depleted of basophils.

IL-5 dose dependently modulates basophil mediator release within a low concentration range of 0.1–3 ng/ml. However, since human IL-5 has been cloned according to its sequence homology to mouse IL-5 only (5), and since natural IL-5 has not been purified, the potency of the human natural product is yet unknown. Also, the role of glycosylation and homodimer formation has been determined only in the murine system (20). Therefore, with regard to basophil activation, the structural requirements for the optimally active form of IL-5 are unclear, and its potency may be underestimated. A particular problem is the definition of units of human IL-5 in the absence of a IL-5-dependent human cell line. The modification of the basophil response described here may thus be a rapid and useful means to standardize the bioactivity of human IL-5.

A large number of cytokines, including IL-2, IL-4, IL-6, G-CSF, IFN-α, IFN-γ, transforming growth factor β and TNF-α, have been examined and found to be ineffective in inducing or modulating basophil mediator release (unpublished results). IL-1β, even at high concentrations, induces only discrete modulation of basophil mediator release. In comparison with the effects of IL-5, IL-3, and GM-CSF, this cytokine must be considered as unimportant in modifying basophil function. Thus, IL-5, IL-3, and GM-CSF belong to a particular set of cytokines with potent modulatory effects on basophil function. It is interesting that the genes of these three cytokines are located in close proximity on human chromosome 5, although they do not share homologies in primary sequence. It is also striking that the same set of cytokines acts on both basophils and eosinophils, which are considered to play a major role in allergic inflammation (9, 10). There is increasing evidence that basophils and eosinophils share many functional and structural similarities. In fact, we believe that basophils are more closely related to eosinophils than to tissue mast cells. Indeed, it has been postulated that both cells derive from a common committed progenitor (21).

Our data indicate that, apart from its relevance in parasitic disease and eosinophilia (22), IL-5, together with IL-3 and GM-CSF, should be considered as a major cytokine responsible for the developmental of inflammatory responses in hypersensitivity diseases. The definition of a set of cytokines with profound influences on eosinophil and basophil responsiveness, and the possibility that these cytokines act through a similar mechanism, could provide the basis for the development of novel antiallergic drugs, capable of interfering at the level of effector cell priming.

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