ORIGINAL ARTICLE
Iran J Allergy Asthma Immunol
June 2014; 13(3):190-197.

Evaluation of The Correlation and Reproducibility between Histamine, IL-4, and IL-13 Release from Human Basophils

Nahid Eskandari[1], Reza Bastan[2], Maryam Ahmadi[1], and Peter T Peachell[3]

[1] Department of Immunology, Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
[2] Department of Immunopharmacology, Faculty of Medicine, Karaj University of Medical Sciences, Alborz, Iran
[3] Department of Immunology, Faculty of Medicine, University of Medical Sciences, Yorkshire, UK

Received: 15 May 2013; Received in revised form: 23 July 2013; Accepted: 21 August 2013

ABSTRACT

Human basophils play a key role in allergic diseases such as asthma and in a variety of immunological disorders. The generation of IL-4 and IL-13 can be induced from basophil by IgE-mediated and non-IgE-mediated mechanisms. Time and stimulus-dependent differences in the regulation of these cytokines could have relevance to their biological effects. The aim of the present study was activation of basophils in order to evaluate the extent of histamine, IL-4, and IL-13 generations.

Basophil-enriched suspensions were prepared by Percoll gradients. The release of histamine and cytokines was assessed after activation with either anti-human IgE (1/1000 or 1/10000, 4 h or 24 h) or IL-3 (100 ng/ ml, 24 h). Results were analysed statistically, using ANOVA test.

Using anti-IgE, there was no significant correlation between the extent of either IL-4 (r=0.24, p=0.35) or IL-13 (r=0.47, p=0.098) and histamine release. Using IL-3 as stimulator, results showed that the extent of IL-13 correlated with histamine release(r=0.44, p=0.036). There was no correlation between the extent of IL-4 and the degree of either histamine (r=0.077, p=0.72) or IL-13 (r=0.162, p=0.5). The reproducibility of cytokines isolated from the same donor (on different occasions) indicated that the ability of anti-IgE to induce cytokines was consistently similar for a given donor.

Our data showed that the pathways leading to IL-3-triggering histamine release and IL-13 generation show similarity. Donor-dependent differences may be responsible for this wide range in the extent of releasibility. The ability of IL-3 to release cytokines from basophils showed a wider range.

Keywords: Allergy; Basophil; Cytokine; Histamine; IL-4; IL-13

Corresponding Author: Nahid Eskandari, MD, PhD; Department of Immunology, Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran. Tel: (+98 311) 7922 431, Fax: (+98 311) 7922 431, E-mail: neskandari@med.mui.ac.ir

Published by Tehran University of Medical Sciences (http://ijaai.tums.ac.ir)

INTRODUCTION

Human basophils play a key role in allergic diseases such as asthma and in a variety of immunological disorders. It is well established that basophils can release a wide variety of mediators that are responsible for the propagation of allergic diseases. [1-6] Allergic responses are dependent on the ability of antigen-specific IgE to bind to basophils via FcεRI receptors with high affinity on the cell surface. Upon appropriate IgE-dependent stimulation by antigen, basophils release and generate a variety of inflammatory mediators, such as histamine, sulfidoleukotrienes (sLTs), and the proallergic cytokines, IL-4 and IL-13. [1, 6-9] While the preformed histamine and de novo-generated sLTs are mainly responsible for the symptoms seen in immediate-type allergic reactions, IL-4 and IL-13 may participate in late phase reactions. [10,11]

Studies have demonstrated that basophils are a rich source of IL-4 and IL-13. [12-14] These cytokines are released to a greater degree by basophils from asthmatics than non-asthmatic controls. In terms of IgE-dependent stimulation, the kinetics of IL-4 release are different from IL-13 generation from basophils. At present, the reasons for these differing kinetics are not known, but factors such as autocrine effects are now being investigated. [15] IL-4 generation occurs earlier, peaking at 4 hours after IgE-dependent stimulation.[12,13,16,17] On the other hand, IL-13 secretion is generally more sustained than IL-4. IL-13 is detectable at 3 h following stimulation and generation steadily increases up to 24 h.[18]

Both IL-4 and IL-13 exert a vital role in the pathogenesis of allergic reactions.[19] IL-4 shares many properties with IL-13 which include the inhibition of cytokine secretion induced by lipoplysaccharide (LPS), down-regulation of monocyte functions (e.g. IL-1, IL-12 secretion), induction of surface antigen on human B cells including CD23 (the low affinity IgE-receptor), and synthesis of Ig class switching to IgE.[20] IL-13 further increases the allergic reaction by promoting the differentiation and survival of eosinophils. Unlike IL-4, IL-13 does not directly affect T cell functions. These cytokines have been shown to bind differently to various inflammatory cell types. Therefore, differences in IL-4 or IL-13 receptor expression on cells could exert different functions in the regulation of immune responses.[21]

Whereas activation through the high-affinity IgE receptor induces the generation of both cytokines in basophils, there is evidence that IL-4 and IL-13 might be differentially regulated in response to IgE-independent stimuli. For example, studies have shown that the function of basophils is strongly regulated by certain cytokines such as IL-3, IL-5, granulocyte-macrophage colony-stimulating factor (GM-CSF) and nerve growth factor (NGF).[22-25] Recent studies have demonstrated that basophils express very prominent and much higher levels of IL-3 receptor, compared to receptors for IL-5, GM-CSF and NGF.[26,27] In addition, IL-3 not only promotes proliferation of immature basophils but also amplifies various aspects of the biological function of basophils such as causing increased generation of mediators and, prolonging survival.[28-30]

Thus, time and stimulus-dependent differences in the regulation of IL-4 and IL-13 generation from basophils could be of relevance to the biological effects of these cytokines. In the present study, therefore, we investigated the effects of IgE-dependent (anti-IgE) and IgE-independent (IL-3) activation of basophils and evaluated the extent of histamine release, IL-4, and IL-13 generations from human basophils.

MATERIALS AND METHODS

Participants

Healthy and normal volunteers participated in the study after giving written informed consent. People with diseases such as allergic or parasitic infections were excluded. The provisions of this study were approved by the Local Research Ethics' Committee. The percentage of male and female donors was 59 and 41%, respectively, and age ranges were from 25 to 45 years with mean age of 35 ± 10.

Basophil Isolation

Basophil-enriched suspensions were obtained by Percoll density gradient centrifugation. Briefly, basophil-enriched preparations were isolated from whole fresh blood. Blood was layered over a two-step discontinuous Percoll gradient consisting of 15 ml of 62% Percoll overlaid with 15 ml of 53% Percoll prepared in 50 ml tubes and centrifuged. A basophil-rich layer (5–15% purity), which was located 1cm above the 53/62% interface, was harvested. The contaminant cells were lymphocytes and monocytes. These cells were washed three times in PIPES buffer

and basophils were investigated for the release of histamine, IL-4 and IL-13.

Mediator Release

The followings were purchased from the sources indicated; goat anti-human IgE, PIPES (free acid), Percoll, BSA; gentamicin and RPMI 1640 (Gibco BRL, Dundee, U.K.); IL-13 (Peprotech, Rocky Hill, NJ, U.S.A.); ELISA kits for human IL-4 and IL-13 (Mast Diagnostics, Amsterdam, Netherlands).

The release of histamine, IL-4 and IL-13 was assessed from basophil-enriched suspension activated with either anti-human IgE or IL-3. Mediator release experiments were performed in RPMI 1640 medium supplemented with BSA (1mg/ml), gentamicin (10 mg/ml) and calcium chloride (made up to 1mM). Basophils (80,000–300,000 basophils per sample) were incubated (15 or 30min) with a RPMI before challenge with a stimulus, typically, in a total reaction volume of 220 ml. Cells incubated (supplemented with Co_2) in RPMI alone served as measures of spontaneous mediator release, and all values cited for stimulus-induced mediator generation were corrected by subtracting this spontaneous mediator release. In experiments monitoring IL-4 generation, basophils were activated for 4h with an optimal releasing concentration of anti-IgE (1:100,000 or 1:10,000 dilutions). In experiments monitoring IL-13 generation, basophils were activated for longer (20 or 24h). These conditions for optimal generation of IL-4 and IL-13 generation have been reported by others[12,13,31] and were confirmed by us in a series of preliminary experiments. In some experiments, cells were activated with IL-3 (100 ng/ml) for 24h for the generation of mediators. After activation, the cells were centrifuged (450 x g, 4min) and the supernatants saved and analysed for mediator release. For the analysis of histamine content, an aliquot (50 ml) of the supernatant, diluted in PBS buffer (950 ml), was analysed using a modification[32] of the automated fluorometric technique of Siraganian.[33] The remainder of the supernatant was assayed for IL-4 and IL-13 content by enzyme-linked immunosorbent assay (ELISA). The limit of sensitivity was 0.2 and 0.5 pg/ml for the IL-4 and IL-13 assays, respectively. The Optical Density (OD) of samples was measured at 450 nM using a Dynatech plate reader.

Data Analysis

Total mediators (histamine and cytokines) content was obtained by incubating cells in the presence of 1.6% perchloric whilst the spontaneous release was determined by incubating cells in buffer and control Mediators release was determined by stimulating cells with stimulators. Stimulated mediators release was calculated as a percentage of the total mediators and then corrected by subtracting the spontaneous release. All experiments were carried out in duplicate.

Data are expressed as means ± s.e.m. EC50 values were determined using GraphPad Prism software (version 2). In order to establish whether stimulator caused statistically significant effects, either paired t - tests or ANOVA, followed by Dunnett's test, was performed. In all instances, the raw data were subjected to statistical analyses.

RESULTS

Correlation and Reproducibility between Histamine IL-4, and IL-13 Release, from Basophils Induced with Anti-IgE

In a further series of experiments, the effects of IL-3 on basophils were investigated. Cells were challenged with IL-3 (100 ng/ml) for 1, 4, 16 or 24 h to evaluate the kinetics of the release of histamine, IL-4 and IL-13 (not shown). Significant ($p<0.05$) levels of histamine release and IL-13 generation were obtained after 16 h incubation of basophils with IL-3. IL-4 generation was also monitored in these experiments but in only two donors (out of four), IL-4 was generated to a considerable degree. Overall, basophils produced higher concentration of IL-13 than IL-4 upon stimulation with IL-3 over 24 h. Histamine was released in a dose-dependent fashion by IL-3 from basophils following 24 h of activation (not shown).

In further experiments, correlations between histamine release, IL-4, and IL-13 generation from basophils were evaluated. Basophils from different donors were exposed to IL-3 for 24 h and mediator generation was assessed.

These experiments showed that the extent of IL-13 generation correlated well with the degree of histamine release (Figure 1b, r=0.44, p=0.036). In contrast, there was no correlation between the extent of IL-4 generation and the degree of either histamine release (Figure 1.a, r=0.077, p=0.72) or IL-13 generation (Figure 1. c r=0.162, p=0.5) in basophils.

These experiments showed that the extent of IL-13

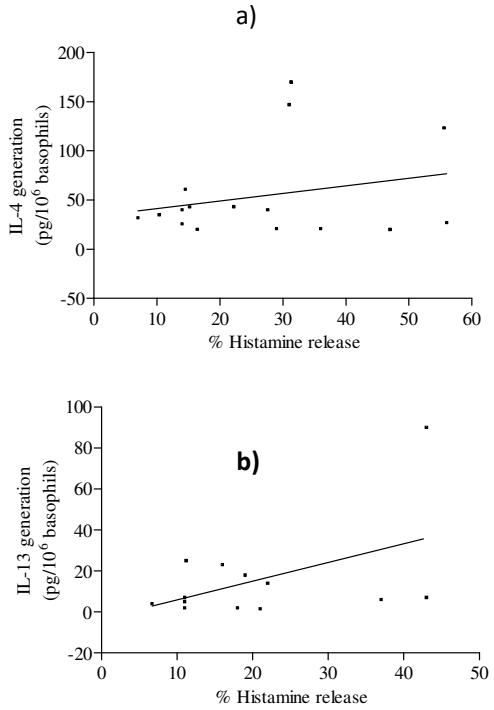


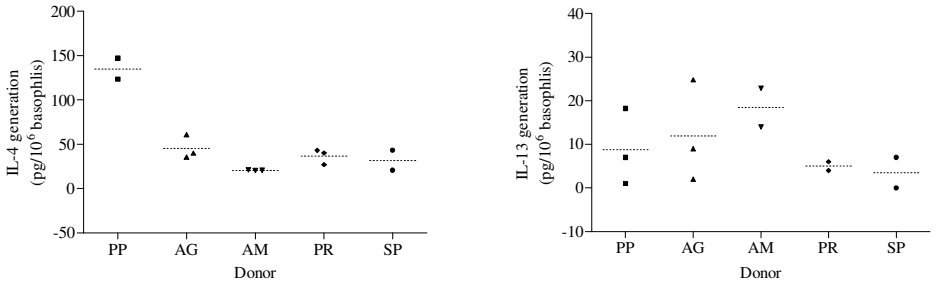
Figure 1. The relationship between histamine release, IL-4, and IL-13 generation in response to anti-IgE from basophils. Cells were incubated for 4 h (IL-4) or 24 h (IL-13) with anti-IgE (1:10000 or 1:100000) for optimal basophil secretion. Supernatants were harvested for determination of histamine, IL-4 and IL-13. Values were plotted as correlations comparing IL-4 against % histamine release (r=0.24, *p*=0.35) (a), and IL-13 against histamine release (r=0.47, *p*=0.098) (b). Each point represents data from a separate donor.

generation correlated well with the degree of histamine release (Figure 1b, r=0.44, *p*=0.036). In contrast, there was no correlation between the extent of IL-4 generation and the degree of either histamine release (Figure 1.a, r=0.077, *p*=0.72) or IL-13 generation (Figure 1. c r=0.162, *p*=0.5) in basophils.

In additional experiments, the reproducibility of IL-3-dependent mediator generation from basophils from the same donors isolated on different occasions was evaluated (Figure 2). Cells were incubated with IL-3 (100 ng/ml) for 24 h and cytokine generation was assessed. In contrast to experiments with anti-IgE, the response of basophils to IL-3 showed greater variability in the extent to which cytokines were generated by a given donor but on different occasions.

Correlation and Reproducibility between Histamine IL-4, and IL-13 Release, from Basophils Induced with IL-3

In a further series of experiments, the effects of IL-3 on basophils were investigated. Cells were challenged with IL-3 (100 ng/ml) for 1, 4, 16 or 24 h to evaluate the kinetics of the release of histamine, IL-4 and IL-13 (Figures 3& 4). Significant ($p<0.05$) levels of histamine release and IL-13 generation were obtained after 16 h incubation of basophils with IL-3. IL-4 generation was also monitored in these experiments but in only two donors out of four, IL-4 was generated to a considerable degree. Overall, basophils produced higher concentrations of IL-13 than IL-4 upon stimulation with IL-3 over 24 h. Histamine was released in a dose-dependent fashion by IL-3 from basophils following 24 h of activation (not shown).



(A) **(B)**

Figure 2. Reproducibility of IL-4 and IL-13 generation from basophils. Basophil-enriched preparations were incubated for 4 h (IL-4) or 24 h (IL-13) with anti-IgE (1:10000 or 1:100000). Supernatants were then harvested for determination of (a) IL-4 and (b) IL-13. For each donor, each point represents data generated from basophils isolated on different occasions. Horizontal broken lines represent mean cytokine generation. Each abbreviation represents data from a separate donor. Asterisks denote allergic donors.

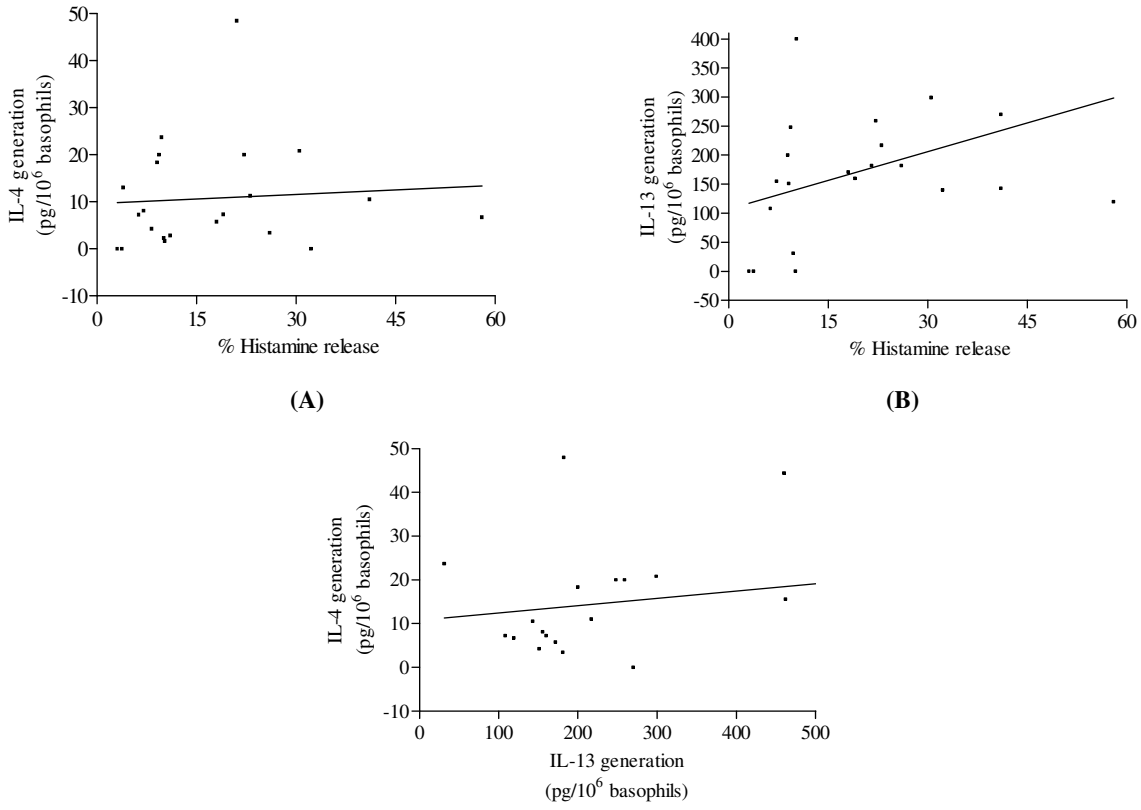


Figure 3. The relationship between histamine, IL-4, and IL-13 generation in response to IL-3 from basophils. Cells were incubated for 24 h with IL-3 (100 ng/ml) for optimal basophil secretion. Supernatants were harvested for determination of histamine, IL-4 and IL-13. Values were plotted as correlations comparing IL-4 generation against histamine release (a), IL-13 generation against histamine release (b), and IL-13 against IL-4 generation (c). Each point represents data obtained from a separate donor.

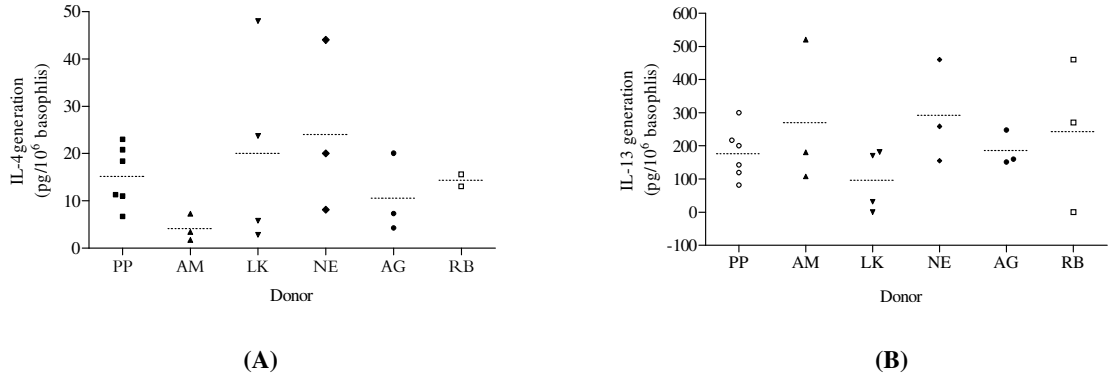


Figure 4. Reproducibility of IL-4 and IL-13 generation from basophils. Basophil-enriched preparations were incubated for 24 h with IL-13 (100 ng/ml). Supernatants were then harvested for the determination of (a) IL-4 and (b) IL-13. For a given donor, each point represents data generated from basophils isolated on different occasions. Horizontal broken lines represent mean cytokine generation. Each abbreviation represents data from a separate donor. Asterisks denote allergic donors.

In further experiments, correlations between histamine release, IL-4, and IL-13 generation from basophils were evaluated. Basophils from different donors were exposed to IL-3 for 24 h and mediator generation was assessed. These experiments showed that the extent of IL-13 generation correlated well with the degree of histamine release (Figure 3b, r=0.44, p=0.036). In contrast, there was no correlation between the extent of IL-4 generation and the degree of either histamine release (Figure 3a, r=0.077, p=0.72) or IL-13 generation (Figure 3c, r=0.162, p=0.5) from basophils.

In additional experiments, the reproducibility of IL-3-dependent mediator generation from basophils from the same donors isolated on different occasions was evaluated (Figure 4). Cells were incubated with IL-3 (100 ng/ml) for 24 h and cytokine generation was assessed. In contrast to experiments with anti-IgE, the response of basophils to IL-3 showed greater variability in the extent to which cytokines were generated by a given donor but on different occasions.

DISCUSSION

The present study attempted to establish whether human basophils were capable of releasing cytokines in response to stimulators such as anti-IgE and IL-3. Initial studies employing different concentrations of anti-IgE indicated that optimal generation of either histamine or IL-4 occurs at different concentrations of anti-IgE. This finding is consistent with other studies which also showed that IL-4 secretion peaks at lower concentrations (ten-fold lower) of anti-IgE than that needed for histamine release.[6,12] By contrast, it has been shown that anti-IgE-induced IL-13 generation parallels histamine release.[31]

In general, we could not detect any significant correlations between the extent which basophils released histamine and generated cytokines in response to anti-IgE. These data suggest that the processes leading to histamine release and cytokine generation, when cells are challenged with anti-IgE, may differ. Similarly, when basophils were challenged with IL-3, there was no correlation between histamine release and IL-4 generation, but there was a significant correlation between the extent of IL-13 generation and histamine release. It is possible, therefore, that the pathways leading to IL-3-triggered histamine release and IL-13 generation show similarity.

Furthermore, in terms of cytokine generation induced by IL-3 or anti-IgE, our data showed that the ability of IL-3 to release cytokines from basophils showed a greater range of levels of generations. This is in agreement with other reports showing more variability in the response of basophils to IL-3.[34] Donor-dependent differences may be responsible for this wide range in the extent of releasibility. Also the reproducibility of IL-3-dependent mediator generation from basophils showed conisderable variability in the extent to which cytokines were generated by a given donor but on different occasions. This is in contrast with anti-IgE induced cytokine generation that was consistently similar for a given donor. This implies that the responsiveness of basophils to IL-3 is less strictly regulated. An individual's status at the time when basophils are isolated, may influence cellular responsiveness to IL-3.

Previous studies have shown that stimulation of basophils with IL-3 induced large magnitude of IL-13 generation but modest levels of IL-4 and negligible levels of histamine release.[26,31,35] Our studies indicated that IL-3 not only induced IL-13 and some modest levels of IL-4 generation from basophils, but also could induce substantial levels of histamine release. The discrepancy between our own data and those of others may relate to incubation time. While studies by others followed histamine release for only 2 h,[36] Our findings showed that the kinetics of histamine release with IL-3 were very slow requiring more than 4 h. IL-3-dependent release differs from IgE-dependent histamine release since the latter is completed by 30-40 min following challenge. Interestingly, a similar slow onset of histamine release from basophils is also seen with LPS (unpublished data). This suggests that the mechanisms by which anti-IgE and IL-3 induce histamine release from basophils, differ. Given the slow kinetics of histamine release, it is possible that IL-3 acts through gene transcription to release histamine. It is known that IL-3 induces STATs (signal transducers and activators of transcription) to initiate transcription and the generation of cytokines.[37,38] It is possible that a similar mechanism may be involved causing slow onset histamine release from basophils. Additional support for this comes from the finding that there was a significant correlation between the extent of histamine release and the degree of IL-13 generation from basophils activated with IL-3. Our studies, comparing the effect of IL-3 on mixed cells and purified basophil preparations (data not shown)

established that IL-3 induced histamine, IL-4 and IL-13 release from basophils and that IL-3 did not mediate effects by interacting with other cell populations. The later data indicated that the basophils could be the major source of releasing IL-4, IL-13 and histamine in mixed leukocyte preparations.

Overall, these findings indicated that basophils were capable of generating cytokines and histamine in response to both IgE- and non-IgE-dependent stimulators. The release of these mediators is likely to contribute to the elaboration of allergic diseases.

ACKNOWLEDGEMENTS

The authors would like to thank to all the people, colleagues and staff for their help in this study.

REFERENCES

1. Warner JA, Kroegel C. Pulmonary immune cells in health and disease: mast cells and basophils. Eur Respir J 1994; 7(7):1326-41.
2. Bochner BS, Busse WW. Allergy and asthma. J Allergy Clin Immunol 2005;115(5):953-9.
3. Dvorak HF, Dvorak AM. Basophilic leucocytes: structure, function and role in disease. Clin Haematol 1975; 4(3):651-83.
4. Schleimer RP, MacGlashan DW, Jr., Peters SP, Naclerio R, Proud D, Adkinson NF, Jr., et al. Inflammatory mediators and mechanisms of release from purified human basophils and mast cells. J Allergy Clin Immunol 1984; 74(4 Pt 1):473-81.
5. Schroeder JT, Kagey-Sobotka A, Lichtenstein LM. The role of the basophil in allergic inflammation. Allergy 1995; 50(6):463-72.
6. Schroeder JT, MacGlashan DW, Jr., Kagey-Sobotka A, White JM, Lichtenstein LM. Cytokine generation by human basophils. J Allergy Clin Immunol. 1994; 94(6 Pt 2):1189-95.
7. Brunner T, Heusser CH, Dahinden CA. Human peripheral blood basophils primed by interleukin 3 (IL-3) produce IL-4 in response to immunoglobulin E receptor stimulation. J Exp Med 1993; 177(3):605-11.
8. Nahum LH. Allergy, Histamine, and the Basophil. Conn Med 1963; 27:367-71.
9. Skov-Stahl P, Norh S, Weeke B. Basophil histamine release in patients with hay fever. Results compared with specific IgE and total IgE during immunotherapy. Clin Exp Immunol 1977; 27(3):432-9.
10. Macfarlane AJ, Kon OM, Smith SJ, Zeibecoglou K, Khan LN, Barata LT, et al. Basophils, eosinophils, and mast cells in atopic and nonatopic asthma and in late-phase allergic reactions in the lung and skin. J Allergy Clin Immunol 2000; 105(1 Pt 1):99-107.
11. Barnes PJ. Cytokines as mediators of chronic asthma. Am J Respir Crit Care Med 1994; 150(5 Pt 2):S42-9.
12. MacGlashan D, Jr., White JM, Huang SK, Ono SJ, Schroeder JT, Lichtenstein LM. Secretion of IL-4 from human basophils. The relationship between IL-4 mRNA and protein in resting and stimulated basophils. J Immunol 1994; 152(6):3006-16.
13. Gibbs BF, Haas H, Falcone FH, Albrecht C, Vollrath IB, Noll T, et al. Purified human peripheral blood basophils release interleukin-13 and preformed interleukin-4 following immunological activation. Eur J Immunol 1996; 26(10):2493-8.
14. Shimizu Y, Shichijo M, Hiramatsu K, Takeuchi M, Nagai H, Takagi K. Mite antigen-induced IL-4 and IL-13 production by basophils derived from atopic asthma patients. Clin Exp Allergy 1998; 28(4):497-503.
15. Falcone FH, Haas H, Gibbs BF. The human basophil: a new appreciation of its role in immune responses. Blood 2000; 96(13):4028-38.
16. Jung T, Wijdenes J, Neumann C, de Vries JE, Yssel H. Interleukin-13 is produced by activated human CD45RA+ and CD45RO+ T cells: modulation by interleukin-4 and interleukin-12. Eur J Immunol 1996; 26(3):571-7.
17. Kon OM, Sihra BS, Till SJ, Corrigan CJ, Kay AB, Grant JA. Unstimulated basophils in atopic and nonatopic subjects express intracellular interleukin-4: detection by flow cytometry. Allergy 1998; 53(9):891-6.
18. Li H, Sim TC, Alam R. IL-13 released by and localized in human basophils. J Immunol 1996; 156(12):4833-8.
19. Schroeder JT, Howard BP, Jenkens MK, Kagey-Sobotka A, Lichtenstein LM, MacGlashan DW Jr. IL-4 secretion and histamine release by human basophils are differentially regulated by protein kinase C activation. J Leukoc Biol 1998; 63(6):692-8.
20. Kraan MC, Versendaal H, Jonker M, Bresnihan B, Post WJ, t Hart BA, et al. Asymptomatic synovitis precedes clinically manifest arthritis. Arthritis Rheum 1998; 41(8):1481-8.
21. Obiri NI, Leland P, Murata T, Debinski W, Puri RK. The IL-13 receptor structure differs on various cell types and may share more than one component with IL-4 receptor. J Immunol 1997; 158(2):756-64.
22. Sin AZ, Roche EM, Togias A, Lichtenstein LM, Schroeder JT. Nerve growth factor or IL-3 induces more

IL-13 production from basophils of allergic subjects than from basophils of nonallergic subjects. J Allergy Clin Immunol 2001; 108(3):387-93.
23. Tedeschi A, Salmaso C, Di Donato M, Lorini M, Miadonna A. Granulocyte-macrophage colony-stimulating factor and interleukin-3 cause basophil histamine release by a common pathway: downregulation by sodium. Immunology 1999; 96(2):164-70.
24. Tedeschi A, Palella M, Milazzo N, Lorini M, Miadonna A. IL-3-induced histamine release from human basophils. Dissociation from cationic dye binding and down-regulation by Na+ and K+. J Immunol 1995; 155(5):2652-60.
25. Miura K, Saini SS, Gauvreau G, MacGlashan DW, Jr. Differences in functional consequences and signal transduction induced by IL-3, IL-5, and nerve growth factor in human basophils. J Immunol 2001; 167(4):2282-91.
26. Ochensberger B, Tassera L, Bifrare D, Rihs S, Dahinden CA. Regulation of cytokine expression and leukotriene formation in human basophils by growth factors, chemokines and chemotactic agonists. Eur J Immunol 1999; 29(1):11-22.
27. Zheng X, Karsan A, Duronio V, Chu F, Walker DC, Bai TR, et al. Interleukin-3, but not granulocyte-macrophage colony-stimulating factor and interleukin-5, inhibits apoptosis of human basophils through phosphatidylinositol 3-kinase: requirement of NF-kappaB-dependent and -independent pathways. Immunology 2002; 107(3):306-15.
28. Valent P, Schmidt G, Besemer J, Mayer P, Zenke G, Liehl E, et al. Interleukin-3 is a differentiation factor for human basophils. Blood 1989; 73(7):1763-9.
29. Hirai K, Morita Y, Misaki Y, Ohta K, Takaishi T, Suzuki S, et al. Modulation of human basophil histamine release by hemopoietic growth factors. J Immunol 1988; 141(11):3958-64.
30. Schleimer RP, Derse CP, Friedman B, Gillis S, Plaut M, Lichtenstein LM, et al. Regulation of human basophil mediator release by cytokines. I. Interaction with antiinflammatory steroids. J Immunol 1989; 143(4):1310-7.
31. Redrup AC, Howard BP, MacGlashan DW, Jr., Kagey-Sobotka A, Lichtenstein LM, Schroeder JT. Differential regulation of IL-4 and IL-13 secretion by human basophils: their relationship to histamine release in mixed leukocyte cultures. J Immunol 1998; 160(4):1957-64.
32. Ennis MP, Wisdom GB. A magnetizable solid phase for enzyme extraction. Appl Biochem Biotechnol 1991; 30(2):155-64.
33. Siraganian RP. An automated continuous-flow system for the extraction and fluorometric analysis of histamine. Anal Biochem 1974; 57(2):383-94.
34. Gibbs BF. Human basophils as effectors and immunomodulators of allergic inflammation and innate immunity. Clin Exp Med 2005; 5(2):43-9.
35. Chen YH, Bieneman AP, Creticos PS, Chichester KL, Schroeder JT. IFN-alpha inhibits IL-3 priming of human basophil cytokine secretion but not leukotriene C4 and histamine release. J Allergy Clin Immunol 2003; 112(5):944-50.
36. Miadonna A, Roncarolo MG, Lorini M, Tedeschi A. Inducing and enhancing effects of IL-3, -5, and -6 and GM-CSF on histamine release from human basophils. Clin Immunol Immunopathol 1993; 67(3 Pt 1):210-5.
37. Numata A, Shimoda K, Kamezaki K, Haro T, Kakumitsu H, Shide K, et al. Signal transducers and activators of transcription 3 augments the transcriptional activity of CCAAT/enhancer-binding protein alpha in granulocyte colony-stimulating factor signaling pathway. J Biol Chem 2005; 280(13):12621-9.
38. Jiang X, Ng E, Yip C, Eisterer W, Chalandon Y, Stuible M, et al. Primitive interleukin 3 null hematopoietic cells transduced with BCR-ABL show accelerated loss after culture of factor-independence in vitro and leukemogenic activity in vivo. Blood 2002; 100(10):3731-40.