Synthesis of Cytokines by Eosinophils and Their Regulation

B.	Bouchaïb	Lamkhioued ^a
D.	Delphine	Aldebert ^a
A.S.	Abdelilah Soussi	Gounni ^a
E.	Emmanuel	Delaporte ^b
M.	Michel	Goldman ^c
A.	André	Capron ^a
M.	Monique	Capron ^a

^aCentre d'Immunologie et de Biologie Parasitaire, Unité INSERM U167, Institut Pasteur, et ^bService de Dermatologie A, Centre Hospitalier et Universitaire, Lille, France; ^cService d'Immunologie, Hôpital Erasme, ULB, Bruxelles, Belgique

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Abstract

In addition to cytotoxic and proinflammatory mediators, eosinophils can produce a variety of cytokines and growth factors. Besides interleukin (IL)-5, we show in the present work that human eosinophils can synthesize interferon (IFN)-γ and IL-10, by RT-PCR, in situ hybridization and immunostaining. Double-labelling procedures revealed the coexpression of IL-5 and IL-10 but not IL-5 and IFN-γ, indicating the existence of subpopulations of eosinophils expressing type 1 or type 2 cytokines. IFN-α efficiently used for the treatment of hypereosinophilic syndromes can significantly decrease eosinophil degranulation and IL-5 release by eosinophils, through binding to a receptor for IFN-α. Thus, eosinophils can represent major sources of cytokines with regulatory functions, especially in allergic diseases and parasitic infections.

Correspondence to: Professor Monique Capron, Unité INSERM U167, Institut Pasteur, 1 rue du Pr. A. Calmette, F-59019 Lille Cédex (France)

Introduction

Over the past 20 years, several lines of evidence have generated interest in the effector function of eosinophils in a variety of clinical states associated with hypereosinophilia, including parasitic and allergic diseases. The differentiation and activation of eosinophils are controlled by hemopoietic growth factors, namely interleukin (IL)-3, granulocyte/ macrophage-colony-stimulating factor (GM-CSF), and specifically IL-5, which bind to the corresponding membrane receptors. Studies on eosinophil mediators have revealed that eosinophils are not only the source of cytotoxic granule basic proteins, and proinflammatory mediators but can also release various cytokines and growth factors. The aim of the present review is to highlight some recent aspects of eosinophil functions with particular emphasis on the synthesis of Th1 versus Th2 cytokines by distinct sub-populations of eosinophils, and the direct effects of interferon (IFN)-α on the release of mediators by eosinophils.

Synthesis of Th1 or Th2 Cytokines by Subpopulations of Eosinophils

Human eosinophils have been shown to synthesize IL-5 in a variety of diseases [1–3]. In patients with bullous pem-phigoid, we could show by in situ hybridization with an IL-5 probe and immunostaining with a monoclonal antibody directed against eosinophilic cationic protein (ECP) that about 50% of eosinophils detected in the bullous fluid expressed IL-5 mRNA. However, both in situ hybridization and immunostaining revealed the absence of IL-5 mRNA and protein in the numerous eosinophils infiltrating the intestinal lesions in patients with Crohn’s disease [4]. These two findings suggested the existence of subpopulations of eosinophils expressing or not IL-5. The demonstration in mice and humans of distinct subpopulations of CD4+ Th cells producing either IL-2 and IFN-γ (Th1 subset) or IL-4, IL-5 and IL-10 (Th2 subset), led us to investigate IFN-γ synthesis by eosinophils. Using in situ hybridization or immu-

nostaining, we could show that some eosinophils expressed IFN- γ mRNA and protein. In the context of the regulatory role of IL-10 on the synthesis of Th1 cytokines, it was interesting to investigate whether eosinophils could express IL-10. The same experimental approaches revealed the expression of IL-10 mRNA and protein by eosinophils. In addition, double in situ hybridization and double immuno-staining revealed coexpression of IL-5 and IL-10, but no coexpression of IL-5 and IFN- γ . These results indicate the existence of subpopulations of eosinophils which may express either IL-5 and IL-10 or IFN- γ . It is therefore reasonable to suspect that eosinophils can represent important sources of cytokines, especially in allergic diseases or parasitic infections.

Effects of IFN- α on the Release of Mediators by Eosinophils

Cross-linked IgA can induce the release of mediators by eosinophils [5]. The release of ECP, eosinophil-derived neurotoxin (EDN) or IL-5 was evaluated after incubating highly purified blood eosinophils with IgA/anti-IgA immune complexes in the presence or absence of IFN- α . According to the concentration, IFN- α could significantly decrease the release of ECP, EDN and IL-5, suggesting an inhibitory effect of IFN- α on eosinophil degranulation. These results prompted us to investigate the existence of a receptor for IFN- α on human eosinophils. Using RT-PCR, we detected the IFN- α receptor message in eosinophil extracts from all patients tested. An immunostaining procedure with biotinylated IFN- α performed on cytocentrifuged preparations of eosinophils revealed a positive staining in eosinophils from 5 of the 6 patients tested. These results provide the first evidence that human eosinophils can express a receptor for IFN- α . This represents one potential basis for the therapeutic effects of IFN- α in patients with HESs.

The interferons constitute a family of secreted proteins that play a leading role in host defense. They are engaged in various biological activities, ranging from inhibition of cell proliferation to induction of differentiation or modulation of the immune system. IFN- α , in particular, has been used as an effective treatment of hairy cell leukemia, early-stage chronic lymphocytic leukemia and hepatitis C. It has been recently used for the treatment of patients with idiopathic hypereosinophilic syndrome (HES) [3, 6]. Clinical improvement was associated, in particular, with a dramatic decrease in peripheral and tissue eosinophil counts, as well as a significant diminution of some blood markers of eosinophil activation [3–6]. These results led us to suggest a direct effect of IFN- α on eosinophils.

Conclusion

Eosinophils can participate in all steps of the immune response, not only as a source of cytotoxic and proinflammatory mediators but also by elaborating a number of cytokines that might contribute to inflammation, chemotaxis, activation and cell growth as well as to the regulation of the immune response. The demonstration of a selective synthesis of distinct cytokines by eosinophil subpopulations and the regulation of their secretion will certainly open new fields of investigation, not only on gene transcription by eosinophils, but also on the development of new therapeutical procedures.

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