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Cytokine generation by eosinophils

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Eosinophils are prominent cells in allergic inflammation, asthma, and immune reactions against parasitic helminths.^{1, 2} The association between eosinophils and asthma has been extensively documented. Large numbers of eosinophils and their granule products have been observed in the airways of patients with asthma,² and an inverse correlation between the degree of bronchial hyperreactivity and peripheral blood eosinophilia was shown in subjects in whom a late-phase response developed after antigen challenge.³ With use of fiberoptic bronchoscopy it was possible to correlate the number of activated eosinophils with the degree of bronchial hyperresponsiveness.⁴ However,

Abbreviations used

GM-CSF:	Granulocyte-macrophage colony-stimulating factor
IFN:	Interferon
IL:	Interleukin
MIP:	Macrophage inflammatory protein
TGF:	Transforming growth factor
TNF:	Tumor necrosis factor

despite this close association, the evidence of a cause and effect relationship between eosinophil products and tissue damage remains unproven.

The accumulation of eosinophils into the site of the inflammatory focus in allergic-type responses is believed to be regulated by a complex series of events that involves T cells and cytokines.^{1, 5, 6} Cytokines, particularly interleukin-3 (IL-3), IL-5, and granulocyte-macrophage colony-stimulating factor (GM-CSF), influence eosinophil growth, maturation, and differentiation. IL-5 is of particular interest because it is unique in that it promotes terminal

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differentiation of the committed eosinophil precursor.⁷ IL-3, IL-5, and GM-CSF all prolong the survival of the eosinophils.⁸⁻¹⁰ These same cytokines, together with interferon- γ (IFN- γ) and tumor necrosis factor- α (TNF- α) also activate eosinophils and prime them for several effector functions.^{11, 12}

Cytokines, which were originally considered to be derived predominantly from lymphocytes and monocytes, are now known to be elaborated by many other cell types. Blood and tissue eosinophils are predominantly "end cells," and therefore by definition have a limited capacity to transcribe and translate new proteins. However, it is clear from studies during the past few years that eosinophils synthesize and secrete several important inflammatory and regulatory cytokines (Table I). In this article we review some current advances in this field, especially as they relate to allergic and inflammatory reactions.

IL-1 α

The early observation of Del Pozo et al.¹³ that murine eosinophils expressed mRNA for IL-1 α , as detected by the technique of *in situ* hybridization, led to subsequent studies on the ability of eosinophils to synthesize and release cytokines. Messenger RNA in murine peritoneal eosinophils, stimulated for 6 hours with lipopolysaccharide, were hybridized with a ³⁵S-labeled cDNA probe for IL-1 α . IL-1 α was also detected in supernatants from these stimulated cells.

The ability of human eosinophils to synthesize IL-1 α was shown by Weller et al.¹⁴ Eosinophils from a hypereosinophilic patient contained transcripts for IL-1 α mRNA detected by Northern blot and *in situ* hybridization both before and after stimulation of cells with phorbol myristate acetate. The expression of IL-1 α protein was also detectable by immunocytochemistry. This group also showed cytokine-induced human leukocyte antigen-DR expression, with eosinophils acting as antigen-presenting cells with the costimulatory cytokine IL-1 α .

TRANSFORMING GROWTH FACTOR- α AND β

Transforming growth factor- α

Wong et al.,¹⁵ while investigating oral squamous carcinoma, known to be associated with increases in the level of tissue eosinophils, detected transforming growth factor- α (TGF- α) at the tumor site. They were able to colocalize mRNA and the protein to the eosinophils. The observation was

confirmed by examining peripheral blood eosinophils from patients with hypereosinophilic syndrome. Eosinophils, both *in vivo* and *in vitro*, appeared to have a constitutive expression of mRNA for TGF- α . This observation was confirmed in rabbit skin tissue after wound healing,¹⁶ which is known to be associated with an increase in the number of eosinophils. Most of the eosinophils, particularly during the peak period of healing, expressed TGF- α mRNA and protein immunoreactivity. Once epithelial wound healing had occurred, TGF- α mRNA disappeared; this was followed by the dispersal of eosinophils from the site. This ability of eosinophils to generate TGF- α was also observed in the Syrian hamster cheek pouch mucosa. In addition, normal hamster bone marrow eosinophils were shown to express TGF- α mRNA and the protein.¹⁷

TGF- β 1

Studies by Wong et al.¹⁸ on eosinophils from patients with blood eosinophilia revealed that, in addition to TGF- α , eosinophils also synthesize and elaborate TGF- β 1. Northern blot analysis, *in situ* hybridization, and immunocytochemistry were used to examine eosinophils from patients with either the hypereosinophilic syndrome or blood eosinophilia. The authors concluded that TGF- β 1 mRNA expression was associated with eosinophils obtained from eosinophilic subjects but not normal subjects. Ohno et al.¹⁹ examined mucosal tissue from nasal polyps with a porcine TGF- β 1 cDNA probe and were able to detect TGF- β 1-specific mRNA. They were also able to localize TGF- β 1 in nasal tissue from a patient with allergic rhinitis but not in normal nasal mucosa. Using a combination of *in situ* hybridization and specific eosinophil staining (carbol chromotrope 2R), approximately 50% of the eosinophils that accumulated in the polyp tissue were TGF- β 1 mRNA⁺. The presence of TGF- β 1 in these cells was confirmed with immunocytochemical staining. TGF- β 1 was also localized to eosinophils in Hodgkin's disease in association with nodular sclerosis, but not other types of Hodgkin's disease.²⁰ Immunoreactivity for TGF- β 1 was detected mainly at the margins of sites of new collagen synthesis in the vicinity of areas rich with Hodgkin/Reed/Sternberg cells. Probing for mRNA for TGF- β 1 revealed that eosinophils, but not Hodgkin/Reed/Sternberg cells, were the major site for TGF- β 1 mRNA expression. These observations are important because TGF- β 1 has a critical role in chronic inflammation and fibrosis;

eosinophil-derived TGF- β 1 may play a repair role in inflammation by promoting fibroblast growth and activation. Furthermore, by exerting their effects on extracellular matrix, including stimulation of collagen synthesis, eosinophils may contribute structural abnormalities such as stromal fibrosis and basement membrane thickening observed in inflammatory conditions. Hamster eosinophils were also shown to express TGF- α and TGF- β in association with cutaneous wound healing.¹⁷

GM-CSF

Moqbel et al.²¹ used in situ hybridization to demonstrate that normal density human eosinophils (obtained by metrizamide gradient separation) transcribed and translated mRNA for GM-CSF after stimulation with either IFN- γ or the calcium ionophore A23187. GM-CSF mRNA was colocalized to the stimulated eosinophil with a combination of in situ hybridization and histochemistry (carbol chromotrope 2R) or immunohistochemistry (EG2).²¹ Kita et al.²² also demonstrated eosinophil-derived GM-CSF after stimulation of cells with ionomycin. Ionomycin was shown to produce GM-CSF-dependent enhanced eosinophil survival that was blocked by cyclosporine in a dose-dependent fashion. This is an important observation because the beneficial effect of cyclosporine in chronic steroid-dependent asthma²³ might be related to the direct effect of the drug on eosinophil cytokine synthesis.

We have recently shown that GM-CSF may be stored in eosinophils from asthmatic subjects in association with crystalloid granules.²⁴ After ultracentrifugation of postnuclear supernatant of eosinophil subcellular components, on a 0% to 40% nycodenz gradient in sucrose buffer, GM-CSF coeluted with granule proteins and enzymes (i.e., major basic protein, eosinophil cationic protein, eosinophil peroxidase, arylsulfatase, and β -hexosaminidase). GM-CSF was not detected in fractions associated with CD9 activity (a marker for eosinophil plasma membrane). The presence of stored GM-CSF, which appears to be residing in association with granules in eosinophils obtained from asthmatic subjects, has important implications in terms of the state of activation of these cells in this disease condition. Thus eosinophils may use endogenous GM-CSF for more effective effector function.

GM-CSF mRNA was also detected in eosinophils in vivo in association with nasal polyposis,²⁵ and immunoreactive GM-CSF was identified in

TABLE I. Cytokines synthesized by and released from human eosinophils

Cytokine/chemokine	Reference No.
TGF- α	15
TGF- β	18, 19
MIP-1 α	35
GM-CSF	21, 22
TNF- α	35, 36
IL-1 α	14
IL-3	22
IL-5	29
IL-6	32, 33
IL-8	34

24-hour culture supernatant of nasal polyp tissue using the ELISA technique. By in situ hybridization and counterstaining with chromotrope 2R, approximately 30% of eosinophils infiltrating the polyp tissue expressed mRNA for GM-CSF. Broide et al.²⁶ confirmed the presence of GM-CSF mRNA expression in human eosinophils with use of cells obtained from bronchoalveolar lavage of asthmatic subjects who underwent endobronchial allergen challenge. These authors also suggested that the expression of GM-CSF by eosinophils at allergic inflammatory foci may provide an autocrine pathway to maintain viability and effector function of these cells.

Thus agents that activate eosinophils for transcription and translation of IL-3, IL-5, and GM-CSF may, in turn, prolong eosinophil survival. For example, adherence of eosinophils to extracellular matrix protein was shown to be an important stimulus for cell activation. Eosinophils adhered to the 40 kd domain of fibronectin via very late activation antigen-4 (α 4 β 1)-dependent mechanisms,²⁷ and this was associated with enhanced survival of eosinophils.²⁸ Survival appeared to be directly related to fibronectin-induced eosinophil synthesis of GM-CSF and IL-3. Thus autocrine production of GM-CSF, IL-3, and IL-5 by eosinophils may modulate their viability (survival) by delaying programmed cell death (apoptosis). In vivo, the latter may be related to the resolution of chronic allergic inflammation. Stern et al.²⁹ reported that eosinophils, like neutrophils, eventually become apoptotic in culture and that this is followed by recognition and "silent" ingestion by macrophages. These workers also showed that apoptosis in eosinophils could be delayed by exogenous IL-5 and GM-CSF, thus providing evidence that autocrine cytokines may modulate cell survival.

IL-3

Kita et al.,²² while studying the release of GM-CSF from eosinophils stimulated with ionomycin, were also able to detect IL-3 in the same supernatants. IL-3 is also known to prolong survival of eosinophils and therefore may be an additional autocrine factor that can be produced and utilized by the eosinophil after stimulation. To date, IL-3 mRNA expression in eosinophils, either in vitro or in vivo, has not been demonstrated.

IL-5

Desreumaux et al.³⁰ made the interesting observation that eosinophils infiltrating mucosa of patients with active coeliac disease express mRNA for IL-5. IL-5 mRNA⁺ cells were found in diseased but not normal tissue and were absent after treatment with a gluten-free diet. By in situ hybridization, mRNA was identified in peripheral blood of eosinophilic subjects. IL-5 mRNA expression in eosinophils in vivo was also demonstrated in bronchoalveolar lavage cells obtained from asthmatic subjects.²⁶ In this study, individual eosinophils exhibited four different cytokine mRNA profiles. Of the eosinophils counted, 34% were IL-5⁺ and GM-CSF⁺, 34% were IL-5⁺ but GM-CSF⁻, 11% were IL-5⁻ but GM-CSF⁺, and only 21% were IL-5⁻, GM-CSF⁻, which suggests that eosinophil IL-5 and GM-CSF expression at sites of allergic inflammation in asthma may provide an autocrine pathway, thus maintaining the viability and effector function of the recruited eosinophils.

Dubucquoi et al.³¹ recently described IL-5 mRNA and immunoreactive IL-5 protein in eosinophils from the blood and tissue of patients with eosinophilic cystitis and the hypereosinophilic syndrome. With the use of electron microscopy and immunogold staining, IL-5 was colocalized with eosinophilic granules and was released after stimulation with IgA-, IgE-, or IgG-immune complexes. Thus they suggested (as described earlier for GM-CSF) that cytokines may be stored in association with eosinophil granules. By simultaneous in situ hybridization and immunocytochemistry on nasal biopsy tissue from atopic rhinitis subjects after allergen exposure, Sun Ying et al.³² were able to colocalize IL-5 mRNA to MBP⁺ eosinophils. However, only 5.4% of the total leukocyte population were IL-5 mRNA⁺/MBP⁺, compared with 83.2% that were IL-5 mRNA⁺/CD3⁺ and 18.5% that were IL-5 mRNA⁺/tryptase⁺. Thus in this model, most cells containing IL-5 mRNA were T cells,

with a much smaller contribution from mast cells and eosinophils.

IL-6

Using a similar approach to that of GM-CSF, IL-6 mRNA was also found in normal density eosinophils.³³ Approximately 20% of unstimulated eosinophils were IL-6 mRNA⁺, whereas the level of expression was enhanced after stimulation with IFN- γ . Translation of mRNA was detected by immunocytochemistry, which showed that staining for IL-6 was "granular." We were also able to measure the release of IL-6 in the supernatant of cultured eosinophils before and after stimulation.³³ This observation has been confirmed by studies of Melani et al.³⁴ that used reverse transcriptase polymerase chain reaction (PCR) and in situ hybridization. In this study, neutrophil granulocytes from healthy persons also expressed variable levels of IL-6, although this was rapidly downregulated when the cells were cultured in vitro. This group also showed constitutive expression of IL-6 in human peripheral blood eosinophils obtained from both normal and hypereosinophilic donors.

With use of a similar fractionation approach to that described for GM-CSF, we have recently demonstrated that IL-6 is a stored cytokine product of eosinophils, again in association with the crystalloid granules.³⁵ The precise significance of eosinophil-derived IL-6 is yet to be clarified. IL-6 plays an important role in the regulation of the immune response by modulating T and B lymphocyte functions and priming granulocytes and endothelial cells.

IL-8

Highly purified eosinophils cultured in vitro with calcium ionophore released IL-8 into the supernatant as shown by specific ELISA.³⁵ This was inhibited both by cyclosporine and cyclohexamide, an inhibitor of protein synthesis. IL-8 mRNA was demonstrated by PCR amplification after stimulation. The presence of immunoreactive IL-8 was also detected using immunocytochemical staining with use of a monoclonal antibody against IL-8. Here again the staining was granular, which suggests that the cytokine resides in the cell in a stored form.³⁶

TNF- α

Again, using the technique of in situ hybridization, 44% to 100% of eosinophils obtained from

the peripheral blood or healthy subjects or patients with hypereosinophilia were positive for TNF- α mRNA.³⁷ The presence of the protein in blood eosinophils from hypereosinophilic subjects was also detected by immunocytochemical staining. When eosinophils were purified from atopic persons, spontaneous release of TNF- α in vitro was inhibitable by cyclohexamide pretreatment. Infiltrating eosinophils in necrotizing enterocolitis were also shown to express TNF- α mRNA. These cells may therefore play a role in pathogenesis of intestinal necrosis.³⁸ In a recent report,³⁹ TNF- α was localized to the matrix compartment by ultrastructural immunogold. Positive signals were observed in 64% of the specific secondary granules. Cells were obtained from patients with the idiopathic hypereosinophilic syndrome.

MACROPHAGE INFLAMMATORY PROTEIN-1 α

In the same study by Costa et al.,³⁷ a high percentage of blood eosinophils (39% to 91%) obtained from hypereosinophilic patients showed positive mRNA expression for the chemokine macrophage inflammatory protein-1 α (MIP-1 α). Eosinophils obtained from normal donors had weak or undetectable expression of this chemokine. In vivo, most eosinophils that infiltrated nasal polyp tissue had strong expression for MIP-1 α mRNA. This observation was confirmed by Northern blot analysis.

CONCLUSIONS

Eosinophils synthesize, store, and release a wide array of cytokines, as well as basic granule-derived proteins and lipid mediators. This functional versatility has several implications for the potential role of the eosinophil in allergic tissue reactions. Eosinophils might act to amplify the allergic response, which, in asthma for example, would enhance tissue damage, but in helminth infections could promote adaptive immunity. On the other hand, eosinophil cytokine production may be a redundant process in the spectrum of immune and inflammatory systems. Conversely, eosinophils may be involved in tissue repair function by, for example, promoting collagen synthesis through release of TGF- α and β . It is not known whether eosinophil-derived cytokines act synergistically with other eosinophil mediators, that is, basic proteins, leukotriene C₄ and platelet-activating factor. Eosinophils have also been shown to express major histocompatibility complex class II

molecules, elaborate IL-1 α , and act as antigen-presenting cells. Eosinophils, therefore, might function as specialized antigen-presenting cells in certain situations, such as helminthic infections.

Although the control and regulation of eosinophilia associated with asthma and allergic disease are not yet fully understood, they are likely to be dependent on IL-3, IL-5, and GM-CSF release from T cells, mast cells, and eosinophils themselves. A better understanding of cytokine regulation by these cell types should aid in the search for precise targets for therapy aimed at inhibiting the selective accumulation of eosinophils in allergy and asthma.

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