

EDITORIAL

Fibroblasts: a cell type central to eosinophil recruitment?

Eotaxin production by fibroblasts

Eosinophilic infiltration is a hallmark of allergic inflammation, and the release of cytotoxic mediators by these cells has been proposed to underlie the tissue damage and dysfunction seen in atopic disorders. The regulation of eosinophil function is believed to be orchestrated by the development of T helper type 2 lymphocytes. These cells are characterized by the production of specific cytokines including interleukin (IL) -4 and IL-5, which promote eosinophil differentiation, maturation and activation. For many years, investigators have searched for the precise mediators and cellular interactions culminating in the selective recruitment of these cells. Then in 1994, a British group led by Professor Tim Williams described a novel eosinophil-specific chemoattractant within the bronchoalveolar lavage fluid of allergen-challenged guinea pigs which they termed eotaxin [1]. This protein has subsequently been shown to have an important local role in stimulating the recruitment of eosinophils from the microvasculature into the tissues at sites of local allergic inflammation [2–5]. The discovery of eotaxin prompted the search for other chemotactic cytokines (termed chemokines) involved in the pathophysiology of allergic inflammation. To date, a variety of leucocyte-specific chemokines have been described as being overexpressed within the local mucosa of atopic disorders and these include eotaxin, RANTES, MCP-1, MCP-3, MCP-4, MIP-1 α . However, eotaxin has commanded considerable attention due to the potency and specificity of its actions on eosinophils.

Following the cloning of human eotaxin in 1996 [4,6], there have been extensive investigations into cellular sources of this chemokine, and its regulation within the respiratory mucosa. In the paper by Terada and coworkers published in this issue of *Clinical Experimental Allergy* [7], they examined whether IL-4 and IL-13, archetypal TH2-type cytokines, are able to induce eotaxin production in cultured human fibroblasts derived from the nasal mucosa. These experiments were prompted by previous reports of IL-4-induced eotaxin production by skin- [8] and lung-derived fibroblasts [9]. The results of this study clearly demonstrate that fibroblasts cultured from the nasal mucosa of subjects with perennial rhinitis are a major source of eotaxin. In comparison, endothelial and epithelial cells, as well as peripheral blood eosinophils, produced far less eotaxin-immunoreactive protein, prompting the suggestion that fibroblasts are central to eosinophil recruitment in allergic disorders.

How do these results relate to those clinical studies investigating the localization of eotaxin expression within the mucosa of individuals with allergic rhinitis and atopic asthma? An initial report by Ponath and colleagues showing eotaxin immunoreactivity in nasal polyps did suggest that fibroblasts were a significant source of eotaxin immunoreactivity [4]. However, since this time there have been several reports of eotaxin immunoreactivity and gene transcription in biopsy samples taken from nasal and bronchial mucosa of patients with allergic rhinitis and atopic asthma. These studies have consistently reported production of eotaxin by airway epithelial cells and submucosal inflammatory cells, including macrophages, eosinophils, mast cells and T cells [10–14]. Interestingly, airway smooth muscle has also been reported as a potential source of eotaxin immunoreactivity and mRNA within the asthmatic airways [14], however, no mention was made of other structural cells including fibroblasts. The above studies were performed in the absence of deliberate allergen challenge, and it is possible that fibroblasts become a major source of eotaxin only within the appropriate cytokine milieu. This question has previously been addressed in a study by Brown and coworkers who investigated the kinetics of eotaxin expression and its relationship to eosinophil accumulation in asthmatic patients following allergen challenge [15]. In bronchial biopsies taken 2 h after allergen challenge, eotaxin mRNA was mainly localized to bronchial epithelial cells, endothelial cells, macrophages, T cells, eosinophils and mast cells. There was no report of fibroblasts being a source of eotaxin in these patients at time points up to and including 24 h after allergen exposure.

So how can we reconcile these findings, and what role does the fibroblast play in the recruitment of eosinophils to the sites of airways inflammation? From the clinical studies described to date, it appears that fibroblasts are a source of eotaxin only in nasal polyps and are not implicated in the recruitment of eosinophils to sites of allergic inflammation. This implies that there are differences in the synthetic capacity of these cells in the various eosinophilic disorders, possibly attributed to the underlying cytokine milieu. It is known for example, that the T lymphocytes infiltrating nasal polyps produce a mixed TH1/TH2 profile of cytokine expression [16], and that these tissues express a preponderance of IFN γ when compared with biopsies from patients with allergic rhinitis [16,17]. Whether differences in the expression of inflammatory mediators can account for the production of eotaxin in nasal polyps remains to be

established. Interestingly, in a eotaxin knockout mouse where this chemokine gene had been replaced by a sequence of DNA encoding β -galactosidase, antigen challenge resulted in positive β -galactosidase staining in stromal cells (fibroblasts/fibrocytes) [18]. However, positive staining was not present within the airways epithelium, and the time course of β -galactosidase expression was not reminiscent of eotaxin production in either clinical or animal studies [1,3]. This was attributed to variations in the allergen challenge protocol which would have resulted in differing profiles of cytokine expression.

Should we focus our research efforts in investigating the expression of eotaxin? While it is pertinent to discuss the role of eotaxin in the recruitment of eosinophils to sites of inflammation, it is obvious from both animal and clinical studies that additional chemotactic agents are operating. These include chemokines such as RANTES, MCP-3, MCP-4 and MCP-5 [19–21]. Moreover, there may be additional chemoattractants acting, since only $\approx 50\%$ of the eosinophil-chemotactic activity in BAL fluid from atopic asthmatics was accounted for by a combination of eotaxin, RANTES and MCP-4 [11]. What is promising from the viewpoint of using specific eotaxin antagonists in the treatment of allergic disorders, is that after allergen challenge of asthmatics, eotaxin release correlates with the numbers of total and activated eosinophils and the level of airflow obstruction at 4 h after allergen exposure [15]. While other eosinophilic chemoattractants may be responsible for the latter stages of eosinophil recruitment, it is early appearance of these cells in the lungs which is predictive of a late-phase response and acute exacerbations of airways responsiveness [22,23].

The study by Terada *et al.* demonstrates that fibroblasts can be a prominent source of eotaxin under the appropriate cytokine stimulation. However, this cell type may make minimal contribution to the production of this chemokine in allergic inflammatory conditions such as atopic asthma and allergic rhinitis. The underlying message is that, to date, we have no indication as to the regulation of eotaxin production by the epithelium and inflammatory cells within the sub-mucosa. Once these mediators or cell–cell interactions have been established then the possibility of blocking eosinophil recruitment into sites of allergic inflammation may become a reality. However, the caveat must be that blocking eotaxin production may unleash a wealth of compensatory mechanisms. Until such time as drugs that specifically regulate eotaxin expression are in clinical trials, we may only surmise its importance in allergic disorders.

References

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