

Microenvironmental influences on inflammatory cell differentiation

Denburg JA. Microenvironmental influences on inflammatory cell differentiation.

Allergy 1995; 50 (suppl 25): 25-28. © Munksgaard 1995.

Airways inflammation involves accumulation of inflammatory cells such as eosinophils, basophils and mast cells, which are derived from progenitors in marrow and blood. The inflamed tissue of the airways, through its structural (epithelium, stroma) and inflammatory cell components, produces an array of cytokines which can influence the differentiation of inflammatory cell progenitors. It is particular mechanism that we have investigated, showing that molecules such as GM-CSF, G-CSF, IL-6, IL-8 and SCF can be produced by airways epithelial cells and fibroblasts in quantities sufficient to induce hemopoietic events, either systemically or locally. Corticosteroids may act therapeutically, at least in part, to block inflammatory cell differentiation, and thus recruitment, into the allergic inflammatory process in the airways.

J. A. Denburg

Division of Clinical Immunology and Allergy,
McMaster University, Hamilton, Ontario, Canada

Key words: inflammation; airway;
microenvironment

J. A. Denburg,
Room 3V46,
McMaster University Medical Centre,
1200 Main Street West,
Hamilton, ON L8N 3Z5,
Canada

Airway inflammation is now recognized to be the basis for various atopic and related conditions of the airways including allergic rhinitis, nasal polyposis and asthma. The cellular and molecular mechanisms involved in the generation of this inflammatory response in the upper and lower airways have been analyzed in the last few years. Work in our laboratory has focused upon the contribution of structural cells of the airways to the generation and perpetuation of this inflammatory response, which includes participation of inflammatory effector cells such as basophils, eosinophils and mast cells. These cells, in turn, are derived from progenitors which circulate in increased numbers in the blood of patients with various forms of airways inflammation (16, 17); these progenitors also fluctuate to allergen challenge or exacerbation of disease and symptoms (9, 10, 16). A dynamic dialogue exists between the structural cells of the airways and these progenitors. In the following brief presentation, several of these pathways of communication between structural cells and inflammatory cells are delineated with reference to the development and maintenance of airway inflammatory diseases.

Cytokines derived from structural cells

Epithelial cells

The epithelium is not a passive participant in the development of airways inflammation. A wide variety of mediators and cytokines can be produced

upon stimulation of the epithelium, either after damage or upon stimulation with various microbial and other challenges. Among the cytokines that have been described as products of the epithelium in airways inflammatory diseases are: various hemopoietic growth factors including granulocyte macrophage colony-stimulating factor (GM-CSF), G-CSF, M-CSF, stem cell factor (SCF) and several not yet fully characterized factors (4) (Table 1). In addition, several pro-inflammatory cytokines such as interleukin 6 (IL-6) and chemokines such as IL-8 are produced by the inflamed airway epithelium (4, 6). We have determined that, in chronic airway inflammation such as nasal polyposis, there is up-regulation of several of these growth factors and pro-inflammatory cytokines, with levels of constitutive or stimulated production of these being much higher than in allergic rhinitis, which is, in turn, higher than normal nasal mucosal epithelial cells (4, 6).

Fibroblasts

The stromal contribution to airway inflammation is principally due to the production of mediators and various cytokines by the fibroblasts in these tissues. A very similar profile, although not identical, of cytokine production by fibroblasts in airways inflammatory diseases *ex vivo* and *in vivo* has been observed (5) (Table 2). Moreover, fibroblasts contribute an array of pro-inflammatory reactants, including enzymes such as metalloproteinases, which are in-

Table 1. Human nasal epithelial cell cytokines

Cytokines	Gene expression	Production	Steroid inhibition
GM-CSF	+	+	+
G-CSF		+	
M-CSF		+	
MDF ^a		+	
IL-3	-	+ ^b	
IL-5		-	
IL-6	+	+	+
IL-8	+	+	+
SCF	+	+	

^a Macrophage differentiation factor. ^b Cell lysates only.

Table 2. Human nasal fibroblast cytokines

Cytokines	Gene expression	Production	Steroid inhibition
GM-CSF	+	+	+
IL-6	+	+	+
IL-8	+	+	+
SCF	+	+	
IL-3		-	
IL-5		-	
BaDF ^a		+	
MDF ^b		-	

^a Basophil differentiation factor. ^b Macrophage differentiation factor.

timately involved in the development and maintenance of chronic inflammation at a variety of sites (11).

Both fibroblasts and epithelial cells respond to signals such as bacterial lipopolysaccharide and the cytokines IL-1 and tumor necrosis factor α (TNF- α), with a production of increased amounts of hemopoietic and pro-inflammatory cytokines, a cascade presumably leading to chronic inflammation (4–6, 11). Substantial literature has also developed on the induction by cytokines from structural cells, of cell adhesion molecules, which allow for the attachment and migration into tissues of inflammatory cells, such as basophils and eosinophils (1, 2).

Inflammatory cell-derived cytokines

Basophils and eosinophils

The basophil and eosinophil contribution to airways inflammation, especially in the late-phase allergic reaction, involves the ingress and recruitment to the tissues of cells with a wide variety of potent mediators. These cells themselves can, upon activation, produce a wide variety of cytokines including: IL-3, IL-4, IL-5, IL-6, IL-8, GM-CSF, TNF- α and transforming growth factor β (TGF- β) (3). Work from our laboratory has focused on the model of nasal polyposis, in which a large number of activated eosinophils is observed to be present, characterized by a specific form of the eosinophil cationic protein

reactive with the monoclonal antibody EG2, as well as the expression and production of TNF- α , GM-CSF and TGF- β (7, 14, 15). These cytokines play an important role in the perpetuation of the inflammatory process, including the development of tissue fibrosis, which characterizes asthma and nasal polyposis alike.

Mast cells

Mast cells also abound in airways inflammatory diseases, especially in nasal polyps, allergic rhinitis and asthma. While the mast cell contribution is thought to be related to the early phase of the immunoglobulin E (IgE)-mediated response, the cytokines derived from these cells may play a crucial role in the development of further airways inflammation. These include: IL-3, IL-4, IL-5, IL-6 and IL-8 as well as TNF- α (8). As can be inferred, the positive feedback that could potentially exist in the development of the inflammatory process involving the ingress and activation of inflammatory effector cells and their production of cytokines is not to be minimized.

Cytokine effects and interactions

Effects on cell differentiation

One of the most important concepts that has driven research in our laboratory is that progenitors derived from the bone marrow and circulating in the blood can receive differentiative signalling from the inflamed tissue itself, leading to recruitment via differentiation and proliferation (9, 10, 16, 17). Although a precise localization of this differentiation process has not yet been fully determined, evidence exists to support the notion that GM-CSF, as well as other factors such as SCF, may play a crucial role in stimulating the bone marrow to produce more progenitors for basophils, eosinophils and mast cells; one cannot exclude the possibility that this process can also occur at a local tissue level (4–6, 11). Moreover, activation of the inflammatory cells themselves at various stages of terminal differentiation could be stimulated by cytokines produced by structural cells and, in autocrine fashion (see below), inflammatory cells themselves. Phenotype control and switching of eosinophils and mast cells can be influenced by several factors derived from tissue structural cells such as GM-CSF, SCF, TGF- β and other as yet not fully identified factors (18, 19). The result is a self-sustained inflammatory process that probably, in some cases, does not require further antigenic stimulation.

Autocrine events

Both eosinophils and mast cells, and to a lesser extent basophils, upon activation can produce cyto-

kines that directly affect further activation and/or differentiation of these cells or their progenitors. These autocrine pathways can be most readily seen in the eosinophil recruitment and presence in nasal polyposis: isolated nasal polyp eosinophils produce GM-CSF, which can prolong the survival and activate eosinophils (Ramis et al., unpublished data). This phenomenon probably exists for several structural cells and inflammatory cells within the context of chronic inflammation in the airways.

Effects of steroids

Topical corticosteroids are the mainstay of therapy in nasal polyposis, allergic rhinitis and asthma. Although the mechanisms for the effects of steroids are complex and beyond the scope of this article, many of the pathways mentioned above, including the cytokines expressed and produced by structural cells or inflammatory cells, can be blocked by corticosteroids applied topically to the airway. Effects on differentiation, activation, phenotype switching as well as cell migration and adhesion can all be seen after the application of the corticosteroids (11). Perhaps this is the reason why prolonged therapy with corticosteroids can continue to bring benefit and improve the histopathology of airway inflammation such as asthma (12, 13). Recently, we have demonstrated that *in vivo* pretreatment with inhaled budesonide blocks allergen-induced bone marrow production of inflammatory cell progenitors (20). This bone marrow contribution to airway inflammation may be closely related to events in the tissue microenvironment.

Conclusion

The process of cell-to-cell signalling involving cytokine networks within inflamed airway tissues are now becoming unravelled. Much needs to be learned about pathways of signal transduction and the specificity of control of the inflammatory process, giving it its characteristic allergic morphology. Moreover, whether or not cytokines are differentially activated in a given context and within a given tissue to produce a self-limited or a self-sustained inflammation needs to be further studied.

Acknowledgements

I acknowledge the expertise and excellent collaborative milieu involving many colleagues, students and assistants in the McMaster Asthma Research Group and Inflammation Group over the last decade. Without this cherished environment, the work summarized herein would never have been accomplished. The work described is supported by grants from the Medical Research Council of Canada and Astra Draco/Astra Canada. Lynne Larocque painstakingly edited the manuscript.

References

1. BOCHNER BS, LUSCINSKAS FW, GIMBRONE MA Jr et al. Adhesion of human basophils, eosinophils and neutrophils to interleukin 1-activated human vascular endothelial cells: contributions of endothelial cell adhesion molecules. *J Exp Med* 1991; 173: 1553-7.
2. BOCHNER BS, PEACHELL PT, BROWN KE, SCHLEIMER RP. Adherence of human basophils to cultured umbilical vein endothelium. *J Clin Invest* 1988; 81: 1355-64.
3. DENBURG JA. Basophil and mast cell lineages *in vitro* and *in vivo*. *Blood* 1992; 79: 846-60.
4. DENBURG JA, DOLOVICH J. *In situ* hemopoietic mechanisms underlying allergic tissue inflammation. In: Johansson SGO, ed. Pharmacia Allergy Research Foundation Award Book. Uppsala, Sweden: Upplands Grafiska, 1988: 20-5.
5. DENBURG JA, DOLOVICH J, OHTOSHI T, COX G, GAULDIE J, JORDANA M. The micro-environmental differentiation hypothesis of airway inflammation. *Am J Rhinol* 1990; 4: 29-32.
6. DENBURG JA, JORDANA M, GIBSON P, HARGREAVE F, GAULDIE J, DOLOVICH J. Cellular and molecular basis of allergic airway inflammation. In: Johansson SGO, ed. Pharmacia Allergy Research Foundation Award Book. Uppsala, Sweden: A.W. Grafiska, 1990: 15-22.
7. FINOTTO S, OHNO I, MARSHALL JS et al. Tumor necrosis factor alpha (TNF α) production by eosinophils in upper airways inflammation (nasal polyposis). *J Immunol* 1993; 153: 2278-89.
8. GALLI SJ. New concepts about the mast cell. *N Engl J Med* 1993; 328: 257-65.
9. GIBSON PG, DOLOVICH J, GIRGIS-GABARDO A et al. The inflammatory response in asthma exacerbation: changes in circulating eosinophils, basophils and their progenitors. *Clin Exp Allergy* 1990; 20: 661-8.
10. GIBSON PG, MANNING PJ, O'BYRNE PM et al. Allergen-induced asthmatic responses: relationship between increases in airway responsiveness and increases in circulating eosinophils, basophils, and their progenitors. *Am Rev Respir Dis* 1991; 143: 331-5.
11. JORDANA M, COX G, OHTOSHI T et al. The 'TDR' concept in chronic airways inflammation: tissue driven response. In: Matsson P, Ahlstedt S, Venge P, Thorell J, ed. Clinical impact of the monitoring of allergic inflammation. London: Academic Press, 1991: 33-46.
12. LAITINEN LA, LAITINEN A, HAAHTELA T, VILKKA V, SPUR BW, LEE TH. Leukotriene E4 and granulocytic infiltration into asthmatic airways. *Lancet* 1993; 341: 989-90.
13. LAITINEN LA, LAITINEN A, HEINO M, HAAHTELA T. Eosinophilic airway inflammation during exacerbation of asthma and its treatment with inhaled corticosteroid. *Am Rev Respir Dis* 1991; 143: 423-7.
14. OHNO I, LEA R, FINOTTO S et al. Granulocyte/macrophage colony-stimulating factor (GM-CSF) gene expression by eosinophils in nasal polyposis. *Am J Respir Cell Mol Biol* 1991; 5: 505-10.
15. OHNO I, LEA RG, FLANDERS KC. et al. Eosinophils in chronically inflamed human upper airway tissues express transforming growth factor β 1 gene (TGF β 1). *J Clin Invest* 1992; 89: 1662-8.
16. OTSUKA H, DOLOVICH J, BEFUS AD, BIENENSTOCK J, DENBURG JA. Peripheral blood basophils, basophil progenitors, and nasal metachromatic cells in allergic rhinitis. *Am Rev Respir Dis* 1986; 133: 757-62.
17. OTSUKA H, DOLOVICH J, BEFUS AD, TELIZYN S, BIENENSTOCK J, DENBURG JA. Basophilic cell progenitors, nasal metachromatic cells, and peripheral blood basophils in ragweed-allergic patients. *J Allergy Clin Immunol* 1986; 78: 365-71.

Denburg

18. SILLABER C, GEISLER K, SCHERRER R et al. Type beta transforming growth factors promote interleukin-3 (IL-3)-dependent differentiation of human basophils but inhibits IL-3-dependent differentiation of human eosinophils. *Blood* 1992; 80: 634–41.
19. VALENT P, SPANBLOCH E, SPERR WR et al. Induction of differentiation of human mast cells from bone marrow and peripheral blood mononuclear cells by recombinant human stem cell factor/kit-ligand in long-term culture. *Blood* 1992; 80: 2237–45.
20. WOOLLEY M, DENBURG J, ELLIS R, DAHLBÄCK M, O'BYRNE PM. Allergen-induced changes in bone marrow progenitors and airway responsiveness in dogs, and the effect of inhaled budesonide on these parameters. *Am J Respir Cell Mol Biol* 1994; 11: 600–6.