

Epithelial Function in Eosinophilic Gastrointestinal Diseases

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Under normal conditions, eosinophils are absent in the esophagus but exist in varying numbers along the rest of the gastrointestinal tract, particularly in the lamina propria.^{1,2} For unknown reasons, eosinophils over the last decade have been increasingly associated with a wide variety of intestinal symptoms. Because of this, their histologic brilliance has created more than just a glancing comment limited to the bedside or the bottom of a pathology report. The enigmatic role of eosinophils in the pathophysiology of gastrointestinal diseases is becoming not only interesting but also increasingly relevant. In particular, because of the close anatomical proximity of eosinophils and epithelial cells and since many of the symptoms associated with eosinophilic gastrointestinal diseases can be attributed to epithelial dysfunction, an increasing number of studies seek to better define this eosinophil/epithelial cell relationship.

EOSINOPHILIC GASTROINTESTINAL DISEASES AND THE ROLE OF THE EPITHELIUM

EGIDs are a heterogeneous group of diseases characterized by gastrointestinal symptoms and large numbers of eosinophils in the intestinal tract. EGIDs include eosinophilic esophagitis (EoE), eosinophilic gastroenteritis, and eosinophilic colitis. For the

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diagnosis of EGIDs to be confirmed, other causes of gastrointestinal eosinophilia must be ruled out. (See the articles by Putnam; Franciosi and Liacouras; and Fleischer and Atkins elsewhere in this issue for related discussion.) Original descriptions of EGIDs separated patients into subtypes according to the anatomic location of their eosinophilia (ie, mucosal, muscular, and serosal disease). Mucosal biopsies are normally taken from the most superficial gastrointestinal surface. Thus, researchers have little data to help understand the precise relationships eosinophils share with other resident cells in this complex immunologic microenvironment. However, studies of the gastrointestinal tract and other organs are now beginning to paint a picture of how eosinophils and epithelial cells interact to produce symptoms consistent with EGIDs. For instance, eosinophil products have been associated with barrier dysfunction, a problem that is increasingly associated with the pathogenesis of a wide variety of inflammatory bowel diseases. Eosinophil relationships with other resident cells, including fibroblasts, mast cells, lymphocytes, and nerves, are not discussed here, but have been reviewed recently.³⁻⁵

EOSINOPHIL MIGRATION TO MUCOSAL SURFACES DIFFERS AMONG ORGANS

The movement of eosinophils to mucosal surfaces, in particular toward the epithelium, is complex and appears to be organ specific. (See the article by Blanchard and Rothenberg on this topic elsewhere in this issue.) The exact mechanisms driving eosinophils and epithelial cells together are likely unique to different organs. For instance, while the lung relies on IL-5 to drive eosinophils into its mucosa, skin eosinophilia appears to be under the control of the chemokine receptor CCR3. In murine studies of esophageal inflammation, IL-5 is critical to chemotaxis, whereas gastric eosinophilia is eotaxin-1 dependent. Finally, baseline intestinal eosinophilia appears to be eotaxin dependent since eotaxin-deficient mice have fewer intestinal eosinophils than control mice do. Studies with intercellular adhesion molecule 1 (ICAM-1)-deficient mice and ICAM-neutralizing antibodies in a dextran sulfate sodium colitis model demonstrated the β 2-integrin/ICAM-1 dependency of colonic eosinophilic inflammation.⁶ Thus, studies regarding the relationship of eosinophils and epithelium need to be viewed with respect to the organ-specific homing signals. Data suggest that a diversity of regulatory mechanisms for the different gastrointestinal microenvironments may ultimately influence future therapeutic interventions.

INFLUENCE OF EOSINOPHILS ON EPITHELIAL FUNCTION

Eosinophils Possess the Ability to Synthesize and Release Potent Biological Mediators

Eosinophils contain a number of preformed granule proteins, including major basic protein (MBP), eosinophilic cationic protein, eosinophilic peroxidase, and eosinophil-derived neurotoxin, which can be released into the tissue microenvironment. While disease-specific patterns of tissue eosinophil degranulation have not yet been identified, a growing body of literature demonstrates evidence of degranulation within murine models of gastrointestinal inflammation and human diseases.

In addition, eosinophils synthesize and release numerous cytokines (IL-2, IL-4, IL-5, IL-10, IL-12, IL-13, IL-16, IL-18, transforming growth factor [TGF] α and β) chemokines (RANTES [regulated on activation, normal T expressed and secreted] and eotaxins), and lipid mediators (platelet activating factor and leukotriene C4).⁷ Previous work demonstrated that these cytokines are capable of inducing a number of different immune responses in inflammatory diseases, such as asthma, atopic dermatitis, rhinitis, and inflammatory bowel diseases.³ IL-5 is particularly critical to eosinophil growth,

chemotaxis, and activation. IL-13 functions as an eosinophil chemoattractant to perpetuate eosinophilic inflammation.⁸ Eosinophils are also a source of profibrotic cytokines and fibrogenic mediators implicated in airway remodeling, such as IL-11, IL-17, IL-17E (IL-25), TGF- α , TGF- β 1, and matrix metalloproteinase 9 (MMP-9). IL-11, a member of the IL-6 family of cytokines, has fibrogenic potential. Its expression within the airways has been localized mainly to epithelial cells and MBP-positive eosinophils.

Chronic skin lesions in atopic dermatitis are also associated predominantly with TGF- β 1 and IL-11 expression produced mainly by eosinophils. This observation further supports the concept that these cells might be involved in the development of structural remodeling in the injured skin of patients with atopic dermatitis.⁹

Eosinophilic Mediators Impact Epithelial Cells

While direct evidence of the eosinophil's impact on the epithelium is difficult to ascertain in vivo and in human studies, a number of in vitro studies have shown that eosinophils can significantly influence epithelial structure and function. The degree of inflammation may be critical in how eosinophils influence the epithelium. For instance, our previous work demonstrated that at concentrations of three eosinophils per epithelial cell, eosinophils diminished epithelial barrier function. This loss of barrier was found to be linked to the highly charged granule protein, MBP. Application of MBP to the basolateral surface led to diminished barrier and MBP-null mice are relatively protected from barrier dysfunction when compared with wild-type mice.¹⁰ In contrast, recent work suggests that at very low eosinophil/epithelial ratios (eg, 0.01), eosinophils may in fact benefit epithelial barrier function.¹¹ These contrasting results may partially explain the pathologic role of large numbers of eosinophils observed during disease states and the physiologic role of low numbers that could address the innate functions of eosinophils in a healthy state.

Eosinophils may also exhibit autocrine functions during inflammation. Eosinophil-derived cytokines appear to be generated in small amounts, suggesting an autocrine, paracrine, or juxtacrine role in regulating the function of the surrounding microenvironment.³ Eotaxins (-1, -2, and -3) are very potent eosinophil chemoattractants. Their secretion by eosinophils indicates their ability to initiate and perpetuate an inflammatory response.¹²

Increased mucosal eosinophil and granule protein deposition has been described in a number of gastrointestinal diseases also associated with altered epithelial barrier dysfunction, including food allergic enteropathy and inflammatory bowel diseases. Eosinophil-derived granule proteins are detected in lavage fluid and in the mucosa of patients with inflammatory bowel diseases and EGIDs. As stated previously, eosinophil-derived MBP has been shown in a coculture model to alter colonic epithelial barrier function.¹⁰

Eosinophils produce significant levels of TGF- β linked to a variety of eosinophil-associated diseases, including asthma.¹³ Human studies have demonstrated that anti-IL-5 reduces levels of airway eosinophils expressing TGF- β , as well as levels of airway remodeling assessed by bronchial biopsies. Moreover, murine models of airway remodeling have provided important insight into potential mechanisms by which TGF- β activation of the Smad-2/3 signaling pathway may contribute to airway remodeling.¹⁴ Some patients with EoE and dense eosinophilia in their esophagus demonstrate evidence of remodeling and fibrosis with isolated strictures, long-segment narrowing, and esophageal fragility.^{15,16}

Eosinophil-derived granule proteins have also been associated with damage to the airway epithelium, and hypersecretion of mucus.¹⁷ For instance, in many asthmatic patients, eosinophils are the main inflammatory cells present adjacent to the airway epithelium. Bronchoalveolar lavage fluid from asthmatics contains elevated numbers

of eosinophils and concentrations of MBP. Increased MBP levels in bronchoalveolar lavage fluid positively correlates with bronchial hyperreactivity in asthmatic patients.¹⁷ Bronchoalveolar lavage was performed on 17 subjects with mild atopic asthma (9 symptomatic, 8 asymptomatic) and on 14 nonasthmatic control subjects (6 hay fever, 8 nonatopic). A significant increase in the eosinophil count and the concentration of MBP in bronchoalveolar lavage fluid in the symptomatic asthmatics was observed. Moreover, there was a significant correlation between the amounts of MBP recovered and the percentage of eosinophils in the bronchoalveolar lavage. These changes were more marked when asthmatics with airway hyperreactivity were compared with subjects with normoreactive airways. Furthermore, there was a significant increase in the percentage of epithelial cells in the hyperreactive asthmatics. This study supports the hypothesis that bronchial hyperresponsiveness is secondary to epithelial cell damage mediated at least in part through eosinophil-derived granule products.¹⁸

Moreover, other eosinophil products are known to stimulate epithelial proliferation. Choe and colleagues¹⁹ showed that, when stretch forces were applied to the airway epithelium, coculture with eosinophils up-regulated epithelial cell airway remodeling genes. In this system, in which human bronchial epithelial cells were layered on a collagen gel embedded with human lung fibroblasts, activated eosinophils and stretch forces increased epithelial thickness, production of mucus, cilia growth, and evidence of tight junctions. This experiment suggests that mechanical strain affects airway wall remodeling synergistically with eosinophilic inflammation.

Another recent study addressed the impact of eosinophils on primary cultures of human bronchial epithelial cells. Pegorier and colleagues²⁰ demonstrated that when primary cultured human bronchial epithelia cells as well as normal human bronchial epithelial cells were exposed to subcytotoxic concentrations of MBP and eosinophilic peroxidase, there was up-regulation of endothelin-1, TGF- α , TGF- β 1, platelet-derived growth factor β , epidermal growth factor receptor, MMP-9, fibronectin, and tenascin genes. In addition, ex vivo modeling of human airway demonstrated that the addition of activated eosinophils to a matrix of fibroblasts and bronchial epithelial cells led to a significant increase in epithelial thickness. Moreover, eosinophil-derived IL-1 α and TGF- β expression participated in this response, thus promoting a role for eosinophils in disruption of extracellular matrices leading to tissue remodeling and fibrosis.²¹ In summary, a growing body of work demonstrates that eosinophil products influence the synthesis of bioactive molecules by epithelial cells that alter the extracellular matrix composition.

Tissue eosinophilia and eosinophilic granule proteins are found in biopsies of atopic dermatitis lesions.²² Moreover, studies in an atopic dermatitis mouse model have shown that tissue eosinophilia correlates with skin hypertrophy and increased thickness of the epidermal and dermal layers, suggesting the involvement of a repair process as a result of exposure to the cytotoxic effects of MBP and eosinophilic cationic protein.²³ Eosinophils are an important source of MMP-9, known to have an important role in cell migration and inflammation.²⁴⁻²⁶ The MMP-9 have relevance to chronic structural airway changes in asthma. They can be generated by structural and inflammatory cells and have the ability to degrade proteoglycans and enhance airway fibrosis and smooth muscle proliferation through their ability to release and activate latent, matrix-bound growth factors.²⁷

Translational and in vitro studies suggest that eosinophils may play a role in the generation of mucus. For instance, rhinopulmonary epithelia associated with mucosal eosinophils have goblet cell hyperplasia and metaplasia, indicative of accelerated mucus production.²⁸ In support of this association, exposure of human airway epithelial cells to supernatants derived from activated eosinophils leads to increased mucin

production. Eosinophil-derived TGF- α and the activation of epidermal growth factor receptor participate in this response.²⁹ Finally, in murine ovalbumin-induced airway eosinophilic inflammation, use of CCR3 monoclonal antibody reduces both eosinophil recruitment to the lung and mucus production.^{30,31}

Recent clinical observations have led to the speculation that eosinophils may lead to epithelial dysfunction in EoE.^{32,33} In support of this hypothesis, Mishra and colleagues³⁴ showed that, in an aeroallergen model of EoE, there is a significant IL-5-dependent accumulation of collagen in the lamina propria and epithelial mucosa. IL-5-deficient mice show reduced basal layer thickness and diminished lamina propria collagen deposition as compared with wild-type mice. An increased level of IL-5 was detected in the esophagus of EoE patients and in the corresponding animal model. The investigators also observed increased expression of IL-5, TGF- β 1 and mucin 5AC in biopsies from EoE patients and in experimental EoE. The Δ dbl-GATA mice are mice unable to produce eosinophils, which are deficient of eosinophils, showed a significant reduction of esophageal remodeling compared with wild-type mice after allergen challenge. In summary, these data provide evidence that eosinophils and IL-5 participate in esophageal remodeling.

EPITHELIA'S IMPACT ON EOSINOPHILS

Epithelial Function

The epithelium is a cellular interface between the external environment and the inside of the body. This interface is limited to a single cell layer except in the esophagus, which has a stratified squamous epithelium. While this monolayer of cells is also protected by a variety of unique organ-specific innate molecules, such as mucous, trefoil factors, defensins, and antibodies, its protective role is not limited to its barrier function alone. In addition, the epithelium serves as a potent reservoir of cytokines and lipid mediators and is functionally active in chloride secretion, which, in a healthy state, cleanses the epithelial surface. When these functions are disrupted or dysregulated, disease develops. For instance, the loss of barrier in the gut leads to bleeding, protein loss, and exposure of the immunologically primed lamina propria to potentially noxious luminal contents. When proinflammatory cytokines, such as TNF- α , are produced in excess, the mucosa is infiltrated with polymorphonuclear cells, resulting in crypt abscess formation. Finally, excess chloride secretion leads to diarrhea with resultant dehydration.

Epithelial Impact on Eosinophils

As mentioned previously, and in the article elsewhere in this issue by Blanchard and Rothenberg, the intestinal epithelia is capable of releasing a number of chemokines, such as eotaxins-1, -2, and -3, that direct eosinophils to specific parts of the gastrointestinal tract. In addition, epithelia promote eosinophil survival by releasing epithelial-derived granulocyte macrophage colony stimulating factor, which delays apoptosis. Neurotrophin levels are known to be increased in bronchoalveolar lavage fluid during allergic asthma. Hahn and colleagues³⁵ investigated the role of neurotrophins as inflammatory mediators in eosinophil-epithelial cell interactions during the allergic immune response. The investigators demonstrated the neurotrophin expression by immunohistochemistry and ELISA in the lung of a mouse model of chronic experimental asthma. For this study, investigators also performed coculture experiments with airway epithelial cells and bronchoalveolar lavage fluid eosinophils. Hahn and colleagues observed that neurotrophin levels increased during chronic allergic airway inflammation, and that airway epithelial cells were the major source of members of the

neurotrophin family, such as nerve growth factor and brain-derived neurotrophic factor within the inflamed lung. Epithelial neurotrophin production was up-regulated by IL-1 β , TNF- α , and T helper 2 cytokines. Lung eosinophils expressed the brain-derived neurotrophic factor and nerve growth factor receptors, and coculture with airway epithelial cells resulted in increased epithelial neurotrophin production and prolonged eosinophil survival. In summary, the study shows that, during allergic inflammation, airway epithelial cells express increased amounts of nerve growth factor and brain-derived neurotrophic factor, which promote the survival of tissue eosinophils. Controlling epithelial neurotrophin production might be an important therapeutic target to prevent allergic airway eosinophilia. This study suggests the presence of an autocrine pathway through which epithelial cells contribute to eosinophil accumulation on the mucosal surface of the asthmatic lung.

Experiments in animal models have shown that intratracheal administration of the cytokine IL-13 induces dose-dependent eosinophil recruitment in the mouse esophagus but not in the stomach. Intratracheal IL-13 induced esophageal epithelial hyperplasia. However, this recruitment is absent in IL-5-deficient mice and the ability of IL-13 to induce EoE was abolished in STAT6-deficient mice (mice deficient in signal transducers and activators of transcription proteins 6). Furthermore, IL-13-induced EoE was significantly diminished in eotaxin-1-deficient mice. As such, IL-13 delivery to the lung in the mouse induces EoE by an eotaxin-1, IL-5, and STAT6-dependent mechanism. These data further establish a close connection between respiratory and esophageal inflammation.³⁶

SUMMARY

As EGIDs present an increasing health care burden to clinicians, our understanding of contribution of eosinophils to the pathogenesis of these diseases is still in its infancy. The intimate anatomic proximity of eosinophils and epithelial cells permits the speculation that eosinophil-epithelial cross talk, as studied in other diseases (eg, asthma and atopic dermatitis), contributes to EGID pathogenesis. Future studies will need to refine our understanding of the histologic patterns of eosinophilia, the impact of eosinophil-specific mediators on epithelial dysfunction, and the expression of epithelial chemokines that drive mucosal eosinophilia. Answers to these questions will provide the groundwork for new diagnostic techniques and therapeutic interventions.

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