Role of Eosinophils in Inflammatory Bowel and Gastrointestinal Diseases

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ABSTRACT

Inflammatory bowel diseases (IBD) are characterized by the invasion of leukocytes into the intestinal mucosa. However, a mixed inflammatory picture is observed that includes neutrophils, lymphocytes, monocytes, and eosinophils. To this day, the role of eosinophils in health and in disease remains unclear. Investigations into their function stem primarily from allergic diseases, asthma, and parasitic infections. This makes it even more difficult to discern a role for the fascinating eosinophil in IBDs because, unlike the lung or the skin, eosinophils reside in normal intestinal mucosa and increase in disease states; consequently, an intricate system must regulate their migration and numbers. These granulocytes are equipped with the machinery to participate in gastrointestinal (GI) inflammation and in the susceptible microenvironment, they may initiate or perpetuate an inflammatory response. A significant body of literature characterizes eosinophils present in the GI microenvironment where they have the potential to interact with other resident cells, thus promoting intestinal remodeling, mucus production, epithelial barrier, cytokine production, angiogenesis, and neuropeptide release. A number of lines of evidence support both potential beneficial and deleterious roles of eosinophils in the gut. Although studies from the gut and other mucosal organs suggest eosinophils affect mucosal GI inflammation, definitive roles for eosinophils in IBDs await discovery.

Key Words: Crohn disease, eosinophil, inflammatory bowel disease, ulcerative colitis

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Enigmatic eosinophils continue to intrigue clinicians and scientists alike. Although their presence in mucosal microenvironments traditionally characterizes allergic diseases, their role in other diseases (rheumatologic, infectious, idiopathic inflammatory) remains unknown. Equally confounding is that, unlike the lung or skin, eosinophils normally reside in intestinal mucosa, suggesting that they play a role in gastrointestinal (GI) health. Despite this knowledge, advancement on the understanding of their exact role in GI health and disease remains limited. With this in mind, we review basic, translational, and clinical studies that focus on proposed functions of eosinophils in the intestinal mucosa, provide an overview of eosinophil trafficking, and speculate as to the role of these intriguing cells in the intestinal microenvironment as they relate to inflammatory bowel diseases (IBDs).

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ARE EOSINOPHILS EQUIPPED WITH MACHINERY TO PARTICIPATE IN GI INFLAMMATION?

Eosinophils are armed with the ability to synthesize and release a number of molecules that reflect their potential physiological diversity and biological influence (Table 1). In the susceptible microenvironment, they may initiate or perpetuate an inflammatory response.

Granule Proteins

Eosinophils are best identified by their abundance of granular proteins, also referred to as eosinophil-derived granule proteins (EDGPs). There are at least 5 proteins secreted from the eosinophil granule including eosinophil peroxidase (EPO), eosinophilic cationic protein (ECP), eosinophil-derived neurotoxin (EDN; eosinophil protein X, or EPX), major basic protein (MBP), and Charcot-Leyden crystal protein. MBP is one of the most abundant proteins produced by eosinophils, and is found as 2 different homologues (MBP1 and MBP2). MBP1 is also produced at much lower levels in basophils; however, MBP2 is eosinophil specific (1,2). ECP and EDN are both ribonucleases and both function to protect the host from infections, mainly, it is thought, through pore formation in pathogens (3–5). EPO is 68% homologous to its neutrophil counterpart myeloperoxidase and functions similarly in antimicrobial or antiviral roles in addition to contributing to superoxide production (6,7). Charcot-Leyden crystal is found in both eosinophils and basophils (8); however, traditionally it has been associated with conditions characterized by eosinophilia, including asthma, allergies, and parasite infection. Indeed in the 1970s, the presence of EDGPs following eosinophil degranulation was predominantly noted at sites of parasitic infection and was thought to represent evidence of antiparasitic activity. These highly charged cationic proteins create pores in cellular membranes resulting in parasite death and host protection (9,10). In mice, increases in parasite burden following thoracic filarial parasitic infection was observed in strains deficient in either EPO or MBP granule proteins (11); however, human EPO deficiency is a rarely reported finding and has no known clinically associated symptoms (12). Thus, eosinophils were thought to act in a protective manner, defending the host from invading pathogens and potential disease.

Although early studies suggested that extracellular deposition of EDGPs represented an important host defense mechanism, present-day studies have also focused on the contribution of EDGPs and other eosinophil-derived factors to disease pathogenesis and

TABLE 1. Eosinophil-derived products with potential targets of action

Eosinophil products	Target cells
IL-3, IL-5, GM-CSF, eotaxins, EDGPs	Autocrine eosinophil activity
T_H1: IL-2, IL-6, IL-12, TNF-α, IFN-γ	Lymphocytes
T_H2: IL-2, IL,4 IL-5, IL-10, IL-13, leukotrienes	
IL-1, IL-3, IL-4, IL-5, IL-9, IL-13, TNF-α, GM-CSF, leukotrienes, prostaglandins, EDGPs	Mast cells
IL-1, IL-4, IL-5, IL-6, IL-13, TGF-β, GM-CSF, leukotrienes, eotaxins, EDGPs	Epithelial cells
IL-1, IL-6, TGF-β, leukotrienes, eotaxins, EDGPs	Endothelial cells
Eotaxins, neurotrophic growth factors, substance P, EDGPs	Neurons
IL-1, IL-5, IL-13, TGF-β, leukotrienes, eotaxins, EDGPs	Smooth muscle cells
IL-1, IL-4, IL-13, TGF-β, eotaxins, EDGPs	Fibroblasts
TGF-α	Goblet cells

EDGP = eosinophil-derived granule protein; GM-CSF = granulocyte macrophage-colony-stimulating factor; IFN = interferon; IL = interleukin; TGF = transforming growth factor; T_H = T helper cell; TNF = tumor necrosis factor.

chronicity, often in the absence of known pathogenic infection. Extensive eosinophil degranulation is often associated with fibrosis in hypereosinophilic syndrome, eosinophilic esophagitis (EoE), IBDs, asthma, and eczema (13–16). EDGPs are known to activate inflammatory mediator release from basophils and mast cells (17–19). Bischoff et al (20) identified the altered presence of eosinophils and mast cell degranulation products in a morphometric study of patients with IBD compared with normal controls.

Cytokines

Eosinophils are classically associated with a T helper 2 cell (T_H2) cytokine profile including interleukin (IL)-4, IL-5, IL-10, and IL-13 (Table 1). IL-5 is critical for eosinophil growth, chemotaxis, and activation, whereas synergistic functions between eotaxin and IL-13 or eotaxin and IL-5 act as an eosinophil chemoattractant mechanism supporting a role for perpetuating eosinophilic inflammation (21,22). Their ability to produce this classical repertoire of T_H2 cytokines supports their role in allergic-type responses. In this regard, eosinophils express a number of cytokine receptors on their surfaces (23) and, therefore, may respond to their local microenvironment. Autocrine activities of IL-3 and granulocyte macrophage-colony-stimulating factor (GM-CSF) on tissue residing eosinophils suggest that they may play an autoregulatory role in which eosinophils could control their own maturation and antiapoptotic mechanisms during disease processes. These cytokines in addition to IL-5 promote eosinophil survival following recruitment to inflamed sites.

In contrast to this association with T_H2–cytokine–mediated diseases, eosinophils also have the capacity to synthesize and secrete T_H1 cytokines in both health and disease (24). Tumor necrosis factor-alpha (TNF-α), the key cytokine in Crohn disease (CD), has been associated with recruitment of eosinophils in IBD (25). Interestingly and in contrast to their roles in other cell types, activation of the TNF receptor 1 and TNF-related apoptosis-inducing ligand in eosinophils is associated with prolonged eosinophil survival (26,27).

The T_H2 cytokine IL-13 is a pivotal player driving the major pathologies associated with asthma, regulating eosinophil recruitment (chemokine induction), mucus secretion (cell differentiation), and airway hyperresponsiveness (smooth muscle activation) (28). During appropriate inflammatory conditions eosinophils produce functional IL-13 protein (29). Eosinophils are also potent sources of the immunoregulatory, profibrotic cytokine transforming growth factor-β (TGF-β). TGF-β is implicated in tissue remodeling in various diseases including pulmonary and esophageal diseases (30). TGF-β is the prototypical ligand for the TGF superfamily of cytokines and growth factors. This family of growth factors is implicated in various downstream functions including control of proliferation and differentiation processes, inflammation, and, most notably, fibrosis. Eosinophils also secrete the anti-inflammatory agents IL-10 and indoleamine 2,3-dioxygenase, all important mediators for the immunoregulation of proinflammatory T_H1-cell activity. Although a strong case for the proinflammatory role of eosinophils exists, there is a growing body of evidence to support a potential regulatory role for eosinophils in mucosal microenvironments (31). For instance, in certain murine allergic pulmonary models, eosinophils are required for the recruitment of effector T cells and the resulting pulmonary pathology associated with murine ovalbumin (OVA)–induced airway hyperresponsiveness (32,33). Jacobsen et al elegantly demonstrated the necessity for pulmonary eosinophilia for the successful recruitment of effector T cells and for the establishment of a T_H2 cytokine environment in this murine pulmonary allergy model (33). In a murine model of *Schistosoma* egg induction of T_H2-associated inflammation, Sabin et al (34) demonstrated the necessity for eosinophils in the early production of the T_H2-driving cytokine IL-4. In the absence of eosinophil recruitment mediated by mast cells and IL-5, there is an ablation of this critical IL-4 production. The role of eosinophils in antiparasitic immunity remains under investigation. A number of infection models in mice chemically or genetically deficient in eosinophil responses found no specific role for the eosinophil (23). In IBD, research suggests an association between elevated eosinophil activation and relapsing disease activity, whereas others suggest a reparative role as eosinophil levels rise during the remission of intestinal inflammation (25,35). Eosinophils also produce potentially anti-inflammatory agents such as arylsulfatase B, histaminases, and phospholipase D, adding to this suggestion (23).

In addition to cytokines, eosinophils secrete chemokines such as eotaxins, RANTES, and macrophage inflammatory protein-α (MIP-1α) (5,36) (Table 1). Eotaxins (−1, −2, −3) are potent eosinophil chemoattractants, and their secretion by eosinophils demonstrates their ability to initiate/perpetuate an inflammatory response (37). Eotaxin attracts eosinophils via interaction with the C-C chemokine receptor 3 (CCR3) receptor, which is expressed almost exclusively by eosinophils (38,39). RANTES stimulates both eosinophil and neutrophil recruitment (40). In contrast, MIP-1 α is important primarily in neutrophil trafficking (41). Thus, eosinophils secrete chemokines involved in their own recruitment, as well as in other leukocyte recruitment and activation. In this light, eosinophils play an important role in mediating the establishment

and maintenance of the local immune microenvironment following activation.

Lipid Mediators

Eosinophils secrete lipid mediators including leukotrienes and platelet-activating factor. In addition, eosinophils express receptors for leukotrienes and prostaglandins (Table 1). These products are generally considered proinflammatory because they increase leukocyte trafficking, endothelial adhesion, smooth muscle contraction, vascular permeability, and mucus secretion (5). The role of lipid mediators in asthma and allergic inflammation has been well defined as they cause bronchoconstriction, mucus hypersecretion, and bronchial hyperresponsiveness. Vieira-de-Abreu et al (42) demonstrated increased in vivo formation of lipid bodies and leukotrienes within infiltrating eosinophils in a mouse model of asthma.

HOW DO EOSINOPHILS TRAVEL TO GI MUCOSAL SURFACES?

Because eosinophils normally reside in the GI tract and increase in disease states, an intricate system must regulate their migration and numbers.

Growth and Development

Hematopoietic stem cells differentiate into myeloid lineage–specific progenitor cells, which give rise to a common precursor cell of both basophil and eosinophil cells in the bone marrow. Eosinophil specification is regulated in this common precursor cell by the control of transcription factors GATA-1, PU.1, and c/EBP. IL-3, IL-5, and GM-CSF play important roles in the development of eosinophils. Eosinophil progenitor cells express the cytokine-specific alpha receptors for each of these cytokines along with the beta-receptor unit shared by all 3. Under the influence of these cytokines in concert with temporal regulation of the transcription factors mentioned above, eosinophils mature and are ready for exit from the bone marrow. The IL-5 cytokine is the most specific of these eosinophilopoietins for eosinophil development, and its actions are essential for the migration of eosinophils into the bloodstream, where they reside for approximately 1 week (5). Mice deficient in IL-5 lack appropriate eosinophil responses during inflammatory states with deficiency in mounting robust eosinophil responses (43,44), whereas transgenic mice engineered to overproduce IL-5 have profound eosinophilia (45). However, other cells are also equipped to respond to this cytokine. Detailed descriptions of the eosinophil life cycle are available (5).

Migration to Intestinal Mucosa

Eosinophil Migration to Intestinal Mucosal Surfaces

Under normal conditions, the vast majority of eosinophils reside in the GI mucosa, and during disease states, these levels increase (5). Understanding signals that drive intestinal eosinophilia is particularly important because unlike the lung and skin, eosinophils are normal inhabitants of the GI mucosa. Mechanistic studies elucidating how eosinophils home to GI surfaces have focused on the role of eotaxin and IL-5. Eotaxin null mice lack intestinal and thymic eosinophils, whereas the induction of allergic airway disease in these mice results in a diminished pulmonary eosinophilia (46,47).

Eosinophils express specific adhesion molecules that allow for their migration out of the periphery and across the endothelium in response to chemoattractants such as eotaxins— a process known as extravasation. This extravasation process is mediated by similar molecules and processes that mediate all leukocyte migration, rolling, adhesion, and transmigration. The exact mechanisms by which eosinophils are recruited to areas of inflammation are beginning to be unraveled. Tissue specificity for eosinophil recruitment is thought to be mediated by the various chemokines, selectins, integrins, and adhesion molecules and their receptors, both on the eosinophil and on the vascular endothelium. Expression of these molecules may be controlled in a microenvironmentally specific manner. For example, Brandt et al (48) found an essential role for β7-integrin in the recruitment of eosinophils to small intestinal inflammation, but found no role for this integrin's expression for eosinophil recruitment to the lung.

Eosinophils constitutively express L-selectin and, in addition, use both E- and P-selectin machinery to slow down and tether to endothelial cells (49–51). P-selectin glycoprotein ligand (PSGL-1) and sialyl-Lewis x, the ligands for endothelial E- and P-selectin, are expressed on eosinophils (52). The recruitment of eosinophils toward peritoneal ragweed sensitization and challenge models in mice deficient in L-, E-, or P-selectin or deficient in combinations of these selectins found a role for each of these molecules in eosinophil adhesion to the endothelium. The authors of this work pointed to a particularly important role for P-selectin. However, they also highlighted the potential for other nonselectin-dependent mechanisms of eosinophil recruitment resulting from the continued recruitment of eosinophils in mice deficient in all 3 selectins (53). Indeed, dextran sodium sulfate (DSS) colitis induced in L-selectin-specific–deficient mice revealed no role for this selectin in this model of acute large intestinal inflammation (54).

Once tethered to the cytokine-activated endothelium, eosinophils roll, spread, and transmigrate between endothelial cells and across the endothelial basement membrane. There, eosinophils make their way through the extracellular matrix to the source of the original chemotaxin and respond to inflammation by potential activation and degranulation. This migration process is controlled by integrins and their receptive endothelial or matrix protein receptors. Eosinophils have overlapping recruitment pathways to mast cells, and basophils, however, distinctively express a large number of adhesion molecules and receptors that specifically control their transmigration, namely α3, α4, α5, α6, αD, αL, αM, αX, and β1, β2, and β7 integrins (55). Eosinophils, in addition, express certain cell adhesion molecules (CAMs) that bind these integrins. Very late antigen (VLA-4) and lymphocyte function–associated antigen (LFA-1) on the eosinophil surface interact with endothelial vascular cell adhesion molecule (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1) in a process regulated by eotaxins. Inhibition of these ligands disrupts the migration of eosinophils into the tissue in experimental models and clinical trials, emphasizing their importance as components in the eosinophil inflammatory response (21,56).

Brandt et al and Forbes et al identified specific adhesion molecules necessary for eosinophil recruitment to the small and large intestinal mucosa. Small intestinal eosinophil recruitment relies on MadCAM-1/α4β7 integrin interactions; however, colonic eosinophil migration relies on β2 integrin molecules (48,54,57). For instance, β7-integrin knockout mice developed less small bowel inflammation compared with wild-type controls in a model of allergic disease (48). Mice exhibited increased circulating eosinophils, indicating no role for this integrin in bone marrow exit and vascular entry. This deficiency is only apparent during inflammation because there is no baseline deficiency in eosinophil presence in the small intestine during homeostasis in β7-integrin–deficient mice. Another method of tissue-specific homing of eosinophils involves the differential regulation of the chemokines

C-C chemokine ligand 25 (CCL25) (TECK) in the small intestine and CCL28 (MEC) in the large intestine (40,58). The receptors for these chemokines, CCR9 and CCR3, have been demonstrated on the surface of eosinophils, as has the eosinophil responsiveness in culture conditions (59,60).

Using ICAM-1 null mice and ICAM neutralizing antibodies in a DSS colitis model, Forbes et al (54) demonstrated the β2-integrin/ICAM-1 dependency of colonic eosinophilic inflammation. In contrast, DSS colitis in a β7-integrin knockout mouse and mice treated with α4-integrin inhibitory antibodies showed no change in the level of eosinophil recruitment to the colon.

Eosinophils use VLA-4 (α4β1) and VLA-6 (α6β1) to interact with basement membrane and extracellular matrix proteins, such as laminin, collagen, and fibronectin to traverse the basement membrane and travel through the lamina propria (61,62). This binding leads to eosinophil priming, and following exposure to inflammatory cytokines, eosinophils become activated and may degranulate upon appropriate stimulation. In the absence of these tissue-recruitment signals or the lack of survival signals such as GM-CSF, IL-5, or TNF, eosinophils will undergo apoptosis (21).

Taken together, these findings suggest a variety of regulatory mechanisms for the different GI microenvironments that may ultimately affect future therapeutic interventions.

Esophageal Mucosa

Normal esophageal mucosa does not contain eosinophils. Eosinophils increase in squamous epithelia of the esophageal mucosa during gastroesophageal reflux disease (GERD) and EoE, but the characteristic numbers and associated histological features of each disease are only now being addressed. For instance, GERD is traditionally associated with a small number of eosinophils in the distal squamous epithelial surface, but recent evidence demonstrates that large numbers (>15 eosinophils/hpf) can be found in both the proximal and distal epithelium of children and adults with GERD (63,64). During the last decade, an emerging body of evidence shows that eosinophils also increase in EoE (65). EoE is a clinicopathological disease characterized by upper intestinal symptoms seen in association with >15 eosinophils/hpf in which GERD and other diseases have been ruled out. Gastric and duodenal biopsies must also be normal.

The mechanisms leading to esophageal eosinophilia have been addressed in several human genetic studies together with a number of murine models. An important study of human esophageal biopsies by Blanchard et al (66) identified a unique transcript signature that reliably identified patients with EoE. Of these genes, eotaxin 3 was the most upregulated gene. Further studies confirmed this association and identified IL-13 as a potent regulator of eotaxin 3 in esophageal biopsies and isolated epithelial cells (67). Thus, these studies define a role for eotaxin 3 in certain patients with EoE. A more recent study (68) of genome-wide associations identified a link between certain patients with EoE and variants at the 5q22 loci. This and future studies will help elucidate the mechanisms by which eosinophils are recruited in individuals and may provide more guidance in the management of this disease.

Mice sensitized to and challenged with the ubiquitous aeroallergen, *Aspergillus fumigatus*, develop significant IL-5–dependent esophageal eosinophilia (69,70). Intratracheal administration of IL-13 promotes eosinophil recruitment to the esophagus in mice; however, this recruitment is ablated in mice genetically deficient in IL-5 (71). Pretreatment with an IL-13–blocking antibody effectively diminished eosinophilia in the same model system (72). Recently published work has additionally pointed to the indoor allergens, house dust mite and cockroach antigens, as potent inducers of experimental eosophageal eosinophilia. In the present study, authors indicate an increase in IL-4 and IL-13 in response to antigen exposure, whereas administration of antigen to Eotaxin1/2 double knockout, CCR3– or IL-5–deficient mice abrogated eosinophil recruitment, indicating an essential role for these molecules in this allergen-induced model of esophageal eosinophilia (73). Together, these studies suggest that an exogenous allergen leads to esophageal eosinophilia that is dependent on T_H2-type cytokines, IL-4, IL-5, and IL-13. Despite these studies indicating the essential role for IL-5 in murine models, recent open-label trials using anti-IL-5 therapies were found to be effective in only a small number of patients (74,75).

Gastric, Small Intestinal, and Colonic Mucosa

Eosinophils localize to the GI tract during perinatal development in an eotaxin- and IL-5–dependent manner (22). Whereas eosinophils are present in the lamina propria of wild-type, 19-day-old mouse embryos, their numbers in intestinal mucosa are significantly diminished in IL-5–deficient mice and eotaxin-deficient mice (22). Interestingly, the same study found no difference in the homeostatic levels of eosinophils in jejunal tissue of GM-CSF–deficient mice. Further investigation found no difference in the number of eosinophils in the bone marrow but decreased levels in circulation, indicating a critical role for these cytokines in exit of eosinophils from the bone marrow. Epithelial overexpression of IL-5 and eotaxin leads to significantly increased numbers of intestinal eosinophils compared with control mice (57). In contrast, studies in isolated eotaxin deficiency show an absence of eosinophils in the intestine, even in the presence of high levels of IL-5, maintaining the essential role for eotaxins in the recruitment of eosinophils into the GI tract (22,57). Finally, mice sensitized by intraperitoneal injection with OVA and later challenged with orally administered OVA develop significant eosinophilic GI inflammation. However, mice deficient in eotaxin under the same conditions have impaired eosinophil recruitment to intestinal tissues and are protected from weight loss and gastromegaly (76). All of these results further support the critical role of IL-5 in the development of eosinophils in the bone marrow; however, tissue eosinophilia is dependent on eotaxin. Thus, these proteins work in concert to induce an efficient eosinophil response in appropriate conditions.

WHAT ARE THE FUNCTIONAL ROLES OF EOSINOPHILS?

A number of lines of evidence support both potential beneficial and deleterious roles for eosinophils in the gut (Fig. 1).

Potential Beneficial Aspects of Eosinophilia

Eosinophils likely benefit human health, but at the present time, these roles are still speculative. Circumstantial evidence for a supportive role stems from their phylogeny that dates back to chordates. Eosinophils are present in normal mammalian mucosa, and genes encoding EDGPs are evolutionarily conserved between numerous species. Interestingly, eosinophils accumulate primarily at body surfaces that border the external environment, such as the GI mucosa, supporting a potential role in host defense (77).

Antiparasitic

Eosinophils have been classically described as antiparasitic leukocytes. Peripheral eosinophilia increases during helminth infection and eosinophils migrate to areas of parasitic infection with terminal endpoints of degranulation at sites of parasitic infiltration (10,78). Epidemiological studies correlate peripheral eosinophilia

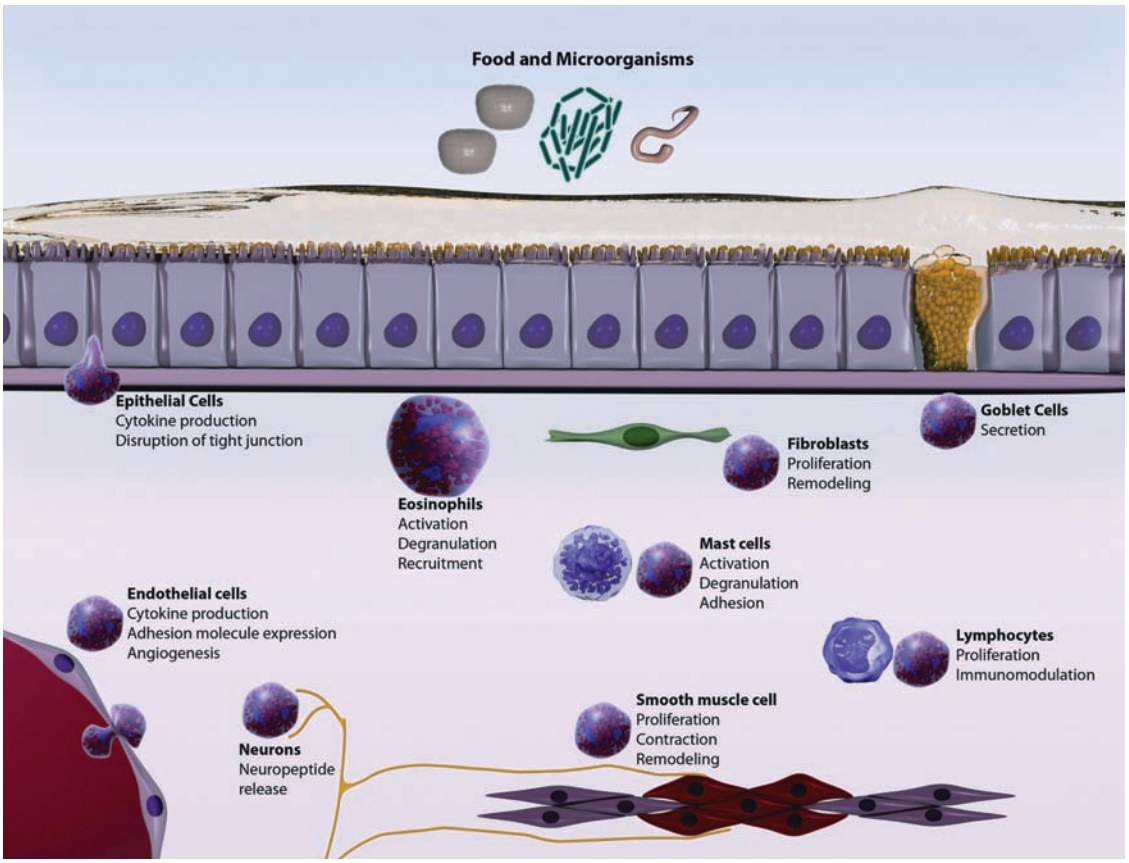

FIGURE 1. Proposed roles for eosinophils within the intestinal mucosa. Based on basic, translational, and clinical studies derived from other organs and the gastrointestinal tract, this figure presents potential mechanisms for eosinophils to interact with resident intestinal cells. Each of these complex and dynamic relationships is described in detail in the body of this review.

with protection against schistosomal infections in Africa. Proposed mechanisms for this response include the ability of EDGPs to induce cell membrane pore formation and mediate antibody- and/or complement-dependent cellular toxicity to parasites (79).

Despite these studies that suggest a role for eosinophils in helminth infection, data from murine models are less certain. Reduction of IL-5, either by genetic manipulation or by antibody depletion, leads to diminished eosinophilia and, in certain infections, more severe parasitic infection compared with mice that have a full complement of eosinophils. For example, IL-5 null mice infected with the nematode *Strongyloides ratti* show increased worm burden, tissue damage, and parasite fecundity. However, infection with the trematode *Fasciola hepatica* does not lead to phenotypic differences in IL-5 null mice compared with wild type (79,80). In addition, mice depleted of eosinophils with the use of anti–IL-5 antibody do not show alterations in *Trichinella* infection compared with untreated mice (81). Finally, IL-5 transgenic mice with marked eosinophilia have no protection from *Trichinella spiralis* infection (82). It is likely that these differences can be attributed to redundancy of effector immune responses to specific pathogens and differences in the animal model that was used (80).

Role in Cancer

Recent studies suggest that, in some circumstances, eosinophils possess antineoplastic properties. For instance, eosinophils are associated with necrotic areas of tumors and within the tumor pseudocapsules. Peripheral eosinophilia is associated with improved prognosis in GI and head and neck cancers, but a poorer prognosis in oral squamous cell carcinoma. Certain forms of human cancer treatments that include cytokines IL-2, IL-4, and GM-CSF promote eosinophilia (83).

Murine studies support a role for eosinophils in decreasing tumor burden. For instance, in a murine model of cancer, malignant cells were transfected to constitutively overproduce IL-4. This leads to tissue eosinophilia at the site of tumors, decreased tumor burden, and improved survival (84). In another murine model, melanoma cells were transfected to express ovalbumin and injected into mice. OVA-specific T_H1 or T_H2 cells were generated and injected into the mice, and lung metastases were measured 18 to 20 days after tumor challenge. Lung metastases regressed in the mice injected with T_H2 but not T_H1 CD4+ cells. Regression of lung metastases was associated with the influx of eosinophils into the tumor sites, and degranulating eosinophils were detected at regressing tumor sites. Eosinophil recruitment and tumor regression was not noted in eotaxin-deficient mice, implicating eotaxin as a key molecule in the recruitment of eosinophils to tumor sites (85). In mice completely void of eosinophils, fibrosarcoma tumor burden is significantly enhanced (86). Finally, recent speculation suggests that eosinophils can respond and traffic to damage-associated molecular pattern molecules (83).

In contrast, eosinophils may promote the growth of certain tumors. For instance, in a hamster model of squamous cell

carcinoma, the administration of anti–IL-5 antibody completely obliterated tumor-associated tissue eosinophilia and subsequently decreased tumor burden and delayed the onset of cancer development (87).

Antiviral

As previously noted, eosinophil granule proteins demonstrate antiviral activities. ECP and EDN are ribonucleases with antiviral activity (88). Eosinophils express Toll-like receptors (TLR)-3, TLR-7, and TLR-9, which recognize dsRNA, ssRNA, and dsDNA, respectively (89,90). Activation of the TLRs generates interferon-beta, thus initiating antiviral host responses (4). Also, in a murine model of respiratory syncytial virus (RSV) infection, IL-5 transgenic mice that harbor profound peripheral eosinophilia show accelerated virus clearance and decreased airway hyperreactivity (4). Transfer of eosinophils, but not IL-5 alone, into RSV-infected wild-type mice leads to accelerated viral clearance and diminished airway hyperreactivity supporting eosinophil specificity of this response. Finally, eosinophil-deficient mice have significantly delayed RSV clearance (4).

Antibacterial

Traditional studies of innate effector cells providing immunity to bacteria have focused on the roles of neutrophils and macrophages. The contribution of eosinophils has been understudied and overlooked. Lehrer et al (91) provided early evidence for the antibacterial role of the eosinophil granule proteins ECP and MBP in vitro. However, 2 recent publications have rehighlighted the potential importance of eosinophils in challenging bacterial infections. Mice deficient in eosinophils had a significant increase in the colony-forming units of *Pseudomonas aeruginosa* bacteria following infection of mouse peritoneal cavities, and the induction of *Pseudomonas* peritonitis. This bacterial burden was abrogated in mice transgenically engineered to have profound eosinophilia (IL-5 transgenic mice) or in mice treated with eosinophil granules following infection (92). Yousefi et al (93) described a previously undetected process by which eosinophils release their mitochondrial DNA in a catapult-like fashion, without subsequent death of the eosinophil, which leads to extracellular bacterial death. This release was detected in response to lipopolysaccharide from Gram-negative bacteria and showed successful killing of *Escherichia coli* in a DNA-dependent fashion in vitro. In support of this antibacterial role for eosinophils, in vivo studies using the mouse bacterial intestinal infection model cecal ligation puncture in mice with high levels of eosinophilia (IL-5 transgenic) found significant improvement in survival and significant reduction in circulating bacterial burden. Although these studies call attention to the beneficial role of eosinophils in fighting bacterial infections, early reports suggested a reduction in circulating eosinophils during the acute phase in bacterial infections in patients (94). It, however, remains possible that eosinophils have been recruited to the tissue site of infection and may not be detectable in the circulation. This has never been systematically studied, thus leaving unanswered the etiology of this reduction and the role of the eosinophil in these infections.

Antigen Presentation

Wang et al (95) provide evidence supporting the eosinophil's role in antigen presentation. Isolated splenic eosinophils, free from antigen-presenting cells, were cultured with GM-CSF and shown to express major histocompatibility complex class II and other co-stimulatory molecules. Eosinophils were then incubated with OVA and transferred into the lung intratracheally. Exposure of eosinophils to OVA-specific CD4+ T cells led to eosinophil proliferation, cytokine secretion, and cell surface activation. These studies provide supportive evidence that eosinophils may process antigen in the lung lumen and function as antigen-presenting cells to CD4+ lymphocytes (95). In another study, Shi et al (96) provided morphological evidence of this process. Following airway challenge, eosinophils were isolated from the airways or the peritoneal cavities of IL-5 transgenic mice and fluorescently labeled ex vivo. Labeled cells were reinstilled into the trachea and were found to home to lymph nodes in an eotaxin-independent manner. Labeled eosinophils expressed major histocompatibility complex class II and co-stimulatory CD80 and CD86 proteins and functioned in vitro as CD80- and CD86-dependent, antigen-specific, antigen-presenting cells.

Innate Mechanisms of Defense

A potential mechanism for eosinophils to protect against microbial invasion is through the stimulation of mucus production. In the lung, eosinophils are associated with induction of mucus production. Exposure of human airway epithelial cells to supernatants derived from activated eosinophils leads to increased mucin production through eosinophil release of TGF-α and activation of epidermal growth factor receptor (EGFR) (97). Rhinopulmonary epithelia associated with mucosal eosinophils have goblet cell hyperplasia and metaplasia, indicative of accelerated mucus production (98). Finally, in OVA-induced airway eosinophilic inflammation, use of gefinitib, an EGFR inhibitor, or CCR3 monoclonal antibody reduced eosinophil recruitment to the murine lung and mucus production (99,100).

Potential Deleterious Aspects of Eosinophilia

Eosinophils also have been implicated as pathogenic effector cells in asthma, atopy, eczema, infection (viral, bacterial, or parasitic), malignancy, EoE, GERD, IBD, allergic colitis of infancy, celiac disease, vasculitis, connective tissue diseases, and hypereosinophilic syndrome as reviewed previously (101). Much evidence supporting a pathological role for eosinophils is derived from morphological and association studies in which eosinophils and their products are present in diseased tissue. Below we highlight the potential pathogenic interactions of eosinophils with resident and recruited cells of mucosal surfaces (Fig. 1).

Epithelium

Eosinophils are the predominant inflammatory cells found in the airway epithelium in asthma. Bronchoalveolar lavage fluid from asthmatics contains increased numbers of eosinophils and levels of MBP. Early studies have shown MBP to be toxic to lung epithelia, leading to increased airway epithelial permeability in vitro. Although other eosinophil products are known to promote epithelial proliferation (102), Pegorier et al (103) demonstrated that lung epithelial cells exposed in culture to MBP or EPO showed a significant increase in TGF-α, TGF-β1, EGFR, platelet-derived growth factor-β, and tenascin mRNA levels.

Smooth Muscle Cells, Fibroblasts, and Nerves

The application of MBP to airway smooth muscle leads to contraction and enhancement of muscle reactivity to acetylcholine and histamine, findings that may explain the contribution of eosinophils to airway hyperreactivity (5,56). Ablation of IL-5 in murine models of asthma leads to decreased eosinophil recruitment to the

airway, attenuated airway hyperreactivity, and diminished lung damage (44). The most compelling evidence implicating eosinophils in the pathogenesis of asthma comes from the PHIL mouse, a genetically engineered mouse that lacks eosinophils. Airway resistance after methacholine challenge is significantly diminished in PHIL compared with wild type, supporting a role for eosinophils in airway dysfunction (104).

Eosinophils may also participate in tissue remodeling. For example, ex vivo modeling of the human airway revealed that the addition of activated eosinophils to a matrix of fibroblasts and bronchial epithelial cells leads to a significant increase in epithelial thickness (102). Gomes et al (14) revealed that coculture of eosinophils with fibroblasts induces fibroblast IL-6 and fibronectin production. In further studies, eosinophil-derived IL-1α and TGF-β were shown to participate in this response, thus promoting a role for eosinophils in modulating extracellular matrices. Studies examining esophageal biopsies from patients with EoE associate eosinophils with tissue remodeling (30). At endoscopy, some patients with EoE demonstrate evidence of remodeling and fibrosis with the presence of isolated strictures, long segment narrowing, or esophageal fragility (16,105). Histological staining of the affected subepithelial layer from patients with EoE reveals increased collagen deposition and increased TGF- β expression compared with patients with GERD and healthy controls (16,30). One of the complexities of intestinal eosinophilia is the lack of reliable clinical outcome measures. Although a number of studies provide circumstantial evidence for a role of eosinophils in esophageal remodeling and fibrosis, the correlation of fibrosis, eosinophilia, and symptoms remains variable.

Eosinophils have direct cell-to-cell contact with both airway neurons in asthma (106) and damaged neurons of the GI tract in IBD (76,106,107); however, the meaning of this interaction remains uncertain. Kingham et al (108) demonstrated that upon coculture with eosinophils, guinea pig parasympathetic nerves undergo dose-dependent shortening. In addition, neuron differentiation is inhibited by eosinophils or MBP in a dose-dependent manner. Eosinophils may also alter nerve remodeling. MBP induced M2 muscarinic receptor expression on cholinergic nerves and reduction in intracellular acetylcholine content in vitro (109). A recent review by Raap and Wardlaw (110) rehighlighted the reciprocal interactions between eosinophils and peripheral nerve cells. In this review they emphasize a number of neuromediator receptors functionally expressed on eosinophils leading to cytokine and granule protein release. The effects of granule proteins on neuron function and viability are addressed (eg, the in vitro neurotoxic activities of EDN and ECP). In addition, the potential indirect interactions between neuropeptides, mast cells, and eosinophils are discussed.

Mast Cells

A number of groups have characterized the influence of eosinophils and EDGPs on mast cells. Zheutlin et al (111) showed that rat mast cells significantly increase histamine release in response to MBP and ECP, but not EDN. MBP induced histamine release, arachidonic acid synthesis, and TNF-α release from murine mast cells with a connective tissue phenotype (112). In contrast, Okayama et al (113) showed that MBP, EPO, EDN, and ECP do not stimulate histamine release from cultured human skin mast cells. Taken together, these studies emphasize the complex and variable role eosinophils may play on mast cell function depending on the microenvironment.

DO EOSINOPHILS PLAY A ROLE IN IBD?

GI tissues affected by IBD demonstrate evidence of mucosal eosinophilia. Although studies from the gut and other mucosal organs suggest that eosinophils affect mucosal GI inflammation, definitive roles for eosinophils in IBD await discovery. Figure 1 demonstrates the potential interactions of the eosinophil with the intestinal mucosa and its resident cells.

Histological Characterization

To date, eosinophils are implicated in IBD because of their morphological association with the diseased tissue. Early studies of mucosal biopsies from patients with IBDs revealed that eosinophils were prominent leukocytes infiltrating the intestinal epithelia (114–117) (Fig. 1). Because of this initial observation, ulcerative colitis (UC) and CD were sometimes described as allergic diseases (118). A complicating factor in determining whether mucosal eosinophilia is pathological is the fact that normal values for GI eosinophilia, distal to the esophagus, have yet to be established. DeBrosse et al (119) retrospectively characterized the quantity and distribution of eosinophils in 28 children. They measured a wide variation from a maximum of 26 eosinophils/hpf in the small intestine to up to 50 eosinophils/hpf in the proximal colon.

Accumulation of eosinophils in IBD has been characterized in a number of histological studies; however, accuracy in true reflection of the numbers and the contribution of eosinophils have been hampered by various factors including use of nonspecific staining, low sample numbers, sample acquisition, and choice of patient population (120). Whereas some studies relied on hematoxylin and eosin staining for eosinophil identification, others were powered with sample sizes as low as 2 per group in some instances. In fact, recent evidence points to the importance of examination of granular protein content in inflamed tissues because examination of hematoxylin and eosin staining alone overlooks the contribution of degranulated eosinophil products in diseased tissues (121). However, taken together, these studies indicate an increase in the numbers of mucosal eosinophils in patients with IBD.

Recent studies characterized mucosal eosinophilia in the colon and associated increased mucosal eosinophilia with IBD. Pensabene et al evaluated the clinical significance of colonic eosinophilia in 69 children seen during an 18-month period. Diagnostic categories included IBD (32%), irritable bowel syndrome (33%), and food allergies (10%), with the remainder receiving a wide range of other diagnoses. The distinguishing features for IBD included high lamina propria cellularity and intracryptal/intraepithelial eosinophils (122).

Secreted Eosinophil Products

Whereas some studies have characterized tissue eosinophilic inflammation in IBD, others have focused on measuring secreted products from eosinophils in the blood, tissue, intestinal lumen, and fecal samples. Because it is well known that eosinophils secrete a number of eosinophil-specific granule proteins such as ECP, EPO, EDN, and MBP, increased levels of these products provide further circumstantial support for their role in IBD. Peripheral eosinophils from patients with active IBD have increased ECP release compared with those with treated quiescent disease. These findings are consistent with similar studies in asthma; patients treated with prednisone have diminished ECP release and IL-5 expression compared with those with active disease (123).

Ultrastructural studies demonstrate that eosinophils release granule products in tissues with IBD. Some of the earliest studies in this regard focus on electron microscopic studies of colonic resection specimens from patients with CD, which identified numerous eosinophils, extracellular eosinophil MBP granule deposition, and cytotoxic tissue changes (10,124). Other studies (125,126)

examining mucosal biopsies from patients with CD reveal increased eosinophils and ECP, and EPO deposition in visually inflamed and normal areas of colon. Dubucquoi et al (127) showed increased mucosal eosinophilia and IL-5 in the resected colon of patients with CD requiring ileocolectomy. This increase in mucosal eosinophils and IL-5 expression in the neoileum was associated with endoscopic recurrence of disease at surveillance endoscopy 3 months later, suggesting that eosinophilia and local IL-5 production was associated with early mucosal damage in CD.

Multiple groups have analyzed the concentration of EDGPs in stool and correlated increased EDGP concentrations with severity of disease. Berstad et al (128) first identified increased levels of fecal ECP in stool samples from active ulcerative colitis (UC) compared with normal, uninflamed controls. Bischoff et al (129) later confirmed these findings in measurements of increased ECP and EPX in stool samples from patients with UC, CD, and food allergy compared with controls. They noted higher concentrations of stool ECP and EPX in patients with evidence of gross mucosal inflammation at endoscopy. Saitoh et al (130) found significantly elevated concentrations of fecal levels of ECP and EPX in active UC and CD compared with clinical and endoscopically inactive UC and CD. Both inactive and active IBD had higher levels of ECP and EPX compared with healthy controls. Also, inactive patients with IBD with higher ECP and EPX fecal levels were more likely to relapse in the following 3 months. Finally, Peterson et al (131) studied fecal EPX levels in patients with UC with endoscopically active disease before and after treatment. They determined that fecal EPX decreased after corticosteroid treatments.

Colonic perfusion fluids from patients with intestinal inflammation also contain increased levels of EDGPs compared with controls. For example, Carlson et al (132) found elevated ECP, EPO, and EPX in colonic perfusion fluids of patients with colitis and isolated proctitis compared with healthy controls. They later found that colonic perfusion levels of ECP, EPO, and EPX decreased following steroid treatment (35). Sangfelt et al (35) found that a reduction of EDGP levels in rectal perfusion fluid was associated with successful response to prednisone treatment in patients with EGIDs. Increased ECP levels in colonic perfusion effluents in children with UC and CD (133) and adults with UC (134) have also been described.

In contrast, Heatley and James (135) analyzed rectal biopsies from patients with UC undergoing surveillance colonoscopy. They found that patients with mild-to-moderate disease who had responded to treatment had significantly raised tissue eosinophil counts compared with patients with aggressive disease that did not respond to treatment. The authors speculated that eosinophils may have contributed to the positive clinical response. Similarly, Lampinen et al (25) found increased eosinophil activation, as defined by CD69 and CD44 staining, in UC in remission compared with active UC, and suggested that eosinophils may contribute to repair of injured epithelia. Finally, Troncone et al (133) found increased ECP levels in gut lavage fluid in children with UC and CD, compared with healthy controls, but ECP levels did not directly correlate with clinical disease activity scores.

Raab et al (136) found a significant elevation in levels of the lipid prostaglandin E2 (PGE2) in rectal and sigmoid perfusates in patients with UC. Increased levels were associated with elevations in ECP, MPO, and TNF-α levels. These mediators were colocalized with eosinophils and macrophages, implicating these 2 cell types in the synthesis of PGE2 in colitis. PGE2 has multiple functions including potential roles in intestinal repair; further studies will define the role of eosinophil-derived lipid mediators in protection against or participation in mucosal injury in IBD (137).

Patients with active IBD present with significant elevation in serum levels of eotaxin when compared with patients with quiescent disease or normal controls, indicating a potential role for eotaxin and its downstream targets in IBD activity (38,39). Other authors found elevated levels of activated eosinophils in pediatric UC. This eosinophilia was determined to positively correlate with disease severity and predominantly resulted from eotaxin-1 production in rectosigmoid colonic specimens (138). Eosinophil recruitment and activation may play an important role in the chronicity of IBD in patients.

Taken together, these studies focus on microscopic evidence of eosinophilia, eosinophil degranulation, cytokine production, and increased eosinophil granule protein products in the stool and colonic perfusion fluid of patients with severe UC or CD. They suggest that the eosinophil is associated with IBD—in other words, present and active at the site of inflammation.

Deleterious Impact of Eosinophil Products on the GI Tract

Guilt by association is not enough to convict the eosinophil as a participant in the pathogenesis of IBD. As described above, a number of clinical and translational studies have shown that eosinophils and their products are increased in tissues affected by IBD and bathe mucosal surfaces at the sites of inflammation. Thus, studies focusing on eosinophils and their products in reductionist and genetically modified murine systems are beginning to tease out the role of this leukocyte. In a reductionist noncontact, coculture model system examining the impact of eosinophils on colonic epithelial cells, eosinophil-derived products were shown to diminish epithelial barrier function as measured by transepithelial resistance. The active soluble product derived from this coculture system was identified as MBP, whereas EDN did not elicit the same impact (139). Xu et al (15) demonstrated that sonicates from eosinophils increase fibroblast proliferation and collagen production in fibroblasts outgrown from biopsies in active CD. A comparative study of peripheral eosinophils between patients with CD and UC indicates differences in chemotactic abilities, adhesion properties, and degranulation activity between these patient subsets (140). Thus, the eosinophil may indeed present in a variety of phenotypes depending on the immune environment and associated disease mechanism.

Several animal models show the eosinophil's impact as an effector cell in models of IBD. For example, MBP null mice exposed to oxazolone colitis were relatively protected from colitis compared with wild-type mice, suggesting a role for MBP (139). Forbes et al (141) also showed that in the murine model of DSS colitis, mice have increased colonic eosinophilia, GI dysfunction, and release of EPO into the colonic lumen. Eotaxin knockout mice have decreased colonic eosinophilia, attenuated experimental UC, and decreased levels of colonic EPO release (54,138). EPO-deficient mice have attenuated experimental colitis, providing further support for the eosinophil's role (141). Shichijo et al (142) examined EDGPs in a rat model of UC. Rats treated with anti-ECP antibody develop attenuated DSS colitis, decreased ECP staining, and improved epithelial healing compared with untreated controls. Finally, Ahrens et al and Vieira et al (138,143) both have shown that mice congenitally deficient in eosinophil development are protected from experimental colitis.

SAMP1/Yit mice develop spontaneous ileitis in association with increased IL-5 and eosinophil infiltration (144). Anti-IL-5 antibody treatment in a model where severe combined immunodeficiency mice are recipients of naïve and effector CD4+ cells from the SAMP1/Yit mouse leads to improvement of ileitis, colitis, and eosinophil infiltration (144). In another study, when IL-5 knockout mice, which have decreased eosinophils at a baseline, undergo DSS colitis no changes in disease severity were seen compared with wild-type controls (43). Thus, although human data remain circumstantial, both cell culture and animal models are providing

increasing evidence for a role for eosinophils and their granule proteins in the pathogenesis of intestinal inflammation. A growing body of literature now exists that examine specific roles of eosinophilia in colitis in genetically engineered mice that are deficient in eosinophil-specific granule proteins, eosinophils, or eosinophil chemokines (eotaxin). Further basic and translational research into the specific mechanisms by which eosinophils participate in intestinal inflammation is still needed.

CONCLUSIONS

Circumstantial evidence places eosinophils at the scene of inflammation. A growing body of basic evidence in other organs, including the gut, implicates eosinophil products with tissue dysfunction. Is the eosinophil the purveyor of tissue damage? Is the eosinophil, the innocent bystander, attacked in the fray along with the intestinal epithelium? Was the eosinophil recruited for tissue repair at the site of damage?

Considering the published literature that examines the gut as well as other organs, it is reasonable to speculate a beneficial and deleterious role for eosinophils in IBDs. Eosinophils are present in healthy intestinal mucosa and increase during inflammation. They possess an armamentarium of biologically active mediators that, in the appropriate microenvironment, may help or harm the host. Although the bulk of evidence supports a pathological role for eosinophils in IBDs, recent microbial studies support a protective role in states of sepsis. Reductionist in vitro experiments, relevant animal models, and translational studies will continue to shed light on this intriguing cell for many years to come.

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