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Eosinophils in Infection and Intestinal Immunity

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Abstract

Purpose of Review—Inflammatory bowel diseases (IBDs; e.g. Crohn's disease and ulcerative colitis) are thought to be a consequence of an uncontrolled inflammatory response against luminal antigens, including commensal bacteria. The observed link between eosinophil levels and severity and remission rates in IBD has led to speculation that eosinophils may contribute to the antimicrobial inflammatory response in IBD.

Recent Findings—Eosinophils express the necessary cellular machinery (innate immune receptors, pro-inflammatory cytokines, antibacterial proteins and DNA traps) to mount an efficient antibacterial response; however, the rapid decline in eosinophil numbers following acute systemic bacterial infection suggests a very limited role for eosinophils in bacterial responses.

Summary—We describe the clinical evidence of eosinophil involvement in IBD; summarize the *in vitro* and *in vivo* evidence of eosinophil anti-bacterial activity and the biology of eosinophils focusing on eosinophil-mediated bactericidal mechanisms and the involvement of eosinophil-derived granule proteins in this response; and conceptualize the contribution of eosinophils to an anti-commensal bacterial response in IBD.

Keywords

Eosinophils; antibacterial immunity; inflammatory bowel diseases

Introduction

While the precise etiologies of inflammatory bowel disease (IBD) (e.g. ulcerative colitis [UC] and Crohn's disease [CD]) remain unclear, experimental and clinical studies indicate that an aberrant intestinal T-cell and macrophage (MΦ) response directed against luminal antigens, including commensal bacteria, is pathognomonic of these diseases [1–3]. Evidence indicates that the commensal intestinal microbiota are important to the exacerbation of the IBD phenotype: surgical diversion of the fecal stream effectively resolves CD inflammation distal to the surgical site [4], and treatment with antibiotics decreases the risk of post-operative recurrence of CD [5]. A common feature of the cellular infiltrate in IBD, particularly UC, is eosinophils [6,7]. While this cell population usually represents only a small percentage of the infiltrating leukocytes, eosinophil level has been shown to correlate with morphological changes to the gastrointestinal (GI) tract, disease severity and GI dysfunction [8–11]. Collectively, this clinical and experimental evidence suggests that eosinophils may play a role in combating commensal intestinal microbiota and infection in intestinal diseases such as IBD.

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Consistent with this possibility, eosinophils possess the biological arsenal to fight bacterial infection. Eosinophils express various pattern recognition receptors (e.g. Toll-like receptors, damage associated molecular patterns (DAMPs)) enabling them to sense bacterial antigens, to produce pro-inflammatory cytokines and cationic proteins (e.g. eosinophil cationic protein [ECP], major basic protein [MBP] and eosinophil peroxidase [EPO]) that possess antibacterial properties and to release mitochondrial DNA-containing “traps” into the extracellular space to kill bacteria. Indeed, recent *in vivo* evidence indicates that mice with elevated eosinophil levels have reduced bacterial burden following infection whereas mice depleted of eosinophils have increased bacterial burden. This inverse association of eosinophil level and post-infection bacterial burden suggests either a direct or indirect role for eosinophils in antibacterial immune response. However, there is clinical and experimental evidence to suggest that this cell population is not a major contributor to antibacterial immunity: systemic bacterial infection is associated with a rapid decline in eosinophil numbers, mice deficient in eosinophils or eosinophil-regulatory molecules (IL-5, CCR3 and eotaxin-1) appear to manage commensal microbe colonization and exposure to steady-state pathogens, and eosinophils reside in the GI tract of germ-free mice. In this review, we discuss eosinophil bactericidal function and its possible role in eosinophil-related GI diseases such as IBD.

Eosinophil-related Gastrointestinal Diseases

Eosinophil accumulation in the GI tract is a common feature of numerous IgE- and non-IgE-mediated GI disorders including eosinophilic gastroenteritis (EGE) [12], eosinophilic esophagitis (EoE) [13,14], IBD [6] and gastroesophageal reflux disease (GERD) [15,16]. However, the function of eosinophils in GI inflammation is not yet fully delineated. Eosinophils can augment GI antigen-specific immune responses by acting as antigen-presenting cells and can potentiate GI inflammation through the release of cytokines, chemokines and lipid mediators, which can modulate GI adhesion systems, leukocyte trafficking, tissue remodeling and cellular activation states. Finally, eosinophils can serve as major effector cells, inducing tissue damage and dysfunction by releasing toxic granule proteins [17,18]. There is an abundance of clinical and experimental evidence to support a pathogenic role for eosinophils in eosinophilic GI disorders (EGID) such as EoE. However, there is also some evidence, at least in IBD, that eosinophils may have a dual function as both an end stage effector cell and immunoregulatory cell [19–23].

Inflammatory Bowel Diseases

The initial descriptions of eosinophil involvement in IBD occurred in the 1950s [24–27]; however, it was not until the 1960s and 1970s more detailed analyses of eosinophil involvement in IBD disease activity and severity were performed. Bercovitz and Sommers reported a 6-fold increase in eosinophil levels in biopsy specimens in clinically active UC and observed that the increased eosinophil numbers in active UC correlated with necrosis, suggesting a pathogenic role for eosinophils in IBD [28]. This potential role was supported by electron microscopy analyses that revealed ultrastructural evidence of eosinophil activation in patients with established CD [29–31] and by immunohistochemical studies that demonstrated extracellular deposits of eosinophil granule proteins in biopsies of patients with CD or UC [8,32,23]. Measuring the levels of eosinophil granule proteins in fecal matter and in intraluminal segmental perfusion fluid revealed an association between the amounts of extracellular granule proteins and disease relapse in CD patients [33,11,9,34]. Extracellular deposits of eosinophil cationic protein are present in crypt abscesses and in areas with damaged surface epithelium but are decreased in inactive UC [9,23,35]. Elevated levels of eosinophils have been observed in colonic biopsy samples from adult UC and CD patients [36,9,37], and increased numbers of this cell and the eosinophil-derived granular

proteins MBP, ECP, EPO and eosinophil-derived neurotoxin (EDN) have been shown to correlate with morphological changes to the GI tract, disease severity and GI dysfunction in UC [8,36,9–11,38].

While the majority of the early patient-based studies demonstrated that eosinophil infiltration and activation were localized to the diseased areas of the GI tract, suggesting a potential role for eosinophils in the initiation of mucosal injury, there is also evidence to indicate that eosinophils may play an immunomodulatory role [17]. Sarin and colleagues demonstrated that there were increased eosinophil counts in active UC compared with inactive disease or non-UC conditions but that there was no correlation between tissue eosinophil counts and clinical severity of UC [39]. Furthermore, Lampinen and colleagues have reported that the level of activated eosinophils is higher in quiescent UC compared with active UC [23]. The colonic mucosa of patients with quiescent UC is free of crypt distortion or active inflammation [40,41], and the decreased eosinophil degranulation in the presence of heightened eosinophil numbers suggests that eosinophils may play a role in the remodeling/repair of injured epithelium [23]. Consistent with this, in other eosinophil-associated diseases including allergic asthma and EoE, eosinophils are thought to contribute to tissue remodeling and repair [42–45]. Tissue remodeling and fibrotic response is mediated primarily via transforming growth factor (TGF)- β through its integral role in the regulation of the extracellular matrix and epithelial-mesenchymal cell transition and function [46]. Increased levels of TGF- β -positive eosinophils have been identified in allergic asthma and EoE, and the loss of these cells was associated with reversal of tissue fibrosis and remodeling [47,48]. Intestinal fibrosis is also a complication of UC, but the mechanism of the fibrotic response is not yet delineated [49,50]. In a previous study, Lampinen and colleagues found increased levels of CD44^{high} colonic eosinophils in quiescent UC [23]. CD44 can be used as a marker of eosinophil activation [51,52], but it may also be associated with tissue remodeling in the resolution phase of inflammation. CD44 is the receptor for hyaluronic acid, and ligation of hyaluronic acid to CD44 has been demonstrated to induce eosinophil TGF- β production [53]. It is interesting to speculate that eosinophils may contribute to the remodeling/fibrotic response in quiescent UC. Consistent with this possibility, eosinophils have been linked to fibroblast activation, fibrosis and stricture formation in CD [54,55].

Eosinophil Biology

Eosinophils develop in the bone marrow under direction of three main classes of transcription factors, zinc finger (GATA-1), ETS family member (PU.1) and CCAAT/enhancer-binding protein family (C/EBP members) [56–58]. GATA-1 is the most important transcription factor for eosinophil lineage specification as mice with a targeted deletion of the high-affinity GATA-binding site in the GATA-1 promoter lack eosinophils [59]. Three cytokines that are particularly important in regulating eosinophil development, interleukin (IL)-3, IL-5 and granulocyte-macrophage colony-stimulating factor (GM-CSF), bind to receptors that share a common beta chain but have unique alpha chains [17,60]. Notably, IL-5 is the most specific cytokine for eosinophil lineage commitment and is responsible for selective differentiation of eosinophils [61]. Furthermore, IL-5 stimulates release of eosinophils from the bone marrow into the peripheral blood [62]. Eosinophils can be activated through the engagement of receptors for cytokines, immunoglobulins and complement. In response to these stimuli, eosinophils can secrete an array of proinflammatory cytokines (IL-2, IL-4, IL-5, IL-10, IL-12, IL-13, IL-16, IL-18, TGF- α and TGF- β), chemokines (RANTES and eotaxin-1) and lipid mediators (platelet-activating factor and leukotriene C4) [18]. These molecules have profound inflammatory effects, including upregulation of adhesion systems, modulation of cellular trafficking and cellular activation states and activation/regulation of vascular permeability, mucus secretion and smooth

muscle constriction [18,17]. Eosinophils can also play a role in remodeling through expression of TGF- β 1, which drives fibroblast proliferation and extracellular matrix deposition [63]. Eosinophils can also activate the adaptive immune response by acting as antigen-presenting cells. They express MHC class II and costimulatory molecules (CD40, CD28, CD86, B7.1 and B7.2) [64–67] and secrete mediators that can promote lymphocyte proliferation, activation and polarization [64,68–70]. Furthermore, eosinophils can release toxic granule proteins (MBP, ECP, EPO, EDN), which have been shown to cause damage to several tissues including the heart, brain and bronchial epithelium [71–73].

Eosinophils and Innate Immunity

Eosinophils are a component of the innate immune system that, at baseline, resides within mucosal tissues, especially the GI tract. Eosinophils are exquisitely sensitive to their environment with expression of a plethora of receptors important in innate immune responses. For example, eosinophils are equipped to respond to pathogen-associated molecular patterns (PAMPs) as well as DAMPs, suggesting a contributing role in responding to pathogens and damaged tissues that may result from focal infections. Upon activation, eosinophils release preformed and *de novo*-synthesized mediators, including granule proteins, cytokines, chemokines, enzymes and growth factors, which mediate the diverse biologic activity of eosinophils in infection and inflammation.

Pattern Recognition Receptors

Eosinophils have also been shown to express a number of toll-like receptors (TLR) including TLR-1, TLR-2, TLR-4, TLR-5, TLR-6, TLR-7, TLR-8, TLR-9 and TLR-10 [74–76]. The level of TLR expression on the eosinophils is low relative to other granulocytes (e.g. neutrophils) except for relatively elevated levels of TLR-7/TLR-8 [74]. Functional analysis using TLR-specific ligands revealed that TLR-7/TLR-8 ligands (R-848) induced eosinophil activation (superoxide production) and prolonged eosinophil survival [77]. Cytokines, including interferon (IFN)- γ , have been shown to regulate the expression of TLR-7/TLR-8 [74].

Eosinophil Granule Proteins

Eosinophil granules contain a crystalloid core composed of MBP-1 (and MBP-2, and a matrix composed of ECP, EDN and EPO [78]. MBP, ECP and EDN are ribonucleases and have been shown to possess antiviral activity, and ECP causes voltage-insensitive, ion-selective toxic pores in the membranes of target cells, possibly facilitating the entry of other cytotoxic molecules [79–82]. ECP also has a number of additional non-cytotoxic activities including suppression of T cell proliferative responses and of immunoglobulin synthesis by B cells, mast cell degranulation and stimulation of airway mucus secretion and of glycosaminoglycan production by human fibroblasts [83]. MBP has been shown to directly alter smooth muscle contraction responses by dysregulating vagal muscarinic M2 and M3 receptor function and to promote mast cell and basophil degranulation [84–86]. MBP has also been recently implicated in regulating peripheral nerve plasticity [87]. EPO catalyzes the oxidation of pseudohalides (thiocyanate [SCN⁻]), halides (chloride [Cl⁻], bromide [Br⁻], iodide [I⁻]) and nitric oxide metabolites (nitrate and nitrite) to form highly reactive oxygen species (hypohalous acids) and reactive nitrogen metabolites (peroxynitrate) respectively. These molecules oxidize nucleophilic targets on proteins, promoting oxidative stress and subsequent cell death by apoptosis and necrosis [88–90].

Eosinophils and DNA Traps

Neutrophils and macrophages are considered the primary cells involved in combating infection. Neutrophils employ the three primary strategies of phagocytosis, degranulation and formation of neutrophil extracellular traps (NETs) to defend against bacteria. Neutrophils can phagocytose the bacteria and subsequently eliminate the microbe in specialized phagolysosome compartments. Neutrophils can also degranulate, whereby the neutrophil releases antimicrobial molecules including defensins, cathelicidins, myeloperoxidase, BPI and serine proteases (e.g. elastase and cathepsin G) to kill bacteria. Additionally, neutrophils can form NETs, which arise from the release of the neutrophil's nuclear contents (as decondensed chromatin) into the extracellular space to interact with the array of antimicrobial peptides released through neutrophil degranulation [91,92]. Recent studies indicate that eosinophils also have the capacity to release mitochondrial DNA-containing "traps" into the extracellular space [93]. Generation of eosinophil-derived extracellular traps can be stimulated by thymic stromal lymphopoietin TSLP, IL-5 or IFN- γ and by a mechanism dependent upon reactive oxygen species [93,94].

Eosinophils and Infection

Eosinophils predominantly reside at mucosal surfaces colonized by microorganisms, such as the GI and respiratory tract and uterus. Under homeostatic noninflammatory conditions, eosinophils are predominantly localized to GI tract and uterus [17]. There is evidence to support increased numbers of eosinophils during bacterial infection. For example, eosinophil levels in the peripheral blood and rectum of patients afflicted with the diarrheal-inducing pathogen *Shigella* are increased [95]. However, a prominent role for eosinophils in clearing infections remains uncertain as a marked decrease in circulating eosinophils, or eosinopenia, has long been associated with acute bacterial infections in patients [96]. Indeed, eosinopenia has been shown to be a sensitive and reliable marker for distinguishing between non-infectious and infection-associated sepsis in the intensive care unit (ICU) setting [97,98]. Increased margination and recruitment of eosinophils to sites of infection may contribute to the acute decline associated with bacterial infections, but the mechanism for prolonged depletion remains undefined. While peripheral blood eosinophil numbers may rapidly diminish with acute infection, this marked reduction can be accompanied by increased serum levels of the eosinophil granule protein ECP, which suggests eosinophil activation and degranulation [99]. Consistent with this possibility, *in vitro* studies indicate that eosinophils can phagocytose and kill bacteria including *Staphylococcus aureus* and *Escherichia coli*, although not as efficiently as neutrophils [100]. Assessment of the diversity of antibacterial activity of human eosinophils revealed that this cell is responsive to gram-positive and gram-negative bacteria [101]. Gram-positive (*Streptococcus. peroris* and *Clostridium. perfringens*) and gram-negative (*Campylobacter. jejuni* and *Escherichia. coli*) organisms induced eosinophil chemotaxis, respiratory burst and degranulation and release of ECP and MBP [101]. Furthermore, incubation of purified murine eosinophils isolated from IL-5 transgenic mice at multiplicity of infection (MOI) of 10, killed 40% of viable with *Pseudomonas aeruginosa* [102]. Notably, isolated eosinophil cationic granule proteins lead to reduced bacteria colony counts, indicating that the antibacterial properties of eosinophils were mediated in part mediated through the release of cationic proteins. These data are consistent with previous *in vitro* studies demonstrating potent antibacterial properties of MBP, ECP and EPO. Human MBP and ECP killed *Staphylococcus aureus* (502A) and *Escherichia coli* (ML-35) in a time-, concentration-, temperature- and pH-dependent manner [103]. Similarly, incubation of partially purified guinea pig EPO killed *Escherichia. coli* (11775) [104]. The molecular basis of eosinophil granule protein antibacterial activity is not fully delineated. However, both MBP- and ECP-mediated bacterial killing appears to involve bacterial ingestion and permeabilization of the outer membrane [103] [105]

combine. ECP binds to lipopolysaccharides and peptidoglycans with high affinity via its N-terminal region, and it is thought that ECP activates cytoplasmic membrane depolarization of *Staphylococcus aureus* and agglutination and death of *Escherichia coli* through this interaction [106]. However, recent evidence indicates that there are regions within ECP that also possess bactericidal activity independent of membrane association and destabilization [106]. EPO activity is primarily via a EPO-hydrogen peroxide-halide bactericidal system [104]. However, EPO causes oxidative damage in presence of nitrite (NO₂⁻) by inducing protein nitration of tyrosyl residues [89]. While cytotoxic granule proteins are thought to be major contributors to the bactericidal potential of eosinophils, there is evidence that superoxide production via eosinophil-derived NADPH oxidase can also kill bacteria [107]. However, this evidence also suggests that majority of the NADPH-oxidase dependent activity is in conjunction with EPO-hydrogen peroxide-halide bactericidal system [108,107].

***In vivo* Evidence**

While multiple *in vitro* studies have demonstrated antibacterial properties for eosinophils, infection-associated eosinopenia has been well-documented (e.g. in experimental models of *Escherichia coli* pyelonephritis and *Streptococcus pneumoniae* abscesses) [96]. Peripheral eosinophil counts have also been noted to decrease in newborn infants that acquire bacterial infections [109]. In addition, studies of adults admitted to the hospital with blood cultures positive for bacterial growth have shown that the percentage of eosinophils in the peripheral blood smear decreased as the number of bacteria-positive blood cultures per patient increased [110]. Further, eosinopenia has been shown to be a sensitive and reliable marker for distinguishing between non-infectious and infection-associated sepsis in the intensive care unit setting [97,98]. Interestingly, intravenous administration of lipopolysaccharide LPS, i.e. endotoxin, to normal human subjects resulted in a long-lasting depression in blood eosinophil counts, suggesting that exposure to microbial products is sufficient to induce eosinopenia [111].

There have also been recent experimental studies assessing the antibacterial properties of eosinophils *in vivo* in mice [102]. Intraperitoneal challenge of IL-5 transgenic mice, which have a profound peripheral blood and tissue eosinophilia, with *Pseudomonas aeruginosa* leads to increased bacterial clearance compared with wildtype mice. Conversely, mice deficient in eosinophils had impaired clearance of *Pseudomonas aeruginosa*. Notably, adoptive transfer of eosinophils improved bacterial clearance, clearly establishing an eosinophil-specific role in *Pseudomonas aeruginosa* clearance [102]. In conjunction with these findings, the demonstration that administration of eosinophil granule proteins was sufficient to improve bacterial clearance *in vivo* suggests that eosinophil-dependent bactericidal effects are mediated via granule proteins [102].

It is important to appreciate that while eosinophils possess bactericidal properties, there is also evidence that suggests that IL-5 can modulate infection independent of eosinophils. Recently, investigators have demonstrated a role for IL-5 in sepsis. Moreover, employing the polymicrobial sepsis model, investigators demonstrated a link between IL-5 deficiency and increased bacterial burden and mortality during sepsis [112]. Conversely, therapeutic administration of IL-5 improved mortality [112]. Notably, IL-5 transgenic mice backcrossed onto an eosinophil-deficient background had similar mortality rates as eosinophil-competent IL-5 transgenic mice, revealing that IL-5-mediated effects are independent of eosinophils; the IL-5-mediated effects appeared to be related to neutrophil and monocyte function. Human neutrophils and monocytes were shown to express IL-5R α , and IL-5 induced cytokine production and macrophage phagocytosis and survival [112]. *In vitro* and *in vivo* data revealed that IL-5 bactericidal activity was dependent on macrophages [112].

Collectively, these studies indicate that IL-5 and eosinophils possess antibacterial activity but that the IL-5-mediated effects can occur independently of eosinophil function.

Conclusion

The contribution of eosinophils to bacterial infection remains elusive. Eosinophils express the necessary innate immune sensors to detect bacteria and cytolytic granule proteins with effective bactericidal activity. However, the experimental and clinical evidence supporting their role as major contributors of intestinal and systemic antibacterial function is limited. Thus, eosinophils may have alternative roles in intestinal inflammatory diseases that are driven by bacterial antigens. Firstly, eosinophils may be involved in tissue repair and remodeling. Several experimental studies indicate an important role for eosinophil-derived cytokines (e.g. IL-13) in fibrotic responses [113,114,44]. Alternatively, eosinophils may orchestrate the antibacterial inflammatory cascade, recruiting and activating other granulocytes and myeloid cells through cytokines, chemokines and lipid mediators to provide an effective bacterial immunity. A number of GI diseases are associated with intestinal epithelial injury; for these diseases, eosinophils could permit re-epithelization of the intestinal wall via released granule proteins which can facilitate clearance of apoptotic host and foreign cells.

Clinical and experimental studies indicate that eosinophils do contribute to the pathogenesis of IBD; however, it remains unclear whether the host eosinophilic response is directed against infection or is directed to promote tissue repair. Further experimental investigation is required to illuminate the roles of eosinophils in infection and intestinal immunity.

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Abbreviations

CD	Crohn's disease
ECP	eosinophil cationic protein
EDN	eosinophil-derived neurotoxin
EoE	eosinophilic esophagitis
EGE	eosinophilic gastroenteritis
EGID	eosinophilic gastrointestinal disorders
EPO	eosinophil peroxidase
GERD	gastroesophageal reflux disease
GI	gastrointestinal
IBD	inflammatory bowel diseases
MΦ	macrophage
MBP	major basic protein
NETs	neutrophil extracellular traps
TLR	toll-like receptors
UC	ulcerative colitis

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Key Bullet Points

Eosinophils are a common feature of the cellular infiltrate in IBD, and their level has been shown to correlate with morphological changes to the GI tract, disease severity and GI dysfunction.

Eosinophils express toll-like receptors, secrete proteins with antibacterial activity and contribute components to neutrophil extracellular traps (NETs).

Eosinophil numbers diminish with acute bacterial infection.

The contribution of eosinophils to bacterial infection and pathogenesis of IBD remains elusive.