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▣ MINI-REVIEW

Eosinophil-Mediated Tissue Inflammatory Responses in Helminth Infection

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Abstract: Eosinophilic leukocytes function in host protection against parasitic worms. In turn, helminthic parasites harbor specific molecules to evade or paralyze eosinophil-associated host immune responses; these molecules facilitate the migration and survival of parasitic helminths in vivo. This competition between eosinophil and worm leads to stable equilibria between them. An understanding of such dynamic host-eosinophil interactions will help us to uncover mechanisms of cross talk between host and parasite in helminth infection. In this review, we examine recent findings regarding the innate immune responses of eosinophils to helminthic parasites, and discuss the implications of these findings in terms of eosinophil-mediated tissue inflammation in helminth infection.

Key words: Eosinophils, Helminth infection, Tissue inflammation, Host-parasite interaction

INTRODUCTION

Eosinophils, terminally differentiated granulocytic leukocytes that reside primarily in vertebrate mucosal tissues and function in host defense, are involved in the tissue pathogenesis caused by parasitic helminth infection [1]. During parasitic infections, the numbers of peripheral blood eosinophils are highly increased under the influence of Th2 cell-derived IL-5, IL-3 and GM-CSF, and eosinophils are recruited from the circulation into inflamed or damaged tissues by the eosinophil selective chemokine, eotaxin [2]. The recruited eosinophils are primed by interaction with connective tissue matrix proteins such as fibronectin and laminin before being activated by cytokines through receptor-mediated signals. The fully activated eosinophils then liberate histotoxic or helminthotoxic reactive oxygen species and granular proteins [3]. Besides these peripheral effector functions, eosinophils modulate immune responses by releasing cytokines and chemokines [4]. Eosinophils possess a variety of cell surface receptors for cell signaling associated with chemotaxis, adhesion, respiratory burst, degranulation, production of cytokines and chemokines, apoptosis or survival [5], all of which may be closely associated with eosinphil-mediated tissue inflammatory responses in helminth infection. Recent experimental studies have demonstrated that eosinophils can function as antigen-presenting cells (APCs). Eosinphils can process and present a variety of microbial, viral, and parasitic antigens [6].

Although the protective role of tissue eosinophilia against tissue-invasive helminths remains controversial, it is clear that eosinophils contribute to tissue inflammatory responses in helminthic infections. In this review, we summarize eosinophil responses to helminthic parasites and discuss the innate roles of eosinophils in related tissue inflammatory responses.

CARDINAL STRUCTURES OF EOSINOPHILS

Eosinophils are characterized by bilobed nuclei and four main granules [7]. The primary granule is the principal site of Charcot-Leyden Crystal protein (CLC; now identified as galectin-10) production [8]. It is possible that CLC is involved in the interactions between eosinphils and the abundant carbohydrate residues that parasitic worms carry on their surfaces [9]. Cytotoxic granular proteins include major basic protein (MBP), eosinphil cationic protein (ECP), eosinophil peroxidase (EPO), and eosinophil neurotoxin (EDN), all of which reside within the crystalloid secondary granule along with a number of cytokines. Eosinophil lipid bodies (LB) contain 5-lipooxygenase, cyclooxygenase, leukotreine C_4 (LTC_4) synthase, and arachidonic acid (AA) for lipid mediator biosynthesis, as well as small granules that store proteins such as arylsulfase B and acid phosphatases.

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EOSINOPHILIA IN HELMINTH INFECTION

Eosinophils originate from $CD34^+$ cells in the bone marrow expressing the IL-5Rα-chain, regulated by the transcription factors GATA-1, GATA-2, and c/EBP [5]. With the help of IL-5, adhesion molecules, and eotaxin-1, eosinophils relocate into the peripheral circulation and travel to specific tissues, predominantly the gastrointestinal (GI) tract, thymus, and mammary glands, where eotaxin-1 is constitutively expressed [5]. The elevation of eosinophil levels in the peripheral circulation and tissues is observed in a wide variety of diseases including diseases of infectious, allergic, neoplastic, and idiopathic origins [10]. Parasitic helminth infections are the most common cause of persistent eosinophilia. Infections by helminths with life cycles that include tissue migratory phases, including trichinosis, ascariasis, filariasis, and paragonimiasis, induce sustained elevated eosinophilia in host blood and tissues. In contrast, sustained eosinophila is usually absent when hosts are infected by parasites that dwell outside the tissues, such as intralumen- (e.g., adult tapeworm), or intracyst- (e.g., *Echinococcus* spp.) dwelling species [10].

EOSINOPHIL TRAFFICKING AND HELMINTHIC PARASITES

It is evident that helminth-induced eosinophilia is accompanied by a profound change in the production of key regulatory cytokines (IL-5, IL-3, GM-CSF) and chemokine (eotaxin) [11]. *Trichinella spiralis* infection induces eosinophil recruitment to infected tissues that is dependent upon eotaxin-1 and -2 [12]. The eosinophils recruited into worm-infected tissues are further activated by various inflammatory stimuli, which may contribute to related eosinophil-mediated tissue inflammatory responses.

It was recently reported that serum levels of eotaxin are increased in human strongyloidiasis [13]. The numbers of positive cells expressing CCR3 receptors for eotaxin are increased during helminth infection [14]. Furthermore, helminths themselves secrete eosinophil-specific chemokinetic molecules showing galectin-like activity [15]. Mammalian galectin-9 is a potent eosinophil chemoattractant [16], and galectin-3 also plays a supporting role in eosinophil trafficking [17]. These results suggest that eosinophils respond to and are activated by worm-secreted factors mimicking mammalian galectin-9, which may amplify eosinophil trafficking to worm-infected tissues. This leads us to hypothesize that eosinophils are well-equipped innate immune cells capable of countering the attempts of parasitic worms to evade host immune responses.

DEGRANULATION AND HELMINTHIC PARASITES

The release of secondary granule proteins such as MBP, ECP, EPO, and EDN may directly damage tissues or infectious worms [5,18]. Immunological stimuli, including sIgA, IgG, C5a, PAF, IL-5, IL-3, and GM-CSF can induce eosinophil degranulation [3]. However, the role of IgE in eosinophil degranulation remains controversial [19,20]. A recent report has shown that eosinophils from allergic donors express approximately 0.5% of the FcεRI that basophils express, and that eosinophils stimulated with human IgE or anti-human IgE do not exhibit effector functions such as production of leukotriene C_4 or superoxide anion, or degranulation [20]. This suggests that helminth-induced IgE production is not critical for eosinphil degranulation, although degranulated eosinophils are frequently observed in the vicinity of damaged parasites in vivo.

There are three modes of eosinophil degranulation, including compound exocytosis, piecemeal degranulation, and cytolytic degranulation (necrosis) [7]. The release of granular proteins via compound exocytosis results from multiple fusions of granules in eosinophils with normal plasma membrane. PAF, which signals via the G-protein coupled receptor (GPCR), is the best-known stimulus for compound exocytosis. IL-5 can induce piecemeal degranulation, which is characterized by emptied secondary granules resulting from the slow leakage of granular proteins. Lastly, degranulation can occur by cytolytic mechanisms as a result of cell death. Recent reports have demonstrated that human eosinphils degranulate in response to helminth-derived excretory-secretory products (ESP) [21]. In particular, 27-kDa cysteine protease in the ESP secreted by newly excysted *Paragonimus westermani* metacercariae (PwNEM) induces EDN release from human eosinophils isolated from peripheral blood [22], whereas PwNEM-secreted 28-kDa cysteine protease did not induce eosinophil degranulation. In addition to their direct toxic effects on worms and tissues, granular proteins have been shown to regulate tissue inflammation by activating various immune cells. For example, MBP has been demonstrated to promote degranulation from mast cells via IgE-independent mechanisms, superoxide anion production, or release of IL-8 and lipid mediators including LTC_4 and $PGF2\alpha$ from eosinophils, neutrophils, and epithelial cells [23]. These results suggest that release of granular proteins from eosinophils in response to specific proteas-

es secreted by helminths play a role in eosinophil-mediated tissue inflammatory responses during tissue invasion by parasitic worms.

NADPH OXIDASE-DERIVED ROS AND HELMINTHIC PARASITES

In addition to toxic granule proteins such as ECP, MBP, and EDN, reactive oxygen species (ROS) are toxic compounds released by eosinophils. They are generated by the NOX family (NOX2) of NADPH oxidase [24], which can be stimulated by PMA, IL-3, IL-5, GM-CSF, C5a, PAF, and eotaxin [3]. It is interesting to note that the capacity of human eosinophils to produce and release ROS such as superoxide anions (O_2^-) is approximately tenfold higher than the capacity of neutrophils [25]. Recent reports have shown that human eosinophils can produce superoxide anions in response to helminth-derived cysteine proteases such as 27-kDa cysteine protease [22]. Besides the cytotoxic role of ROS, they also participate in inflammatory responses mediated by T cells and eosinophils [26,27]. These results suggest that ROS production by eosinophils stimulated by helminth-derived secretory products may contribute to eosinophil-mediated tissue inflammation in helminthic infection.

RELEASE OF LIPID MEDIATORS AND HELMINTHIC PARASITES

Human eosinophils isolated from peripheral blood produce both eicosanoids and PAF. The major eicosanoid produced by eosinophils is leukotriene C_4 (LTC_4), which is rapidly converted to LTD_4 and LTE_4 in the extracellular environment [28]. LTC_4, LTD_4, and LTE_4 are collectively referred to as cysteinyl leukotrienes. These molecules contribute to the constriction of bronchi and increase airway responsiveness, vascular permeability, and mucus secretion in the airways of bronchial asthmatic patients.

In *Nippostrongylus brasiliensis*-infected mice, elevation in PAF synthesis is correlated with significant elevation in histologically detectable eosinophils in the jejunum [29]. Human eosinophils secrete LTC_4 after adhering to IgG- or IgE-coated schistosomules of *Schistosoma mansoni* [30]. A recent report suggests that leukotrienes play a protective role in controlling parasite burden in murine strongyloidiasis [31]. However, there is no available information regarding whether eosinophils can be activated to release lipid mediators such as LTC_4 or prostaglandin (PG) when directly stimulated by worm-derived secretions or products. Recently, there has been intriguing evidence that various parasites secrete lipid mediators to communicate with host immune cells [32]. In particular, eosinophils possess well-equipped cells bearing receptors for lipid mediators [33]. Therefore, further studies of the role of helminth-secreted lipid mediators on eosinophil-mediated tissue inflammation are warranted.

PRODUCTION OF CYTOKINES AND HELMINTHIC PARASITES

Human eosinophils produce cytokines, chemokines, and growth factors [5]. For example, cytokines include IL-1α, IL-2, IL-3, IL-4, IL-5, IL-6, IL-9, IL-11, IL-12, IL-13, IL-16, IL-17, leukemia inhibitory factor, interferon-γ, tumor necrosis factor α (TNF-α, and GM-CSF. A variety of chemokines including epithelial cell-derived neutrophil activation peptide (ENA-78/CXCL5), eotaxin, growth-related oncogene (GROα/CXCL1), IL-8, IFN-γ-inducible protein (IP-10/CXCL10), IFN-inducible T-cell α chemoattractant (I-TAC/CXCL11), macrophage inflammation protein 1α (MIP-1α), monocyte chemoattractant protein 1 (MCP-1/CCL3), MCP-3 (CCL7), MCP-4 (CCL13), and RANTES (CCL5) are generated by eosinphils. Eosinophils produce growth factors such as heparin-binding epidermal growth factor-like binding protein (HB-EGF-LBP), nerve growth factor (NGF), platelet-derived growth factor (PDGF), stem cell factor, transforming growth factor α (TGF-α) and TGF-β1. Among secreted proteins, IL-2, IL-4, IL-5, IL-6, TNF-α, GM-CSF, eotaxin, RANTES and TFG-α are stored as preformed mediators within eosinophil crystalloid granules [34]. It is interesting to note that eosinophils express two pro-inflammatory cytokines, IL-12 and IFN-γ, which serve to down-regulate allergic inflammation [5]. Indeed, IL-12 has been shown to inhibit allergen-induced Th2 cytokine responses [35] and eosinophil degranulation [36]. These results suggest that eosinophils may have the ability to release cytokines or chemokines for regulation of eosinophil-mediated tissue inflammation in helminth infection.

Recent studies have demonstrated that helminthic parasites can regulate immune responses via the production of cytokines. For example, infection with *Fasciola hepatica* has been demonstrated to attenuate autoimmunity via TGF-β-mediated immune suppression of Th17 and Th1 responses [37]. In addition, Th2 cell-derived IL-4 production facilitates eosinophil and lymphocyte recruitment and Th2 cytokine production associated with *N. brasiliensis* infections [38]. Infection with *Strongyloides stercoralis* induces enhanced serum levels of eotaxin and IL-5 [13].

However, information regarding cytokine production by eosinophils in response to helminthic parasites is limited. Recently, we have shown that *P. westermani*-secreted products directly stimulate human eosinophils to produce GM-CSF [39] and IL-8 [40]. GM-CSF plays an important role in maintaining the viability and inducing the effector function of eosinophils [3,41]. In addition, IL-8 is a highly potent chemotactic cytokine for eosinophils as well as neutrophils [42]. It is of particular that that lower, but not higher concentrations of ESP secreted by PwNEM exhibit strong stimulatory effects on the production of GM-CSF and IL-8 by human eosinophils [39,40]. The stimulatory effect of the ESP on autocrine production of GM-CSF is nicely matched with enhanced longevity of eosinophils [39]. These results suggest that eosinophils may be actively responded to the light infection of the worms to release cytokines or chemokines associated with induction of eosinophil-mediated tissue inflammation, which might pain the worms to lose their original way to final destination. In contrast, eosinophils seem to be passively responded in response to the heavy infection to silence eosinophil's responses which might be favorable for host to block the severe tissue damage. In our previous study [39], we also found an interesting result that pretreatment of high concentrations of the ESP secreted by PwNEM with heat at 100℃ for 5 min showed a pro-survival effect on eosinophils [39]. This suggests that eosinophils may be directly activated by heat-resistant molecules secreted by helminthic parasites to release cytokines and chemokines, which in turn may play a role in promoting eosinophil-mediated tissue inflammatory responses during helminth infection. Further studies on this issue are required.

APOPTOSIS AND HELMINTHIC PARASITES

The life span of eosinophils may be prolonged in the presence of IL-5 GM-CSF, IL-3 [41], IL-9 [43], IL-13 [44], IL-33 [45], lipid mediators such as PGE_2 [46], and microbial-derived lipopolysaccharides (LPS) [47]. In contrast, eosinophils undergo spontaneous death through apoptosis within four days without the presence of eosinophil active cytokines in vitro. In order to assess the innate role of eosinophils in helminth infection, recent studies have focused on the direct effects of helminth-secreted products on the viability of human eosinophils. It has been demonstrated that *P. westermani*- or *F. hepatica*-secreted ESP induces apoptosis of eosinophils in a caspase-dependent manner [48,49]. Moreover, *F. hepatica*-derived ESP has been reported to cause mitochondrial-membrane depolarization of eosinophils leading to the release of cytochrome c, and also induced intracellular ROS generation, which preceded mitochondrial injury for apoptosis [50]. Since most apoptotic tissue eosinophils progress to the pro-inflammatory cellular fate of secondary necrosis [51], it is possible that eosinophil apoptosis induced by helminth-derived ESP may cause severe tissue inflammation that helps to combat infectious worms. *P. westermani*-secreted ESP has also death effect on eosinophils stimulated with pro-survival cytokines including GM-CSF, IL-5 and IL-3 [48]. The pro-death effect the ESP was completely abolished by heat treatment. These results suggest that heat labile factors contained in the helminth-derived ESP can induce eosinophil apoptosis, which may be closely associated with orchestration of eosinophil-mediated tissue inflammation for host defense against tissue migratory helminthic worms. Further studies are necessary to determine what factors secreted by helminthic worms and how trigger the pro-apoptotic signals associated with eosinophil death.

MECHANISMS THAT HELMINTHIC PARASITES USE TO EVADE EOSINPHIL-MEDIATED HELMINTHOTOXICITY

Helminth-derived products harbor specific components leading to the down-regulation of eosinophil- or mast cell-associated allergic responses. This allows parasitic worms to evade host immune responses. For example, the immunization of proteins from adult *Toxascaris leonine* inhibits allergic specific Th2 response [52]. *Anisakis simplex*-derived peptide has also been found to inhibit eosinophil-mediated inflammatory responses in the airways in ovalbumin-induced bronchial asthmatic mice [53]. *Heligmosomoides polygyrus* infection down-regulates eotaxin concentrations and CCR3 expression in lung eosinophils in a allergic pulmonary inflammation mouse model [54].

Recent reports have suggested that helminthic worms themselves secrete specific molecules to interfere with eosinophil-mediated tissue inflammatory responses during helminth infection. For example, *Toxocara canis* larval excretory/secretory proteins impair the eosinophil-dependent resistance of mice to *N. brasiliensis* [55]. *P. westermani*-derived proteases attenuate the effector functions of eosinphils triggered by IgG [56]. Cathepsin L proteinase secreted by *F. hepatica* prevents antibody-mediated eosinophil attachment to newly excysted juveniles in vitro [57]. Moreover, eosinophil selective chemokine eotaxin has been re-

ported to be specifically cleaved by hookworm metalloproteases, which block the chemotactic effects on eosinophils in vitro and in vivo [58]. Furthermore, it is interesting to note that filarial nematode-secreted products inhibit IgE-mediated mast cell responses [59], considering the fact that there are immunological interactions between human eosinophils and mast cells [60]. These results suggest that tissue-migratory helminthic parasite-secreted products might contribute to reduction of eosinophil-mediated tissue inflammation, which provides an immunological milieu for the worms to complete their long journey during the tissue-migratory phase in vivo.

CONCLUSION

Eosinophils are end-stage cells that reside in mucosal tissues and function in host defense against helminth infection. Recent studies regarding immunological interactions between eosinophils and helminthic parasites have made important advances in understanding the innate role of eosinophils in controlling eosinophil-associated tissue inflammation involved in infection by tissue migratory helminthic parasites. In this review, we emphasize two points. The first is that eosinophils are well-equipped immune cells that directly recognize helminth-derived immunomodulating agents and mount tissue inflammatory responses for host defense. The second is that tissue-migratory helminthic worms have evolved to attenuate eosinophil-mediated tissue inflammatory responses for their survival in hosts. Future studies regarding the signaling mechanisms of cross talk between hosts and parasitic worms are warranted. Furthermore, deeper investigation to elucidate the role of galectin-10, which is expressed on the surface of eosinophils, in host defense against helminthic parasites is recommended.

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