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Eosinophils: Nemeses of Pulmonary Pathogens?

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Abstract

Purpose of Review: Eosinophils are short-lived granulocytes that contain a variety of proteins and lipids traditionally associated with host defense against parasites. The primary goal of this review is to examine more recent evidence that challenged this outdated role of eosinophils in the context of pulmonary infections with helminths, viruses, and bacteria.

Recent Findings: While eosinophil mechanisms that counter parasites, viruses and bacteria are similar, the kinetics and impact may differ by pathogen type. Major antiparasitic responses include direct killing, immunoregulation, as well as some mechanisms by which parasite survival/growth is supported. Antiviral defenses may be as unembellished as granule protein-induced direct killing or more urbane as serving as a conduit for better adaptive immune responses to the invading virus. Although sacrificial, eosinophil DNA emitted in response to bacteria help trap bacteria to limit dissemination. Herein, we discuss the current research redefining eosinophils as multifunctional cells that are active participants in the host defense against lung pathogens.

Summary: Eosinophils recognize and differentially respond to invading pathogens, allowing them to deploy innate defense mechanisms to contain and clear the infection, or modulate the immune response. Modern technology and animal models have unraveled hitherto unknown capabilities of this surreptitious cell that indubitably has more functions awaiting discovery.

Keywords

helminth; virus; bacteria

Introduction

Eosinophils are granulocytes derived from $CD34^+$ pluripotent hematopoietic stem cells in the bone marrow and belong to the innate branch of the immune system. While sharing some phenotypic and functional similarities with other members of the granulocyte family, eosinophils maintain their individualilty by their granule structure and contents, and the sophisticated means by which they are released. Although previously described by other investigators, Paul Ehrlich is credited for the identification and appellation of eosinophils in

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1879 based on their unique staining properties from eosin uptake by granules [1]. Eosinophils have been evolutionarily preserved across organisms; invertebrates like annelids, insects, and crabs, contain eosinophil-like cells, while vertebrates including fish, reptiles and even lampreys have cells that are morphologically similar to the classical mammalian eosinophils [2, 3].

Eosinophils are regarded as terminally differentiated cells that reside in mucosal tissues. Pluripotent $CD34^{+}$ stem cells commit to the myeloid lineage through expression of GATA-1, PU.1, and c/EBP transcription factors and develop into mature eosinophils when stimulated with IL-3, GM-CSF, and IL-5 [4]. Their presence in the bone marrow may help sustain plasma B cell populations long-term, thereby contributing to overall humoral memory especially to vaccines [5, 6]. Once released into the blood stream, eosinophils migrate to the thymus, mammary glands, gastrointestinal tract, and the uterus, where they may function in organ development and remodeling during homeostasis and disease [7, 8]. Resting eosinophils are maintained in the bone marrow, blood, and spleen [9]. Chemokines (primarily eotaxins) as well as IL-5 released in response to stimuli, signal eosinopoiesis and emigration to the trigger site where their survival depends on microenvironmental availability of growth factors, especially IL-5 [4, 10].

Despite the wealth of information garnered over the past 140 years resulting in 46,250 articles (at the time of writing) on PubMed dating back to 1911, the exact biophysical function of eosinophils and the reason for their evolutionary conservation remains unclear. Eosinophil deficiency in humans and mice appears to have no impact [8, 11], and yet, eosinophils and their products are generally considered injurious agents during allergic asthma [12, 13]. Their presence in stimulated tissues appears to be the focus point for investigation into their functions and contribution to disease. The structural composition of eosinophil granules is unique with an electron dense core mainly consisting of major basic protein (MBP) and an electron lucent matrix, containing other eosinophil-specific cationic proteins (high affinity for acidic dyes) in addition to a variety of cytokines, demarcated by a trilaminar membrane [14, 15]. Functions of eosinophil cationic proteins range from affecting mitogenic and motogenic properties of other cells, to inducing tissue injury and promoting repair [7, 16]. Lipid bodies in the cytoplasm permit additional functions for eosinophils as regulators of lipid metabolism and eicosanoid production sites [17, 18]. The number of lipid bodies contained in eosinophils increases with inflammation [18] further emphasizing the dynamic and responsive nature of these cells.

Largely owing to their presence in the targeted tissues, eosinophils are deemed to be detrimental in diseases like allergic asthma. Reducing the number of circulating eosinophils through anti-IL-5/IL-5R antibodies (mepolizumab, reslizumab, and benralizumab) in patients with severe asthma correlates with reduced asthma exacerbations, however, this effect is also noted in non-eosinophilic asthmatics [19]. Given that asthma inflammation is rich in leukocytes both in variety and abundance, it is difficult to ascertain cells that are causative from those that are recruited but have spectator impacts. Since a number of other leukocytes are responsive to IL-5 (B cells [20], mast cells [21], basophils [22]), alleviation of symptoms with anti-IL-5 therapies may be due to a variety of other factors that influence asthma inflammation and a definite tissue-destructive role for eosinophils may not be

assigned. Similarly, their abundance in tissues hosting parasites led to the notion that anti-helminth immunity was the *raison d'être* for eosinophils. The LIAR (local immunity and/or remodeling/repair) hypothesis [3] suggests instead that eosinophils are recruited to locales of tissue damage where they engage in contributory effector functions at the inflammatory foci together with other cells to regain tissue homeostasis. The multitude of mediators contained within [23] basically makes this cell a miniature immune system capable of a broad range of functions [7, 8, 10, 23] which underscores their importance to host immunity (Figure 1).

Akin to other organ systems, the respiratory system performs secondary functions such as host defense, acid balance, optimizing cardiac output, and filtration [24–26]. Mainly owing to the large surface area and vasculature for their primary function of gas exchange, the lungs are incessantly at risk for pathogen infections. In addition to mucosal defenses that include antimicrobial peptides, muco-ciliary escalator, surfactants, and the physical barrier that the airway lining provides, resident cells of the pulmonary system like macrophages engage in routine antigen clearance to prevent infection and maintain lung homeostasis. Recently, lung resident eosinophils were identified to perform a similar function [27]. While best known functions of eosinophils have been delineated in pulmonary disease triggered by allergens and parasites, eosinophil responses to respiratory viruses and bacteria are now being rapidly elucidated. Readers are referred to a number of excellent reviews that discuss eosinophil responses to allergens [28, 29] and their potential role in asthma [13, 30, 31]. The purpose of this article is to provide a compendium of the literature that focuses on the functions of eosinophils during pulmonary stages of parasite infections as well as during viral and bacterial infections of the lungs.

Eosinophils and Worms: In Sickness and in Health

Helminths are now considered "old world" pathogens because morbidities associated with them only affect small fraction (albeit hundreds of millions) of the world's population at present [32]. However, helminths are likely an important aspect of the "old friends" hypothesis suggesting that their elimination in the human host may have led to an increase in aberrant diseases like asthma. Nematodes, trematodes, and cestodes have lung migration and/or dwelling phases in their life cycles that can trigger inflammation with an eosinophil predominance in the blood and tissue that occurs within hours to days after infection [33, 34].

Defense against extracellular multicellular organisms generally involves humoral and cellular components of innate and adaptive immunity, as phagocytosis may not be feasible due to size. Eosinophil granule proteins, MBP, eosinophil peroxidase (EPO), and eosinophil cationic protein (ECP) are all cytotoxic to parasites [16], and eosinophils rapidly aggregate around helminths killing them within minutes [35] as a display of their lethality. The immunoregulatory roles played by MBP and EPO during parasite infection is evident in studies that have utilized mice deficient in these proteins [36]. Both MBP and EPO deficient mice have increased worm burden and size, and altered macrophage and T cell functions in response to nematode infection [37]. Additionally, eosinophil derived neurotoxin (EDN) is an alarmin that promotes dendritic cell (DC) polarization toward T_H2 [38] thereby setting the stage for a T_H2 immune response during helminth infections. Other eosinophil secretory

products such as IL-4, IL-5, TGF-β may accompany granule proteins during eosinophil degranulation to regulate the landscape surrounding helminths during lung infection [7, 39, 40].

While fully capable of killing helminths directly, it is unclear whether eosinophils perform this action *in vivo* [39]. Studies utilizing eosinophil deficient mice show little [36, 41] to no [39, 42] benefit during helminth infection suggesting that eosinophil responses to parasites may be situational and redundant [43]. Furthermore, eosinophils are necessary for the survival of *Trichinella spiralis* in mouse skeletal muscles [42], with enhanced recruitment of neutrophils observed in their absence resulting in nitric oxide mediated killing of the parasite, and reduced numbers of IL-4 producing $CD4^+$ T cells [44]. Since T cells are incapable of directly killing these large extracellular multicellular organisms, it is speculated that T cells orchestrate parasite damage through disabling, degrading, and dislodging effects [40] of which eosinophils are particularly useful for degrading effects which destroy parasite integrity. Anti-helminth properties of eosinophils may be redefined as more sophisticated functions of eosinophils are identified. It is possible that eosinophils are recruited to the lungs during parasite infections as an effector cell to directly harm the parasite as well as an immunomodulatory cell to enhance cell-cell crosstalk at the infection site to expel the parasite and promote wound repair mechanisms or temporally safeguard the parasite to maintain a ‘healthy’ antigen burden in the tissue to help reduce allergies (Figure 2).

When Eosinophils Meet Viruses

Common respiratory viruses such as respiratory syncytial virus (RSV), rhinovirus (RV), and influenza A virus (IAV) annually infect millions worldwide and cause severe morbidity and mortality incurring a significant economic burden to society. Infection of the respiratory epithelia triggers the release of cytokines and chemokines that may inadvertently incur eosinophil recruitment to the lungs. Additionally, eosinophils can be recruited to the airways during chronic lung conditions, where they may encounter invading respiratory pathogens. Allergic asthma is often characterized by the presence of eosinophils in the peribronchovascular areas of the lungs, in sputum, and in the blood, although it should be noted that not all asthmatics have eosinophilia [45] and severe asthma can develop even in eosinophil deficient patients [11]. Virus-induced wheezing seems to predispose children to asthma later in life [46–48], and although correlation does not necessarily intimate causation, this observation led to the hypothesis that early virus exposure preconditions the lungs to subsequent reactions to environmental agents. Conversely, the presence of eosinophils in the allergic airways may alter host responses to virus infections. As such, investigating the function of eosinophils during respiratory infections is of benefit. Eosinophils undergo piecemeal degranulation in response to IAV [49], and RSV [50], although the kinetics and dynamics of granule protein release has not been determined. Once released, granule proteins may directly impact viral infectivity/load, or influence resident leukocytes (dendritic cells, neutrophils [51] and macrophages [52]) and the epithelial cells [53] to indirectly hinder virus dissemination. While it is accepted that eosinophil granule proteins are released in response to viruses, the mechanisms by which they reduce viral infectivity or impact viral pathogenesis is still unclear.

Perhaps the most attention drawn to eosinophils in the context of viruses arose during the unfortunate first RSV vaccine trial in which infants that received the formalin inactivated virus had more severe disease when naturally infected and vaccinated children that died had heightened eosinophilia in the lungs [54]. Herein, eosinophil recruitment and degranulation were thought to have contributed to sustained inflammation and tissue damage that aggravated virus-associated pathophysiology [55]. Formalin-inactivated RSV vaccinated monkeys were demonstrated to have elevated T_H2 responses with eosinophilia and severe disease after virus challenge [56]. Although similar findings have been reported in murine models of RSV, the function of eosinophils in the tissue during the infection is unclear [57]. Domachowske *et al*. demonstrated *in vitro* that eosinophils reduce RSV infectivity in a dose-dependent manner [58]. Since then, many others have reported the antiviral role of eosinophils against respiratory virus infection, although it appears that the mechanisms employed by eosinophils for antiviral immunity varies by virus family.

Eosinophils have been showcased as active contributors to innate immunity against virus infection rather than bystanders [55, 59, 60]. Their recruitment kinetics into the virus-infected tissue suggests that they may be required for tissue healing [61, 62], although it has not been specifically investigated. Indeed, eosinophils are capable of responding to rhinovirus [63], RSV [64], pneumonia virus of mice [65], IAV [49], and parainfluenza virus [66]. The arsenal of immune regulators within eosinophils allow these cells to act directly or indirectly in response to respiratory viruses. Eosinophil granule proteins have clear antiviral functions wherein virus infectivity is reduced in the presence of ECP, eosinophil derived neurotoxin (EDN), and EPO [58, 67]. While MBP has been demonstrated to induce cytopathology in epithelial cells [68], it is unclear whether MBP plays a direct antiviral role against respiratory viruses. In our hands, recombinant MBP does not affect IAV infectivity (unpublished data). Eosinophil degranulation and products thereof have been reported in RSV patients [55, 69] thereby providing a clinical justification to investigate pathways of eosinophil recruitment, activation, and functions during respiratory virus infections.

Eosinophils also use other components in their arsenal in defense against viruses. Nitric oxide (NO), a free radical gas produced by nitric oxide synthase (NOS) using L-arginine, is a mediator of numerous biological functions including neurotransmission, vasodilation, inflammation, immune regulation and host defense [70]. Eosinophils generate NO [71] that reacts with superoxide anion (O_2-) to form peroxynitrite (ONOO-) which functions as a cytotoxic compound. Eosinophil-derived NO can mediate antiviral responses to parainfluenza virus [66] and RSV [72] through viral load reduction. Interestingly, NO synthesis by eosinophils is dependent on interferon responses during virus infection [66]. As producers of a variety of cytokines, eosinophils themselves may contribute to the local cytokine milieu during virus infections as we have found them to release IFNγ in response to IAV [49]. Therefore, maintaining the intricate balance between T_H1 and T_H2 immune responses supports antiviral immunity.

More targeted immune responses through cellular and humoral immunity are required to fully clear virus, stop ongoing inflammation, and regain homeostasis. Specific antigen presentation and co-stimulation are required to activate T cells to initiate the adaptive immune cascade. Ovalbumin-pulsed eosinophils transferred intratracheally, migrate to the

draining lymph nodes and present peptide to trigger ovalbumin-specific T cell activation in mice [73–76] showcasing their ability to moonlight as antigen presenting cells. In the context of IAV and other virus infections, effective viral clearance largely depends on $CD8^+$ T cell activation [77–79]. Our studies established that eosinophils upregulate MHCI and CD86 in response to IAV, are found in the T cell zones when transferred into infected mice, engage in direct interaction with $CD8^+$ T cells, and promote the recruitment of virus-specific $CD8^+$ T cells into the lungs to enhance antiviral immunity in the host [49]. It is still unclear how eosinophils obtain viral peptides for presentation, and while our work suggests that antigen availability may be due to susceptibility to infection [49], it may also be possible that eosinophils obtain viral antigen from the environment through phagocytosis, a function which they are capable of [80]. Rather than being activated directly by virus binding/sensing, eosinophil responses to respiratory viruses may be governed by other leukocytes. It has been reported that human eosinophils degranulate in response to RSV, RV or parainfluenza virus only in the presence of $CD4^+$ T cells and DCs [81].

Eosinophils may tailor their antiviral responses to virus type, and multiple mechanisms may partake independently, or in combination (Figure 2). Granule proteins are clearly virucidal *in vitro* against a variety of viruses, however, it is still unclear if such a function occurs or is important *in vivo* during an active infection. Since piecemeal degranulation occurs in response to viruses, it is necessary to determine the kinetics and sequence of granule contents that are released in response to each type of virus. If eosinophils do indeed function as putative antigen presenters to elevate T cell responses, it is important to determine the antigen processing and presentation processes within these cells.

Eosinophils Trap Bacteria

Although eosinophils have been historically implicated in allergy and helminth infection, they also possess the ability to recognize, ingest and kill bacteria [82, 83]. The importance of eosinophils in host defense against bacteria has been demonstrated *in vivo*. Transgenic mice overexpressing IL-5 subjected to cecal ligation puncture or infected intraperitoneally with *Pseudomonas aeruginosa,* show prolonged survival compared to control mice without eosinophilia [84, 85]. Conversely, there is higher outgrowth of *P. aeruginosa* following intraperitoneal infection of eosinophil-deficient PHIL mice than wild-type mice, a phenotype that is rescued by the adoptive transfer of eosinophils prior to infection [84]. Although eosinophils are phagocytic, both uptake and intracellular killing of bacteria are significantly lower than for other phagocytes [82, 86, 87]. Therefore, it is likely that the contribution of eosinophils during bacterial infection is related to their potent killing of extracellular bacteria by mechanisms such as released antimicrobial granule proteins and generation of extracellular DNA traps.

Eosinophil granule proteins, in particular the cationic proteins, have been ascribed antimicrobial properties since the 1970s, and treatment of mice with purified granule proteins significantly reduces *P. aeruginosa* burden *in vivo* [84]. Following interaction with specific triggers, eosinophils can generate an extracellular web of either mitochondrial [85] or nuclear [88] DNA that can physically trap pathogens and act as a scaffold for granule proteins such as MBP and ECP [85, 89]. Of significance, the generation of nuclear DNA

nets occurs during a specific cytolytic process termed ‘eosinophil extracellular trap cell death’ (EETosis) [88], whereas cells that extrude mitochondrial DNA retain viability [85, 90]. In addition to granule proteins, intact eosinophil granules can also be enmeshed in the extracellular DNA traps, some of which are able to respond to cytokines and secrete their contents within the tissue [88]. It is likely that by facilitating the co-localization of bacteria and antimicrobial granule proteins, eosinophil extracellular DNA traps provide a mechanism to optimize bacterial killing while limiting non-specific damage to surrounding tissue.

Many cationic proteins and peptides have been implicated in bacterial defense due to their innate affinity to negatively charged lipid membranes, and similarly EPO, MBP and ECP have defined antibacterial functions. In 1978, Migler *et al*. reported that a lysate of eosinophils enriched from a patient with eosinophilia possessed potent bactericidal activity against *Staphylococcus aureus* and *Escherichia coli* when combined with hydrogen peroxide and a halide, which they attributed to the heme peroxidase EPO [91]. Jong *et al*. (1980) later confirmed this assumption by reproducing the *E. coli* killing using purified guinea pig EPO [92]. Human EPO is also bactericidal against *Mycobacterium tuberculosis;* interestingly, killing can occur in the absence of exogenous hydrogen peroxide, albeit at a slower rate than when hydrogen peroxide is supplemented [93]. Although rapid bacterial killing is observed *in vitro*, *Epx* null mice with *Alternaria alternata*-induced eosinophilia cleared *Haemophilus influenzae* from the airways equally as well as wildtype mice, despite having fewer recruited eosinophils, and eosinophils that were present were less likely to express TLR4 [94]. This disparity between the *in vitro* and *in vivo* findings needs to be clarified with further studies. Following its release in response to pathogen sensing, MBP, which exists as an inert nanocrystal within mature eosinophil granules, is converted to a cytotoxic entity by granule acidification and the subsequent formation of extracellular amyloids [16]. Protein aggregation is crucial to the bactericidal activity of MBP, and disruption of amyloid formation significantly reduces its ability to kill *E. coli* [95]. Similarly, ECP also forms amyloid-like aggregates [96, 97], and has bactericidal activity against both Gram-positive and -negative bacteria [98]. Human ECP has a high affinity for both peptidoglycan, highly expressed in the cell wall of Gram-positive bacteria, and lipopolysaccharide (LPS), a constituent of the outer membrane of Gram-negative bacteria [99]. While ECP binding to peptidoglycan does not trigger autolysis or result in visible cell damage of Gram-positive bacteria, ECP causes considerable depolarization of the outer membrane and promotes bacteria agglutination in Gram-negative bacteria [99]. Both non-aggregating ECP mutants and *E. coli* LPS truncation mutants reduce bacterial agglutination and killing [97, 100] suggesting that, following the recognition of LPS by ECP, the formation of amyloid-like aggregates on the surface of Gram-negative bacteria cause the disruption of the lipid bilayer. Although EDN shares 89% cDNA sequence homology with ECP [101] and has reported antiviral activity [102], it has not been reported to directly kill bacteria. Instead, EDN augments bacterial clearance by recruiting and activating dendritic cells [103, 104].

The release of granule proteins in response to bacterial stimuli is surprisingly discriminatory, with some bacteria stimulating global degranulation, while others promote the selective release of granule components by piecemeal degranulation [105]. *In vitro* studies indicate that ECP is secreted by human eosinophils predominantly in response to Gram-negative bacteria, whereas EPO and MBP are released following exposure to a selection of both

Gram-negative and -positive bacteria [106]. EDN is released upon stimulation with heat-killed *Clostridium difficile* and *Staphylococcus aureus*, but not with *H. influenzae*, *Prevotella sp*, or *Bifidobacterium bifidum* [107, 108]. The mechanisms dictating these discrete eosinophil responses to bacteria can be attributed to distinct pathogen sensing mechanisms. Human eosinophils express complement receptors [109, 110], Fc receptors [111, 112], and a wide repertoire of pattern-recognition receptors, including all toll-like receptors (except TLR-8), nucleotide-binding oligomerization domain (NOD)-like receptors (NLR) 1 and 2, and the C-type lectin receptor Dectin-1 [113–120]. The expression of these receptors on eosinophils can vary during disease conditions and upon stimulation by bacterial components during infection [115]. For example, Driss *et al*. reported that eosinophils from individuals with eosinophilia express TLR-2 and TLR-4 on their surface, whereas eosinophils from healthy patients did not [115]. The release of EPO, which has antimicrobial activity against mycobacteria, occurs following TLR-2-mediated activation of human eosinophils by *M. bovis* bacillus Calmette-Guerin, along with the generation of α-defensin and reactive oxygen species [115]. Furthermore peptidoglycan, another TLR-2 ligand, causes eosinophils to selectively release intracellular stores of proinflammatory cytokines IL-1β, IL-6, IL-8 and GRO-α, a process that is abolished by a TLR-2 neutralizing antibody [120]. The release of ECP from granules can be stimulated by LPS sensing through TLR-4 and CD14 on eosinophils [113]. The ability of eosinophils to selectively release granule content upon recognition of pathogen motifs is an elegant mechanism to prevent the excessive inflammation and damage to the surrounding host cells, while promoting the killing of local bacteria.

Cell-to-cell crosstalk may play a crucial role in inflammatory responses triggered by eosinophils during bacterial infections. Activated eosinophils can express MHCII on their surface, as evident in eosinophils recovered from the blood, sputum and airways of asthmatics [121–123] and can be induced *in vitro* by incubation with GM-CSF [124]. *S. aureus* superantigens SEA and SEB (staphylococcal enterotoxins A and B) and TSST-1 (toxic shock syndrome toxin) bind to MHCII on eosinophils inhibiting apoptosis [125] and promoting MHCII-TCR crosslinking [126] to activate $CD4^+$ T cells. However, although GM-CSF-activated eosinophils stimulate resting $CD4^+$ T cells after incubation with SEA and SEB [127], studies defining eosinophils as antigen presenting cells capable of processing and presenting bacterial antigens are limited and conflicting. Weller and colleagues reported that HLA-DR^+ eosinophils incubated with tetanus toxoid then fixed with paraformaldehyde were able to promote T cell proliferation whereas cells fixed prior to toxoid pulsing were not, indicating that antigen processing was required for the proliferative effect [128]. Conversely, Mawhorter *et al*. did not observe proliferation of *M. tuberculosis* purified protein derivative (PPD)-specific $CD4^+$ T cells during co-culture with PPD-pulsed eosinophils [127].

While eosinophils are indeed capable of responding to pathogenic bacteria (Figure 2), their exact functions during an active infection *in vivo* are yet to be elucidated. Since eosinophil recruitment in macrophage CD14 deficient allergic mice infected with IAV is stunted [129], it is possible that similar intercellular crosstalk predominates during bacterial infections in the lungs where eosinophils may help modulate immune responses and help in the reparative processes that follow neutrophilic inflammation.

Conclusion

Eosinophils are multifunctional cells of the immune system equipped with an arsenal of specialized proteins with clear antihelminthic, antiviral, and antibacterial properties (Figure 2). In addition, the storage of a plethora of cytokines and chemokines, neuropeptides, and growth factors provide them with the necessary tools to regulate the microenvironment including the leukocytes that may surround them in an inflamed tissue. Recent evidence strongly negates the antediluvian notion that the sole purpose of the eosinophil is to counter parasites. In contrast, the evolutionary conservation of these cells certainly suggests that they serve an important, albeit redundant, role in the pulmonary immune response both in sickness and in health.

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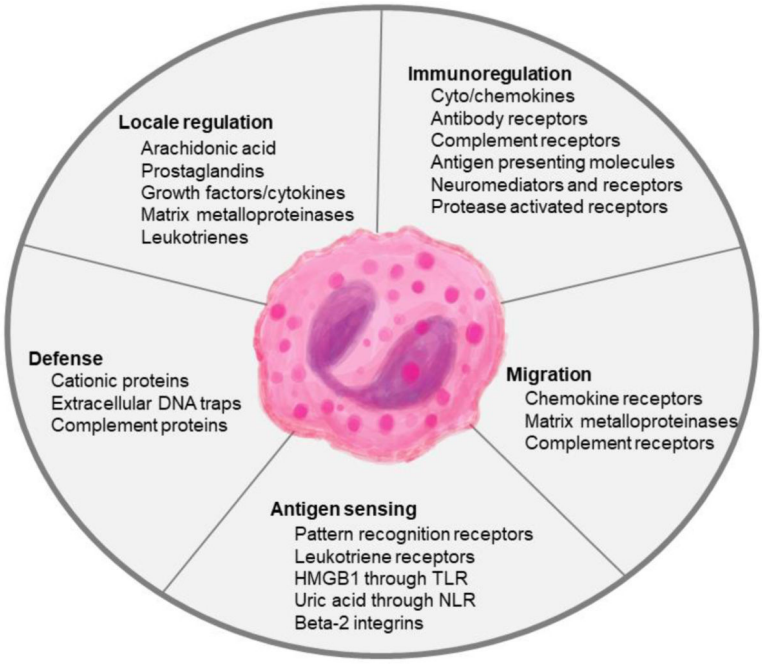

Figure 1. Functions of eosinophils during lung infections.

Eosinophil granule contents including granule proteins and cytokines promote direct defense strategies to counter pathogens in addition to enhancing the functions of surrounding immune cells. The expression of a variety of receptors on the eosinophil surface allows the cells to sense and respond to the environment in real-time.

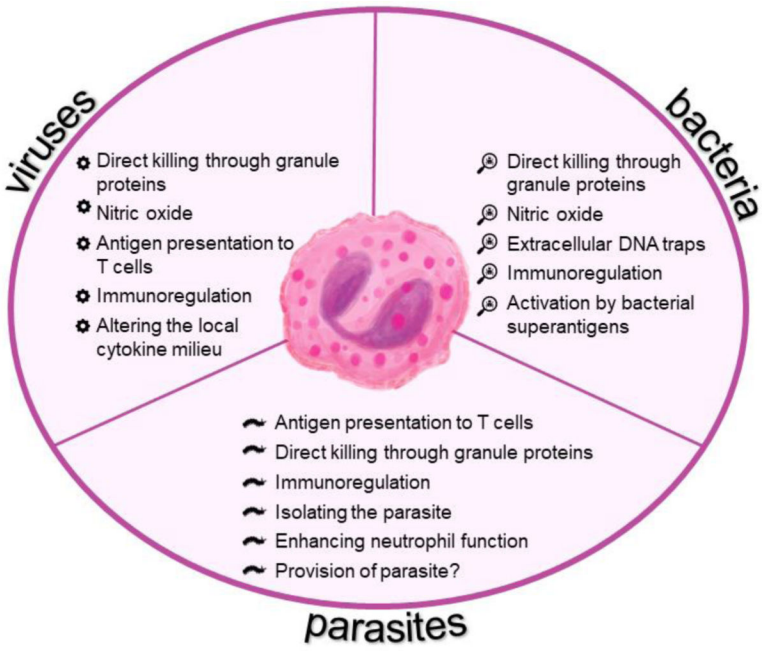

Figure 2. Anti-pathogen responses of eosinophils during lung infections.

Broad anti-pathogen functions of eosinophils are applicable to respiratory viruses and bacteria as well as the lung-phase of parasites.