A Player and Coordinator: The Versatile Roles of Eosinophils in the Immune System

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Summary

Eosinophils have traditionally been associated with allergic diseases and parasite infection. Research advances in the recent decades have brought evolutionary changes in our understanding of eosinophil biology and its roles in immunity. It is currently recognized that eosinophils play multiple roles in both innate and adaptive immunity. As effector cells in innate immunity, eosinophils exert a pro-inflammatory and destructive role in the Th2 immune response associated with allergic inflammation or parasite infection. Eosinophils can also be recruited by danger signals released by pathogen infections or tissue injury, inducing host defense against parasitic, fungal, bacterial or viral infection or promoting tissue repair and remodeling. Eosinophils also serve as nonprofessional antigen-presenting cells in response to allergen challenge or helminth infection, and, meanwhile, are known to function as a versatile coordinator that actively regulates or interacts with various immune cells including T lymphocytes and dendritic cells. More roles of eosinophils implicated in immunity have been proposed including in immune homeostasis, allograft rejection, and anti-tumor immunity. Eosinophil interactions with structural cells are also implicated in the mechanisms in allergic inflammation and in *Helicobacter pylori* gastritis. These multifaceted roles of eosinophils as both players and coordinators in immune system are discussed in this review.

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Introduction

Eosinophils develop from hematopoiesis in the bone marrow and migrate into blood, making up about 1–6% of white blood cells. These special granulocytes were first observed by Wharton Jones in 1846 and named by Paul Ehrlich in 1879, because they contain abundant intracellular granules that are intensely stained by the acidophilic dye eosin [1]. Therefore, eosinophils can be easily differentiated from other granulocytes such as neutrophils and basophils in morphology by their brightly brick-red appearance under hematoxylin and eosin staining.

Historically, eosinophils have long been perceived as important immune cells responsible for two aspects of events: i) combating multicellular parasites or helminthes, and ii) participating in hypersensitivity or allergic response, for example the pathological mechanisms of allergic asthma, along with mast cells. With an arsenal of toxic granule proteins and other pro-inflammatory mediators contained in its granules, eosinophils can cause tissue damage by its degranulation process upon inflammation-triggering signals. Therefore eosinophils have traditionally been considered as end-stage cells in innate immunity that contribute to anti-parasitic immunity or allergy by their pro-inflammatory and destructive effects.

In the recent decades, many more new roles of eosinophils have been identified in various pathological processes, including not only host protection against other microbes, such as certain types

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of fungi, bacteria, and viruses, but also allograft rejection, anti-tumor immunity, and a number of idiopathic eosinophilic diseases [2–4]. These have dramatically enriched our knowledge on this specific granulocyte in regard to its functions and relevant molecular mechanisms in health and disease.

According to current understanding, apart from the pro-inflammatory and destructive effects as end-stage cells in innate immunity, eosinophils may also be involved in tissue repair, fibrosis, and remodeling as well as in modulation of adaptive immune responses [4–6]. Specially, eosinophils can actively promote Th2-type immune responses by producing a range of immunoregulating cytokines and molecules [5] and acting as antigen-presenting cells (APCs) [7, 8]. Eosinophils are also implicated in the mechanisms of allograft rejection [9] and anti-tumor immunity [10–12]. Here we will mainly review the multifaceted roles of eosinophils as both effectors and regulators of the immune system, with the molecular basis and functions discussed.

The Biological and Molecular Basis of Eosinophil Functions

Eosinophils are equipped with a preformed armamentarium of cationic granule proteins, cytokines, chemokines, growth factors, lipid mediators (e.g. leukotrienes, prostaglandins), and other immunomodulatory molecules, including matrix metalloproteinases, serving as the fundamental basis for the immunobiological functions of eosinophils [7]. Most of these products are stored primarily within intracellular granules or vesicles of eosinophils and can be secreted or released immediately in response to certain stimuli, affecting the immune microenvironment and causing relevant immune responses. Meanwhile, eosinophils express a broad variety of surface receptors and molecular makers, mediating signals in different immunobiological processes [3, 8]. The different functional mechanisms associated with these eosinophil-derived products and eosinophil receptors have been comprehensively discussed in several previous reviews [6, 7, 13, 14] and thus will not be described here in detail. We just briefly summarize the different groups of molecules relevant to eosinophil functions.

The Preformed, Functional Granule Contents and Eosinophil Degranulation

Eosinophils are characterized by their numerous intracellular secretory granules in the cytoplasm, which store the majority of cationic granule proteins and a variety of cytokines, chemokines, and growth factors. Compared to T lymphocytes that require hours or days to generate and secrete cytokines upon activation, eosinophils can release their preformed granule contents by degranulation immediately when triggered by certain stimuli or signals through cell surface molecules.

Among these granule contents, eosinophil-derived cationic granule proteins include major basic protein (MBP), eosinophil-derived neurotoxin (EDN), eosinophil cationic protein (ECP), and eosinophil peroxidase (EPO). With a highly basic nature, these cationic proteins are highly toxic to parasitic helminthes and human airway epithelium because they can damage cells by binding to negatively charged cell membranes and thus disordering the lipid bilayer, or by affecting the activity of enzymes within tissues [15].

A variety of cytokines, chemokines, and growth factors are also harbored in the specific granules. These contents secreted by eosinophils can affect the immune microenvironment and function in several different aspects: i) the eosinophilopoietins, IL-5 and granulocyte-macrophage colony-stimulating factor (GM-CSF), and the key chemoattractant CCL11 (eotaxin) act on eosinophils themselves as an autocrine regulation [8], which plays critical roles in eosinophil chemotaxis and survival within tissues; ii) immunomodulatory cytokines such as IL-4 [16], IL-13 [16], and IL-25 [17] promote and/or enhance the Th2 immunity, participating in the pathogenesis of allergy and anti-parasite immune responses [5]; iii) pro-inflammatory cytokines such as IL-6 and tumor necrosis factor α (TNF-α) participate in the augment of inflammatory response and may cause tissue damage, indicating an immediate-reaction role of eosinophils in innate immunity; and iv) transforming growth factor β (TGF-β) enhances proliferation and collagen synthesis of fibroblasts and plays a crucial role in tissue remodeling and fibrosis, which are implicated in the chronic pathologic process of various eosinophil-associated inflammatory diseases, including asthma [18] and eosinophilic esophagitis (EoE) [19].

Eosinophils are a major source of lipid mediators such as leukotrienes, prostaglandins, and 5-hydroxyeicosatetraenoic acid (5-HETE) as well as of platelet-activating factor (PAF), which have broad inflammatory effects. Besides, a number of proteinases, e.g. matrix metalloproteinase 9 (MMP-9), and other pro-inflammatory enzymes have been identified in eosinophils, many of which are implicated in the innate immune responses, including wound healing and tissue remodeling.
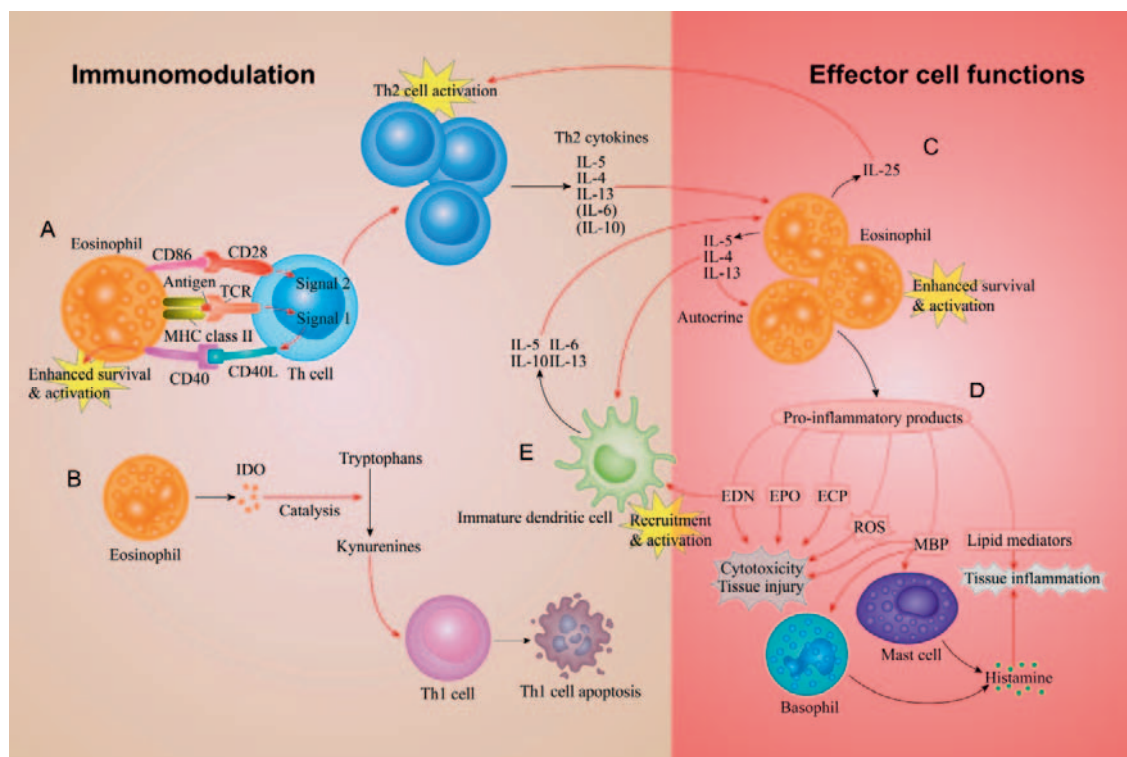
Eosinophil Receptors and Surface Markers

The eosinophil expresses a broad variety of surface receptors and molecular makers, each with specific roles to play. Comprehensive lists of these surface molecules as well as their corresponding ligands and biological functions have been previously summarized in several excellent reviews [5, 7].

According to their different immunobiological functions, we briefly summarize them in several groups as follows:
– *Pattern-recognition receptors (PRRs):* PRRs are surface molecules that help eosinophils to probe pathogens and/or host-derived damage signals. Namely, PRRs either directly recognize pathogen-associated molecular patterns (PAMPs), the specific microbial molecular signatures expressed by certain pathogens, or recognize damage-associated molecular patterns (DAMPs), the signals released by necrotic or damaged cells [20, 21]. When responding to these pathogen- or tissue damage-related signals,

Fig. 1. An illustration of the mechanisms involved in the immunomodulatory functions and the effector cell functions of eosinophils in Th2 immunity, a common immune response present in allergic inflammation and host defense against parasite infection. **A.** The eosinophil presents antigens to the Th cell. MHC class II molecules of the eosinophil present antigens to TCR receptors on the Th cell, producing 'Signal 1', and the costimulating molecule CD86 binds to CD28 of the Th cell, serving as 'Signal 2'. These signals promote the Th2 immune response characterized by Th2-cell activation and production of Th2 cytokines, i.e. IL-5, IL-4, and IL-13. Meanwhile, upon activation by the two signals, the Th cell expresses CD40L and binds to CD40 expressed on eosinophils, promoting eosinophil activation. **B.** Eosinophils express IDO, an enzyme that catalyzes the catabolism of tryptophans to kynurenines, which leads to Th1-cell apoptosis and thus favors the polarization of Th2 immunity. **C.** The regulatory effects of Th2 cytokines lead to eosinophil differentiation, recruitment, survival and activation. The activated eosinophils, in turn, release cytokines including IL-5, IL-4, IL-13, and IL-25, enhancing their own activity as an autocrine regulation and contributing to the Th2 polarization by regulating Th cells and immature DCs. **D.** Activated eosinophils release various pro-inflammatory products, including lipid mediators (e.g. leukotrienes), ROS, and granule proteins EDN, EPO, ECP, and MBP, which posing different effects such as cytotoxicity, tissue injury, and tissue inflammation. Of note, MBP can stimulate mast cells and basophils to release histamine, contributing to the tissue inflammation. **E.** EDN can also serve as an innate immune alarmin that recruits immature DCs and induces their differentiation into a Th2-promoting phenotype.

PRRs can activate downstream signaling cascades, leading to release of pro-inflammatory cytokines and type I IFNs [21].

– *Cytokine receptors, chemokine receptors, adhesion molecules, and receptors for immunoglobulins, complements, proteases, and lipid mediators:* These are implicated in, but not limited to, eosinophil development, adhesion and transmigration into tissues, chemotaxis, activation, and inflammatory responses [7, 22].

– *Receptors involved in Th2 immunity:* Major histocompatibility complex (MHC) class II [23] and the costimulatory receptors CD80, CD86 [24] and CD40 [25] are key molecules for eosinophils to present antigens to T cells and stimulate antigen-specific T-cell proliferation, initiating Th2-type immune response (fig. 1).

– *Apoptosis-inducing or inhibitory receptors:* These receptors expressed on eosinophils, e.g. sialic acid-binding immunoglobulin-like lectin 8 (siglec-8), serve as extinguishers of inflammation by inducing apoptosis of eosinophils. Siglec-8 ligation with cross-linking antibodies can rapidly generate caspase-3-like activity and induce pronounced apoptosis of eosinophils [26].

Eosinophils as Effector Cells in Innate Immunity: Pro-Inflammatory, Cytotoxic and Fibrogenic Effects

Pro-Inflammatory and Destructive Effects in Allergic Inflammation

Eosinophil infiltration is a common feature in the pathologic sites of allergic inflammatory diseases, which is recruited and enhanced mainly by Th2-cell-secreted IL-5 and eotaxin-1. For example, tissue eosinophilia is present in and tightly associated with the inflammation of the airway in asthma [27] and rhinosinusitis [28], of the gastrointestinal tract in eosinophilic esophagitis (EoE) [29, 30] and eosinophilic gastroenteritis [31, 32], and of the skin lesions in atopic dermatitis [33].

Eosinophils play key effector roles in the inflammation process provoked by allergens. Upon activation, eosinophils release its cytotoxic granule proteins and other granule contents via degranulation process. These released proteins, cytokines, and chemokines as well as lipid mediators and proteinases exert pro-inflammatory and destructive effects and cause inflammation or damage to the tissue (fig. 1). Notably, eosinophil granule proteins and reactive

Table 1. Different mechanisms of eosinophil-mediated host defense against various types of microbial pathogens

Types of antimicrobial immunity	Pathogen recognition by eosinophils	Eosinophil-mediated innate immune responses	Eosinophil-mediated adaptive immune responses	Ref.
Anti-parasitic	eosinophils are stimulated by sIgA-, IgA- and IgG-coated helminthes *in vitro* via the immunoglobulin receptor FcαR	i) cytotoxic granule proteins (MBP, EPO, ECP, and EDN) are released onto helminthic parasites via eosinophil degranulation (compound exocytosis), causing parasite-killing effects; ii) eosinophils down-regulate parasite-induced IgE responses and airway goblet cell mucus production during infection with *Brugia malayi* microfilariae	eosinophils present parasite-specific antigens to T cells, promoting polarization of Th2 response and production of parasite-specific IgM; enhance host immunity upon reinfection; and promote schistosomiasis-induced liver fibrosis by production of profibrotic mediators IL-13 and Th2 polarization	[5, 36, 37, 131, 132]
Anti-fungal	eosinophil PAR-2 receptor is cleaved by aspartate proteases produced by *Alternaria alternata*, exposing neo-ligands that activate eosinophils	the activated eosinophil adheres to the fungi *Alternaria alternata* by the binding of its CD11b integrin to the fungal cell wall component, β-glucan, leading to eosinophil degranulation and release of cytotoxic granule proteins (MBP and EDN) and chemokines (MIP-1α, MCP-1, IL-8)	N/A	[133, 134]
Anti-bacterial	eosinophil surface receptor PRRs, e.g. TLRs, NOD-like receptors, recognize specific PAMPs expressed on bacteria	i) ingesting bacteria by phagocytosis, and thereafter killing these bacteria in phagocytic vacuoles with MBP and ECP translocated from cytoplasmic granules; ii) bactericidal activity of MBP and ECP, and (or) oxygen-dependent killing by superoxide and EPO, towards extracellular bacteria; iii) eosinophil extracellular traps, comprised of mitochondrial DNA and granule proteins, bind to and kill the trapped bacteria	N/A	[3, 5, 21, 135]
Anti-viral	eosinophil surface receptor PRRs, e.g. TLR7, recognize specific PAMPs of viruses	i) eosinophil-derived EDN has ribonuclease activity with anti-ssRNA virus effect; ii) in RSV infection, stimulation of TLR7-MyD88 signaling by viral ssRNA binding induces expression of anti-viral mediators including IRF-7, NOS-2, and ribonucleases EAR-1 and EAR-2; iii) in RSV or PVM infection, viral replication in eosinophils results in release of infectious virions and proinflammatory mediator IL-6	eosinophils present viral peptides (e.g. RV16 virus) to antigen-specific T lymphocytes, inducing T-cell proliferation and IFN-γ production	[21, 136–140]

MIP-1α = Macrophage inflammatory protein 1α; MCP-1 = monocyte chemotactic protein 1; NOD = nucleotide-binding oligomerization domain; TLRs = Toll-like receptors; PRRs = pattern-recognition receptors; PAMPs = pathogen-associated molecular patterns; RSV = respiratory syncytial virus; PVM = pneumonia virus of mice.

oxygen species (ROS) cause direct injury to epithelial cells and other tissues [15]. Lipid mediators such as cysteinyl leukotrienes, enhance the airway smooth muscle contraction, mucus production and vascular permeability, and also promote the eosinophils' autocrine secretion of IL-4 [34]. Moreover, another two important effectors in allergic immune response, mastocytes and basophils, can be activated to release histamine upon stimulation by MBP, one of the eosinophil-derived cationic granule proteins [35].

The mechanism how eosinophil degranulation is triggered has been an intriguing question. Recent studies have found that epithelial cell-derived thymic stromal lymphopoietin and tissue stromal cell-derived IL-33 play crucial roles in modulating eosinophil infiltration and degranulation in the mechanisms of allergic inflammation. We will discuss these mechanisms later in this review in 'Epithelial or Tissue Stromal Cells, Eosinophils, and Allergic Inflammation'.

Host Defense against Different Pathogens

Traditionally, eosinophils have been recognized as the effector cells in killing parasites in the presence of antibody and/or complement, which was mediated by the cytotoxic granule proteins released onto the helminthes via eosinophil degranulation [5]. In re-

cent decades, eosinophils have also been known as APCs and may enhance the parasite-specific immune response against helminthes such as *Strongyloides stercoralis* [36, 37]. With regards to eosinophils' important role in modulation of the adaptive immunity, this will be discussed later in 'Immunomodulatory Functions of Eosinophils'. Apart from the anti-parasitic activity, eosinophils also participate in the host defense against other microbial pathogens, including fungi, bacteria and viruses, which have been discussed in detail in previously published reviews [3, 5, 7]. The different mechanisms of eosinophil-mediated host defense against these distinct pathogens are summarized in table 1.

Response to Tissue Damage Signals and Promotion of Tissue Remodeling

When alarmins or DAMPs are released from necrotic cells, the PRRs expressed on eosinophils recognize these endogenous danger signals and subsequently activate the eosinophil and enhance its survival [5]. For example, the binding to high mobility group box-1 (HMGB1), a necrosis signal molecule, by the receptor for advanced glycation end products (RAGE) expressed on eosinophils can mediate the chemotactic migration of eosinophils and their response to areas of tissue injury or necrosis [20]. It has been inferred that these effects might be beneficial to the healing of tissue wound or injury, especially for maintaining the epithelial barriers of gastrointestinal tract and airway.

However, a 'side effect' of this eosinophil response is the fibrogenic effect that may result in an outcome of tissue remodeling. Indeed, in some eosinophilic inflammatory diseases, including asthma, EoE, and certain eosinophilic skin dermatoses such as granuloma faciale, a pro-inflammatory effect of eosinophils often dominates in the early or acute phase, whereas a fibrogenic process gradually features the chronic phase in the pathological process [29, 38, 39]. In these chronic inflammation settings, a broad spectrum of eosinophil-derived mediators, including TGF-β, Th2 cytokines (e.g. IL-13, IL-4), MMPs, and granule proteins MBP and EDN, play crucial roles in promoting epithelial and/or smooth muscle cell hyperplasia, myofibroblast differentiation, extracellular matrix reorganization and tissue fibrosis [5]. These effects contribute to a variety of chronic inflammatory conditions associated with eosinophilia, including not only airway remodeling in severe asthma [38, 40], stromal fibrosis in chronic rhinosinusitis with nasal polyposis [41] and esophageal subepithelial fibrosis in EoE [29] but also endomyocardial fibrosis in hypereosinophilic syndrome (HES) [42].

Angiogenesis is another feature involved in eosinophil-associated tissue remodeling. Several pro-angiogenic factors, such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF) and angiogenin, are also released by eosinophils, which contribute to the pathological process of eosinophilic inflammatory disorders. For example, these factors are associated with eosinophil infiltration in asthma and are implicated in the increase of peribronchial vessels and vascular permeability in the asthmatic airway [40, 43].

Immunomodulatory Functions of Eosinophils

Protecting the Immune Homeostasis: Roles in Bone Marrow, Gut, and Thymus

Eosinophils are produced from pluripotent stem cells in the bone marrow, released into the peripheral circulation, and finally home into tissues such as the gastrointestinal tract, the thymus, mammary glands, and the uterus. The presence of eosinophils plays essential roles in maintaining the immune homeostasis in these tissues. For example, depletion of eosinophils in mice results in increased apoptosis of plasma cells in the bone marrow, while restoration of eosinophils can rescue this defect [44]. Indeed, eosinophils co-localize with plasma cells in bone marrow and secrete a proliferation-inducing ligand (APRIL), known as a critical plasma cell chemokine, and IL-6, sustaining the survival of plasma cells [44].

A major population of eosinophils is preserved in the gastrointestinal tract, regulating the immune homeostasis in the gut in various ways. First of all, eosinophils are implicated in the retention of IgA-producing plasma cells in Peyer's patches, also by secretion of APRIL [45]. This may play a role in the maintenance of microbial homeostasis of commensal organisms in the gut. Secondly, recent studies have shown that eosinophils in lamina propria are able to induce the differentiation of regulatory T (Treg) cells by producing TGF-β1 and all-trans retinoic acid (ATRA) [46]. Moreover, in mouse models of acute peritonitis or acute colitis, eosinophil-deficient mice developed significantly more severe inflammation than wild-type mice, which suggests that eosinophils play protective roles in terminating acute inflammation, possibly due to their production of the anti-inflammatory lipids such as protectin D1 (PD1) [47, 48].

Eosinophils in the thymus may play important roles in the negative selection of T cells. In neonatal thymus, eosinophils have an activated phenotype and are localized primarily in the corticomedullary regions, which are the sites of negative selection of double-positive thymocytes [49]. However, these findings from mouse studies have not been confirmed in humans yet.

Promoting Th2 Immune Response: Roles as APCs and Immunomodulators in Allergy and Anti-Helminth Immunity

While the important roles of eosinophils as effector cells in Th2 immune response have been well documented, either in allergic inflammation or host defense against parasitic infection, eosinophils also play an active, modulatory role in the induction and propagation of Th2 immunity. It has been observed that, in a number of experiments with murine models of allergic airway inflammation induced by allergen challenge, depletion of eosinophils in mice results in significant inhibition of pulmonary T-cell recruitment, blockade of Th2-associated cytokine production (IL-4, IL-5, and IL-13) as well as in attenuated airway inflammatory outcomes such as pulmonary mucus secretion and/or the airway hyperresponsive-

ness [50, 51]. Notably, adoptive transfer of eosinophils, together with Th2-polarized T cells or with delivery of eotaxin-1 into the lung, can restore the pulmonary T-cell infiltration, the Th2 immune responses, and the airway inflammation in these eosinophil-deficient mice, while adoptive transfer of T cells alone does not show this reversal [52, 53]. In addition, Th2-mediated peanut food allergy and anaphylaxis are impaired in eosinophil-deficient mice, and this defect can be restored by adoptive transfer of eosinophils into these mice [54]. Other studies focusing on anti-parasitic immunity have demonstrated that antigen-pulsed eosinophils, injected intraperitoneally into naive or immunized mice, are sufficient to induce the primary or boost the secondary Th2 immune responses to *Strongyloides stercoralis* in these mice, causing increased production of IL-4, IL-5, and the parasite antigen-specific immunoglobulins IgM and IgG [36]. Although there is lack of human data, these results provide compelling evidence for the crucial roles of eosinophils in the T-cell recruitment and Th2 immune response in allergen-induced inflammation and anti-parasitic immunity in mice. The possible mechanisms are discussed in the following, with both studies on humans and data from animal experiments.

Eosinophils as Nonprofessional APCs

In the recent decades, one of the breakthrough findings about eosinophils is their functions as APCs. APCs generally include two categories: professional APCs and nonprofessional APCs. Professional APCs, such as dendritic cells (DCs) and macrophages, constitutively express surface MHC class II molecules and costimulatory molecules, and are capable of processing antigen and presenting it to resting T cells. However, nonprofessional APCs, such as B cells and endothelial cells, usually do not express surface MHC class II molecules or costimulatory molecules unless activated by cytokines, and their functions of processing and presenting antigens also largely rely on cytokine-induced activation.

There has been sufficient evidence in human and murine models that eosinophils belong to the category of nonprofessional APCs in allergic inflammation and in anti-parasitic immune responses. Eosinophils in resting state do not constitutively express MHC class II molecules or costimulatory molecules (e.g. CD80/CD86, CD40) on the surface and are unable to present antigens to T cells [55, 56]. However, MHC class II molecules can be expressed on eosinophils upon activation by the cytokines GM-CSF, IL-4, IFN-γ and IL-5 [55–58], and are also expressed on in vivo activated eosinophils isolated from the bronchoalveolar lavage (BAL) fluid of patients with eosinophilic pneumonia [23]. In addition, expression of costimulatory molecule CD86 (also known as B7.2) has also been identified on the surface of human eosinophils activated by IL-3 [59]. On the other hand, eosinophils are not fully competent in antigen processing even if stimulated by cytokines that signal via the β-chain, because eosinophils activated by IL-5 or GM-CSF are only able to present superantigen and antigenic peptides, but not native antigens, to T cells [58, 59].

Data from murine studies are consistent with the above findings. Eosinophils isolated from mice infected with the parasitic nematode *Brugia malayi* [60] express MHC class II molecules. Activated eosinophils isolated from mice challenged by airway allergen [61] and eosinophils challenged by *Strongyloides stercoralis* antigens [62] also express the costimulatory molecule CD86.

The antigen-presenting function of activated eosinophils has been demonstrated both in vitro and in vivo. It has been observed that eosinophils treated with GM-CSF and IL-5 are able to present antigens to activated T cells, although much less efficiently than macrophages can [55, 58, 63]. As indicated by in vivo studies, eosinophils can express MHC class II and costimulatory molecules upon cytokine-induced activation, and stimulate antigen-specific CD4+ T-cell proliferation in a cell-cell contact manner, promoting Th2 cytokine production [36, 64, 65]. Meanwhile, CD40 on the surface of eosinophils can bind to CD40L, a costimulatory molecule expressed on the T cells upon signaling via antigen presentation process, leading to enhanced survival and GM-CSF release of eosinophils [25] (fig. 1).

Other Immunomodulatory Effects of Eosinophils Contributing to Th2 Immunity

Although the mechanisms are not completely clear, an immunomodulatory role of eosinophils in the induction and prosperity of Th2 immune response has been proposed. There is evidence that, in response to allergens or Th2-eliciting pathogens, eosinophil recruitment occurs prior to the infiltration of Th2 cells, i.e., in a manner independent of adaptive immunity [66, 67]. In this early stage of response, eosinophils are a dominant source of the Th2-polarized cytokines IL-4 and IL-13 (fig. 1), because these cytokines are preformed and stored in eosinophil granules and can be rapidly released upon stimulation. Meanwhile, the granule protein EDN released by eosinophils may serve as an alarmin to immature DCs, which induces the recruitment and differentiation of DCs into a Th2-promoting phenotype [68] (fig. 1). Recent studies have also suggested that the enzymatic activity of EPO, another eosinophil granule protein, promotes activation of DCs in vitro, activates intestinal and extraintestinal DCs in mice, and induces their mobilization to lymph nodes in vivo, which is necessary for Th2 priming [54]. On the other hand, indoleamine 2,3-dioxygenase (IDO), an enzyme constitutively expressed by eosinophils, catalyzes the conversion of tryptophans to kynurenines, which induce apoptosis of IFN-γ-producing T cells (Th1 cells), but not IL-4-producing T cells (Th2 cells) [69] (fig. 1). Thus all these regulatory effects favor the polarization of Th2 immunity at an early stage of immune response to allergen challenge or parasite infection.

Eosinophils may also exert a critical role in promoting polarization of Th2 immune response during allergic inflammation via cytokine IL-25. IL-25, released by eosinophils, enhances the expansion and cytokine production of the allergen-specific Th2 memory cells [17] (fig. 1). This regulatory effect on memory cells could be of crucial significance in Th2 immune response elicited by re-exposure of allergens or re-infection of parasites. Moreover, recent findings with in vitro experiments have indicated that eosinophils can modulate CD4+ T-cell responses via eosinophil-secreted HMGB1 in the pathogenesis of asthma [70].

Regulating Other Activities in the Immune System

Eosinophils also promote humoral immune responses. The IgM-mediated host protection against parasitic larval *S. stercoralis* is impaired in IL-5 knockout mice and can be rescued by reconstitution of eosinophils at the time of immunization [37]. Similarly, eosinophil-deficient mice also show inhibited production of antigen-specific IgM when immunized by alum antigen, while adoptive transfer of eosinophils into these mice can correct this defect in early antibody response [71]. These results have suggested a crucial role of eosinophils in augmenting B-cell activation and early antigen-specific IgM synthesis.

A recent study has evoked an interest in the role of eosinophils in helminth parasites-elicited protection against autoimmunity. Using mice with experimental autoimmune encephalomyelitis (EAE), a mouse model of multiple sclerosis, Finlay and colleagues [72] observed a clinical improvement with increased eosinophils after treating these mice with the parasitic *Fasciola hepatica* excretory-secretory products (FHES). However, this protection against EAE induced by FHES and the associated accumulation of eosinophils were absent in IL-33–/– mice and upon neutralization of IL-5, which, in turn, could be restored by transfer of FHES-induced or IL-33-induced eosinophils into these mice [72].

Roles of Eosinophils in Allograft Rejection

Acute Allograft Rejection: Eosinophils Functioning as Effectors

After the first observations of eosinophil infiltration of rejected allografts in transplant recipients, a number of studies have followed and collectively demonstrated the diagnostic and prognostic values of eosinophils in acute rejection of allografts. Weir et al. [73] have reviewed the clinical course of 132 consecutive renal transplant recipients and found that the elevated eosinophil counts in peripheral blood and/or increased presence of eosinophils in allograft biopsy specimens show an adverse prognosis for acute rejection outcome. Similar correlation with a poor prognosis was reported in other studies on patients receiving transplantation of kidneys [74, 75], livers [76, 77] or lungs [78].

The mechanisms how eosinophil infiltration in the allografts participates in allograft rejection have been investigated, mainly through experimental animal models [9]. Le Moine et al. [79] observed a dense, aggressive eosinophil infiltrate in the MHC class II-disparate skin allografts that had been acutely rejected after transplanted in C57BL/6 mice. They also found that lymphocytes isolated from lymph nodes draining rejected skin allografts were primed for IL-5 secretion, and IL-5 mRNA was present within rejected allografts [79]. These results suggested a possible role of eosinophil infiltration in allograft destruction, dependent on IL-5 regulation, which was evidenced by the delayed rejection of the same skin allograft in IL-5-deficient mice. The destructive effect of eosinophils recruited into rejected allografts and its dependence on IL-5 were also identified in animals depleted of CD8+ T cells and

transplanted with fully mismatched cardiac allografts [80]. Moreover, experiments in vitro shows that IL-5 secretion can be inhibited by the presence of CD8+ T cells and/or IFN-γ, which is consistent with the in vivo experimental finding that eosinophilia is present in allografts rejected by IFN-γR-deficient recipients. On the other hand, studies on eosinophil-deficient ΔdblGATA1 mice transplanted with allogeneic heart grafts or allogeneic splenocytes have shown that eosinophils are not required for the formation or maintenance of alloantibody, namely, the donor-specific antibodies [81].

It is postulated that two possible mechanisms are involved in acute allograft rejection: CD8+ T-cell-mediated damage stimulated by IL-2, IFN-γ or other cytokines, and eosinophil-directed tissue damage regulated by IL-5 or other cytokines produced by CD4+ T cells [9, 77, 82]. Csencsits et al. [83] studied the CD4+ cell-mediated rejection response to indirectly presented alloantigen by transplanting cardiac allografts deficient for class II transactivator (CIITA) into recipient mice depleted of CD8+ T cells. Indeed, an acute rejection with a strong Th2 response characterized by eosinophil influx into the graft was observed in the BALB/c mice depleted of CD8+ T cells, whereas in recipients not depleted of CD8+ cells, these CIITA–/– allografts induced a polarized Th1 response instead [83]. Thus it is proposed that the role of eosinophils as effector cells in allograft damage becomes crucial when classical pathways of rejection are inhibited and Th2 cells dominate the alloimmune response. However, how the alloantigen was indirectly presented to CD4+ T cells remains to be elucidated.

Whether or not these possible roles of eosinophils and their mechanisms in murine models are the same in acute allograft rejection of humans remains largely unknown. A recent study with clinical data from 86 heart transplant patients has observed that patients with acute cellular rejection had a lower eosinophil count in peripheral blood compared with those without rejection, indicating an association between a high eosinophil count and non-occurrence of allograft rejection [84]. This new finding challenges the traditional knowledge that elevated eosinophil counts predict adverse prognosis of allograft rejection. Further investigation into this paradoxical issue is warranted.

Chronic Allograft Rejection: Regulatory Roles of Eosinophils in Alloimmunity

Eosinophil infiltration is also implicated in chronic allograft rejection, but possibly playing a regulatory role in the alloimmune responses, which is different from its destructive roles in acute rejection. Nolan et al. [85] evaluated the presence of eosinophils with epifluorescence on Fisher-Giemsa-stained sections, which is a highly sensitive method, and found that, among the 15 examined patients with chronic renal allograft rejection, 14 (93%) had eosinophil infiltration in the allografts. These infiltrated eosinophils were primarily localized in the intimal, adventitial, and tubulointerstitial compartments. Further, eosinophil-conditioned medium showed a stimulatory effect on DNA synthesis in both rat and human vascular smooth muscle cells, suggesting a potential regula-

tory role of eosinophils in promoting intimal smooth muscle proliferation [85]. This might indicate a possible pathogenic effect of eosinophil-derived products in the pathogenesis of obliterative arteriopathy, a characteristic pathologic change in chronic vascular rejection of renal allografts, although it remains to be elucidated which cytokines or products released by eosinophils are the key molecules and how they impose the effect.

It has also been hypothesized that eosinophils, similar to NK cells, could induce maturation of DCs. When stimulated by CpG ODN 2395 (CpG-C), a surrogate molecule of PAMPs, eosinophils enhance DC maturation via a direct cell-cell interaction [86]. In addition, whereas the eosinophil granule protein EDN does not contribute to this maturing effect, MBP, another granule protein released by these stimulated eosinophils, are taken up and internalized by DCs [86]. Thus it is hypothesized that eosinophils may be activated by host-derived DNA in the setting of necrosis-associated chronic inflammation and may subsequently induce DC maturation, contributing to the pathogenesis of chronic allograft rejection.

Le Moine et al. [87] established a mouse model of chronic rejection using C57BL/6 mice injected with the 145–2C11 anti-CD3 mAb and transplanted with MHC class II-disparate bm12 skin allografts. A marked infiltration of eosinophils and accumulation of IL-4 and IL-5 were present in the chronically rejected graft. Notably, the tissue eosinophilia and interstitial dermal fibrosis in these grafts were inhibited by in vivo blockage of either IL-5 or IL-4, while the characterized obliterative intimal vasculopathy in these grafts could only be prevented by blockage of IL-4, but not IL-5 [87]. Apparently, the eosinophil involvement in chronic rejection may also be dependent on IL-5 and IL-4, possibly either with a role different to the other. However, mechanisms of this regulation still need further investigation.

Roles of Eosinophils in Anti-Tumor Immunity

Tumor-associated tissue eosinophilia (TATE) and/or presence of eosinophil degranulation have been observed for a long time in various cancers, including both solid tumors and hematological malignancies. While many studies suggested a favorable prognosis associated with tissue eosinophilia in different solid cancers, a poor prognosis was indicated in Hodgkin lymphoma with TATE [12], and the exact mechanisms of how eosinophils participate in anti-tumor immunity remain largely unclear and even controversial [10, 11]. A variety of receptors and mediators expressed by eosinophils have been suggested to function in their anti-tumor activities. Briefly, eosinophils are proposed to exert anti-tumor effects either by direct cytotoxicity or by immunomodulatory functions in Th2 immune response, especially IL-4-mediated anti-tumor response [5, 12]. However, there are also studies indicating the role of eosinophils in promoting tumors, e.g., by enhancing tumor angiogenesis and promoting the connective tissue formation adjacent to tumors [10]. Two recent reviews that discuss these mechanisms in an extensive magnitude are recommended for more detailed understanding of eosinophils' roles in anti-tumor immunity [11, 12].

Recent Advances on Eosinophil Interactions with Structural Cells

Epithelial or Tissue Stromal Cells, Eosinophils, and Allergic Inflammation

Regulation of Eosinophils by Epithelial Cell-Derived Thymic Stromal Lymphopoietin in Allergy

Thymic stromal lymphopoietin (TSLP), a cytokine mainly secreted by epithelial cells in response to allergen or other environmental stimuli [88, 89], is known as a key molecule in the development of allergic inflammatory response [90]. Increased expression of TSLP has been observed in the skin lesions of patients with atopic dermatitis [91, 92], in the nasal epithelium of patients with allergic rhinitis and nasal polyps [93], and also in airway epithelial cells in patients with allergic asthma being correlated with the severity of allergic inflammation in asthma [94, 95]. TSLP has been linked with atopic dermatitis and allergic asthma also by the association with single nucleotide polymorphisms (SNPs) in the *TSLP* gene [90, 96].

For a long period, it is only known that TSLP mainly binds to the thymic stromal lymphopoietin receptor (TSLPR) expressed on myeloid DCs, by which the myeloid DCs are activated to polarize naive T cells into a Th2 phenotype [91]. More recently, research advances have indicated that eosinophils, expressing TSLPR, are also positively regulated by epithelial-derived TSLP, which contribute to the Th2-type immunity in allergic inflammatory response. Cook et al. [97] have observed that eosinophil expression of TSLPR is upregulated in the presence of TNF-α and IL-3, and thereafter TSLP directly activates eosinophils and leads to eosinophil degranulation, STAT5 phosphorylation, and increased eosinophil viability and survival. Experimental findings with mouse models also support the crucial roles of eosinophils in TSLP-induced systemic Th2 inflammatory response [98]. Meanwhile it is known that, in the presence of IL-3, TSLP significantly stimulates human hematopoietic progenitors via TSLP-TSLPR interactions to produce eosinophils and basophils colony forming units, promoting the involvement of eosinophils in allergic inflammation [99]. Another interesting recent finding is that TSLP can directly stimulate eosinophils to produce and release eosinophil extracellular traps, one of the efficient machineries for extracellular bacterial killing [100].

Regulation of Eosinophils by Tissue Stromal Cell-Derived IL-33 in Allergy

IL-33, a recently described cytokine of the IL-1 family, has also been recognized as an important mediator in Th2 immune response [101]. Expressed by tissue stromal cells in lung, skin and other tissues, IL-33 exerts diverse effects on different hematopoietically derived cell types by binding to a heterogeneous receptor complex consisting of IL-33R α-chain (ST2L) and IL-1R accessory protein (IL-1RAcP) [102, 103]. Both SNP in *IL33* and its cognate receptor, *IL1RL1* [104, 105] and increased expression of IL-33 in the airway epithelium [106], have been identified in patients with allergic asthma and have been shown to be associated with the de-

velopment of this allergic inflammatory disease. In addition, airway inflammation is ameliorated in *Il33–/–* mice, and exacerbated in mice overexpressing IL-33 [107, 108].

Recent evidence has shown that eosinophils are regulated by IL-33 in the mechanisms of allergic inflammatory response. IL-33 can activate human eosinophils in vitro [109–111]. Upon its ligation to receptors on eosinophils, NF-κB and mitogen-activated protein kinase (MAPK) pathways are activated [110], promoting cell surface expression of β2-integrin CD11b and intercellular cell adhesion molecule-1 (ICAM-1) and production of the pro-inflammatory cytokines IL-13, IL-6, and IL-8 [109]. More recent studies have demonstrated that dual-specificity phosphatase 5 (DUSP5), a member of mitogen-activated protein kinase phosphatases, negatively regulates IL-33-mediated extracellular regulated protein kinase activation, and thus abrogates IL-33-induced eosinophil survival and function [112]. IL-33 also directly stimulates eosinophil differentiation from CD117+ hematopoietic progenitor cells in an IL-5-dependent manner [113]. Studies in mice with allergic airway inflammation have observed an inhibitory effect of either anti-IL-33 antibody or vaccination against IL-33 on eosinophil infiltration and the allergic inflammation, demonstrating an essential role of IL-33 in regulating eosinophilic inflammation [114, 115].

Interaction between Gastric Epithelial Cells and Eosinophils in the Mechanisms of Helicobacter pylori *Gastritis*

Increased Eosinophil Infiltration in H. pylori Gastritis

As early as in 1991, it was observed that *H. pylori*-positive chronic gastritis had significantly greater eosinophil infiltration and degranulation in gastric mucosa than *H. pylori*-negative chronic gastritis or normal individuals [116]. Consistent findings were confirmed in a larger sample size by a later study with specimens from 44 *H. pylori*-positive patients and 20 *H. pylori*-negative patients [117]. In specimens of chronic *H. pylori* gastritis, the severity of gastritis was significantly correlated with that of eosinophil infiltration [116], although no difference in the severity of eosinophil infiltration was observed between gastritis with ulcer and those without gastric ulcer among *H. pylori*-positive patients [117]. Another intriguing phenomenon is that eosinophil infiltration in the gastric mucosa remains at a relatively high level even at 1 year after therapeutic clearance of *H. pylori* [118]. These data implied a possible link between *H. pylori* infection and tissue eosinophilia in the inflammatory process present in *H. pylori* gastritis. However, the mechanisms remain largely unknown until recent studies have shed light on mechanisms of the host-bacterium interaction in the gastric mucosa through which *H. pylori* regulates eosinophil recruitment and degranulation.

H. pylori, Gastric Epithelial Cells, and Eosinophils: Interactive Roles in the Mechanisms of H. pylori *Gastritis*

The crosstalk between *H. pylori* and gastric epithelial cells not only causes epithelial cell inflammatory injury, but also impacts on eosinophil infiltration and function in *H. pylori* gastritis (fig. 2).

Gastric epithelial cells exposed to *H. pylori* for 24 h can overproduce the chemokines CCL2, CCL5, and GM-CSF, which serve as chemoattractants and enhance eosinophil recruitment to colonized gastric mucosa. It has been further confirmed that these chemokine production and eosinophil recruitment effects are mediated by MAPK pathway in gastric epithelial cells, and also by the cag pathogenicity island of *H. pylori* [119], a strain-specific virulence locus associated with enhanced risk of peptic ulceration and gastric adenocarcinoma [120].

H. pylori outer membrane vesicles (OMVs), which refer to the vesicular compartments derived from the bacterial outer membrane and released from the *H. pylori* bacteria, are considered as key factors in the mechanisms of eosinophil degranulation affected by *H. pylori* infection. OMVs contain surface elements of the bacterium such as lipopolysaccharide (LPS), and act as a vehicle for vacuolating cytotoxin (VacA) of the bacterium [121]. Uptake of *H. pylori* OMVs by gastric epithelial cells can cause apoptosis, release of the pro-inflammatory cytokine IL-8 [121], and increased expression of ICAM-1 on cell surface [122]. Eosinophils recruited from the lamina propria of gastric mucosa, expressing the β2 integrin CD11b/CD18, can recognize the ICAM-1 molecules and interact with gastric epithelial cells to cause degranulation [122]. *H. pylori* OMVs can also directly trigger the release of granule proteins from human eosinophils by an ICAM-1- and CD11/CD18-dependent mechanism [122].

Meanwhile, a recent study has proposed that eosinophils may play a role in the repair of gastric mucosa tissue during *H. pylori* infection. Exposure to the *H. pylori*-derived peptide Hp(2–20) stimulates eosinophil migration and production of VEGF-A and TGF-β, which are two key mediators for tissue remodeling [123]. In vivo experiments also found that Hp(2–20) could cause eosinophil infiltration in rat gastric mucosa with indomethacin-induced injury [123].

Future Directions

Research advances in the recent decades have fundamentally broadened our understanding of eosinophil biology and its multifaceted roles in immunity. Advances in eosinophil biology have also shed light on a series of potential therapeutic targets, such as IL-5 and siglec-8, for eosinophilic diseases including allergic asthma [124, 125]. Inspiringly, a series of novel drugs or monoclonal antibodies (mAb) that specifically inhibit eosinophils have come into the horizon [124, 126]. For example, mepolizumab, the first anti-IL-5 mAb applied in clinical trial for treating asthma, has proved to be effective in both inhibiting eosinophilia and reducing exacerbations rates in asthma [127].

Challenges, however, still remain in current research heading to decipher the various effects of eosinophils and their exact mechanisms in different immunobiological milieus. These difficulties are largely due to the complex immune regulation network, e.g., in the sophisticated scenarios like allograft rejection and anti-tumor immunity. Moreover, the origin and the mechanisms of eosinophilia

Fig. 2. The role of eosinophils and its mechanisms in *H. pylori* gastritis. **A.** OMVs continuously shed from the surface of *H. pylori* in the gastric lumen. OMVs contain LPS and VacA. Part of *H. pylori* form biofilms on the surface of gastric epithelium. **B.** Upon the uptake and internalization of *H. pylori* OMVs, gastric epithelial cells show increased apoptosis and release of IL-8, causing pro-inflammatory effect. **C.** Internalization of *H. pylori* OMV causes gastric epithelial cells to actively express ICAM-1 and release chemokines CCL2, CCL5, and GM-CSF that recruit eosinophil migration from the lamina propria to the epithelium. **D.** Infiltrated eosinophils, expressing the β2 integrin CD11b/CD18, are stimulated by the gastric epithelial cells via binding to ICAM-1, leading to eosinophil degranulation and IL-8 production, which contributes to the inflammatory response. **E.** Eosinophils can also transmigrate through the epithelium into the gastric lumen, where contact with *H. pylori* OMVs may stimulate eosinophil expression of CD11b/CD18, release of RANTES and IL-8, and also eosinophil degranulation, participating in the inflammatory response. **F.** *H. pylori* can probably induce eosinophils in the gastric lumen to produce VEGF-A and TGF-β, accelerating tissue remodeling and would healing of gastric mucosa.
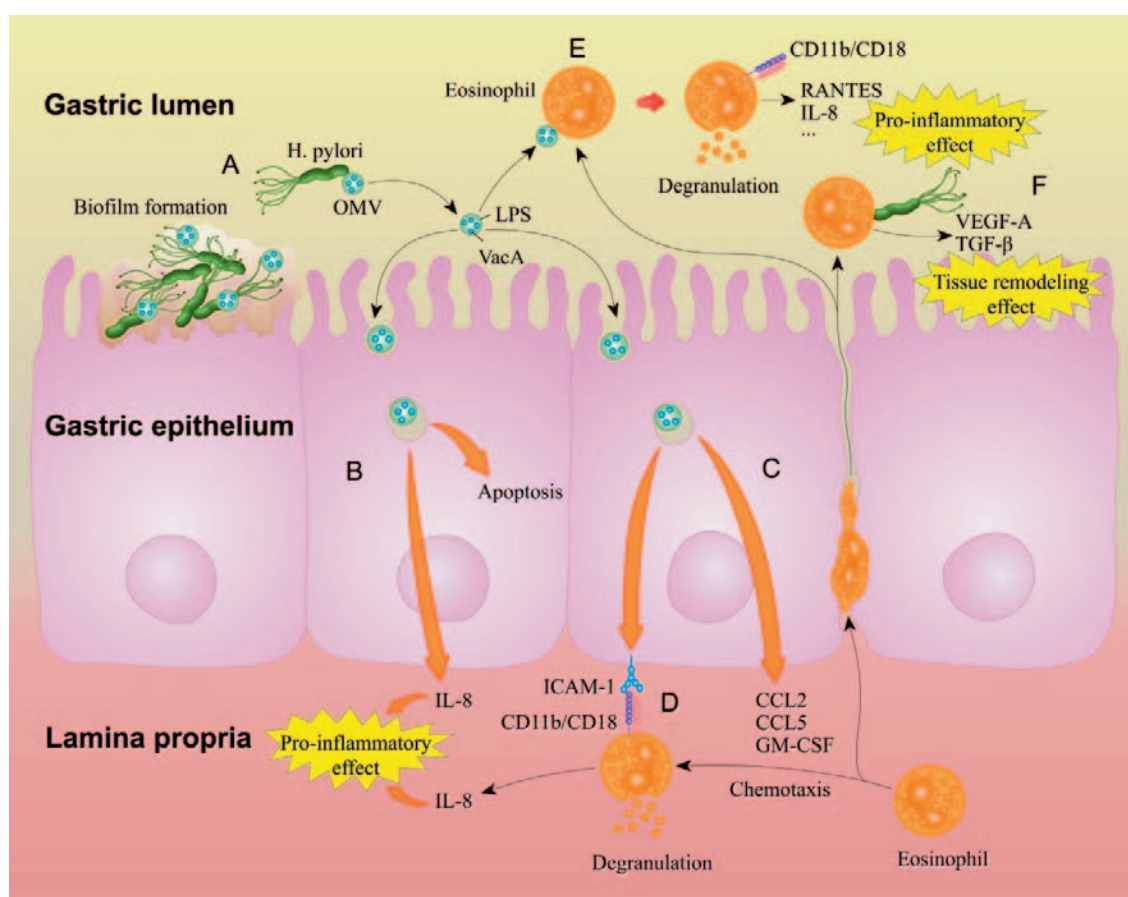
in a broad spectrum of eosinophilic disorders remain to be elucidated, e.g., idiopathic hypereosinophilic syndrome [128] and some eosinophilic skin diseases such as eosinophilic fasciitis, eosinophilic cellulitis, and eosinophilic pustular folliculitis [39].

A fascinating question is the possible relationship between eosinophils, helminth parasitic infection, and protection of autoimmunity. The recent finding that treatment with the parasitic FHES achieves clinical improvement in EAE mice, as mentioned in 'Regulating Other Activities in the Immune System', has demonstrated an essential role of eosinophils in this helminth parasites-induced therapeutic effect on autoimmunity [72]. Interestingly, two recent publications reported that treatment with the phosphorylcholine from certain parasitic helminths can lead to improved clinical findings of autoimmune diseases in murine models of lupus nephritis and those of collagen-induced arthritis [129, 130]. Is it possible that eosinophils also contribute to this therapeutic effect? Further investigation will be needed to unveil the exact role of eosinophils in helminth-elicited protection against autoimmunity. Genetically

engineered mouse models depleted of eosinophils could be of great value for further investigations [8, 22]; however, we should be cautious when applying the conclusion from mice studies in humans.

Disclosure Statement

The authors declare that they have no conflict of interest.

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