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Eosinophils: A Friend or Foe in Human Health and Diseases

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Abstract

Background: Since their discovery, around 150 years, eosinophils research has been a field of changing perspective, and new directions are emerging since then. ***Summary:*** Initially, eosinophils were perceived as terminally differentiated cytotoxic effector cells. Clearly, eosinophils are capable of playing functions other than immune responses, which is not surprising given their intricate interactions with pathogens as well as other circulating leukocytes. Attempts to comprehend the eosinophil biology and functions have yielded remarkable insights into their roles in human health and sickness. The use of FDA-approved eosinophils-targeting biologics has provided exciting opportunities to directly explore the contributions of eosinophils in disease etiology in humans. ***Key Messages:*** In this review, we will focus on the eosinophils' lifecycle and discuss the current state of knowledge from mouse models and retrospective human studies demonstrating eosinophils' roles in the pathogenesis of human diseases such as asthma, cancer, and kidney disorders. Despite three recently approved anti-eosinophil agents, a number of key questions and challenges remain far from settled, thereby generating opportunity to further explore this enigmatic cell. A comprehensive understanding of eosinophils biology and function will surely aid in developing improved therapeutic strategies against eosinophils-associated disorders.

Introduction

Eosinophils are an important yet less common type of white blood cells, making 1–5% of all circulating leukocytes [1–3]. In normal conditions, eosinophil numbers range from 0 to 500/μL of blood in humans, which may increase drastically (by nearly 20 folds) under certain disease conditions. Mostly, a routine blood test can determine the eosinophilic phenotype in asthmatic patients. Evolutionary conservation of eosinophils (or eosinophil-like cells) in vertebrates suggests the vital and favorable

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role of these cells in health and well-being [1, 4]. For long, eosinophils have been believed to favorably impact the innate immunity against parasites and inflammatory diseases; however, eosinophils heterogeneity hints their varying role in health and disease conditions. Over the past decade, their role in homeostasis and immunoregulation has become increasingly popular [2, 5]. Advent of advanced pharmacological tools and the availability of eosinophil-deficient mice strains made it possible to challenge and test the role of eosinophils in immune responses [6, 7]. Precision pharmacology provided approved biological agents to selectively and effectively target eosinophils in humans suffering from eosinophil-related diseases [8]. Development of such agents is providing intriguing insights to understanding the role of eosinophils in health and sickness [2, 9]. Novel eosinophil targeting therapies have renewed the interest in understanding eosinophil biology. Although preliminary observations suggest the involvement of eosinophils in several fundamental process such as glucose homeostasis [10] and antibody production [9, 11, 12], the precise role remains unclear. In this review, we will focus (briefly discuss) on the lifecycle of eosinophils and review their functions in human diseases, while highlighting the recent advances and gaps in our understanding of these roles.

Eosinophilopoiesis (Development of Eosinophils)

Eosinophils, like other circulating lymphocytes, develop from the multipotent hematopoietic stem cells (HSCs) in bone marrow. HSCs expressing CD34 give rise to unique progenitor cells, among which eosinophil-committed progenitors (EoPs) are terminally differentiated into mature eosinophils in the presence of several growth factors (such as cytokines) and transcription factors [11]. Among several receptors expressed on the surface of EoPs, IL-5Rα (high-affinity alpha subunit of IL-5 receptor) is acquired early in the eosinophilopoiesis, and under IL-5 influence, these IL-5Rα+ EoPs exclusively differentiate into mature eosinophils [10] and enter the blood stream to reach different organs (spleen, thymus, gastrointestinal [GI] tract, and lymph nodes). Eosinophils numbers have been reported to have age-linked decline [13]. During their transit from bone marrow to the tissue via bloodstream, eosinophils interact with endothelial cells via integrins and selectins; similarly, they also interact with epithelial cells at the mucosal surfaces [14, 15]. Moreover, eosinophils also interact with other leukocytes and regulate their functions (shown in Fig. 1), ranging from their role in the T-cell selection [16], to enhancing the macrophages' ability to phagocytose the apoptotic thymic cells [17]. When exposed to inflammatory signals, eosinophils enter the lungs or other inflamed tissues, where they function as main mediators of effector function and innate immunity, as well as participate in the adaptive immune responses. Eosinophils can circulate in blood for ~8–12 h and can survive for further ~8–12 days in the tissues in the absence of any stimulation [18].

Although eosinophils are usually found in blood circulation, tissue-resident eosinophils also exist [15]. Under homeostatic conditions, the eosinophils are particularly enriched in the lamina propria of the GI tract (20–30% of leukocytes) and are also present in the thymus, adipose tissue (≤4% of the stromal/vascular fraction), lungs (≤1% of leukocytes), and female reproductive system [19]. Presence of tissue-resident eosinophils at mucosal sites (GI tract, stomach, and intestine) allows them to participate in homeostatic process and perform tissue protective functions. Data have also suggested the positive role of eosinophils in the adaptive immune response via secretion of activation and proliferation-induced ligand, which is required for plasma cell (PC) survival. Further, Lombardi and colleagues have reviewed the eosinophils' role involved in maintaining the tissue integrity and are important in tissue remodeling [20]. In contrast to the lung-resident eosinophils, the eosinophils in the thymus and GI tract are independent of the tissue microbiota [21]. GI-resident eosinophils are maintained throughout life, compared to short-lived thymus eosinophils (decrease ~2 weeks post-birth) [19]. Influence of tissue microbiota on resident eosinophils survival and maintenance implies that eosinophils can respond to and integrate "tissue-tropic" specific signals. Emergence of different methods to detect tissue-resident eosinophils is setting ways for their use as prognostic markers in some malignancies [22, 23].

Eosinophils have been shown to play multiple roles in the allergic and inflammatory conditions. Studies have explored the different roles of eosinophils in homeostasis and in disease conditions. In healthy individuals, under homeostatic conditions, the development and differentiation of eosinophils is regulated by a unique interplay of several important transcription factors, including GATA-1 [24], friend of GATA, and PU.1 (a member of ets family) [25]. Expression of GATA-1 is regulated by an eosinophil-lineage-specific enhancer in *GATA-1* gene itself [12]. Transgenic deletion of a high-affinity double GATA binding site (a unique palindromic sequence) in the HS-2 enhancer region of *GATA-1* gene resulted in the eosino-

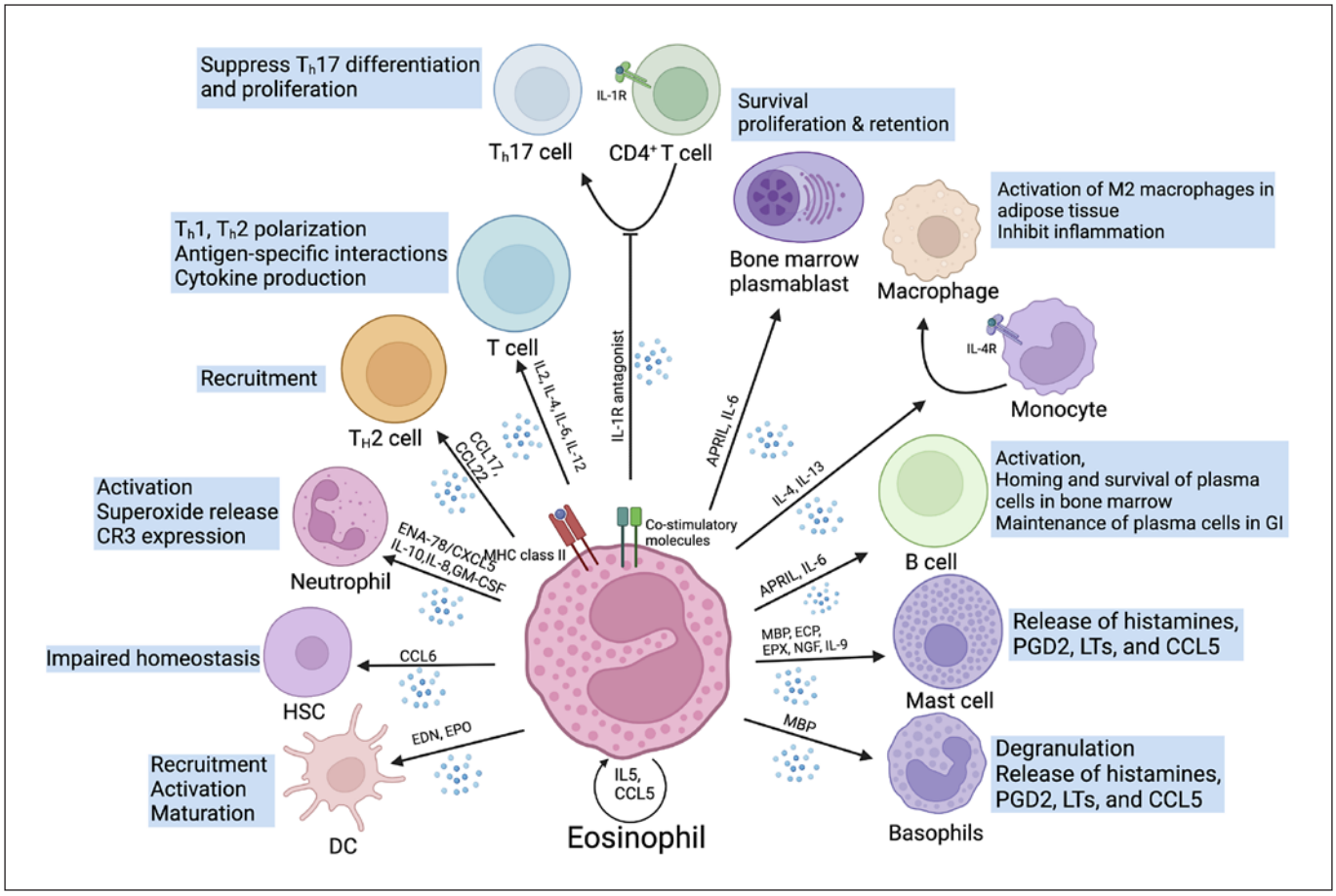

Fig. 1. Map of eosinophils-mediated regulation of other leukocytes functions. Besides acting as effector cells in immune responses, eosinophils can also modulate the functions of several other leukocytes. Eosinophil-derived CCL6 has been shown to negatively regulate the homeostasis of hematopoietic stem cells (HSCs). Eosinophils can secrete GM-CSF, IL-8, and IL-10 to attract neutrophils, which are activated by the eosinophil-derived major basic protein (MBP), and triggers the release of IL-8 and superoxide, increasing their cell surface expression of integrin complement receptor 3 (CR3). Human neutrophils can be directly activated by eosinophil-derived ENA-78/CXCL5. Eosinophils can exhibit cell surface expression of MHC-2 and co-stimulatory molecules and thus can process antigens and stimulate T-cells proliferation as well as antigen-specific cytokine production. Eosinophils can maintain homeostasis of intestinal immunity by suppressing Th17 differentiation via IL-1R release. Moreover, eosinophils-mediated antigen priming of B cells triggers antigen-specific IgM production; in addition, eosinophils play role in the activation, and homing, and sustain the long-term survival of plasmablasts in bone marrow by secreting IL-6 and APRIL (a proliferation-inducing ligand) and are also involved in the maintenance of PCs in GI tract. In response to allergen sensitization or challenge, eosinophils can also regulate the recruitment of Th2 cells, by secreting CCL22 and CCL17. Further, CpG DNA-stimulated eosinophils can release EDN (eosinophil-derived neurotoxin) and induce DC maturation. In addition, intestinal eosinophils release EPO to activate DCs and trigger their migration to draining lymph nodes. Eosinophils can also influence macrophages in adipose tissues via IL-13 and IL-14 secretion and maintain metabolic homeostasis by inhibiting inflammation. Also, EPO is positively involved in the regulation of macrophage phagocytosis. Moreover, eosinophils-derived eosinophil peroxidase (EPX), MBP, eosinophil cationic protein (ECP), and IL9, which trigger activation of mast cells. Activated mast cells then promote eosinophil activation by releasing histamine, prostaglandins (PGD2), chemokines (CCL5), and leukotrienes (LTs), which are known mediators of airway inflammation. MBP has also been shown to trigger airway inflammation, disturb the GI barrier function, and elicit basophil/mast-cell degranulation. Likewise, NGF (nerve growth factor) from eosinophils helps prolong survival of mast cells. Finally, eosinophils are able to extend self-survival by releasing CCL5 and IL5.

phil deficiency in mouse (ΔdoubleGATA, an eosinophil-deficient mouse strain); however, other GATA requiring hematopoietic lineages remained unaffected [12]. Not only these GATA-1 binding sites autoregulate the eosinophilic expression of GATA-1 in mice, these sites functionally activate the transcription of eosinophil-specific

genes [1], including those encoding the major basic protein-1, eosinophil peroxidase, eosinophil-derived neurotoxin, Charcot-Leyden crystal protein/galcetin-10, the eotaxin receptor CCR3, and the IL-5Rα chain [1]. Besides GATA-1, downregulation of FOG-1, low levels of PU.1, and the temporally regulated expression of C/EDP family members (C/EBPα and C/EBPε), the latter of which is expressed as a series of transcriptional repressor and activator isoforms [26], are needed for the eosinophils' terminal differentiation. Finally, the baseline development and differentiation of eosinophils is regulated in part by miRNAs and lncRNAs [27–29], as well as epigenetically by the higher-order regulatory mechanisms that are now being studied in mice models.

The discovery of critical functions of GATA transcription factors and IL-5 along with other key steps in eosinophilopoiesis played instrumental roles in the development of several novel animal models (especially mouse) to study eosinophil-related disorders. Among these innovative mouse models are the Δdbl-GATA-1 and PHIL eosinophil-deficient mice strains [12], recently developed major basic protein-1/EPX double-knockout eosinophil-deficient mice [30], and the Cre-recombinase eosinophil transgenic mice [31]. A relatively recent adding to this list is the *Xbp1*-null mouse, in which the deletion of transcription factor *Xbp1* in multi-lineage hematopoietic progenitor cells results in lineage-specific late maturation arrest during the development of eosinophils (which could be, at least partly, attributed to the dysregulated synthesis and assembly of granule proteins) and a complete lack of circulating eosinophils [32]. Because early developmental stages of eosinophils are not affected and EoPs appear normal in the *Xbp1*-null mice, this model could provide intriguing insights into the importance of eosinophil granule-protein packaging toward the terminal differentiation of eosinophil, as well as a lineage-specific therapeutic target to treat eosinophilic disorders.

Roles of Eosinophils in Health and Diseases

Soon after Ehrlich coined the name for "eosinophils," a relationship between eosinophilia and helminth infection was reported [33, 34]. This gave rise to the hypothesis that eosinophils had roles in anti-pathogen responses, especially against helminth. As with the advancement in health science, the helminth infection became rare today, yet eosinophils persisted. This rose questions about the roles of eosinophils in human health and well-being. Later on, besides their purported protective role in parasitic infections, several studies suggested the involvement of eosinophils in several fundamental homeostatic processes [4], including their role in the fat and glucose homeostasis, to their roles in tumor surveillance, wound healing, and reproductive biology as well as immunoregulation and in terminal differentiation of PCs to produce antibodies against pathogens [4, 6, 35, 36]. Majority of these studies employed either transgenic or inducible eosinophil-deficient mice [37]. Most of these ideas, however, remain to be confirmed in humans. To this end, the critical role of mouse eosinophils in the development of IgA-producing PCs [38, 39] has been recently challenged [40]. Likewise, the controversial role of eosinophils in cancers remains unsettled [41]. Besides their proposed favorable roles under homeostatic conditions, abnormal levels of eosinophils in blood or tissues under unfortunate circumstances may result in the pathogenesis of several diseases in various organs. Multiple disorders have been recognized involving blood eosinophilia (eosinophilic count >500/μL of blood) [42], abnormal accumulation of eosinophils in lungs, liver, kidney, GI tract, and other sites. Fortunately, majority of these disorders are rare; however, in relatively common conditions such as asthma, and other type-2 diseases, occurrence of eosinophilia is a common finding. Despite evidence of their involvement in these conditions, the precise roles of eosinophils as trouble makers or simply a bystander, is far from settled. One such example is the unresolved role of eosinophils in airway remodeling during asthma, both in human and mouse studies [37].

The discovery and advances in the development of eosinophil-deficient animal models, both transgenic and pharmacological, made it possible to explore several aspects of eosinophil biology and functions in vivo, both in health and disease conditions. Now, there are several approved eosinophil-eliminating therapies available against human diseases such as asthma, hypereosinophilic syndromes (HESs), and/or EGPA (eosinophilic granulomatosis with polyangiitis) [43] and the others entering in clinical trials. Such drugs target IL-5/IL-5R, CCR3, Siglec-8, and CRTH2, as well as other less common pathways in eosinophilopoiesis, which is not novel [44–46]. Therapeutically targeting eosinophils have exposed the complex and heterogenous nature of eosinophil-linked diseases. However, with the research ongoing and new information becoming available, new dimensions of the eosinophil's roles are being revealed, providing new answers. Peripheral blood eosinophilia (PBE) has also been observed in several conditions (Table 1). Since the range of eosinophil-linked diseases is rather broad [47], we have

Table 1. Other causes of PBE

Category	Disease
Respiratory	•EGPA, allergic bronchopulmonary aspergillosis •Sarcoidosis
Hematological and neoplastic	•Myeloproliferative HES, lymphocytic-variant HES •Systemic mastocytosis •Certain leukemias and lymphomas •Solid tumors – squamous cell carcinomas, adenocarcinomas, large cell lung carcinomas, transitional cell carcinoma of the bladder
Infective	•Parasitic infection, in particular helminths •Human immunodeficiency virus
Dermatological	•Eczema •Scabies infestation
Iatrogenic	•Certain drug hypersensitivity reactions •Graft versus host disease

selectively reviewed the roles of eosinophils in three human diseases in the sections below, including asthma pathogenesis, tumor surveillance, and kidney diseases in particular, as well as provided an updated discussion on the therapeutic advances in this area.

Defining the Role of Eosinophils in Asthma

Asthma is a chronic inflammatory disorder of lungs, which is characterized by the reversible obstruction of airways that become inflamed and constricted in response to nonspecific spasmogenic stimuli, resulting in symptoms such as shortness of breath coupled with wheezing and coughing [2]. While asthma pathogenesis can vary among asthmatic patients, abnormal accumulation of eosinophils in lungs is generally observed in such patients [48, 49]. In response to inflammatory signals in lungs and airways during asthma, eosinophils are recruited to these sites by the cytokines released from activated Th2 cells and chemokines (mostly of eotaxin family) [2]. Recently, our group reported the release of eosinophil-derived chemokines mCCL6 and hCCL15/23 as well, which interact with CCR1 and promote eosinophilic airway inflammation [50]. Concordantly, OVA-challenged CCL6$^{-/-}$ mice showed significant reduction not only in the airway eosinophils but also in the bone marrow eosinophil precursors. Moreover, BX471 (a CCR1 antagonist) showed similar effect in OVA-challenged asthma model. Since CCL15/23 (human orthologs of CCL6) is significantly elevated in the circulating eosinophils in asthmatic patients, it implies that CCR1 antagonism could be a therapeutic strategy against eosinophilic inflammation in asthma.

Eosinophils role in asthma has been characterized as destructive, and a plethora of literature, mostly from the studies on mouse models of acute or chronic allergic airway disease, supports the pathogenic role of eosinophils in some forms of asthma [44, 51]. At first, the eosinophil role in allergic respiratory inflammation was considered correlative, and then Shen et al. [52] showed a causative association of eosinophils with allergen-induced pulmonary pathologies. The varying contributions of cytokines among asthmatic patients further complicates the asthma pathophysiology. Core features of asthma pathophysiology include airway hyperresponsiveness (AHR), mucus hypersecretion, and tissue damage, as well as airway remodeling. And eosinophils play multiple roles in asthma pathophysiology (including mucus production, tissue damage, air hyperresponsiveness, and airway remodeling). Higher eosinophil count in the peripheral blood and bronchoalveolar lavage fluid of asthmatic individuals compared to healthy controls was observed long ago and has been validated by a relatively recent prospective cohort study involving 130,000 asthmatic patients [53]; however, noneosinophilic asthma conditions have also been recognized [54]. Analysis revealed higher levels of Th2 cytokines in the bronchoalveolar lavage fluid of atopic asthma patients [55], including IL-5, that are linked with the eosinophilic inflammation. Generally, the increase in eosinophil count (degree of eosinophilia) is associated with the severity of disease and exacerbation frequency [53].

Eosinophils secrete several cytokines, such as IL-13, which cause AHR, as well as enhance the differentiation of goblet cells, thereby promoting mucus hypersecretion. Shen and colleagues [56] showed that instead of simply blocking IL-5 production in the airways, corticosteroids (a first-line therapy against eosinophilia) alleviate allergen-induced airway inflammation by suppressing the bone marrow eosinophilopoiesis. Moreover, eosinophil lipid bodies produce leukotrienes (lipid mediators), which also contribute to AHR and in mucus hypersecretion [57]. Chronic inflammation and smooth muscle hypertrophy during asthma may result in reduced lung function which could be difficult to reverse; therefore, it is important to eliminate eosinophils from the airways to control asthma. To this end, our group revealed the anti-eosinophil role of ABT-199, which is a common inhibitor of Bcl-2 (highly expressed on the outer surface of mito-

chondria in inflammatory cells) [58]. For targeted delivery to the bronchial inflammatory cells' mitochondria, we synthesized a pH-sensitive nano-formulated ABT-199, which significantly alleviated the airway inflammation by inducing eosinophils' apoptosis along with alleviating other symptoms of AHR [59].

Discovery and development of anti-eosinophil therapies in asthma led us to a new era of understanding the eosinophils' role in asthma pathogenesis and exacerbations. At a glance, the eosinophil targeting (anti-eosinophil) therapy seems really favorable in treating asthma. To this end, Kuang and Bochner [43] have reviewed in detail and compared both anti-IL-5 (mepolizumab [60–63] and reslizumab [64]) and anti-IL-5 receptor alpha chain (IL-5RA) (benralizumab [65–68]) phase 3 trials that attained FDA approval to treat asthma. In these trials, the most commonly occurring adverse events included viral infection of the upper-respiratory tract, nasopharyngitis, and the asthma exacerbations, with each event covering 7–30% in long-term extension trials [69–72]. However, the overall, anti-eosinophil therapeutic studies on asthma demonstrate that a complete elimination or reduction in the eosinophil count certainly results in improved lung functions and relevant clinical outcomes in patients with reversible lung dysfunction [43]. While some previous studies demonstrating anti-IL-5 can partially reverse airway remodeling are interesting [73], clearly, long-term studies on prolonged eosinophil depletion to explore their effect in protecting or maintaining the lung function are needed [69].

Eosinophils in Cancer Biology

Despite the diverse and complicated etiology of cancers, eosinophils are commonly found in human cancer, including but not limited to, uterine, cervical, GI, bladder, mammary, glioblastoma, pancreatic, and oral cancers [6]. Recently, our group provided evidence of the eosinophils' prometastatic activity via CCL6 axis, which was effectively inhibited by targeting CCR1 (receptor of CCL6), thus providing a strategy to prevent metastatic diseases [74]. Korbecki et al. [75] has reviewed the pro- or anti-cancerous role of chemokine receptors in detail. Although the eosinophil differentiation is common occurrence in cancers, the precise role of eosinophils in cancer growth and progression is complex depending on the tissue type [41, 76], and our understanding of their contributions to tumorigenesis is still evolving.

Eosinophils are recruited at tumor sites by cancer cells and the necrosis they induce, along with the other immune cells that secrete eosinophil attractants [77]. It was demonstrated that type-2 cytokines, IL-5 in particular, secreted by cancer cells [78] attract eosinophils to the tumor site. Moreover, eotaxin 1 (CCL11) and GM-CSF also contribute to the recruitment as well as activation of eosinophils [79, 80]. Regarding the function of eosinophils in tumor growth, researchers have presented conflicting results. IL-4 cytokine has been reported to play anti-tumor function by recruiting eosinophils to the tumor site as well as inducing local expression of eotaxin [81, 82]. Recently, Hollande et al. [83] demonstrated that eotaxin-1-mediated eosinophil recruitment contributes to increased tumor control. Eotaxin's role in cancers can be highlighted by their expression in the human cancer tissues [84].

Exploring the anti-tumor roles of eosinophils in cancers, Lucarini and colleagues demonstrated in mouse model of melanoma that eosinophils recruitment is inversely related to the tumor growth or even incidence. Mechanistically, in addition to the direct cytotoxic effect and metastasis inhibition via degranulation [82], they promote the recruitment, activation, and maturation of other immune cells to enhance tumor rejection [85–88]. Scientists have demonstrated that eosinophil-mediated recruitment of cytotoxic $CD8^+$ T cells to tumor site was essential for controlling tumor in a mouse model of melanoma [87]. A relatively recent study demonstrated that anti-tumor role of eosinophils relies on their IFN-γ signaling [89].

Nonetheless, a plethora of studies have shown the protumor effects of eosinophils. For instance, tumor-produced TSLP-mediated activation of eosinophils promoted tumor growth in a model of cervical cancer [90]. Concordantly, tumor growth was reduced in an oral carcinoma model upon inhibition of eosinophil infiltration [91, 92]. Mechanistically, eosinophils may recruit Tregs [93], release IL-13 to induce immune-suppressive phenotype, or induce macrophage polarization [94]. Overall, several growth factors are released from eosinophils that may directly influence the growth of tumor as well as metastasis, tumor-associated angiogenesis, or even the remodeling of matrix [76]. It appears that functional plasticity of eosinophils enables them to play opposing roles in the tumor pathogenesis [41, 95], and like other immune cells, the role eosinophils play in the cancers could vary depending on the surrounding environmental stimuli [96, 97].

Recent understanding comes from the tumor biopsies, used to analyze the correlation between prognosis and

eosinophils' count in the tumor microenvironment [41, 77]. For instance, given the advantage of these approaches in solid tumors, eosinophilia-linked prognosis can be of pro- (e.g., melanoma, breast cancer), anti- (e.g., lung cancer, Hodgkin's lymphoma), or of unclear significance (e.g., brain cancer) [1, 95]. The downside of this strategy lies in its lack of insight it provides into the precise role of eosinophils in tumorigenesis, considering the eosinophilia could merely be result of type 2 inflammation. Furthermore, methodologies to quantitate tissue eosinophilia and relevant transcriptomic signatures await the discovery and validation.

Studies conducted on mepolizumab treatment in hypereosinophilia (HE) [67, 74] followed the longest treatment and follow-up [98, 99]. The first study reported 7 malignancies, among which 2 were T-cell lymphoma and angioimmunoblastic T-cell lymphoma [98]. However, the study did not contain the control arm, so in comparison to general population, the risk of malignancies was increased. The second study was retrospective involving HES patients treated with high dose of mepolizumab, compared with patients who did not receive mepolizumab treatment for at least 5 years [99]. Results from this study revealed that number of malignancies did not differ significantly between the groups. However, it is worth mentioning that 1 patient developed angioimmunoblastic T-cell leukemia, carrying the similar surface marker that was found on the circulating T-cell clones driving the HES over these years. Another patient was diagnosed with several colonic polyps and later diagnosed with an attenuated form of familial adenomatous polyposis that leads to a weaker colorectal cancer phenotype.

Future studies might be directed to explore the eosinophils' role in malignancies, while considering the individual risks and different cancer types. As suggested by Kuang and Bochner [43], one strategy could be "to take a malignancy with well-understood natural history, e.g., colon cancer, and assess whether an increase or decrease is observed in the frequency or types of polyps or lesions while screening colonoscopies." Currently, a rather broad range of cancers reported in individuals undergoing anti-eosinophil therapy is rather broad and may represent lymphoproliferative illnesses that could present with eosinophilia and hence be misdiagnosed as HE [100] or the elevated risk of hematologic malignancy associated with lymphoid HES, such as discovered by our group's previous study that the eosinophil-derived CCL6 impairs homeostasis of HSCs [101, 102]. Both findings appear encouraging, at least for now, in terms of eosinophils depletion not displaying any consistent or concerning signal for an elevated risk of acquiring malignancies. And it is important to note that neither eosinophil-deficient mice nor eosinophil-deficient humans appear to be at elevated risk of cancer development [1].

Eosinophils in Kidney Disorders

In the past decade, research has led us to believe that eosinophils are more than just an end point in pathogen clearance after an infection [103] or a maladaptive response to allergic reactions such as asthma. Despite the renal involvement being rare in the HES disorders [104], eosinophilia has been commonly reported in many renal diseases [105–107]. However, the data linking idiopathic HE to renal disorders are rare [108]. A retrospective study conducted by Disckin and colleagues on 1,339 patients, who were referred to nephrology service after hospitalization, showed multiple associations with eosinophilia [109]. In a relatively recent case-control study by Tariq et al. [110], they demonstrated that peripheral eosinophilia is an independent predictor of tissue eosinophilia and subsequent progression to end-stage kidney disease. Given that ~20–70% of cholesterol crystal embolism patients present eosinophilia [111–116], Mochida et al. [117] demonstrated in a single-centered cohort study that eosinophilia served as a prognostic factor for renal death among cholesterol crystal embolism patients. Besides, Gauckler and colleagues [118] also reviewed acute or chronic kidney diseases and other special condition associated with eosinophilia. Studies have shown association of PBE with several other renal pathologies in some cases. For instance, PBE rarely occurs in the diabetic nephropathy, and might be linked to a drug-induced hypersensitivity reaction [119, 120], or might result from an accompanying interstitial nephritis [121]. Moreover, a prospective study compared the leukocyte counts among US veterans and showed slightly elevated eosinophil count in peripheral blood of chronic kidney disease patients [122]. Among diabetics (type-2 diabetes), eosinophilia was linked to albuminuria [123]. Further, uremic patients had bone marrow eosinophilia without increased PBE but higher level of circulating eosinophil cationic protein. This abnormal homeostasis pointed toward a uremia-induced accelerated turnover of peripheral eosinophils [124, 125].

Hemodialysis-associated eosinophilia (HAE) usually occurs among patients on hemodialysis. Components of the dialysis circuit often cause allergic reactions which result in HAE [126]. In the 1970s, dialyzer reactions oc-

curred quite frequently, with reported PBE prevalence in up to 39 percent of all patients on maintenance dialysis [127]. A commonly used sterilizing agent at that time, ethylene oxide, was linked with allergic reactions and HAE [128–130]. Later, the prevalence of hemodialysis-associated reactions was decreased by gamma irradiations and steam as sterilization techniques, as well as by replacing the traditional cuprophane or cellophane membrane with ester-modified cellulose or synthetic polymer-base membranes [126]. Comparatively, the PBE is usually mild and episodic in patients on peritoneal dialysis, while often being linked to peritoneal fluid eosinophilia (PFE) [131]. In comparison to HAE, the occurrence of peritoneal dialysis-associated eosinophilia has diminished over the past decades. Compared to an earlier study (reporting PFE prevalence of 60.8%), a more recent prospective study on patients undergoing continuous ambulatory peritoneal dialysis reported only a smaller prevalence (>10%) of PFE, with no correlation to PBE [132]. Usually, following catheter replacement, PBE is detected in asymptomatic patients and resolves shortly after; therefore, steroid treatment is not suggested. However, in severe cases where it becomes chronic or with permanent changes in the function of membrane, the corticosteroid therapy has been found beneficial in several cases. Moreover, montelukast (leukotrienes receptor antagonist) has shown therapeutic efficacy in one case report and hence could be a therapeutic option [133].

Both the tissue eosinophilia and PBE are associated with AAR (acute allograft rejection) in the kidney transplant recipients and therefore (tissue eosinophilia in particular) should be considered as the predictors of poor transplant outcomes [134]. Gauckler et al. [118] reviewed retrospective studies on patients with AAR. One study showed PBE occurrence in 20–36% patients, and a higher mean prevalence (1.5–3%) of PBE in AAR was found compared to controls (0–0.9%). Severity of the AAR outcomes was correlated to the PBE percentage in second study. However, the absolute eosinophil count was not significantly correlated. A more recent study confirmed tissue eosinophils with impaired allograft outcome, but did not detect PBE, which could be attributed to the high daily dose (10 mg) of prednisone among patients under study [135]. Former two studies imply that PBE is slightly increased in AAR and associated corticosteroid therapy possibly hinders the diagnosis.

Gauckler et al. [118] suggested a three-step strategy in the management of patients suffering from unexplained PBE and acute kidney injury (refer to Fig. 3 in their review). Briefly, they suggested a primary assessment to exclude any classical eosinophilic disorders, such as allergies, parasitic infections, and hematologic neoplasia [118]. Next, a screening for PBE-linked kidney disorders along with a comprehensive assessment of renal function parameters should be made to narrow down the probable kidney disorders. In the absence of any specific urinary findings, PBE could be a beneficial diagnostic marker for acute interstitial nephritis (AIN). In acute kidney injury settings, AIN is discovered in about 5–18% of biopsies, with increasing prevalence over the last years [136]. Given the three-quarter prevalence of drug-induced AIN among all the cases, Gauckler et al. recommend a screening for the recently made changes in the patient's medications, particularly focusing on any PPIs, NSAIDs, or antibiotics; however, any drug can induce AIN. Any potential triggers should be withdrawn promptly and the kidney function should be monitored for 3–5 days. Unfortunate failure to recover the kidney function during this time should be followed by kidney biopsy, and an early steroid treatment [137, 138], and a more targeted immunosuppressive measure should be taken.

Therapeutic Implication against Eosinophilia and Long-Term Safety of Anti-Eosinophil Strategies/ Eosinophil Deficiency

Among the available FDA-approved strategies to target eosinophils in HES, corticosteroid is the first-line strategy; however, its long-term usage has been linked to significant toxicity and lack of response in some patients [139]. A second-line treatment biologic (interferon-α, hydroxyurea, methotrexate, and imatinib) is generally chosen based on the clinical subtype of HES and its linked medical problems as well as the cost and preference of patient and physician. Owing to the varying response rate and associated side effects, discontinuation of second-line therapy is common. Some of the new and improved targeted agents with increased efficacy and lower cytotoxicity have currently either gained FDA approval (mepolizumab, reslizumab, and benralizumab) or are in clinical trials (lirentelimab [AK002], dexpramipexol [AZD1981], fevipiprant [GW766994], and timapiprant) [1, 43].

Recent clinical trials of mepolizumab led to the FDA approval of these agents in eosinophilic asthma and EGPA, with specific dosage indications. Shortly after, reslizumab and benralizumab were also approved in the treatment of eosinophilic asthma [1, 20, 140]. Mechanistically, both (mepolizumab and reslizumab) these agents are the monoclonal antibodies and neutralize IL-5, which

is a critical cytokine for the eosinophil lifecycle (development, activation, and survival). On the other hand, benralizumab is an "afucosylated monoclonal antibody against IL-5RA," which is expressed on the cell surface of eosinophils as well as basophils and mast cells. Once benralizumab binds to the IL-5RA, it attracts IgG receptors on the macrophages and NK cells that can perform antigen-dependent cellular phagocytosis/cytotoxicity, respectively, and eliminate the target cell. In terms of eosinophil depletion efficiency, anti-IL-5 therapy could be described as partial or significant depletion strategy compared to anti-IL-5RA therapy which results in near-complete depletion of eosinophils [43, 141].

More recently, our groups' research presented the pathogenic role of CCR1 in eosinophilic asthma and that CCR1 antagonist alleviated the eosinophilic inflammation [50]. Chemokines, predominantly expressed by the airway epithelial cells, attract eosinophils to the airways. Since the chemokine receptors are G-protein-coupled receptors, they can block small molecules that can be taken orally as tablets, a clear advantage over inhaler-based therapies or expensive injectable biologics. Although several CCR1 antagonists (including MLN3897, BMS-817399, CP-481, and CX-354) have been tested and well tolerated in the clinical studies, they failed in phase 2 and did not progress to clinical development. Clearly, further research and improved biologics are required to support the CCR1 antagonists in clinical development. Structural studies have suggested models to develop biased antagonists with expectedly greater efficiency and lesser adverse effects. Our groups' recent research has revealed that "although the native form of CCL15 produces balanced agonism, different N-truncated forms of CCL15 interact with CCR1 to produce biased agonism, and shorter forms induce reduced recruitment of β-arrestin and therefore greater signaling through Gi" [142]. This implies that more effective CCR1 antagonists that can produce biased agonisms would have improved efficacy and might be possible in coming years.

Safety of anti-eosinophil therapies or eosinophil deficiency is an important area to consider while benefiting from these therapeutic options [69, 143]. Prolonged administration of anti-eosinophil biologics may have different impact on the health. Kuang and Bochner have beautifully reviewed the safety of anti-eosinophil therapies and their "immediate and short-term" effects and discussed their associated risk of infections as well the effect of eosinophil deficiency on metabolism, wound healing, and pregnancy [43]. Although several mouse models have shown the capability of eosinophil-deficient mice to survive and reproduce [12, 144], congenital eosinophilic deficiency in humans has not been reported. It could be attributed to the underreporting due to absence of any characteristic clinical phenotype. An analysis at university of Pittsburgh, involving 24,300 patients, found no case of unexplained eosinophilia. Rare cases of acquired deficiency, however, was reported, mostly in the patients suffering from Good's syndrome [145], and did not show any characteristic clinical features [146]. Despite the absence of any problematic safety signals to date, outcomes of the long-term eosinophils deficiency remain unidentified [8]. To this end, along with careful pharmacovigilance, clinical studies should be designed to assess the effects of eosinophil deficiency on homeostatic pathways. Nevertheless, long-term prospective studies on chronic depletion of eosinophils will certainly advance our knowledge of eosinophils' role in health and sickness.

Conclusion and Future Perspective

Since their discovery, the understanding of eosinophil biology and their role in health and disease has tremendously evolved. Past decade has seen major developments in the eosinophil-targeting therapies, ranging from those targeting eosinophils based on their surface-markers to growth factors, including those whose mechanism of action remains unknown. Of prime interest are the innovative mouse models which lack eosinophils, either congenitally or conditionally. These mouse models have improved our understanding of eosinophil functions in human diseases, as well as revealed their unexpected roles in homeostatic conditions.

Discovery and approval of eosinophil-targeting biologics has not only allowed better management and therapeutic care of patient but also provided insights into disease pathogeneses and human physiology. In clinic, use of three FDA approved anti-eosinophil agents (4) has demonstrated efficacy against eosinophil-associated disorders, such as asthma, EGPA, and HES, thereby firmly cementing the eosinophils' pathogenic role in these diseases. Ongoing clinical studies might expand this list in future; however, comparison studies are also needed to optimize the eosinophil depleting strategies in patients suffering from different eosinophil-associated diseases. Finally, long-term perspective studies on after eosinophils' depletion with continued monitoring of associated safety signals are mandatory and will help advance our understanding on eosinophils' contribution in human health and disease.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Author Contributions

Madiha Zahra Syeda wrote the manuscript. Tu Hong helped in writing the manuscript. Chao Zhang, Songmin Ying, and Huahao Shen provided guidance and supervised the final version of the manuscript. All authors approved the final version.

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