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Targeting Eosinophils in Allergy, Inflammation and Beyond

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Abstract

Eosinophils can regulate local immune and inflammatory responses, and their accumulation in the blood and tissue is associated with several inflammatory and infectious diseases. As such, therapies aimed at eosinophils may help control diverse diseases, including atopic disorders such as asthma and allergy, and diseases not primarily associated with eosinophils such as autoimmunity and malignancy. Recently, eosinophil-targeted therapeutic agents aimed at blocking specific steps involved in eosinophil development, migration and activation have entered clinical testing and have produced encouraging results and insights into the role of eosinophils. Herein, we describe recent advances in the development of first generation eosinophil-targeted therapies and highlight strategies for using personalized medicine approaches for eosinophilic disorders.

Introduction

Eosinophilia (see text box), defined as a peripheral blood eosinophil count greater than 450 cells per microliter, is associated with numerous disorders including allergies, drug reactions, helminth infections, Churg-Strauss syndrome [glossary], some malignancies and metabolic disorders, eosinophilic gastrointestinal disorders, and hypereosinophilic syndrome. Eosinophils are bone marrow-derived leukocytes that are normally less than 5% of leukocytes in the blood, but can be found in higher numbers in tissues such as the bone marrow and gastrointestinal. Recruitment of activated eosinophils from the bloodstream into tissues can occur under a variety of conditions and lead to the release of preformed and newly synthesized products, including cytokines, chemokines, lipid mediators and cytotoxic granule proteins, that can initiate, quickly escalate and sustain local inflammatory and remodeling responses.

Eosinophil-rich inflammation has long been associated with parasitic infestation and allergic inflammation. A body of evidence including clinical studies and animal models of asthma has demonstrated a causal role for eosinophils in asthma pathogenesis including airway hyper-reactivity, elevated mucus production and airway remodeling. These studies include elegant experiments in eosinophil-lineage-deficient mice that have protection against features of asthma, although not in all cases[1,2]. Clinical studies have revealed an important role for eosinophils in asthma exacerbations[3,4]. Recent evidence also supports a broader role for eosinophils in health and disease with their emerging role in malignancy and in regulating antibody production[5,6]. In addition, eosinophils can frequently be found surrounding solid tumors[6,7] and can participate in tumor immune surveillance influencing the incidence of tumor formation[8,9]. Recent studies have proposed a role for eosinophils in humoral immunity as an important source of pro-survival factors for long-lived plasma cells in the bone marrow[10,11]. In autoimmune disease in which plasma cells have a pathologic role via autoantibody production, eosinophils may prove to be an attractive therapeutic target. Thus, treatments that specifically target eosinophils are likely to be effective in controlling a number of important and prevalent diseases in the fields of allergy, infectious disease, autoimmunity and malignancy. The increasing incidence of eosinophil-associated

disorders, including eosinophilic gastrointestinal disorders and asthma, in high income and low income countries highlights the important and expanding need for eosinophil-targeted therapies[12,13].

There have traditionally been two major approaches to drug development for eosinophilic diseases: blocking recruitment of eosinophils into organs and impairing the survival of mature eosinophils. As discussed below, innovative new strategies for future drug development include blocking eosinophil production in the bone marrow and inhibiting eosinophil activation.

Pathogenic actions of eosinophils

Eosinophils develop in the bone marrow from hematopoietic stem cells[14,15]. During human hematopoiesis, common myeloid progenitors give rise to a $CD34^{+}IL\text{-}5R\alpha^{+}$ eosinophil progenitor[14], which is increased in numbers in several diseases including allergies, helminth infections [glossary] and hypereosinophilic syndrome [glossary], suggesting that increased production of eosinophil progenitors is an important checkpoint in disease-associated eosinophilia[14,16]. Mature human eosinophils contain crystalloid secondary granules, which are primarily composed of highly charged basic proteins, including two major basic proteins, eosinophil cationic protein, eosinophil-derived neurotoxin and eosinophil peroxidase[17]. Deposition of granules released from eosinophils in tissues is a common finding in eosinophil-associated diseases and likely contributes to disease pathogenesis[18–22]. Major basic protein and eosinophil peroxidase are toxic to a number of different cell types, including airway epithelial cells[23,24] and cardiac muscle cells[25], and may contribute to tissue damage and organ dysfunction in patients with asthma or hypereosinophilic syndrome. Eosinophil-derived neurotoxin, eosinophil cationic protein belong to the RNase A family of granule proteins that have ribonuclease activity[26], are associated with host defense against viruses[27] and may have a role in tissue remodeling[28]. In addition to these cationic proteins, eosinophil granules contain a plethora of preformed cytokines, chemokines, enzymes and growth factors, which results in diverse biological activity for eosinophils in infection and inflammation[29]. In addition to preformed mediators stored in the granules, eosinophils can release upon activation *de novo*-synthesized mediators including IL-4, which has the capacity to stimulate adaptive immunity.

Current therapies and moving forward

Glucocorticoids are the most effective current therapy used to reduce eosinophil numbers in the blood and tissue (Table 1), but the pleiotropic effects of corticosteroids can result in potentially harmful side effects and limit their therapeutic use. Glucocorticoids promote eosinophil clearance both by directly inducing apoptosis and by inhibiting pro-survival signals induced by cytokines such as IL-3, IL-5 and GM-CSF[30–32]. The tyrosine kinase inhibitor imatinib, the first and only drug approved for hypereosinophilic syndrome, can be an effective treatment to reduce blood eosinophil levels, but only for patients who harbor genetic alterations that involve fusion genes that result in hypereosinophilic syndrome, such as the fusion of the *FIP1L1* gene with *PDGFRA*[33,34]. Therapy directed against the eosinophil growth factor IL-5 is effective in animal studies[35] and has recently been tested in clinical trials (as discussed below); while it results in a substantial decrease in blood eosinophil counts in several different diseases, such as hypereosinophilic syndrome, eosinophilic asthma and eosinophilic esophagitis, the reduction of tissue eosinophilia and improvements in symptoms have been variable depending upon the disease and patient subgroup[4,36–38]. These and other new drugs that are based on an improved understanding of the mechanism of eosinophilia and eosinophil effector functions are thus desperately needed.

Blockade of Eosinophil Recruitment

A network of cytokines, adhesion molecules, chemoattractants and receptors regulate eosinophil trafficking[17]. A number of these molecules have been investigated as candidates for blocking eosinophil accumulation in tissues.

CCR3 and CCL11

CCR3, a seven-transmembrane cell surface G-protein-coupled receptor, is a promiscuous chemokine receptor that has up to eleven different ligands[39,40]. These ligands include the eotaxins [CCL11 (also known as eotaxin-1), CCL24 (also known as eotaxin-2) and CCL26 (also known as eotaxin-3)], which are high-affinity agonists for CCR3, a chemokine receptor that is selectively and abundantly expressed on eosinophils and promotes the accumulation of eosinophils. In addition to eosinophil chemoattraction, eotaxin-mediated activation of CCR3 triggers the respiratory burst apparatus, induces eosinophil degranulation and upregulates expression of adhesion molecules[41,42].

The CCR3-CCL11 axis is crucial for the recruitment and accumulation of eosinophils in numerous disease states including experimental models of asthma and eosinophilic gastrointestinal disorders[43–46]. In addition, increased expression of CCR3 and its ligands correlates with severity of disease in patients with asthma[47]. Thus, antagonism of CCR3 had been a promising target for therapeutic intervention in eosinophil-associated inflammation. In preclinical studies, low-molecular-weight CCR3 antagonists reduced airway eosinophilia in chronic experimental asthma models[48,49]. A selective, competitive antagonist for CCR3 was evaluated in a Phase II trial (NCT01160224) for effectiveness in reducing sputum eosinophilia in subjects with mild to moderate asthma, but no results have been reported. A neutralizing antibody, bertilimumab, directed against CCL11 (eotaxin-1), has been evaluated for reducing nasal congestion in a Phase II trial; allergen-induced nasal obstruction was significantly reduced, and there was a trend toward reduced numbers of eosinophils in nasal mucosa biopsies, although this trend did not reach statistical significance, perhaps due to the small sample size of patients[50]. The application of this drug for other eosinophil-associated disorders, such as subgroups of patients with ulcerative colitis, is currently being pursued (NCT01671956).

Although *in vitro* and *in vivo* preclinical studies have supported a crucial role for CCR3 and its ligands in recruiting eosinophils into inflamed tissues, the lack of significant efficacy in clinical trials to date may be related to redundant pathways in the diseases being studied. The redundancy of the chemokine and chemokine receptor system and the exquisite sensitivity of eosinophils to other chemoattractant molecules likely contribute to the decreased therapeutic potential of CCR3 blockade. However, there are likely to be some diseases that are more selectively driven by an eotaxin-dependent pathway, such as eosinophilic esophagitis, in which CCL26 is the most highly induced gene in the esophagus and there is limited induction of other major eosinophil chemoattractants[51]. Indeed, mice genetically engineered to be deficient in CCL11 or CCR3 are protected from the development of esophageal eosinophilia[51,52]. In addition, since eotaxin elicits eosinophilia in concert with other eosinophil-directed cytokines such as IL-5, combination therapy with IL-5-targeted and eotaxin- or CCR3-targeted therapy may be more effective. Indeed, mice with targeted ablation of IL-5 and eotaxin-1 have increased protection against experimental asthma compared with ablation of either gene alone[53].

Adhesion Molecules

Eosinophil migration from the bloodstream into various tissues results from a specific interaction between integrins on the surface of eosinophils with adhesion receptors on the

surface of the vascular endothelium[17]. In experimental models, recruitment of eosinophils into the lung in response to allergen challenge is dependent on VLA-4 (Very Late Antigen-4, an integrin dimer composed of CD49d and CD29)[54], prompting investigations into targeting VLA-4 to inhibit eosinophil accumulation in inflamed lungs. Preclinical studies demonstrated that VLA-4 blockade using a CD49d-specific antibody inhibited airway eosinophilia in an experimental asthma model[55]. Small-molecule VLA-4 antagonists have also been evaluated for potential clinical utility, with studies demonstrating inhibition of eosinophil adhesion to VLA-4 and a significant reduction (up to 80%) in skin eosinophilia induced by intradermal injection of CCL11 in mice[56].

Of note, marked peripheral blood eosinophilia (more than 2000 cells per mm^3) in three patients with multiple sclerosis has been reported to develop following treatment with natalizumab, a humanized monoclonal antibody against CD49d[57]. Whether this was mediated by a direct inhibitory effect on eosinophil adhesion resulting in retention of eosinophils in the bloodstream is worthy of determining. Taken together, these data suggest that while blockade of integrin and adhesion receptor interaction could result in decreased eosinophil accumulation in tissues, there is the potential for inducing secondary blood eosinophilia with its associated risks, which could limit the therapeutic benefit of this strategy.

CRTH2 and PGD_2

Prostaglandin D_2 (PGD_2) is a product of arachidonic acid metabolism that is generated and released by activated mast cells during an allergic response[58]. PGD_2 induces eosinophil chemotaxis and mobilization of mature eosinophils from the bone marrow[59,60]. The effects of PGD_2 are mediated through two G-protein-coupled receptors, DP1 and CRTH2 (Chemoattractant Receptor of Th2 cells; also known as DP2, GPR44 and CD294). CRTH2 is expressed on the surface of Th2 cells, eosinophils and basophils[61].

In experimental asthma models, CRTH2 mediates eosinophil recruitment into the lung[61,62]. Furthermore, PGD_2 activates eosinophils via CRTH2 resulting in release of granule proteins and respiratory burst activity[63]. As PGD_2 signaling results not only in eosinophil recruitment but also in eosinophil activation and mobilization of mature eosinophils from the bone marrow, the potential for clinical benefit from intervening in this pathway is high. Thus, antagonizing CRTH2 has been pursued as a potentially useful strategy for treatment of eosinophil-associated disorders. Low-molecular-mass CRTH2 antagonists partially attenuate pulmonary eosinophilia in a number of different models[64,65]. A published Phase II study of the effectiveness of a CRTH2 antagonist in patients with moderate persistent asthma showed a significant reduction in the geometric mean sputum eosinophil count from 2.1% to 0.7% after treatment[66]. While this may appear to be a small difference, reductions in sputum eosinophils (even at this low level) correlates very well with improved asthma control[67]. Another Phase II study is in progress to evaluate CRTH2 effects on reducing sputum eosinophilia in patients with persistent asthma (NCT01545726). Preliminary data from a clinical trial treating patients with active eosinophilic esophagitis with a CRTH2 antagonist show a moderate reduction in tissue eosinophilia[68]. More clinical studies are needed to evaluate the effectiveness of blockade of CRTH2, and possibly DP1, on blood and tissue eosinophilia in human disease.

Histamine H4 Receptor

The histamine H4 receptor is a G-protein-coupled receptor expressed on cells of the immune system, including eosinophils. Activation of the H4 receptor by its ligand histamine results in eosinophil chemotaxis to sites of allergic inflammation and increased expression of adhesion molecules on the surface of eosinophils[69,70]. Small-molecule antagonists of the H4

receptor inhibit eosinophil migration *in vitro*[71,72]. In addition, antagonism of the H4 receptor inhibit eosinophil infiltration into the esophageal epithelium in an allergen-induced model of eosinophilic esophagitis in guinea pigs[73]. To date, only preclinical assessment of candidate drugs targeting H4 receptors have been completed, but the results from these studies advocate the H4 receptor as a drug target for the treatment of eosinophil inflammatory disorders[72,74].

Interleukin-13 and Interleukin-4

Numerous studies to date support an important role for IL-13 in eosinophil-associated disorders[75,76]. In animal models, IL-13 is a key cytokine that regulates the recruitment of eosinophils into inflammatory sites, primarily through induction of chemokine expression[77,78]. For example, a whole genome expression analysis of primary human esophageal epithelial cells showed that *CCL26* exhibited the greatest increase in expression levels following induction with IL-13[79].

In patients with asthma, expression of IL-13 has been associated with eosinophil recruitment into the airway in response to allergen challenge[80,81]. Thus, it has been hypothesized that IL-13 neutralization would inhibit allergen-induced eosinophil inflammation. However, when the effectiveness of two fully humanized IL-13–specific antibodies on allergen-induced responses in mild asthmatics was recently assessed, there were no changes in peripheral blood eosinophil numbers or sputum eosinophils[82]. Treatment of patients with uncontrolled asthma with lebrikizumab, a humanized monoclonal antibody that binds IL-13, resulted in modestly increased peripheral blood eosinophil counts, suggesting that IL-13 blockade decreased eosinophil recruitment from the bloodstream into the lungs, but in patients with persistently increased eosinophil production this may lead to blood eosinophilia[83]. In addition, an IL-13-blocking antibody had no effect on nasal lavage eosinophil numbers in patients with allergic rhinitis in a nasal allergen challenge model[84].

These studies suggest that IL-13 blockade alone may be insufficient to inhibit tissue eosinophilia and blood eosinophilia, likely due to overlapping roles of IL-13 and IL-4 in promoting eosinophil-rich inflammation[85,86]. Accordingly, the therapeutic effects of pitrakinra, an IL-4 variant and fully human monoclonal antibody against IL-4Rα that blocks both IL-4 and IL-13 activity, have been investigated in Phase II clinical trials[87,88]. However, inhibition of the biological activity of both IL-4 and IL-13 resulted in no significant change in the number of sputum eosinophils[87,88] or peripheral blood eosinophils[88] in atopic asthmatics.

Summary of Blockade of Eosinophil Recruitment

Preclinical studies suggest that blockade of eosinophil migration from the bloodstream into tissues has the potential to be therapeutically useful, but there has been limited clinical success to date with current targets and approaches. Studies have emphasized the importance of selecting patients to participate in clinical trials on the basis of mechanism of action of the drug[4,83,89] and that the lack of efficacy may be due to inclusion of patients not likely to respond to the drug on the basis of the patients' varying phenotypes[90]. For example, the effectiveness of lebrikizumab treatment was greater in patients with high periostin [glossary] and blood eosinophil levels, suggesting that these biomarkers could be used to identify patients with an asthma phenotype that is driven by IL-13[83]. It is notable that these may be the specific group of patients that are more likely to respond to specific and effective anti-eosinophil therapeutics either alone or in combination with anti-IL-13/IL-4 blockers. More work is needed to identify those patients who would be most likely to respond to migration-targeted therapy. The lack of effectiveness of current targets may also be due to the complex regulation of eosinophil recruitment into inflammatory tissue, especially the lung, which is

often the first organ for which eosinophil-targeted therapy is tested (because of the large potential market for asthma); a single target may be insufficient to block tissue eosinophilia and prevent eosinophil-mediated pathology.

Inhibition of Eosinophil Survival

Eosinophils are differentiated from multipotent stem cells in the bone marrow under the influence IL-3, GM-CSF and IL-5[91]. The most eosinophil-specific of these cytokines is IL-5, which has key roles in proliferation and maturation of the committed progenitors, as well as in migration and survival of mature eosinophils[92,93]. As differentiation and maturation of the developing eosinophil progresses, the cell loses the capacity to proliferate. The life cycle of the terminally differentiated mature eosinophil usually ends physiologically by apoptosis, although necrosis with release of functionally active granules, especially following cellular activation, can also occur. It is notable that eosinophilic inflammatory tissue often contains abundant and intact granules that are extracellular to the eosinophil, suggesting that these may be functionally relevant in the pathogenesis of disease[94]. Eosinophils have high rates of spontaneous apoptosis[95], and a several mediators, including IL-5, promote eosinophil survival[32,96,97]. Agents that interfere with survival signals for eosinophils are being actively developed and have begun to be tested for therapeutic value.

IL-5 andIL-5Rα

As IL-5 signal transduction has been shown to participate in eosinophil development, survival and effector function, IL-5 and its specific receptor subunit IL-5Rα have been attractive therapeutic targets for eosinophil-associated disorders[93]. Two different humanized IL-5–specific antibodies, mepolizumab and reslizumab, have been developed and tested in clinical trials for asthma[3,4,89], hypereosinophilic syndrome[36], eosinophilic esophagitis [glossary][37,98,99] and nasal polyposis[100]. Treatment with IL-5-targeted therapy results in a dramatic decline in blood eosinophilia but has variable efficacy in reducing tissue eosinophilia and no effect on the numbers of eosinophil progenitors in the bone marrow. IL-5-targeted therapy reduced esophageal eosinophil infiltration[99] and intraepithelial eosinophil counts[37,101] in patients with eosinophilic esophagitis but had variable effects on symptoms, which was in part likely to be related to the use of non-disease-specific patient-reported outcome measures[37,101]. In asthma, initial studies showed no improvement in lung function in patients with asthma who were treated with reslizumab, but post-hoc analysis of patients to identify those with sputum eosinophilia at baseline showed a significant increase in pulmonary function for patients receiving reslizumab compared with placebo[3,102]. In other studies that included patients with persistent asthma and with baseline sputum eosinophilia, reductions in severe exacerbations[4] and in daily corticosteroid dose[89] and improvements in lung function[3,38] were observed for those patients receiving IL-5-targeted therapy. These findings emphasize the importance of selecting patients with eosinophilia in disease-related tissues such as the airway in patients with asthma for maximum therapeutic benefit.

Another approach to blocking eosinophils is to therapeutically target the IL-5 receptor with a neutralizing and cytotoxic antibody. Benralizumab is a humanized monoclonal antibody that binds to IL-5Rα and blocks the biological activity of IL-5. Importantly, benralizumab also induces apoptosis of eosinophils through antibody-dependent, cell-mediated cytotoxicity[103]. As benralizumab reduced the numbers of peripheral blood eosinophils and eosinophil precursors in the bone marrow of non-human primates[103], there is considerable potential in targeting IL-5Rα for clinical efficacy in eosinophil-associated diseases. In early Phase I/II studies, benralizumab treatment resulted in significant and prolonged peripheral blood eosinopenia [glossary] in patients with mild atopic asthma[104].

Another strategy used to inhibit IL-5-mediated effects of eosinophils is through downregulation of the other subunit of the IL-5 receptor, the common β chain (βc chain), which is shared with IL-3, IL-5 and GM-CSF receptors. The inhaled antisense oligonucleotide [glossary] drug candidate TPI ASM8 contains antisense oligonucleotides directed against the mRNA for human CCR3 and βc. In an open-label study, TPI ASM8 reduced allergen-induced sputum eosinophil and eosinophil progenitor recruitment into the airway[105]. Further studies are ongoing to test the clinical usefulness of this strategy of downregulating receptors that are important for growth and recruitment of eosinophils via degradation of their respective mRNA. Improvements in the delivery and longevity of antisense oligonucleotides will help increase the clinical potential of this technology[106,107]. Another possibility, although not yet tested for eosinophil-associated diseases, is promoting the expression of the soluble form of IL-5Rα through the use of splice-switching oligonucleotides [glossary]. This strategy was effective in mouse models of arthritis in which a splice-switching oligonucleotide switched expression from a membrane-bound form of the TNF-α receptor to a secreted, soluble form that bound TNF-α in the bloodstream and antagonized its activity[108].

Siglec-8

Sialic acid-binding immunoglobulin-like lectins (siglecs) are surface proteins expressed predominately by leukocytes. Siglec-8 is selectively expressed on human eosinophils and mast cells, while its murine functional paralog Siglec-F is expressed by eosinophils but not mast cells[109]. Engagement of Siglec-8 on the surface of eosinophils by a cross-linking antibody results in pronounced cell death via apoptosis[110]. Preclinical studies with Siglec-F-deficient mice demonstrated that Siglec-F is important in regulating eosinophil survival in experimental models of asthma[111]. Further, administration of Siglec-F-targeted antibodies to mice over-expressing IL-5 which leads to hypereosinophilia, resulted in induction of eosinophil apoptosis and rapid reduction in blood and tissue eosinophilia[112]. Treatment of mice with Siglec-F-targeted antibody also resulted in decreased eosinophil accumulation in the intestinal mucosa and decreased blood and bone marrow eosinophilia in a model of allergen-induced gastrointestinal inflammation[113].

Together, these preclinical studies strongly support continued investigations into Siglec-8-targeted therapies for eosinophil-associated disorders, as engagement of Siglec-8 results in robust and selective apoptosis of eosinophils. Active research is currently underway to fully characterize the endogenous ligands for Siglec-8 and the enzymes required for its synthesis[114].

Immunoglobulin E

Omalizumab is a recombinant monoclonal antibody that binds immunoglobulin E (IgE) and prevents it from binding to its receptor FcεRI on the surface of mast cells and basophils. Several clinical trials have demonstrated that omalizumab is effective in reducing exacerbations, corticosteroid use and other clinical outcomes in patients with moderate to severe asthma [115–118]. In studies where eosinophilia was measured, there was evidence that IgE-targeted treatment had an impact on eosinophilia. For example, individuals with allergic asthma receiving omalizumab therapy had reduced mean percentages of sputum eosinophils (6.6 to 1.7%) and bronchial eosinophils (8 to 1.5 cells/mm^2) compared to patients receiving placebo[119].

Pooled analysis from five randomized, double-blinded, placebo-controlled trials with patients with moderate-to-severe persistent asthma revealed a decrease in baseline mean blood eosinophils by a median of 18.8% post treatment with omalizumab (compared to 2.1% with placebo)[120]. The mechanism by which the reduction in circulating IgE with

omalizumab therapy also leads to a reduction in blood and tissue eosinophils remains unclear. Omalizumab-treated patients have increased levels of eosinophil apoptosis compared to placebo-treated patients, but the reason for the increased apoptosis is undefined[121].

In a small open-label trial evaluating omalizumab in patients with eosinophilic gastrointestinal disorders, mean blood eosinophil counts were significantly decreased (47%) with omalizumab treatment[122]. Eosinophils in the duodenum and stomach declined but not significantly, and esophageal eosinophilia remained unchanged. Studies focused on understanding how IgE modulates blood and tissue eosinophilia are needed and may yield potential new therapeutic targets.

Inhibitory Receptors

Immune responses are regulated by an intricate network of positive and negative signals[123]. While a vast majority of studies have focused on activation receptors on cells of the immune system, recent evidence supports an important role for inhibitory receptors in maintaining immune homeostasis[124]. Eosinophils are known to express a number of different inhibitory receptors in addition to Siglec-8 (described above)[125,126]. Preclinical studies have emphasized a key role for inhibitory receptors in the regulation of eosinophil survival and activation. The inhibitory receptor CD300a can has been shown to override eosinophil survival signals mediated by IL-5, IL-3 and GM-CSF[127]. In addition, a recent study provides evidence for the inhibitory receptor CD172a as a negative regulator of eosinophil survival, as well as eosinophil degranulation, in the intestine[128]. Eosinophil chemotaxis is also counter-regulated by inhibitory receptors[129], emphasizing that inhibitory receptors are key regulators not only of cell survival but also of effector functions. The potential for targeting these inhibitory receptors in eosinophil-rich inflammatory states was shown in a study in which treatment with a bispecific antibody fragment that recognized both CD300a and CCR3 reversed airway eosinophilia in an experimental model of chronic asthma[130].

Thymic stromal lymphopoietin

Thymic stromal lymphopoietin (TSLP) is an IL-7-like cytokine expressed primarily by activated epithelial cells that signals through a heterodimeric receptor (comprised of a TSLP-specific binding chain and the IL-7Rα chain)[131]. TSLP has diverse effects, but its primary target appears to be dendritic cells, through which it promotes differentiation of Th2 cells that produce IL-4, IL-13 and IL-5[132–134]. Transgenic mice that overexpress TSLP have elevated serum levels of IL-5, suggesting TSLP has a role in the promotion of eosinophilia via induction of Th2 cytokine expression[135].

TSLP has also been shown to have direct effects on human eosinophils – providing pro-survival signals, modulating expression of adhesion molecules on the surface and stimulating bacterial killing by eosinophils[136,137]. A human sequence variant associated with elevated blood eosinophil counts was identified in the 5q22 chromosomal region, which contains *TSLP*, supporting an association between eosinophilia and TSLP[138]. In a genome-wide association study aimed at identifying susceptibility loci for eosinophilic esophagitis, *TSLP* at chromosome 5q22 was identified as an important candidate gene in disease pathogenesis, with *TSLP* being overexpressed in esophageal biopsies from patients with eosinophilic esophagitis compared to controls[139]. These and other studies have prompted the development of therapeutic agents targeting TSLP, such as a fully monoclonal antibody (AMG 157) that blocks interaction of TSLP with its receptor. A phase I trial (NCT01405963) is underway to evaluate the efficacy, safety and pharmacokinetics of AMG 157 in mild atopic asthma.

Strategies for the Future

Eosinophil Activation

The clinical severity of many eosinophil-associated disorders is believed to be a reflection of the extent of eosinophil activation in the tissues. Indeed there is a subgroup of patients with marked blood eosinophilia but no evidence of clinical pathology or organ dysfunction[140]. The eosinophils from these patients have reduced markers of activation when compared to those from patients with eosinophil-mediated organ damage, and their eosinophils show little to no evidence of degranulation when examined by electron microscopy. In contrast, studies have shown that airway eosinophils isolated from patients with asthma after allergen challenge display enhanced responsiveness to numerous mediators, with greater superoxide generation and degranulation compared to blood eosinophils[141,142]. The increased capacity of tissue-derived eosinophils to respond to mediators results from a process referred to as "priming" and has been recapitulated *in vitro* via exposure to IL-5, GM-CSF and other cytokines[143,144].

Collectively, these studies suggest that inhibiting eosinophil priming and activation in patients may result in decreased tissue eosinophilia and organ damage. It is notable that IL-5-specific antibody therapy reduces levels of circulating eosinophil-derived neurotoxin[36] and responsiveness of eosinophils to CCL11, providing evidence that anti-IL-5 may be the first agent that selectively inhibits eosinophil effector function[145].

In addition to mediators such as PGD_2 and IL-5 (discussed above) several other mediators can induce eosinophil activation, and as such might be beneficial therapeutic targets. The cytokine IL-33, a member of the IL-1 family of cytokines and a ligand for ST2 [glossary], is a potent eosinophil activator[146–148]. In preclinical studies, treatment with an IL-33-blocking antibody and soluble ST2 markedly decreased tissue eosinophilia in experimental models of asthma and allergic rhinitis[149–151], supporting further investigations into this activating pathway.

Similar to priming of eosinophils by cytokines, Notch signaling has a role in regulating eosinophil activation state and effector functions[152,153]. The Notch pathway is an evolutionarily conserved signaling pathway that has a key role in deciding the fate of progenitor cells[154] as well as regulating immune cell activation[155]. In addition to eosinophil priming, Notch signaling regulates eosinophil maturation[152,156]. These findings are relevant as treatment with an inhibitor of Notch signaling (LY450139 dihydrate) in a clinical trial for Alzheimer disease resulted unexpectedly in a statistically significant mean increase (47%) in blood eosinophils in patients[157].

Further studies are needed to identify key regulators and potential checkpoints that result in eosinophil activation and priming and thereby lead to enhanced tissue infiltration, degranulation and synthesis of mediators, as knowledge of these regulators and checkpoints may lead to the design of novel therapeutics.

Eosinophil Production

Atopy [glossary], helminth infections and allergen challenge have all been shown to be associated with increased eosinophil progenitor cells ($CD34^+IL\text{-}5R\alpha^+$ cells) in the bone marrow, highlighting the importance of the bone marrow in contributing to eosinophil-associated disorders[14–16]. Furthermore, increased numbers of eosinophil progenitors have been identified within allergic nasal and airway mucosa and in sputum from patients with asthma patients, suggesting eosinophil differentiation *in situ* may contribute to the accumulation of effector eosinophils in tissues[158–160].

While IL-5-targeted therapy is very effective in reducing mature eosinophil counts in the blood and bone marrow, the number of eosinophil progenitors and capacity to produce eosinophils from the bone marrow is unchanged,[161] which has important implications for patients when therapy is discontinued. Agents directed at specifically blocking production or survival of the eosinophil progenitor has the potential to be a long-lasting and specific therapy. As mentioned above, eosinophil precursors in the bone marrow of non-human primates were reduced following treatment with benralizumab[103], indicating that targeting progenitors via cell surface markers is a viable approach to inhibiting eosinophilia. Research focused on further characterizing the biology of the eosinophil progenitor to identify specific surface markers, as well as proliferative and survival signals, may indeed result in new approaches to target eosinophils.

Sub-phenotyping Eosinophilic Disorders

Post-hoc analyses of data from clinical trials have emphasized the importance of including patients that will likely receive the most therapeutic benefit from a specific agent. For example, in a clinical study in subjects with severe persistent asthma there was an increase in lung function (mean increase in FEV1 [glossary] of 0.29L) after receiving IL-5-specific antibody therapy in a subgroup of subjects with baseline sputum eosinophil levels greater than 3%[102]. In subjects with baseline sputum eosinophils less than 3%, there was no difference in change in lung function between those receiving IL-5-specific antibody therapy or placebo, emphasizing the importance of phenotyping patients for baseline eosinophilia to maximize therapeutic benefit. It is interesting to note that eosinophilic asthmatic patients are particularly sensitive to the effects of anti-IL-5 and anti-IL-13 when separately used[38,83]. Elevated levels of serum periostin correlate with eosinophil levels and responsiveness to anti-IL-13, raising the possibility that this subgroup of patients should also be treated with anti-eosinophil therapy, either alone or in combination with anti-IL-13. Blood and tissue eosinophilia can occur in a wide variety of disease processes[162] and hypereosinophilic syndrome is a heterogeneous disorder that often has no identifiable cause[163]. Thus, it is necessary to identify sub-phenotypes of patients with eosinophilic disorders in order to predict treatment responses on the basis of a patient's genetics or gene expression profiles of affected organs and to tailor therapy for their eosinophil-associated disease accordingly. This approach has proven very effective in patients with hypereosinophilic syndrome, with treatment plans being selected on the basis of the mechanism of eosinophilia (i.e. fusion-gene expression), and we believe this should now should be implemented in other more prevalent eosinophilic disorders such as eosinophilic asthma and eosinophilic gastrointestinal disorders.

Indeed, whole-genome transcript expression profile analysis has identified a disease-specific tissue transcriptome in the esophagus of patients with eosinophilic esophagitis[51,79]. The transcriptome analysis has been limited to esophageal biopsies which typically represent mucosa (epithelium and lamina propria) rather than deeper layers of the esophagus. Notably, the transcript is not enriched for eosinophil-specific genes because eosinophils contain relatively low amounts of mRNA compared with other inflammatory and resident cells. Rather, the eosinophilic esophagitis transcriptome provides insight into effector pathways involved in eosinophilic inflammation and can distinguish patients with differing levels of mucosal inflammation as well patients who have been exposed to specific drugs such as topical glucocorticoids[164]. As such, the use of tissue transcript profiling enables an eosinophilic esophagitis diagnostic panel to be derived to monitor disease diagnosis, patient prognosis and responsiveness to therapy[51,164–166]. It is anticipated that patient-specific information, derived from tissue transcriptome or cytokine expression analysis, would enable and customize key decisions about the degree and mechanism of tissue inflammation,

the compliance with medications and the responsiveness to therapeutic intervention[51,165,167].

Conclusions

Eosinophil accumulation in the blood and tissue is associated with a number of prevalent infectious and inflammatory disorders. Traditionally, therapy for eosinophilic disorders has primarily focused on glucocorticoids, but these agents are often toxic and variable degrees of drug resistance are common. More recently, drug development has focused on blocking eosinophil recruitment into organs and impairing their survival and activation. Clinical trials with first-generation eosinophil-targeted therapeutic agents are now underway and appear particularly promising, especially those that target IL-5 and its receptor. Challenges that need to be addressed as new agents are evaluated include residual tissue eosinophilia as reported in the trials to evaluate the efficacy of IL-5-specific antibodies and refractory response as seen in some patients treated with glucocorticoids. In addition, as therapeutic agents become more effective in blocking eosinophilia, the potential beneficial role for eosinophils in maintaining good health may come to the forefront and need to be addressed. Another substantial challenge for the future is identifying the sub-phenotypes of patients with other complex eosinophilic diseases, such as allergic asthma and eosinophilic gastrointestinal disorders, and determining how particular sub-phenotypes respond to specific agents on the basis of their disease characteristics and pathophysiology. Indeed, a personalized medicine approach has already proven to be crucial and effective, as demonstrated by patients with the *PDGFRA*-associated myeloproliferative form of hypereosinophilic syndrome, who are generally very responsive to the tyrosine kinase inhibitor imatinib. Application of tissue transcriptome analysis offers opportunity to further advance personalized and predictive medicine for eosinophilic disorders, particularly eosinophilic esophagitis, as tissue biopsies are standard-of-care and such analysis has already proven feasible and useful.

Glossary

Churg-Strauss Syndrome	is a rare systemic necrotizing vasculitis affecting small to medium-sized vessels, and characterized by late-onset asthma, blood eosinophilia, and eosinophil-rich granulomatous inflammation in affected tissues. First-line treatment is corticosteroids.
Eosinophilopoiesis	is the process of eosinophil production in the bone marrow.
Blood eosinophilia	is defined as greater than 450 eosinophils per microliter of blood.
Tissue eosinophilia	is greater than normal numbers of eosinophils in a particular tissue.
Helminth infection	is an infection with a parasitic worm and the most common cause of eosinophilia world-wide. Helminth infections are most common in the developing world. Infections with helminths can arise through mosquito transmission, eating infected food, drinking contaminated water and walking on contaminated soil.
Hypereosinophilic Syndromes	are a heterogenous group of disorders characterized by a persistently elevated peripheral blood eosinophil count (>1500/mm3) without any recognizable cause and evidence of tissue eosinophilia.

Periostin	is a extracellular matrix protein that interacts with integrin molecules on epithelial and leukocyte cell surfaces. Periostin expression is induced by Th2 cytokines, such as IL-4 and IL-13, and has recently been shown to promote allergic inflammation, including the accumulation of eosinophils in the skin.
Eosinophilic esophagitis	is a chronic disease characterized by symptoms of esophageal dysfunction, evidence eosinophil infiltration of at least 15 eosinophils per high-power microscopy field on esophageal biopsy, and exclusion of other possible causes of esophageal eosinophilia, especially gastrointestinal reflux induced esophageal eosinophilia.
Eosinopenia	is where the number of eosinophils in the blood or tissue is lower than expected. Eosinopenia can be caused by stress reactions, bacterial infections and the use of corticosteroids.
Antisense oligonucleotides	are synthesized strands of nucleic acid (DNA or RNA) that are complementary to a specific messenger RNA. They bind to their target messenger RNA to promote degradation of the messenger RNA and prevent translation from occurring. This can ultimately lead to decreased expression of a particular protein.
Splice-switching oligonucleotide	are similar to antisense oligonucleotides in that they target and bind to a particular messenger RNA; however, instead of promoting degradation of the messenger RNA of targeted genes they can be designed to promote favorable splice variants.
ST2	is a component of the receptor for IL-33 that is widely expressed by innate immune cells and a subset of T cell lymphocytes.
Atopy	is the predisposition to develop allergic hypersensitivity (IgE-mediated) reactions. Atopy results from both hereditary and environmental components.
FEV1	(forced expiratory volume) is the maximal amount of air that an individual can forcefully exhale in one second as calculated during pulmonary function testing. A normal FEV1 is predicted based on height, weight and race. A lower than normal FEV1 is a marker of an obstructive process such as asthma.
Eotaxin family of chemokines	is a subset of structurally related chemokines that bind to the eotaxin receptor (CCR3) and are involved in selectively activating and chemoattracting eosinophils.

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Text Box- Blood and Tissue Eosinophilia

Eosinophilia, more than normal numbers of eosinophils, can be found in both the peripheral blood and/or tissues in a variety of disorders, including helminthic parasite infections, atopic and allergic diseases, and adverse drug reactions[163,168–170]. In the peripheral blood, eosinophilia can be characterized as mild (450–1500 eosinophils per microliter), moderate (1500–5000 eosinophils per microliter) or severe (greater than 5000 eosinophils per microliter). Hypereosinophilia refers to blood eosinophils level greater than 1500 eosinophils per microliter. In general, blood eosinophilia results from enhanced eosinophilopoiesis (i.e. increased production of eosinophils in the bone marrow). Peripheral blood eosinophilia can be further categorized as primary, secondary and idiopathic. Primary eosinophilia usually occurs in the context of hematologic malignancies and proliferative disorders that result in increased numbers of progenitors leading to increased numbers of eosinophils in the bone marrow and blood. Secondary eosinophilia is the most common form of eosinophilia and often occurs in response to other primary disease processes such as overproduction of the cytokine IL-5 (often by T-cell lymphocytes) leading to elevated production of eosinophils. Idiopathic eosinophilia is often associated with moderate to severe eosinophilia with no identifiable cause.

In a healthy individual, tissue eosinophils normally can be found primarily in the bone marrow and gastrointestinal tract, but can also be found in smaller numbers in the thymus. The number of eosinophils that normally reside in tissues can vary dramatically, even within the same organ system. For instance, in a healthy gastrointestinal tract eosinophils can be found in increasing numbers from the stomach to the colon, but no eosinophils are present in the normal esophagus. Tissue eosinophilia usually results from increased recruitment of activated eosinophils from the bloodstream. Once recruited into the tissues, activated eosinophils have the capability to cause tissue damage and dysfunction. Tissue eosinophilia does not always correlate with blood eosinophilia. Blood eosinophil numbers can be normal, but increased migration of activated eosinophils from the blood results in significantly increased eosinophil numbers in organs, as is found in patients with eosinophilic esophagitis and eosinophilic pneumonias. In contrast, blood eosinophilia can occur without any evidence of increased tissue eosinophilia likely due to the absence of activating signals in the blood stream.

Table 1

Current therapies to treat severe eosinophilia

Therapy	Mechanism of action
Corticosteroids (systemic, topical and inhaled)	Inhibits eosinophil survival and promotes eosinophil clearance from tissues
Imatinib	Inhibits receptor tyrosine kinase activity
Hydroxyurea	Cytotoxic agent, precise mechanism unclear.
Interferon-α	Inhibits eosinophil development and functional responses

Table 2

New therapeutic strategies for eosinophilia

Strategy	Class	Example	Phase	Reference
Recruitment Blockade	CCR3 and CCL11 inhibitors	Small molecule CCR3 antagonists (piperidine derivative LH31407)	II	48
		eotaxin-1 specific antibody (bertilimumab)	II	50
	Adhesion molecule inhibitors	CD49d specific antibody (natalizumab)	NE	57
		Small molecule VLA-4 antagonists (compound 1)	Pre-clinical	56
	CRTH2 and PGD2 inhibitors	CRTH2 antagonists (OC000459)	II	66
	Histamine 4 receptor blockade	Small-molecule H4 antagonist (INCB38579)	Pre-clinical	71
	IL-13 and [or and/or] IL-4 blockade	IL-13 specific antibody (Lebrikizumab)	II	83
		IL-4Rα antagonist (AMG 317)	II	87
		IL-4 variant (pitrakinra)	II	88
Inhibition of Survival	IL-5 and/or IL-5Rα blockade	IL-5 specific antibodies (mepolizumab, reslizumab)	IV	89
		IL-5Rα specific antibody (benralizumab)	II	104
		Antisense oligonucleotides directed against common beta chain (TPI ASM8)	II	105
	Siglec-8 agonists	Siglec-8 specific antibody	Pre-clinical	113
	IgE blockade	IgE specific antibody (omalizumab)	IV	118
	Inhibitory receptor activation	CD300a specific antibody	Pre-clinical	127
	TSLP inhibitors	TLSP specific antibody (AMG 157)	I	
Inhibition of Activation	IL-33 blockade	Anti-IL-33 specific antibody	Pre-clinical	149
	Notch inhibitors	Notch signaling inhibitor (LY450139)	Pre-clinical, NE	157
Eosinophil Production Blockade	IL-5R blockade	IL-5Rα specific antibody (benralizumab)	II	104

NE – not tested for efficacy in an eosinophil-associated disorder, but found to have an effect on eosinophilia in clinical trials for other disorders.