The role of eosinophilopoietins and integrins on eosinophils biology in asthma

EOZINOFILOPOETINŲ IR INTEGRINŲ V AIDMUO EOZINOFILŲ BIOLOGINĖMS SAVYBĖMS SERGANT ASTMA

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Summary. Asthma is a chronic inflammatory airway disease that affects about 300 million people worldwide, and the incidence is continuously increasing. Patients with asthma are most commonly diagnosed with type 2 inflammation, which is characterized by eosinophilia, which is an increased amount of eosinophils in the blood and airways. Asthma with predominant eosinophilic inflammation is characterized by a more severe course of the disease, more frequent exacerbations, and more intense symptoms. To reduce symptoms, facilitate the course of the disease, and treat asthma more effectively is important to understand asthma pathogenesis better. Eosinophils survival maturation, activation, and quantity in the lungs are promoted by cytokines, of which eosinophilopoietins – interleukin (IL) 3, IL-5, and granulocyte-macrophage colony-stimulating factor (GM-CSF) are the most important. Eosinophilia is also associated with the activation of integrins present on the surface of eosinophils. Integrins are responsible for eosinophils adhesion to airway structural cells, thus prolonging their survival leading to more intense airway eosinophilia. Eosinophilopoietins, their receptors, and integrins might be suitable targets reducing eosinophilia in blood and airway, as well as airway inflammation. Humanized monoclonal antibodies are used for this purpose. Biological therapy allows for the specific inhibition of relevant asthma pathways and offers patients individualized treatment. This review will discuss the biological significance of eosinophilopoietins and their receptors, integrins on eosinophils functions, anti-cytokine and anti-integrin therapy efficiency in asthma.

Keywords: eosinophils, eosinophilopoietins, interleukin 3, interleukin 5, granulocyte-macrophage colony-stimulating factor, integrins, asthma.

INTRODUCTION

Asthma is one of the most common chronic diseases which affects about 300 million people worldwide. This disease affects people in all countries; however, the prevalence of asthma is greatest in developed western countries. People with asthma experience shortness of breath, cough, wheezing, and tightness in the chest. All these symptoms are associated with airway obstruction caused by bronchial hyperresponsiveness and airway inflammation. Immune cells exposed to cytokines and growth factors cause various structural changes in the airways called airway remodeling [1]. Although asthma is usually easily controlled with standard treatment, nevertheless, disease control is not always...
Eosinophils are specialized granulocytes that are involved in the defense against parasites and viruses. They are also associated with allergic reactions, asthma, and certain forms of cancer. Eosinophils are a subset of leukocytes, which are white blood cells that help fight off infections.

Eosinophils have a unique set of functions that are important for maintaining health and preventing disease. They play a role in inflammatory processes, immune responses, and cell development. Eosinophils are involved in the development of asthma and other respiratory diseases, as well as in the regulation of immune responses.

Eosinophils differentiate from hematopoietic precursors in the bone marrow and are released into the bloodstream. They have a short lifespan of about 1–2 weeks, during which they are released into the tissues and live there for about 2 to 5 days. Eosinophils are terminally differentiated, bone marrow-derived, granule-containing leukocytes, as are neutrophils, basophils, and mast cells. The number of eosinophils generated from the bone marrow in healthy individuals is low, resulting in relatively few cells circulating systemically. Eosinophils were identified and described by Paul Ehrlich in 1879 after eosin dyes were first used. Typically, 0.5 × 10^9/L absolute eosinophil counts are the upper limit of normal and eosinophil counts exceeding ≥0.5 × 10^9/L are reported as elevated. An increased number of eosinophils in the tissues and/or blood are called eosinophilia.

Eosinophils in the blood live from 16 to 36 hours. After circulating in the blood, eosinophils migrate into the tissues and live there from 2 to 5 days. Eosinophils in the blood and tissues of individuals with asthma have been shown to live longer than in healthy individuals. Eosinophil apoptosis can be delayed by a variety of factors, with a prolongation of survival of up to 1–2 weeks.

Eosinophils are involved in defensive reactions against parasites and viruses, and are known to promote allergic reactions. After migrating to the tissues, these cells actively regulate various immune responses through the release of biologically active substances. Eosinophils typically contain about 200 morphologically distinct cytoplasmic granules, containing many toxic proteins and other mediators that enhance the inflammatory response and cause tissue damage. Eosinophils themselves are a source of over 35 cytokines, chemokines, and growth factors. The link between eosinophils and asthma was first established about a century ago. A close relation between eosinophilia, exacerbations of asthma, and deterioration in lung function have been proven.

Airway eosinophilia also contributes to the development of airway remodeling, and eosinophils’ role in disturbing local homeostasis is indisputable.

### METHODS

The scientific review presents information obtained from freely accessible scientific periodicals published abroad with a citation rate in the Clarivate Analytics Web of Science, Scopus, and Springerlink databases.

### ROLE OF EOSINOPHILPOIETINS ON EOSINOPHILS FUNCTIONS

Airway inflammation in asthma is regulated by the cytokine network [3] that owns excess of 50 cytokines [20]. The main cytokines that affect eosinophils are the β-chain cytokines (IL-3, IL-5, GM-CSF), which belong to the β-common chain cytokines, eosinophilopoietins, IL-3, IL-5, GM-CSF, β-chain-signaling cytokines receptors, integrins, anti-cytokine, and anti-integrin therapy.
IL-3, IL-5, and GM-CSF. They belong to the β-chain cytokines family [8]. These cytokines are called eosinophilopoietins [8, 21]. IL-3, IL-5, and GM-CSF are mostly produced by activated T cells and characterized by the same receptor structure, comprising a cytokine-specific α chain and a common β chain (βc) [22]. Eosinophilopoietins cause eosinophils maturation, activation and accumulation in the lungs [21]. Excessive expression of IL-3, IL-5, GM-CSF can lead to excessive signal transduction and alter the course of the disease [23].

IL-3, IL-5, and GM-CSF have wide-ranging effects on eosinophils [24]. IL-3 and GM-CSF are far more pleiotropic than IL-5, but all three are thought to have mostly redundant functions on eosinophils [25]. IL-5 promotes eosinophils proliferation and differentiation; IL-3, IL-5, and GM-CSF have important effects on survival, trafficking, degranulation, and also activation of eosinophils (Figure 1). IL-3 and IL-5 are expressed mainly by activated T lymphocytes and mast cells. GM–CSF is produced by T cells, epithelial cells, and macrophages [23]. The impact of each cytokine on eosinophil biology is similar but has some different aspects. IL-3 and GM-CSF are crucial in the early eosinophils development stages, while IL-5 is important for final maturation during eosinophil differentiation. Human bone marrow activated with IL-5 forms colonies of highly pure and mature eosinophils, while IL-3 or GM-CSF forms more colonies, but with less mature eosinophils [8]. All three β-chain cytokines play a vital role in the growth and survival of eosinophils [26]. IL-3, IL-5, and GM-CSF have similar effects on eosinophil adhesion and comparable efficacy to induce eosinophil transmigration through a layer of epithelial cells via the β2 integrin [8]. Due to the above-mentioned properties, IL-3, IL-5, and GM-CSF are considered as a potential target in asthma therapeutics [27]; however, IL-5 was selected as a priority target to reduce eosinophilia because it is highly specific for eosinophilic inflammation [28].

Not only cytokines but also their receptors play an important role in the recruitment process of eosinophils in asthma. IL-3, IL-5, and GM-CSF share a common β-chain and have their cytokine-specific α-chains. The IL-5 receptor is fairly specific since it is only expressed on eosinophils and basophils, while receptors for IL-3 and GM-CSF are present on many haematopoietic cells [28]. Despite all three cytokines sharing a standard beta (β) chain receptor subunit, each differentially affects eosinophils biology due to alpha (α) chain subunit-specific properties [27]. The cytokines attach to their respective α-chain with low affinity (nanomolar); on the other hand, subsequent recruitment of the β-chain contributes to a conformational change to a great affinity (picomolar) binding complex [8]. Assembly of the IL-3, IL-5, and GM-CSF receptors are shown in Figure 2.

Activation of β-chain cytokines receptors by eosinophilopoietins leads to eosinophils pre-activation, required for regulation of their surface proteins expression, including integrins [30]. Eosinophils activation by IL-3, IL-5, or GM-CSF depends on the concentration of these cytokines and the amount of β-chain cytokines receptors on eosinophils surface. However, exist and important cross-regulation between these cytokines concentrations and expression of their receptors [31]. The study demonstrated that all eosinophilopoietins down-regulate IL-5Rα and up-regulate IL-3Rα expression, while GM-CSFRα is down-regulated by GM-CSF itself, but are not affected by IL-3 or IL-5. This study was completed with healthy subjects eosinophils.

**Figure 1. The effect of major stimulatory cytokines on eosinophils [24]**

IL-5 promotes eosinophil differentiation and proliferation. IL-5, GM-CSF, and IL-3 all have important effects on trafficking, survival, degranulation, and activation of eosinophils. IL-3 – interleukin-3; IL-5 – interleukin-5; GM-CSF – granulocyte-macrophage colony-stimulating factor.

**Figure 2. Assembly of the IL-3, IL-5, and GM-CSF receptors [29]**

IL-3Rα, IL-5Rα, and GM-CSF Rα exist as monomers on unstimulated cells. Each Ra chain provides cytokine binding specificity. On ligand binding, βc is recruited to the Ra/ligand complex and interacts with the Ra-bound cytokine to activate signal transduction and physiologic response. Ra – receptor α; IL-3Rα – interleukin-3 receptor α chain; IL-5Rα – interleukin-5 receptor α chain; GM-CSFRα – granulocyte-macrophage colony-stimulating factor receptor α chain; βc – β chain.
Adhesion

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ICAM-1
VCAM-1
FG VN

Adhesion
Migration

aM*
β1

VCAM-1

aD*
β2

aX*

αL

MAdCAM-1

Adhesion

Viability

aL*
β2

Figure 3. Integrins of eosinophils [12]

Functions and ligands assigned to integrins have been deduced in various assays using eosinophils. * Subunits that contain the insert (I)-domain. Subunits that are underlined contain the I-like domain. MAdCAM-1, Mucosal addressin cell adhesion molecule-1; FG, fibrinogen; LN, laminin; VN, vitronectin. ICAM-1 – intercellular adhesion molecule-1; VCAM-1 – vascular cell adhesion molecule; FG – fibrinogen; VN – vitronectin; LN – laminin; MAdCAM-1 – Mucosal addressin cell adhesion molecule-1.

However, in asthma, the cross-regulation is similar. It was revealed that serum levels of IL-3 do not change during asthma, however, expression of this cytokine’s receptors in eosinophils is significantly up-regulated. The concentration of GM-CSF is increased in the serum of allergic and severe non-allergic eosinophilic asthma (SNEA) patients. Still, the expression of its receptors do not change in eosinophils from SNEA patients and is significantly reduced in allergic asthma (AA) phenotype. Finally, the dominance of the IL-5 receptor in eosinophils from SNEA patients is significantly up-regulated and can control cell biologies, such as growth, division, survival, cellular differentiation, and apoptosis [41]. αMβ2 is influenced greatly by activation with IL-5, which enhances αMβ2-mediated adhesion of blood eosinophils to ICAM-1 or modules 1 or 4 of VCAM-1 [42]. IL-5-related αMβ2 activation could be a potential target to reduce eosinophilia, as IL-5 levels are significantly increased in asthma [43]. Moreover, it is known that IL-5, IL-3, or GM-CSF stimulated eosinophils to adhere to periostin through αMβ2 integrin leading to increased eosinophils infiltration in the lungs, as periostin levels are also increased in AA and SNEA patients [40].

ROLE OF INTEGRINS ON EOSINOPHILS FUNCTIONS

Eosinophils 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 and cells in the tissues that mediate transmigration process. Blood eosinophils can enter the airways after firm adhesion to vascular endothelium cells and diapedesis [33]. Eosinophils express αβ7, αβ1, αMβ2, αXβ2, αDβ2, and αβ2 integrin dimers (Figure 3). All of them regulate the extravasation of eosinophils from the bronchial circulation to the airway wall and airspace under the control of several chemoattractants [12, 34]. Whereby integrins on circulating eosinophils become activated, eosinophils tether inflow, and roll on bronchial endothelial cells (Figure 4). With continued cytokine activity, eosinophils activation continues, and eosinophils with the help of adhesion molecules migrate to the airways. Integrins expression and their activation state are essential for more stable and increased adhesion, and adhesion-related eosinophils activation after interacting with counter-receptors on other cells or ligands in the extracellular matrix [11, 26].

αMβ2 and αMβ3 are the most important and most studied eosinophils integrins [35]. αβ1 and αMβ2 are differentially expressed following exposure to GM-CSF and different redox agents. αβ1 largely responsible for the arrest of blood eosinophils in vessels of the asthmatic lung, while αMβ2 is involved in subsequent eosinophils recruitment to and persistence in the extracellular matrix of the bronchi in asthma [35]. Previously was demonstrated that gene expression of αM, β2, α4, and β1 integrins subunits are enhanced in eosinophils from stable AA patients [36]. Moreover, another study revealed that αM, α4, and β1 subunits are differentially expressed in SNEA patients, compared with AA [32]. Altered integrins expression suggest their potential role as a target for eosinophilic inflammation treatment in asthma.

Eosinophils can interact with ligands, including vascular cell adhesion molecule protein 1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1), laminin, fibrinogen/fibrin, vitronectin, and periostin [38–40]. Integrin-dependent adhesion also acts as a signal transducer and can control cell biologies, such as growth, division, survival, cellular differentiation, and apoptosis [41]. αMβ2 is influenced greatly by activation with IL-5, which enhances αMβ2-mediated adhesion of blood eosinophils to ICAM-1 or modules 1 or 4 of VCAM-1 [42]. IL-5-related αMβ2 activation could be a potential target to reduce eosinophilia, as IL-5 levels are significantly increased in asthma [43]. Moreover, it is known that IL-5, IL-3, or GM-CSF stimulated eosinophils to adhere to periostin through αMβ2 integrin leading to increased eosinophils infiltration in the lungs, as periostin levels are also increased in AA and SNEA patients [40].

ANTI-CYTOKINE AND ANTI-INTEGRIN THERAPY IMPACT ON EOSINOPHILS FUNCTIONS IN ASTHMA PATIENTS

Profound studies of the molecular mechanisms of asthma carried out since the 1990s, implicated cytokines, and their receptors in the maintenance and initiation of asthma. These findings led to anti-cytokine therapy to become a potential asthma treatment. Many of the eosinophil’s functions are controlled...
by IL-5. Two ways are available to regulate IL-5 and the eosinophil's participation in asthma. One of them is a monoclonal antibody directed against the cytokine IL-5, another – a monoclonal antibody that targets its receptor. Both approaches are effective in reducing circulating eosinophils, and with a reduction in circulating eosinophils, fewer of these cells are available for migration to the airway. Mepolizumab and reslizumab are directed against IL-5, benralizumab – against the IL-5R. All of these medications lower the asthma exacerbation rate, improve quality of life, and ameliorate asthma symptoms [44, 51–58].

One of the limiting issues with monoclonal antibodies is their access to the inflammation site where the cytokines are acting. Thus, an anti-IL-5 antibody will not shorten the survival of eosinophils already present in the airway. In contrast anti-receptor antibodies can bind to tissues eosinophils and shorten the survival of already infiltrated eosinophils as well. It is an important difference between anti-cytokine and anti-receptor antibodies. That causes the higher capacity of anti-IL-5 to eliminate tissue eosinophils in contrast to anti-IL-5 antibodies [45].

The initial results of clinical trials investigating mepolizumab were disappointing. Mepolizumab diminished blood eosinophils but did not manage to improve any clinically important outcome. It is believed that this happened because asthma is a heterogeneous disease, and anti-IL-5 antibodies are effective only for some asthma phenotypes. The patients included in the initial study were not selected by eosinophil count [46]. Later in trials were involved patients who had at least two exacerbations in the previous year despite receiving high-dose of inhaled corticosteroids and with blood eosinophil counts of ≥300 cells/μL or sputum eosinophils count ≥3 percent. Mepolizumab efficacy has been investigated in a total of five trials [47, 51–55]. Phase 3 studies on mepolizumab for severe eosinophilic asthma are presented in Table 1.

Reslizumab efficacy has been investigated in four trials [47, 48, 56]. Initial data from the early stages of the reslizumab clinical development program were discouraging. It was because of a lack of patient selection. A phase 1 pilot trial of reslizumab in a small number of patients with severe persistent asthma failed to demonstrate a significant improvement in asthma symptoms and lung function [49, 66]. However, this study has important implications as it was the first to demonstrate that reslizumab can effectively and safely decrease eosinophil counts in patients with asthma. This study highlighted the importance of adequately preselection of patients whose asthma is dependent on the eosinophilic inflammation pathway, and this led the incorporation of appropriate patient selection. The main phase II 3 studies results are presented in Table 1. It is important to mention that in the studies with reslizumab asthmatics were enrolled with baseline blood eosinophils > 400 cells/μL. Reslizumab is different from other anti-IL-5 antibodies because it is currently available as an intravenous formulation, and the development of a subcutaneous formulation is ongoing [49].

Benralizumab is a biologic drug that specifically binds to the IL-5 receptor, thus preventing the interaction with its ligand and the consequent pro-inflammatory effects [50]. It is efficacy has been investigated in six clinical trials. Clinical trials have revealed the high efficacy and good tolerability of benralizumab in patients with eosinophilic asthma. Two of the trials were the 2 phase [48]. Benralizumab was tested in a phase 2a and phase 2b randomized, dose-ranging trials. The results showed that benralizumab improved expiratory volume (FEV1) within 1 second, caused a marked decrease in the number of peripheral blood eosinophils, reduced the number of exacerbations of...
asthma, and improved asthma control. Phase 3 studies on benralizumab for severe eosinophilic asthma are presented in Table 1. This medication seems to be theoretically more powerful than mepolizumab and reslizumab in mediating a sustained control of type-2 inflammation [60].

GM-CSF and IL-3 are implicated in the pathogenesis of a range of diseases. Although the role of GM-CSF and IL-3 in mediating emergency myelopoiesis has been known for a long time, uncovering their role as mediators of innate immune memory has paved the way for new mechanistic investigations on the effects of GM-CSF and IL-3 on the innate immune system. GM-CSF and IL-3 are now considered critical modulators of the innate immune response by acting directly on mature immune cells. These cytokines are still under investigation as therapeutic targets for some diseases, including asthma. Phase 1/2 clinical trials are currently underway. Some of these trials already showing that blocking antibodies against GM-CSF and IL-3-specific receptor α subunits or βc subunits can be safe and effective in inflammatory diseases [61]. Phase 2, randomised placebo-controlled trial to evaluate the efficacy and safety of an anti-GM-CSF antibody in patients with inadequately controlled asthma results show that FEV1 in prespecified groups of participants with alpha GM-CSF antibody in patients with inadequately controlled asthma results show that FEV1 in prespecified groups of participants treated with anti-GM-CSF compared with placebo showed improvements in patients with eosinophilic asthma [62]. There is evidence that IL-3 through alpha subunit-specific properties uniquely influences eosinophil biology and may serve as a potential therapeutic target also [27].

Anti-cytokine therapies have not succeeded in asthma treatment in all patients at the moment. Therefore, newer therapies are being developed that target pathways involved in asthma pathogenesis [22]. Therapies that broadly target integrins would offer the possibility of potently suppressing eosinophil-related pathologies with greater specificity and with lesser side-effects compared with current treatments. Such therapy could target recruitment mechanisms involving 4 and 2 integrins [12]. One of the integrins suppressing agent is RGDS (Arg-Gly-Ser-Asp) peptide as a non-selective integrin receptor antagonist working through α4 integrin or αMβ2 integrin [63]. It was shown that integrins suppression by this peptide reduced eosinophils adhesion, decreased the effects of eosinophils on TGF-β1, WNT-5a, and extracellular matrix protein gene expression in airway smooth muscle cells together with their proliferation [36]. Moreover, RGDS reduced the in vivo-allergen activated eosinophils effect on airway smooth muscle cells COL1A1 and FN gene expression [64].

Several inhibitors that target impact integrin heterodimers have been devised to prevent the recruitment or quantity of eosinophils in the airways of asthmatic patients and thus, reducing eosinophilic airway. Most therapeutic strategies involving integrins of eosinophils have targeted 4, the common subunit of 41, the most important counter-receptor of eosinophils recognizing VCAM-1, and 47, potentially important in recognition of MAdCAM-1 [12]. Blockade of integrin and adhesion receptor interaction could result in decreased eosinophils accumulation in tissues [38]. That is why, as a means to suppress the impact of inflammation on airway remodeling and airway structural cells, has emerged as a potential therapeutic approach for asthma [39]. Integrins are validated drug targets of the US FDA for acute coronary syndromes, psoriasis, and multiple sclerosis, respectively. For example, efalizumab is for the treatment of psoriasis. It was observed that this medication reduce the accumulation of eosinophils in the airway and attenuates the late asthmatic response of human subjects with atopic asthma. However, none has been approved for indications related to respiratory diseases yet [63]. The effectiveness of integrins has

### Table 1. Phase 3 studies on anti-IL-5 therapies for severe eosinophilic asthma

| Study       | Medication | Patients | Duration | Primary outcomes                        | References |
|-------------|------------|----------|----------|------------------------------------------|------------|
| DREAM study | Mepolizumab| 621      | 52       | Reduced number of exacerbations          | [51]       |
| MENSA study | Mepolizumab| 576      | 52       | Reduced number of exacerbations          | [52]       |
| SIRIUS study| Mepolizumab| 135      | 20       | Reduced oral corticosteroid dose         | [53]       |
| OSMO study  | Mepolizumab| 145      | 32       | Reduced number of exacerbations          | [54]       |
| MUSCA study | Mepolizumab| 551      | 24       | Improvement in the SGRQ total score       | [55]       |
| Two phase 3 study (study 1 and study 2) | Reslizumab | 953      | 24       | Reduced number of exacerbations          | [56]       |
| SIROCCO study | Benralizumab| 1,205    | 48       | Reduced number of exacerbations          | [57]       |
| CALIMA study | Benralizumab| 1,306    | 56       | Reduced number of exacerbations          | [58]       |
| ZONDA study | Benralizumab| 220      | 28       | Reduced oral corticosteroid dose         | [59]       |
| BORA study  | Benralizumab| 1,578    | 56       | Validated 2-year safety of benralizumab use | [60]       |

FEV1 – forced expiratory volume in the first second; ACQ – asthma control questionnaire; AQLQ – asthma quality of life questionnaire; SGRQ – Saint George’s respiratory questionnaire.
been studied in several clinical trials. The first phase 1 clinical trial was published in 2002. This trial and later trials results showed that anti-integrin therapy decreases allergen-induced airway inflammatory and airway hyperresponsiveness, reduces the percentage of eosinophils in sputum, prevents eosinophil extravasations [13]. In general, clinical trials that have been performed demonstrated clinically significant benefits in many patients, leading to continued interest in the further development of novel integrin inhibitors [65].

CONCLUSION

Eosinophilopoietins are important cytokines responsible for eosinophil maturation and activation and are the primary target for controlling eosinophil functions. So far, only anti-IL-5 or anti-IL-5R therapy has achieved sufficient success, and research with anti-IL-3 and anti-GM-CSF therapy due to lack of specificity for eosinophils is slow. Integrins are another important class of eosinophil surface molecules that are closely related to their functions. Blockade of eosinophil integrins may inhibit their functions, contributing to the reduced airway infiltration and further adverse effects of eosinophils. Antibodies to integrins are not yet widely used, but further research is needed in this area.

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