We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Endothelial Cells in Asthma

Andrew Reichard and Kewal Asosingh

Abstract

The occurrence of new blood vessel formation in the airway wall of asthma patients was reported more than a century ago. It was long thought that angiogenesis in asthma was an epiphenomenon of airway inflammation. Therefore, little research has been performed on the role of endothelial cells in this disease. We are moving away from this misconception as an increasing number of clinical studies and findings in murine models of asthma demonstrate a causal link between angiogenesis in the airway and genesis of allergic asthma. In this chapter, we review the evidence supporting key roles for the endothelium and other angiogenic cells in the pathogenesis of asthma.

Keywords: endothelium, angiogenesis, VEGF, inflammation, PACs, Th2

1. Introduction

Allergic asthma is a chronic inflammatory disease of the conducting airways. The incidence of asthma is steadily increasing, and it has become a major health problem worldwide. The disease presents with airway inflammation, bronchoconstriction, and remodeling of the airway wall including mucus or goblet cell metaplasia, airway fibrosis, increased microvascular permeability, and angiogenesis [1].

Generally, blood vessels exhibit a two-part response upon tissue inflammation. In the first phase, which lasts about 24 hours, functional changes occur in existing blood vessels as endothelial cells are activated and vessel permeability increases. Following this initial phase, vessel remodeling and angiogenesis occur, ensuring adequate blood and nutrient delivery to tissues for survival [2–4]. When inflammation becomes chronic, immune and inflammatory cells continually infiltrate tissues, causing simultaneous damage and repair and allowing the angiogenic response to become permanent [2, 5, 6].

Chronic inflammation and the associated angiogenic response play a role in several inflammatory diseases. For example, in inflammatory bowel disease (IBD), continuous ulceration and regeneration in the bowel rely on immune-driven angiogenesis which leads to the enhanced microvessel density associated with IBD [7, 8]. Psoriatic arthritis presents with tortuous, elongated blood vessels along with an increase in the number of blood vessels of the synovial membrane, contributing to the joint inflammation which is a hallmark of the disease [9]. Rheumatoid arthritis also presents with increased vascularity and inflammation of the synovial membrane due to angiogenesis, but blood vessels exhibit normal branching and structure [10]. In cancer, tumors require angiogenesis in order to continue growth and are not hindered by the disorganized, leaky, tortuous vessels that result from the associated inflammation [11].

Over a century ago, researchers first observed the presence of excess small blood vessels crowded closely together in the asthmatic airway. These early studies aimed to determine the pathology of asthma and involved examining ejected sputum from asthmatic patients and extracted lungs from patients post mortem following sudden asphyxic asthma death (SAAD), or death by asthma attack. In addition to finding excess small blood vessels, these early studies also showed thickening and scarring of the bronchial wall, accumulation of leukocytes and eosinophils in the asthmatic airway, and the formation of dense, mucus-filled plugs or blockages in the lumen of the airway [12]. A subsequent study identified a dense exudate located in the bronchial lumen, likely similar to those masses observed a half century earlier, containing accumulations of eosinophils which were recruited to the airway [13]. This study also uncovered other features now firmly associated with angiogenesis and asthma, including dilated capillary blood vessels and swollen, activated endothelial cells. Around the same time, allergic inflammation in the asthmatic airway was also found to contribute to the formation of the dense exudate along with vessel engorgement, dilation, and permeability [14, 15]. Since these seminal studies, it has become well established that along with these symptoms, asthma presents with angiogenic remodeling of the vascular bed throughout the bronchial wall [1, 16]. Another study reported that angiogenesis is initiated in the early phases of adult asthma, suggesting that this process may play a role in the genesis of the disease [17].

Like in any other inflammatory diseases, the airway endothelium plays a classical role in asthmatic airway inflammation by recruiting inflammatory cells. Angiogenesis exacerbates this inflammatory response by facilitating the influx of inflammatory cells to the lungs through the newly formed blood vessels, and the permeability of these new vessels contributes to airway edema due to vessel leak [18–21]. Inflammatory cells arriving in the lungs migrate through the endothelial layer into the airway walls and induce tissue damage via the release of various mediators [22]. When specific endothelial cell adhesion molecules are lacking, inflammatory cell influx into the lungs decreases, resulting in reduced transendothelial migration and a reduction of airway hyperresponsiveness [23]. Thus, the surface receptors of endothelial cells in the lungs are a potential target for preventing airway inflammation and bronchoconstriction. This review is focused on angiogenic mechanisms in asthma, beyond their classical roles in the recruitment of immune cells.

2. Angiogenesis and its mechanism relevant to asthma

Neovascularization is the formation of new blood vessels, including vasculogenesis, arteriogenesis, and angiogenesis [1, 24, 25]. Angiogenesis is the formation of new blood vessels as an extension of pre-existing vessels. Under conditions of homeostasis, a balance exists between angiogenic activators and inhibitors, and a state of vascular quiescence is maintained in which there is no net change in vascularization [1].

Patients with asthma are no longer maintaining vascular quiescence in the bronchial wall and thus have reached a pro-angiogenic state. This pathological angiogenesis occurs due to overproduction of angiogenic factors, underproduction of inhibitors, or a combination of each of these issues, leading to increased vascularization [1]. Increased numbers of blood vessels in the bronchial wall is strongly correlated to the severity of asthma [19–21]. Increased vascularity in the airway and the increased vessel permeability which occurs concurrently contribute to the thickening of the inner airway wall and the development of airway edema [18, 19]. These symptoms lead to narrowing of the airway lumen which reduces airflow and leads to

the obstructive symptoms of asthma [18–21, 26]. In healthy patients, airway smooth muscles contract, causing the luminal boundary to buckle. The luminal wall conforms to a distinct folding pattern which allows normal lung function. When the airway wall thickens as a result of asthma, fewer luminal folds are able to form upon contraction and buckling, leading to the airway obstruction observed in asthmatic patients [27].

The most studied angiogenic factor associated with increased airway vascularity in asthma is vascular endothelial growth factor (VEGF) [28]. Angiogenesis is dependent upon VEGF and its tyrosine kinase receptors (VEGFR) [29]. The VEGF family consists of VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor (PlGF) [30]. The members of the VEGF family bind to one or multiple types of VEGFR, which are denoted as VEGFR-1, VEGFR-2, and VEGFR-3 [30]. Each VEGFR is predominantly expressed on specific cell types: VEGFR-1 on monocytes and macrophages, VEGFR-2 on vascular endothelial cells, and VEGFR-3 on lymphatic endothelial cells and endothelial cells of sprouting blood vessels [31]. However, each receptor type plays multiple roles in angiogenesis and other processes through lower level expression on other cell types and through binding multiple ligands of the VEGF family. VEGFR-1, the only receptor which binds PlGF and VEGF-B, plays a role in controlling angiogenesis through functions associated with both endothelial and non-endothelial cells [32]. VEGFR-1 and VEGFR-2 both bind to VEGF-A, which is the prototypical member of the VEGF family and is often denoted as simply VEGF [32]. VEGFR-2 has been shown to be the primary mitogenic receptor for VEGF in the angiogenesis pathway, binding VEGF which has been released by nearby tissues in a paracrine fashion [33, 34]. VEGFR-2 and VEGFR-3 each bind to VEGF-C and VEGF-D, inducing angiogenic and lymphangiogenic activity [32]. It is important to note that VEGF-C, while commonly viewed as controlling lymphangiogenesis specifically, can also induce blood vessel angiogenesis by stimulating endothelial cell migration and proliferation when binding to VEGFR-3 on blood vessel endothelial cells [35–38]. Blocking VEGFR-3 through specific antagonistic antibodies has been shown to decrease the number of proliferating endothelial cells, directly linking this receptor to angiogenesis [39]. VEGF is also responsible for activating the extracellular signal-regulated kinase (ERK) pathway [40]. The ERK pathway helps to control migration, proliferation, and apoptosis of endothelial cells and therefore plays a significant role in angiogenesis [41].

Two cell types directly involved in angiogenesis are pro-angiogenic hematopoietic progenitor cells and endothelial colony-forming cells. Pro-angiogenic hematopoietic progenitor cells (PACs) are a heterogeneous population of cells serving in a paracrine function to promote angiogenic activity. This heterogeneous population of pro-angiogenic cells is made up of subsets of hematopoietic progenitor cells but can also include mature blood cells such as monocytes [42–45]. The hematopoietic stem or progenitor cells are typically committed to the myeloid lineage and stimulate local angiogenic responses through a paracrine release of growth factors [46–50]. PACs are known to play a significant role in asthma due to their pro-angiogenic activity [49, 51–55]. Endothelial colony-forming cells (ECFCs), sometimes referred to as late outgrowth endothelial cells (OECs), are true endothelial cell precursors which proliferate to form new blood vessels as part of the angiogenic process [42–45, 56]. ECFCs are rare in circulation but incorporate into existing microvessels, functioning as the building blocks of new vasculature by dividing and proliferating quickly [1, 46–48, 57]. ECFCs and PACs participate synergistically in the process of neovascularization, and both cell types are required in an angiogenic response [58]. These two cell types were originally collectively referred to as endothelial progenitor cells (EPCs) [59]. However, it became apparent that a variety of blood and endothelial cells were being grouped together under this umbrella term [60, 61]. The lineage relationships among EPCs that led to their suggested

reclassification and the removal of this umbrella term have been reviewed [42]. PACs and ECFCs do in fact share a common embryonic origin, the hemangioblast, which is capable of developing into both hematopoietic and endothelial precursor cells [62]. Hemangioblasts have been shown to play a significant role in embryologic development as bipotent stem cells and have recently been found to remain active during adult development, most notably in the bone marrow [62]. It has been proposed that the synergy and dependence between PACs and ECFCs observed in angiogenesis are a result of the common developmental origin of the vascular and hematopoietic system, centered on the hemangioblast [26]. PACs and ECFCs also share similar functions, cell markers, and *in vitro* phenotypes, again most likely stemming from their common origin [26]. However, more recent analysis has revealed that PACs are in fact hematopoietic cells derived from the bone marrow which differ from the ECFCs studied in angiogenesis [42, 49, 56, 63, 64]. This leads us to the current classification used to distinguish the two cooperating but distinct cell types involved in asthma-related angiogenesis.

Recruitment of PACs into the lungs is an early step in initiating airway wall angiogenesis in asthma. C-X-C motif chemokine receptor 2 (CXCR2) and C-X-C motif chemokine receptor 4 (CXCR4) are important receptors in inflammatory and angiogenic pathways [55, 65, 66]. CXCR2 and CXCR4 are expressed by PACs and vascular endothelial cells and are activated by one of eight known ligands [54, 56]. These ligands are released within hours of lung allergen exposure and act as chemoattractants to promote the activation and lung-homing of PACs [54, 55]. The accumulation of PACs in the lungs and perivascular tissue promotes inflammation and accumulates VEGF, leading to increased angiogenesis [67–69]. Blocking CXCR2 receptors has been shown to reduce the accumulation of PACs in the lungs and the occurrence of airway angiogenesis, proving the essential nature of recruiting PACs in the angiogenic pathway [70].

Another receptor that has been shown to play a pivotal role in pathological angiogenesis is C-C motif chemokine receptor 3 (CCR3). CCR3 is expressed by angiogenic endothelial cells and eosinophils and acts as a receptor for eotaxin [53, 71–73]. Eotaxin is a chemokine expressed by endothelial cells, epithelial cells, and PACs, among others, and presents at particularly high levels in the lung endothelium in asthmatic patients and allergen-exposed mice [53]. Eotaxins have traditionally been known to act as the major chemoattractant of eosinophils, which contribute to the airway inflammation in allergic asthma. Asthmatic patients are therefore known to express higher levels of eotaxins [52]. However, eotaxins have also been shown to induce migration and angiogenic tube formation by CCR3-expressing lung endothelial cells [72]. This confirms the role of eotaxins as major angiogenic factors, alongside VEGF, contributing to airway remodeling in allergic asthma.

3. Animal models

Murine models are utilized to study the underlying mechanisms of asthma and to conduct preclinical testing of novel therapeutic strategies. Allergen exposure in murine models allows the induction of an allergic response in a controlled setting that is meant to resemble the symptoms of asthma seen in patients. This is an insightful alternative to observing established asthma in clinical studies. Two common murine models of allergic asthma used in research are the house dust mite extract (HDME) model and the ovalbumin (OVA) model [52, 74–76].

Experiments in the OVA model showed that chronic allergen exposure induces mobilization and lung-homing of PACs, increasing vascularity of the airway wall through angiogenesis, endothelial activation, and airway resistance within hours

of allergen exposure [51–55, 77]. Blocking CXCR4 resulted in reduced lung-homing of PACs along with reduced airway inflammation and airway hyperresponsiveness, blunting the effects of OVA challenge [55]. Type 2 helper (Th2) cells are immune cells which contribute to the Th2-mediated inflammatory response in asthma following allergen challenge by promoting eosinophilia and stimulating the production of specific cytokines involved in asthma pathogenesis [78–80]. These Th2 cells cooperate with type 1 helper (Th1) cells to contribute to the asthmatic phenotype [16, 81–83]. OVA challenge induces angiogenesis, promoting the Th2 inflammatory response, also known as the type 2 immune response, through the production of pro-Th2 cytokines. Interleukin-25 (IL-25), also known as IL-17E, is an upstream master regulator of Th2-mediated inflammation [84–88]. IL-25 is expressed by various cell types, including epithelial and endothelial cells, mast cells, T cells, and eosinophils [84, 88–93]. It was recently shown that endothelial cells facilitate the type 2 immune response in asthma by producing IL-25. Th2 activation complements the release of thymic stromal lymphopoietin (TSLP) by lung-recruited PACs [51]. TSLP is a pro-Th2 cytokine expressed in endothelial cells, epithelial cells, neutrophils, macrophages, and mast cells which plays a role in the maturation of T cells and eosinophils [94, 95]. The combined effects of IL-25 and TSLP contribute to angiogenesis and eosinophilia by inducing the expression of eotaxins by PACs and other cell types [53].

More recent studies have utilized the HDME model, which is clinically relevant as house dust mite allergens are a potent inducer of asthma worldwide [96]. HDME-exposed mice present with increased accumulation of PACs, increased vascularity of the airway, airway inflammation, and airway hyperresponsiveness [77, 97]. VEGFR-3 and its ligand VEGF-C are critical in new vessel sprouting in asthmatic angiogenesis [97]. VEGFR-3 is expressed exclusively in blood vessels actively undergoing angiogenesis, and this VEGFR-3 expression is known to increase when cells are exposed to HDME [97]. HDME exposure promotes differentiation and proliferation of PACs, induces secretion of VEGF-C, and upregulates protease-activated receptor 2 (PAR-2) [97–102]. PAR-2 is a key house dust mite allergen-sensing receptor mainly expressed on airway epithelial cells, endothelial cells, and dendritic cells [103–109]. PAR-2 initiates the Th2 inflammatory responses to HDME and is also an important regulator of angiogenesis [98, 99, 110]. House dust mite proteases penetrate deep into the airway mucosa, activating endothelial cells via PAR-2 and triggering the onset of angiogenesis in the airway [97]. This endothelial activation of PAR-2 induces the production of pro-Th2 cytokines including interleukin-1 α (IL-1 α) and granulocyte-macrophage colony-stimulating factor (GM-CSF) [109, 111–113]. IL-1 α activates dendritic cells and controls the Th2 inflammatory response by inducing release of GM-CSF and TSLP by other cells [113]. GM-CSF activates dendritic cells which stimulate Th2 cells [113–118]. Together, these results show that house dust mite proteases induce angiogenesis, airway inflammation, and airway hyperresponsiveness through the activation of endothelial cells, mobilization of PACs, and upregulation of VEGFR-3 and VEGF-C.

The timeline of the progression and development of angiogenesis has also been studied in murine asthma models. PACs are recruited to the lungs within a few hours of allergen challenge, creating a pro-angiogenic environment in the lungs within 48 hours. However, the influx of inflammatory cells, namely, eosinophils, observed in the asthmatic airway following allergen challenge does not reach its peak until 4–6 days after allergen challenge [16]. This indicates that angiogenesis starts in the lungs before bulk inflammation occurs, suggesting that endothelial cell activation in asthma occurs independently of inflammation and reinforcing the importance of researching the angiogenic mechanisms in asthma. Other reports confirmed that PAC recruitment and neovascularization occur prior to airway inflammation [1, 119].

Recent research has focused on developing strategies to inhibit angiogenesis in the lungs as a novel therapeutic approach in asthma. Targeting PACs has proven to be an effective method of controlling angiogenesis in the asthmatic airway in a murine model. AMD3100, a chemokine receptor antagonist, was administered to mice during OVA allergen challenge. Accumulation of PACs in the airway was attenuated, as was eosinophilic inflammation, airway hyperresponsiveness, and airway vascularity due to the mitigation of angiogenesis [55]. Mice with established asthma symptoms that were treated with AMD3100 exhibited only partially reversed airway hyperresponsiveness despite the reduction of PAC and eosinophil accumulation and angiogenesis. This suggests that early detection and treatment of asthmatic angiogenesis may be crucial for clinical benefit. Drugs that prevent transendothelial migration of inflammatory cells, limiting inflammation that typically occurs in the asthmatic airway as the disease progresses, have also been explored [22]. Theophylline is an anti-inflammatory natural small molecule commonly used in asthma treatment to prevent inflammation and transendothelial migration [120]. Montelukast is a drug which serves as a leukotriene receptor antagonist, preventing the inflammatory response in the airway as well [121]. VUF-K-8788 is a histamine H1 antagonist that is able to reduce eosinophil adherence to endothelial cells in vitro while also reducing eosinophil accumulation and adherence in the airway of a guinea pig asthma model, preventing airway inflammation associated with the disease [122]. Discovering new inhibitors to target PACs and endothelial cells in the asthmatic airway will be crucial in future animal studies to explore potential therapeutic interventions for pathological angiogenesis.

4. Clinical studies

Clinical studies of patients with allergic asthma have played a key role in developing the current knowledge of neovascularization in this disease. Endobronchial biopsies are commonly performed to quantify airway inflammation and airway remodeling. A biopsy punch is used to extract tissues from the airway wall which are then studied to assess the current state of a patient's airway. For example, endobronchial biopsies have been used to compare VEGF mRNA levels in asthmatic and healthy control patients [123]. Increased VEGF mRNA indicates increased angiogenesis in asthmatic patients, as VEGF controls vascular remodeling of the airway through angiogenesis, as previously discussed. Increased VEGF mRNA levels in the airway wall may explain the elevated levels of VEGF in sputum and serum from asthmatic patients which correlate to the severity of the disease [124–129]. In another study, asthmatics presenting with airway inflammation and hyperresponsiveness underwent allergen inhalation prior to endobronchial biopsy. The endobronchial biopsy tissues showed increased presence of PACs in addition to elevated vessel numbers and size, indicative of angiogenesis [54]. Bronchoalveolar lavage (BAL) is another clinical technique used to quantify the presence of various cell types by flushing the bronchial and alveolar spaces with fluid in order to collect cells. For example, one BAL study compared the presence of PACs and total vessel density in asthmatic and healthy patients. Total vessel number was shown to be increased in the airway walls of asthma patients, as was the accumulation of PACs [17]. Increased vascularity observed in medium-sized airways in the lungs may contribute to airflow limitation, as an enhanced vascular network in the airway develops in early phases of chronic adult asthma [17].

Clinical studies of nitric oxide (NO) have also contributed to explaining endothelial cell activation in asthma. NO in circulation originates from the endothelium, while exhaled NO originates in the epithelium. When patients underwent allergen

challenge by inhalation, a significant increase in serum NO levels was observed after 4 hours, while exhaled NO did not increase [53]. This indicates that endothelial cells in the airway are activated prior to epithelial cells in the airway during a controlled asthma attack induced by inhaled allergens [53]. Thus, activation of the airway endothelium is one of the earliest responses to an induced asthma attack, triggering the vascular endothelium to release NO and mobilizing PACs to initiate angiogenesis.

5. Conclusion

Despite historical studies reporting angiogenesis in asthma more than a century ago, understanding of the endothelial contribution to asthma is still in its infancy. Clinical studies show a strong correlation between neovascularization and asthma severity. Whole-lung allergen studies suggest that airway inflammation and bronchoconstriction are preceded by rapid activation of the endothelium and accompanied by mobilization and recruitment of bone marrow-derived pro-angiogenic cells into the airway, resulting in angiogenesis. Murine model studies recapitulate the clinical findings and further indicate that endothelial cells are capable of sensing allergens just as the airway epithelium and dendritic cells do. Overall, a pro-Th2 angiogenic response may have a causal role in the genesis of allergic asthma (Figure 1).

Figure 1.
Angiogenic mechanisms in asthma.

Inhaled allergen proteases breach the airway epithelial barrier allowing them to penetrate into the airway mucosa. PAR-2 expressing bone marrow-derived PACs and lung-resident endothelial cells sense the mucosal presence of house dust mite allergens and respond by releasing angiogenic factors (eotaxin, VEGF-A, VEGF-C) and Th2-promoting cytokines (TSLP, IL-1α, GM-CSF). Additional PACs

expressing CXCR2 and CXCR4 receptors are recruited into the lungs. Eotaxins play a dual role by inducing angiogenesis and attracting circulating eosinophils into the lungs via CCR3 receptors. Thus, a pro-Th2 angiogenic response fuels the innate allergen sensing in the airway mucosa and promotes airway inflammation and bronchoconstriction.

Acknowledgements

The authors thank David Schumick of the Cleveland Clinic Center for Medical Art and Photography for his illustration work on **Figure 1**.

Conflict of interest

The authors declare no conflicts of interest.

Author details

Andrew Reichard and Kewal Asosingh*
Department of Inflammation and Immunity, Lerner Research Institute,
The Cleveland Clinic, Cleveland, Ohio, USA

*Address all correspondence to: asosink@ccf.org

IntechOpen

© 2019 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

References

- [1] Asosingh K, Erzurum SC. Angioplasticity in asthma. *Biochemical Society Transactions*. 2009;**37**(Pt 4):805-810
- [2] Majno G. Chronic inflammation: Links with angiogenesis and wound healing. *The American Journal of Pathology*. 1998;**153**(4):1035-1039
- [3] Cines DB, Pollak ES, Buck CA, Loscalzo J, Zimmerman GA, McEver RP, et al. Endothelial cells in physiology and in the pathophysiology of vascular disorders. *Blood*. 1998;**91**(10):3527-3561
- [4] Carmeliet P. Mechanisms of angiogenesis and arteriogenesis. *Nature Medicine*. 2000;**6**(4):389-395
- [5] Frantz S, Vincent KA, Feron O, Kelly RA. Innate immunity and angiogenesis. *Circulation Research*. 2005;**96**(1):15-26
- [6] Danese S, Dejana E, Fiocchi C. Immune regulation by microvascular endothelial cells: Directing innate and adaptive immunity, coagulation, and inflammation. *Journal of Immunology*. 2007;**178**(10):6017-6022
- [7] Alkim C, Savas B, Ensari A, Alkim H, Dagli U, Parlak E, et al. Expression of p53, VEGF, microvessel density, and cyclin-D1 in noncancerous tissue of inflammatory bowel disease. *Digestive Diseases and Sciences*. 2009;**54**(9):1979-1984
- [8] Alkim C, Alkim H, Koksar AR, Boga S, Sen I. Angiogenesis in inflammatory bowel disease. *International Journal of Inflammation*. 2015;**2015**:970890
- [9] Cantatore FP, Maruotti N, Corrado A, Ribatti D. Angiogenesis dysregulation in psoriatic arthritis: Molecular mechanisms. *BioMed Research International*. 2017;**2017**:5312813
- [10] Reece RJ, Canete JD, Parsons WJ, Emery P, Veale DJ. Distinct vascular patterns of early synovitis in psoriatic, reactive, and rheumatoid arthritis. *Arthritis and Rheumatism*. 1999;**42**(7):1481-1484
- [11] Ramjiawan RR, Griffioen AW, Duda DG. Anti-angiogenesis for cancer revisited: Is there a role for combinations with immunotherapy? *Angiogenesis*. 2017;**20**(2):185-204
- [12] Ellis AG. The pathological anatomy of bronchial asthma. *The American Journal of the Medical Sciences*. 1908;**186**(3):407-428
- [13] Dunnill MS. The pathology of asthma, with special reference to changes in the bronchial mucosa. *Journal of Clinical Pathology*. 1960;**13**:27-33
- [14] Segal M, Attinger E. Bronchial asthma. In: Gordon B, editor. *Clinical Cardiopulmonary Physiology* (American College of Chest Physicians). New York: Grune and Stratton; 1957. pp. 283-327
- [15] Florey H. The secretion of mucus and inflammation of mucous membranes. In: Florey H, editor. *General Pathology*. 2nd ed. London: Lloyd-Luke; 1958. pp. 120-142
- [16] Asosingh K, Swaidani S, Aronica M, Erzurum SC. Th1- and Th2-dependent endothelial progenitor cell recruitment and angiogenic switch in asthma. *Journal of Immunology*. 2007;**178**(10):6482-6494
- [17] Hashimoto M, Tanaka H, Abe S. Quantitative analysis of bronchial wall vascularity in the medium and small airways of patients with asthma and COPD. *Chest*. 2005;**127**(3):965-972
- [18] Li X, Wilson JW. Increased vascularity of the bronchial mucosa

- in mild asthma. *American Journal of Respiratory and Critical Care Medicine*. 1997;**156**(1):229-233
- [19] Salvato G. Quantitative and morphological analysis of the vascular bed in bronchial biopsy specimens from asthmatic and non-asthmatic subjects. *Thorax*. 2001;**56**(12):902-906
- [20] Vrugt B, Wilson S, Bron A, Holgate ST, Djukanovic R, Aalbers R. Bronchial angiogenesis in severe glucocorticoid-dependent asthma. *The European Respiratory Journal*. 2000;**15**(6):1014-1021
- [21] Pascual RM, Peters SP. Airway remodeling contributes to the progressive loss of lung function in asthma: An overview. *The Journal of Allergy and Clinical Immunology*. 2005;**116**(3):477-486 quiz 87
- [22] Green CE, Turner AM. The role of the endothelium in asthma and chronic obstructive pulmonary disease (COPD). *Respiratory Research*. 2017;**18**(1):20
- [23] Tang ML, Fiscus LC. Important roles for L-selectin and ICAM-1 in the development of allergic airway inflammation in asthma. *Pulmonary Pharmacology & Therapeutics*. 2001;**14**(3):203-210
- [24] Carmeliet P. Angiogenesis in health and disease. *Nature Medicine*. 2003;**9**(6):653-660
- [25] Semenza GL. Vasculogenesis, angiogenesis, and arteriogenesis: Mechanisms of blood vessel formation and remodeling. *Journal of Cellular Biochemistry*. 2007;**102**(4):840-847
- [26] Duong HT, Erzurum SC, Asosingh K. Pro-angiogenic hematopoietic progenitor cells and endothelial colony-forming cells in pathological angiogenesis of bronchial and pulmonary circulation. *Angiogenesis*. 2011;**14**(4):411-422
- [27] Wiggs BR, Hrousis CA, Drazen JM, Kamm RD. On the mechanism of mucosal folding in normal and asthmatic airways. *Journal of Applied Physiology (Bethesda, MD: 1985)*. 1997;**83**(6):1814-1821
- [28] Chetta A, Zanini A, Foresi A, D'Ippolito R, Tipa A, Castagnaro A, et al. Vascular endothelial growth factor up-regulation and bronchial wall remodelling in asthma. *Clinical and Experimental Allergy*. 2005;**35**(11):1437-1442
- [29] Leung DW, Cachianes G, Kuang WJ, Goeddel DV, Ferrara N. Vascular endothelial growth factor is a secreted angiogenic mitogen. *Science*. 1989;**246**(4935):1306-1309
- [30] Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. *Nature Medicine*. 2003;**9**(6):669-676
- [31] Koch S, Tugues S, Li X, Gualandi L, Claesson-Welsh L. Signal transduction by vascular endothelial growth factor receptors. *The Biochemical Journal*. 2011;**437**(2):169-183
- [32] Cao Y. Positive and negative modulation of angiogenesis by VEGFR1 ligands. *Science Signaling*. 2009;**2**(59):re1
- [33] Fong GH, Rossant J, Gertsenstein M, Breitman ML. Role of the Flt-1 receptor tyrosine kinase in regulating the assembly of vascular endothelium. *Nature*. 1995;**376**(6535):66-70
- [34] Shalaby F, Rossant J, Yamaguchi TP, Gertsenstein M, Wu XF, Breitman ML, et al. Failure of blood-island formation and vasculogenesis in Flk-1-deficient mice. *Nature*. 1995;**376**(6535):62-66
- [35] Joukov V, Pajusola K, Kaipainen A, Chilov D, Lahtinen I, Kukk E, et al. A novel vascular endothelial growth factor, VEGF-C, is a ligand for the Flt4

(VEGFR-3) and KDR (VEGFR-2) receptor tyrosine kinases. *The EMBO Journal*. 1996;**15**(2):290-298

[36] Cao Y, Linden P, Farnebo J, Cao R, Eriksson A, Kumar V, et al. Vascular endothelial growth factor C induces angiogenesis in vivo. *Proceedings of the National Academy of Sciences of the United States of America*. 1998;**95**(24):14389-14394

[37] Witzenbichler B, Asahara T, Murohara T, Silver M, Spyridopoulos I, Magner M, et al. Vascular endothelial growth factor-C (VEGF-C/VEGF-2) promotes angiogenesis in the setting of tissue ischemia. *The American Journal of Pathology*. 1998;**153**(2):381-394

[38] Tammela T, Zarkada G, Nurmi H, Jakobsson L, Heinolainen K, Tvorogov D, et al. VEGFR-3 controls tip to stalk conversion at vessel fusion sites by reinforcing Notch signalling. *Nature Cell Biology*. 2011;**13**(10):1202-1213

[39] Tammela T, Zarkada G, Wallgard E, Murtomaki A, Suchting S, Wirzenius M, et al. Blocking VEGFR-3 suppresses angiogenic sprouting and vascular network formation. *Nature*. 2008;**454**(7204):656-660

[40] Wu LW, Mayo LD, Dunbar JD, Kessler KM, Baerwald MR, Jaffe EA, et al. Utilization of distinct signaling pathways by receptors for vascular endothelial cell growth factor and other mitogens in the induction of endothelial cell proliferation. *The Journal of Biological Chemistry*. 2000;**275**(7):5096-5103

[41] Wang S, Cao W, Xing H, Chen YL, Li Q, Shen T, et al. Activation of ERK pathway is required for 15-HETE-induced angiogenesis in human umbilical vascular endothelial cells. *Journal of Receptor and Signal Transduction Research*. 2016;**36**(3):225-232

[42] Richardson MR, Yoder MC. Endothelial progenitor cells: Quo vadis? *Journal of Molecular and Cellular Cardiology*. 2011;**50**(2):266-272

[43] Chao H, Hirschi KK. Hemato-vascular origins of endothelial progenitor cells? *Microvascular Research*. 2010;**79**(3):169-173

[44] Ingram DA, Mead LE, Tanaka H, Meade V, Fenoglio A, Mortell K, et al. Identification of a novel hierarchy of endothelial progenitor cells using human peripheral and umbilical cord blood. *Blood*. 2004;**104**(9):2752-2760

[45] Yoder MC. Defining human endothelial progenitor cells. *Journal of Thrombosis and Haemostasis*. 2009;**7**(Suppl 1):49-52

[46] Wilson JW, Hii S. The importance of the airway microvasculature in asthma. *Current Opinion in Allergy and Clinical Immunology*. 2006;**6**(1):51-55

[47] Yoder MC. Is endothelium the origin of endothelial progenitor cells? *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2010;**30**(6):1094-1103

[48] Yoder MC, Mead LE, Prater D, Krier TR, Mroueh KN, Li F, et al. Redefining endothelial progenitor cells via clonal analysis and hematopoietic stem/progenitor cell principals. *Blood*. 2007;**109**(5):1801-1809

[49] Rose JA, Erzurum S, Asosingh K. Biology and flow cytometry of proangiogenic hematopoietic progenitors cells. *Cytometry. Part A*. 2015;**87**(1):5-19

[50] Wara AK, Croce K, Foo S, Sun X, Icli B, Tesmenitsky Y, et al. Bone marrow-derived CMPs and GMPs represent highly functional proangiogenic cells: Implications for ischemic cardiovascular disease. *Blood*. 2011;**118**(24):6461-6464

- [51] Asosingh K, Cheng G, Xu W, Savasky BM, Aronica MA, Li X, et al. Nascent endothelium initiates Th2 polarization of asthma. *Journal of Immunology*. 2013;**190**(7): 3458-3465
- [52] Asosingh K, Hanson JD, Cheng G, Aronica MA, Erzurum SC. Allergen-induced, eotaxin-rich, proangiogenic bone marrow progenitors: A blood-borne cellular envoy for lung eosinophilia. *The Journal of Allergy and Clinical Immunology*. 2010;**125**(4):918-925
- [53] Asosingh K, Vasanthi A, Tipton A, Queisser K, Wanner N, Janocha A, et al. Eotaxin-rich proangiogenic hematopoietic progenitor cells and CCR3+ endothelium in the atopic asthmatic response. *Journal of Immunology*. 2016;**196**(5):2377-2387
- [54] Imaoka H, Punia N, Irshad A, Ying S, Corrigan CJ, Howie K, et al. Lung homing of endothelial progenitor cells in humans with asthma after allergen challenge. *American Journal of Respiratory and Critical Care Medicine*. 2011;**184**(7):771-778
- [55] Doyle TM, Ellis R, Park HJ, Inman MD, Sehmi R. Modulating progenitor accumulation attenuates lung angiogenesis in a mouse model of asthma. *The European Respiratory Journal*. 2011;**38**(3):679-687
- [56] Medina RJ, O'Neill CL, Sweeney M, Guduric-Fuchs J, Gardiner TA, Simpson DA, et al. Molecular analysis of endothelial progenitor cell (EPC) subtypes reveals two distinct cell populations with different identities. *BMC Medical Genomics*. 2010;**3**:18
- [57] Melero-Martin JM, Khan ZA, Picard A, Wu X, Paruchuri S, Bischoff J. In vivo vasculogenic potential of human blood-derived endothelial progenitor cells. *Blood*. 2007;**109**(11):4761-4768
- [58] Yoon CH, Hur J, Park KW, Kim JH, Lee CS, Oh IY, et al. Synergistic neovascularization by mixed transplantation of early endothelial progenitor cells and late outgrowth endothelial cells: The role of angiogenic cytokines and matrix metalloproteinases. *Circulation*. 2005;**112**(11):1618-1627
- [59] Asahara T, Murohara T, Sullivan A, Silver M, van der Zee R, Li T, et al. Isolation of putative progenitor endothelial cells for angiogenesis. *Science*. 1997;**275**(5302):964-967
- [60] Yoder MC, Ingram DA. Endothelial progenitor cell: Ongoing controversy for defining these cells and their role in neoangiogenesis in the murine system. *Current Opinion in Hematology*. 2009;**16**(4):269-273
- [61] Steinmetz M, Nickenig G, Werner N. Endothelial-regenerating cells: An expanding universe. *Hypertension*. 2010;**55**(3):593-599
- [62] Loges S, Fehse B, Brockmann MA, Lamszus K, Butzal M, Guckenberg M, et al. Identification of the adult human hemangioblast. *Stem Cells and Development*. 2004;**13**(3):229-242
- [63] Rehman J, Li J, Orschell CM, March KL. Peripheral blood "endothelial progenitor cells" are derived from monocyte/macrophages and secrete angiogenic growth factors. *Circulation*. 2003;**107**(8):1164-1169
- [64] Hur J, Yang HM, Yoon CH, Lee CS, Park KW, Kim JH, et al. Identification of a novel role of T cells in postnatal vasculogenesis: Characterization of endothelial progenitor cell colonies. *Circulation*. 2007;**116**(15):1671-1682
- [65] Sukkar A, Jenkins J, Sanchez J, Wagner EM. Inhibition of CXCR2 attenuates bronchial angiogenesis in the ischemic rat lung. *Journal of Applied*

Physiology (Bethesda, MD: 1985).
 2008;**104**(5):1470-1475

[66] Hristov M, Zerneck A, Bidzhekov K, Liehn EA, Shagdarsuren E, Ludwig A, et al. Importance of CXC chemokine receptor 2 in the homing of human peripheral blood endothelial progenitor cells to sites of arterial injury. *Circulation Research*. 2007;**100**(4):590-597

[67] Asagoe K, Yamamoto K, Takahashi A, Suzuki K, Maeda A, Nohgawa M, et al. Down-regulation of CXCR2 expression on human polymorphonuclear leukocytes by TNF- α . *Journal of Immunology*. 1998;**160**(9):4518-4525

[68] Matsuo Y, Raimondo M, Woodward TA, Wallace MB, Gill KR, Tong Z, et al. CXC-chemokine/CXCR2 biological axis promotes angiogenesis in vitro and in vivo in pancreatic cancer. *International Journal of Cancer*. 2009;**125**(5):1027-1037

[69] Li X, Chen Y, Chang Y, Li S, Zhao Z, Zhang H. CXCR2 is involved in pulmonary intravascular macrophage accumulation and angiogenesis in a rat model of hepatopulmonary syndrome. *Clinical Science (London, England)*. 2017;**131**(2):159-168

[70] Jones CP, Pitchford SC, Lloyd CM, Rankin SM. CXCR2 mediates the recruitment of endothelial progenitor cells during allergic airways remodeling. *Stem Cells*. 2009;**27**(12):3074-3081

[71] Salcedo R, Young HA, Ponce ML, Ward JM, Kleinman HK, Murphy WJ, et al. Eotaxin (CCL11) induces in vivo angiogenic responses by human CCR3+ endothelial cells. *Journal of Immunology*. 2001;**166**(12):7571-7578

[72] Takeda A, Baffi JZ, Kleinman ME, Cho WG, Nozaki M, Yamada K, et al. CCR3 is a target for age-related macular

degeneration diagnosis and therapy. *Nature*. 2009;**460**(7252):225-230

[73] Ponath PD, Qin S, Post TW, Wang J, Wu L, Gerard NP, et al. Molecular cloning and characterization of a human eotaxin receptor expressed selectively on eosinophils. *The Journal of Experimental Medicine*. 1996;**183**(6):2437-2448

[74] Hammad H, Plantinga M, Deswarte K, Pouliot P, Willart MA, Kool M, et al. Inflammatory dendritic cells—not basophils—are necessary and sufficient for induction of Th2 immunity to inhaled house dust mite allergen. *The Journal of Experimental Medicine*. 2010;**207**(10):2097-2111

[75] Plantinga M, Guillems M, Vanheerswynghe M, Deswarte K, Branco-Madeira F, Toussaint W, et al. Conventional and monocyte-derived CD11b(+) dendritic cells initiate and maintain T helper 2 cell-mediated immunity to house dust mite allergen. *Immunity*. 2013;**38**(2):322-335

[76] Xu W, Ghosh S, Comhair SA, Asosingh K, Janocha AJ, Mavrikakis DA, et al. Increased mitochondrial arginine metabolism supports bioenergetics in asthma. *The Journal of Clinical Investigation*. 2016;**126**(7):2465-2481

[77] Sivapalan N, Wattie J, Inman MD, Sehmi R. Lung-homing of endothelial progenitor cells and airway vascularization is only partially dependant on eosinophils in a house dust mite-exposed mouse model of allergic asthma. *PLoS One*. 2014;**9**(10):e109991

[78] Romagnani S. Th1/Th2 cells. *Inflammatory Bowel Diseases*. 1999;**5**(4):285-294

[79] Cazzola M, Polosa R. Anti-TNF- α and Th1 cytokine-directed therapies for the treatment of asthma.

Current Opinion in Allergy and Clinical Immunology. 2006;**6**(1):43-50

[80] Umetsu DT, McIntire JJ, Akbari O, Macaubas C, DeKruyff RH. Asthma: An epidemic of dysregulated immunity. *Nature Immunology*. 2002;**3**(8):715-720

[81] Li XM, Schofield BH, Wang QF, Kim KH, Huang SK. Induction of pulmonary allergic responses by antigen-specific Th2 cells. *Journal of Immunology*. 1998;**160**(3):1378-1384

[82] Randolph DA, Carruthers CJ, Szabo SJ, Murphy KM, Chaplin DD. Modulation of airway inflammation by passive transfer of allergen-specific Th1 and Th2 cells in a mouse model of asthma. *Journal of Immunology*. 1999;**162**(4):2375-2383

[83] Randolph DA, Stephens R, Carruthers CJ, Chaplin DD. Cooperation between Th1 and Th2 cells in a murine model of eosinophilic airway inflammation. *The Journal of Clinical Investigation*. 1999;**104**(8):1021-1029

[84] Fort MM, Cheung J, Yen D, Li J, Zurawski SM, Lo S, et al. IL-25 induces IL-4, IL-5, and IL-13 and Th2-associated pathologies in vivo. *Immunity*. 2001;**15**(6):985-995

[85] Fallon PG, Ballantyne SJ, Mangan NE, Barlow JL, Dasvarma A, Hewett DR, et al. Identification of an interleukin (IL)-25-dependent cell population that provides IL-4, IL-5, and IL-13 at the onset of helminth expulsion. *The Journal of Experimental Medicine*. 2006;**203**(4):1105-1116

[86] Owyang AM, Zaph C, Wilson EH, Guild KJ, McClanahan T, Miller HR, et al. Interleukin 25 regulates type 2 cytokine-dependent immunity and limits chronic inflammation in the gastrointestinal tract. *The Journal of Experimental Medicine*. 2006;**203**(4):843-849

[87] Wang YH, Angkasekwinai P, Lu N, Voo KS, Arima K, Hanabuchi S, et al. IL-25 augments type 2 immune responses by enhancing the expansion and functions of TSLP-DC-activated Th2 memory cells. *The Journal of Experimental Medicine*. 2007;**204**(8):1837-1847

[88] Angkasekwinai P, Park H, Wang YH, Wang YH, Chang SH, Corry DB, et al. Interleukin 25 promotes the initiation of proallergic type 2 responses. *The Journal of Experimental Medicine*. 2007;**204**(7):1509-1517

[89] Ikeda K, Nakajima H, Suzuki K, Kagami S, Hirose K, Suto A, et al. Mast cells produce interleukin-25 upon Fc epsilon RI-mediated activation. *Blood*. 2003;**101**(9):3594-3596

[90] Dolgachev V, Petersen BC, Budelsky AL, Berlin AA, Lukacs NW. Pulmonary IL-17E (IL-25) production and IL-17RB+ myeloid cell-derived Th2 cytokine production are dependent upon stem cell factor-induced responses during chronic allergic pulmonary disease. *Journal of Immunology*. 2009;**183**(9):5705-5715

[91] Pan G, French D, Mao W, Maruoka M, Risser P, Lee J, et al. Forced expression of murine IL-17E induces growth retardation, jaundice, a Th2-biased response, and multiorgan inflammation in mice. *Journal of Immunology*. 2001;**167**(11):6559-6567

[92] de Boer OJ, van der Meer JJ, Teeling P, van der Loos CM, Idu MM, van Maldegem F, et al. Differential expression of interleukin-17 family cytokines in intact and complicated human atherosclerotic plaques. *The Journal of Pathology*. 2010;**220**(4):499-508

[93] Sonobe Y, Takeuchi H, Kataoka K, Li H, Jin S, Mimuro M, et al. Interleukin-25 expressed by brain

capillary endothelial cells maintains blood-brain barrier function in a protein kinase Cepsilon-dependent manner. *The Journal of Biological Chemistry*. 2009;**284**(46):31834-31842

[94] Ying S, O'Connor B, Ratoff J, Meng Q, Mallett K, Cousins D, et al. Thymic stromal lymphopoietin expression is increased in asthmatic airways and correlates with expression of Th2-attracting chemokines and disease severity. *Journal of Immunology*. 2005;**174**(12):8183-8190

[95] West EE, Kashyap M, Leonard WJ. TSLP: A key regulator of asthma pathogenesis. *Drug Discovery Today: Disease Mechanisms*. 2012;**9**(3-4):83-88

[96] Platts-Mills TAE, de Weck AL, Aalberse RC, Bessot JC, Bjorksten B, Bischoff E, et al. Dust mite allergens and asthma—A worldwide problem. *The Journal of Allergy and Clinical Immunology*. 1989;**83**(2 Pt 1):416-427

[97] Asosingh K, Weiss K, Queisser K, Wanner N, Yin M, Aronica M, et al. Endothelial cells in the innate response to allergens and initiation of atopic asthma. *The Journal of Clinical Investigation*. 2018;**128**(7):3116-3128

[98] Belting M, Dorrell MI, Sandgren S, Aguilar E, Ahamed J, Dorfleitner A, et al. Regulation of angiogenesis by tissue factor cytoplasmic domain signaling. *Nature Medicine*. 2004;**10**(5):502-509

[99] Uusitalo-Jarvinen H, Kurokawa T, Mueller BM, Andrade-Gordon P, Friedlander M, Ruf W. Role of protease activated receptor 1 and 2 signaling in hypoxia-induced angiogenesis. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2007;**27**(6):1456-1462

[100] Wara AK, Foo S, Croce K, Sun X, Icli B, Tesmenitsky Y, et al. TGF-beta1

signaling and Kruppel-like factor 10 regulate bone marrow-derived proangiogenic cell differentiation, function, and neovascularization. *Blood*. 2011;**118**(24):6450-6460

[101] Wara AK, Manica A, Marchini JF, Sun X, Icli B, Tesmenitsky Y, et al. Bone marrow-derived Kruppel-like factor 10 controls reendothelialization in response to arterial injury. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2013;**33**(7):1552-1560

[102] Milia AF, Salis MB, Stacca T, Pinna A, Madeddu P, Trevisani M, et al. Protease-activated receptor-2 stimulates angiogenesis and accelerates hemodynamic recovery in a mouse model of hindlimb ischemia. *Circulation Research*. 2002;**91**(4):346-352

[103] Tomee JF, van Weissenbruch R, de Monchy JG, Kauffman HF. Interactions between inhalant allergen extracts and airway epithelial cells: Effect on cytokine production and cell detachment. *The Journal of Allergy and Clinical Immunology*. 1998;**102**(1):75-85

[104] Cocks TM, Fong B, Chow JM, Anderson GP, Frauman AG, Goldie RG, et al. A protective role for protease-activated receptors in the airways. *Nature*. 1999;**398**(6723):156-160

[105] Ricciardolo FL, Steinhoff M, Amadesi S, Guerrini R, Tognetto M, Trevisani M, et al. Presence and bronchomotor activity of protease-activated receptor-2 in guinea pig airways. *American Journal of Respiratory and Critical Care Medicine*. 2000;**161**(5):1672-1680

[106] Cocks TM, Moffatt JD. Protease-activated receptor-2 (PAR2) in the airways. *Pulmonary Pharmacology & Therapeutics*. 2001;**14**(3):183-191

[107] Schmidlin F, Amadesi S, Vidil R, Trevisani M, Martinet N, Caughey G,

et al. Expression and function of proteinase-activated receptor 2 in human bronchial smooth muscle. *American Journal of Respiratory and Critical Care Medicine*. 2001;**164**(7):1276-1281

[108] Pichavant M, Charbonnier AS, Taront S, Brichet A, Wallaert B, Pestel J, et al. Asthmatic bronchial epithelium activated by the proteolytic allergen Der p 1 increases selective dendritic cell recruitment. *The Journal of Allergy and Clinical Immunology*. 2005;**115**(4):771-778

[109] Adam E, Hansen KK, Astudillo Fernandez O, Coulon L, Bex F, Duhant X, et al. The house dust mite allergen Der p 1, unlike Der p 3, stimulates the expression of interleukin-8 in human airway epithelial cells via a proteinase-activated receptor-2-independent mechanism. *The Journal of Biological Chemistry*. 2006;**281**(11):6910-6923

[110] Lambrecht BN, Hammad H. The airway epithelium in asthma. *Nature Medicine*. 2012;**18**(5):684-692

[111] Sun G, Stacey MA, Schmidt M, Mori L, Mattoli S. Interaction of mite allergens Der p3 and Der p9 with protease-activated receptor-2 expressed by lung epithelial cells. *Journal of Immunology*. 2001;**167**(2):1014-1021

[112] Asokanathan N, Graham PT, Stewart DJ, Bakker AJ, Eidne KA, Thompson PJ, et al. House dust mite allergens induce proinflammatory cytokines from respiratory epithelial cells: The cysteine protease allergen, Der p 1, activates protease-activated receptor (PAR)-2 and inactivates PAR-1. *Journal of Immunology*. 2002;**169**(8):4572-4578

[113] Willart MA, Deswarte K, Pouliot P, Braun H, Beyaert R, Lambrecht BN, et al. Interleukin-1 α controls allergic sensitization to inhaled house dust mite

via the epithelial release of GM-CSF and IL-33. *The Journal of Experimental Medicine*. 2012;**209**(8):1505-1517

[114] Stampfli MR, Wiley RE, Neigh GS, Gajewska BU, Lei XF, Snider DP, et al. GM-CSF transgene expression in the airway allows aerosolized ovalbumin to induce allergic sensitization in mice. *The Journal of Clinical Investigation*. 1998;**102**(9):1704-1714

[115] Ohta K, Yamashita N, Tajima M, Miyasaka T, Nakano J, Nakajima M, et al. Diesel exhaust particulate induces airway hyperresponsiveness in a murine model: Essential role of GM-CSF. *Journal of Allergy and Clinical Immunology*. 1999;**104**(5):1024-1030

[116] Cates EC, Fattouh R, Wattie J, Inman MD, Goncharova S, Coyle AJ, et al. Intranasal exposure of mice to house dust mite elicits allergic airway inflammation via a GM-CSF-mediated mechanism. *Journal of Immunology*. 2004;**173**(10):6384-6392

[117] Bleck B, Tse DB, Jaspers I, Curotto de Lafaille MA, Reibman J. Diesel exhaust particle-exposed human bronchial epithelial cells induce dendritic cell maturation. *Journal of Immunology*. 2006;**176**(12):7431-7437

[118] Zhou Q, Ho AW, Schlitzer A, Tang Y, Wong KH, Wong FH, et al. GM-CSF-licensed CD11b⁺ lung dendritic cells orchestrate Th2 immunity to *Blomia tropicalis*. *Journal of Immunology*. 2014;**193**(2):496-509

[119] Asosingh K, Aldred MA, Vasanji A, Drazba J, Sharp J, Farver C, et al. Circulating angiogenic precursors in idiopathic pulmonary arterial hypertension. *The American Journal of Pathology*. 2008;**172**(3):615-627

[120] Choo JH, Nagata M, Sutani A, Kikuchi I, Sakamoto Y. Theophylline attenuates the adhesion of eosinophils to endothelial cells. *International*

Archives of Allergy and Immunology.
2003;**131**(Suppl 1):40-45

[121] Virchow JC Jr, Faehndrich S, Nassenstein C, Bock S, Matthys H, Luttmann W. Effect of a specific cysteinyl leukotriene-receptor 1-antagonist (montelukast) on the transmigration of eosinophils across human umbilical vein endothelial cells. *Clinical and Experimental Allergy*. 2001;**31**(6):836-844

[122] Takizawa T, Watanabe C, Saiki I, Wada Y, Tohma T, Nagai H. Effects of a new antiallergic drug, VUF-K-8788, on infiltration of lung parenchyma by eosinophils in guinea pigs and eosinophil-adhesion to human umbilical vein endothelial cells (HUVEC). *Biological & Pharmaceutical Bulletin*. 2001;**24**(10):1127-1132

[123] Hoshino M, Nakamura Y, Hamid QA. Gene expression of vascular endothelial growth factor and its receptors and angiogenesis in bronchial asthma. *The Journal of Allergy and Clinical Immunology*. 2001;**107**(6):1034-1038

[124] Kanazawa H, Hirata K, Yoshikawa J. Involvement of vascular endothelial growth factor in exercise induced bronchoconstriction in asthmatic patients. *Thorax*. 2002;**57**(10):885-888

[125] Asai K, Kanazawa H, Otani K, Shiraishi S, Hirata K, Yoshikawa J. Imbalance between vascular endothelial growth factor and endostatin levels in induced sputum from asthmatic subjects. *The Journal of Allergy and Clinical Immunology*. 2002;**110**(4):571-575

[126] Asai K, Kanazawa H, Kamoi H, Shiraishi S, Hirata K, Yoshikawa J. Increased levels of vascular endothelial growth factor in induced sputum in asthmatic patients. *Clinical and Experimental Allergy*. 2003;**33**(5):595-599

[127] Papadaki G, Bakakos P, Kostikas K, Hillas G, Tsiligianni Z, Koulouris NG, et al. Vascular endothelial growth factor and cysteinyl leukotrienes in sputum supernatant of patients with asthma. *Respiratory Medicine*. 2013;**107**(9):1339-1345

[128] Abdel-Rahman AM, el-Sahrigy SA, Bakr SI. A comparative study of two angiogenic factors: Vascular endothelial growth factor and angiogenin in induced sputum from asthmatic children in acute attack. *Chest*. 2006;**129**(2):266-271

[129] Lee HY, Min KH, Lee SM, Lee JE, Rhee CK. Clinical significance of serum vascular endothelial growth factor in young male asthma patients. *The Korean Journal of Internal Medicine*. 2017;**32**(2):295-301