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Mini-Review

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Angiogenesis Factors as Emerging Circulating Biomarkers in Asthma

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ABSTRACT

Angiogenesis is an important event in the development of allergic inflammation as well as in the pathophysiology of tissue remodeling in asthma. Increased angiogenesis is a well-documented feature of airway remodeling in asthma. Angiogenesis refers to the formation of new blood vessels from pre-existing endothelium. Angiogenesis can be initiated by endogenous angiogenic factors released from mesenchymal cells or inflammatory cells. Under physiological conditions, angiogenesis is controlled by an equilibrium between pro-endogenous and anti-endogenous angiogenic factors released from the extracellular matrix to become bioavailable. The presence of increased size and number of bronchial blood vessels indicates that angiogenesis plays a crucial role in tissue growth and remodeling in asthma. However, the diagnostic significance of circulating angiogenic factors in asthma remains unclear. This review summarizes the role of angiogenesis in airway remodeling in asthma, and the potential diagnostic implications of circulating angiogenetic factors.

Keywords: Angiogenesis; biomarkers; airway remodeling; asthma

INTRODUCTION

Asthma is an important non-communicable disease affecting people of all ages and represents a major global health problem. It is a heterogeneous disease characterized by chronic airway inflammation. Dysregulated immune and inflammatory pathways ultimately affect lung tissue cells, causing the cardinal features of asthma, including airway inflammation and hyperreactivity.[1] Asthma manifests symptoms such as wheezing, chest tightness, coughing, and shortness of breath, resulting from factors including airway inflammation, bronchoconstriction, hyperresponsiveness, and airway remodeling.[1] Initially, the key feature of asthma was known as the constriction of airway smooth muscle (ASM) due to excessive airway responsiveness to external stimuli. Currently, it is recognized that airway inflammation is a cardinal feature of asthma, along with structural changes in the airways and lungs known as airway remodeling.[1] The main pathology of asthma includes wall remodeling and lumen narrowing,[2,3] with the involvement of small airways increasingly recognized, particularly in severe asthma.[4,5]

Angiogenesis or the increased size and numbers of bronchial blood vessels is the essential component of tissue growth and remodeling in asthma.[6] Angiogenesis is initiated by endogenous angiogenic factors released from mesenchymal cells or inflammatory cells.[7] Under physiological conditions, angiogenesis is controlled by an equilibrium between pro-endogenous and anti-endogenous angiogenic factors that are released from the extracellular matrix to become bioavailable.[7] Angiogenesis is an important event in the development of allergic inflammation and the pathophysiology of tissue remodeling in asthma,[7] with increased angiogenesis being a well-documented feature of airway remodeling.[8-10]

This review summarizes the role of angiogenesis in airway remodeling in asthma, and the potential diagnostic implication of circulating angiogenetic factors.

AIRWAY REMODELING IN ASTHMA

Airway remodeling involves hypertrophy and hyperplasia of ASM cells, leading to reduced lung function and recurrent exacerbations.[11] The pathophysiology of asthma encompasses a multifaceted interplay of molecular and cellular components, including cytoskeletal proteins and inflammatory mediators.[12-14]

Airway remodeling, a crucial phenomenon in respiratory diseases such as asthma, entails structural changes in the airway that profoundly impact pathological alterations and disrupt normal physiological functions. These structural changes include epithelial damage, increased number of goblet and mucus cell causing excessive mucus production, subepithelial fibrosis leading to increased airway rigidity, ASM hypertrophy leading to heightened airway constriction, and structural modifications in airway vasculature.[15,16]

Angiogenesis, a critical component of airway remodeling, contributes to chronic inflammation by creating a network of blood vessels that facilitates eosinophil migration into the bronchial mucosa.[17] Angiogenesis plays a pivotal role in asthma progression, and analyzing its association with clinical outcomes could improve understanding of asthma endotypes and aid in identifying novel therapeutic targets and biomarkers.

Invasive methods offer valuable insights into structural alterations occurring in the airways but are often accompanied by ethical and practical challenges.[18] Recently, non-invasive approaches, including a computed tomography (CT) scan and biomarker-based methods, have been used to evaluate airway remodeling. CT scans assess airway parameters including bronchial wall thickness, luminal diameter, lumen area, wall area, total area, and the percentage of wall area to total area (WA/TA or wall area %). These parameters can be correlated with lung function, making it a valuable tool for assessing airway remodeling.[19-21]

BIOMARKERS IN ASTHMA

Until now, various biomarkers of asthma have been identified (**Table 1**). Airway inflammation in eosinophilic asthma can be indicated by sputum eosinophilia, determined by an eosinophil count exceeding 2%–3% of the total cells in sputum samples.[22] Because sputum induction and quantification are complex and time-consuming processes, researchers are increasingly focusing on alternative diagnostic biomarkers linked to eosinophilic inflammation.

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Eosinophilic asthma is often indicated by peripheral blood eosinophil counts frequently linked to the severity of asthma exacerbations.[23,24] Interestingly, eosinophil counts in the sputum strongly correlate with those in the blood. Elevated levels of eosinophil-derived neurotoxin and eosinophil peroxidase were observed, exhibiting a significant correlation with symptom severity scores ($P < 0.0001$) and eosinophil counts ($P < 0.0001$). These findings indicate the activation of eosinophilic biomarkers in individuals with eosinophilic asthma.[25,26] In addition to evaluating sputum and blood/serum eosinophil counts, they can be assessed by eosinophils in bronchoalveolar lavage fluid (BALF) or biopsies of the airway mucosa. Elevated fractional exhaled nitric oxide (FeNO) levels, particularly those exceeding 25 parts per billion (ppb), are indicative of eosinophilic airway inflammation and can predict responsiveness to corticosteroids.[27] A meta-analysis has shown that FeNO demonstrates fair accuracy and sensitivity in diagnosing asthma.[28] Recent insights suggest that combining FeNO levels with blood eosinophil counts can further optimize asthma management.[27] Exhaled breath condensate offers a noninvasive method for assessing severe eosinophilic asthma by measuring compounds such as cysteinyl leukotrienes and volatile organic compounds, which correlate with asthma exacerbations.[29,30] Standardizing collection methods and validating analysis techniques are needed for broader application. The progression of eosinophilic asthma results in significant changes in the composition of urine metabolites.[31] Bromotyrosine (BrTyr) and other urinary markers have been identified as valuable indicators of the disease progression. Notably, elevated BrTyr levels were a significant predictor of asthma exacerbation at follow-up, with participants exhibiting a 4.0-fold increased risk of exacerbation during the follow-up period (95% confidence interval, 1.1–14.7; $P = 0.03$) compared to those with lower BrTyr levels.[25] These markers not only offer insights into the progression of eosinophilic asthma but also serve as important tools for assessing the efficacy of steroid therapy.[32]

Table 1. Biomarkers in asthma

Biomarker	Sample	Associated asthma endotype	References
EDN	Sputum, blood	T2-high	25
EPO	Blood	T2-high	26
FeNO	Exhaled breath	T2-high	27,28
CysLTs	Exhaled breath	T2-high	29
VOCs	Exhaled breath	Not determined	30
Bromotyrosine	Urine	T2-high	31
miRNAs	Bronchoscopy	T2-high	33,34,35
Periostin	Sputum, blood	T2-high	36,37
Siglec-8	Sputum, exhaled breath	T2-high	38
CD11b	Blood	T2-high	39
CD62L	Sputum, blood	T2-high	39
CD69	Blood	T2-high	39
CX3CR1	Blood	T2-high/T2-low	39
B7-2/CD86	Blood	T2-high	39
IL-6TS	Sputum	T2-low	40
TSLP	Blood	T2-high	41
Nectin-4	Blood, tissue	T2-high	43
Claudins	Blood, tissue	T2-high	44,45
JAM-A	Blood, tissue	T2-high	46
Fibronectin	Blood	T2-high	47
Collagen types I, III, and V	Bronchial biopsy	T2-high	47
Laminin	Tissue, blood	T2-high	47
Tenascin	Blood	T2-high	47
Versican	Tissue, BAL fluid	T2-low	47
Annexin	Blood, tissue	T2-high	48

EDN, eosinophil-derived neurotoxin; EPO, eosinophil peroxidase; CysLT, cysteinyl leukotriene; VOC, volatile organic compound; miRNA, micro RNA.

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Genetic markers and proteomic studies of airway tissues are unveiling potential therapeutic targets and elucidating the underlying molecular landscape of asthma.[33] MicroRNAs (miRNAs) play a significant role in Th2-driven airway inflammation in eosinophilic asthma. A wide range of miRNAs, including miR-21, miR-135a, miR-142, miR-143, miR-146b, miR-193b, miR-223, miR-365, miR-375, miR-452, and miR-1165-3p, have been implicated in this process.[33] Analysis of miRNA-338 and miRNA-145 in sputum samples effectively distinguishes patients with severe eosinophilic asthma from those with chronic obstructive pulmonary disease (COPD).[34] Also, miRNA-338-3p has emerged as a promising early biomarker for predicting response to reslizumab and mepolizumab treatments in severe eosinophilic asthma.[35] Profiling these miRNAs can aid in distinguishing severe asthma patients from healthy individuals and in predicting responses to treatment.[33] Periostin plays a crucial role in tissue remodeling and inflammation and has emerged as a potential diagnostic and prognostic biomarker for asthma. Elevated serum periostin levels and increased bronchial epithelial cell proliferation are linked to frequent asthma exacerbations and persistent eosinophilic airway inflammation, even with corticosteroid treatment. Periostin is released in response to interleukin (IL)-4 and IL-13 signaling, and therapies targeting these pathways have been shown to reduce periostin levels.[36] Specific treatments such as omalizumab, Lebrikizumab, and Tralokinumab have effectively decreased periostin levels in the airways, suggesting their potential role in managing asthma-related tissue remodeling and inflammation.[36,37] Siglec-8, a surface molecule expressed on eosinophils, correlates with eosinophilic airway inflammation when measured in sputum or exhaled breath.[38] Markers of eosinophil activation, such as CD11b, CD62L, CD69, CX3CR1, and B7-2/CD86, could provide real-time information about ongoing inflammation and serve as prognostic biomarkers due to their increased expression upon eosinophil activation.[39] Elevated IL-6 trans-signaling levels offer insights into asthma, including eosinophilia, phenotypic differences, and increased immune cell infiltration in the airway submucosa.[40] Elevated levels of mast cell tryptase in severe asthma patients indicate its significance, particularly when combined with thymic stromal lymphopoietin and blood eosinophil count, in assessing exacerbation risks.[41]

The airway epithelium in asthmatic individuals undergoes significant phenotypic alterations, leading to a loss of epithelial integrity through epithelial shedding and increased mucus production via mucous gland hyperplasia.[42] The bronchial epithelial cells collectively create a selective permeability barrier that regulates fluid loss, prevents pathogen entry, and curbs inappropriate immune responses in the subepithelial lung mucosa.[43] Many studies have also revealed structural alterations in the airway epithelium of asthmatic patients, including disruption of tight and adherens junctions. Plasma proteins of cell barrier proteins, such as JAM-A, Claudins and Nectin-4, were related to the exacerbation of asthma and chronic obstructive lung disease.[43-46]

A notable and frequent characteristic of asthmatic airway remodeling is the thickening of the ASM layer. Abnormal thickening of the ASM layer with increased deposition of fibronectin, collagen types I, III, and V, laminin, tenascin, and versican, annexin has been observed in patients with mild to severe and fatal asthma in several studies.[42,47,48]

Proteomic analysis offers a roadmap for identifying potential biomarkers associated with eosinophilic asthma.[42] Imaging biomarkers and artificial intelligence, in conjunction with cluster analyses, could enhance the effectiveness of models that determine responses to specific biologic therapies.[49]

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Table 2. Angiogenesis markers in asthma

Biomarker	Sample	Associated asthma endotype	References
VEGF	Sputum, tissue	T2-high	55,56
VEGF-A	Sputum, blood, BAL fluid	T2-high	57,58,59
TGF-β	Blood, tissue	T2-low	61,62
FGF-2	Sputum, BAL fluid	T2-high	61
MMPs	Sputum, blood, BAL fluid	T2-low	61,62
SDF-1	Tissue, blood, BAL fluid	T2-high	63
Angiopoietin-1	Sputum, blood	T2-high	64,65,66
Angiopoietin-2	Sputum, blood	T2-high	64,65,66
SOX18	Blood	T2-high	67
Angiomotin	Blood, tissue	T2-high/T2-low	68,69
Angiostatin	Blood, tissue	T2-high/T2-low	68,69

VEGF, vascular endothelial growth factor; TGF, transforming growth factor; FGF, fibroblast growth factor; MMP, matrix metalloproteinase; SDF, stromal cell-derived factor.

ANGIOGENESIS IN ASTHMA

Although numerous asthma biomarkers have been identified (**Table 2**), research on angiogenesis remains limited. One feature central to the pathophysiology of this respiratory condition is the increased microvascular network within the asthmatic airway wall. Studies suggest that increased blood flow to the airway tissue promotes a chronic influx of inflammatory mediators, abnormal cell growth and proliferation, and thickening of the airway wall, all of which contribute to the pathophysiology of asthma.[50,51] The abnormal expansion of the vascular network has been reported in a series of publications which identified increased blood vessel numbers, vessel density (number of vessels/mm^2) and percentage vascular area in the sub-epithelial space, including the lamina propria and submucosa, of asthmatic airways.[52] Given that vascular remodeling is a critical component in the pathophysiology of asthma, this process needs to be addressed in the therapeutic management. Neovascularization and vascular leakage are commonly observed in asthma[53]; consequently, the blood vessels in the asthmatic lung exhibit characteristics similar to the dysfunctional, permeable vessels found in tumors.[54] Thus, the same anti-angiogenic strategies may provide new avenues for combating the angiogenic component of airway remodeling associated with asthma.

Vascular endothelial growth factor (VEGF) is a key pro-angiogenic factor that plays a critical role in vascular remodeling, inflammation, and increased blood vessel permeability.[55] VEGF levels were elevated in induced sputum and biopsy specimens from asthma patients, with VEGF mRNA-expressing cells in the airway mucosa correlating with vascular permeability and airway hyperresponsiveness.[55,56] Asthmatic serum, sputum, BALF and airway tissue showed increased levels of the pro-angiogenic factor VEGF-A compared to non-asthmatic controls.[57] VEGF-A stimulated vascular network expansion, vasodilation, and plasma leakage.[58] VEGF-A together with IL-8 could be used as diagnostic biomarkers of Asthma-COPD overlap syndrome.[59] Interestingly, asthma treatments with budesonide, montelukast, and diosmetin attenuated the expression of VEGF. These findings suggest that targeting VEGF could offer therapeutic benefits in asthma management.[60] BALF from asthmatic patients exhibits pro-angiogenic properties, including increased levels of pro-angiogenic mediators.[56] Many pro-inflammatory mediators increased in asthma, including transforming growth factor (TGF)-β, fibroblast growth factor-2 and matrix metalloproteinases (MMPs), also have pro-angiogenic properties.[61] They can stimulate quiescent vascular expansion or increase endothelial cell permeability, either by direct contact or indirectly through the stimulation of inflammatory and accessory cells.[62] The pilot study demonstrated that serum levels of MMP-1 and TGF-β1

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are significantly elevated in individuals with chronic asthma, suggesting their potential utility as adjunct biomarkers for differentiating between moderate and severe forms of the disease.[62] Increased vascularity of the bronchial mucosa in asthmatic subjects is closely related to the expression of stromal cell-derived factor (SDF)-1, a member of the chemokine family with both angiogenic and angiostatic properties.[63] SDF-1 is released at concentrations 15 times higher in the BALF of asthma patients compared to healthy subjects. This chemokine correlated with cell recruitment within asthmatic airways.[63] SDF-1 release from asthmatic airways may contribute to increased airway vascularity and decline in lung function.[63]

Previous studies have demonstrated the physiologic roles of angiopoietin-1 and angiopoietin-2 as regulatory factors in airway microvascular phenomena. The finding that levels of angiopoietin-1 and angiopoietin-2 in induced sputum were significantly higher in asthmatic patients than in healthy control subjects suggests dysregulated vascular function in the airways of individuals with asthma.[64,65] Regression analysis showed a significant positive association between angiopoietin-1, angiopoietin-2, and eosinophil counts in severe refractory asthma.[66] This dysregulation could potentially contribute to increased permeability of blood vessels in the airway, which may exacerbate inflammation and other asthma-related symptoms. SOX18, a transcription factor, participates in various physiological processes, including endothelial cell differentiation in the formation of new blood vessels. Plasma SOX18 increased more during exacerbation than in stable state, suggesting its association with asthma exacerbation related to angiogenesis and airway remodeling.[67] Moreover, we reported that angiomotin and angiostatin exhibit distinct functions in angiogenic signaling associated with the pathogenesis of asthma.[67,68] Angiomotin and angiostatin, when analyzed together, represents important parameters for distinguishing between stable and exacerbated states in asthma patients, demonstrating greater effectiveness than either biomarker alone.[68] These results suggest that they could serve as potential biomarkers and offer possibilities for the development of asthma therapeutics.[68,69]

Circulating vasoactive factors may provide insights into disease development and novel therapeutic strategies in asthma (**Figure**).[70,71] Interestingly, some studies suggest that anti-VEGF monoclonal antibodies shows potential for asthma treatment.[58,72] Despite these insights, there are no widely used pharmacological agents specifically targeting angiogenesis in asthma. This presents several challenges, including an incomplete understanding of underlying mechanisms, difficulty identifying effective targets, potential side effects of angiogenesis inhibition, and the inherent heterogeneity among asthma patients. However, targeting angiogenesis remains a promising therapeutic strategy for asthma, highlighting the need for further investigation in this field.

CONCLUSION

Angiogenesis, the formation of new blood vessels from existing ones, is a process not exclusive to asthma. To address the issue of specificity, researchers and clinicians should adopt a broader approach by combining angiogenic biomarkers with asthma-specific factors, such as eosinophil counts, immunoglobulin E levels, or Th2 cytokines (*e.g.*, IL-4, IL-13). Additionally, assessing local angiogenesis in the airways through bronchial biopsies or imaging could help develop more targeted treatments that focus on the fundamental mechanisms of angiogenesis in asthma, distinguishing it from the systemic inflammation observed in other diseases.

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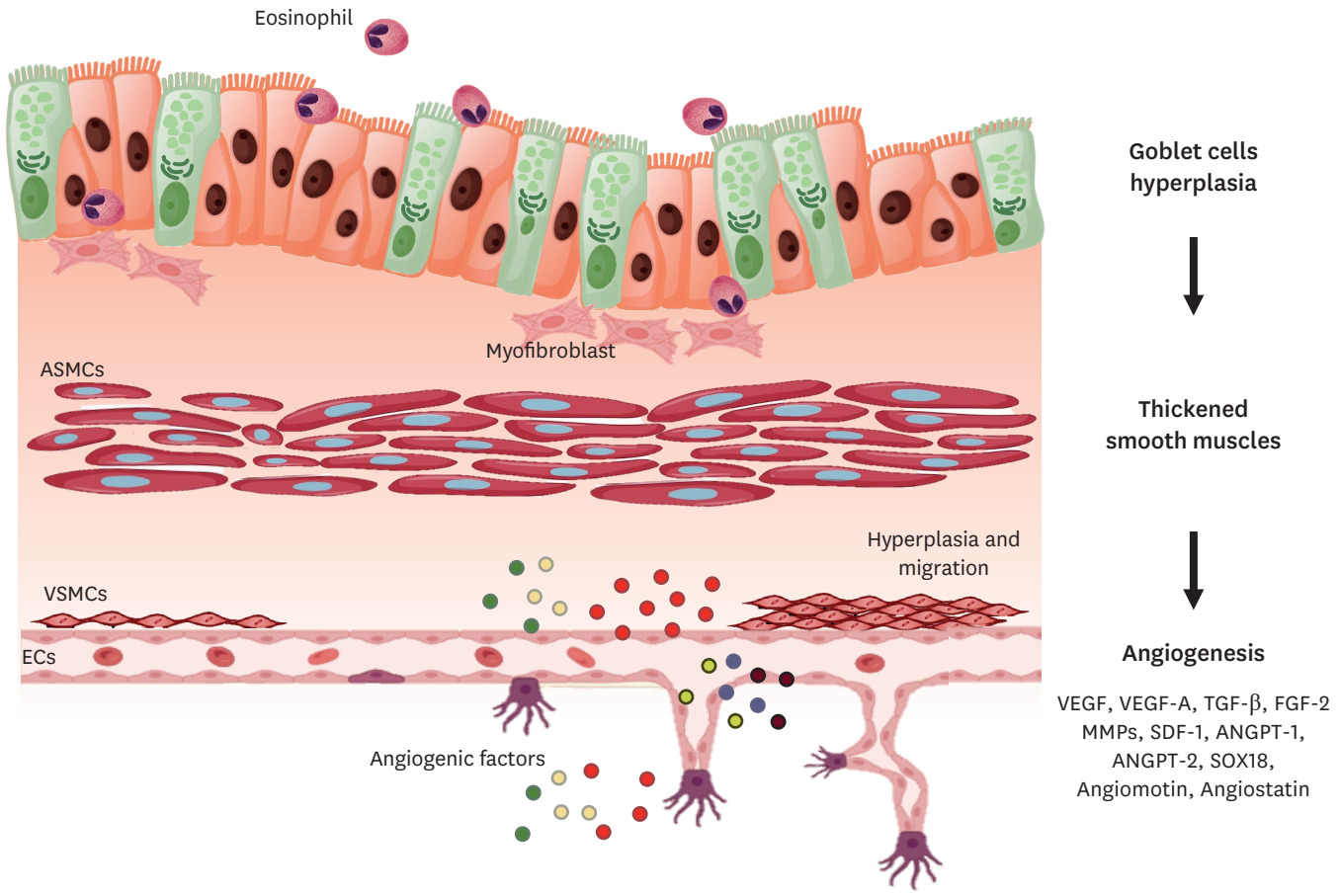

Figure. Angiogenesis and therapeutic targets for airway remodeling in asthma. Features of airway remodeling include epithelial cell mucus metaplasia, smooth muscle hypertrophy/hyperplasia, subepithelial fibrosis and angiogenesis. Studies on airway remodeling in asthma suggest an important role of angiogenic factor released from inflammatory or structural cells. Pro-angiogenic factors such as VEGF, VEGF-A, TGF-β, FGF-2, SDF-1, ANGPT-1, and Angiomotin are secreted and bind the receptors expressed on endothelial cells, promoting angiogenesis. In contrast, ANGPT-2 and angiostatin serve as anti-angiogenic factors, inhibiting excessive blood vessel growth. MMPs exhibit a dual role by mediating extracellular matrix remodeling, which is critical for both angiogenesis and the maintenance of vascular stability.
ASMC, airway smooth muscle cell; VSMC, vascular smooth muscle cell; VEGF, vascular endothelial growth factor; TGF, transforming growth factor; FGF, fibroblast growth factors; MMP, matrix metalloproteinases; SDF, stromal cell-derived factor; ANGPT, angiopoietin.

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REFERENCES

1. Global Initiative for Asthma. Global strategy for asthma management and prevention 2021 [Internet]. Fontana (WI): Global Initiative for Asthma; 2021 [cited 2022 Jan 1]. Available from: www.ginasthma.org.
2. Shimizu K, Tanabe N, Oguma A, Kimura H, Suzuki M, Yokota I, et al. Parenchymal destruction in asthma: fixed airflow obstruction and lung function trajectory. J Allergy Clin Immunol 2022;149:934-942.e8.
PUBMED | CROSSREF
3. Oguma T, Hirai T, Fukui M, Tanabe N, Marumo S, Nakamura H, et al. Longitudinal shape irregularity of airway lumen assessed by CT in patients with bronchial asthma and COPD. Thorax 2015;70:719-24.
PUBMED | CROSSREF

4. Postma DS, Brightling C, Baldi S, Van den Berge M, Fabbri LM, Gagnatelli A, et al. Exploring the relevance and extent of small airways dysfunction in asthma (ATLANTIS): baseline data from a prospective cohort study. Lancet Respir Med 2019;7:402-16. PUBMED | CROSSREF
5. Mauad T, Silva LF, Santos MA, Grinberg L, Bernardi FD, Martins MA, et al. Abnormal alveolar attachments with decreased elastic fiber content in distal lung in fatal asthma. Am J Respir Crit Care Med 2004;170:857-62. PUBMED | CROSSREF
6. 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. Clin Exp Allergy 2005;35:1437-42. PUBMED | CROSSREF
7. McDonald DM. Angiogenesis and remodeling of airway vasculature in chronic inflammation. Am J Respir Crit Care Med 2001;164 Suppl 2:S39-45. PUBMED | CROSSREF
8. Al-Muhsen S, Johnson JR, Hamid Q. Remodeling in asthma. J Allergy Clin Immunol 2011;128:451-62. PUBMED | CROSSREF
9. Kristan SS, Malovrh MM, Silar M, Kern I, Flezar M, Kosnik M, et al. Airway angiogenesis in patients with rhinitis and controlled asthma. Clin Exp Allergy 2009;39:354-60. PUBMED | CROSSREF
10. Hoshino M, Takahashi M, Aoike N. Expression of vascular endothelial growth factor, basic fibroblast growth factor, and angiogenin immunoreactivity in asthmatic airways and its relationship to angiogenesis. J Allergy Clin Immunol 2001;107:295-301. PUBMED | CROSSREF
11. James AL, Elliot JG, Jones RL, Carroll ML, Mauad T, Bai TR, et al. Airway smooth muscle hypertrophy and hyperplasia in asthma. Am J Respir Crit Care Med 2012;185:1058-64. PUBMED | CROSSREF
12. Jang YH, Choi JK, Jin M, Choi YA, Ryoo ZY, Lee HS, et al. House dust mite increases pro-Th2 cytokines IL-25 and IL-33 via the activation of TLR1/6 signaling. J Invest Dermatol 2017;137:2354-61. PUBMED | CROSSREF
13. Khapchaev AY, Shirinsky VP. Myosin light chain kinase MYLK1: anatomy, interactions, functions, and regulation. Biochemistry (Mosc) 2016;81:1676-97. PUBMED | CROSSREF
14. Inam A, Shahzad M, Shabbir A, Shahid H, Shahid K, Javeed A. Carica papaya ameliorates allergic asthma via down regulation of IL-4, IL-5, eotaxin, TNF-α, NF-κB, and iNOS levels. Phytomedicine 2017;32:1-7. PUBMED | CROSSREF
15. Davies DE. The role of the epithelium in airway remodeling in asthma. Proc Am Thorac Soc 2009;6:678-82. PUBMED | CROSSREF
16. Munakata M. Airway remodeling and airway smooth muscle in asthma. Allergol Int 2006;55:235-43. PUBMED | CROSSREF
17. Ding Z, Yu F, Sun Y, Jiao N, Shi L, Wan J, et al. ORMDL3 promotes angiogenesis in chronic asthma through the ERK1/2/VEGF/MMP-9 pathway. Front Pediatr 2022;9:708555. PUBMED | CROSSREF
18. Yang MS, Choi S, Choi Y, Jin KN. Association between airway parameters and abdominal fat measured via computed tomography in asthmatic patients. Allergy Asthma Immunol Res 2018;10:503-15. PUBMED | CROSSREF
19. de la Hoz RE, Liu X, Celedón JC, Doucette JT, Jeon Y, Reeves AP, et al. Association of obesity with quantitative chest CT measured airway wall thickness in WTC workers with lower airway disease. Lung 2019;197:517-22. PUBMED | CROSSREF
20. Kozlik P, Zuk J, Bartyzel S, Zarychta J, Okon K, Zareba L, et al. The relationship of airway structural changes to blood and bronchoalveolar lavage biomarkers, and lung function abnormalities in asthma. Clin Exp Allergy 2020;50:15-28. PUBMED | CROSSREF
21. Gono H, Fujimoto K, Kawakami S, Kubo K. Evaluation of airway wall thickness and air trapping by HRCT in asymptomatic asthma. Eur Respir J 2003;22:965-71. PUBMED | CROSSREF
22. Walsh CJ, Zaihra T, Benedetti A, Fugère C, Olivenstein R, Lemière C, et al. Exacerbation risk in severe asthma is stratified by inflammatory phenotype using longitudinal measures of sputum eosinophils. Clin Exp Allergy 2016;46:1291-302. PUBMED | CROSSREF
23. Price D, Wilson AM, Chisholm A, Rigazio A, Burden A, Thomas M, et al. Predicting frequent asthma exacerbations using blood eosinophil count and other patient data routinely available in clinical practice. J Asthma Allergy 2016;9:1-12. PUBMED
24. Zeiger RS, Schatz M, Dalal AA, Chen W, Sadikova E, Suruki RY, et al. Blood eosinophil count and outcomes in severe uncontrolled asthma: a prospective study. J Allergy Clin Immunol Pract 2017;5:144-153.e8. PUBMED | CROSSREF
25. Kim CK. Eosinophil-derived neurotoxin: a novel biomarker for diagnosis and monitoring of asthma. Korean J Pediatr 2013;56:8-12. PUBMED | CROSSREF
26. Sanz ML, Parra A, Prieto I, Diéguez I, Oehling AK. Serum eosinophil peroxidase (EPO) levels in asthmatic patients. Allergy 1997;52:417-22. PUBMED | CROSSREF

27. Couillard S, Laugerud A, Jabeen M, Ramakrishnan S, Melhorn J, Hinks T, et al. Derivation of a prototype asthma attack risk scale centred on blood eosinophils and exhaled nitric oxide. Thorax 2022;77:199-202. PUBMED | CROSSREF

28. Karrasch S, Linde K, Rücker G, Sommer H, Karsch-Völk M, Kleijnen J, et al. Accuracy of FENO for diagnosing asthma: a systematic review. Thorax 2017;72:109-16. PUBMED | CROSSREF

29. Baraldi E, Carraro S, Alinovi R, Pesci A, Ghiro L, Bodini A, et al. Cysteinyl leukotrienes and 8-isoprostane in exhaled breath condensate of children with asthma exacerbations. Thorax 2003;58:505-9. PUBMED | CROSSREF

30. Meyer N, Dallinga JW, Nuss SJ, Moonen EJ, van Berkel JJ, Akdis C, et al. Defining adult asthma endotypes by clinical features and patterns of volatile organic compounds in exhaled air. Respir Res 2014;15:136. PUBMED | CROSSREF

31. Loureiro CC, Duarte IF, Gomes J, Carrola J, Barros AS, Gil AM, et al. Urinary metabolomic changes as a predictive biomarker of asthma exacerbation. J Allergy Clin Immunol 2014;133:261-3.e1. PUBMED | CROSSREF

32. Tiotiu A. Biomarkers in asthma: state of the art. Asthma Res Pract 2018;4:10. PUBMED | CROSSREF

33. Boudewijn IM, Roffel MP, Vermeulen CJ, Nawijn MC, Kok K, Terpstra MM, et al. A novel role for bronchial micrornas and long noncoding RNAs in asthma remission. Am J Respir Crit Care Med 2020;202:614-8. PUBMED | CROSSREF

34. Lacedonia D, Palladino GP, Foschino-Barbaro MP, Scioscia G, Carpagnano GE. Expression profiling of miRNA-145 and miRNA-338 in serum and sputum of patients with COPD, asthma, and asthma-COPD overlap syndrome phenotype. Int J Chron Obstruct Pulmon Dis 2017;12:1811-7. PUBMED | CROSSREF

35. Rial MJ, Cañas JA, Rodrigo-Muñoz JM, Valverde-Monge M, Sastre B, Sastre J, et al. Changes in serum microRNAs after anti-IL-5 biological treatment of severe asthma. Int J Mol Sci 2021;22:3558. PUBMED | CROSSREF

36. Sonnenberg-Riethmacher E, Miehe M, Riethmacher D. Periostin in allergy and inflammation. Front Immunol 2021;12:722170. PUBMED | CROSSREF

37. Humbert M, Taillé C, Mala L, Le Gros V, Just J, Molimard M, et al. Omalizumab effectiveness in patients with severe allergic asthma according to blood eosinophil count: the STELLAIR study. Eur Respir J 2018;51:1702523. PUBMED | CROSSREF

38. Legrand F, Cao Y, Wechsler JB, Zhu X, Zimmermann N, Rampertaap S, et al. Sialic acid-binding immunoglobulin-like lectin (Siglec) 8 in patients with eosinophilic disorders: receptor expression and targeting using chimeric antibodies. J Allergy Clin Immunol 2019;143:2227-2237.e10. PUBMED | CROSSREF

39. Hussain M, Liu G. Eosinophilic Asthma: Pathophysiology and Therapeutic Horizons. Cells 2024;13:384. PUBMED | CROSSREF

40. Jevnikar Z, Östling J, Ax E, Calvén J, Thörn K, Israelsson E, et al. Epithelial IL-6 trans-signaling defines a new asthma phenotype with increased airway inflammation. J Allergy Clin Immunol 2019;143:577-90. PUBMED | CROSSREF

41. Guillet C, Steinmann S, Lang C, Maul JT, Schmid-Grendelmeier P. Eosinophil-mast cell interaction: Mepolizumab leads to a reduction of clinical symptoms and serum tryptase in a patient with eosinophilic asthma and idiopathic mast cell activation. J Allergy Clin Immunol Pract 2021;9:1393-1395.e1. PUBMED | CROSSREF

42. Joseph C, Tatler AL. Pathobiology of airway remodeling in asthma: the emerging role of integrins. J Asthma Allergy 2022;15:595-610. PUBMED | CROSSREF

43. Lee PH, Choi SM, An MH, Hwang DY, Park S, Baek AR, et al. Nectin4 is a potential therapeutic target for asthma. Front Immunol 2022;13:1049900. PUBMED | CROSSREF

44. Kim BG, Lee PH, Lee SH, Park CS, Jang AS. Impact of ozone on claudins and tight junctions in the lungs. Environ Toxicol 2018;33:798-806. PUBMED | CROSSREF

45. Lee YG, Lee SH, Hong J, Lee PH, Jang AS. Titanium dioxide particles modulate epithelial barrier protein, Claudin 7 in asthma. Mol Immunol 2021;132:209-16. PUBMED | CROSSREF

46. An MH, Lee PH, Choi SM, Hwang D, Kim JH, Park MC, et al. Impact of the junction adhesion molecule-A on asthma. Yonsei Med J 2023;64:375-83. PUBMED | CROSSREF

47. Hsieh A, Assadinia N, Hackett TL. Airway remodeling heterogeneity in asthma and its relationship to disease outcomes. Front Physiol 2023;14:1113100. PUBMED | CROSSREF

48. Lee SH, Lee PH, Kim BG, Seo HJ, Baek AR, Park JS, et al. Annexin A1 in plasma from patients with bronchial asthma: its association with lung function. BMC Pulm Med 2018;18:1. PUBMED | CROSSREF

49. Zhan J, Chen W, Cheng L, Wang Q, Han F, Cui Y. Diagnosis of asthma based on routine blood biomarkers using machine learning. Comput Intell Neurosci 2020;2020:8841002. PUBMED | CROSSREF

50. Bergeron C, Tulic MK, Hamid Q. Airway remodelling in asthma: from benchside to clinical practice. Can Respir J 2010;17:e85-93. PUBMED | CROSSREF

51. Zanini A, Chetta A, Imperatori AS, Spanevello A, Olivieri D. The role of the bronchial microvasculature in the airway remodelling in asthma and COPD. Respir Res 2010;11:132. PUBMED | CROSSREF

52. Grigoraş A, Căruntu ID, Grigoraş CC, Mihăescu T, Amălinei C. Relationship between immunohistochemical assessment of bronchial mucosa microvascularization and clinical stage in asthma. Rom J Morphol Embryol 2012;53:485-90. PUBMED

53. Olivieri D, Chetta A. Therapeutic perspectives in vascular remodeling in asthma and chronic obstructive pulmonary disease. Chem Immunol Allergy 2014;99:216-25. PUBMED | CROSSREF

54. Carmeliet P. Angiogenesis in life, disease and medicine. Nature 2005;438:932-6. PUBMED | CROSSREF

55. Debeljak J, Korošec P, Lopert A, Fležar M, Košnik M, Rijavec M. Asthma treatment response to inhaled corticosteroids is associated with variants in VEGFA gene. Gene 2021;783:145573. PUBMED | CROSSREF

56. Simcock DE, Kanabar V, Clarke GW, Mahn K, Karner C, O'Connor BJ, et al. Induction of angiogenesis by airway smooth muscle from patients with asthma. Am J Respir Crit Care Med 2008;178:460-8. PUBMED | CROSSREF

57. Meyer N, Akdis CA. Vascular endothelial growth factor as a key inducer of angiogenesis in the asthmatic airways. Curr Allergy Asthma Rep 2013;13:1-9. PUBMED | CROSSREF

58. Yuksel H, Yilmaz O, Karaman M, Bagriyanik HA, Firinci F, Kiray M, et al. Role of vascular endothelial growth factor antagonism on airway remodeling in asthma. Ann Allergy Asthma Immunol 2013;110:150-5. PUBMED | CROSSREF

59. Ding Q, Sun S, Zhang Y, Tang P, Lv C, Ma H, et al. Serum IL-8 and VEGFA are two promising diagnostic biomarkers of asthma-COPD overlap syndrome. Int J Chron Obstruct Pulmon Dis 2020;15:357-65. PUBMED | CROSSREF

60. Tota M, Łacwik J, Laska J, Sędek Ł, Gomułka K. The role of eosinophil-derived neurotoxin and vascular endothelial growth factor in the pathogenesis of eosinophilic asthma. Cells 2023;12:1326. PUBMED | CROSSREF

61. Carmeliet P. Mechanisms of angiogenesis and arteriogenesis. Nat Med 2000;6:389-95. PUBMED | CROSSREF

62. Prabha A, Lokesh KS, Chaya SK, Jayaraj BS, Malamardi S, Subbarao MVSS, et al. Pilot study investigating diagnostic utility of serum MMP-1 and TGF-β1 in asthma in 'real world' clinical practice in India. J Clin Pathol 2022;75:222-5. PUBMED | CROSSREF

63. Negrete-García MC, Velazquez JR, Popoca-Coyotl A, Montes-Vizuet AR, Juárez-Carvajal E, Teran LM. Chemokine (C-X-C motif) ligand 12/stromal cell-derived factor-1 is associated with leukocyte recruitment in asthma. Chest 2010;138:100-6. PUBMED | CROSSREF

64. Kanazawa H, Tochino Y, Asai K. Angiopoietin-2 as a contributing factor of exercise-induced bronchoconstriction in asthmatic patients receiving inhaled corticosteroid therapy. J Allergy Clin Immunol 2008;121:390-5. PUBMED | CROSSREF

65. Lee PH, Kim BG, Seo HJ, Park JS, Lee JH, Park SW, et al. Circulating angiopoietin-1 and -2 in patients with stable and exacerbated asthma. Ann Allergy Asthma Immunol 2016;116:339-43. PUBMED | CROSSREF

66. Tseliou E, Bakakos P, Kostikas K, Hillas G, Mantzouranis K, Emmanouil P, et al. Increased levels of angiopoietins 1 and 2 in sputum supernatant in severe refractory asthma. Allergy 2012;67:396-402. PUBMED | CROSSREF

67. Hong J, Lee PH, Lee YG, Leikauf GD, Jang AS. Augmented angiogenic transcription factor, SOX18, is associated with asthma exacerbation. J Asthma 2021;58:1143-54. PUBMED | CROSSREF

68. Lee PH, An M, Hwang D, Jang AS. Impact of circulating angiomotin and angiostatin on clinical variables in patients with asthma. Ann Allergy Asthma Immunol 2024;133:101-3. PUBMED | CROSSREF

69. Lee PH, Choi S, An M, Hwang D, Park S, Baek AR, et al. Angiomotin and angiostatin as asthma biomarkers: implications for the regulation of airway remodeling and inflammation. Allergy 2023;78:1674-7. PUBMED | CROSSREF

70. Koczy-Baron E, Grzanka A, Jochem J, Gawlik R, Kasperska-Zajac A. Evaluation of circulating vascular endothelial growth factor and its soluble receptors in patients suffering from persistent allergic rhinitis. Allergy Asthma Clin Immunol 2016;12:17. PUBMED | CROSSREF

71. Bikov A, Bohacs A, Eszes N, Weiszhar Z, Ivancso I, Muller V, et al. Circulating and exhaled vascular endothelial growth factor in asthmatic pregnancy. Biomarkers 2012;17:648-54. PUBMED | CROSSREF

72. Türkeli A, Yilmaz Ö, Karaman M, Kanik ET, Firinci F, XMLLink_XYZnan S, et al. Anti-VEGF treatment suppresses remodeling factors and restores epithelial barrier function through the E-cadherin/β-catenin signaling axis in experimental asthma models. Exp Ther Med 2021;22:689. PUBMED | CROSSREF