Genes & Diseases (2023) 10, 1537–1551

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REVIEW ARTICLE

The multifaceted role of placental growth factor in the pathogenesis and progression of bronchial asthma and pulmonary fibrosis: Therapeutic implications

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Received 13 August 2022; accepted 19 October 2022
Available online 14 November 2022

KEYWORDS
AHR;
Airway remodeling;
Bronchial asthma;
Chronic airway inflammation;
PlGF

Abstract Placental growth factor (PlGF) is a glycosylated dimeric protein that is homologous to vascular endothelial growth factor (VEGF). PlGF expression is upregulated in patients with bronchial asthma, suggesting that it plays a role in the pathogenesis of asthma. Bronchial asthma is characterized by chronic airway inflammation and airway hyperresponsiveness (AHR). After recurrent asthma attacks, pulmonary fibrosis develops and leads to airway remodeling and a further decline in lung function. In this review, we focused on the pivotal role of PlGF in chronic airway inflammation, AHR, and airway remodeling during bronchial asthma. Furthermore, we summarized data showing that PlGF may be a potential therapeutic target in bronchial asthma.

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Peer review under responsibility of Chongqing Medical University.
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https://doi.org/10.1016/j.gendis.2022.10.017

Introduction

Bronchial asthma (hereinafter termed asthma) is a chronic inflammatory disease of the airways, involving a variety of inflammatory cells (such as eosinophils, mast cells, lymphocytes, and macrophages) and inflammatory factors. The main characteristics of asthma include chronic airway inflammation, airway hyperresponsiveness (AHR), and airway remodeling. The mechanisms of airway inflammation and remodeling are diverse and complex. After stimulation by allergens, inflammatory cells are recruited and infiltrate the bronchial epithelium, where they act together with epithelial cells, fibroblasts, smooth muscle cells, and other structural tissue cells,[1] releasing a series of mediators, cytokines, and chemokines.[2] This results in an acute inflammatory response that is characterized by vascular leakage, excessive mucus secretion, and epithelial shedding. If the inflammatory infiltration persists, the airway wall structure changes, including collagen deposition under basement membranes, mucus gland hyperplasia, bronchial smooth muscle hypertrophy, and changes in bronchial microcirculation, leading to airway wall thickening and airway lumen stenosis.[3–5] The final outcomes are irreversible airway obstruction and progressive decline in pulmonary function.[6] Importantly, bronchial mucosal inflammation is the basis of AHR.[7] Furthermore, asthma was responsible for over 21 million disability-adjusted life years in 2019,[8] and approximately half of the children and adolescents with asthma had severe symptoms, representing a significant personal and socioeconomic burden.[9]

Our previous studies found that in asthma patients, especially asthmatic smokers, placental growth factor (PlGF) levels in the induced sputum and serum are significantly higher than in healthy controls. Furthermore, PlGF levels are negatively correlated with lung function.[10] These data are consistent with the research of Bobic et al[11] and suggest that PlGF may become a new asthma biomarker. PlGF was first discovered in the human placenta by Persico in 1991.[12] While PlGF is mainly expressed in the placenta, transcripts are also detected in the lung, heart, thyroid, and skeletal muscle.[13] PlGF is a glycoprotein homodimer encoded by a single gene that produces four isomers (PlGF1–4) in humans due to selective splicing.[14–16] PlGF-1 and PlGF-2 are the most important isoforms in humans,[12,17,18] but only one form of PlGF is expressed in mice, which is equivalent to human PlGF-2.[19]

Structurally, PlGF shares significant sequence homology at the amino acid level with vascular endothelial growth factor (VEGF)-A, the most active member of the VEGF family.[20,21] VEGF-A binds and activates two tyrosine kinase receptors, VEGFR-1 (also known as Flt-1 in humans and mice) and VEGFR-2 (also known as KDR in humans and Flk-1 in mice).[22,23] Unlike VEGF-A, PlGF specifically binds only to VEGFR-1,[24] however, PlGF may also activate VEGFR-2 through indirect manners. PlGF may compete with VEGF-A to bind VEGFR-1 and, therefore, promote the binding of VEGF-A to VEGFR-2.[25] Another possibility is that PlGF and VEGF-A may heterodimerize and then bind and activate VEGFR-2 or induce VEGFR-1/VEGFR-2 dimer on the cell surface.[17,26,27] Additionally, with additional heparin-binding domains, PlGF-2 promotes endothelial cell migration by binding the two coreceptors neuropilin-1 and -2 that were discovered as coreceptors of class 3 semaphorins.[28]

VEGFR-1 expresses two types of mRNA, one for a full-length receptor (Flt-1) and another for a soluble short protein known as soluble VEGFR-1 (sFlt-1).[29] VEGFR-1 is expressed not only in vascular endothelial cells but also in monocytes and macrophages.[30–32] VEGFR-1 negatively regulates physiological vasculogenesis by suppressing pro-angiogenic signals to establish a critical balance essential for physiological vascular formation during embryogenesis.[33] Nevertheless, in adulthood, VEGFR-1 expression is upregulated in activated macrophages in inflammatory diseases,[30,34] and in turn, VEGFR-1 promotes the activation and migration of macrophages, stimulates angiogenesis, and increases vascular permeability through its kinase activity.[35] VEGFR-2 is mainly expressed in endothelial cells, promoting the growth, migration, and tubular formation of endothelial cells, and enhancing vascular permeability.[36]

PlGF is secreted by bronchoalveolar epithelial cells, intrapulmonary macrophages, and fibroblasts.[37,38] Activating VEGFR-1 and VEGFR-2, by direct or indirect binding, respectively, PlGF influences the inflammatory response, angiogenesis, vascular leakage, and other pathological changes related to the pathogenesis of asthma. Therefore, PlGF may play an important role in the pathogenesis of asthma. We have summarized the different effects of PlGF on asthma-related cells in Table 1.

PlGF expression in asthma

During lung development in mice and humans,[39,40] PlGF derived from pulmonary macrophages and epithelial cells is highly expressed before alveolization. PlGF is then rapidly downregulated when alveolization is accomplished, thus maintaining a stable low level in adulthood.[19,41] Our previous studies showed that PlGF levels in the serum and induced sputum of asthmatic smokers are significantly higher than in healthy controls.[10] PlGF is also markedly elevated in the induced sputum and bronchial biopsies of patients with house dust mite (HDM)-allergic asthma or rhinitis.[11] As the PlGF receptor, VEGFR-1 expression is also upregulated in $CD34^+$ cells, macrophages, and T cells in asthma patients.[42] Additionally, expression of PlGF and downstream transcription factors (endothelin-1 and early growth response factor-1 (Egr-1)) regulated by PlGF significantly increases in the nasal airway epithelial cells of asthma patients.[43–46] In asthma models, PlGF expression is significantly increased in airway epithelial cells and bronchoalveolar lavage fluid (BALF).[11] Moreover, activation of the Th2 cytokine/STAT6 pathway is able to induce PlGF expression in respiratory epithelial cells, alveolar macrophages, and eosinophils.[43]

Allergen exposure induces PlGF expression in airway epithelial cells, alveolar macrophages, and eosinophils.[43] Inflammatory mediators such as interleukin (IL)-1β, tumor necrosis factor (TNF)-α, transforming growth factor (TGF)-β, and epidermal growth factor (EGF) stimulate bronchial epithelial cells to secrete PlGF.[47] EGF and TGF-α/β can also induce the production of PlGF in keratinocytes (Fig. 1).[48] PlGF mRNA expression is significantly increased in hypoxic lung tissues,[49] thus hypoxia is also an important stimulator of PlGF expression. Hypoxia-inducible factor (HIF)-1α can directly

Table 1 Specific effects of PlGF on cells in bronchial asthma.

Cells in bronchial asthma	Effect on cells	Reference
Eosinophil	Promote eosinophil recruitment to the airway	43
Neutrophil	Promote neutrophil migration to airway, lung tissue, or inflammatory sites	69–73
Monocyte	Induce monocyte activation	45,60,61
	Promote monocytes to secrete cytokines (TNF-α, IL-6 and IL-1β) and chemokines (MCP-1, MIP-1 and TNF-α)	59–63
Macrophage	Induce macrophages to migrate to inflammatory sites	30,59,65–67
	Induce macrophage migration to blood vessels	81,161,177–179
	Stimulate the activation of macrophages	30,64
	Prolong the survival time of macrophages	75
	Induce M2 polarization of macrophages	52,80,81
	Induce macrophages to secrete TGF-β, the key cytokines that stimulate extracellular matrix synthesis	80,83
Alveolar epithelial cell	Induce autophagy and apoptosis of lung epithelial cells	34,41,47,54,122,126
	Inhibit the proliferation of lung epithelial cells	41
	Induce EMT-like changes in AECs, manifested by the decrease of E-cadherin and the increase of vimentin and fibronectin	144
Fibroblast	Stimulate the proliferation of human lung fibroblasts and the expression of collagen I	142
Vascular endothelial cell	Upregulate the expression of VEGFR-1 and VEGFR-2 in endothelial cells	91
	Increase the proliferation of pulmonary vascular endothelial cells	10,25,26,165
	Inhibit apoptosis of pulmonary vascular endothelial cells that improved their survival rate	164
	Increase the migration of human pulmonary microvascular endothelial cells	10
	Promote the mobilization, chemotaxis, and recruitment of bone marrow-derived endothelial progenitor cells to ischemic tissues	167
Smooth muscle cell	Recruit smooth muscle cells to the vascular endothelium to mediate the maturation and stability of new blood vessels	164

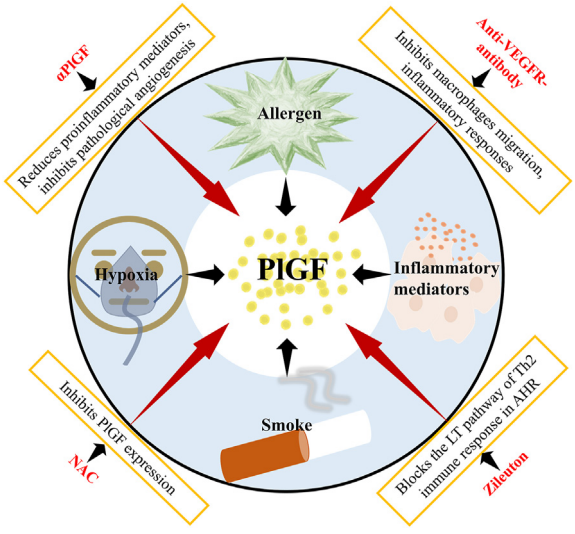

Figure 1 Factors that upregulate PlGF expression or inhibit PlGF action. Allergens, inflammatory mediators, hypoxia, and smoking induce PlGF expression in airway epithelial cells, alveolar macrophages, eosinophils, and/or keratinocytes. The antioxidant NAC may inhibit PlGF expression via the ROS/ERK-1/2 (MAPK)/Egr-1 pathway. Anti-PlGF antibodies (αPlGF), anti-VEGFR-1 antibodies, and the 5-LO inhibitor zileuton may block PlGF function in asthma. The black arrow represents promotion and the red arrow represents inhibition.

activate PlGF transcription in endothelial cells and hepatic stellate cells.[50–53] Hypoxia also induces PlGF production by fibroblasts (Fig. 1).[38] In addition, smoking may potentially stimulate PlGF expression because cigarette smoke extract (CSE) induces PlGF production and secretion in human bronchial epithelial cells.[54,55] These data suggest that the PlGF signaling pathway is activated in asthma (Fig. 1).

PlGF and chronic airway inflammation

Chronic airway inflammation, one of the characteristics of asthma, is caused by the recruitment and infiltration of inflammatory cells such as T cells, eosinophils, and macrophages into lung tissue.[56] A predominant Th2 immune response leading to Th1/Th2 imbalance is one of the pathogenic mechanisms of airway inflammation in asthma. The Th2 inflammatory environment includes cytokines (IL-6, IL-13, and IL-1β) and other inflammatory factors such as monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1 (MIP-1), and TNF-α.[57] The recruitment and activation of macrophages are also related to airway inflammation in asthma.[57,58] PlGF promotes the secretion of inflammatory factors, stimulates recruitment and activation of macrophages, and induces alternative activation (also known as M2 polarization) of macrophages. All these mechanisms are involved in airway inflammation in asthma (Fig. 2).

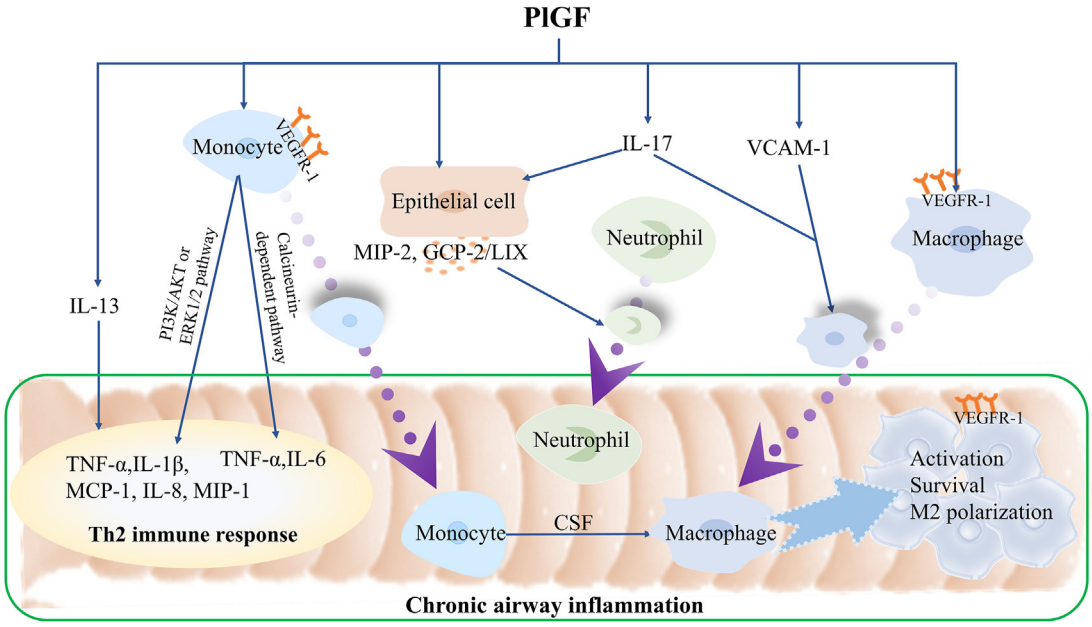

Figure 2 PlGF and chronic airway inflammation. PlGF stimulates inflammatory and epithelial cells and participates in the crosstalk between inflammatory cells and inflammatory factors, as well as the formation of a Th2 inflammatory environment. PlGF also promotes the secretion of inflammatory factors, increases chemotaxis of monocyte-macrophages, and induces alternative activation of macrophages, all of which may play a role in the Th2 inflammatory environment. CSF, colony-stimulating factor; IL, interleukin; MIP-1, macrophage inflammatory protein-1; MIP-2 (CXCL-2), macrophage inflammatory protein-2 (C-X-C motif chemokine ligand 2); TNF, tumor necrosis factor; VCAM-1, vascular cell adhesion molecule-1. The purple arrow represents migration.

PlGF stimulates the secretion of inflammatory factors

After binding with VEGFR-1 in monocytes, PlGF induces monocyte activation (Fig. 2).[45,59,60] PlGF then stimulates monocytes to secrete cytokines (TNF-α, IL-8, and IL-1β) and chemokines (CCL2 and MIP-1) via the phosphoinositol 3-kinase (PI3K)/protein kinase B (AKT) and extracellular signal-regulated kinase 1/2 (ERK-1/2) pathways,[59–62] or trigger TNF-α and IL-6 production through a calcineurin-dependent pathway.[63] PlGF also promotes a Th2 immune response through IL-13 in lung tissue after HDM exposure.[43] Targeted anti-PlGF antibody (αPlGF) therapy can reduce lung inflammation and cause a significant decrease in pro-inflammatory markers (MCP-1 and CD68).[37] PlGF knockdown (*Plgf* $^{-/-}$) by small interfering RNA in mice significantly inhibits pro-inflammatory cytokine (TNF-α and IL-1β) and chemokine (MCP-1) expression in the fibrotic liver.[64] Moreover, in a murine model of allergic asthma, *Plgf* $^{-/-}$ mice had fewer neutrophils and lower expression of macrophage inflammatory protein-2 (MIP-2), granulocyte chemotactic protein-2/LPS induced CXC chemokine (GCP-2/LIX, the IL-8 analogue in mice) and IL-17 in BALF compared with *Plgf* $^{+/+}$ mice.[11] *Plgf* $^{-/-}$ mice also had decreased eosinophil aggregation and mucus secretion in airway walls.[43]

PlGF recruits macrophages

Macrophages are one of the leading players in asthma, participating in a series of pathogenic mechanisms, including lung inflammation and injury, pulmonary fibrosis, and airway remodeling.[55] PlGF increases chemotaxis of monocytes and macrophages in a dose-dependent manner[34,45,64] and PlGF knockdown inhibits macrophage recruitment.[53] PlGF may recruit macrophages via binding to VEGFR-1 expressed in monocytes and promoting the secretion of monocyte chemokines. PlGF may also stimulate macrophage activation and prolong macrophage survival, thus increasing macrophage infiltration in inflammatory sites.

The combination of PlGF and VEGFR-1 expressed in monocytes can directly induce monocytes and macrophages to migrate to inflammatory sites (Fig. 2).[30,59,65–67] Anti-VEGFR-1 antibody treatment greatly inhibits macrophage migration and the inflammatory response by interrupting the PlGF/VEGFR-1 signaling axis.[64] Furthermore, PlGF-induced monocyte migration is eliminated in monocytes isolated from VEGFR-1 knockdown (*Vegfr-1* $^{-/-}$) mice.[68] Consequently, the PlGF/VEGFR-1 signaling pathway may be a master regulator of monocyte and macrophage migration.

PlGF promotes the secretion of monocyte chemokines to recruit macrophages. For example, PlGF may recruit pulmonary monocytes and macrophages by promoting IL-17 secretion. IL-17, a monocyte chemokine, acts on epithelial cells to promote the secretion of MIP-2 and GCP-2/LIX, both of which participate in the recruitment of neutrophils to inflammatory sites.[69–72] Moreover, in *Plgf* $^{-/-}$ mice, the concentrations of neutrophils and neutrophil chemotactic agents (IL-17 and GCP-2/LIX) are reduced in lung tissue and PlGF treatment rescues IL-17 expression in the lung.[11] PlGF can also recruit macrophages via enhancing the expression of vascular cell

adhesion molecule-1, a key molecule in monocyte and macrophage adhesion and rolling and endothelial cell activation on the side of the arterial lumen.[59,73] The recruited monocytes differentiate into macrophages under the influence of colony-stimulating factors and then the activated macrophages can recruit more inflammatory cells to stimulate angiogenesis.[74]

In addition, PlGF treatment stimulates macrophage activation, while PlGF deficiency inhibits macrophage activation (Fig. 2).[30,64] PlGF can also prolong the survival time of macrophages,[75] thereby increasing their infiltration in inflammatory sites.

PlGF-mediated mechanisms of M2 polarization

Allergens can induce M2 polarization of macrophages in asthma patients.[76–79] Furthermore, M2 macrophages may promote lung injury and airway remodeling in asthma by releasing inflammatory cytokines.[57,58]

In bone marrow-derived macrophages, PlGF treatment markedly increases the expression of F4/80+ and $CD163^{+}$, which are classical surface markers of M2 macrophages.[80] PlGF also promotes the transformation of tumor-associated macrophages (TAMs) from a tumor-inhibiting M1-like phenotype to a pro-angiogenic M2-like phenotype that promotes tumor progression.[81] In contrast, *Plgf* $^{-/-}$ macrophages tend to transition to an M1-like phenotype.[52] M2 macrophages induced by PlGF not only promote cell proliferation, regeneration, and tissue remodeling,[82] but also secrete TGF-β to stimulate endothelial cell growth, thus promoting the growth and neovascularization of non-small cell lung cancer.[83] In conclusion, PlGF induces M2 polarization of macrophages and stimulates the secretion of asthma-related inflammatory molecules. Notably, there is still a lack of research on the direct relationship between M2 polarization and asthma. The specific mechanism by which PlGF promotes M2 polarization requires further study.

PlGF and AHR

AHR is an important feature of asthma and leads to the recurrence of symptoms such as wheezing, dyspnea, chest tightness, and cough.[84,85] Small airway inflammation and obstruction are associated with persistent AHR.[85–88] During AHR, the body encounters an allergen and inflammatory cells are recruited into the bronchial wall where they secrete inflammatory factors and cause a chronic inflammatory reaction in the bronchial mucosa. This is manifested by increased vascular permeability and inflammatory edema of the airway wall, which further narrows the airway and aggravates asthma.[85] PlGF not only promotes the secretion of Th2 cytokines,[43] but also increases vascular permeability.[89–91] In contrast, PlGF deficiency inhibits AHR by reducing inflammatory cell recruitment and expression of Th2 cytokines such as IL-13 in allergen-exposed mice.[43] Therefore, PlGF may contribute to AHR by enhancing the Th2 immune response and aggravating airway edema.

PlGF acts on inflammatory pathways

After allergen exposure, the Th2 immune response promotes secretion of Th2 cytokines (IL-4 and IL-13),[92] stimulates contraction of airway smooth muscle, recruits inflammatory cells, and increases mucus secretion, thus driving AHR and lung inflammation.[43,57] In the pathogenesis of AHR, PlGF can participate in the Th2 immune response directly via the Th2 pathway or by acting as a link between the Th2 and leukotriene (LT) pathways (Fig. 3).[43]

The Th2 pathway consists of IL-4 and IL-13/STAT6. Allergen exposure induces PlGF expression in respiratory epithelial cells, alveolar macrophages, and eosinophils by IL13-mediated STAT6 activation. IL-13 levels are significantly lower in *Plgf* $^{-/-}$ mice after HDM exposure than in control mice, suggesting that PlGF may increase the Th2 immune response via upregulating IL-13 expression.[43] In addition, PlGF also participates in IL-13-mediated IL-4/eotaxin (the eosinophil chemokine)-independent AHR,[93] thereby increasing airway smooth muscle reactivity.[93,94] Therefore, there may be a positive feedback loop between the Th2 immune response and PlGF. PlGF expression may be upregulated through activation of the Th2 cytokine/STAT6 pathway induced by allergens. In turn, PlGF may further modestly augment the Th2 immune response through enhancing the IL-4/IL-13 signal that induces AHR.

The LT pathway comprises Leukotriene D_4 (LTD_4) and cysteine leukotriene (CysLT)/cysteine leukotriene receptor 1 (CysLTR 1). LTD_4 combines with CysLTR 1 and then stimulates lung type 2 innate lymphocytes to secrete a large amount of IL-4.[95] CysLT, an effective contractile agonist of airway smooth muscle cells and vascular wall cells,[96,97] induces the production of eosinophils and recruitment of blood and airway eosinophils.[98–100] PlGF induces expression of HIF-1α and Egr-1 transcription factors, which mediate the upregulation of 5-lipoxygenase activating protein (FLAP) and arachidonic acid-5-lipoxygenase (ALOX5), respectively (Fig. 3). These are key molecules in the LT pathway in human pulmonary endothelial cells and monocytes.[44,60] PlGF also induces 5-lipoxygenase (5-LO, encoded by ALOX5) that generates LTs and directly promotes CysLT and CysLTR1 expression, thus increasing the number of eosinophils in the blood and lung and aggravating AHR in allergic asthma mice.[43] Similarly, IL-13 upregulates CysLT and CysLT receptor expression.[101–104] Furthermore, CysLT mediates an increased Th2 response and eosinophil infiltration in the lung.[105,106] In summary, the LT and Th2 pathways are mutually enhanced in asthmatic mice.[95,103,104,107] PlGF may be a new link connecting these two pathways.

PlGF promotes vascular permeability and airway edema

In asthma, small airway obstruction may be associated with AHR.[87,88] Airway edema further aggravates small airway obstruction, thus participating in AHR. PlGF and its receptor VEGFR-1, play an important role in vascular leakage, therefore it is considered a key mediator promoting the

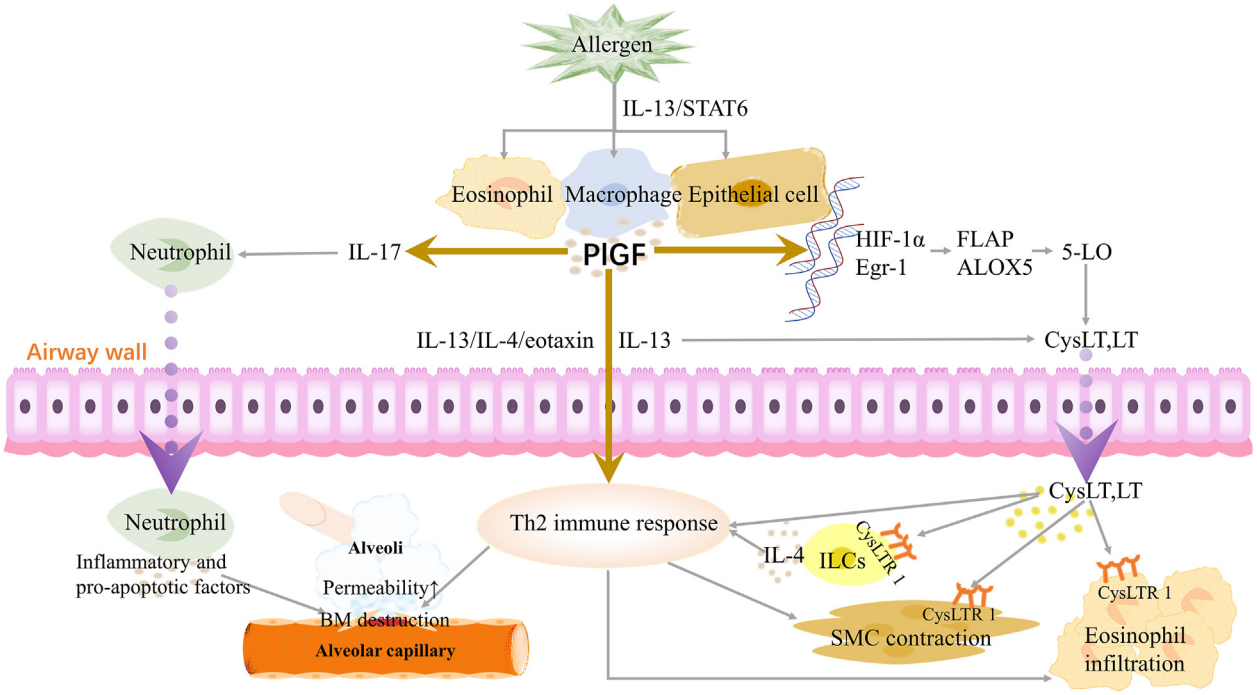

Figure 3 PlGF and AHR. PlGF enhances the Th2 immune response and aggravates airway edema, thus contributing to AHR. Allergen exposure induces PlGF expression in airway epithelial cells, alveolar macrophages, and eosinophils. PlGF then participates in the Th2 immune response through the Th2 and LT pathways and promotes airway smooth muscle contraction and eosinophil recruitment. In addition, PlGF promotes IL-17 secretion, contributing to chronic neutrophil activation, which increases alveolar-capillary barrier permeability and exacerbates airway edema. ALOX5, arachidonic acid-5-lipoxygenase; CysLT, cysteine leukotriene; CysLTR 1, cysteine leukotriene receptor 1; Egr-1, early growth response factor-1; FLAP, 5-lipoxygenase activating protein; HIF-1α, hypoxia-inducible factor-1α; 5-LO, 5-lipoxygenase; LT, leukotriene; ILC2, lung type 2 innate lymphocytes. The purple arrow represents migration. The brown arrow represents the direct effect of PlGF.

development of bronchial epithelial edema (Fig. 3). In a murine model of asthma, the wet/dry ratio of lung tissue, a marker of tissue edema, is markedly reduced in ovalbumin-challenged *Plgf* $^{-/-}$ mice. In contrast, intranasal PlGF perfusion or PlGF overexpression in mice increases lung tissue edema and enhances vascular permeability.[11,91] In addition to lung tissue, PlGF directly affects skin vascular permeability and induces skin edema by stimulating vascular remodeling during acute skin inflammation.[56] Similarly, *Plgf* $^{-/-}$ mice have reduced tissue edema and vascular leakage in response to skin injury,[108] while exogenous PlGF injection into the epidermis induces vascular leakage.[89] Hence, PlGF has a marked effect in maintaining vascular permeability and inducing vascular leakage.[25,108]

PlGF may work alone or cooperate with VEGF-A to significantly increase vascular permeability.[25,89,90] The VEGFR-2 specific ligand VEGF-E significantly increases vascular permeability.[35] VEGF can also activate VEGFR-1 directly, but the effect of VEGF on VEGFR-1 is approximately 10 times weaker than on VEGFR-2.[109] These indicate that VEGFR-2 is a direct signal converter for vascular permeability. PlGF from tumor cells increases the permeability of tumor capillaries,[110] whereas PlGF deficiency or inhibition reduces plasma extravasation.[25] Therefore, to increase vascular permeability and promote pulmonary edema during the pathogenesis of asthma, PlGF binds specifically to VEGFR-1 directly or indirectly activates VEGFR-2 through the synergistic effect of VEGF-A as mentioned above.[17,24–27,111] Moreover, PlGF is associated with edema mediated by bronchial neutrophilic inflammation in allergic asthma and participates in the migration of neutrophils to inflammatory sites by promoting secretion of IL-17.[69,70] Prolonged activation of neutrophils releases inflammatory and pro-apoptotic factors, resulting in destruction of the basement membrane and increased permeability of the alveolar-capillary barrier (Fig. 3).[112–115] PlGF also contributes to the increased pulmonary vascular permeability in acute lung injury.[116]

PlGF and airway remodeling

Airway remodeling refers to structural changes in the airways of asthma patients. These changes include damage to epithelial integrity, bronchial epithelial fibrosis, angiogenesis, thickening of the airway smooth muscle layer, and hyperplasia of mucous glands, all of which lead to the thickening and hardening of airway walls.[117] PlGF may contribute to bronchial epithelial cell apoptosis and epithelial fibrosis, as well as angiogenesis, thus aggravating the pathological changes of airway remodeling in asthma (Fig. 4).

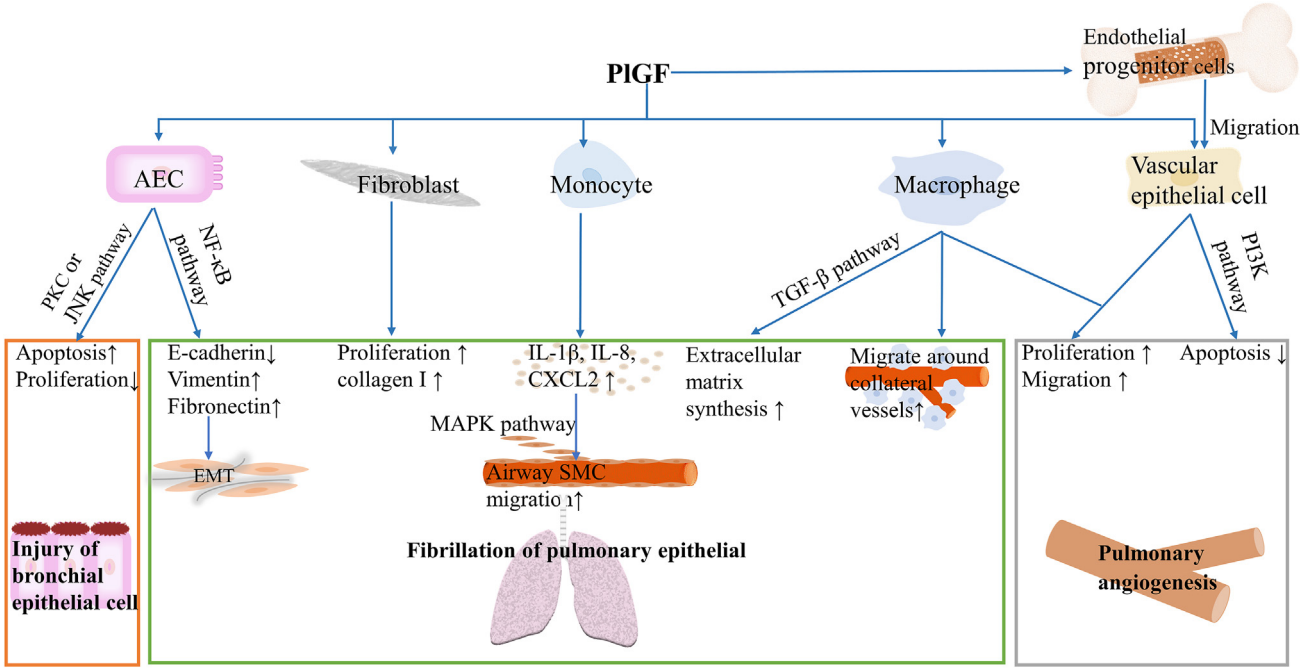

Figure 4 PlGF and airway remodeling. PlGF affects the development and progression of airway remodeling in asthma. Multiple cellular signaling pathways involving PlGF promote bronchial epithelial injury, subepithelial fibrosis, and neovascularization. AECs, type II alveolar epithelial cells; EMT, epithelial—mesenchymal transition; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; MIP-2 (CXCL-2), macrophage inflammatory protein-2 (C-X-C motif chemokine ligand 2); PKC, protein kinase C; SMC, smooth muscle cell.

PlGF participates in bronchial epithelial cell injury

The phenomenon of epithelial cell injury and exfoliation occurs in the airways of asthma patients.[118,119] Epithelial injury and basement membrane denudation weaken the defense functions of airway epithelium,[120] and therefore, small airway injury is a risk factor for exacerbation of asthma.[121] PlGF induces apoptosis of type II alveolar epithelial cells (AECs),[41,47,122] and a VEGFR-1 inhibitor can eliminate cell death and apoptosis.[47] In chronic asthma, cytokines produced by the Th2 immune response open tight junctions at the apical side of the columnar cells, resulting in loss of epithelial integrity.[123,124] Moreover, T cells and eosinophils synergistically induce apoptosis of bronchial epithelial cells in asthma.[120,125] As mentioned above, PlGF not only participates in the Th2 immune response,[43,57] but also recruits eosinophils to inflammatory sites,[43] which may contribute to epithelial cell apoptosis in asthma.

In terms of mechanism, PlGF inhibits MLE-15 cell (mouse pulmonary type II epithelial cell) proliferation in a dose-dependent manner.[41] Moreover, PlGF promotes apoptosis in MLE-15 cells and BEAS2B cells (a human bronchial epithelial cell line) through the c-Jun N-terminal kinase (JNK) and p38 (mitogen-activated protein kinase (MAPK)) pathway.[39,126] Smoking induces neutrophil elastase expression and promotes PlGF secretion. PlGF then induces apoptosis of lung epithelial cells by the downstream JNK and protein kinase C (PKC) δ signaling pathways (Fig. 4).[54] PlGF overexpression in mouse lungs leads to autophagy and apoptosis of AECs.[41] Conversely, PlGF knockdown protects mice against elastase-induced pulmonary emphysema.[127] Overall, these results suggest that PlGF may play a potential role in the pathogenesis of airway remodeling in asthma through promoting bronchial epithelial apoptosis.

PlGF is associated with fibrosis of pulmonary epithelium

PlGF is highly expressed in fibrotic liver and PlGF deficiency significantly reduces the severity of liver inflammation and fibrosis.[53,64] Subepithelial fibrosis is an important feature of airway remodeling. PlGF may be involved in pulmonary epithelial fibrosis by inducing the expression of pro-fibrotic factors and promoting fibroblast proliferation and bronchial epithelial—mesenchymal transition (EMT) (Fig. 4).

Fibrosis is usually associated with impaired angiogenesis and sustained local tissue hypoxia. Hypoxia promotes the development of fibrosis and angiogenesis through the HIF-mediated pathway.[53,128] HIF-1α expression is increased in lung mucosa biopsy specimens of asthma patients,[129] indicating tissue hypoxia in the asthmatic airway. PlGF expression is also markedly increased in hypoxic lung tissue.[49] Hypoxia may induce PlGF expression by accompanying HIF-1α activation.[53] HIF-1α is able to directly activate PlGF transcription in endothelial cells and hypoxia is an important stimulator of PlGF expression.[50,51] VEGFR-1 expression is also directly regulated by hypoxia and HIF in endothelial cells.[130] Interestingly, PlGF-specific small interfering RNA can inhibit the expression of HIF-1α in

fibrotic livers.[53] In summary, PlGF expression increases with hypoxia, and PlGF, together with HIF, may be involved in subepithelial fibrosis in asthma patients.

The main cause of subepithelial fibrosis is the imbalance of matrix synthesis and breakdown. As a key cytokine stimulating extracellular matrix synthesis,[131] TGF-β expression is significantly increased in pulmonary fibrosis,[132] and its expression level is related to the degree of subepithelial fibrosis.[133–136] Interestingly, TGF-β upregulates PlGF expression[137] and, in turn, PlGF and VEGFR-1 overexpression induces macrophages to secrete TGF-β.[80,81] Therefore, PlGF may be involved in the subepithelial fibrosis mediated by TGF-β. Additionally, C-X-C motif chemokine ligand (CXCL) 2 and CXCL3 that are induced by TGF-β, VEGF, IL-1β and IL-17 promote airway smooth muscle cell (SMC) migration through the MAPK pathway, thus contributing to airway remodeling.[138] PlGF can recruit and activate monocytes and promote the secretion of inflammatory factors (IL-1β and IL-8) and chemokines (CXCL2 and CCL2), so as to contribute to airway epithelial fibrosis.[11,59]

Excessive accumulation of extracellular matrix causes airway remodeling and fibrosis in asthma patients.[139] As connective tissue cells, pulmonary fibroblasts can synthesize and secrete collagen fibers, which are the main source of extracellular matrix in subepithelial fibrosis.[140,141] A common cause of airway remodeling in asthma patients is the proliferation and activation of fibroblasts, leading to the accumulation of type I collagen around small bronchi. Interestingly, PlGF stimulates the proliferation of cultured human lung fibroblasts and type I collagen expression *in vitro* in a concentration-dependent manner,[142] suggesting another mechanism by which PlGF may induce fibrosis (Fig. 4).

During airway remodeling, EMT exacerbates subepithelial fibrosis.[143] E-cadherin is downregulated and vimentin is upregulated in the airway epithelial cells of HDM-asthmatic mice,[143] suggesting that the pathogenesis of asthma is related to EMT. *In vitro*, exogenous PlGF induces EMT-like changes in AECs by activating NF-κB signaling, decreasing E-cadherin, and increasing vimentin and fibronectin (Fig. 4).[144] Furthermore, PlGF induces EMT-like changes in cervical cancer SiHa cells and breast cancer MCF-7 cells.[145,146] Therefore, PlGF may help drive fibrotic lesions by promoting EMT transformation in the pulmonary epithelium.

Relationship between PlGF and pulmonary angiogenesis

As a significant feature of asthma patients, airway wall neovascularization is manifested by an increase in the number and size of bronchial vessels. These changes are closely related to the airway wall thickness and airway remodeling.[147,148] Angiogenesis is mediated by angiogenic factors, such as VEGF, angiopoietin-1, and angiopoietin-2, all of which contribute to airway remodeling and airflow obstruction.[149–152] Our previous studies showed significantly higher PlGF levels in the serum and induced sputum of asthmatic smokers than in healthy controls,[10] demonstrating the potential role of PlGF in pathological angiogenesis in lung tissues of asthma patients. PlGF is a strong stimulator of angiogenesis, especially in pathological conditions and an increased PlGF level can offset ischemic damage.[153] Furthermore, αPlGF is able to effectively and selectively inhibit pathological angiogenesis with a good safety profile.[25,66,154,155]

VEGF-A has a clear influence on angiogenesis.[156,157] PlGF acts synergistically with VEGF-A in angiogenesis.[25] PlGF only binds VEGFR-1, while VEGF-A binds both VEGFR-1 and VEGFR-2. Compared with VEGFR-1, VEGFR-2 has higher tyrosine kinase activity.[24] Surprisingly, in transgenic mice, PlGF overexpression simultaneously upregulates the expression of VEGFR-1 and VEGFR-2 in endothelial cells.[91] On the one hand, PlGF indirectly activates VEGFR-2 via enhancing the binding of VEGF-A and VEGFR-2 or forming PlGF/VEGF-A heterodimers.[25,27,158] PlGF also activates VEGFR-1—VEGFR-2 crosstalk by connecting with VEGFR-1. It means that activation of VEGFR-1 leads to intermolecular phosphorylation of VEGFR-2, thereby amplifying VEGF-A-driven angiogenesis through VEGFR-2.[159] On the other hand, PlGF upregulates other angiogenesis factors, such as VEGF, basic fibroblast growth factor (FGF2) and matrix metalloproteinases (MMPs).[160,161] Therefore, PlGF and VEGF-A cooperate to participate in angiogenesis.

Microvascular endothelial cells have the ability to migrate and form capillary-like structures and play a key role in angiogenesis induced by growth factors.[162] Human lung microvascular endothelial cells (HLMECs) actively participate in airway wall vascular remodeling in asthma patients.[163] Our previous research showed that stimulation of HLMECs with recombinant human PlGF can significantly increase their proliferation and migration, and markedly increase the formation of stress fibers and capillary-like networks in a concentration-dependent manner.[10] These data indicate that PlGF directly acts on existing endothelial cells to influence neovascularization.[147,163] PlGF and PlGF/VEGF-A may also maintain angiogenesis by upregulating the anti-apoptotic protein (B-cell lymphoma-2 (Bcl-2)) through the PI3K pathway and thus improving the survival of endothelial cells (Fig. 4).[164] Besides that, PlGF mediates the maturation and stability of new blood vessels by stimulating the migration of SMCs and pericytes to vascular endothelium.[75,164] Generally speaking, as a chemokine of endothelial growth factor to regulate the growth of endothelial cells,[165] PlGF directly stimulates the growth, migration, and survival of endothelial cells,[25,26,66,75,166] and promotes the mobilization, chemotaxis, and recruitment of endothelial progenitor cells from the bone marrow to ischemic tissues. Therefore, PlGF promotes the healing of injured blood vessels.[167]

Macrophages induce angiogenesis by producing angiogenic cytokines and growth factors (VEGF-A and FGF-2) to promote the proliferation and migration of endothelial cells and the formation of vascular buds.[168–170] It is important that the expression of angiogenic cytokines and growth factors is higher in M2 macrophages than in M1 macrophages.[171] *In vivo* and *in vitro*, IL-4-induced M2a and IL-10-induced M2c macrophages both promote angiogenesis, but M2c macrophages induce angiogenesis depending on PlGF signaling.[172] Conversely, M2c macrophages produce the highest levels of PlGF and MMP2.[173,174] Furthermore, PlGF induces polarization of TAMs and then promotes TGF-β production and lung cancer angiogenesis.[52,80,81,175,176] The angiogenic effect of PlGF may also come from direct VEGFR-1 activation in endothelial cells or indirect VEGFR-1 activation

in monocytes. Recruited monocytes produce angiogenic factors and proteolytic enzymes to promote angiogenesis and arterialization of microvessels.[155,159,177] Moreover, PlGF attracts macrophages and bone marrow progenitor cells to gather around collateral vessels,[81,161,177–179] and further stimulates angiogenesis by releasing VEGF.[155] Therefore, PlGF interacts with angiogenesis-stimulating macrophages.

PlGF affects lung function in asthma patients

Our previous clinical data showed that PlGF levels correlate negatively with post-bronchodilator forced expiratory volume in 1 s (FEV1) and the FEV1/forced vital capacity (FVC) in asthmatic smokers.[10] The upregulation of PlGF in serum, sputum, and BALF of COPD patients is negatively correlated with FEV1, and the level of PlGF in BALF is higher in patients with severe airflow limitation.[11,47]

PlGF promotes fibroblast proliferation and induces EMT of bronchial epithelium, thus contributing to airway remodeling.[141,144] Fibroblast numbers and airway SMC size are negatively associated with prebronchodilator and postbronchodilator FEV1 values in asthma patients.[180] In non-smoking patients with asthma, there is a negative correlation between PlGF in sputum and diffusion capacity for carbon monoxide of the lung (D_{LCO}, one of the indicators of pulmonary fibrosis). These data indicate that PlGF production exacerbates pulmonary diffusion dysfunction in these patients.[10] Continuous EMT may lead to airway remodeling in asthma and ultimately cause a progressive decline in lung function.[181] EMT also induces changes in airway epithelial sensitivity and affects the therapeutic effect of glucocorticoids in severe asthma.[182] In addition to that, PlGF is involved in edema of the airway wall. Airway obstruction is closely related to AHR because reduced baseline FEF_{25-75}% (maximal mid-expiratory flow (MMEF)) values with normal FEV1 and FEV1/FVC may predict AHR at asthma onset and a greater FEF_{25-75}% reduction may be associated with a more severe AHR.[88] High-resolution CT scores are related to the severity of asthma and airflow obstruction.[183] In asthma patients, PlGF levels in the serum and induced sputum are positively associated with the wall thickness of the posterior basal segmental bronchus (designated as RB10) and the development of severe expiratory flow restriction.[10] These data show that PlGF hurts lung function in asthma patients. However, further studies are required to confirm this correlation.

Treatment outlook

Our previous study showed that PlGF expression is increased in asthma patients.[10] As we outlined above, PlGF may be involved in the pathogenesis of asthma. Consequently, PlGF may be an attractive therapeutic target for asthma. In recent years, there have been relevant studies on PlGF inhibition or PlGF-targeted therapy using specific anti-PlGF antibodies (αPlGF) (Fig. 1). Blocking PlGF function by αPlGF or blocking LT production by the 5-LO inhibitor zileuton reduces AHR attacks in a sickle cell anemia mouse model (Fig. 1).[43] αPlGF also prevents the infiltration of vasoactive macrophages and inhibits pathological angiogenesis,[66,155] which may attenuate airway remodeling in asthma. Remarkably, using an anti-VEGFR1 antibody to block the PlGF/VEGFR1 signaling axis significantly inhibits macrophage migration and the inflammatory response.[64] Moreover, our experimental data suggest that the ROS/ERK-1/2 (MAPK)/Egr-1 pathway plays a major role in the regulatory mechanism of CSE-induced PlGF production. Furthermore, the antioxidant NAC can partly abolish these effects and, therefore, may be beneficial to asthma patients (Fig. 1).[55] Nevertheless, these inhibitors affect other signaling pathways and have pleiotropic effects. Therefore, the development of selective PlGF inhibitors is crucially important.

Many studies have demonstrated the effects of PlGF deficiency and/or neutralization on different pathological processes in asthma and other respiratory disease models. Blocking PlGF effectively inhibits inflammatory cell recruitment and reduces pathological angiogenesis and vascular leakage. Although these data emphasize the possible therapeutic effect of anti-PlGF, this therapy has not been considered for asthma treatment. Currently, further studies are needed to understand how PlGF blockade may treat asthma. For example, anti-PlGF antibodies may attenuate Th2 inflammation and reduce asthma attacks or may work by inhibiting angiogenesis and pulmonary fibrosis. Using anti-VEGFR1 antibodies to block VEGFR1 on macrophages or neutrophils may delay the progression of airway remodeling induced by pulmonary fibrosis. Interestingly, PlGF silencing robustly reduced liver fibrosis and inflammation in a murine model of chronic liver disease.[53] The potential effect of anti-PlGF therapy in suppressing pulmonary fibrosis may also apply to patients with poor response to other anti-asthma therapies, but further evidence is needed. It is also important to clarify the downstream pathways of PlGF so that the pro-inflammatory effect of PlGF can be indirectly inhibited by pathway inhibitors such as zileuton. In addition, methods to inhibit PlGF production in asthma patients can be considered, but the relationship between PlGF and the severity of asthma and decline in lung function must be further elucidated. It is unclear whether PlGF inhibition can be used as a separate treatment for asthma, or can be used in combination with or as an alternative to current asthma treatment strategies.

Conclusion

Chronic airway inflammation, AHR, and airway remodeling are the main pathological characteristics of asthma. Among them, recurrent asthma leads to pulmonary fibrosis, thickening of airway walls, and further narrowing of airways, which is an important factor affecting the prognosis of asthma patients. The PlGF-related mechanisms in asthma are multiplex and complex, and thus it is necessary to further study the details of the PlGF pathway. Interestingly, targeted therapy to inhibit PlGF can attenuate or slow down asthma-related pathological changes. However, it is still unclear whether these effects are sufficient to have a lasting impact on asthma patients by improving fixed airflow obstruction and slowing the decline in lung function. Therefore, anti-PlGF treatment may be an effective auxiliary asthmatic therapy, although further studies are required.

Author contributions

Dan Huang: conceptualization (lead), methodology (lead), and writing - original draft (equal); Zhiyi Xu: writing - original draft (lead); Gege Liu: writing - review & editing (lead); Shushu Chen, Cuili Wang, Dewei Liu, and Jiahao Cao: writing - review & editing (equal); Bin Wu: supervision (lead); Junfen Cheng: resources (lead); Dong Wu: conceptualization (lead) and project administration (lead). All authors read and agreed to the published version of the manuscript.

Conflict of interests

The authors declare no conflict of interests, and they agreed to the publication of this manuscript.

Funding

This work was supported by the National Science Foundation of Guangdong Province, China (No. 2022A1515011731 and 2021A1515011062); Guangdong Provincial Administration of Traditional Chinese Medicine (China) (No. 20221211); Project of Zhanjiang City, Guangdong, China (No. 2020A01016, 2020B01346, 2021A05077, and 2016B01062); and Affiliated Hospital of Guangdong Medical University (China) (No. 4SG21231G, LCYJ2017A003, CLP202113001, CLP2021B001, LCYJ2020B008, and BK201616).

Acknowledgements

We thank Leah Cannon, Ph.D., from Liwen Bianji (Edanz) (www.liwenbianji.cn/), for editing the English text of a draft of this manuscript.

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