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REVIEW

Biomarkers in COPD-Associated PH/CCP: Circulating Molecules and Cell-Intrinsic Marker

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Abstract: Chronic obstructive pulmonary disease (COPD) is a chronic progressive disease of the airways and lungs characterized by persistent respiratory symptoms and airflow limitation. Under hypoxic conditions, endothelial cells and immune cells secrete inflammatory mediators and growth factors, promoting the proliferation of pulmonary vascular smooth muscle cells and fibroblasts, leading to vascular remodeling. Considering the high morbidity and mortality of pulmonary hypertension (PH) in patients with COPD, we investigated the molecular mechanisms underlying vascular remodeling in COPD-related PH. Neurohumoral factor N-terminal brain natriuretic peptide (NT-proBNP), inflammatory mediators, growth factors, and forkhead box M1 (FOXM1) were evaluated as auxiliary diagnostic markers for COPD with PH and chronic cor pulmonale (CCP), aiming to facilitate early PH screening, prevention, and improvement of patient survival and quality of life. Circulating biomarkers (NT-proBNP, inflammatory mediators, growth factors) can be detected via clinical blood sampling, offering non-invasive, convenient diagnostic approaches with high specificity and sensitivity—ideal tools for disease screening. Intracellular molecular marker FOXM1, requiring tissue or enriched cell detection, serves as a histopathological marker and potential target for liquid biopsy, positioning it as a promising future screening tool.

Keywords: COPD, pulmonary hypertension, PH, chronic cor pulmonale, CCP, biomarkers, inflammatory cytokines, growth factors, FOXM1

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive respiratory condition characterized by persistent symptoms and airflow limitation that is not fully reversible with bronchodilator therapy. It has become a significant global health issue.[1] According to the World Health Organization, COPD was the third leading cause of death worldwide in 2019, accounting for 3.23 million deaths. Additionally, it ranks as the seventh leading cause of poor health globally, as measured by disability-adjusted life years. The prevalence of COPD is notably higher among current and former smokers, and it increases with age.[2]

It has been shown that the pathogenesis of COPD is closely related to abnormal inflammatory response, protease-antiprotease imbalance, and oxidative stress damage. Inflammatory cells release pro-inflammatory factors such as interleukin (IL-6, IL-8) and tumor necrosis factor alpha (TNF-α), leading to thickening of the airway wall, excessive mucus secretion, and ciliary dysfunction. Chronic inflammation further damages the alveolar structure, leading to emphysema and small airway fibrosis. In addition, protease-antiprotease imbalance and the imbalance between oxidative stress and antioxidation, exacerbate lung tissue damage and inflammation amplification. As the pathophysiology of COPD progresses, it can lead to an increase in mean pulmonary arterial pressure (mPAP). This increase is primarily driven by three key mechanisms: first, hypoxic pulmonary vasoconstriction contributes to increased pulmonary circulation resistance; second, the loss of small pulmonary vessels and pulmonary vascular remodeling—characterized by intimal proliferation of poorly differentiated smooth muscle cells and deposition of elastic and collagen fibers—also plays a significant role; third, hypoxia induces an increase in red blood cell count and blood viscosity. These three factors

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can contribute to pulmonary hypertension (PH) either individually or simultaneously.[3] The prevalence of PH is very high in patients with advanced COPD. A meta-analysis shows that the combined prevalence of COPD-related PH is 39.2%, and the prevalence of PH increases with the severity of COPD.[4] A study in patients with severe airway obstruction indicates that up to 90% of such patients have an mPAP greater than 20 mmHg.[5] In COPD, PH is typically of moderate severity and progresses slowly, often without affecting right ventricular function in most patients. However, a small percentage (1–3%) may experience disproportionate PH, where pulmonary arterial pressure significantly exceeds the degree of airway impairment.[6] Persistent PH leads to increased right ventricular afterload, ultimately causing right ventricular remodeling and functional failure, known as chronic cor pulmonale (CCP). Furthermore, since COPD and cardiovascular disease share common risk factors—such as advanced age, smoking, and systemic inflammation—COPD can lead to chronic systemic inflammation in addition to pulmonary inflammation. This systemic inflammation may result in myocardial inflammation and subsequent fibrosis, which affect the mechanical, electrical, and vasomotor functions of the myocardium. Consequently, this also increases the risk of cardiovascular disease in COPD patients, particularly right heart failure due to PH.[7] Importantly, a key characteristic of COPD is that an individual's prognosis is significantly influenced by comorbidities, with PH and cardiovascular disease increasingly recognized as exacerbating factors associated with higher mortality rates in COPD patients.[8] A research displays that the 5-year all-cause mortality of COPD patients is significantly higher in combined with PH group than without PH group (32.0% vs 13.0%).[9] The mPAP and pulmonary vascular resistance values are negatively correlated with survival rates. Reports indicate that the five-year survival rate for COPD patients with mPAP values greater than 25 mmHg is only 36%. Additionally, pulmonary hemodynamics have been shown to be a stronger predictor of survival than forced expiratory volume in one second (FEV1) or gas exchange variables.[10]

Recognizing PH can be challenging, as its symptoms often overlap with those of COPD. A high index of suspicion for PH is warranted if clinical deterioration does not correlate with a decline in pulmonary function, especially in cases of profound hypoxemia or significant reductions in carbon monoxide diffusion capacity.[6] Patients with suspected PH should undergo evaluation by Doppler echocardiography, a widely accepted non-invasive diagnostic tool that uses ultrasound to generate cardiac images. PH can be diagnosed when pulmonary artery systolic pressure exceeds 50 mmHg, in conjunction with a clinical diagnosis. The gold standard for diagnosing PH, however, is catheterization, which involves inserting a catheter into the pulmonary artery to directly measure pressure, with PH defined as an mPAP of 25 mmHg or higher. Despite its accuracy, this invasive technique presents challenges in clinical practice due to its complexity and associated risks.[11] In view of the high incidence of PH and CCP in COPD patients, along with the associated adverse outcomes, there is an urgent need for convenient and non-invasive diagnostic methods that offer good specificity and sensitivity. Circulating biomarkers and intracellular molecular markers in COPD patients are expected to play a key role in diagnosing the presence of PH and CCP, complementing existing diagnostic methods.

Brain Natriuretic Peptide

Brain natriuretic peptide (BNP) is a biologically active molecule composed of 32 amino acids, primarily synthesized in the cardiac ventricles and released into circulation in response to pressure overload, volume expansion, and increased myocardial wall stress. Its precursor, pro-BNP, is cleaved by blood proteases to produce BNP and N-terminal pro-BNP (NT-proBNP). BNP has a half-life of approximately 22 minutes, while NT-proBNP has a half-life of about 120 minutes, making NT-proBNP relatively stable and potentially more accurate for disease diagnosis.[12] COPD accompanied by PH results in increased pulmonary vascular pressure and right heart afterload, which heightens the strain on the ventricular wall and triggers the release of NT-proBNP. This mechanism may be a significant contributor to the upregulation of NT-proBNP levels in these patients.[13] Secondly, hypoxia has been identified as a potential contributor to elevated NT-proBNP levels. A study by Hopkins et al on adult patients with cyanotic congenital heart disease demonstrated a significant increase in BNP levels, highlighting that hypoxia serves as a direct stimulus for BNP secretion in human cardiac myocytes.[14] Casals et al conducted in vitro experiments using cultured human ventricular myocytes and demonstrated that hypoxia may stimulate the synthesis and secretion of BNP in these cells through the enhanced transcriptional activity of hypoxia-inducible factor 1 (HIF-1).[15] Oxygen therapy can significantly reduce pulmonary artery pressure and NT-proBNP levels in COPD patients. Non-invasive positive pressure ventilation can decrease the risk

of acute exacerbation and improve prognosis in patients with severe-to-very-severe COPD complicated by PH.[16] Finally, the elevation of NT-proBNP levels can also be linked to the activity of various pro-inflammatory cytokines. Previous studies have indicated that cytokines such as IL-1β, TNF-α, and IL-6 may act as stimuli for the release of NT-proBNP from cardiac myocytes.[17]

Historically, BNP has been closely associated with heart failure (HF). In cases of left ventricular heart failure (LVHF), elevated BNP levels have been linked to reduced exercise tolerance and a poorer prognosis.[18] Additionally, it has been reported that even in the absence of LVEF, PH secondary to end-stage lung disease can further exacerbate right ventricular afterload, potentially leading to right heart failure in COPD patients. This condition can also result in increased BNP concentrations.[19] A meta-analysis showed that compared to COPD patients without PH and HF, patients with combined PH and HF had significantly elevated NT-proBNP levels. Moreover, compared to the stable COPD group, the NT-proBNP levels in acute exacerbation of chronic obstructive pulmonary disease (AECOPD) patients were significantly elevated. Elevated NT-proBNP levels are associated with a higher mortality risk in hospitalized AECOPD patients and serve as an important prognostic indicator for poor outcomes in these individuals.[20] The study by Agoston-Coldea et al demonstrated that NT-proBNP levels have significant predictive value for right ventricular dysfunction, with an area under the receiver operating characteristic (ROC) curve (AUC) of 0.945 ($p < 0.0001$), indicating extremely strong diagnostic accuracy. When using 311 pg/mL as the optimal cutoff value, NT-proBNP exhibited 100% sensitivity and 84.0% specificity. These findings suggest that at this threshold, NT-proBNP can serve as a highly effective screening tool for right ventricular dysfunction.[21] It is worth pondering whether NT-proBNP can differentiate between right heart failure caused by isolated HF and right heart failure induced by COPD combined with CCP. In the study by Dewan et al, 12.3% of HF patients with reduced ejection fraction were found to have COPD. Compared to those without COPD, participants with COPD exhibited higher levels of NT-proBNP, experienced more severe symptoms and functional limitations, and faced a higher risk of composite outcomes, including HF deterioration and cardiovascular death.[22] Another study found no significant difference in NT-proBNP levels between patients with HF combined with COPD and those with HF alone.[20] Therefore, although NT-proBNP cannot differentiate between right heart failure caused by isolated HF and that caused by COPD combined with CCP, it can still serve as a useful exclusion criterion for COPD-induced PH and CCP. A normal NT-proBNP level effectively rules out these complications.

Inflammatory Mediators

The histopathological characteristics of PH include thickening of the vascular intima and media, muscularization of distal pulmonary arteries, vascular occlusion, and the presence of complex plexiform lesions. These features are closely associated with pulmonary artery smooth muscle cells (PASMCs), endothelial cells (ECs), and immune cells.[23,24] ECs and immune cells secrete growth factors and inflammatory cytokines, triggering a phenotypic shift in PASMCs from a contractile or differentiated state to a proliferative or dedifferentiated state. This shift promotes and sustains PASMC proliferation and contributes to vascular remodeling.

Macrophages are key effectors of pulmonary inflammation in patients with PH. Among them, alveolar macrophages contribute to local immune homeostasis and possess surfactant properties, while pulmonary interstitial macrophages, such as perivascular macrophages, play a predominant role in driving pulmonary inflammation.[25] Florentin et al's study further demonstrated that hypoxia results in a gradual depletion of alveolar macrophages and a substantial increase in interstitial macrophages. The reduction in alveolar macrophages under hypoxic conditions may be attributed to increased expression of cleaved caspase-3, which promotes apoptosis, along with decreased levels of granulocyte colony-stimulating factor (G-CSF), which is insufficient to stimulate macrophage proliferation. The increase in interstitial macrophages under hypoxic conditions may be attributed to elevated levels of chemokines and their receptors. Both animal experiments and clinical studies of PH patients have shown higher chemokine levels: hypoxic mice exhibited elevated pulmonary levels of chemokines such as chemokine (C-X3-C motif) ligand 1 (CX3CL1) and C-C chemokine ligand (CCL2), while PH patients showed increased levels of pulmonary chemokines including CCL1, CCL2, CCL3, CCL4, CCL18, and CX3CL1, which promote monocyte migration. Additionally, expression of corresponding chemokine receptors like C-C chemokine receptor 1 (CCR1), CCR2, CCR5, and CX3CR1 was found to be elevated in the circulating monocytes of PH patients. The increase in lung chemokines and the upregulation of chemokine receptor

expression on blood monocytes trigger the mobilization of inflammatory monocytes to the lungs in PH patients, where they subsequently differentiate into interstitial perivascular macrophages.[25] Inflammation in the right ventricle (RV), driven by the activation of the nucleotide-binding domain, leucine-rich repeat-containing family, pyrin domain-containing-3 (NLRP3) inflammasome in macrophages, contributes to increased RV fibrosis and worsening RV function. The specific pathway of action includes the following steps: 1. Priming and Activation: Initiated by various signals, such as damage-associated molecular patterns, potassium efflux, calcium influx, and mitochondrial dysfunction; 2. Aggregation: Formation of the apoptosis-associated speck-like protein containing a caspase activation and recruitment domain, which is a key adaptor molecule in inflammasome signaling; 3. Gasdermin D Pore Formation and IL-1β Release: Activation leads to the formation of gasdermin D pores and subsequent release of IL-1β; 4. Induction of Pro-inflammatory Response: IL-1β triggers a pro-inflammatory response in the RV, including the release of additional inflammatory cytokines such as IL-6; 5. Downstream IL-6 Signaling: IL-6 signals downstream through signal transducer and activator of transcription 3 (STAT3) in monocytes, aiding in the recruitment of new monocytes/macrophages to the RV. Animal models have confirmed that the inflammatory and fibrotic changes associated with PH are chamber-specific. When comparing the RV and left ventricle, only the RV shows elevated levels of collagen-III, atrial natriuretic peptide, and macrophage counts.[26] Xingchen et al demonstrated that treatment with the glutaminase 1 inhibitor BPTES significantly ameliorated pulmonary artery pressure, right ventricular function, and pulmonary vascular remodeling in a rat model of PH. Concurrently, this intervention suppressed M1 macrophage polarization, NLRP3 inflammasome activation, and the release of pro-inflammatory cytokines. These findings further validate that macrophage inhibition may represent a promising therapeutic approach for PH.[27]

The T-helper 17 (Th17) and T-helper 2 (Th2) subsets of CD4+ T cells are pivotal in the development of chronic hypoxia-induced PH. IL-6, in combination with transforming growth factor-β (TGF-β), promotes the differentiation of naive T cells into Th17 cells and sustains STAT3 activation.[28] Th17 cells then produce the pro-inflammatory cytokine IL-17, which has multiple roles in promoting airway inflammation. IL-17 facilitates the recruitment of neutrophils by inducing CXC chemokines such as CXCL2, which is also known as macrophage inflammatory protein-2 (MIP-2), and upregulating G-CSF expression. Additionally, IL-17 binds to TNF-α, stabilizing mRNA and enhancing the production of other pro-inflammatory cytokines like IL-6 and IL-8, thereby intensifying airway inflammation.[29–32] Moreover, IL-17 stimulates the release of matrix metalloproteinase-12 (MMP-12), contributing to tissue degradation.[33,34] It also activates the Wnt3a/β-catenin/CyclinD1 pathway in pulmonary artery endothelial cells (PAECs), leading to PAECs dysfunction.[35] This dysfunction further stimulates PASMCs proliferation, intensifying hypoxia-induced vascular remodeling. The cytokine IL-4, produced by Th2 cells, is a multifunctional cytokine that not only stimulates antibody production by B lymphocytes but also plays a pivotal role in Th2-mediated inflammatory responses.[36] IL-4 is crucial for the collagen accumulation and proliferative effects of hypoxia-induced mitogenic factor (HIMF) in pulmonary arteries (PAs). Additionally, HIMF significantly enhances the expression of vascular endothelial growth factor (VEGF) and themonocyte chemoattractant protein-1 (MCP-1, also known as CCL2) in pulmonary microvascular endothelial cells through an IL-4-dependent pathway, facilitating the recruitment of circulating monocytes. This suggests that HIMF, in the presence of IL-4, fosters a pro-inflammatory and chemotactic microenvironment. Therefore, IL-4 signaling likely plays a critical role in HIMF-induced pulmonary inflammation and vascular remodeling.[37–39]The pathways by which the above inflammatory factors affect vascular remodeling are summarized in Figure 1.

It is worth noting that the above inflammatory cytokines produced by immune cell-related pathways are closely associated with the diagnosis of comorbidities and disease severity in COPD patients, demonstrating significant clinical significance. Xu et al's research has demonstrated that CCL18 and CX3CL1 are significantly elevated in patients with COPD and CCP (COPD&CCP). The combination of CCL18 and CX3CL1 shows high precision for discriminating COPD&CCP with high AUC values (0.828), sensitivity (66.1%), and specificity (92.5%). The combined detection of the two can achieve high-specificity differentiation of COPD&CCP and reduce misdiagnosis (such as differentiation from simple COPD or LVEF). Moreover, both are independent predictors of poor clinical outcomes, associated with reduced therapeutic benefits and an unfavorable prognosis in COPD&CCP patients.[40] Eissa et al's study shows that IL-1 can be used for early warning and initial screening of COPD-PH. ROC analysis of IL-1 in predicting the probability of PH shows a significant AUC value of 0.722, indicating its moderate predictive ability for

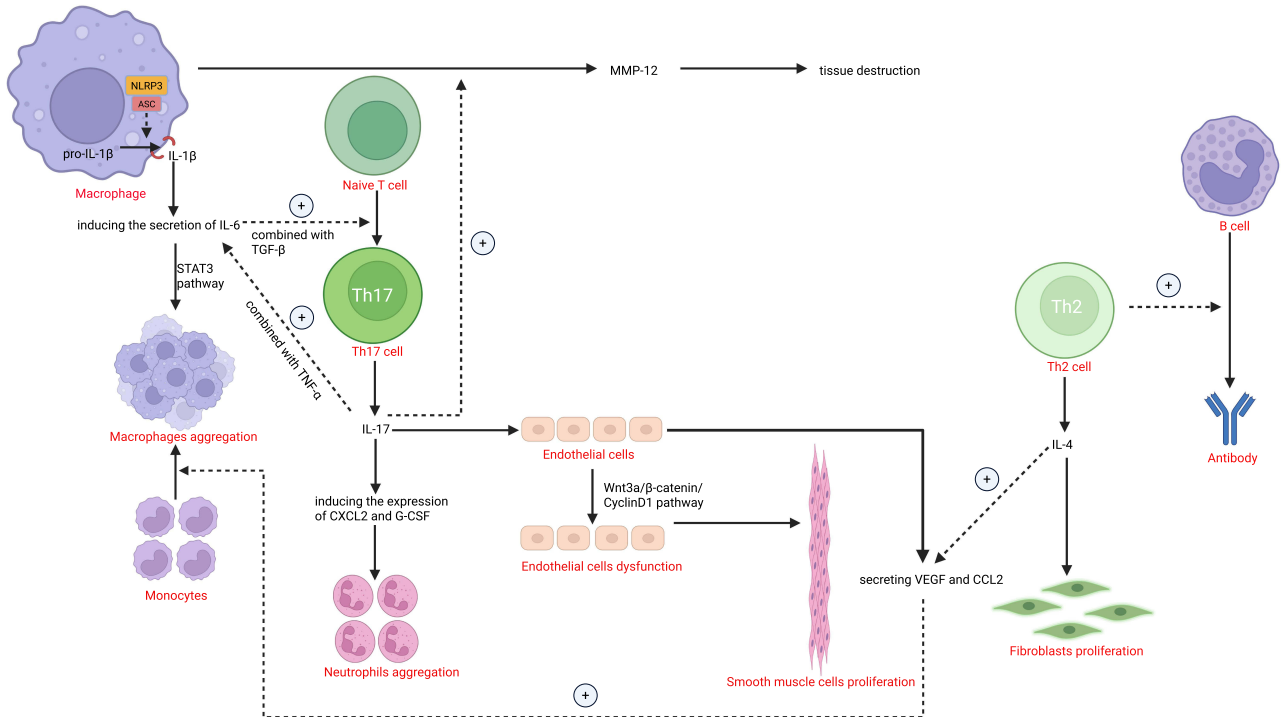

Figure 1 The pathways of inflammatory factors involved in vascular remodeling.
Abbreviations: ASC, Apoptosis-associated speck-like protein; B cell, B lymphocyte; CCL2, Chemokine (C-C motif) ligand 2; CXCL2, Chemokine (C-X-C motif) ligand 2; IL, Interleukin; G-CSF, Granulocyte Colony-Stimulating Factor; MMP-12, matrix metalloproteinase −12; NLRP3, Nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3; STAT3, Signal and transducer of transcription 3; TGF-β, Transforming growth factor-β; Th cell, T helper cell; TNF-α, Tumor necrosis factor-α; VEGF, Vascular endothelial growth factor.

PH risk. The best cutoff point is >86, with a sensitivity of 78.6% at this point, meaning it can identify approximately 79% of COPD-PH patients. However, the specificity is 58.1%, indicating some false positives, so clinical exclusion of interference such as infection is required.[41] Yang et al's study confirmed that IL-6 demonstrated significant value in the diagnosis and treatment of COPD&PH. ROC analysis showed that the AUC of IL-6 for diagnosing COPD&PH reached 0.929, approaching perfect predictive efficacy. When the cutoff value was set at 98.99 pg/mL, its sensitivity was 87.27%, meaning it can accurately identify over 80% of COPD&PH patients, and the specificity was 89.47%, effectively reducing misdiagnosis. These results indicated that IL-6 can serve as a non-invasive and highly efficient screening marker to assist in the early clinical detection of high-risk populations for COPD&PH. The study further confirmed that elevated IL-6 levels were an independent risk factor for the onset of COPD&PH (OR value: 2.564, 95% confidence interval: 1.114–4.789), suggesting that IL-6 is not only useful for diagnosis but also a potential target for monitoring disease progression. Clinically, dynamic monitoring of IL-6 levels helps assess disease severity and guide treatment decisions.[42] Interestingly, a study by Zou et al demonstrated that serum IL-1β and IL-17 levels in the AECOPD group were significantly higher than those in the stable COPD group or control group. These findings suggest that serum IL-1β and IL-17 may serve as critical biomarkers for distinguishing COPD patients from healthy subjects and could be instrumental in evaluating the severity of COPD and predicting clinical outcomes.[43]

Inflammatory mediators contribute to the pathogenesis of PH in COPD patients by affecting PASMCs, leading to an imbalance between vasoconstriction and vasodilation and promoting vascular remodeling.[44] Nitric oxide (NO), produced by endothelial nitric oxide synthase (eNOS), possesses vasodilatory and anti-proliferative properties. Bao et al demonstrated that NO expression is significantly downregulated in AECOPD patients combined with PH. Moreover, decreased NO levels were identified as an independent risk factor for concurrent PH in this population and can help clinically predict the occurrence of PH.[45] Similarly, prostacyclin I2 (PGI2) is a vasodilator that also inhibits vascular remodeling and is synthesized via prostacyclin synthase activity. In patients with COPD and PH, both the synthesis and release of

NO in the lungs are diminished, and the expression of prostacyclin synthase mRNA is reduced.[46,47] Inflammatory mediators that contribute to vasoconstriction and vascular remodeling include angiotensin II (AngII), thromboxane A2 (TxA2), prostaglandin E2 (PGE2), 5-hydroxytryptamine (5-HT), and endothelin-1 (ET-1).

Ang II is generated from angiotensin I through the catalytic action of angiotensin-converting enzyme (ACE). Ang II functions as a vasoconstrictor and also promotes the proliferation of PASMCs.[44] An animal experiment demonstrated that during the progression of hypoxic PH, there is an increase in local ACE expression and Ang II production within the pulmonary artery walls. This increase promotes vascular contraction and induces distal muscularization of typically non-muscular vessels, ultimately contributing to the development of PH.[48]

Like PGI2, TXA2 and PGE2 are prostaglandins—lipid mediators produced through the cyclooxygenase-initiated metabolism of arachidonic acid.[49] TXA2 induces contraction of PAs by binding to the thromboxane receptor. PGE2 regulates various functions of lung fibroblasts, including proliferation, migration, and collagen synthesis.[50] Multiple factors stimulate the endogenous production of PGE2 in lung fibroblasts, including IL-1, TNF-α, and TGF-β. Notably, TGF-β promotes fibroblast-mediated contraction of the collagen matrix, which serves as an indicator of repair function. In contrast, IL-1 and TNF-α inhibit this contraction. This suggests that PGE2 may play a regulatory role in fibroblast-mediated tissue repair functions in the lung under different condition.[51,52] PGE2 mediates its effects through four specific receptors, with the vasoconstrictive receptor EP3 being particularly notable for its response to hypoxic conditions. In both human and mouse PASMCs, the expression of the EP3 receptor is upregulated in response to hypoxia. This upregulation may contribute to pulmonary vasoconstriction under hypoxic conditions, as the EP3 receptor is associated with reduced cAMP levels, often leading to contraction and other vasoconstrictive effects.[53] The specific pathways involved in this process include: 1. Rho/ROCK-dependent actin remodeling: This mechanism facilitates the trafficking of membrane type 1–matrix MMP (MT1-MMP) to the cell surface; 2. MT1-MMP activity: Once on the cell surface, MT1-MMP cleaves extracellular pro-MMP-2, enhancing the activity of extracellular MMP-2. This process degrades the extracellular matrix and vascular basement membrane, promoting angiogenesis; 3. Promotion of TGF-β signaling: Hypoxia-activated pathways increase TGF-β signaling and the expression of fibrotic proteins, leading to vascular wall remodeling; 4. Feedback loop with TGF-β1 and PGE2: TGF-β1 further stimulates the release of endogenous PGE2, potentially amplifying the response. In PASMCs lacking the EP3 receptor, MT1-MMP is less present on the membrane and more retained within the cytoplasm, resulting in decreased extracellular MMP-2 activity. Conversely, reintroducing EP3a and EP3b isoforms in these cells restores membrane-localized MT1-MMP, enabling them to respond more effectively to hypoxic conditions.[54]

5-HT, commonly known as serotonin, plays a role in promoting cell mitosis. Research indicates that hypoxia serves as a potent inducer of serotonin transporter (5-HTT) expression.[55] Both in vitro and in vivo exposure to hypoxia has been shown to increase 5-HTT expression twofold in PASMCs via a transcriptional mechanism, specifically by upregulating 5-HTT mRNA. This increase makes PASMCs more sensitive to the growth-promoting effects of 5-HT. The induction of 5-HTT expression by hypoxia may ultimately influence the degree of pulmonary vascular remodeling and the severity of PH in patients with advanced hypoxic COPD.

Growth Factors

Growth factors, including basic fibroblast growth factor (FGF), VEGF, platelet-derived growth factor (PDGF), and epidermal growth factor (EGF), play crucial roles in vascular remodeling in PH. Specifically, FGF-1 enhances the expression of the endothelin-1 subtype A receptor (ET-AR) in PASMCs and activates ET-AR through endothelin-1 (ET-1)—a primary mediator of hypoxia-induced PH—leading to PASMCs contraction. In addition, FGF-2 and VEGF are considered the strongest activators of angiogenesis, which can stimulate the migration and proliferation of endothelial cells in existing blood vessels to generate and stabilize new blood vessels.[56] A recent study has demonstrated that elevated serum levels of FGF-2 and VEGF in COPD patients are strongly correlated with an increased likelihood of developing PH. Clinically, serum FGF-2 and VEGF concentrations may serve as valuable biomarkers for assessing PH risk. Furthermore, serum FGF-2 and VEGF levels were significantly higher during acute exacerbation phase than in the remission and stable phases in COPD, indicating a direct association with disease severity in COPD patients.[57] Another study investigated VEGF levels in sputum samples of COPD patients, demonstrating a significant positive correlation

between exercise-induced PH severity and sputum VEGF concentrations. As a non-invasive diagnostic modality, sputum analysis offers direct insights into airway inflammation, epithelial injury, and vascular remodeling due to its direct origin from the respiratory tract. However, sputum specimen integrity is susceptible to multiple confounders, including salivary contamination, insufficient sputum volume, or tenacious consistency. Future research may optimize diagnostic accuracy by standardizing sputum collection protocols, integrating serum biomarker profiling, and incorporating echocardiographic pulmonary artery pressure assessments.[58]

The generation of growth factors requires transcriptional activation factors HIF-1a and STAT3.[59] Research has shown that, compared to normoxia (20% O_2), exposure to moderate hypoxia (5% O_2) increases the proliferation response of PASMCs to mitogens such as FGF-2 and PDGF, a process likely associated with hypoxia-inducible factors (HIFs).[60] HIFs refer to a group of heterodimeric transcription factors composed of α and β subunits. Targeted deletion of either the α or β subunit of HIF-1 is lethal to early embryos and is associated with vascular developmental defects, which play a crucial role in the proliferation and/or survival of PASMCs during early vascular development.[61] We searched for literature on the effects of HIF-1α and growth factors on PH over the past 10 years and summarized the findings in Table 1. Hypoxia increases the intracellular level of HIF-1α. Then the α subunit binds to the β subunit into a heterodimer, which binds to numerous promoters containing hypoxia response elements (HREs), and finally promotes the expression of growth factors and the development of PH.[62] Knockdown of HIF-1α with specific small interfering RNAs inhibited FGF-2-stimulated and PDGF-stimulated proliferation of PASMCs,[60] reduced the muscularization of small pulmonary arterioles.[63] Hypoxia serves as the primary stimulus for the upregulation of HIF-1α. Under hypoxic conditions, the expression of OTU deubiquitinase 6B (Otud6b) increases, reducing the rate of ubiquitin-mediated degradation.[64]

Table 1 Hypoxia Facilitates Vascular Remodeling by Enhancing the Expression of Growth Factors

Sample Sources	Control Group	Experimental Group		Testing Methods/ Indicators	Results	Refs
HPASMCs	Nor (20% O2)	Hyp (5% O2 or 1% O2)		Western blot	Hypoxia stimulated HIF-1α expression and enhanced the mitogenic effects of PDGF, FGF-2, and EGF.	[60]
	Hyp + nonspecific siRNA	Hyp + HIF-1α-specific siRNA			Knockdown of HIF-1α inhibited FGF-2- and PDGF-induced HPASMC proliferation.	
WT mice	Nor (20% O2)	Hyp (10% O2)		Flow cytometry, RT-PCR, Western blot	Lung macrophages accumulated and Pdgfb was upregulated in lung macrophage in hypoxia.	[69]
					The HIF-1α level was upregulated in hypoxia.	
	Be administered with liposomes loaded with PBS	Be administered with liposomes loaded with clodronate		Flow cytometry, RVSP, Fulton index, the number of alveolar myofibroblasts	The clodronate-loaded liposomes reduced macrophages, attenuating distal muscularization, PH and RVH.	
WT mice in Hypoxia (10% O2)	Carrying no LysM or CSF1R	Carrying LysM+ or CSF1R+ cells		RT-PCR, RVSP, Fulton index, the number of alveolar myofibroblasts	Pdgfb deletion in the LysM+ or CSF1R+ cells attenuated distal muscularization and PH.	
	HIF-1α fl/fl mice carrying no LysM or CSF1R	HIF-1α fl/fl mice carrying LysM+ or CSF1R+ cells			HIF-1α deletion attenuated hypoxia-induced Pdgfb expression, distal muscularization, PH and RVH.	
	Be administered with the anoparticles loaded with Scr RNA	Be administered with the nanoparticles loaded with siRNA targeting Pdgfb			Nanoparticle delivery of siRNA targeting Pdgfb attenuated distal muscularization, PH and RVH.	
HPASMCs	Nor (20% O2)	Hyp (3% O2)	Hyp + CAPE	RT-PCR, Western blot, MTT	Hypoxia increased the expression of HIF-1α, the AKT phosphorylation and the proliferation of HPASMCs, which were reversed by administration of CAPE.	[70]
			Hyp + LY294002	Western blot	The inhibitor of PI3-kinase (LY294002) inhibited hypoxia-induced AKT phosphorylation and HIF-1α expression, suggesting that hypoxia induced HIF-1α expression via a pathway involving AKT.	

(*Continued*)

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Table 1 (Continued).

Sample Sources	Control Group	Experimental Group			Testing Methods/ Indicators	Results	Refs
HPASMCs	Nor (20% O2)	Hyp (3% O2)		Hyp + atorvastatin	Western blot, CCK-8, Flow cytometry	Hypoxia increased the level of HIF-1α through the AKT/ERK signaling, and increased cell viability, which were reversed by atorvastatin.	[71]
WT mice	Nor (21% O2)	Hyp (10% O2)		Hyp + DSY	RVSP, Fulton index, Masson trichrome stain and microscope	Hypoxia increased the vascular remodeling, which was reversed by DSY administration.	[72]
HPAECs and HPASMCs	Nor (21% O2)	Hyp (1% O2)		Hyp + DSY	CCK-8, Western blot	Hypoxia upregulated the expressions of phosphorylation of AKT, STAT3, HIF-1α, and VEGF, causing the proliferation of HPAECs and HPASMCs, which were reversed by DSY.	
WT mice	Nor (21% O2)	Hyp (10% O2)			Western blot	Hypoxia upregulated the expression of the HIF-1α, VEGF and NF-kB.	[73]
HPAECs	Nor (21% O2)	Nor + AdPOSTIN	Hyp (1% O2)	Hyp + AdPOSTN	RT-PCR, Western blot, microscope	1. Hypoxia increased the levels of HIF-1α, VEGF and POSTIN, and the tube formation. 2. In both normoxic and hypoxic conditions, the overexpression of POSTN increased the levels of HIF-1α and VEGF, and the tube formation.	[68]
	Hyp, with siNC	Hyp, with siHIF-1α			Microscope	SiRNA-mediated knockdown of HIF-1α abolished the proangiogenic effect of POSTN, indicating HIF-1α is a downstream mediator of the effects of POSTN.	
	Nor, with AdPOSTIN + siNC	Nor, with AdPOSTIN + siHIF-1α					
	Hyp, with AdPOSTIN + siNC	Hyp, with AdPOSTIN + siHIF-1α					
WT mice	Nor (21% O2)	Hyp (10% O2)			RT-PCR, Western blot, ELISA	Hypoxia increased the expression levels of inflammatory factors TNF-α, IL-1β and IL-6, as well as Otud6b.	[65]
	Nor + siNC	Nor + siOtud6b	Hyp + siNC	Hyp + siOtud6b	RVSP, mPAP, Fulton index, PAT/ ET, H&E staining and immunostaining, ELISA	1. Hypoxia induced vascular remodeling, which was reversed by siOtud6b treatment. 2. SiOtud6b treatment decreased the expression levels of inflammatory factors TNF-α, IL-1β and IL-6.	
HPAECs and HPASMCs	Nor (21% O2)	Hyp (3% O2)	Hyp + MDL	Hyp + YC-1	RT-PCR, Western blot, ELISA	Hypoxia increased the expressions of Otud6b, HIF-1α and inflammatory factors TNF-α, IL-1β and IL-6.	
	Nor + siNC	Nor + siOtud6b	Hyp + siNC	Hyp + siOtud6b		1.The expressions of Otud6b, and HIF-1α were decreased in siOtud6b treated group. 2.The expression levels of inflammatory factors TNF-α, IL-1β and IL-6 proteins in the siOtud6b treatment group were reduced.	
HPAECs	Nor (21% O2)	Nor + Otud6b	Hyp	Hyp + Otud6b		Otud6b increased HPAECs production of HIF-1α, ET-1 and VEGF.	
HPSMCs	Nor (21% O2)	Hyp (2% O2)	Hyp + ASIV		Western blot, MTT, TUNEL	Hypoxia increased the levels of HIF-1α and Bcl-2, promoting HPASMCs proliferation and inhibiting apoptosis, which were reversed by ASIV.	[74]
HPAECs					Western blot	Hypoxia increased the HIF-1α and VEGF protein levels, which were reversed by ASIV.	
					ELISA	Hypoxia increased the concentrations of TNF-α and IL-1β, which were reversed by ASIV.	
PASMCs of rats	Nor (21% O2)	Hyp (10% O2 or 1% O2)			RT-PCR, Western blot	Hypoxia increased the expression levels of SUMO-1, HIF-1α and VEGF.	[66]
		Nor +SUMO-1-RNAi-LV	Hyp +SUMO-1-RNAi-LV	Nor +SUMO-1-LV	Hyp +SUMO-1-LV	SUMO-1 silencing reduced SUMO-1, HIF-1α and VEGF levels, while its overexpression increased SUMO-1, HIF-1α and VEGF levels.	

(*Continued*)

Table 1 (Continued).

Sample Sources	Control Group	Experimental Group	Testing Methods/ Indicators	Results	Refs
HPASMCs	Nor (21% O2)	Hyp (3% O2)	RT-PCR, Western blot, flow cytometry	Hypoxia increased the expressions of HIF-1α and VEGF, promoted the proliferation and migration of HPASMCs.	[75]
HPASMCs	Nor (21% O2)	Hyp (0% O2)	RT-PCR, MTT, wound healing, RVSP, mPAP, Fulton index	Hypoxia increased the expression levels of HIF-1α, VEGF and FGF-2, promoted cell viability, cell migration, and vascular remodeling.	[76]
WT rats	Nor (21% O2)	Hyp (5% O2)	Western blot, ELISA, mPAP, Fulton index	Hypoxia activated the PI3K/AKT signaling pathway, increased the expressions of NF-kB, Bcl-2, TNF-α, IL-6, HIF-1α, and VEGF, promoted vascular remodeling.	[77]
WT rats	Nor (21% O2)	Hyp (10% O2)	RT-PCR, RVSP, Fulton index, Immunostaining and microscope	Hypoxia increased the expression of HIF-1α, the number of c-kit+ /VEGF-R2+ cells, promoted vascular remodeling.	[78]
PASMCs of rats	Nor (21% O2)	Hyp (1% O2)	RT-PCR, Western blot, CCK-8, EdU staining	Hypoxia increased the expression of HIF-1α and VEGF, promoted the proliferative ability of PASMCs.	[79]
WT rats	Nor (21% O2)	Hyp (10% O2)	RT-PCR, Western blot, mPAP, Fulton index, microscope	Hypoxia increased the expressions of HIF-1α and VEGF, promoted vascular remodeling.	[80]

Abbreviations: CCK-8, Cell Counting Kit-8; ELISA, Enzyme-Linked Immunosorbent Assay; HPAECs, Human pulmonary arterial endothelial cells; HIF-1α, Hypoxia-inducible factor 1α; HPASMCs, Human pulmonary artery smooth muscle cells; Hyp, Hypoxia; mPAP, Mean pulmonary artery pressure; MTT, 3-(4,5)-dimethylthiahiazo (-z-y1)-3,5-di-phenytetrazoliumromide; Nor, Normoxia; NF-kB, Nuclear factor-kappa B; RT-PCR, Reverse Transcription-Polymerase Chain Reaction; RVSP, Right ventricular systolic pressure; TUNEL, Terminal dUTP Nick End Labeling; WT, Wild type.

Simultaneously, the expression of small ubiquitin-like modifier 1 (SUMO-1) also increases, which, in contrast to ubiquitin, is thought to primarily prevent proteasome-mediated protein degradation.[65] Consequently, the expression of HIF-1α increases. Additionally, during hypoxia, the expression of the matrix protein periostin rises, which is believed to interact with various integrins, including αVβ3, αVβ5, and α6β4. This interaction initiates processes such as cell proliferation, cell migration, and epithelial-to-mesenchymal transition. Nie et al found that the increased periostin is mainly localized at the nuclear section of cells, where it may interact with HIF-1α.[66,67] In addition to hypoxia, RAS mutations, phosphatase and tensin homolog (PTEN) deficiency, increased expression of EGFR, and the interaction between MMP-2 and integrin-αVβ3 can also upregulate the level of HIF-1α by activating the PI3K/AKT/mTOR pathway.[68] Activation of the PI3K/mTOR pathway increases HIF-1α protein levels without altering HIF-1α mRNA levels, possibly by increasing HIF-1α translation.[61,63]

In COPD patients, ECs and macrophages produce various regulatory mediators, including IL-6, IL-8, and TGF-β. These pro-inflammatory markers can activate the STAT3 pathway, leading to increased STAT3 phosphorylation.[81,82] STAT3 forms homodimers and binds with HIF-1α simultaneously to the VEGF promoter, where they form a molecular complex with the transcription coactivators CBP/p300 and Ref-1/APE. Moreover, the negative expression of HIF-1α or STAT3 significantly impairs promoter activity, leading to a reduction in VEGF expression. This finding suggests that the cooperative binding of both STAT3 and HIF-1α to the VEGF promoter is essential for optimal transcription of VEGF mRNA in response to hypoxic conditions. The resultant upregulation of growth factors enhances the proliferation, migration, and proteoglycan synthesis in lung fibroblasts, thereby facilitating vascular remodeling.[83,84]

The Forkhead Box M1 Transcription Factor

The forkhead box M1 (FOXM1) transcription factor belongs to the FOX family of transcription factors, with the FOXM1 gene located on human chromosome 12p13.3, encoding a protein of 747 amino acids.[85] The FOXM1 transcription factor is recognized as a key regulator of cell cycle progression, promoting the G1/S and G2/M transitions, which in turn advances mitotic progression through its downstream targets. It is widely acknowledged for its role in promoting the

proliferation of cancer cell lines.[86] However, FOXM1 is also essential for normal pulmonary vascular development and plays an important role in the proliferation of PASMCs stimulated by hypoxia.[87]

Two additional members of the FOX family, FOXO1 and FOXO3, have been demonstrated to regulate FOXM1 transcription. In COPD patients, on the one hand, hypoxia and exposure to cigarette smoke promote oxidative stress, leading to an increase in the expression of miR-214 in PASMCs while simultaneously reducing the expression of PTEN.[88] Conversely, dysfunctional ECs secrete multiple factors, such as PDGF-B, CXCL12, ET-1, and MIF, which activate the PI3K/Akt pathway. This activation leads to the phosphorylation and subsequent nuclear exclusion of FOXOs, thereby diminishing their transcriptional inhibition of FOXM1 and resulting in the upregulation of FOXM1 expression.[89]

In addition to HIF-2α and FOXOs, the expression of FOXM1 in PASMCs is also regulated by miR-204 and the epigenetic reader bromodomain-containing protein 4 (BRD4). Hypoxia has been shown to reduce poly ADP ribose polymerase 1–dependent miR-204 expression in PASMCs, resulting in overexpression of BRD, ultimately leading to the pro-proliferative and anti-apoptotic phenotype in these cells. The specific molecular mechanisms underlying this process include: 1. Inhibition of the cell cycle regulator p21, thereby promoting cell proliferation; 2. Activation of the nuclear factor of activated T cells; 3. Upregulation of pulmonary hypertension-related oncogenes, such as B-cell lymphoma 2 (Bcl-2) and survivin; 4. Mitochondrial membrane hyperpolarization in PASMCs, leading to increased resistance to apoptosis and enhanced proliferation.[90] Furthermore, BRD4 can bind to the promoters of pro-inflammatory cytokines, such as IL-6 and TNF-α, thereby enhancing their expression in activated macrophages in chronic inflammatory diseases. This increased expression can lead to DNA damage in PASMCs, resulting in elevated expression and activation of PARP1. Consequently, this cascade further downregulates miR-204.[91,92] Thus, BRD4 may not only play a role in the onset of PH, but also in the sustainability of PH by maintaining this inflammatory state.

Additionally, the promotion of PASMCs proliferation through increased FOXM1 expression may be associated with several factors. First, FOXM1 has been demonstrated to directly enhance the expression of multiple genes involved in metabolic reprogramming, particularly in glycolysis and cell cycle progression. Key targets include GLUT1, HK2, Cyclin D1, and STAT3, all of which are linked to the progression of PH.[93–95] Secondly, studies indicate that FOXM1 could enhance the activity of Nuclear Factor Kappa-B (NF-κB) and β-catenin, two transcription factors that significantly influence various mechanisms of PH progression. These mechanisms encompass stress responses, cell proliferation, survival, and immune responses.[96,97] Additionally, it is associated with decreased TGF-β/ Smad3-dependent signaling, resulting in down-regulated expression of contractile proteins in PASMCs. This downregulation represents a de-differentiated phenotype in these cells.[98] Finally, FOXM1 enhances DNA repair capacity by stimulating the expression of DNA damage sensor protein Nijmegen breakage syndrome 1(NBS1), thereby promoting hyperproliferation of PASMCs and contributing to disease progression.[99] We summarized that hypoxia promotes vascular remodeling through FOXM1 pathway as shown in Figure 2. In patients with COPD, FOXM1 contributes to the development of PH through the aforementioned pathways. As an intracellular molecular marker, FOXM1 requires detection via tissue biopsy or enriched cell analysis, positioning it as a promising tool for disease screening.

Conclusion

Comorbid PH and CCP in patients with COPD are associated with dismal prognoses and heightened mortality, underscoring the urgent need for early detection, precise diagnosis, and timely intervention. This review synthesizes emerging evidence on promising biomarkers for COPD-PH/CCP, highlighting their roles in improving diagnostic accuracy and guiding therapeutic strategies. Hypoxia-driven crosstalk between endothelial cells and immune cells orchestrates the release of proinflammatory cytokines (such as IL-1, IL-6, IL-17), chemokines (such as CCL18, CX3CL1), and angiogenic growth factors (such as VEGF, FGF), which synergize with the neurohumoral marker NT-proBNP to form a quantifiable diagnostic network. These biomarkers exhibit significant upregulation in COPD-PH/CCP patients, with robust diagnostic performance characterized by high sensitivity and specificity. Their utility in non-invasive screening and risk stratification offers clinical advantages over traditional imaging, particularly in resource-limited settings. The transcription factor FOXM1, a key driver of vascular remodeling, represents a novel intracellular molecular marker. While current detection requires tissue biopsy or enriched cell analysis, future advancements in liquid biopsy technologies may enable peripheral blood-based FOXM1 quantification, overcoming current limitations in accessibility. Beyond conventional oxygen

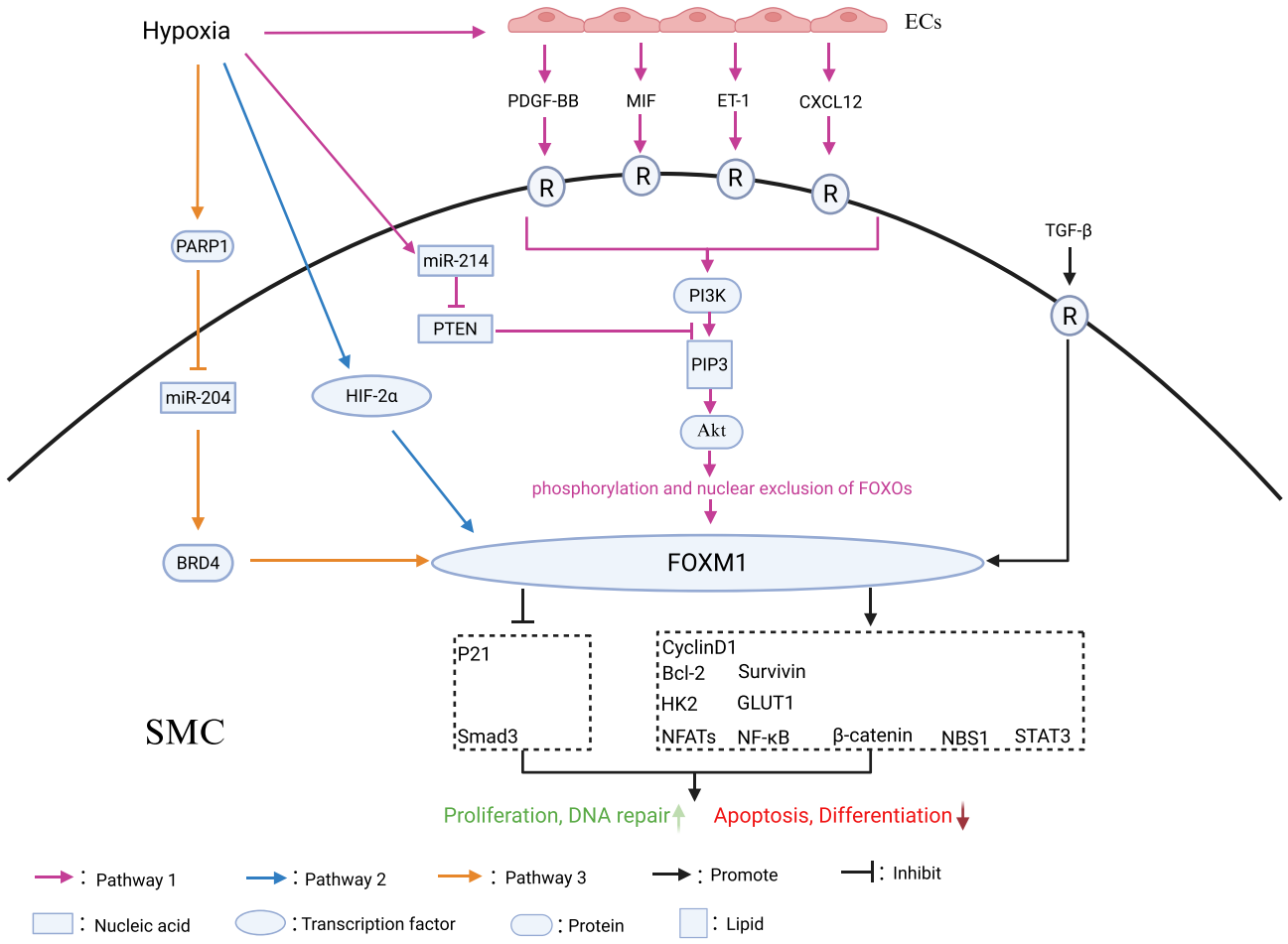

Figure 2 Hypoxia promotes vascular remodeling through the FOXM1 pathway.
Abbreviations: Akt, Protein Kinase B, PKB; Bcl-2, B-cell lymphoma-2; BRD4, Bromodomain-containing protein 4; CXCL12, Chemokine (C-X-C motif) ligand 12; ET-1, Endothelin-1; FOXM1, Forkhead box M1; GLUT1, Glucose Transporter 1; HIF-2α, Hypoxia-inducible factor 2α; HK2, Hexokinase 2; IL-6, Interleukin-6; MIF, Macrophage migration inhibitory factor; NBS1, Nijmegen breakage syndrome protein 1; NFATs, Nuclear factor of activated T cells; NF-kB, Nuclear factor-kappa B; PARP1, Poly (ADP-ribose) polymerase 1; PDGF-BB, Platelet-derived growth factor; PI3K, Phosphatidylinositol 3-kinase; PIP3, Phosphatidylinositol phosphate 3; PTEN, phosphatase and tensin homolog deleted on chromosome ten; P21, Cyclin-dependent kinase inhibitor 1A; STAT3, Signal and transducer of transcription 3; TGF-β, Transforming growth factor-β; TNF-α, Tumor necrosis factor-α.

therapy and supportive care, biomarker-guided precision therapies are emerging as transformative approaches. Targeting interleukin pathways or chemokine-receptor interactions may disrupt the vicious cycle of inflammation and vascular remodeling. FOXM1 related inhibitors are being explored in preclinical models to block smooth muscle cell proliferation and pulmonary artery thickening. Integrating circulating biomarkers (eg, NT-proBNP, VEGF) with tissue-based FOXM1 analysis could enable dynamic risk assessment and personalized treatment adjustment. Prospective studies are needed to validate these biomarkers in large, diverse cohorts and to define their roles in predicting treatment response. Additionally, translating targeted therapies from bench to bedside requires addressing drug specificity and systemic safety. By bridging biomarker discovery with mechanistic insights, this framework holds promise for achieving early detection, early intervention, and improved outcomes in COPD-PH/CCP, ultimately reducing morbidity and mortality in this vulnerable population.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

There are no conflicts of interest to declare.

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