Research progress in the etiology of pulmonary hypertension

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Abstract

Pulmonary hypertension (PH) is a progressive disorder affecting the pulmonary circulation, characterized by a grim prognosis that often culminates in right heart failure and mortality. Pulmonary vascular remodeling stands out as the predominant feature in the pathogenesis and pathological alterations of PH. Whereas, the pathogenic factors of PH are intricate, involving multiple interacting elements, and the mechanism behind pulmonary vascular remodeling remains not entirely comprehended. In this context, inflammation, chemokines, and gut microbiota may make a intricate and interrelated difference during the process of pulmonary vascular remodeling.

Keywords: pulmonary hypertension; inflammation; chemokines; INTESTINAL Microbiota

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Introduction

Pulmonary hypertension (PH) is a fatal pulmonary circulation disease with multiple causes, featured by progressive pulmonary vascular occlusive lesions in small and medium-sized arteries [1], resulting in incremental pulmonary vascular resistance and declining pulmonary arterial compliance, leading to right heart failure and death in the end [2]. In the first World Symposium on Pulmonary Hypertension in 1973, PH was defined as a mean pulmonary arterial pressure (mPAP) at rest of ≥ 25 mmHg, a definition that has been used ever since. However, data from normal subjects showed that the normal mPAP was 14.0 ± 3.3 mmHg, and two standard deviations above this mean indicated an upper limit of mPAP > 20 mmHg (above 97.5% of normal), so the 6th World Symposium on Pulmonary Hypertension in 2018 recommended that PH is recognized as mPAP > 20 mmHg, normal left atrial pressure, and pulmonary vascular resistance ≥ 3 Wood during right cardiac catheterization [3]. In 2022, the ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension adjusted the diagnostic criteria for hemodynamics to mPAP > 20 mmHg. PH is a multifactorial disease characterized by pathological growth of the vascular wall and functional impairment caused by imbalances in mediators that regulate vascular tone, ultimately leading to occlusive lesions. The median survival in PH is only 5–7 years, with an in-hospital mortality rate of 6% [4]. In addition to poor prognosis, limitations in exercise capacity also affect the quality of life and employment of PH patients. In the past 20 years, PH has transformed from a rapidly progressive fatal disease to a chronic illness with relatively high quality of life but still suboptimal prognosis, with a 5-year survival rate of 61.2% for new diagnosed cases [5].

Current Status of Drug Therapy for PH

Before the 1990s, there were no effective drugs for the treatment of PH at home or abroad, and calcium channel blockers and lung transplantation were the only treatment method for PH. With the progress of international research, targeted drugs have played an important role in the treatment of PH. Currently, targeted therapies for PH target three main pathogenic pathways, namely the prostacyclin pathway, nitric oxide pathway, and endothelin (ET) pathway. These drugs have been shown to improve symptoms, exercise tolerance, hemodynamics, or can prolong the time before clinical deterioration [6]. With in-depth research into the pathogenesis of PH, new targeted drugs for PH, such as prostacyclin receptor agonists, soluble guanylate cyclase activators, tyrosine kinase inhibitors, and Ras homologous (Rho) kinase inhibitors, have gradually become hotspots in the field of PH research. There are six main classes of drugs for specific treatment: (1) calcium channel blockers: nifedipine, diltilazem, amlodipine, and felodipine, (2) endothelin receptor antagonists: anira cetam, albesantan, bosentan, and macitentan, (3) prostacyclin analogs and prostacyclin receptor agonists: e.g., iloprost, iloprost, treprostatin, and beclomethasone, (4) prostacyclin receptor agonists, e.g., Streptozotocin and Seroquel, (5) PHOSPHODIESTERASES (PDE-5) inhibitors such as sildenafil, tadalafil, and vardenafin, (6) Soluble sGC agonists, such as leucovorin. These drugs are mainly used to reduce PH through vasodilatory and antiremodeling effects. Despite the significant progress made in the treatment of PH with these drugs, the 5-year morbidity and mortality rates are still high, with 5-year survival rates ranging from 20% to 60%. PDE-5 inhibition prevents the cGMP catalobism, and the sGC stimulator, leucovorin, stabilizes the nitric oxide(NO)-sGC binding, which results in the increase of the sGC's sensitivity to NO, and stimulates the cGMP cascade directly in the sGC, thus increasing the cGMP cascade. sGC, thereby increasing cGMP synthesis and decreasing PH. Given the tremendous advances in pharmacological development, targeting drug send to the lungs and pulmonary arteries is still a big challenge. Drug nanocrystals are favorable for accumulation in the lungs due to their spherical shape. A PTX (paclitaxel)-loaded nano-crystal particle (NPs) system was established as a carrier, enabling the co-delivery of PTX and caspase 3 targeting, which, through non-covalent interactions such as hydrogen bonding and π-π superposition, will Through non-covalent interactions such as hydrogen bonding and π-π stacking, the active protein caspase-3 was co-loaded onto metal-phenolic network encapsulated paclitaxel nanoparticles, and the co-delivery system was encapsulated with glucuronid acid to target glucose transporter-1, which is an essential component of pulmonary arterial smooth muscle cells (PASMCs) [7]. PTX can up-regulate FoxO1 expression and inhibit the proliferation of PASMCs, and works synergistically with caspase-3. PTX, a commonly used chemotherapeutic drug, can up-regulate FoxO1 and inhibit the proliferation of PASMCs. Metal-phenolic network can stabilize drug nanocrystals to prevent aggregation with low toxicity. The targeted co-delivery system can effectively promote apoptosis of PASMCs and inhibit pulmonary arterial remodeling, thus improving right ventricular function and hemodynamics. This has ushered in a new era in the treatment of PH.

Due to the complexity of the pathogenesis of PH, combination drug therapy in PH has significant potential, and the concept of first-line combination therapy is increasingly receiving attention. Based on extensive evidence gathered from numerous randomized controlled trials, the fifth World PH Symposium recommended the use of sequential combination therapy in PH patients who do not respond adequately to monotherapy, as well as the first use of first-line therapy in patients with advanced disease. Recently, many PH experts have used combinations of targeted drugs to treat patients [8]. The AMBITON study revealed that early combined treatment with tadalafil and ambrisantan reduces the primary endpoint of first clinical failure events (hospitalization due to worsening of PH, disease progression, death, or long-term clinical outcomes that are not satisfactory) by 50% compared to each monotherapy alone. In fact, with the extension of lifespan and the improvement of quality of life, the achievements in PH management are largely attributed to combination therapy, as most patients use more than one drug.

Research progress of PH etiology

The pathological features of PH are pulmonary vascular constriction, vascular wall remodeling, and in situ thrombus formation, leading to an increase in pulmonary vascular resistance. The mechanism of pulmonary vascular remodeling in PH is still not fully understood, and the pathogenic factors of PH are complex, with multiple factors coexisting and interacting to promote the occurrence and development of PH.

Inflammatory Pathways

Increasing evidence indicate that inflammatory cells play a complex role in the process of pulmonary vascular remodeling and functional impairment [9]. Around blood vessels, obvious perivascular inflammation is present in human PH and experimental animal models, which is related to pulmonary vascular remodeling. Inflammation involves a variety of cells and mediators such as macrophages, neutrophils, interleukin-6 (IL-6), and others, and the interaction with other mechanisms in the vascular wall promotes the development of the disease.

Previous studies have shown macrophage infiltration in PH [10]. Macrophages respond to polarized environmental signals and are divided into classical activation (M1), selective activation (M2), and anti-inflammatory (regulatory) macrophages. M1 macrophages exhibit cytotoxic and pro-inflammatory phenotypes, characterized by strong pathogen and tumor cell clearance capabilities. M2 macrophages are mainly activated by CCL2, IL-6 and IL-13, inhibiting immune and inflammatory responses, and participating in tissue remodeling and tumor progression by promoting nutrition, fibrosis, and angiogenesis. The concrete role and activation condition of macrophages in PH is not completely clear. However, the supernatant in culture medium of hypoxic M2 macrophages promotes the multiplication of PASMCs, indicating that these cells have a function in promoting the disease. The activation of macrophages is also
closely related to epigenetic changes, which mediate the interaction between macrophages/fibroblasts and promote the proliferation of fibroblasts in PH [11]. This interaction is actuated by metabolic shifts to oxidative stress, involving the activation of pro-inflammatory cytokines mediated by leukotriene B4 (LTB4) and histone deacetylase 1 Macrophage-colony stimulating factor signaling [12] and it has been proposed that the synergistic interaction between these pathways can regulate the gene expression of inflammatory macrophages [13]. Macrophage-derived LTB4 generate PASMCs hypertrophy and pulmonary artery endothelial cell damage. However, interference with LTB4 signaling has been shown to Revert experimental PH.

Utilizing information obtained from the three-dimensional structures of biomolecular targets and their corresponding ligand-target complexes is an effective approach in the molecular docking design of novel drugs for important diseases. It is also an ideal method for conducting large-scale database screening. Macrophage migration inhibitory factor (MIF) is a promising target of treatment in several inflammatory disorders involving PH. A novel series of N-(phenylmethyl)-benzoaxole-2'-thiones 5-32 has been synthesized and designed to target the MIF tautomerase active site [14]. By studying the structure-activity relationship, especially at position 5 of the benzoaxazole core, compound 31 was discovered. This compound exhibits potent inhibition of cell survival in pulmonary endothelial cells derived from patients with idiopathic pulmonary arterial hypertension. Molecular docking studies helped elucidate the initial structure-activity relationship associated with MIF mutant enzyme inhibition and identified the preferred binding mode of compound 31 within the MIF mutant enzyme active site. Interestingly, daily treatment with compound 31, starting two weeks after a subcutaneous monocrotaline injection, resulted in regression of established pulmonary hypertension in rats.

Neutrophils and neutrophil-derived mediators are involved in detrimental remodeling and vascular dysfunction in PH. Elevated levels of neutrophil elastase (NE) have been found in patients with idiopathic pulmonary arterial hypertension (IPAH) and in PASMCs of experimental PH models [15]. NE can influence the integrity of pulmonary arterioles by leaving bioactivator from the extracellular matrix. NE also activates complement system components, further promoting inflammatory responses. Myeloperoxidase (MPO) is an enzyme with fibrictic and effective vascularconstrictive properties that is highly expressed in neutrophils and has been revealed to aggravate to experimental PH [16], MPO deficiency protects Sugen/hypoxia-induced PH in rats, and intervention with MPO inhibitors also reduced PH in the rat model.

Among the inflammatory mediators associated with PH pathology, IL-6 is particularly important. IL-6 mediates its biological effects through two different pathways: the classical (or cis-signaling) pathway and the trans-signaling pathway. The classical IL-6 signaling pathway plays a crucial role in promoting anti-inflammatory activity during acute immune responses and is of significant importance. On the other hand, the trans-signaling pathway of IL-6 has pro-inflammatory activity [17]. A recent study showed that the IL-6 receptor (IL-6R) plays a key role in PASMCs and in inflammatory cells in vivo and in vitro [18]. Furthermore, IL-21 has been identified as a downstream target of IL-6 signaling that promotes hypoxia-induced PH by enhancing M2 macrophage polarization [19]. However, how IL-6 promotes the progression of PH is still not fully understood, and further research is needed on downstream signaling pathways of both classical and trans-signaling of IL-6.

The inflammatory process is closely related to changes in inflammatory cell metabolism in the vasculature. Michelakis et al. recently reported increased levels of pyruvate dehydrogenase kinase (mitochondrial pyruvate dehydrogenase inhibitors) in the pulmonary arteries of PH patients compared to healthy lungs [20]. Pioglitazone is a peroxisome proliferator-activated receptor gamma agonist that can back up serious PH by regulating metabolic, transcriptional, and changes undesirable epigenetic [21].

Anti-inflammatory drugs act on many aspects of the inflammatory response, inhibiting inflammation-induced PH and vascular remodeling. Quercetin, a flavonoid found in fruits and vegetables, has unique biological properties that may improve bodily functions and reduce the risk of infection. Flavonoids act as potent antioxidants and reduce the risk of chronic diseases. Quercetin increases the antioxidant response by enhancing the liveness of Nuclear factor-erythroid 2-related factor 2 and decreasing the levels of pro-inflammatory cytokines. Quercetin inhibits the inflammatory enzymes cyclooxygenase and lipoxygenase and reduces inflammatory mediators containing prostaglandins and leukotrienes. Quercetin inhibits signaling pathways associated with inflammatory processes, including phosphorylation of mitogen-activated protein kinases (MAPKs), α/β inhibitors of 1B kinase, c-Jun, cAMP response binding protein. P response binding protein can block the translocation of NF-κB phosphatase to the nucleus by blocking MAPK and NF-κB signaling pathway, and improve the inflammatory response.

Compound dasheen dropping pills (CDDP) is a combination of traditional Chinese medicine and modern medical technology. CDDP has antioxidant and anti-inflammatory properties in the cardiovascular system, and has been widely used in the prevention and treatment of acute myocardial ischemia (AMI) and other cardiovascular diseases for more than 25 years. CDDP improves the oxygen saturation of blood, and prevents or alleviates the symptoms and tissue damage caused by hypoxia of AMI. CDDP can improve blood oxygen saturation, prevent or alleviate AMI-associated symptoms and hypoxia-induced tissue damage. CDDP alleviates ROS enhanced by low-pressure hypoxia by improving Superoxide dismutase and glutathione Peroxidase-1, and inhibits pro-inflammatory cytokines and NF-κB expression. CDDP reduces hypoxia-induced D-dimer, erythrocyte aggregation, and blood rheology, and promotes the expression of aquaporin-1 and nuclear factor erythroid-2-related factor 2. Experiments have shown that CDDP can inhibit NF-κB expression, reduce the production of inflammatory factors such as TNF-α, IL-6, ICAM-1 and reduce the edema of inflamed tissues by promoting the expression of aquaporin-1 [22].

**Chemokines and their receptors**

In recent years, chemokines have received increasing attention, and research suggests that chemokines and their receptors have a significant impact on every step of the pulmonary vascular remodeling process in PH. CXCR4 and its unique ligand CXCL12 were initially found to mediate leukocyte migration to inflamed areas, and their interaction is crucial for the migration of progenitor cells during embryonic development of the central nervous systems, hematopoietic, and cardiovascular. Dai [23] et al. demonstrated that the absence of prolyl hydroxylase 2 structure in pulmonary artery endothelial cells (PAECs) can cause a significant increase in CXCL12 content, leading to PASMC proliferation and vascular plexiform lesions.

CCL2 is a chemokine for monocytes and also an activator of monocytes, promoting the release of reactive oxygen species and lysosomal enzymes and the production of IL-6. The CCL2/CCL2 pathway is involved in the pulmonary vascular remodeling and inflammatory reaction in the progress of PH.

Several other chemokines and their receptors have been shown to be associated with PH, including CXCL13, CCL20, CCL7, CCR5, CCL21, CXCL4, and CCR7 [24]. The expression of several chemokine receptors, such as CCR9, CCR6, and CCR7, is decreased instead of increased during the development of PH, indicating the possible existence of negative feedback mechanisms to limit excessive activation or prolong signaling of chemokine receptors [25]. In summary, inflammatory/immune responses exist in the early stages of PH. Dysregulation of chemokine and anti-inflammatory cytokines signaling may be involved in the occurrence and development of PH, providing new insights into the pathogenesis of PH.

Chemokines and their receptors are involved in inflammatory infiltration and pulmonary vascular remodeling during the development of PH, and many studies have made some progress in treating PH by using them as specific targets. For example, Amsell
et al. [26] investigated the effects of CCR5 receptor antagonists on PASMC and inflammatory response in a mouse model of PH and found that activation of the CCL5/CCR5 pathway directly led to PASMC proliferation and macrophage recruitment, a process that was significantly inhibited by CCR5 receptor antagonists. The results suggest that the CCL5/CCR5 pathway may serve as a therapeutic target for PAH caused by human immunodeficiency virus or other factors.

Hypoxia evaluated the effect of CCR4 on ET-1 function of human PAECs and demonstrated that activation of CCRX4 by its endogenous agonist constitutes a protective mechanism that attenuates endothelial barrier damage caused by thrombin under disease conditions and that this protection is enhanced by treatment with an exogenous CCRX4 agonist. Treatment with exogenous CCRX4 agonists enhances this protective response, further demonstrating that CCRX4 can serve as a therapeutic target. In PAH mice, Bordeneve et al. found that the CXCL12 neutralizer LIT-927 blocked the binding of CXCL12 to CCRX4 and CCRX7, and that treatment with LIT-927 was more effective than the CCRX4 receptor antagonist AMD3100 in reducing pulmonary blood pressure and pulmonary vascular remodeling. In conclusion, more and more chemokines and their receptors have been shown to play a role in PAH, and their control at the molecular level may become a trend for the prevention and treatment of PH in the future.

Oxygen sensing, ET and reactive oxygen species
Specialized organs are adapted to perceive small changes in airway oxygen levels and arterial oxygen, and these tissues form the homeostatic oxygen-sensing system (HOSS). The HOSS responds to changes in environmental oxygen levels by altering respiration, vascular tone, and neurosecretion. Hypoxia stimulation can cause mitochondria to produce ROS, which is an key factors in promoting pulmonary vascular remodeling. ROS activate prolyl hydroxylase and induce the excitation of hypoxia-inducible factor 1 (HIF-1), an essential step for triggering vascular remodeling and pulmonary arterial stenosis. Furthermore, these ROS are transformed to the conductive signaling molecule hydrogen peroxide (H2O2) by the enzyme (SOD2). H2O2 then move away from the mitochondria and regulates ion channels and enzymes, leading to changes in cellular membrane potential, intracellular Ca2+ levels, and Ca2+ sensitivity. This ultimately controls acute and adaptive responses to hypoxia, including changes in neurotransmitter release, vascular tone, and ventilation. Disruption of this oxygen-sensing pathway promotes disease progression in PH. Mitochondrial oxygen sensing provides new therapeutic targets for the treatment of PH. It is a promising experimental therapeutic strategy for PH that recovering mitochondrial calcium regulation [27].

Lee et al. studied the results of ambisentan treatment in a rat model of PH induced by monocrotaline. The authors reported that ambisentan treatment led to weight and right ventricular hypertrophy recovery, reduced right ventricular pressure, and restored the protein expression levels of ET-1 and enrin oxide synthase, thus demonstrating the interaction between endothelin and ROS in causing PAH and vice versa. However, unexpectedly, the expression level of NOX4 was not affected [28], possibly due to the limitations of the study such as the fixed (low) dose of ambisentan, insufficient treatment time, and limited number of animals used in the study. Therefore, further research is needed to elucidate the relationship between endothelin and NOX4 and demonstrate the interactions between different cells in the lung tissue of PH. A better understanding of the complex interactions between different vascular cell types in PH may help identify new therapeutic targets and reduce the future incidence and mortality associated with PH [29].

Research finding that lixiobacil normalized the expression of serotonin-related genes and renal injury markers immonocrotaline-induced experimental PAH rats. However, Xu et al. [30] using a low-pressure chlorpyrifos-induced rat model found that the therapeutic effect of riocloiril was minimal, suggesting that riocloiril may not be as effective as drugs such as macitentan and Selexipag in the treatment of hypoxic injury-induced PH, although the exact reason for this has not yet been elucidated. In addition, a study on the combination of the PDE5 inhibitor Lodenalf and human umbilical cord mesenchymal stem cells in a SuHx-induced rat model reversed Right Ventricular Hypertrophy and mesenchymal cell infiltration in the SuHx-induced rat model, which is considered a potential therapeutic strategy for PH [31]. Endothelin is a potent vasoconstructor and smooth muscle mitogen, acting through ET A and ET B receptors. ET-1 plays a key role in the regulation of pulmonary vascular tone. Endothelin receptor antagonists (e.g., bosentan) are used in the treatment of PH. Bosentan and macitentan are dual endothelial receptor antagonists that block ET A and ET B receptors and downstream signaling pathway activation. Bosentan only reduces resting pulmonary arterial pressure and is not effective in active PAP. Bosentan has not been widely used in PH, and a study that included highland residents with PH showed that endothelin levels were higher in PH and that treatment with bosentan reduced pulmonary artery systolic pressure more than oxygen. Bosentan restores the activity of pulmonary vascular endothelial cells (ECs) and NOS, promotes NO synthesis, resists hypoxia-induced pulmonary vasoconstriction, dilates the pulmonary arteries, lowers pulmonary arterial pressure, reduces fluid infiltration into the alveoli, blocks lipid peroxidation of ECs, and reduces inflammation, slowing the development of PH [32].

Intestinal microbiota and immune disorders
The human intestine contains trillions of microorganisms, collectively known as the “intestinal microbiota”, including various fungi, bacteria, parasites, and viruses. The intestinal microbiota can prevent pathogen colonization, enhance intestinal immune function, aid in digestion, and the host provides them with a favorable living environment [33]. Exercise, diet, genetic factors and medications determine its function and composition of the individual gut microbiota [34]. Gut dysbiosis are mean any damage of the natural balance between the host and the gut microbiota, which is associated with the immunopathogenesis of various diseases [35]. The typical characteristics of intestinal dysbiosis are the decrease in the richness and diversity of microbial communities, the decrease of acetic acid and butyric acid producing bacteria, the increase of lactic acid producing bacteria and bacteria, and the increase of the ratio of Firmicutes to bacteroidetes (F/B) [36]. This increases intestinal permeability, which in turn causes bacterial translocation and the release of endotoxins into the internal circulation.

Some research results in preclinical models and patients with PH suggest that gut and circulating microbiota dysbiosis may be involved in the development of PH [37]. Firstly, gut dysbiosis was observed in experimental PH: rats exposed to Sugen and low oxygen for 2 weeks showed gut dysbiosis and changes in serum metabolites [38]. From a time perspective, changes in gut microbiota may have a pathogenic effect in the early mechanism of PH pathogenesis. Secondly, Intestinal dysbiosis give rise to enhance intestinal permeability and secondary translocation of intestinal bacteria and/or bacterial products (such as endotoxins). Elevated levels of serum endotoxins were detected in experimental models of pulmonary vascular disease [39]. The endotoxin is first released from the gut into the portal vein and later into the pulmonary circulation, activating macrophages in the blood vessels. Endotoxins interact with TLR4 receptors on macrophages and activate the NF-kB signaling pathway, contributing to incremental cytokines . Gut bacterial translocation, serum endotoxemia, and macrophage activation also occur in human PH. Compared with healthy controls, patients with idiopathic or hereditary PH have increased levels of serum endotoxins and soluble CD14, and both are parallel to increased TLR4 expression [40]. In addition, patients with Abernethy malformation usually have pulmonary vascular disease [41], but there is no hemodynamic change from left-to-right shunting, which cannot explain the development of pulmonary hypertension. The possible mechanism is that symbiotic bacteria and toxins in the intestine bypass the liver through the portal system, avoiding their absorption and deactivation by the liver, entering the pulmonary circulation through the right heart, activating macrophages in the lungs, and causing pulmonary arteriovenous malformations, capillary

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dilation, and distal pulmonary arterial proliferative arteriopathy. Similarly, Wedgewood et al. also suggested that gut dysbiosis may affect remote organs including the lungs and promote the development of PH [42]. In this study, gut dysbiosis occurred in PH rats induced by postnatal growth restriction, and probiotic treatment reduced PH. Considering these results, the authors believe that changes in gut microbiota may be a partial cause of PH. Thenappan et al. also suggested that gut dysbiosis may be related to vascular inflammation in the early development of PH [43].

The mechanism that the imbalance of gut ecology and circulating microbiota leads to PH may be: 1. Increased gut permeability allows microorganisms to translocate within the gut and increases the levels of microbiota or microbiota products in circulation. 2. Changes in microbial community structure produce pro-inflammatory metabolic groups (decreased anti-inflammatory metabolites or increased pro-inflammatory metabolites). Liver detoxification and filtration function are lost, either secondary to portal shunt or cirrhosis can lead to the progression of PH. Similarly, an increased genetic susceptibility, such as BMPR2 mutation, can enhance sensitivity to pro-inflammatory signals, leading to the development of PH.

Therefore, regulating intestinal microbiota may be a potential therapeutic target for treating PH. Antibiotics, diet, prebiotics, and intestinal microbiota transplantation (IMT) can regulate the composition of gut microbiota. IMT can be said to be the most effective method of changing the patient's gut microbiota, and has been clinically used in the treatment of refractory Clostridium difficile infection.

However, although intestinal dysbiosis has been linked to the early pathogenesis of PH, several key issues need to be addressed before regulating intestinal microbiota as a treatment option for PH. Firstly, intestinal dysbiosis has not been studied in human PH patients. Secondly, rigorous experimental studies are needed to determine the causes of intestinal dysbiosis and the role of changes in circulating flora in the pathogenesis of PH. Various methods, such as regulating the composition of intestinal microbiota through antibiotic treatment, changing the diet to increase the production of short-chain fatty acids (such as acetate or butyrate), or using germ-free mice with intestinal microbiota transplanted from PH experimental models or human PH patients, can be used to demonstrate the causal relationship between intestinal dysbiosis and PH. Thirdly, future research should determine whether the increase in circulating microbiota and/or endotoxins in PH is secondary to intestinal dysbiosis, secondary to right heart failure, or both. Addressing these issues will help develop potential intervention strategies that target the microbiota of PH patients.

Probiotics help to improve the intestinal environment, balance the immune response and regulate metabolic activities. Probiotics such as Lactobacillus and Bifidobacterium can inhibit the growth of harmful bacteria, regulate the homeostasis of intestinal flora, and improve the intestinal flora dysbiosis. Probiotics were found to reduce the synthesis of trimethylamine/trimethylamine N-oxide in intestinal flora and improve intestinal flora dysbiosis to further prevent and treat PH. Fecal microbiota transplantation is an effective way to prevent and treat PH. Fecal microbiota transplantation has been widely proved to be a targeted method to restore microbial homeostasis. For the first time, it was demonstrated that overexpression of ACE2 prevented gut dysbiosis in a PH model, and that transplantation of feces from mice overexpressing ACE2 stabilized the gut flora and alleviated hypoxia-induced right ventricular systolic pressure and right ventricular hypotrophy in wild-type mice. Fecal microbiota transplantation can alleviate PH by re-establishing normal intestinal flora through transplantation of beneficial bacteria [44].

Conclusion

Pulmonary vascular remodeling is the most critical pathological change in PH. Secondary pulmonary vascular and right ventricular changes can ultimately lead to right heart failure and even death. The pathogenic mechanisms of pulmonary arterial remodeling in PAH are not fully understood and involve multiple factors, including immune-inflammatory responses, hypoxia, dysbiosis of the gut microbiota, as well as various vasoactive molecules and signaling pathways. Intestinal dysbiosis causes pulmonary vascular remodeling and pulmonary hypertension by disrupting the intestinal mucosal barrier, triggering immune responses and perivascular inflammation. Improving intestinal dysbiosis is important for the prevention and treatment of PH. Diet, probiotics, and fecal microbiota transplantation are potential complementary therapeutic approaches. The existing targeted drugs primarily focus on addressing endothelial dysfunction in pulmonary vasculature and are unable to reverse pulmonary vascular remodeling or alter the progression of the disease. Immune-inflammatory responses, oxygen sensing systems, and gut microbiota have the potential to become new directions for the future treatment of PH.

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