Targeting Molecular and Cellular Mechanisms in Pulmonary Hypertension

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Abstract

Pulmonary hypertension (PH) is described as an elevated mean pulmonary artery pressure (mPAP) of 25 mmHg or above, measured at rest by right-heart catheterization. The precise worldwide occurrence of PH is not easily measured, majorly as a result of its complex etiology, and its progression is likely to be underestimated. Extensive reports on the pathophysiology of PH and incidence etiology at the cellular and molecular level have been well documented. In addition, basic clinical research studies have shown promising potentials of popular and widely known cardiovascular biomarkers, but with limited clinical significance in the management and diagnosis of PH as a result of decreased specificity as well as several other cardiovascular complications of patients with PH. Conversely, a large panel of experimental research studies reveal novel cellular and molecular mechanisms, drug targets, and biomarkers following the principle of the evidence-based medicine. Unfortunately, the basic extrapolation of these finding results to clinical practice is not straightforward because of large complex nature of the pathophysiology of PH. Hence, there is the need for more translational medicine research to fully comprehend the pathophysiological

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classification of PH and define accurately its biomarkers and therapeutic approach for PH treatment. We discuss in this chapter the types of PH, the novel therapeutic options available, and the molecular mechanism behind PH and its possible drug targets for treatments at the cellular and molecular level. Several factors like oxidative stress, cell signaling, inflammation, and mechanisms of immune systems are highlighted that may be responsible for the pathophysiology of PH and its complications. Each of these processes is discussed separately, for clarity purpose, but most importantly, crucial cross functions will occur among the pathways in PH patients.

Keywords

Pulmonary hypertension · Mean pulmonary artery pressure · Cardiovascular disease · Pathophysiology · Lung disease

17.1 Introduction

Hypertension (HP) is a global health burden because of its rising observed cases and its increased risk factor for cardiovascular diseases (CVDs). HP occurs when there is persistent elevation of artery's blood pressure, thus bringing about damages of organs and an increase in the world mortality rate [1]. When there is a rise in cardiac output and systemic vascular resistance, it results in blood pressure. Blood pressure has been found to elevate the risk of cardiovascular disease globally. Blood pressure is reported as two numbers which are obtained from the diastolic and systolic pressure [2]. The highest pressure in the arteries when the heart beats and fills the arteries is termed the systolic pressure, while the least pressure in the arteries when the heart rests between beats is termed the diastolic pressure.

During aging process, there is stiffness of blood vessels; this prevents the free movement of blood from the heart, thus bringing about an increase in systolic pressure as aging occurs. "In most cases, increased cardiac output occurs in younger age while in adults, systemic vascular resistance is observed; this may be a result of elevated α-adrenoreceptor stimulation; it could be that peptides like angiotensin are constantly released. Elevated increase of calcium in the cytosolic medium of vascular smooth muscle results in vasoconstriction. Other factors such as growth factors can also increase vascular smooth muscle, thus causing vasoconstriction, stiffening of the aorta and arteries which results in pulse pressure increase" [3]. It has been established that CVD is one of the major causes of global deaths; thus, the treatment and management of several CVDs have been put into consideration to reduce mortality rate worldwide.

Hypertension has been considered to be one of these CVDs and it occurs when there is a persistent elevation in the blood pressure of arteries. "Hypertension contributes majorly to increased risks for coronary heart disease, stroke, and several other heart-related diseases. It has been confirmed to be one of the major contributors to global deaths. In recent times, lots of studies and researches were carried out to

combat the occurrence of hypertension worldwide. Hypertension was classified into primary hypertension which occurs as a result of genetic factors or nonspecific lifestyles such as excess salt in diet, excess body weight, physical inability, smoking, and secondary hypertension described as persistent diseased state such as chronic kidney disease. Treating of hypertension has been linked to a significant reduction in the occurrence of certain disease conditions, namely heart diseases, stroke, myocardial infarction, and other cardiovascular related diseases [2]. The autonomic nervous system is well documented to play a crucial function in the regulation of blood pressure as patients with hypertension have elevated peripheral sensitivity to certain hormones like norepinephrine; in addition, increased responsiveness to stressful stimuli is also observed in hypertensive patients" [2, 3].

17.2 Consequences and Complications of Hypertension

There is no gauge for complications to arise, as an increase in blood pressure is linked with increased morbidity across the whole blood pressure ranges of measurement. "Persistent increase in blood pressure brings about increase in muscle mass, thickening of the artery wall resulting in left ventricular hypertrophy (a condition that impairs diastolic function and slows ventricular relaxation) which is a separate risk factor for CVDs. Arterial hypertension is one of the major factors that increase the occurrence of coronary artery disease. It has been established that poorly controlled or untreated hypertensive patients are prone to having myocardial ischemia and myocardial infarction as a result of pressure-related increased demand for oxygen or a coronary oxygen supply depletion. Other complications of hypertension are heart failure, stroke, etc. which could be from intracranial hemorrhage or thrombosis" [2].

17.2.1 Treatment of Hypertension

Hypertension has greatly increased the world's mortality rate; therefore, there is a quick response to the search for its treatment and management. The first line of treatment and management of HP is modification in the way of living, which includes restriction in sodium intake, weight reduction, decreased alcohol intake, and frequent exercises. "The use of drug therapy has also been introduced in the treatment and management of hypertension. The mechanism of action of most hypertensive drugs differs from each other but every antihypertensive drug acts majorly by reducing the cardiac output, resistance of vascular tissues, or both. Some of the most common class of antihypertensive drugs include β-blockers, inhibitors of angiotensin-converting enzyme (ACE), thiazide diuretics, antagonists of the angiotensin II receptors, blockers (calcium channel, α-adrenoceptor, combined α- and β-blockers), etc." [3, 4].

17.3 Pulmonary Hypertension (PH)

PH occurs when the resting mean pulmonary artery pressure is 25 mmHg or above at the resting stage [1]. "It could occur due to pulmonary vascular disease, left-heart disease, lung disease or hypoxia, chronic thromboembolic disease, and a variety of disorders, including hemolytic anemias and sarcoidosis. Globally, it is estimated that over 100 million people have been affected. Currently, there exists no curative treatment for PH despite advancement in the study of the disease pathology but there are improved diagnostic markers and therapeutic approaches for patients. Patients with PH tend to show the following pathogenic features: prolonged pulmonary vasoconstriction, remodeled small pulmonary artery vasculature, in situ thrombosis, and elevated stiffness of the vascular wall, leading to increased pulmonary arterial pressure (Fig. 17.1) [1, 2]. One major feature of PH is an increased resistance of the vascular walls resulting in progressive elevations in pulmonary artery pressure [1]. Clinically, these pulmonary vascular changes come with some symptoms, such as syncope, chest pain, unexplained dyspnea on exertion, and fatigue.

17.3.1 Pulmonary Arterial Hypertension (PAH)

Pulmonary arterial hypertension (PAH) is a primary subdivision of PH which has a prominent characteristic of a gradual increase in resistance from the pulmonary vascular tissues due to unregulated remodeling of pulmonary vasculature, prolonged vasoconstriction, and in situ thrombosis (Fig. 17.2) [3]. The advancement in extensive clinical classification of PH, diagnostic indices, and novel therapeutic approach produced improved survival rate in PH in the past years [4].

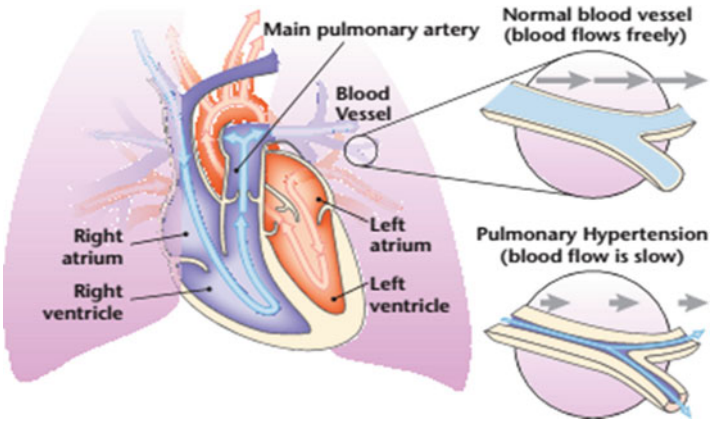

Fig. 17.1 The flow of blood in pulmonary hypertension [2]

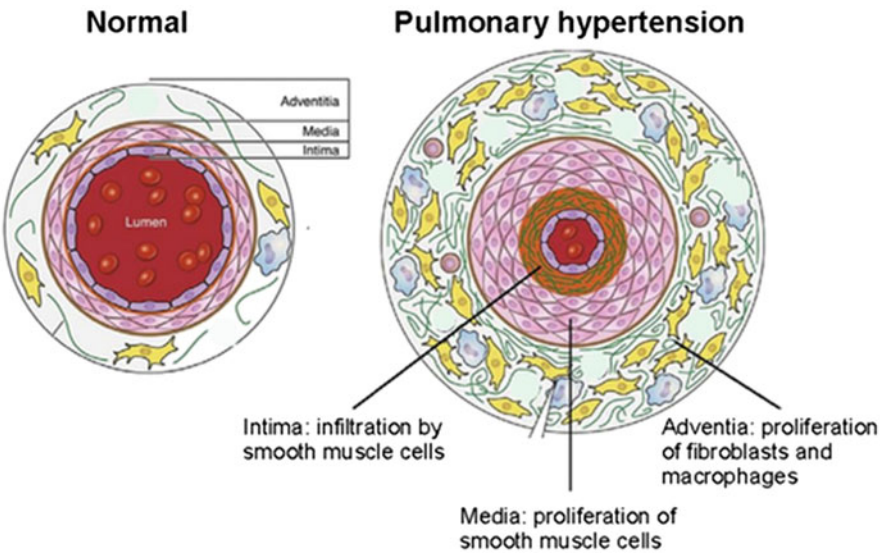

Fig. 17.2 Vascular framework in pulmonary hypertension. Cross-sectional diagram of a normal pulmonary arteriole and a pulmonary arteriole in pulmonary hypertension

17.3.2 Clinical Classification of Pulmonary Hypertension

PH was subdivided into groups based on the report of World Health Organization (WHO) that anorexigen is capable of inducing PAH. PH was then classified into five groups (Fig. 17.3).

17.3.2.1 Group 1: Pulmonary Arterial Hypertension (PAH)

This occurs when arteries in the lungs become narrowed, thickened off, or stiff. The right side of the heart must work harder to push blood through these narrowed arteries [4]. The major feature of PH in this category is a persistent rise in pulmonary vascular resistance (PVR) and mean pulmonary artery pressure (mPAP) due to an obstruction within the pulmonary vasculature [5]. The identified causes of PAH include idiopathic, heritable such as human immunodeficiency virus (HIV) infection, bone morphogenetic protein receptor 2 (BMPR2), toxin- and drug-induced and associated disorders, portal hypertension, and congenital heart diseases. Many mutations in the gene like BMPR2 predispose people to the incidence of PAH [3].

17.3.2.2 Group 2: PH Due to Left-Heart Disease (PH-LHD)

The PH in this category is a result of left-heart diseases. It is defined as mPAP $\geq$25 mmHg and pulmonary artery wedge pressure (PAWP) >15 mmHg. The prominent characteristics of this class of PH are a rise in mPAP, declining pulmonary vascular remodeling, failure of the right ventricle, and death [6]."

Fig. 17.3 Classification of pulmonary hypertension

17.3.2.3 Group 3: PH Due to Lung Diseases and/or Hypoxia

Group 3 class of PH is linked with hidden conditions like developmental lung abnormalities, interstitial lung diseases (ILD), chronic obstructive pulmonary disease (COPD), obstructive sleep apnea (OSA), and other pulmonary diseases [7]. Hypoxic vasoconstriction and extermination of the pulmonary vascular bed are the two main pathophysiologic bottom-line features of PH ascribed with hypoxia and COPD [6]. It has been documented that hypoxia is a major player in the incidence of endothelial cell damage, molecule release like endothelin giving birth to spasm reactions, and proliferation in the neighboring smooth muscle cells [3, 7]. The major therapeutic strategy to the management of group 3 PH is addressing the hidden disease process.

17.3.2.4 Group 4: Chronic Thromboembolic PH (CTEPH)

PH occurs as a result of chronic thromboembolic disease, giving birth to protracted occlusion of the pulmonary vasculature, thus resulting in abnormal mechanisms of

fibrinolysis and autoimmune disorders. This condition greatly contributes to poor resolution of thrombi [5].

17.3.2.5 Group 5: PH with Unclear Multifactorial Mechanisms

PH with unclear many-sided mechanisms is classified as group 5 PH. It is sometimes called the orphan disease. Group 5 PH is a significant diversified group of diseases that comprises PH secondary to multifaceted mechanisms. In this diseased state, the precise incidence, etiology, and therapy remain unclear.

17.4 Pathophysiology of Pulmonary Hypertension

The classification of PH into groups has enhanced the gradual understanding of its mechanism of action; most especially, the pathophysiological mechanism of group 1 PAH has been greatly understood leading to diverse discoveries of potential drug targets; however, groups 2, 3, 4, and 5 have not been fully understood. However, there is a dearth of information on the mechanism behind the other groups of PH [2]. Moreover, they share some common denominators in their mechanism of action among all groups of PH [8]. The foundational mechanisms of increases in PVR in PAH include prolonged vasoconstriction, uncontrolled pulmonary vascular remodeling, and in situ thrombosis. The incidence and progression of PAH involve multiple factors and a plethora of several cell types inside the pulmonary artery vessel wall like primary pulmonary artery smooth muscle cells (PASMC), pulmonary artery endothelial cells (PAECs), fibroblasts, inflammatory cells, and platelets that are contributory factors in the disease process (Fig. 17.4).

17.4.1 Genetics and Genomics of PAH

17.4.1.1 Transcript Mapping and Positional Cloning of the Gene Underlying PAH

Genes with similar biological properties with PAH are characterized by direct Sanger sequencing; this leads to the recognition of the gene bone morphogenetic receptor type II (BMPR2) [10]. "BMPR2 is an approximately large gene, comprising 13 coding exons displaying over 190 kb of genomic DNA. At the transcriptional level, its start site is at base pair position 1148 very close to the initiation codon adenine. It has a remarkably long 3'UTR of an estimated size of 11 kb [9]. BMPR2 encodes the transmembrane bone morphogenetic receptor type II of the TGF-β superfamily of signaling molecules [10]. TGF-β molecules perform important functions in cellular activities such as migration, differentiation, proliferation, and apoptosis." (Fig. 17.5).

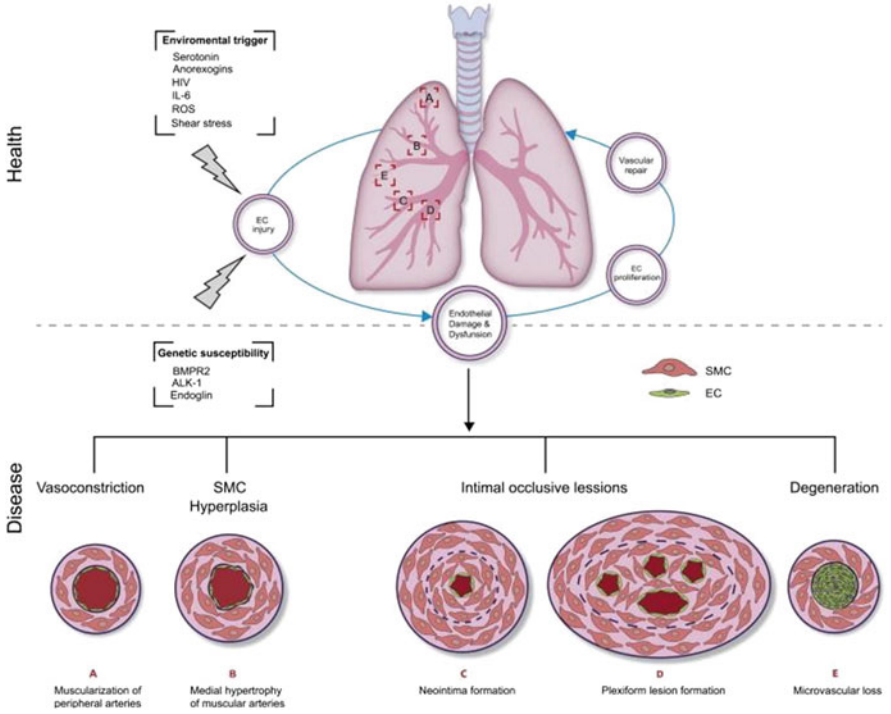

Fig. 17.4 Pathophysiological mechanisms of PAH

17.4.2 Role of Inflammation in PH

Inflammatory mechanisms appear to perform a crucial function in some types of PH including cases of rats induced with monocrotaline and PAH of several sources in humans. This inflammation has also been implicated in connective tissue diseases and human immunodeficiency virus infection. "Remarkably, some patients with serious PAH linked with systemic lupus erythematosus got better with immunosuppressive therapy, highlighting the importance of inflammation in this subset of patients [11]. Some immunological disturbances have been observed with idiopathic PAH patients which further supports the assertion that inflammation is implicated in the incidence and development of this disease. Undoubtedly, a cross section of PAH patients have circling autoantibodies which include antinuclear antibodies, together with increased rotating levels of proinflammatory cytokines IL-1 and IL-6. Histopathology of the lungs also shows inflammatory infiltrates (macrophages and lymphocytes) in the spectrum of plexiform lesions in severe PAH together with an elevated expression of chemokines RANTES and fractalkine" [12].

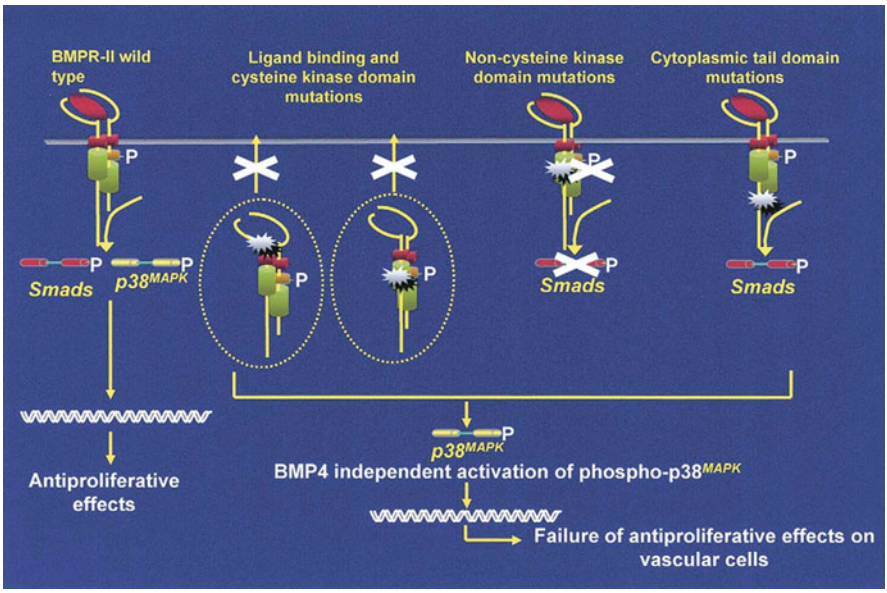

Fig. 17.5 Consequences of bone morphogenetic protein type II (BMPR2) receptor mutations on signaling [10]

17.4.3 Caveolin-1 Mutation in PH

Caveolin-1 is usually the point where many signaling cascades begin due to their interaction with G proteins, TGF-β-receptor 1, endothelial nitric oxide synthase (eNOS), and nitric oxide synthase 2A [13]. Caveolin-1 is a scaffolding protein and a major component of caveolae that connects with many signaling molecules including the ones implicated in PH and it is involved in their modulation [14]. The interruption and ongoing loss of endothelial caveolin-1 with reciprocal activation of proliferative pathways occur prior to the inception of PH, and the recapture of caveolin-1 impedes proliferative pathways and mitigates PH [15]. A comprehensive loss to the endothelial cells happens during the development of PH with resultant enhancement of caveolin-1 expression in the smooth muscle cells. In the smooth muscle cells, caveolin-1 moves from having an antiproliferative role to a proproliferative one and engages in cell proliferation and cell movement, probably going towards an irreversible process of PH [13, 15]. However, the interruption of endothelial caveolin-1 is not noticed in the reversible form of PH known as hypoxia. In contrast, proliferative pathways are activated in this model, suggesting a dysfunction in caveolin-1 function. Hence a dysfunction or disruption of endothelial caveolin-1 promotes PH, and the status of caveolin-1 may determine whether PH is reversible or irreversible [15, 16].

17.5 Metabolism Alterations in Pulmonary Hypertension

17.5.1 Energetic Metabolism in PH

Warburg effect, a phenomenon involving the substitution of energy acquisition in the Krebs cycle with glycolysis, is a characteristic of cancer cells and cells in PH patients (Fig. 17.6). Pyruvate, a key product of glycolysis in aerobic conditions, is metabolized into acetyl-CoA by the enzyme pyruvate dehydrogenase (PDH) which then enters into the tricarboxylic acid cycle (TCA cycle). The reduction in PDH activity as well as the conversion of pyruvate to lactate by the enzyme lactate dehydrogenase A (LDHA) in PAH PAECs has been proved and reported [17]. Increased fatty acid metabolism is the second metabolic deviation observed in PAH cells [17]. The third metabolic change is the glutaminolysis [18, 19]. The

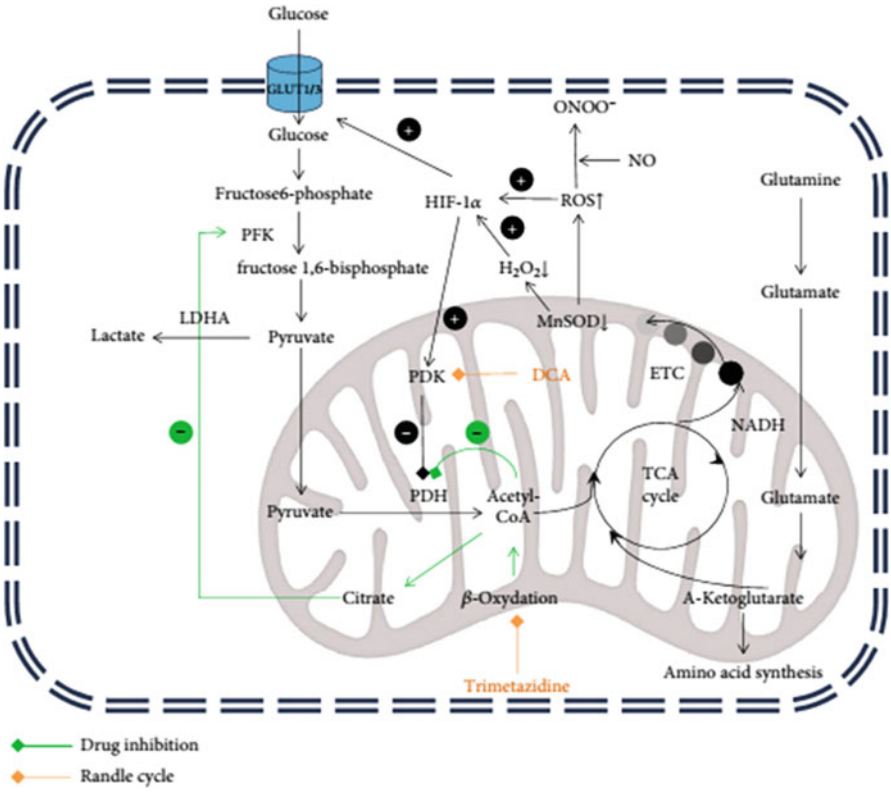

Fig. 17.6 Metabolism alteration in pulmonary hypertension [20]. *DCA* dichloroacetate, *ETC* electron transport chain, *HIF-1α* hypoxia inducible factor, *LDHA* lactate dehydrogenase A, *MnSOD* mitochondrial superoxide dismutase, *PDH* pyruvate dehydrogenase, *PFK-6* 6-phosphofructo-1-kinase, *ROS* reactive oxygen species, *TCA cycle* tricarboxylic acid cycle. Orange arrow: drug inhibition; green arrow: Randle cycle

additional significant changes relate to mitochondrial dysfunction. The function of mitochondria includes generation of ATP; they also act as oxygen sensors [20, 21].

17.6 Conclusion

To date, basic clinical research studies have shown promising potentials of popular and widely known cardiovascular biomarkers, but with limited clinical significance in the management and diagnosis of PH resulting from their decreased precision as well as several other cardiovascular complications of patients with PH [22, 23]. Conversely, a large panel of experimental research studies reveal novel cellular and molecular mechanisms, drug targets, and biomarkers following the principle of the proof-based medicine. Regrettably, the plain extrapolation of these findings to clinical application is not straightforward because of large complex nature of the pathophysiology of PH. Hence, there is the need for more translational medicine research to better understand the pathophysiological classification of PH and define accurately its biomarkers and therapeutic strategy for PH treatment.

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