The Pathobiology of Pulmonary Arterial Hypertension

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KEYWORDS

• Pulmonary arterial hypertension • Endothelial cell • Smooth muscle cell • Fibroblast • Inflammation

KEY POINTS

- Pulmonary arterial hypertension is a disease of the pulmonary arterioles, characterized by abnormal remodeling and obstruction.
- Pulmonary arterial hypertension leads to increased resistance in the pulmonary vessels and right ventricular afterload, eventually resulting in right heart failure.
- Over the past decades, a number of important pathobiological mechanisms have been found to contribute to pulmonary arterial hypertension.
- These changes are in endothelial function, smooth muscle cell proliferation, fibroblast activation, inflammation, and metabolism.
- A number of molecular mechanisms underlie these pathophysiological changes, including alterations in type II bone morphogenetic protein receptor and transforming growth factor-β signaling, changes in vasoactive mediators, chemokine and cytokine signaling, ion channel activity, transcription factors, and microRNAs and other epigenetic changes.

THE PATHOLOGY OF PULMONARY ARTERIAL HYPERTENSION

Human Pathology

Pulmonary arterial hypertension (PAH) is characterized by lesions in the distal arterioles, ranging from 50 to 500 μm in size.[1,2] Grossly, this results in a decrease in distal perfusion and the classic "pruning" of the distal pulmonary vasculature observed on a chest radiograph or pulmonary angiography.[3] This in turn results in increased right ventricular (RV) afterload and right heart failure. The histopathologic findings of PAH include medial hypertrophy or hyperplasia, intimal and adventitial fibrosis, and plexiform lesions, the pathognomonic lesions for PAH.[1,2] Recent detailed histologic analyses have demonstrated that plexiform lesions are complex lesions that arise from arteriolar obstruction followed by collateralization of the vasa vasorum and bronchial arteries.[4,5] Thus, these lesions represent a compensatory mechanism to maintain distal perfusion through the pulmonary arterial system. In additional to pulmonary arterioles, remodeling of the pulmonary capillaries and venules is also observed in all PH groups.[6] Beyond the pulmonary vasculature, systemic vascular abnormalities in PAH support the emerging paradigm of PAH as a systemic vasculopathy.[7] With their constant exposure to the entire cardiac output, the pulmonary arterioles are most susceptible to vascular remodeling.

Animal Models

Because clinical studies and patient sample studies are limited in offering insights into the pathogenesis of PAH, complementary animal models

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are used to better understand the cellular and molecular basis of disease and for testing potential therapies. The earliest and simplest model is chronic, hypoxia-induced PAH. This state was first observed in cattle living at high altitude and was coined "brisket disease."[8] High altitude decreases oxygen tension, causes reactive hypoxic vasoconstriction, and results in abnormal medial hypertrophy of pulmonary arterioles. Although chronic hypoxia-induced PAH was observed initially in large animals, the observations has been extended to small animals (ie, mice and rats). Today, small animals are the most commonly used models for examining PAH.[9,10] Because pathology induced by chronic hypoxia does not recapitulate all the features of human disease, the focus of many studies has been on 2-hit approaches to induce severe pulmonary vascular remodeling. For example, mice are relatively resistant to hypoxic stress and generally develop mild pulmonary remodeling and PH when exposed to chronic hypoxia. However, transgenic technology in mice allows the flexibility to examine the contribution of specific molecules, pathways, and cell types to disease pathogenesis. Genetic modifications in combination with hypoxia can lead to severe PH in mice, for example, exposing mice with lung-specific overexpression of IL-6 to hypoxia.[11] Other 2-hit approaches, including combining SU5416 injections, a vascular endothelial growth factor receptor 2 antagonist that can cause endothelial injury, with hypoxia, pneumonectomy, induction of allergic inflammation, or other genetic modifications,[9] can also enhance the severity of PH.

Similar strategies have also been applied to rat models that, compared with mice, generally develop significantly more extensive vascular remodeling with severe pulmonary hypertension. Although mice are resistant to monocrotaline (MCT) toxicity, MCT administration is commonly used to induce PH in rats, where a single subcutaneous injection of MCT results in progressive, severe pulmonary remodeling, right heart failure, and fatal PH.[10] MCT is thought to act as a toxin to the endothelium, although its effects are complex and not organ-specific. The SU5416-hypoxia model results in severe and sustained PH,[12] which can be fatal depending on the strain of rat used.[13] Together, the use of these models has been invaluable in probing the pathobiology and pathophysiology of PAH.

THE PATHOPHYSIOLOGY OF PULMONARY ARTERIAL HYPERTENSION

The pathophysiology of PAH is complex, with contributions from multiple cell types in the pulmonary vasculature and the right heart. Here we highlight some of the major mechanisms that contribute to pulmonary vascular remodeling (**Fig. 1**) and RV dysfunction in PAH.

Endothelial Dysfunction

PAH is characterized by microvascular rarefaction. Pulmonary artery endothelial cell (PAEC) injury leading to EC dysfunction and apoptosis are triggers for the development of PAH. Both animal models of PH (ie, MCT and SU5416-hypoxia models) and human type II bone morphogenetic protein receptor (BMPR2) mutation-associated PAH are characterized by lung PAEC apoptosis.[14] Chronic PAEC apoptosis results in microvascular destruction and rarefaction. In addition, apoptosis leads to the selection of apoptosis resistance and proliferative PAECs causing occlusive arterial remodeling.[15] Cultured PAECs isolated from human patients with PAH demonstrate increased proliferation compared with nondiseased controls.[16] Idiopathic PAH (IPAH) PAECs also have metabolic abnormalities, with decreased mitochondrial numbers per cell and a higher glycolytic rate.[17] It is unclear as to which of these processes—a primary loss of vessels owing to EC apoptosis versus a secondary loss of vessels owing to obliteration from apoptosis-resistant ECs—is central to PAH pathogenesis.[18] Additionally, these processes may play roles in different phases of the disease.[19] Another aspect by which the EC contributes to PAH is endothelial-to-mesenchymal transition, where ECs can transition to smooth muscle cell (SMC)-like cells that upregulate twist and vimentin.[20]

Smooth Muscle Cell Hypertrophy and Proliferation

Hypertrophy, proliferation, migration, and apoptosis resistance of medial SMCs in the pulmonary arterioles (PASMCs) plays a central role in PAH. PASMCs in normal adult lung are quiescent with a contractile and nonmigratory phenotype. In the setting of tissue injury, SMCs can transition to a proliferative phenotype, resulting in vessel remodeling. Pathologic distal arteriole muscularization results from proliferation of preexisting SMCs and recapitulates many aspects of arterial wall development, including SMC dedifferentiation, distal migration, proliferation, and then redifferentiation.[21] Some of the cues for this process are regulated by nonclassical monocytes and macrophages that sense hypoxia and are predicted to promote pulmonary vascular remodeling and SMC proliferation.[22] For example, macrophage-derived factors such as platelet-derived growth

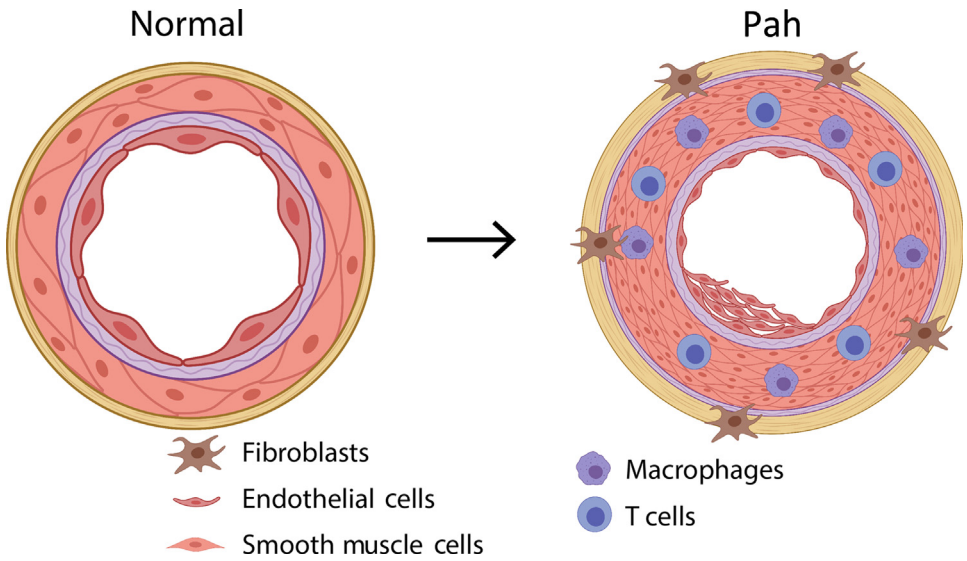

Fig. 1. Cell types that contribute to pulmonary vascular remodeling. Pulmonary vascular remodeling involves all layers of the vascular wall (the intima, primarily composed of ECs; the media, primarily composed of SMCs; and the adventitia, primarily composed of fibroblasts) along with infiltration with immune cells such as macrophages and T cells. This results in the selection of apoptosis-resistant ECs, the proliferation of SMCs, and the activation of fibroblasts. Much of this is driven by signaling from immune cells such as macrophages and T cells. See text for details. Created with BioRender.com.

factor-β are upregulated in PAH and promote SMC proliferation.[23] There are also cell autonomous factors that contribute to SMC proliferation. This process is exemplified by SMC-specific knockout of BMPR1A, which resulted in attenuated SMC proliferation, decreased hypoxia-mediated muscularization of distal vessels, and the preservation of peripheral pulmonary arteries.[24]

Fibroblasts and Fibrosis

Obliterative thickening of vessels in PAH are largely composed of SMCs and myofibroblasts. Frank fibrosis has been noted in PAH pathologic samples, especially in those with PAH associated with connective tissue disease.[2] Adventitial fibroblasts from calves with severe hypoxia-induced PH and humans with IPAH display increased aerobic glycolysis. Treatment of these mice with a pharmacologic agent for an nicotinamide adenine dinucleotide–sensitive transcription corepressor resulted in decreased glycolysis and expression of inflammatory genes, attenuated proliferation, and decreased remodeling of the distal pulmonary vasculature.[25] These fibroblasts also activate macrophages through paracrine signaling via IL-6–activated STAT3 to promote pulmonary vascular remodeling.[26]

Immune Cells and Inflammation

Inflammation is known to be an important mediator of vascular dysfunction in the pathogenesis of PAH. Accumulation of immune cells, including T cells, B cells, monocytes, macrophages, and mast cells, has been observed in all animal models of PH and human disease.[27,28] The predominant cell types are T cells, monocytes, and macrophages. These cells are found mostly in the perivascular regions, but also observed within the plexiform lesions.[29] T cells, monocytes, and macrophages can directly or indirectly, via paracrine signaling, modulate the activation, proliferation, transformation, migration, and survival of vascular mural cells (ie, EC, vascular SMCs, and adventitial fibroblasts), modify extracellular matrix, and regulate remodeling of all parts of the vascular wall. Altering immune cell populations and balance in both adaptive and innate immune compartments modulates vascular remodeling and PH severity. For example, athymic animals develop severe pulmonary remodeling and PH spontaneously owing to the absence of the protective effect of $CD4^+$ T regulatory cells.[30,31] In contrast, Th1 and Th17 cells secrete proinflammatory cytokines such as IL-6, IL-1, IL-21, and tumor necrosis factor-α, and IFN-ɣ, and promote vascular remodeling.[32,33] Additionally, Th17 cells also promote PH through the secretion of IL-17A.[34] Although Th1 cells and IFN-ɣ are required for the development of pneumocystis-induced PAH[32]; Th2 cells, through production of IL-4 and IL-13, exacerbate schistosomiasis-induced and other forms of PAH.[35–37] Thus, the balance of Th1 versus Th17 or Th2 versus T regulatory cell populations determine the immune milieu and its effects on vascular remodeling.[33]

Monocytes and macrophages are also involved in multiple aspects of PAH pathogenesis. Recent studies have shown that macrophages are derived from both fetal precursors or circulating monocytes; the function of macrophages depends on their origin, anatomic microenvironment, and specific stimuli.[38–41] Consistent with this paradigm, depletion strategies that differentially affect various populations of monocytes and macrophage can either promote or ameliorate PAH severity.[42–44] Preferential polarization of macrophages to alternative phenotype (M2-like) spectrum, characterized by signaling through STAT3, and promote cellular proliferation and is believed to drive PAH. However, in animal models of PAH, both M1-like and M2-like macrophages have been described.[45] M1-like macrophages are potent producers of interferon, which is a known driver of vascular remodeling and PAH. Moreover, the M1/M2 classification is an oversimplification of macrophage involvement in PAH.[46] Macrophage recruitment and activation are modulated by many factors produced by both vascular mural and other immune cells, including a decrease in BMPR2 signaling, secreted macrophage inhibitory factor by dysfunctional ECs, leukotriene T4, and chemokines (eg, CCL2, CCL1, and CX3CL1).[33,47–50] These molecules and pathways are being explored as potential therapeutic targets for PAH. In addition to T cells and macrophages, mast cells and eosinophils have been implicated in PAH pathogenesis.[51–55] With the complexity of different immune cell populations and responses, immune cell dysregulation generally promotes the abnormal vascular mural cell phenotype in PAH.

Metabolism

As noted elsewhere in this article, many of the cell types in pulmonary vasculature display changes in their metabolic state. Paulin and Michelakis[56] have proposed that many of the pathobiological abnormalities in PAH promote mitochondrial suppression, with an inhibition of glucose oxidation, which in turn results in many of the observed molecular abnormalities noted in PAH. It has been proposed that these metabolic abnormalities are similar to those seen in cancer and explain features of the PAH vascular phenotype, including the enhancement of proliferation and apoptosis resistance. Notably, insulin resistance is also common in PAH and is characterized by alterations in lipid and lipoprotein levels, and elevated levels of circulating medium- and long-chain acylcarnitines.[57,58] These defects in fatty acid oxidation contribute to lipotoxicity in the RV in PAH.[59] Metabolic profiling has also been used to identify signatures of RV–pulmonary valve dysfunction, consistent with the pulmonary release of tryptophan metabolites.[60] Although it is likely an oversimplification to reduce all of the complex abnormalities in PAH to a single underlying cause of metabolic changes, these studies clearly demonstrate that metabolic abnormalities contribute to PAH pathogenesis and phenotype.

Right Ventricular Dysfunction

The majority of basic pathobiology studies in PAH focus on abnormalities in the pulmonary vasculature, but the RV in PAH also has an abnormal response to increased afterload.[61] The increased afterload from pulmonary vascular remodeling results in right heart failure, characterized by decreased RV function that leads to insufficient cardiac output and/or increased filling pressure at rest or exercise. In response to the increased afterload, the RV displays an adaptive hypertrophic response, but over time this can transition to a maladaptive phenotype.[62] Notably, patients who display preserved RV function in PH have significantly better survival than those who have decreased RV function at follow-up. Adaptive remodeling is characterized by the preservation of a normal cardiac output, RV ejection fraction, filling pressures, and exercise capacity. Adaptive remodeling consists primarily of concentric hypertrophy with minimal dilatation and fibrosis.[62] Maladaptive remodeling is associated with increased filling pressures and a decreased cardiac output and RV ejection fraction; it consists primarily of RV dilatation and fibrosis. With these compensatory mechanisms, RV–pulmonary arterial coupling (typically quantified by the ratio of RV end-systolic elastance and arterial elastance) with efficient energy transfer is maintained initially in adaptive remodeling. However, it is then overwhelmed gradually[61] and transitions from adaptive to maladaptive remodeling. In MCT-induced PH rat models, this transition is associated with a decrease in angiogenesis, a decrease in glucose uptake, and a reversion toward normal metabolism.[63] However, a detailed analysis of human samples with stereology[64] demonstrated that, in advanced PH, there was a significant increase in the RV vasculature in the setting of RV hypertrophy, consistent with compensatory angiogenesis in severe PAH. Similar results were observed in Su5416-hypoxia PH models,[65] where a compensatory angiogenic response was observed, but with a modest decrease in arterial delivery of metabolic substrates owing to an increase in the radius of tissue served per vessel. Metabolomics

revealed major metabolic alterations and reprogramming, but without evidence of tissue hypoxia or depletion of key metabolic substrates. This finding suggested that the major driver of RV maladaptation was related to direct changes in cardiomyocytes and not secondary to vascular rarefaction and decreased substrate delivery. Despite these findings supporting the importance of RV function on outcomes, there are currently no PAH therapies that directly target the RV.

MOLECULAR MECHANISMS OF PULMONARY ARTERIAL HYPERTENSION

Multiple molecular mechanisms contribute to the pathophysiological axes discussed elsewhere in this article. We highlight a number of these mechanisms in Fig. 2 and elsewhere in this discussion.

Type II Bone Morphogenetic Protein Receptor and Transforming Growth Factor-β Signaling

BMPR2 mutations account for 70% of heritable PAH and are also found in 20% of patients with IPAH.[66] BMPR2 is a member of the transforming growth factor (TGF)-β receptor superfamily. While TGF-β receptors promote signaling through Smad2/3 transcription factors, BMPR2 promotes signaling through Smad1/5 transcription factors.[67] A large meta-analysis also identified that patients with BMPR2 mutations, whether idiopathic, heritable, or anorexigen-associated, presented at a younger age with more severe disease and were at a higher risk of death compared with those without BMPR2 mutations.[68] Mutations of a number of proteins important in the TGF-β superfamily have been identified as potentially pathogenic in next-generation sequencing studies in PAH.[69] Although some of these genetic links have been known for some time,[70] the complex pharmacology of this system has made it difficult to identify the specific receptor hetereomers and their ligands that were responsible for signaling in the pulmonary vascular endothelium.[71] A breakthrough was made with the discovery that BMP9 is the preferred ligand for preventing apoptosis and enhancing endothelial integrity.[72] Additionally, the administration of BMP9 reversed established PAH in mice carrying a heterozygous knock-in allele of human BMPR2 (R899X) mutation.[72] More recently, an approach of targeting the

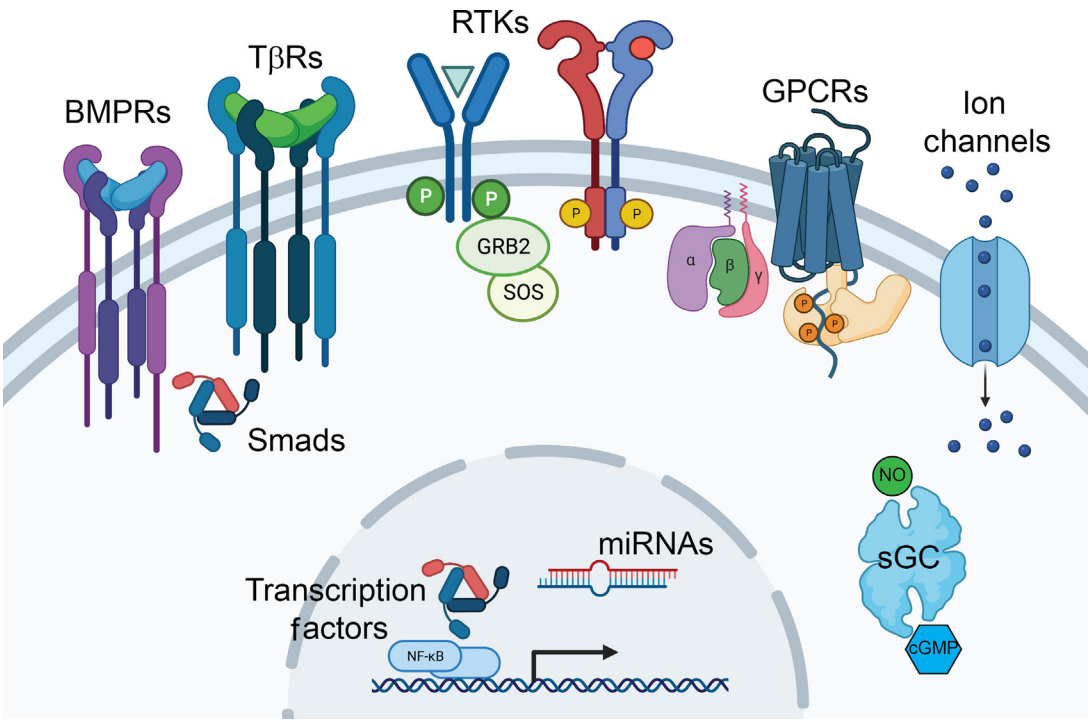

Fig. 2. Molecular mechanisms that contribute to PAH. Multiple molecular mechanisms contribute to the development of PAH, including signaling by BMPRs and TGF-β receptors through Smads, growth factor signaling via receptor tyrosine kinases (RTKs), growth factors and vasoactive mediator signaling via G protein-coupled receptors, the activation of ion channels, nitric oxide signaling via soluble guanylate cyclase (sGC), the activation of transcription factors and epigenetic mechanisms such as microRNAs (miRNAs). See text for details. Created with BioRender.com.

balance of activin/growth differentiation factor and BMP signaling via BMPR2 has demonstrated preclinical efficacy.[73] Although activins and growth differentiation factors promote signaling via Smad2/3, BMPs promote signaling via Smad1/5/9. Treatment with a potent growth differentiation factor 8/11 and activin ligand trap inhibited Smad2/3 signaling, resulting in decreased proliferation and enhancement of apoptosis in the vascular wall, and attenuated PH.[73] These findings suggest that new approaches to target BMPR2 signaling will be useful as a therapeutic strategy in PAH.

Growth Factors

The dysregulation of a range of growth factors, many of which target receptor tyrosine kinases (RTKs), promote abnormal vascular proliferation and play a central role in PAH pathobiology.[74] Markers of angiogenesis, such as vascular endothelial growth factor, have been noted in plexiform lesions.[75] In the setting of vascular destruction and obstruction in PAH, this likely reflects an angiogenic response to form collaterals from bronchial/vasa vasorum to the pulmonary arterial circulation. KDR heterozygosity (the gene encoding vascular endothelial growth factor receptor 2) is strongly associated with PAH that occurs later in life.[76] Levels of fibroblast growth factor 2 (FGF2) are elevated in the remodeled pulmonary vascular endothelium of patients with IPAH; and FGF2 knockdown decreased PASMC growth.[77] In an animal model, the inhibition of FGF receptor 1, a receptor for FGF2, reverses established PH, suggesting this receptor as a potential therapeutic target. Similarly, platelet-derived growth factor (PDGF) promotes PASMC proliferation and migration; and expression of PDGF receptor (PDGFR) is increased in the lung tissue of patients with PAH.[78] The PDGFR antagonist, imatinib, can reverse advanced pulmonary vascular disease in MCT-PH rats and hypoxia mice.[78] Consistent with this finding, imatinib significantly improved exercise capacity and hemodynamics in a clinical trial. Unfortunately, it was also associated with a significant increase in subdural hematomas in patients who were on anticoagulation.[79] In PAH, epidermal growth factor (EGF) activates its receptor (EGFR) to promote cell proliferation and survival. However, the effects of different EGFR antagonists in MCT PH have been noted to be variable, with only some improving RV systolic pressure and hypertrophy.[80] Notably, none of them significantly improved RV systolic pressure or pulmonary vascular remodeling in mice with chronic hypoxic PH. Consistent with this finding, EGFR expression in lungs was not altered in patients with IPAH. Targeting a range of tyrosine and serine/threonine kinases with sorafenib decreased RV hypertrophy and pulmonary arterial muscularization in MCT-treated rats.[81] An approach using multiple agents to target RTKs (ie, FGFR, EGFR, and PDGFR), was successful in regressing established MCT PH. Treatment decreased the activation of the adapter protein p130(Cas), which works downstream of RTKs to promote cell migration and proliferation.[82] With their central roles in regulating cell migration, proliferation and survival, these growth factors are excellent drug targets in PAH if their potential systemic effects can be limited.

Vasoactive Mediators: Prostacyclins, Endothelins, and Nitric Oxide

Vasoactive mediators have long been known to contribute to PAH pathophysiology, with low levels of vasodilators such as prostacyclin[83] and high levels of vasoconstrictors such as endothelin-1[84] noted in patients with PAH. Only a small percentage of patients with PAH are vasodilator responsive,[85] displaying an acute decrease in pulmonary pressures after treatment with a pulmonary vasodilator such as inhaled nitric oxide, adenosine or epoprostenol.[86] Vasodilator responders display an excellent long-term therapeutic response to calcium channel blockers.[87] Regardless of their acute response to vasodilators, patients with PAH demonstrated a positive response to treatments, such as prostacyclin infusion, in early studies.[88] These initial discoveries translated to the first therapy for PAH, intravenous epoprostenol.[89,90] Although long-term treatment with therapies such as prostacyclins have been shown to be beneficial, they do not seem to reverse PAH pathology fully. As noted in an autopsy study of a PAH patient maintained on long-term therapy who died of a different cause, vascular abnormalities are still evident.[91] All 3 pathways currently targeted by PAH-specific therapies—the prostacyclin pathway (targeted by prostacyclin receptor agonists), the nitric oxide/cyclic guanosine monophosphate axis (targeted by phosphodiesterase 5 inhibitors and soluble guanylate cyclase stimulators), and the endothelin pathway (targeted by endothelin receptor antagonists)—have direct vasoactive effects. It is possible that other vasoactive pathways, such as angiotensin[92,93] and other mediators,[94] would also have beneficial effects in PAH, but they have not been tested in large clinical trials in the PAH population. Notably, although these drugs are thought to primarily act through vasodilation, with prolonged exposure, they likely also act as

antiproliferative agents, because vasoconstriction is closely linked to other complex changes in the vasculature.[95]

Chemokines

Chemokines, also known as chemotactic cytokines, are a group of more than 40 small proteins that regulate cell migration and function. Chemokines bind to more than 20 chemokine receptors, which are G protein-coupled receptors. Chemokine receptors are categorized into 5 families based on their activating chemokine ligand (CXCR, CCR, CX3CR, or XCRs), with an additional group of atypical chemokine receptors that bind chemokines of different families, but primarily act as scavenger or decoy receptors. Chemokines bind to negatively charged glycosaminoglycans on the EC surface or extracellular matrix, resulting in a chemokine concentration gradient that promotes immune and inflammatory cell recruitment.[96,97] Chemokine levels have been correlated with disease severity, pulmonary hemodynamics, and RV function in multiple studies. For example, CCL2 and CXCL10 levels are associated with disease severity.[98–101] CCL2, CXCL8, CXCL10, CXCL12, and CXCL13 levels are correlated with hemodynamics such as pulmonary vascular resistance,[100,102–104] right atrial pressure,[98,102] cardiac output,[102] and cardiac index.[98,100,102] With respect to harder outcomes, CCL2, CCL21, and CXCL12 levels have been associated with adverse outcomes and mortality.[105–108] Some of these chemokines may increase as part of an adaptive mechanism; for example, elevated levels of CXCL10 are associated with improved survival in patients with PAH.[109] In addition, some chemokines could serve as biomarkers for monitoring disease progression or treatment effect. For example, the beneficial effects of epoprostenol treatment on functional and hemodynamic status in patients with PAH were associated with increased levels of CCL2.[104] Despite these strong associations with disease severity, chemokines have been challenging to target owing to their complex pharmacology, but novel approaches may make these targets more druggable.[110]

Ion Channels

Ion channels play a central role in the membrane potential and regulate vascular tone of the pulmonary circulation. Voltage-gated potassium channels play a central role in hypoxic vasoconstriction.[111] Mice with mutation of Kv1.5 display impaired hypoxic vasoconstriction.[112] Fawn-hooded rats have a chromosomal abnormality that disrupts a mitochondria–reactive oxygen species–hypoxia inducible factor–Kv pathway, resulting in a loss of voltage-gated potassium channel activity. These rats develop pulmonary hypertension spontaneously.[113] A familial form of PAH is due to heterozygous loss-of-function mutations in KCNK3,[114] which encodes the TASK-1 potassium channel. Consistent with this finding, MCT-treated rats have decreased expression of KCNK3, and the pharmacologic activation of KCNK3 improved PH.[115] Such findings suggest that ion channels may serve as drug targets in PAH treatment.

Transcription Factors and Nuclear Receptors

Transcription factors are the downstream targets of a wide range of signals, such as hypoxia, growth factors, cytokines, and chemokines, that result in the reprogramming of cells to a PAH-promoting phenotype. Hypoxia inducible factor-1α mediates much of the transcriptional response to hypoxia, and its activity in macrophages results in the activation of pro-proliferative signals to PASMCs. For example, FoxO1 is responsible for signaling downstream of many growth factors and inflammatory mediators, and inactivation of specific isoforms results in the pro-proliferative and antiapoptotic phenotype of PASMCs in PAH.[116] Similarly, the related transcription factor FoxM1 promotes PASMC proliferation in PAH.[117] PPAR-γ and β-catenin have been shown to promote BMPR2 signaling via apelin, resulting in improved PAEC survival. In mice, this effect was recapitulated with apelin treatment leading to PAH reversal.[118]

MicroRNAs and Long Noncoding RNAs

A number of epigenetic changes have been noted in PAH. Noncoding RNAs, such as microRNAs (miRNAs) and long noncoding RNAs (lncRNAs), have been identified as being dysregulated in PAH. The miRNAs are small noncoding RNAs that inhibit gene expression and are critical in gene regulation.[119] Recently, a number of groups have identified changes in miRNA expression in PAH that seem to contribute to PAH pathobiology. Of these miRNAs, miR-29, -124, -140, and -204 have been reported as dysregulated in PAH, where they seem to play distinct roles.[120] miR-124, -140, and -240 inhibit cellular proliferation, and miR-29 promotes proliferation but inhibits vasoconstriction. However, it has been challenging to interpret some of these studies, because the effects are not always consistent between patients and different disease models.[120] More recently, lncRNAs have been implicated in PAH pathogenesis. The lncRNA H19 was described recently as a new biomarker

for right heart failure in PAH. The lncRNA H19 is upregulated in the decompensated RV of patients with PAH and also in rat disease models.[121] Silencing H19 improved RV fibrosis and capillary rarefaction, suggesting that targeting these lncRNAs could be a potential therapeutic strategy. The lncRNA TYKRIL has been shown to be upregulated in pericytes and PASMCs in cells exposed to hypoxia and patients with IPAH.[122] Expression of PDGFRβ strongly correlated with TYKRIL expression and TYKRIL knockdown decreased PDGFRβ expression, suggesting another approach for targeting pathogenic signaling in PAH.

SUMMARY

The pathobiology of PAH is complex, with contributions from multiple pathophysiologic processes that are regulated by a variety of molecular mechanisms. This finding likely explains the limited efficacy of our current therapies, which only target a small portion of the pathobiological mechanisms that underlie advanced disease. It is likely that different therapies that target these multiple axes will need to be used in combination, as is being used with our currently available therapies,[86] to improve outcomes in this devastating disease.

CLINICS CARE POINTS

- Multiple cellular and molecular mechanisms contribute to vascular remodeling in the development of PAH.
- Current PAH therapies focus on targeting vasoactive mechanisms, including prostacyclin receptor agonists, endothelin receptor antagonists, phosphodiesterase 5 inhibitors, and soluble guanylate cyclase stimulators.
- Novel PAH therapies that are being developed target other signaling pathways including the type II bone morphogenetic protein receptor and growth factor receptors.
- All of these pathways regulate endothelial function, smooth muscle cell proliferation, fibroblast activation, inflammation, and metabolism that underlie PAH pathogenesis.

DISCLOSURE

The authors have no commercial or financial conflicts of interest.

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