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Pulmonary Arterial Hypertension Research Advancement through the Years

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Abstract

Pulmonary arterial hypertension (PAH) is a rare disease with a high mortality rate. Although treatment options have improved over the past two decades, patients still die prematurely from right heart failure. Although rare, they are heterogeneous at the genetic and molecular level, and understanding and exploiting this fact is key to developing more effective treatments. BMPR2, which encodes bone morphogenetic receptor type 2, is the most commonly affected gene in both familial and non-familial PAH, although rare mutations have been identified in other genes. Transcriptome, proteomics, and metabolomics studies to search for endophenotypes are ongoing. Although there is no shortage of potential new drug targets in PAH, their selection and prioritization is a challenge for the research community.

Keywords: Pulmonary hypertension; BMPR2; Bone morphogenetic receptor type 2;New drug targets

Introduction

In contrast to the systemic circulation, the normal adult pulmonary circulation is a low-pressure, low-resistance vascular bed. Pulmonary hypertension (PH) is diagnosed when the resting mean pulmonary artery pressure (mPAP) is at least 25 mmHg and is divided into five major subgroups based on clinical and hemodynamic criteria. As a result, the workload of the right ventricle increases, which, if hypertrophied and uncoordinated, can lead to premature death.

PH is not uncommon in left ventricular failure where risk grading is increasingly recognized such that even borderline elevations in mPAP contribute to mortality. Pulmonary arterial hypertension (PAH) is less common. Incidence rates of 1.1 to 17.6 per million adults per year have been reported, and prevalence rates of 6.6 to 26.0 per million adults have been reported, suggesting that increased mPAP is due to precapillary resistance to lung perfusion [1]. In the absence of airway or parenchymal lung disease, or chronic thromboembolism. PAH is clinically heterogeneous, with PAH without a definite cause (referred to as idiopathic PAH [IPAH]), hereditary PAH, drug-induced PAH, and related congenital heart disease, connective tissue disease, HIV, phyla. Hypertension or schistosomiasis [2] histology at postmortem or lung transplantation shows marked pulmonary artery remodeling with vascular cell proliferation invading the vessel lumen.

Molecular Signatures of Pulmonary Arterial Hypertension

The current clinical classification of PAH is acknowledged to be inadequate from both diagnostic and drug development perspectives. Combining detailed analysis of genetics and molecular phenotypes is expected to define key drivers and novel drug targets of PAH, opening the possibility of more personalized medicine [3]. His associated national PAH cohort study has facilitated the collection of biological samples from his PAH patients across the UK, with deep representations such as metabolomics and proteomics that can be cross-checked with genetic data from the NIHRBR effort [4]. We are starting to provide type data.

A subgroup of her PAH patients, less than 10%, responded well to calcium channel blockers, suggesting that this pharmacological phenotype should have distinct molecular signatures. This is supported by transcriptomic signatures reported in small patient populations that require further prospective validation 14 . It has been shown that the metabolic profile of patients who respond to calcium channel blockers resembles that of healthy subjects more than those who do not respond to PAH [5].

High-throughput techniques such as aptamer-based assays, nuclear magnetic resonance, and mass spectrometry have been applied to plasma samples and used for patient risk stratification. Prognostic panels developed from this approach can add valuable information to clinical assessments. For example, a panel of nine proteins has been shown to improve risk stratification in combination with N-terminal pro-brain natriuretic peptide (NT-proBNP) or the registry risk equation REVEAL (Registry to Evaluate Early and Long-term PAH) [6]. It has been. Formula created from patient clinical assessment and comorbidities. An advantage of panels of circulating biomarkers is that they are more objective than functional class assessment and more accessible than imaging. Also, combinations of molecules reporting different disease states (proliferation, inflammation, coagulation, metabolic dysfunction, etc.) provide more detailed information than a single biomarker. (eg brain natriuretic peptide).

But the real power of these techniques lies in their potential to identify important and treatment-relevant subsets of patients in the clinic. An initiative funded by the US National Heart, Lung and Blood Institute wants to explore this. The PVDOMICS (Pulmonary Vascular Disease Phenomics Program) consortium aims to “redefine pulmonary hypertension through the phenomenon of pulmonary vascular disease” [7]. The goal is to enroll his 1,500 participants with PH and healthy controls for comprehensive clinical and omics analysis. Recruitment was initiated and an analysis plan was outlined. Data integration challenges cannot be underestimated, but if successful, will provide the basis for molecular taxonomy and biologically relevant insights in pH.

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New Drugs

Current therapy for PAH consists of four classes of drugs (prostanoid analogues, endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, and soluble guanylate cyclase) that treat endothelial dysfunction and reduce vasomotor tone stimulant) [9]. Although they relieve symptoms and improve function, there is limited evidence that these drugs slow the progression of his PAH and prolong the patient's survival. To do this, the drug must at least support right ventricular function and, even better, reverse pulmonary artery remodeling.There is no shortage of potential new drug targets for PAH.

Targets From Genetics

Impaired BMPR2 signaling causes an imbalance of TGFβ/BMP signaling in favor of TGFβ and may underlie vascular remodeling in PAH patients with and without BMPR2 mutations. Beyond the pursuit of gene therapy, many therapeutic strategies have been proposed, including pharmacological approaches such as chloroquine (to prevent lysosomal degradation of BMPR2), atallen (to detect missense mutations), and increasing BMP9 levels. I'm here [10]. To date, tacrolimus is the only treatment used in clinical trials that targets his BMPR2 signaling. The drug binds to all three her BMP type 1 receptors and removes FKBP12, activating BMPR2-mediated signaling in the absence of exogenous ligand and her BMPR2. Although some patients showed marked increases in her BMPR2 expression, improvement in 6-minute walking distance (6MWD) and heart failure serological and echocardiographic parameters, changes were not observed in all patients [11]. There is none. An alternative approach is to inhibit TGFβ activity using a novel activin receptor fusion protein (Sotatercept) that competitively binds to and neutralizes TGFβ superfamily ligands. Although this approach is developing into clinical trials, the effects of increased hematocrit associated with this treatment need to be carefully monitored and understood.

Growth Factors

Much has been said about the similarities between dysregulated growth of vascular cells and tumor cell growth, leading to interest in repurposing oncology drugs. Research on the tyrosine kinase receptor inhibitor imatinib has led the field. In addition to inhibiting the bcr-abl tyrosine kinase, imatinib inhibits platelet growth factor (PDGF) receptors α and β and c-KIT. PDGF is a trophic factor for vascular cells and PAH lungs show increased expression of her PDGF receptor [12]. A phase 3 trial reported an increase in mean placebo-corrected treatment effect and a decrease in pulmonary vascular resistance at 6MWD 32 m. However, there was no improvement in time to clinical deterioration, and serious adverse events and treatment discontinuation occurred more frequently with imatinib.Of particular concern were the eight patients receiving imatinib and anticoagulant therapy It was a subdural hematoma that occurred in Although further development of imatinib as a treatment has been discontinued, there remains interest in understanding patient characteristics that may provide significant benefit [13]. The ability to identify potential responders, coupled with the avoidance of concomitant anticoagulant therapy, would support the argument to reconsider imatinib as a treatment. Concerns about toxicity remain, as use of dasatinib in other indications is rarely associated with the development of PH. There is strong interest in elastase inhibitors that have been shown to prevent and reverse experimental pH [14]. Elafin, an endogenously produced low molecular weight elastase inhibitor, induces apoptosis of human pulmonary artery smooth muscle cells and reduces neointimal lesions in lung organ cultures. Enhanced BMPR2 signaling, which is dependent on the stabilization of caveolin-1 at the plasma membrane, has also been implicated as a mechanism of action.

Metabolism

The "metabolic theory" of PAHs is based on the observation that proliferating cells switch cellular metabolism from oxidative phosphorylation to glycolysis for ATP production. Increased expression of pyruvate dehydrogenase kinase (PDK), which inhibits pyruvate dehydrogenase, is one factor underlying this switch, although other PDK-independent factors (e.g., SERT3 or UCP2, which predict decreased protein function) (destroying variants) can also contribute and actually impair functionality [15]. Clinical response to inhibition of PDK by dichloroacetate (DCA). His 16-week study of his DCA treatment in PAH showed a reduction in pulmonary arterial pressure, along with a reduction in pulmonary parenchymal glucose uptake, in genetically susceptible patients [16].

Aside from the metabolic disturbances observed in proliferating cells, insulin resistance is common in PAH31. Although the explanation underlying this association is unclear, preclinical data support further evaluation of insulin resistance therapeutics for repurposing in PAH [17]. These include rosiglitazone, metformin, and glucagon-like peptide 1 (GLP-1) receptor agonists.

Oestrogen Signalling

Modulation of estrogen levels is another potential therapeutic approach to treat PAH, although results from preclinical and clinical trials are different. A variant in the promoter region of the aromatase gene, which encodes the enzyme responsible for converting androgens to estrogens, is associated with elevated circulating levels of 17b-estradiol (E2) and an increased risk of PAH in patients with cirrhosis. Strozol or metformin therapy also reduced PH and right ventricular hypertrophy in an in vivo pH model [18]. These observations culminated in a randomized clinical trial of 18 patients in which anastrozole (1 mg/day) significantly reduced serum E2 levels and increased 6MWD compared to placebo. , another Phase 2 trial is underway.

Oxidative Stress

Attempts to reduce oxidative stress in PAHs have included inhibition of apoptosis signaling-regulating kinase 1 (ASK1) and treatment with bardoxolone methyl. Pharmacological inhibition of ASK1 has shown efficacy in many preclinical PAH models, but failed to demonstrate clinical benefit in phase 2 clinical trials [19].

Bardoxolone methyl induces activation of the nuclear factor erythroid 2-related factor 2 (Nrf2), a transcription factor that regulates antioxidant proteins, and the pro-inflammatory factor nuclear factor kappa light chain enhancer of activated B, orally. Semi-synthetic triterpenoid available cells (NF-κB) [20]. Initial reports of Phase 2 trials have reported some indications of efficacy, and Phase 3 trials are underway. Eramipretide, a small mitochondrial-targeted tetrapeptide (D-Arg-dimethylTyr-Lys-Phe-NH2), reduces the production of toxic reactive oxygen species (ROS) and increases cardiolipin for the treatment of mitochondrial diseases is currently under development.

Hypoxic Stress and Iron Homeostasis

Hypoxia-inducible factor (HIF) is upregulated in remodeled pulmonary vessels. Selective deletion of either HIF1α or HIF2 provides protection against hypoxia-induced PH in mice. A mutation that results in a dysfunctional von Hippel-Lindau (VHL) protein causes her PH in a patient with Chuvash polycythemia. Iron deficiency

without anemia is common in PAH and associated with poor survival. The cause is unknown. It cannot be explained by inflammation [21]. Orally administered iron is poorly absorbed by patients with PAH. His two open-label studies of intravenous iron supplementation in PAH reported improvements in athletic performance measures. A randomized, double-blind trial is nearing completion.

Serotonin

The 5-HT1B receptor is highly expressed in human pulmonary arteries, is upregulated in PAH patients, and mediates serotonin-induced vasoconstriction and remodeling. 5-HT1B effects are specific to the lung, as 5-HT2A receptors mediate these effects systemically. Both the 5-HT1B receptor and the serotonin transporter (SERT) are critical for her Nox1-derived ROS production and serotonin-mediated vascular effects in PAH. However, so far, clinical studies evaluating pharmacological manipulation of serotonergic activity in PAH have been disappointing. Current interest is in the inhibition of tryptophan hydroxylase 1 (TPH1), the rate-limiting enzyme of serotonin biosynthesis. KAR5585, a prodrug of KAR5417, is a function-selective inhibitor of TPH1. Dose-dependent inhibition of serum serotonin and its plasma and urinary degradation product 5-hydroxyindoleacetic acid (5-HIAA) has been demonstrated in healthy volunteers. In preclinical models of PAH, KAR5585 dose-dependently reduced serum, intestinal, and pulmonary levels of serotonin and 5-HIAA, and significantly reduced pulmonary artery pressure and pulmonary vessel wall thickness and occlusion.

DNA Damage

Dysregulation of DNA damage and repair mechanisms has been identified as a trigger for disease progression in PAH, and inhibition of poly (ADP-ribose) polymerase (PARP) reverses PAH in several animal models. A safety study has been proposed to repurpose olaparib, an orally available PARP inhibitor approved for the treatment of BRCA-associated breast cancer, for PAH.

Conclusion

These opportunities come with challenges. Animal models do not faithfully mimic the human condition and have a poor track record in predicting efficacy. Not suitable for development of drugs targeting vascular remodeling. Clinical trials must compete for relatively small patient pools.

References

1. Hoeper MM, Humbert M, Souza R, Idrees M, Kawut SM, et al. (2016) A global view of pulmonary hypertension. Lancet Respir Med 4: 306-322.
2. Maron BA, Hess E, Maddox TM, Opotowsky AR, Tedford RJ, et al. (2016) Association of Borderline Pulmonary Hypertension With Mortality and Hospitalization in a Large Patient Cohort: Insights From the Veterans Affairs Clinical Assessment, Reporting, and Tracking Program. Circulation 133: 1240-1248.
3. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, et al. (2016) 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 37: 67-119.
4. Stenmark KR, Meyrick B, Galie N, et al (2009) Animal models of pulmonary arterial hypertension: the hope for etiological discovery and pharmacological cure. Am J Physiol Lung Cell Mol Physiol 297:L1013-L1032.
5. International PPH Consortium, Lane KB, Machado RD, Pauciulo MW, Thomson JR, et al. (2000) Heterozygous germline mutations in BMPR2, encoding a TGF-beta receptor, cause familial primary pulmonary hypertension. Nat Genet 26: 81-84.
6. Deng Z, Morse JH, Slager SL, Cuervo N, Moore KJ, et al. (2000) Familial primary pulmonary hypertension (gene PPH1) is caused by mutations in the bone morphogenetic protein receptor-II gene. Am J Hum Genet 67: 737-744.
7. Gräf S, Haimel M, Bleda M, Hadinnapola CM, Southgate L, et al. (2018) Identification of rare sequence variation underlying heritable pulmonary arterial hypertension. Nat Commun 9: 1416.
8. Evans JD, Girerd B, Montani D, Wang XJ, Galiè N, et al. (2016) BMPR2 mutations and survival in pulmonary arterial hypertension: an individual participant data meta-analysis. Lancet Respir Med 4: 129-137.
9. Ma L, Roman-Campos D, Austin ED, Eyries M, Sampson KS, et al. (2013) A novel channelopathy in pulmonary arterial hypertension. N Engl J Med 369: 351-361.
10. Kerstjens-Frederikse WS, Bongers EM, Roofthooft MT, Leter EM, Douwes JM, et al. (2013) TBX4 mutations (small patella syndrome) are associated with childhood-onset pulmonary arterial hypertension. J Med Genet 50: 500-506.
11. Hadinnapola C, Bleda M, Haimel M, Screaton N, Swift A, et al. (2017) Phenotypic Characterization of EIF2AK4 Mutation Carriers in a Large Cohort of Patients Diagnosed Clinically With Pulmonary Arterial Hypertension. Circulation 136: 2022-2033.
12. Rhodes CJ, Wharton J, Ghataorhe P, Watson G, Girerd B, et al. (2017) Plasma proteome analysis in patients with pulmonary arterial hypertension: an observational cohort study. Lancet Respir Med 5: 717-726.
13. Rhodes CJ, Ghataorhe P, Wharton J, Rue-Albrecht KC, Hadinnapola C, et al. (2017) Plasma Metabolomics Implicates Modified Transfer RNAs and Altered Bioenergetics in the Outcomes of Pulmonary Arterial Hypertension. Circulation 135: 460-475.
14. Hemnes AR, Trammell AW, Archer SL, Rich S, Yu C, et al. (2015) Peripheral blood signature of vasodilator-responsive pulmonary arterial hypertension. Circulation 131: 401-409.
15. Benza RL, Miller DP, Gomberg-Maitland M, Frantz R, Foreman AJ, et al. (2010) Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). Circulation 122: 164-172.
16. Hemnes AR, Beck GJ, Newman JH, Abidov A, Aldred MA, et al. (2017) PVDOMICS: A Multi-Center Study to Improve Understanding of Pulmonary Vascular Disease Through Phenomics. Circ Res 121: 1136-1139.
17. Long L, Yang X, Southwood M, Lu J, Marciniak SJ, et al. (2013) Chloroquine prevents progression of experimental pulmonary hypertension via inhibition of autophagy and lysosomal bone morphogenetic protein type II receptor degradation. Circ Res 112: 1159-1170.
18. Morrell NW, Bloch DB, ten Dijke P, Goumans MJ, Hata A, et al. (2016) Targeting BMP signalling in cardiovascular disease and anaemia. Nat Rev Cardiol 13: 106-120.
19. Spiekerkoetter E, Sung YK, Sudheendra D, Scott V, Rosario PD, et al. (2017) Randomised placebo-controlled safety and tolerability trial of FK506 (tacrolimus) for pulmonary arterial hypertension. Eur Respir J 50: 1602449.
20. Komrokji R, Garcia-Manero G, Ades L, Prebet T, Steensma DP, et al. (2018) Sotatercept with long-term extension for the treatment of anaemia in patients with lower-risk myelodysplastic syndromes: a phase 2, dose-ranging trial. Lancet Haematol 5: e63-e72.
21. Schermuly RT, Dony E, Ghofrani HA, Pullamsetti S, Savai R, et al. (2005) Reversal of experimental pulmonary hypertension by PDGF inhibition. J Clin Invest 115: 2811-2821.