



Pulmonary Arterial Hypertension Research Advancement through the Years

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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

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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 NIHRBRIE cohort [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 [4]. 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 “redesign 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 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 TGF β /BMP signaling in favor of TGF β 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), atalenu (to detect missense mutations), and increasing BMP9 levels. Imvumab [10]. To date, imvumab is the only treatment used in clinical trials that targets BMPR2 signaling. The drug binds to all three human BMP type 1 receptors and removes FKBP12, activating BMPR2-mediated signaling in the absence of exogenous ligand and human BMPR2. Although some patients showed marked increases in human 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 TGF β activity using a novel activin receptor fusion protein (Sotatercept) that competitively binds to and neutralizes TGF β 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

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.

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