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Commentary

Novel Therapeutics for Pulmonary Arterial Hypertension: Targeting Disease Pathways beyond Vasodilation

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DESCRIPTION

Pulmonary Arterial Hypertension (PAH) represents a progressive and devastating form of pulmonary hypertension characterized by pathological remodeling of pulmonary arterioles, resulting in increased pulmonary vascular resistance, right ventricular failure, and premature mortality. Despite significant advances in therapeutic options over the past three decades that have improved quality of life and survival for many patients, PAH remains an incurable disease with a 5-year survival rate of approximately 60%. Contemporary treatment strategies have largely focused on restoring the balance between vasoconstrictive and vasodilatory mediators through three established pathways: the prostacyclin pathway, the endothelin pathway, and the nitric oxide-soluble guanylate cyclase-cyclic guanosine monophosphate pathway. While these approaches have demonstrated clinical benefit, their predominant mechanism of vasodilation fails to adequately address the complex pathobiology of PAH, which involves proliferation, inflammation, fibrosis, and metabolic dysfunction.

The pathogenesis of PAH is now recognized as a multifaceted process extending well beyond simple vasoconstriction. A central feature is the abnormal phenotype of Pulmonary Arterial Smooth Muscle Cells (PASMCs) and endothelial cells, characterized by enhanced proliferation, resistance to apoptosis, metabolic reprogramming, and production of inflammatory mediators. Genetic insights, particularly the discovery of mutations in the Bone Morphogenetic Protein Receptor Type 2 (*BMPR2*) gene in heritable PAH, have illuminated key signaling pathways involved in disease development and progression. These advances in understanding the molecular underpinnings of PAH have catalyzed the development of novel therapeutic approaches targeting disease-modifying pathways.

Growth factor signaling represents a promising therapeutic target given its role in promoting pulmonary vascular cell proliferation and survival. Platelet-Derived Growth Factor (PDGF) stimulates PASMC proliferation and migration, with evidence of increased PDGF receptor expression in PAH lungs. Imatinib, a tyrosine kinase inhibitor with activity against PDGF receptors, demonstrated improvements in pulmonary hemodynamics and exercise capacity. However, serious adverse events, including subdural hematomas, led to its discontinuation for this indication. More selective approaches to growth factor inhibition are under investigation, including specific PDGF receptor antagonists and inhibitors of downstream signaling molecules such as mitogen-activated protein kinases. Transforming Growth Factor-β (TGF-β) superfamily signaling, which encompasses Bone Morphogenetic Protein (BMP) signaling, plays a crucial role in maintaining pulmonary vascular homeostasis. *BMPR2* mutations, present in approximately 80%of familial Pulmonary Arterial Hypertension (PAH) cases and 20% of idiopathic PAH cases, result in reduced Basic Metabolic Panel (BMP) signaling and enhanced TGF-β signaling, promoting vascular remodeling.

Metabolic dysregulation has emerged as a fundamental feature of PAH pathobiology, with pulmonary vascular cells exhibiting a cancer-like metabolic phenotype characterized by enhanced glycolysis despite adequate oxygen availability, altered mitochondrial function, and lipid metabolism abnormalities. dichloroacetate, which inhibits pyruvate dehydrogenase kinase and promotes glucose oxidation over glycolysis, has demonstrated promising results in preclinical models and small clinical studies. Inflammation and immune dysregulation contribute significantly to PAH pathogenesis, with numerous inflammatory cells and mediators implicated in disease development and progression. DNA damage and genomic instability are increasingly recognized features of PAH, potentially contributing to the proliferative vascular phenotype. Poly ADP-Ribose Polymerase (PARP) inhibitors, used in cancer therapy, have demonstrated efficacy in preclinical PAH models by reducing excessive PARP activation and preserving endothelial function. Similarly, histone deacetylase inhibitors, which modulate chromatin structure and gene expression, have shown promising effects on pulmonary vascular remodeling in experimental settings. Sex hormone signaling modulation has gained attention given the female predominance of PAH despite worse outcomes in males. Estrogen metabolites may contribute

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to pulmonary vascular disease through proliferative effects, while estrogen receptor beta activation appears protective. Anastrozole, an aromatase inhibitor that reduces estrogen production, is currently being evaluated in the phantom trial, while selective estrogen receptor modulators represent another approach under investigation.

CONCLUSION

Cell-based therapies aim to regenerate damaged pulmonary vasculature and restore endothelial function. Endothelial progenitor cells and mesenchymal stem cells have shown promise in preclinical studies, with potential mechanisms including direct incorporation into the pulmonary vasculature, paracrine effects through secreted factors, mitochondrial transfer, and immunomodulation. Early-phase clinical trials have reported safety and preliminary efficacy signals, though optimal cell types, delivery routes, and patient selection criteria remain to be established.