Trends in Molecular Medicine

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Review

Targeting Vascular Remodeling to Treat Pulmonary Arterial Hypertension

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Pulmonary arterial hypertension (PAH) describes a group of conditions with a common hemodynamic phenotype of increased pulmonary artery pressure, driven by progressive remodeling of small pulmonary arteries, leading to right heart failure and death. Vascular remodeling is the key pathological feature of PAH, but treatments targeting this process are lacking. In this review, we summarize important advances in our understanding of PAH pathogenesis from novel genetic and epigenetic factors, to cell metabolism and DNA damage. We show how these processes may integrate and highlight exploitable targets that could alter the relentless vascular remodeling in PAH.

Pulmonary Vascular Remodeling in PAH: Many Problems, Few Solutions

Pulmonary hypertension (PH) is defined by a mean pulmonary artery pressure of greater than 25 mmHg at rest [1]. Diagnostic groups are further classified according to clinical, etiological, and hemodynamic features (Table 1), but share common symptoms of increased breathlessness on exertion, right heart failure, and ultimately result in premature death [1]. PAH (see Glossary) is characterized by sustained vasoconstriction and progressive obliteration of small-resistance pulmonary arteries and arterioles through a process of intimal and medial thickening and the formation of **angioproliferative plexiform lesions** [2]. Pulmonary vascular insults cause **endothelial dysfunction** and apoptosis, thereby impairing endothelial-mediated suppression of quiescent smooth muscle cells [3]. This, coupled with clonal expansion of apoptosis-resistant endothelial cells, promotes a **proliferative vasculopathy** that also involves complex interplay with adventitial fibroblasts, perivascular inflammatory cells, and the extracellular matrix [3]. Despite considerable advances in PAH treatment, this devastating disease still carries a prognosis worse than many cancers, with a 3-year survival of 68–70% [4,5]. Current therapies predominantly target **pulmonary vasoconstriction** rather than proliferative vascular remodeling and, therefore, new strategies are urgently required to directly address the pathological remodeling that underpins the disease.

PAH constitutes diagnostic Group 1 (Table 1) and is characterized by added hemodynamic criteria that define **precapillary pulmonary hypertension** with absence of left-sided heart disease (Group 2), lung diseases (Group 3), or **thromboembolic disease** (Group 4). However, Group 1 comprises patients with a range of conditions that are associated with the development of PAH and, thus, within this group, there may be considerable mechanistic heterogeneity at a molecular and pathophysiological level. Consequently, we limit this review by focusing on key pathogenic processes of **idiopathic PAH** (IPAH) and its heritable form (HPAH), rare conditions with a combined annual incidence of approximately one to two per million [4,6].

The breadth of disruption of pulmonary vascular cell biology in PAH is becoming apparent. Recent studies of genetic and epigenetic factors, **DNA damage**, and disordered metabolism

Trends

Advances in high-throughput sequencing and 'omic technologies have generated new insights into the disease mechanisms of PAH, highlighting problems of metabolism, DNA repair, inflammation, and epigenetics.

Close collaboration among national and international networks and consortia will maximize the chances of identifying and validating causal rare variants in PAH.

By increasing our understanding of the mechanisms regulating proliferative vascular remodeling in PAH and using multiple disease models and patient cells, we may be moving closer to the translation of preclinical discoveries.

The pleotropic effects of impaired type 2 bone morphogenetic protein receptor (BMPR-II) signaling continue to emerge and emphasize the potential importance of restoring or enhancing this pathway therapeutically.

Recent studies have highlighted mechanisms, independent of genetic mutations, that also result in the down-regulation of BMP signaling, identifying putative drug targets.

Numerous miRNAs have been targeted with beneficial effects in animal models of pulmonary hypertension, but challenges remain in the delivery and translation of these agents to humans.

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Table 1. Clinical Classification of PH[a]

WHO group	Classification	Hemodynamics	Subclassification
1	PAH	Precapillary mPAP ≥25 mmHg; PAWP ≤15 mmHg	Idiopathic; heritable; drug and toxin induced. Associated with: connective tissue disease; HIV infection; portal hypertension; congenital heart disease; schistosomiasis
1'	PVOD and/or PCH	Precapillary	
2	PH due to left heart disease	Postcapillary mPAP ≥25 mmHg; PAWP >15 mmHg	Systolic dysfunction; diastolic dysfunction; valvular disease; outflow/inflow tract obstruction; congenital cardiomyopathies
3	PH due to lung disease and/or hypoxia	Precapillary	Chronic obstructive pulmonary disease; interstitial lung disease; sleep-disordered breathing; alveolar hypoventilation; chronic exposure to high altitude; developmental lung diseases
4	Chronic thromboembolic PH	Precapillary	Thromboembolic disease
5	PH with unclear multifactorial mechanisms	Precapillary or combined pre- and postcapillary	Hematological disorders (e.g., splenectomy; chronic hemolytic anemia; myeloproliferative disorders; systemic disorders (e.g., sarcoidosis); pulmonary histiocytosis; metabolic disorders (e.g., glycogen storage disease, Gaucher's disease); others (e.g., tumors, chronic renal failure)

[a]Abbreviations: mPAP, mean pulmonary artery pressure; PCH, pulmonary capillary hemangiomatosis; PAWP, pulmonary artery wedge pressure; PVOD, pulmonary veno-occlusive disease.

have yielded important mechanistic insights into established disturbances of endothelial function and smooth muscle cell proliferation. We discuss the central importance of **bone morphogenetic protein** receptor 2 (BMPR-II) signaling in PAH and focus on approaches to rescue the disease-associated suppression of this pathway. Other new genetic leads are explored and the rapidly expanding field of miRNA biology and its relevance to PAH are discussed. Furthermore, work on triggers for PAH development has added to our understanding of the role of inflammation and hypoxia in PAH, and we highlight key recent findings in these areas. Although it is not yet clear how all of these problems combine temporally and mechanistically, these advances bring enormous potential for new therapeutic approaches that specifically target vascular remodeling, providing fresh hope of significant impact on disease progression and improved patient outcomes.

The Ups and Downs of BMPR-II Signaling in PAH

Since the identification of mutations in the gene encoding BMPR-II (*BMPR2*) in families with PAH [7,8], *BMPR2* has become the predominant genetic factor in heritable forms of the disease, with a large amount of evidence implicating it as a central molecular player in PAH. BMPR-II is a member of the transforming growth factor beta (TGF-β) receptor family that forms a dimer with an activin receptor-like kinase (ALK) [9]. There are multiple ALKs and each heterodimeric combination confers different ligand affinity [10]. Thus, differential expression in tissues may alter sensitivity to specific bone morphogenetic protein (BMP) ligands. Notably, the BMPR-II/ALK-1 heterodimer signals with relative specificity in response to BMP9 and BMP10 in human microvascular endothelial cells (ECs) [11], while BMPR-II/ALK-3 or -6 signals in response to BMP2 or BMP4 in smooth muscle cells [12]. Upon ligand binding, the receptor phosphorylates **SMAD proteins** (mothers against decapentaplegic homologs) that complex and translocate to the nucleus, regulating in turn the expression of target genes [e.g., inhibitor of DNA binding (**ID**) proteins] through SMAD binding elements (Figure 1) [13].

Glossary

Anastrozole: a drug used to reduce the conversion of androgens to estrogens.
Angioproliferative plexiform lesions: disorganized growth of EC characteristic of PAH. Other histological changes include thickening of intimal and medial layers, muscularization of distal pulmonary arteries, and vascular occlusion.
Blood outgrowth endothelial cells: cells cultured from human peripheral blood samples. These cells develop a typical cobblestone morphology characteristic of EC monolayers and express mature EC surface markers.
Bone morphogenetic proteins (BMPs): members of the TGF-β superfamily, known to regulate embryonic patterning and organogenesis. BMPs also have a range of roles as endocrine mediators of cardiovascular, metabolic, and hematopoietic functions.
Chuvash polycythemia: autosomal recessive form of familial erythrocytosis endemic to Chuvashia, caused by a mutation in the *VHL* gene.
Dichloroacetate (DCA): a pyruvate dehydrogenase kinase inhibitor that inhibits glycolysis (typically enhanced in PAH tissue and the right ventricle) and promotes oxidative phosphorylation.
DNA damage: DNA is vulnerable to damage from multiple endogenous and exogenous insults, including oxidative stress, radiation, and inflammation. While multiple repair pathways exist, errors can occur during repair, leading to sequence alterations, deletions, and translocations.
Endothelial dysfunction: an imbalance of vasoactive mediators released from the pulmonary vascular endothelium resulting in vasoconstriction and failure to suppress smooth muscle cell proliferation.
Endothelial-to-mesenchymal transition (EndoMT): process by which EC acquire a mesenchymal phenotype in association with the expression of smooth muscle cell histological markers and genes.
Forkhead box O1 (FoxO1): belongs to the Forkhead family of transcription factors and regulates a variety of