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New Molecular Targets of Pulmonary Vascular Remodeling in Pulmonary Arterial Hypertension

Importance of Endothelial Communication

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Pulmonary arterial hypertension (PAH) is a disorder in which mechanical obstruction of the pulmonary vascular bed is largely responsible for the rise in mean pulmonary arterial pressure, resulting in a progressive functional decline despite current available therapeutic options. The fundamental pathogenetic mechanisms underlying this disorder include pulmonary vasoconstriction, in situ thrombosis, medial hypertrophy, and intimal proliferation, leading to occlusion of the small to mid-sized pulmonary arterioles and the formation of plexiform lesions. Several predisposing or promoting mechanisms that contribute to excessive pulmonary vascular remodeling in PAH have emerged, such as altered crosstalk between cells within the vascular wall, sustained inflammation and dysimmunity, inhibition of cell death, and excessive activation of signaling pathways, in addition to the impact of systemic hormones, local growth factors, cytokines, transcription factors, and germline mutations. Although the spectrum of therapeutic options for PAH has expanded in the last 20 years, available therapies remain essentially palliative. However, over the past decade, a better understanding of new key regulators of this irreversible pulmonary vascular remodeling has been obtained. This review examines the state-of-the-art potential new targets for innovative research in PAH, focusing on (1) the crosstalk between cells within the pulmonary vascular wall, with particular attention to the role played by dysfunctional endothelial cells; (2) aberrant inflammatory and immune responses; (3) the abnormal extracellular matrix function; and (4) altered BMPRII/KCNK3 signaling systems. A better understanding of novel pathways and therapeutic targets will help in the designing of new and more effective approaches for PAH treatment.

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ABBREVIATIONS: 5-HT = serotonin; AngII = angiotensin II; BMPRII = bone morphogenetic protein receptor II; EC = endothelial cell; ECM = extracellular matrix; ET = endothelin; FGF = fibroblast growth factor; MCP = monocyte chemoattractant protein; MIF = migration inhibitory factor; miRNA = microRNA; MMP = matrix metalloproteinase; mPAP = mean pulmonary arterial pressure; NO = nitric oxide; PAH = pulmonary arterial hypertension; PGI2 = prostacyclin; PH = pulmonary hypertension; SMC = smooth muscle cell; TGF = transforming growth factor; Treg = regulatory T lymphocyte

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Pulmonary hypertension (PH) is a complex and multifactorial cardiopulmonary disorder characterized by a progressive sustained increase in mean pulmonary arterial pressure (mPAP), leading to right-sided heart failure and death. PH can result from precapillary (arterial) or postcapillary (venous) pathomechanisms. The current PH clinical classification gathers groups of PH that share similar hemodynamic criteria and types of pulmonary vascular lesions to optimize therapeutic approaches, predict patient outcomes, and facilitate research strategies.[1]

Group 1 PH corresponds to pulmonary arterial hypertension (PAH). PAH is characterized by precapillary PH (mPAP $\geq$ 25 mm Hg, with a normal pulmonary capillary wedge pressure $\leq$ 15 mm Hg) due to major pulmonary arterial remodeling. In the absence of specific treatments, patients have a mean survival of 2.8 years.[1,2] Specific therapies that have been approved for use to manage PAH include agents that have important vasoactive effects, modulating abnormalities in three main pathobiologic pathways for PAH: endothelin (ET)-1, prostacyclin (PGI2), and nitric oxide (NO). However, these current therapeutic options only partially improve symptoms and survival, and lung transplantation remains an important treatment in eligible patients with severe PAH refractory to medical management.

Irreversible remodeling of the pulmonary vascular bed is the cause of increased mPAP in PAH and frequently leads to progressive functional decline in patients despite the available medical treatments. The increasing knowledge about PAH pathogenesis clearly underscores the importance of microenvironmental alterations and, in particular, of the crosstalk between pulmonary vascular-wall cells in PAH development and/or progression. Among these intercell communications, the crosstalk between dysfunctional endothelial cells (ECs) and the other components of the pulmonary vascular wall, such as smooth muscle cells (SMCs), myofibroblasts, and pericytes, or the circulating immune cells, represent a key feature of PAH pathogenesis.

This article reviews the current knowledge of the intrinsic abnormal properties of pulmonary ECs from patients with PAH and their functional effects on the different vascular-wall cell types. In addition, we profile the innovative research into novel pathways and therapeutic targets that may lead to the development of targeted agents for use in PAH.

Basic Pathomechanisms Contributing to the Development and/or Progression of PAH

Pulmonary vascular lesions occurring in patients with PAH (as well as in animal models of the disease) include, to varying degrees, abnormal muscularization of distal and medial precapillary arteries, loss of precapillary arteries, thickening of the pulmonary arteriolar wall with concentric or eccentric laminar lesions, neointimal formation, fibrinoid necrosis, and the formation of complex lesions commonly named "plexiform lesions."[3] Although different forms of PAH could reflect distinct pathomechanisms, current evidence strongly suggests that a common denominator underlying many of the established molecular and cellular elements is altered crosstalk between cells within the vascular wall (ie, SMCs, myofibroblasts, pericytes, and ECs) and also sustained inflammation and dysimmunity, altered energy metabolism, inhibition of cell death, and excessive activation of some growth factor-stimulated signaling pathways, in addition to the interaction of systemic hormones, local growth factors, cytokines, and transcription factors.

The understanding of the etiology of PAH continues to evolve, including many disease-predisposing and/or contributing factors, such as inflammation, pulmonary endothelial dysfunction, aberrant vascular-wall cell proliferation, and several gene mutations (Fig 1).[3-6] Therefore, the molecular and cellular bases of the pulmonary vascular remodeling associated with PAH needs clarification to better understand the disease and to propose new, more adapted, and more powerful therapeutic tools.

Restoration of Functional Cellular Crosstalk Between Cells Within the Vascular Wall

Clinical and preclinical studies strongly support the idea that the aberrant local microenvironment in the pulmonary vascular wall plays a critical role in either initiation and/or perpetuation of the characteristic progressive pulmonary arterial obstruction in PAH. Investigations provide evidence that the pulmonary endothelium in PAH is a critical local source of several key mediators for vascular remodeling, including growth factors (fibroblast growth factor [FGF]-2, serotonin [5-HT], angiotensin II [AngII]), and vasoactive peptides (NO, PGI2, ET-1), cytokines (IL-1, IL-6, macrophage migration inhibitory factor [MIF]), and chemokines (monocyte chemoattractant protein [MCP]-1), adipokines (leptin).[7-13] Indeed, our group has underscored altered crosstalk between cells within the vascular wall and, more specifically, between pulmonary ECs and