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Review

Cellular interplay in pulmonary arterial hypertension: Implications for new therapies

Rita Nogueira-Ferreira [a,b,*], Rita Ferreira [a], Tiago Henriques-Coelho [b]

[a] QOPNA, Department of Chemistry, University of Aveiro, Aveiro, Portugal
[b] Department of Physiology and Cardiothoracic Surgery, Faculty of Medicine, University of Porto, Porto, Portugal

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ABSTRACT

Pulmonary arterial hypertension (PAH) is a complex and multifactorial disease characterized by vascular remodeling, vasoconstriction, inflammation and thrombosis. Although the available therapies have resulted in improvements in morbidity and survival, PAH remains a severe and devastating disease with a poor prognosis and a high mortality, justifying the need of novel therapeutic targets. An increasing number of studies have demonstrated that endothelial cells (ECs), smooth muscle cells (SMCs) and fibroblasts of the pulmonary vessel wall, as well as platelets and inflammatory cells have a role in PAH pathogenesis. This review aims to integrate the interplay among different types of cells, during PAH development and progression, and the impact of current therapies in cellular modulation. The interplay among endothelial cells, smooth muscle cells and fibroblasts present in pulmonary vessels wall, platelets and inflammatory cells is regulated by several mediators produced by these cells, contributing to the pathophysiologic features of PAH. Current therapies are mainly focused in the pulmonary vascular tone and in the endothelial dysfunction. However, once they have not been effective, novel therapies targeting other PAH features, such as inflammation and platelet dysfunction are emerging. Further understanding of the interplay among different vascular cell types involved in PAH development and progression can contribute to find novel therapeutic targets, decreasing PAH mortality and morbidity in the future.

1. Introduction

Pulmonary arterial hypertension is a progressive and life-threatening disease, multifactorial in nature [1,2]. Although the "trigger" that leads to the disease is still unknown, a complex interplay among different types of cells occurs and multiple alterations are verified: (i) intimal hyperplasia; (ii) medial hypertrophy and hyperplasia; (iii) adventitia proliferation; (iv) neointima formation and (v) occurrence of plexiform lesions. In addition, these changes are accompanied by vasoconstriction, local inflammation and thrombosis in situ [3–6].

Endothelial cells, located in the inner layer of the pulmonary artery wall, have several O_2-sensing mechanisms, including O_2-sensitive NADPH oxidases, endothelial nitric oxide synthase, and heme oxygenases [7,8]. Vascular smooth muscle cells, located in the medial layer, have multiple stretch-sensing mechanisms, and are able to convert a mechanical stimulus into an intracellular signal that leads to modulation of gene expression and cellular function, such as contraction, proliferation, apoptosis and migration [9]. Fibroblasts, present in the adventitial compartment, may be considered the principal injury-sensing cells. They may experience functional changes due to stimuli such as vascular injury (Fig. 1) [10].

Abbreviations: 5-HT, serotonin; 5-HT_{1B}, serotonin type 1B receptor; 5-HT_{2A}, serotonin type 2A receptor; 5-HT_{2B}, serotonin type 2B receptor; 5-HTT, serotonin transporter; ADP, adenosine diphosphate; ATP, adenosine triphosphate; AVD, apoptotic volume decrease; BMP, bone morphogenetic protein; BMPRII, bone morphogenetic protein receptor type II; cAMP, cyclic adenosine monophosphate; cav-1, caveolin-1; CCBs, calcium channel blockers; cGMP, cyclic guanosine monophosphate; DNA, deoxyribonucleic acid; ECM, extracellular matrix; ECs, endothelial cells; eNOS, endothelial nitric oxide synthase; EPCs, endothelial progenitor cells; ET-1, endothelin-1; ET_A, endothelin-1 type A receptor; ET_B, endothelin-1 type B receptor; FKN, fractalkine; HA, hyaluronic acid; MCT, monocrotaline; MMPs, matrix metalloproteinases; mRNA, messenger ribonucleic acid; NADPH, nicotinamide adenine dinucleotide phosphate; NO, nitric oxide; PAECs, pulmonary artery endothelial cells; PAH, pulmonary arterial hypertension; PAI-1, plasminogen activator inhibitor-1; PASMCs, pulmonary artery smooth muscle cells; PDE-5, phosphodiesterase type 5; PDGF, platelet-derived growth factor; PGI_2, prostacyclin; RANTES, Regulated upon Activation, Normal T-cell Expressed and Secreted; ROCK, Rho kinase; SMCs, smooth muscle cells; SM-MHC, smooth muscle-myosin heavy chain; SNAPs, soluble ATPase N-ethylmaleimide-sensitive factor association proteins; SNAREs, SNAP receptors; TASK-1, two pore-related acid-sensitive potassium channel-1; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α; t-PA, tissue plasminogen activator; TXA_2, thromboxane A_2; VDCC, voltage-dependent calcium channels; α-SMA, α-smooth muscle actin

* Corresponding author at: Chemistry Department, University of Aveiro, Campus de Santiago, 3810-193 Aveiro, Portugal. Tel.: +351 234370700; fax: +351 234370084.
E-mail address: rmferreira@ua.pt (R. Nogueira-Ferreira).

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Table 1
Current and novel therapies for pulmonary arterial hypertension.

Current therapies	Novel therapies
Endothelial cells	
Prostacyclin analogs	Rho kinase inhibitor
Epoprostenol	Fasudil
Treprostinil	
Iloprost	
Endothelin-1 receptor antagonists	Dual endothelin-1 receptor antagonist
Bosentan	Macitentan
Ambrisentan	Pyruvate dehydrogenase kinase inhibitor
	Dichloroacetate
	Endothelial progenitor cells
Smooth muscle cells	
Phosphodiesterase inhibitors	Soluble guanylate cyclase stimulator
Sildenafil	Riociguat
Tadalafil	
Calcium channel blockers	Prostacyclin receptor agonist
Nifedipine	Selexipag
Diltiazem	
Amlodipine	
Fibroblasts	
	Elastase inhibitors
Inflammatory cells	
	Rapamycin
	Tryptolide
	Thymulin
Platelets	
	Thromboxane synthesis inhibitors
	Ozagrel
	Furegrelate

Given the role of these cell types in the regulation of several vascular processes, the next points intend to detail various aspects of the contribution of these cell types to development and progression of PAH as well as of platelets and inflammatory cells. The mediators that regulate the interplay between these distinct cell types during PAH development and progression will also be analyzed envisioning novel therapeutic targets.

2. Endothelial cells

2.1. Role in pathophysiology of PAH

Endothelial damage is a key initial event in PAH. Although the mechanisms that mediate this damage are largely unknown, insults such as chronic hypoxia, inflammation, viral infection, mechanical stretch or shear stress, can activate the endothelial apparatus and induce cell apoptosis [11]. The death of ECs leads to the appearance of apoptotic-resistant and hyper-proliferative ECs, contributing to the vascular remodeling [12]. Endothelial cells not only contribute to the vascular remodeling linked to PAH development, but also regulate the related vasoconstriction and thrombosis processes, through the production and release of several mediators [2].

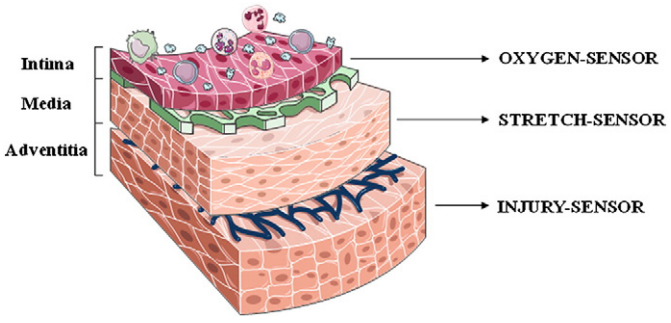

Fig. 1. "Sensing" mechanisms in the different layers of the pulmonary artery wall. Endothelial cells of the intima are equipped with mechanisms to sense differences in the oxygen supply. Medial smooth muscle cells have multiple stretch-sensing mechanisms that participate in the modulation of their functions. Fibroblasts, present in the adventitia, are considered the principal injury-sensing cells.

Endothelial cell migration and proliferation were thought to be responsible for the regeneration of injured endothelium. However, additional mechanisms were shown to replace the denuded or injured arteries. It has been reported that endothelial progenitor cells (EPCs) exert important functions in repairing and maintaining the integrity of the endothelial monolayer by replacing denuded parts of the artery [13]. After several pre-clinical studies demonstrate the beneficial effects of EPC administration, which was translated into a decrease of right ventricle systolic pressure, as well as a decrease in pulmonary and cardiac remodeling [14], clinical trials were performed. Autologous EPC administration in adult and pediatric idiopathic PAH patients showed an improvement on pulmonary hemodynamics and exercise capacity [15,16]. These results contrast with the finding that EPCs can contribute to PAH-related vascular remodeling [17]. However, given the promising results observed in clinical studies, the use of EPCs as a therapeutic option continues to be investigated. The results of the clinical trial PH (pulmonary hypertension) and Cell Therapy (PHACeT trial; ClinicalTrials.gov Identifier: NCT00469027), performed with the aim of evaluating the safety of administering autologous progenitor cells transduced with eNOS in idiopathic PAH patients are awaited. Furthermore, a combined therapy with autologous bone marrow-derived EPCs and sildenafil (a phosphodiesterase type 5 inhibitor) showed a superior efficacy than either bone marrow-derived EPCs or sildenafil alone in preventing monocrotaline (MCT)-induced PAH [18]. This combined therapy successfully abolished PAH-induced hemodynamic impacts on the right ventricle. Despite these encouraging results, it is yet unclear what is the EPC mechanism of action in PAH treatment. In this setting, a study reported that EPC infusion prevented MCT-induced PAH in athymic nude rats through a mechanism that requires the presence of natural killer cells [19].

2.2. Intracellular pathways modulated by PAH

The increase of endothelial cell permeability seems to have a huge contribution to PAH pathogenesis [20]. Stimuli that activate RhoA/ROCK, like thrombin, increase endothelial permeability. Stimuli that stimulate Rac1/p21-activated kinase, like prostacyclin (PGI_2), promote barrier integrity [20,21]. The net effect of EC permeability favors the release of mediators like endothelin-1 (ET-1), nitric oxide (NO), PGI_2 and thromboxane-A_2 (TXA_2) on SMCs and platelets. In addition, endothelial dysfunction in PAH can be reflected by a reduction in vasodilators/growth inhibitors like NO and PGI_2, and an increase in vasoconstrictors/co-mitogens like ET-1 and TXA_2 [20].

Another pathway that seems to contribute to EC permeability is the bone morphogenetic protein (BMP) signaling pathway. Recently, the loss of bone morphogenetic protein type II receptor (BMPRII) in ECs was reported to promote the extravasation of leucocytes into the pulmonary artery wall, increasing the susceptibility to inflammation [22]. Bone morphogenetic proteins are members of the transforming growth factor-β (TGF-β) family and signal via BMP type I and II receptors, which are serine/threonine kinase transmembrane receptors. This interaction with the receptors usually activates Smad1/5/8 that form complexes with Smad4 and translocate to the nucleus, regulating gene expression through the interaction with transcription factors. Besides the canonical Smad signaling, non-Smad pathways, such as the MAPK (mitogen-activated protein kinase), can also be involved [23,24]. As it is known, several gene mutations that lead to BMPRII loss of function have been associated to heritable PAH [25,26]. However, BMPRII expression is reduced in the pulmonary vasculature of patients with heritable and idiopathic PAH, independently of whether they present or not the BMPRII gene mutation [27]. In ECs, BMPRII activation seems to promote cell proliferation, migration and survival [28,29]. Loss of BMPRII function in these cells was reported to induce apoptosis, contributing to the