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Medicine in focus

Pulmonary arterial hypertension: New pathophysiological insights and emerging therapeutic targets

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ABSTRACT

Pulmonary arterial hypertension (PAH) encompasses a group of clinical entities characterized by sustained vasoconstriction and progressive vascular remodeling that act in concert to elevate pulmonary vascular resistance. The current treatments for PAH are mainly dedicated to target the process of vasoconstriction and do not offer a cure. There is now accumulating evidence that expansion of pulmonary artery cells due to increased proliferation and apoptotic evasion is a key pathological component of vascular remodeling that occurs in PAH. Thus, vascular lesions seen in advanced PAH patients present some cancer-like characteristics offering important avenues for exploration and expanding treatment options. In this review article, we will discuss recent advances into mechanisms underlying disease progression, with a focus on pulmonary artery smooth muscle cells.

1. Introduction

Pulmonary arterial hypertension (PAH) is a progressive and fatal disease characterized by vasoconstriction and vascular remodeling of distal pulmonary arteries (PAs), resulting in a persistent elevation of the mean PA pressure above 25 mmHg at rest, and ultimately in right heart failure (Lau et al., 2017). PAH is classified into subgroups based on etiology, including idiopathic, heritable (corresponding mostly with heterozygous germline Bone morphogenetic protein receptor-type 2, BMPR2 mutations), drug-induced (e.g. appetite suppressants, methamphetamine, etc.) and associated with other conditions (e.g. scleroderma, HIV, etc.) (Lau et al., 2017). Regardless of their etiology, all forms of PAH exhibit similar pulmonary vascular lesions suggesting shared pathological mechanisms. Mounting evidence supports the concept that development of PAH follows a biphasic pattern; a model supported by studies showing that apoptotic drugs able to reverse advanced PAH (Schermuly et al., 2005), at the expense of severe side effects (Hoeper et al., 2013), also predispose to development of the disease (Guignabert et al., 2016). Indeed, due to genetic predisposition and exposition to numerous insults (e.g. oxidative and shear stresses, inflammation), PA endothelial cell (PAEC) dysfunction is recognized as the primary event that causes PAH. In this model, PAECs that undergo apoptosis liberate a variety of cytokines and growth factors creating conditions that subsequently stimulate vessel constriction along with favoring the emergence of highly proliferative and apoptosis-resistant PA vascular cells, including PA smooth muscle cells (PASMCs), adventitial fibroblasts, but also PAECs themselves (Figs. 1 and 2). These alterations lead to a gradual narrowing of the vascular luminal and possibly to complete occlusion. Currently approved drugs for PAH, mainly dedicated to reduce the pulmonary vasomotor tone, do not cure the disease and only confer modest mortality and quality of life benefits (Lajoie et al., 2016). In view of this, the pathogenic paradigm of PAH has gradually shifted away from vasoconstriction towards much greater focus on vascular remodeling with significant research effort directed toward deciphering the molecular mechanisms allowing PA cells (especially PASMCs) to survive and hyper-proliferate, notwithstanding exposure to chronic damaging stresses (Boucherat et al., 2017). Considering that the phenotype of PAH cells in an advanced stage of the disease is quite similar to that observed in cancer cells, this suggests that lessons learned from the field of oncology may provide valuable insights into PAH pathogenesis, and indirectly that drugs currently used in cancer and demonstrating safety profiles could be repurposed to tackle PAH. While inflammation and genetic abnormalities are key factors of PAH pathogenesis, determining the role of DNA damage response, metabolic reprogramming, endothelial-mesenchymal transition and epigenetics have become a major focus in PAH research and substantial effort are directed towards identifying clinical targets.

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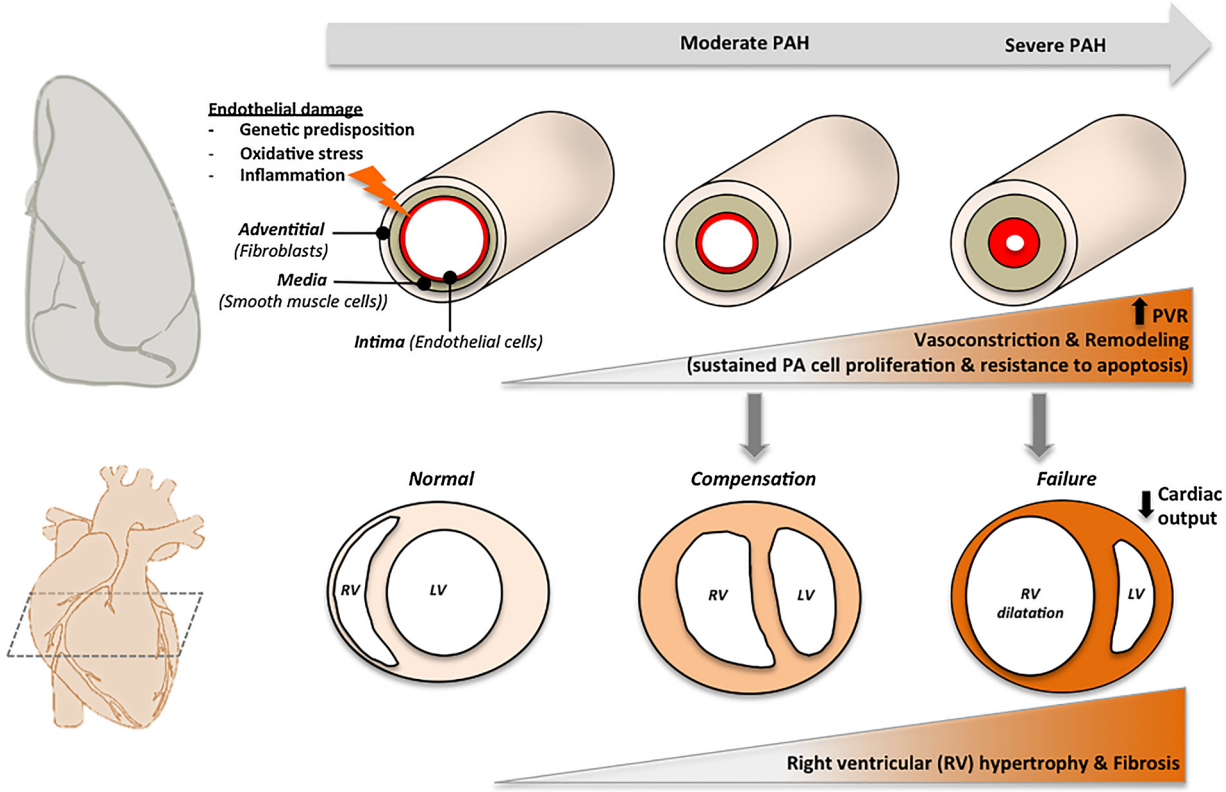

Fig. 1. Schematic progression of pulmonary arterial hypertension. Following endothelial dysfunction, distal pulmonary arteries (PAs) undergo progressive vascular remodeling associated with exaggerated proliferation and resistance to apoptosis of PA resident cells. This structural change progressively results in occlusion of the pulmonary vascular lumen and contributes to elevations of pulmonary vascular resistances (PVR) and PA pressure. As a result of pressure-overload, the right ventricle (RV) initially compensates by an increase in hypertrophy and contractibility to maintain cardiac output (CO). In most of patients, however, these compensatory mechanisms fail and premature death occurs.

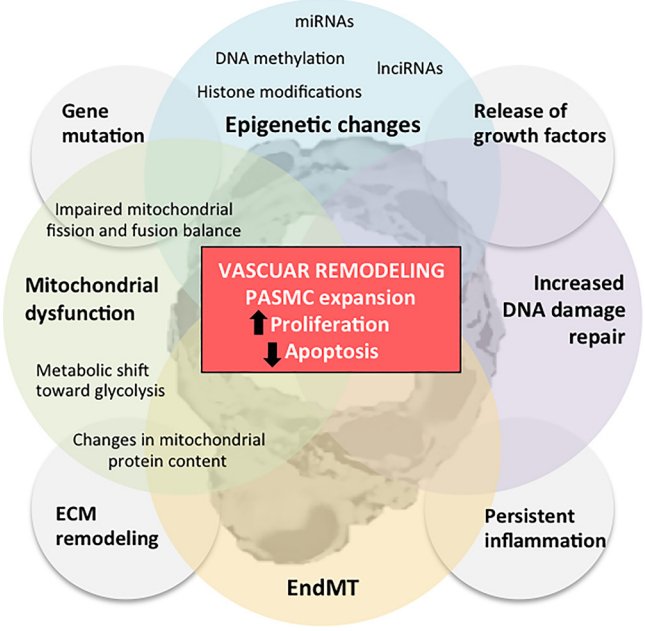

Fig. 2. Pathological factors contributing to vascular remodeling in PAH by stimulation of pulmonary artery smooth muscle cell (PASMC) expansion. ECM, extracellular matrix.

2. Pathogenesis

2.1. Immune dysregulation

As a result of perivascular accumulation of immune cells (such as macrophages, lymphocytes, dendritic and mast cells), a myriad of pro-inflammatory mediators have been documented to be increased in PAH patients, collectively contributing to the initiation and progression of vascular remodeling (Kuebler et al., 2018). Among them, the interleukin-6 (IL-6) is considered one of the primary target, as (i) its serum concentration is elevated in PAH patients (Humbert et al., 1995) and predicts survival (Soon et al., 2010); (ii) its overexpression induces pulmonary hypertension (PH) in mice (Steiner et al., 2009); and (iii) inhibition of its signaling pathway prevents and reverses PH in animal models by, at least in part, reducing the apoptosis-resistant threshold in PASMCs (Tamura et al., 2018). Although other evidence connect immune dysregulation to PAH, such as protection against PH development in xenograft lung cancer models in immunodeficeint mice (Pullamsetti et al., 2017) and the presence of circulating autoantibodies (Kuebler et al., 2018), the beneficial effect of anti-inflammatory treatments remains limited in some human PAH subtypes.

2.2. DNA damage response

Efficient detection and repair of DNA damage is crucial for cell survival. In agreement with the two-step model for PAH development, it has been demonstrated that early PAEC dysfunction was associated with an enhanced susceptibility to DNA damage, a condition amplified by genetic loss of BMPR2 signaling or hypoxia (Diebold et al., 2015; Li et al., 2014). However, in the setting of disease progression, PAH cells exhibit sustained proliferation and survival, indicating that cells have