COPD-PH Pathogenesis

The major pathologic determinants of increased PVR in COPD are pulmonary vascular remodeling and reduced vascular density, or vascular pruning. Pulmonary vascular remodeling, consisting mainly of thickening of the intimal layer in pulmonary arteries (PA) and arterioles, is highly prevalent in COPD, even in patients without PH and also in smokers without airflow obstruction.(1-3) In non-severe COPD-PH, hypertrophy of the muscular layer and muscularization of the arterioles has been described, while in severe COPD-PH prominent muscularization of pulmonary arterioles becomes apparent.(4-6)

Pulmonary vascular remodeling in COPD-PH includes proliferation of endothelial cells (ECs), smooth muscle cells (SMCs), and fibroblasts leading to intimal hyperplasia and medial hypertrophy of arteries or arterioles in concert with endothelial injury and reduced capillary density.(1, 7-9) Endothelial dysfunction plays a central role in the pathogenesis of PH in COPD.(7, 8) It is associated with changes in the availability/release of vasoactive mediators with an imbalance favoring vasoconstriction, cell proliferation and vascular remodeling.(1, 2, 7, 8, 10) Reduced endothelium-dependent relaxation of PA has been shown across a spectrum of COPD severity and correlates with the severity of vessel remodeling.(1, 2)

Proliferation of SMCs includes differentiation from resident precursor cells, de-differentiation of mature SMCs from the media that migrate to the intima, trans-differentiation of EC to SMCs, or recruitment from circulating bone marrow-derived progenitor cells.(7, 8, 11) In addition, hypoxic vasoconstriction, cigarette smoke, and inflammatory mechanisms are thought to contribute to COPD-PH.(2, 7, 8, 12) These mechanisms are interdependent, modulated by genetic factors, and may be influenced by comorbidities such as sleep-disordered breathing, left ventricle (LV) failure and chronic pulmonary thromboembolism.

Vascular pruning found histologically in the lungs of COPD patients with severe PH can also be assessed by computed tomography (CT) measurements of small vessel density itself inversely related to PA pressure in COPD.(5, 13, 14) The severity of emphysema is unrelated to pulmonary vascular remodeling and the association between small vessel density and PH severity is only apparent in patients with mild emphysema, suggesting that pulmonary vascular pruning is not due to emphysema.(3, 15, 16)

Cigarette smoking (CS) is considered a triggering event, and its effects are synergistic with those of hypoxia and inflammation in activating common signaling pathways.(2, 7, 8) The nitric oxide (NO)-soluble guanylate cyclase (sGC)-cyclic guanosine monophosphate pathway is of particular interest as COPD-PH vasculature demonstrates reduced endothelial NO synthase (eNOS) and sGC.(2, 7) In rodent models, exposure to CS, sGC stimulators or phosphodiesterase-5 (PDE-5) inhibitors attenuate PH, pulmonary vessels and right ventricle (RV) remodeling and, interestingly, the development of emphysema.(17-19)

Prostacyclin and redox pathways may also be involved in the pathogenesis of COPD-PH. Beraprost, a prostacyclin analogue, the thromboxane-A synthase receptor antagonist daltroban, and the selective cyclooxygenase-2 inhibitor celecoxib significantly inhibited CS-induced proliferation of human PA SMCs and EC.(20) Inhibition of calpain, a regulator of reactive oxygen species production, has been shown to attenuate the proliferation of PA SMCs induced by CS extract in vitro, as well as the development of PH and pulmonary vascular remodeling in rats exposed to CS.(21)

In hypoxia-induced PH rodent models, inhibition of several miRs and epigenetic modulators has been shown to attenuate pulmonary vascular and RV remodeling. In addition, there was suppression of in vitro SMC proliferation and migration through the modulation of different downstream pathways (cyclin-dependent kinase inhibitor 1A, bone morphogenetic protein receptor type 2 (BMPR2) and nitric oxide synthase 1 (NOS)).(22)

ILD-PH Pathogenesis

Pathogenesis

The current understanding of PH pathogenesis in ILD incorporates multiple contributory mechanisms, rather than the previously held prominence accounted to the role of hypoxia. The postulated mechanisms of ILD-PH include hypoxic vasoconstriction, disrupted angiogenesis resulting in decreased vascularity in fibrotic areas and increased microvascular density in nonfibrotic areas, neoangiogenesis, reduced capacitance and elastance of the vascular bed due to parenchymal destruction, as well as compression of peripheral lung vessels by collagen-rich fibrosis. In addition, shared pathways are dysregulated between fibrogenesis and PH causing remodeling of vasculature with intimal fibrosis and medial hypertrophy with hyperplasia of SMCs and fibroblasts, as well as endothelial-to-mesenchymal cell transition.(8, 23-25) Variable forms of neoangiogenesis exist in different ILDs (i.e. aberrant sprouting angiogenesis in UIP and misguided intussusceptive angiogenesis in NSIP).(26) Cigarette smoke (CS) appears to play an independent role in the development of a pulmonary vasculopathy through complex mechanisms including the decreased expression of endothelial NOS.(27) In addition, there is emerging data on the role of air pollution on endothelial function in ILD.(28) In IPF) specifically, pulmonary veins show constrictive remodeling in both preserved and fibrotic areas, even in the absence of arterial remodeling.(29)

On the molecular level, disruption in endothelial NOS, transforming growth factor (TGF)-β1, hypoxia inducible factor-1 alpha, vascular endothelial growth factor (VEGF)-A, tumor necrosis factor (TNF)-α, platelet derived growth factor (PDGF), fibroblast growth factor (FGF), profibrogenic leukotrienes, miRs, and transcription factor Slug/prolactin-induced protein are all thought to play a role.(8, 23, 27)

Little is known about the genetic variability that may contribute to the pathogenesis of ILD-PH. Patients with IPF-PH have a specific gene signature including expression of mediators of PA SMC and EC proliferation, Wnt signaling, complement system activation, and extracellular matrix (ECM) remodeling and apoptosis.(8, 23, 30) Several studies have linked the reduced expression of bone morphogenic protein receptor (BMPR) 2 (and imbalance in P-SMAD 1/5/8 versus P-SMAD 2/3) to the development of vasculopathy in ILD.(31, 32) A recent neuronal network analysis suggested that there is shared genetic and protein dysregulation in EC proliferation and migration in patients with IPF, PAH and pulmonary veno-occlusive disease (PVOD) with similarities in anti-inflammatory, anti-angiogenic and anti-apoptotic pathway dysregulation in IPF and PVOD cohorts.(33)

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