LEARNING THE ROPES: PULMONARY HYPERTENSION

Novel concepts in the endothelial pathobiology of pulmonary arterial hypertension: Piecing the puzzle together

NICHOLAS D. COBER^{1,2} & DUNCAN J. STEWART^{1,2,3}

¹Sinclair Centre for Regenerative Medicine, Regenerative Medicine Program, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada. ²Department of Cellular and Molecular Medicine, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada

³Division of Cardiology, University of Ottawa Heart Institute, Canada

DOI: 10.30824/2103-6

Pulmonary hypertension (PH) is defined as mean pulmonary arterial pressures >20mmHg, assessed by right heart catheterization¹. Based on the underlying etiology, PH can be further sub classified into 5 categories, whereby Group 1 PH, or pulmonary arterial hypertension (PAH), results from progressive pruning of the lung arteriolar bed leading to increases in pulmonary vascular resistance (PVR) and pulmonary arterial pressures. Hallmarks of PAH include intimal and medial pulmonary arterial thickening and the formation of obliterative 'plexiform' arterial lesions². Although there has been considerable progress in the elucidation of the mechanisms that lead to vascular abnormalities in PAH over the last 3 decades, there is still no consensus on a unified pathway from initial endothelial injury to the development of advanced disease. Current PAH therapies address only symptoms, delaying but not preventing disease progression; therefore, it is of the utmost importance that a more complete, end-to-end understanding of the pathobiology of PAH be established to guide the development of potentially curative treatments. In this brief review we will outline three major paradigms for the endothelial pathobiology of PAH which we will attempt to reconcile into a cohesive conceptual framework for the pathophysiology of this devastating disease.

Endothelial dysfunction in PAH

The concept of endothelial dysfunction as a major mechanism in the pathogenesis of PAH emerged in the late 1980s and early 90s with the discovery that endothelial cells (EC) play a critical role in the regulation of vascular tone and structure³. Nitric oxide, prostacyclin, and endothelin-1 are potent endothelial-derived vasomotor factors, the levels of which are profoundly altered in PAH. Endothelial dysfunction is characterized by decreased levels of endothelial nitric oxide synthase (eNOS) and prostacyclin synthase in pulmonary vessels, and increased levels of the potent vasoconstrictor, endothelin-1 which contribute to increased vasoconstriction as well as smooth muscle cell proliferation and medial thickening resulting in narrowing of lung arteries^{1,3}. Currently approved PAH-specific therapies seek to mitigate the hemodynamic consequences of endothelial dysfunction using medications that target each of these three pathways, including prostanoids (parenteral, inhaled and oral), endothelin receptor blockers, and PDE5 inhibitors or soluble guanylate cyclase stimulators⁴. While current therapies have been beneficial in improving symptoms and outcomes for PAH patients, the 5-year mortality remains high (~50%)⁴ suggesting that targeting endothelial dysfunction alone is not sufficient to reverse the underlying vascular pathology in this disease.

Endothelial apoptosis leading to dysregulated vascular cell growth: the proliferative hypothesis

Many of the manifestations of severe PAH, including the formation of complex plexiform lesions, can be reproduced in a rat model of PAH in which EC apoptosis is induced by inhibition of VEGF signaling with SU5416 (SU), combined with a 3-week exposure to hypoxia (Hx)⁵. In this model, the appearance of growth dysregulated, cancer-like vascular cells is thought to drive the formation of complex arterial lesions which can obliterate the arterial lumen thus contributing to increased vascular resistance and disease progression. This paradigm has garnered considerable interest and has generated a plethora of possible mechanisms mediating dysregulated vascular cell growth as potential therapeutic targets^{2,6}, some of which are now in the early stages of clinical development.

However, there are aspects of the pathogenesis of PAH that are not well explained by the proliferative paradigm, particularly relating to the early phases of the disease in which pulmonary arterial pressures may be elevated even preceding the appearance of obliterative arteriopathy. In particular, a recent study using the rat SU-Hx model of PAH has demonstrated that reducing pulmonary blood flow by banding one pulmonary artery can reverse obliterative arterial remodeling in the banded lung, suggesting that perturbation in pulmonary hemodynamics related to increased intimal shear stress is a prerequisite for the development of complex arterial remodeling⁷. In other words, occlusive arteriopathy maybe a consequence but not the cause of the hemodynamic abnormalities in PAH, which begs the question of what mechanisms underlies the initial development of this disease.

Endothelial injury leading to arteriolar 'drop-out': the degenerative hypothesis

We have argued that the initial onset of hemodynamic abnormalities in PAH can occur as a direct result of EC injury and apoptosis⁸. In this paradigm, EC loss leads to 'drop out' of fragile precapillary arterioles, which consist of little more than endothelial tubes with occasional mural cells. This results in functional pruning of the distal lung arterial circulation which directly increases arterial resistance and pressure, creating the hemodynamic conditions that can give rise to proliferative arterial remodeling. With the progressive loss of lung arterial area, the remaining microvascular bed needs to accommodate the cardiac output which results in marked increases in intimal shear stress⁹. Indeed,

this recapitulates the hemodynamic abnormalities which underly the development of PAH in patients with congenital heart disease (CHD) and a large left to right shunt in which pathological intimal shear forces are thought to cause ongoing endothelial injury leading to progressive pulmonary arterial remodeling⁵.

Persistent cycle of endothelial injury and failed repair in PAH: the final piece of the puzzle?

Thus far, we have connected three of the puzzle pieces in the pathophysiology of PAH (Figure): 1) Endothelial dysfunction increases pulmonary arterial tone and medial thickness contributing to early increases in arterial resistance; 2) Endothelial apoptosis leads to drop-out of fragile precapillary vessels, arteriolar pruning and the worsening lung hemodynamic abnormalities, which in turn perpetuate EC injury through pathological levels of intimal shear stress and; 3) Persistent hemodynamic abnormalities lead to the development of proliferative arterial remodeling and occlusive arteriopathy. However, the link between EC loss and the emergence of growth dysregulated vascular cells remains unclear. It is likely that EC proliferation, which is apparent even in the early stages of the SU-hypoxia model, represents an attempt to repair the endothelial damage and restore the lung microvasculature. But endothelial repair may be overwhelmed by ongoing EC loss caused by protracted intimal injury. Over time, this cycle of ongoing injury and repair could lead to exhaustion and senescence of regenerative cells, amplifying proliferative and inflammatory signaling through the senescence associated secretory phenotype. Indeed, Van der Fenn et al. have recently demonstrated that reversibility of arterial remodeling may be time-limited in a model of CHD associated PAH induced by monocrotaline combined with the creation of a surgical aortocaval shunt. They showed that the reversal of complex arterial remodeling after transplantation of a PAH lung into a normal host was lost after 21 days, which coincided with the appearance of markers of EC senescence¹⁰. Thus, these data are consistent with the concept of a vicious cycle of ongoing EC injury and repair during the development of PAH which eventually leads to exhaustion of reparative mechanisms (Figure). Therefore, targeting EC repair and senescence may represent another potential therapeutic target for PAH.

These paradigms provide a conceptual framework for understanding the complex pathobiology of PAH and suggest new opportunities to develop novel therapies for this devastating disease. Ultimately, the validity and relative importance of

each of these concepts will be established by the effectiveness of therapeutic strategies developed to target these interrelated mechanisms. After many decades and intensive research, it is only by embracing these new ideas that a curative therapy for PAH may one day be found.

References

1. Evans, C. E., Cober, N. D., Dai, Z., Stewart, D. J. & Zhao, Y.-Y. Endothelial Cells in the Pathogenesis of Pulmonary Arterial Hypertension. *Eur. Respir. J.* 2003957 (2021). doi:[10.1183/13993003.03957-2020](https://doi.org/10.1183/13993003.03957-2020)
2. Humbert, M. et al. Pathology and pathobiology of pulmonary hypertension: state of the art and research perspectives. *The European respiratory journal* vol. 53 (2019). DOI: [10.1183/13993003.01887-2018](https://doi.org/10.1183/13993003.01887-2018)
3. Kurakula, K. et al. Endothelial Dysfunction in Pulmonary Hypertension: Cause or Consequence? *Biomedicines* 9, 57 (2021). doi: [10.3390/biomedicines9010057](https://doi.org/10.3390/biomedicines9010057)
4. Lau, E. M. T., Giannoulatou, E., Celermajer, D. S. & Humbert, M. Epidemiology and treatment of pulmonary arterial hypertension. *Nature Reviews Cardiology* vol. 14 603–614 (2017). doi: [10.1038/nrcardio.2017.84](https://doi.org/10.1038/nrcardio.2017.84)
5. Dickinson, M. G., Bartelds, B., Borgdorff, M. A. J. & Berger, R. M. F. The role of disturbed blood flow in the development of pulmonary arterial hypertension: lessons from preclinical animal models. *Am J Physiol Lung Cell Mol Physiol* 305, 1–14 (2013). doi: [10.1152/ajplung.00031](https://doi.org/10.1152/ajplung.00031)
6. Bourgeois, A., Omura, J., Habbout, K., Bonnet, S. & Boucherat, O. Pulmonary arterial hypertension: New pathophysiological insights and emerging therapeutic targets. *International Journal of Biochemistry and Cell Biology* vol. 104 9–13 (2018). doi: [10.1016/j.biocel.2018.08.015](https://doi.org/10.1016/j.biocel.2018.08.015)
7. Abe, K. et al. Haemodynamic unloading reverses occlusive vascular lesions in severe pulmonary hypertension. *Cardiovasc. Res.* 111, 16–25 (2016). doi: [10.1093/cvr/cvw070](https://doi.org/10.1093/cvr/cvw070)
8. Chaudhary, K. R., Taha, M., Cadete, V. J. J., Godoy, R. S. & Stewart, D. J. Proliferative Versus Degenerative Paradigms in Pulmonary Arterial Hypertension. *Circ. Res.* 120, 1237–1239 (2017). doi: [10.1161/CIRCRESAHA.116.310097](https://doi.org/10.1161/CIRCRESAHA.116.310097)
9. Postles, A., Clark, A. R. & Tawhai, M. H. Dynamic blood flow and wall shear stress in pulmonary hypertensive disease. in 2014 36th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBC 2014 vol. 2014 5671–5674 (Institute of Electrical and Electronics Engineers Inc., 2014). doi: [10.1109/EMBC.2014.6944914](https://doi.org/10.1109/EMBC.2014.6944914)
10. Van Der Feen, D. E. et al. Cellular senescence impairs the reversibility of pulmonary arterial hypertension. *Sci. Transl. Med.* 12, (2020). doi: [10.1126/scitranslmed.aaw4974](https://doi.org/10.1126/scitranslmed.aaw4974)

Figure: Piecing together the paradigms of

endothelial pathobiology of PAH. Endothelial dysfunction results in increased vascular tone and narrowing, while endothelial cell (EC) apoptosis leads to arteriolar pruning. The resultant perturbed hemodynamics and increased intimal shear stress contributes to a cycle of persistent injury and endothelial repair. Failed arteriolar repair and EC senescence contribute to emergence of hyper-proliferation and complex arteriolar remodeling. Created with BioRender.com

Nicholas D. Cober - nicober@ohri.ca

Duncan J. Stewart - djstewart@toh.ca