Pulmonary arterial hypertension is believed to be a proliferative disease, triggered by endothelial cell injury and apoptosis and leading to the formation of occlusive vascular lesions caused by growth-dysregulated "cancer-like" cells. However, the current experimental and clinical evidence is not entirely consistent with this paradigm and suggests an alternate interpretation, specifically that microvascular rarefaction may be due to a degenerative process, driven by sustained endothelial cell apoptosis. The "degenerative" paradigm has important implications, not the least of which is that proliferative lesions may be a secondary manifestation of disease rather than the primary cause of microvascular rarefaction, and that regenerative strategies may be needed to restore the microcirculation in established disease.

Although there remains much debate about the precise mechanisms of pulmonary arterial hypertension, it is generally accepted that there is functional microvascular rarefaction, resulting in a marked decrease in pulmonary vascular cross-sectional area. Two distinct, and seemingly mutually exclusive, mechanisms have been proposed for the loss of lung microvasculature. The first is a proliferative process that leads to arteriolar occlusion and obliteration, and the second is a degenerative process that leads to drop-out and loss of fragile lung vasculature.

The Proliferative Hypothesis
Let's first consider the proliferative hypothesis. The so-called "cancer paradigm" of pulmonary arterial hypertension (PAH) is based on the idea that dysregulated endothelial cell (EC) growth can lead to disordered angiogenesis with the heaping up of intimal cells within the lumen causing arteriolar occlusion and obliteration. Indeed, dysregulated vascular cell growth is integrally linked to the development of plexiform lesions, which represent hallmark features of PAH. This is supported by evidence of changes in biochemical and molecular cellular activity in PAH, similar to those seen in cancer, including a shift in glucose metabolism from mitochondrial glucose oxidation to glycolysis (Warburg effect), activation of cell growth pathways, increased expression of apoptosis inhibitors, and evidence of increased DNA damage and defects in repair. Similar abnormalities in growth regulation have been demonstrated in medial smooth muscle cells and adventitial fibroblasts in PAH, all contributing to the marked arterial remodeling.

Important insights into the mechanisms underlying dysregulated cell growth have come from a new model of severe PAH in which the receptor tyrosine kinase inhibitor, SU5416 (SU), is used to block VEGF (vascular endothelial growth factor) receptor 2, followed by a 3-week exposure to hypoxia. Inhibition of VEGF receptor 2 results in widespread lung microvascular EC apoptosis, which is thought to result in the selection of apoptosis-resistant and hyper-proliferative cells. These growth-dysregulated cells then result in obliteration of distal arterioles and a progressive increase in pulmonary vascular resistance. This model produces a particularly severe and progressive PAH phenotype in rats, persisting even after animals had been returned to a normoxic environment, and characterized by obliterator lesions that closely resemble plexiform lesions seen in human patients. The SU hypoxia (SUHx) model has now been widely adopted as possibly the most relevant preclinical model for PAH. The concept of EC apoptosis playing a central role in triggering PAH has been bolstered by reports that BMPR2, which is by far the most common gene implicated in PAH, mediates EC survival, and that disease-causing BMPR2 mutations are associated with increased susceptibility to EC apoptosis. So a picture of the pathogenesis of PAH has begun to emerge, beginning with lung microvascular EC injury and apoptosis, which leads to the emergence of apoptosis-resistant, growth-dysregulated vascular cells resulting in obliterator arterial remodeling and PAH.

Fact Check—Are We Missing Something?
But how does this paradigm stand up to the evidence? Let's begin with the SUHx model that inspired this paradigm in the first place. If this idea were correct, one would expect a close correlation between the development of occlusive vascular lesions and the onset and progression of PAH. But in fact, this does not appear to be the case. Severe PAH is apparent as early as 3 weeks post SU while widespread occlusive lesions...
generally do not appear until after 5 weeks. Moreover, Abe et al. have recently reported that the development of these occlusive lesions is dependent on hemodynamic abnormalities, rather than the other way around. This group showed that banding of the left pulmonary artery in the SUHx rat model prevented complex lesion formation in the downstream lung, and lesions were only seen in the contralateral, nonbanded lung. Moreover, unilateral pulmonary artery banding 5 weeks after administration of SU reversed established lesions. Thus, abnormal pulmonary hemodynamics appear to be necessary for plexiform lesion formation, implying that a mechanism other than proliferative arterial obliteration is responsible for causing the hemodynamic abnormalities in the first place. This is consistent with the evidence of regression of plexiform arteriopathy after single lung transplantation in the nontransplanted lung, presumably driven by resolution of hemodynamic abnormalities.

The Clinical Evidence

A recent report from the REVEAL registry showed that the number and extent of plexiform and occlusive lesions correlated poorly with functional and hemodynamic abnormalities, again suggesting dissociation between complex vascular remodeling and the severity of PAH. Case reports have also pointed to discrepancies between complex arteriopathy and severity of disease in patients with PAH. For example, a patient who was well controlled on long-term parenteral prostaglandin, and succumbed to an unrelated illness, was found to have extensive plexogenic arteriopathy at autopsy, disproportionate to her functional status. The authors even speculated that prostacyclin, the gold-standard therapy for this disease, may have contributed to the extensive vascular remodeling in this patient. Finally, an intriguing report from Abman group suggests that plexiform lesions may not even arise in the pulmonary circulation in the first place. Rather, they argue that these lesions may originate in the bronchial systemic bed as a result of opening of intrapulmonary bronchial anastomoses in response to increasing pulmonary arterial pressures. The resulting overload in the bronchial microcirculation initiates complex remodeling and plexiform lesions. If correct, this would have profound implications; for example, if plexiform lesions do not actually occur within the pulmonary bed, then how can they contribute directly to increased pulmonary vascular resistance?

The Degenerative Paradigm

These observations point to a mechanism other than proliferative arteriopathy in the development of hemodynamic abnormalities in PAH. An obvious possibility is that EC apoptosis itself may contribute directly to the loss of lung microvasculature through the degeneration and drop out of fragile precapillary arterioles (Figure). Lung distal arterioles consist of little more than endothelial tubes, supported by scant matrix and the occasional pericyte. Thus, it is not hard to imagine that there would be little left to maintain the integrity of these small vascular structures after the disintegration of the endothelial monolayer. Interestingly, there has been much less interest in exploring the direct (rather than the indirect) consequences of EC apoptosis on the integrity of the lung microvascular bed in PAH. In part, this may relate to the inherent difficulties in studying the lung microcirculation, and the challenge of visualizing a discrete microvascular loss. Much of our understanding of the histopathology of PAH has come from the examination of thin sections of lung tissue in which it is easy to see evidence of proliferative arterial remodeling. In contrast, the demonstration of loss of the lung vasculature requires methods that are better suited for 3-dimensional imaging, such as micro-computerized tomography and fluorescent microangiography. By these methods it is evident that massive loss occurs rapidly in the lung microvasculature in experimental models of PAH, mainly in the distal arterioles of 100 µm or less. Moreover, areas of arteriolar “drop-out” exhibit a paucity of cells, rather than hypercellularity, consistent with a degenerative mechanism.

Therapeutic Implications

The degenerative hypothesis of PAH carries far-reaching implications. To the extent that abnormal cell proliferation is a
Consequence, rather than a cause, of hemodynamic abnormalities, then targeting proliferation per se may not be the most effective therapeutic strategy. Our hypothesis suggests that a novel approach would be to target the degenerative process itself, either by blocking EC apoptosis as the driver of arteriolar degeneration or by promoting lung microvascular repair and regeneration. Inhibition of EC apoptosis as a therapeutic strategy for PAH may seem like a heretical idea for many readers, especially as there is increasing interest in doing just the opposite; namely promoting smooth muscle cell apoptosis as a therapeutic strategy to reverse vascular remodeling in this disease. This notwithstanding, there is already data showing that the inhibition of EC apoptosis with Z-Asp-CH2-DCB can prevent the severe PAH phenotype in both the SUHx1 and the monocrotaline rat models, while the therapeutic value of proapoptotic strategies largely remain to be established.

However, it is important to recognize that inhibition of apoptosis may carry significant long-term risks by interfering with a fundamental mechanism of control of cell growth, and thus potentially favoring the development of neoplasia. Targeting repair and regeneration of lung microvasculature is perhaps a safer approach that could restore lung microcirculation lost by degenerative changes, or even produce functional channels that could effectively “bypass” occlusive lesions. Indeed, the potential efficacy of this “angiogenic” strategy is supported by preclinical and even some early clinical evidence. For example, we have shown that endothelial progenitor cells, transiently transfected with endothelial nitric oxide (NO)-synthase, can reverse established pulmonary hypertension in the monocrotaline model. Moreover, gene therapy with endothelial NO-synthase or VEGF, both of which promote angiogenesis, was effective in reversing established monocrotaline-induced PH, with evidence of regeneration of lung microcirculation. Therapy with endothelial NO-synthase gene-enhanced endothelial progenitor cells has been also translated into an early phase clinical study, the PHACeT (Pulmonary Hypertension and Angiogenic Cell Therapy), and a phase II study is expected to commence early 2017.

Conclusions
The intent of this viewpoint was to stimulate debate about the fundamental mechanisms in the pathogenesis of PAH. Some readers may strongly disagree with the paradigm that is being put forward; however, we believe at the very least it is time to focus more attention on the direct consequences of EC apoptosis, namely arteriolar degeneration and loss of lung microvasculature, as an important mechanism leading to progressive vascular rarefaction in PAH and as a potential therapeutic target. It is our hope that this will stimulate more interest and research into this paradigm and, in the end, it will be the data, not our individual biases, that should settle this debate.

Sources of Funding
This study was supported by Canadian Institutes for Health Research Foundation award (RIRI 997393265) to Dr Stewart.

Disclosures
Dr Stewart is the founding scientist of Northern Therapeutics. The other authors report no conflicts.

References

Key Words: apoptosis || endothelial cell || hemodynamics || hypertension, pulmonary || mutations
Proliferative Versus Degenerative Paradigms in Pulmonary Arterial Hypertension: Have We Put the Cart Before the Horse?

Ketul R. Chaudhary, Mohamad Taha, Virgilio J.J. Cadete, Rafael S. Godoy and Duncan J. Stewart

Circ Res. 2017;120:1237-1239
doi: 10.1161/CIRCRESAHA.116.310097

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/120/8/1237

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/