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Commentary: The pressure to treat pulmonary artery hypertension

Andrew F. Feczko, MD, and Siva Raja, MD, PhD

Pulmonary artery hypertension (PAH) is a severe health condition affecting 20 to 70 million people worldwide.^{1,2} Multiple different etiologies can lead to PAH and current therapies for the disease focus on modulating signaling pathways that lead to the vasoconstriction of PAs already narrowed by medial hypertrophy and neointimal proliferation.^{2,3} These therapies have improved patient symptoms without decreasing mortality (approximately 10% per year) or reversing the changes associated with the disease.^{1,2} The battle to find a cure for this chronic condition rages on.

In the study by Miao and colleagues,⁴ combinations of known proangiogenic (eg, hepatocyte growth factor and vascular endothelial growth factor) and vascular stabilization factors (eg, angiopoietin 1, platelet-derived growth factors, and transforming growth factor beta) were transfected into a rat model of monocrotaline-induced PAH using a lentivirus vector.⁴ They hypothesized that stable neoangiogenesis would demonstrate improvement in the hemodynamic parameters associated with the disease. Through a variety of immunohistochemical and perfusion-based techniques, the authors tested different permutations of angiogenesis and stabilization factors to determine the value (if any) of their combination. The combinations of hepatocyte growth factor + angiopoietin 1 and vascular endothelial growth factor + angiopoietin 1 were shown to promote the development of increased numbers of histologically mature blood vessels. These combinations also showed improved function, with lower PA pressures and decreased right ventricular weights (a surrogate for right ventricular hypertrophy), compared with controls at 4 weeks.

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Siva Raja, MD, PhD (left), and Andrew Feczko, MD (right).

CENTRAL MESSAGE

Neoangiogenesis is a novel treatment for pulmonary artery hypertension but is it ready for prime time?

By building off prior investigations by Zhang and colleagues,⁵ this study suggests the possibility of leapfrogging the biology underlying PAH; that is, using stable neoangiogenesis to bypass the hypertensive vasculature and reverse the cardiopulmonary effects of the disease. These results stand firmly in the realm of basic science but there are a number of issues that temper initial enthusiasm. The monocrotaline induction model of PAH, although inexpensive and easy to use, is a notably reversible and variable animal model, potentially promoting a positive result in a limited representation of the disease.⁶ Moreover, the rapid induction and resolution of PAH with the experimental treatment may not accurately reflect the potential for stable neoangiogenesis to reverse the chronic hemodynamic/functional changes in PAH. Lastly, this model is only 1 of many approximating PAH and may not capture all of the mechanisms underlying PAH.

Nevertheless, a journey of 1000 miles begins with a single step, and if you cannot improve the system, build a new system. Miao and colleagues⁴ suggest a potentially novel approach to PAH, but in doing so they have embarked on an arduous path to move from an interesting idea to a real paradigm shift. The authors will need to show long-term and durable results from this technique as well as demonstrate the specificity of their vector for the development of pulmonary vasculature, addressing the possibility of unwanted angiogenesis in other tissues. Once over these hurdles, their perseverance will be rewarded with the technical, ethical, and regulatory challenges of applying these gene-editing therapies in humans and finding out if these results hold true from rat to human. Although the work by Miao and

colleagues⁴ is preliminary, they should be recognized for contributing to the foundation on which new treatments can be built. With increasing numbers of patients being diagnosed with PAH, the pressure to find effective treatments remains high.

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Commentary: A new treatment strategy for pulmonary arterial hypertension

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Despite remarkable improvements in understanding the pathobiology¹ and medical treatment for pulmonary arterial hypertension (PAH), it remains to be a severe and progressive disease. Pathologically, PAH is associated with a severe arteriopathy leading to small vascular occlusion, increased pulmonary artery pressure, right ventricular failure, and death. Current therapies are mainly targeted to 3 pathways: prostacyclin, nitric oxide, and endothelin. These therapies are very effective and have markedly improved the prognosis of patients with PAH, including idiopathic PAH. However, these therapies are not to cure PAH but to improve pulmonary hemodynamics by dilating pulmonary small vessels. When all medical treatment fails, lung transplantation remains to be the last hope.

In this issue of the *Journal*, Miao and colleagues² report a rat experimental study to develop a new treatment strategy for PAH.³ The purpose of this study was to select a suitable

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CENTRAL MESSAGE

The combination of proangiogenic and vascular stabilization factor transfection may promote angiogenesis and vascular maturation and thus may be a new treatment for pulmonary arterial hypertension.

combination of angiogenic and vascular stabilization factors to improve the proliferation and maturity of neovascularization of lung tissue. The contrast medium filling time and right pulmonary artery root diameter and hemodynamic parameters in hepatocyte growth factor + angiopoietin-1 (Ang-1) and vascular endothelial growth factor + Ang-1 groups were significantly decreased compared with the vehicle group. The authors concluded that hepatocyte growth factor + Ang-1 transfection and vascular endothelial growth factor + Ang-1 transfection alleviate PAH by promoting maturation and stability of new blood vessels,

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