Editorial

Stem Cell INVESTIGATION

Inducible pluripotent stem cells and pulmonary arterial hypertension: the future is now!

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Provenance: This is an invited Editorial commissioned by Editor-in-Chief Zhizhuang Joe Zhao (Pathology Graduate Program, University of Oklahoma Health Sciences Center, Oklahoma City, USA).

Comment on: Gu M, Shao NY, Sa S, *et al*. Patient-Specific iPSC-Derived Endothelial Cells Uncover Pathways that Protect against Pulmonary Hypertension in BMPR2 Mutation Carriers. Cell Stem Cell 2017;20:490-504.e5.

Received: 14 April 2017; Accepted: 25 April 2017; Published: 13 June 2017.

doi: 10.21037/sci.2017.05.10

View this article at: http://dx.doi.org/10.21037/sci.2017.05.10

The pulmonary circulation is responsible for directing venous (low-oxygen) blood to the gas exchange regions of the lung, where oxygen uptake takes place before arterial (oxygen-rich) blood leaves the heart via the systemic circulation. Compared to the systemic circulation, the pulmonary circulation is a low-pressure/low resistance system that maximizes the amount of venous blood entering the lungs through the pumping action of the right ventricle. However, disorders associated with abnormal increase in pressure and/or resistance can adversely affect the capacity of the right ventricle to pump blood into the lungs and reduce the oxygen content in arterial blood. This is the case with pulmonary arterial hypertension (PAH), a rare but life-threatening disorder associated with abnormally increased pulmonary pressures and right heart failure (1). Despite the availability of 14 FDA approved therapies, none are capable of curing PAH, likely due to their inability to prevent progression and/or reverse vascular pathology. Therefore, there is an unmet need to understand the pathological mechanism involved in pulmonary vascular remodeling and use this knowledge to test novel approaches to treat the disease.

While the cause of PAH remains poorly understood, the last two decades have shed light on cellular and genetic mechanism responsible for predisposition to vascular remodeling in PAH. In particular, it has been shown that the endothelial cells (ECs) in PAH are dysfunctional, as evidenced by their excessive proliferation, limited angiogenic capacity and abnormal distribution within vascular lesions (2). One of the major genetic mechanisms driving this endothelial phenotype appears to be loss of function mutations in bone-morphogenetic-protein receptor 2 (BMPR2), a member of the transforming growth factor beta superfamily. Although only 20% of the population with this mutation develops PAH, it is found in almost 70% of the familial and ~25% of sporadic patients with PAH (3). Our incomplete understanding of the risk factors for BMPR2 mutation carriers is in part due to lack of a reliable source of tissues from these patients to perform in depth genetic and functional mechanistic studies.

There have been different efforts to try to understand the cellular and molecular mechanisms of PAH using different animal models that mimic some of the vascular pathology (4). However, none of the available animal can recapitulate the full range of vascular changes seen in PAH. Another complementary strategy has been to collect cells and tissues from patient lungs obtained at the time of transplant; however, progress in this area has been limited by the scarcity of lung tissue due to the low number of lung transplants performed each year for PAH and lack of institutional resources to ensure consistent collection and processing of the materials. Thus, there is an urgent need for alternative experimental models to help researchers access patient derived material in a reliable fashion and without the need to rely on transplantation.

The last decade has seen tremendous progress in the

field of stem cell research and its application to the study and treatment of various diseases. The use of the so-called "Yamanaka factors" (5) has revolutionized the field of stem cell by allowing researchers to generate induced pluripotent stem cells (iPSCs) from mature cells. The use of iPSC has quickly become a powerful experimental platform to model common diseases such as hereditary cardiomyopathies, diabetes and Alzheimer (6,7) but its application to PAH has not been tested until now.

The paper by Gu et al expands on previous work by the same group (8) and presents a novel and elegant approach that takes advantage of IPSCs derived ECs (iPSC-ECs) as a tool to analyze cell phenotypic and genotypic variations between healthy donors and BMPR2 mutation-carriers who are either unaffected (UMC) or suffering from familial PAH (FPAH) (9). While there was a significant reduction in BMPR2 expression when compared to healthy donors, levels of BMPR2 in UMC and FPAH iPSC-ECs were comparable, indicating that reduced expression alone is not sufficient to produce PAH in the UMC. However, it was noted that FPAH demonstrated significantly reduced adhesion properties in a wide range of matrix substrates along with increased susceptibility to apoptosis following environmental stressors. Interestingly, in contrast to UCM, FPAH iPSC-ECs failed to recover migration and capacity for angiogenesis despite treatment with BMP-4, a BMPR2 ligand. The authors go on to explore signaling pathways that could be responsible for the phenotypic differences observed, documenting a direct link between p38 activation and adhesion. Lack of p38 activation in FPAH was associated with reduced adhesion and use of pharmacological p38 activators was able to partially improve their adhesion to matrix substrates. Through a series of comprehensive molecular studies, the authors identify differences in expression of critical molecules responsible for tuning BMPR2 mediated downstream p38 activation and adhesive properties of UCM and FPAH cells. In the last part of the manuscript, gene editing with CRISPR/Cas9 is used to correct the BMPR2 mutation in one of the FPAH iPSC-ECs to show recovery of angiogenic response to BMP-4, increased adhesion and p38 activation.

This study is the first to apply an iPSCs based model to systematically study why some carriers of BMPR2 mutations are more prone to PAH by demonstrating greater endothelial dysfunction. The implications of the study are exciting since it brings us closer towards the possibility of implementing personalized medicine in the field of PAH. As an example, screening for relevant genetic signatures together with cell-based assays using iPSCs-ECs from UMC and FPAH could help identify asymptomatic BMPR2 mutation carriers at greater risk of developing PAH. For these patients, a more aggressive screening strategy could be implemented that could lead to early diagnosis and improved clinical outcomes. Another exciting possibility is that iPSC-ECs could serve as a platform to select the most effective drug regime for a given patient and to conduct high throughput screening for novel drugs. However, it is important to remember that iPSCs-ECs are not necessarily representative of pulmonary ECs since these are derived from either blood or skin cells. Since the vascular pathology in familial and sporadic PAH seems to spare the systemic circulation, it is reasonable to speculate whether the findings reported here could also apply to EC in other vascular beds. Unfortunately, there are no systematic studies that can help answer this question and efforts to characterize these cells via the Human Cell Atlas project are ongoing. A thorough comparison between ECs from different organs and the iPSCs-derived ECs should be done to narrow the vascular phenotype and improve our odds of discovering therapeutic targets specific to the pulmonary circulation. Despite this limitations, use of iPSCs represents a step forward in the field of PAH research since these cells can be used to generate other relevant cell types associated with PAH vascular pathology (e.g. smooth muscle cells, fibroblasts) and to generate cardiomyocytes for studies centered in mechanisms of right ventricular failure.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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doi: 10.21037/sci.2017.05.10
Cite this article as: Lopez MR, de Jesus Perez V. Inducible pluripotent stem cells and pulmonary arterial hypertension: the future is now! Stem Cell Investig 2017;4:53.

