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Advances in PH Journal

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What is the Current State of Stem Cell Research in PAH?

We know from clinical experience with patients undergoing pneumonectomy for lung cancer that reducing the pulmonary vascular bed by 50% does not result in overt pulmonary hypertension. However, most patients with PAH have a much greater reduction in perfused pulmonary microvasculature. By the time a patient with PAH arrives at the PH clinic in WHO functional class 3, their functional microvascular surface area may be decreased to 20-25% of normal.[1] This reduction is due to obstruction and flow restriction in small precapillary arterioles, and the therapeutic challenge that PAH clinicians face is to somehow regain some of the lost vascular bed. Our current therapies may offer some benefit in that direction, although the direct evidence for this is lacking. Strategies to deal with the excess cellular proliferation seen in PAH might include trying to encourage cellular apoptosis, trying to re-seed the bed with healthier cells, or trying to induce a local environment within the microvasculature that would support healthy cells and select against the abnormal cells. Strategies that utilize all these approaches may ultimately prove to be the most successful.

Given that much of the vascular obstruction is from obliterative cellular proliferation by abnormal endothelial cells and other cell types, using vascular cell therapy as a reparative tool may be a reasonable strategy. Certainly, it is fortunate that the lung circulation can act as a sieve, trapping cells that are injected into the systemic venous or pulmonary arterial circulations. Circulating endothelial progenitor cells (EPC) have been identified in humans and can be harvested safely via leucopheresis. These autologous cells can be induced to proliferate *in vitro*, yielding large numbers for injection, and they can be manipulated genetically to increase expression of potentially beneficial molecules then injected into the pulmonary circulation. Presently, it is unclear what role circulating EPC have in PAH. Are they reparative or do they further contribute to the endothelial proliferation seen in PAH? Are presumably dysfunctional EPC in PAH patients able to effect any vascular repair at all?

Two groups have been exploring EPC therapy in PAH. Chen and colleagues from Zhejiang University in China have injected unmodified autologous EPC into PAH patients and shown improved 6-minute walk distance and hemodynamics after 12 weeks (NCT 00257413).[2] Stewart and colleagues are injecting autologous EPC that have been transfected with endothelial nitric oxide synthase (eNOS) to produce high levels of nitric oxide. The enhanced EPC have shown great benefit in animal models and seem to be able to increase the amount of perfused microvasculature.[3] A phase 1 human trial (PHACeT) is still recruiting (NCT 00469027). What is remarkable in the human studies is the lack of adverse events. Specifically, there has been no evidence to date that the cells are detrimental. I participate in the latter trial, and the cells have been well tolerated, both in the short term and after several years. After successful completion of these pioneering trials, the likely next step will be to provide patients with repeated injections at regular intervals to assess long-term efficacy. It is unknown whether the EPC will arrest or reverse the proliferative process, and how much of the vascular bed must be regained to provide a human with a normal prognosis.

While marked progress has been achieved, the field of cell-based therapy is in its infancy and much work needs to be done. It is hopeful to consider that successful evolution of this field may potentially be the key in our ability to further treat PAH.

1. Langleben, D, Orfanos, SE, Giovinazzo, M. Pulmonary capillary endothelial metabolic dysfunction: severity in pulmonary arterial hypertension related to connective tissue disease versus idiopathic pulmonary arterial hypertension. Arthritis Rheum. 2008;58:1156–1164.
2. Wang, XX, Zhang, FR, Shang, YP. Transplantation of autologous endothelial progenitor cells may be beneficial in patients with idiopathic pulmonary arterial hypertension: a pilot randomized controlled trial. J Am Coll Cardiol. 2007;49:1566–1571.
3. Zhao, YD, Courtman, DW, Deng, Y. Rescue of monocrotaline-induced pulmonary arterial hypertension using bone marrow-derived endothelial-like progenitor cells: efficacy of combined cell and eNOS gene therapy in established disease. Circ Res. 2005;96:442–450.

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- Cell Therapy for Pulmonary Arterial Hypertension: Potential Efficacy of Endothelial Progenitor Cells and Mesenchymal Stem Cells
- Design and Validation of an Endothelial Progenitor Cell Capture Chip and its Application in Patients with Pulmonary Arterial Hypertension
- Endothelial Cells Caught in the Crosshairs of Pulmonary Arterial Hypertension
- Rescuing the BMPR2 Pathway: How and Where Can We Intervene?
- Prognostication in Pulmonary Arterial Hypertension and Use of Current Risk Prediction Models

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