Endothelial Cell Global Positioning System for Pulmonary Arterial Hypertension
Homing in on Vascular Repair

Natasha M. Rogers, Jeffrey S. Isenberg

Pulmonary arterial hypertension (PAH), defined as a mean pulmonary artery pressure exceeding 25 mm Hg in the presence of a normal capillary wedge pressure, is an infrequent (reported incidence, 1–2 per million), chronic, and eventually fatal disorder characterized by obliterator microvascular changes, endothelial cell (EC) dysfunction, and vascular smooth muscle cell overgrowth. The cause of PAH varies (idiopathic, familial, or secondary to autoimmune phenomena and infections such as human immunodeficiency virus), but overall outcome (median survival, 2.8 years) is universally poor. Such strategies have evolved from bone marrow transplantation and are now the subject of intense interest to regulate the innate and adaptive immune system after solid organ transplantation. This has provided a platform for the use of other cell types (including stem and terminally differentiated cells) in a variety of disease processes (www.clinicaltrials.gov).

The chemotactic cytokine interleukin 8 (CXCL8), also known as interleukin-8 (IL-8), is produced by phagocytic cells to promote neutrophil accumulation at sites of injury. CXCL8 is also produced by EC (in response to hypoxic stress), vascular smooth muscle cell, and epithelial cells. CXCL8 is implicated in lung injury arising from a variety of causes, including ischemia–reperfusion injury, aspiration, and sepsis. Although not specifically documented in PAH, induction of proinflammatory cytokines (including CXCL8) has been associated with increased mortality. The 2 CXCL8 receptors, interleukin 8 receptor A (CXCR1) and interleukin 8 receptor B (CXCR2), share sequence homology and high affinity for the ligand and promote via ligand–receptor binding, G protein, and phospholipase C activation. Downstream effector mechanisms through Ras, Akt, and mitogen-associated protein kinase trigger neutrophil adhesion, transmigration, and degranulation.

In a novel and interesting study by Fu et al in this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, the infusion of EC transplanted to express IL8RA/B reduced acute pulmonary inflammatory cell influx and cytokine release to mitigate endothelial damage after monocrotaline injury. A single infusion of IL8RA/B-expressing EC resulted in a beneficial effect on the development of monocrotaline-driven PAH with attenuated right ventricular hypertrophy and decreased pulmonary vascular smooth muscle cell overgrowth. The authors also found restoration of alveolar and arteriolar endothelial nitric oxide synthase–positive cells and reduced inflammatory cell (macrophage and neutrophil) infiltrate.

This study and others from the same group use terminally differentiated EC and thus represent a departure from previous investigations using cells with greater self-renewal capacity. Endothelial progenitor cells have been shown to contribute to repair of damaged endothelium through neoangiogenesis. Unlike other EC populations, endothelial progenitor cells do express CXCR2 (IL8RB), which mediates adhesion to both matrix in vitro and recruitment to areas of carotid arterial injury in vivo in a CXCR2-dependent manner. Pathological changes within damaged organs may also affect cell homing; for example, chronic hypoxia may increase peripheral endothelial progenitor cell mobilization, but pulmonary recruitment is limited.

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Current treatment algorithms involve general supportive measures and pharmacotherapy (calcium channel blockers, anticoagulants, diuretics), as well as targeting major pathways that regulate pulmonary vascular tone: endothelin, nitric oxide, and cAMP. Therapeutic agents, such as endothelin receptor antagonists (bosentan), CGMP-specific phosphodiesterase type 5 inhibitors (sildenafil), soluble guanylate cyclase activators (riociguat), and prostacyclin analogs that increase cGMP-specific phosphodiesterase type 5 inhibitors (sildenafil), soluble guanylate cyclase activators (riociguat), and prostacyclin analogs that increase cAMP production (epoprostenol), provide symptomatic benefit and increased functional capacity. However, they fail to substantially improve life expectancy or reverse the underlying disease process. Potentially curative therapies, other than lung transplantation (which itself has significant attendant morbidity secondary to chronic immunosuppression), that directly modulate the underlying pathogenesis of PAH remain elusive.

Although there remains much to understand regarding the cause of PAH, novel therapeutic interventions have been developed to enable mitigation of disease in preclinical (animal) models by targeting known activated pathways in PAH. Preventing disease progression by lung microvasculature repair is one such emerging therapeutic intervention. Given the success arising from proof-of-concept animal studies, cellular therapy has become an increasingly attractive avenue for potential clinical application, reaching phase II and III trials (NCT01795950). Such strategies have evolved from bone

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is potentially relevant because the right ventricle, although not a direct target of monocrotaline, nonetheless experiences injury in PAH and may represent another location for transfused cell homing.

One disadvantage of cell-based therapies is the substantial proportion of cells lodging within the pulmonary vasculature after intravenous injection. Hence, only a small percentage of effector cells remain capable of reaching the systemic circulation, although this obstacle is exploited when the target organ is the lung as in the present study. Nonetheless, the use of cells transfected with homing devices may facilitate tracking of cells to the site of damage as in the present situation where monocrotaline-mediated endothelial damage initiates CXCL8 production to putatively attract infused CXCL8 receptor-bearing EC.

So, how to proceed from here? Several critical questions should be answered if cell therapies are to become a platform for treatment of disease: (1) precisely where do these cells travel after infusion? (2) do these cells maintain physiological function? and (3) what is their longevity in vivo? The new work by Fu et al suggests several other interesting questions (Figure). How are these transfected, terminally differentiated EC cheating death in vivo, now that they no longer have a tissue scaffold or growth factor support, and then how are they mediating vascular repair? Are these cells themselves providing a reparative mechanism for the endothelial layer, modulating healthy or damaged EC function to initiate repair, or are they instead preventing vascular damage by acting as a dominant-negative (decoy) receptor for released IL-8 to reduce inflammatory cell homing? As with all animal models, the relevance of this type of treatment to human PAH, which typically lacks an inciting acute inflammatory event, remains to be established. Also important for the future pursuit of cell-based therapy is the regard for the overall safety of manipulated, albeit autologous, cells.

In conclusion, the field of PAH has yielded to cellular therapy as a potential future therapeutic opportunity, with novel targets and techniques to recover vascular function.

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References


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