Pulmonary arterial hypertension (PAH), defined as a mean pulmonary artery pressure exceeding 25 mm Hg in the presence of a normal capillary wedge pressure,1 is an infrequent (reported incidence, 1–2 per million), chronic, and eventually fatal disorder characterized by obliterative 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.2

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),7,8 vascular smooth muscle cell,9,10 and epithelial cells.11,12 CXCL8 is implicated in lung injury arising from a variety of causes, including ischemia–reperfusion injury,13 aspiration,14 and sepsis.15 Although not specifically documented in PAH, induction of proinflammatory cytokines (including CXCL8) has been associated with increased mortality.16 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.17 Downstream effector mechanisms through Ras, Akt, and mitogen-associated protein kinase trigger neutrophil adhesion, transmigration, and degranulation.18

In a novel and interesting study by Fu et al19 in this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, the infusion of EC transfected 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 study19 and others from the same group20,21 use terminally differentiated EC and thus represent a departure from previous investigations using cells with greater self-renewal capacity.22 Endothelial progenitor cells have been shown to contribute to repair of damaged endothelium through neoangiogenesis.23,24 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.25 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.26 This
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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