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 oblitative microvascular changes, endothelial cell (EC) dysfunction, and eventual 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.

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 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 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. This
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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Disclosures
J.S. Isenberg is Chair of the SAB for Vasculox, Inc, and Radiation Control Technologies, Inc, and has equity interest in the same. N.M. Rogers reports no conflicts.

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