Joshua M. Diamond, MD

University of Pennsylvania
Philadelphia, PA

Clinical and Biomarker Risk Evaluation of Pulmonary Hypertension in Lung Transplantation

Pulmonary arterial hypertension (PAH) is a severe, progressive disorder with a median survival of 2.8 years if left untreated. While certain therapies are effective, these treatments do not cure PAH and do not appear to benefit patients with pulmonary hypertension (PH) secondary to parenchymal lung disease (WHO Group 3). Lung transplantation remains the only available therapeutic option for PAH refractory to treatment and severe WHO Group 3 PH.

Unfortunately, PH related to either PAH or parenchymal lung disease significantly increases the risk of post-lung transplant primary graft dysfunction (PGD), a form of acute lung injury that is the major cause of early post-transplant morbidity and mortality. Patients with severe PH have double the risk of PGD after transplant compared with those without PH, and those with PAH have more than three times the risk of PGD. Despite the enormous adverse impact of PH on transplant, there is poor understanding of the clinical predictors and biochemical mechanisms linking PH to PGD, preventing the institution of potential preventative or treatment strategies before or early after surgery.

Long pentraxin-3 (PTX3) is produced by macrophages and dendritic cells as a result of interleukin-1 (IL-1) and toll-like receptor (TLR) signaling pathways, and indicates activation of innate immunity. We have preliminary data showing that higher plasma PTX3 in PH may increase the risk of PGD in these patients. We have demonstrated that elevated post-transplant plasma complement levels are associated with PGD and higher post-transplant plasma PTX3 levels are associated with increased risk of PGD. We have also found that genetic variation in PTX3 is associated with PGD risk. Furthermore, recent study case-control study demonstrated higher mean plasma PTX3 concentrations in patients with PAH compared to control subjects, suggesting that PTX3 levels may serve as an effective diagnostic biomarker for PAH. **The clinical and biochemical risk factors that determine which patients with PH (including PAH and PH with parenchymal lung disease) will develop PGD will be the focus of this application.**