Angela V. Ghatnekar, PhD

Medical University of South Carolina
Charleston, South Carolina

The Role of GATA-6 in Pulmonary Arterial Hypertension

Our recent data revealed that GATA-6, a zinc-finger transcription factor, is strikingly down-regulated at the mRNA and protein level in endothelial cells (ECs) lining all vessel types, both occluded and non-occluded, in idiopathic pulmonary arterial hypertension (PAH) patients, as well as systemic sclerosis-associated PAH patients. In addition, we have found that GATA-6 transcript levels are reduced in the lungs of the monocrotaline rat model of PAH at an early time point in disease onset. Furthermore, in vitro data suggest that loss of GATA-6 in ECs leads to a reduction in EC markers and an increase in markers of vascular remodeling. Based on our preliminary findings, we hypothesize that loss of GATA-6 after vessel injury may be an important component of EC activation/dysfunction. Moreover, reduction of GATA-6 may be an important early feature of PAH. To study the potential role of GATA-6 in PAH, we propose to investigate the functional consequences of reduced GATA-6 in ECs, both in cultured human pulmonary artery endothelial cells (HPAECs) and in mouse lungs in vivo. In specific aim 1, we will investigate changes in gene expression patterns in HPAECs with reduced GATA-6 using Human Endothelial Cell Biology PCR arrays. Putative direct transcriptional targets will be validated using quantitative RT-PCR, western blotting, and chromatin immunoprecipitation (ChIP) analysis. In specific aim 2, we propose to investigate the functional consequences of decreased GATA-6 levels in pulmonary endothelial cells in vivo using

Angela V. Ghatnekar, PhD

transgenic mice (Cre/loxP system) with conditional GATA-6 knockdown in endothelial cells. GATA-6 conditional knockout mice will be characterized by performing hemodynamic analyses and lung tissue analyses with respect to vascular abnormalities. Lung endothelial cells will also be isolated to check for differential expression of markers identified in Aim 1, which may be specifically altered in response to GATA-6 down-regulation. We expect that once these experiments are complete, they will provide us with novel insights about the molecular mechanisms contributing to vascular remodeling in PAH.