

Patients with sickle cell disease (SCD) experience recurrent episodes of vaso-occlusive crises (VOC). Following a VOC, patients often develop pulmonary symptoms resulting in a potentially life-threatening condition termed acute chest syndrome (ACS). ACS is the second most common cause of mortality in sickle cell disease. In the National Acute Chest Study, 38% of ACS cases were attributed to infection, fat embolism and pulmonary infarction, while no identifiable cause was found in the remaining 62% of cases. Recruitment of monocytes/polymorphonuclear neutrophils (Mo/PMN) into the alveolar compartment is an important feature of acute lung injury. Leukocytosis, in the absence of infection, is commonly seen in SCD patients and is a predictor of disease severity and of ACS. Studies in transgenic sickle mice (Tg HbS) reveal increased accumulation of leukocytes in the lung in response to an experimental lung insult. We find that endothelin-1 (ET-1) is released from cultured human pulmonary endothelial cells (HPEC) in response to deoxygenated sickle RBCs and initiates leukocyte transmigration. The goal of this project is to test the hypothesis that the interaction of SS RBCs with HPEC initiates cellular signaling to cause Mo/PMN to transmigrate from the lumen of the blood vessel into the alveolar compartment, wherein activated Mo/PMN cause injury to the pulmonary alveolar epithelial cells (PAEC).