Hypoxia-induced acute lung injury in murine models of sickle cell disease

Abstract: Vaso-occlusive events are the major source of morbidity and mortality in sickle cell disease (SCD); however, the pathogenic mechanisms driving these events remain unclear. Using hypoxia to induce pulmonary injury, we investigated mechanisms by which sickle hemoglobin increases susceptibility to lung injury in a murine model of SCD, where mice either exclusively express the human alpha/sickle beta-globin (halphabetaS) transgene (SCD mice) or are heterozygous for the normal murine beta-globin gene and express the halphabetaS transgene (mbeta+/-, halphabetaS+/-; heterozygote SCD mice). Hypoxia further decreased association of HSP90 with eNOS in lungs of SCD and heterozygote SCD mice, but not in the control lungs. These data support the hypotheses that hypoxia increases XO release from ischemic tissues and that the local increase in XO-induced oxidative stress can then inhibit HSP90 interactions with eNOS, decreasing *NO generation and predisposing the lung to vaso-occlusion.