

HEMOLYSIS AND THE PATHOPHYSIOLOGY OF VASCULAR COMPLICATIONS

Rationale:

Erythrocytes provide a physical barrier that shields the endothelial lining of blood vessels from heme, a highly reactive redox moiety critical for hemoglobin (Hb)-mediated gas exchange. The sickle cell mutation engenders a diversity of anomalies that render the erythrocyte susceptible to lysis in the intravascular space. Chronic hemolysis eventually overwhelms the adaptation to intravascular hemolysis, as SCD patients become deficient in haptoglobin and hemopexin, the scavenger molecules that clear Hb and heme from the circulation. Sickle cell patients living in sub-Saharan Africa (SSA) bear an additional burden of hemolysis due to malaria. Although the overall disease burden, and the associated public health impact of hemolysis in SSA is widely acknowledged, exactly how this phenomenon contributes to the development of end-organ damage, and early mortality among individuals who have SCD is uncertain.

The impact of hemolysis on human health is modulated by at least two intrinsic factors, a) the hemolytic event itself (controlled by innate erythrocyte factors), and b) the host-response to hemolysis (controlled by cytoprotective factors). What genetic and environmental factors influence the ease with which sickle erythrocytes lyse in individual SCD patients of the same ethnic group (e.g. Bantu), and at the population-level, what are the major factors that control variation in the hemolytic rate among SCD patients. Malaria adds an extrinsic modulating factor, presumably with its own intrinsic variables related to the hosts' response to infection. With respect to the host response to hemolysis, the master transcriptional factor nuclear erythroid-2 factor 2 (Nrf2), is likely to play a dominant role. Nrf2 controls the expression of >200 genes involved in cellular detoxification. Emerging evidence indicates that heme oxygenase-1 (HO-1) and other Nrf2-regulated genes attenuate the vascular damage in SCD. It will be important to understand this process, and develop appropriate therapeutics to mimic this natural

antidote to hemolytic stress. The Ofori-Acquah laboratory is funded to pursue this idea in transgenic SCD mice and has developed tools that can be readily applied to studies in SCD patients. A longitudinal observation study offers the most rigorous approach to systematically investigate the role and mechanisms of hemolysis in SCD.

Aims:

1. Determine the spectrum of clinical outcomes and organ dysfunction associated with hemolysis in a longitudinal cohort of SCD patients.
2. Determine the activation of hemolysis and oxidative stress protective pathways in neonates and children with SCD and the deterioration of this protection with disease progression and aging longitudinally
3. Determine the genetic factors that attenuate and exacerbate hemolysis, and modulate the response to hemolysis, in SCD patients using a whole genome approach, and test for their association with clinical outcomes and organ dysfunction.
4. Determine the expression of putative hemolysis-modifying genes and transcripts