Sickle Cell Disease: Insights into the Pathophysiology of Vaso-occlusion using Murine Models of Sickle Cell Disease

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The major cause of morbidity and mortality in sickle cell disease (SCD) is tissue ischemia and infarction due to vascular occlusion that results in progressive organ damage. Despite a detailed understanding of the genetics, molecular biology and biochemistry of sickle haemoglobin (HbS) and its effect on the sickle erythrocyte, the pathogenesis of the profound vascular and organ dysfunction observed in SCD remains incompletely understood. Murine models can aid in dissecting the pathophysiology of complex human diseases such as SCD. The "Berkeley" murine model of sickle cell disease exclusively expresses human alpha, gamma, and beta^S haemoglobins with genotype [Tg(Hu-miniLCRα1^{G}γ ^{A}γδβ^s) *Hba^0*//*Hba^0 Hbb^0*//*Hbb^0*]. Berkeley SCD mice have a phenotype that closely mimics many features of severe SCD in man. This includes a moderately severe haemolytic anemia (haematocrit ~25%, >30% reticulocytes) and irreversibly sickled red cells on the blood smear. Berkeley SCD mice have multiorgan pathology including prominent sites of vascular congestion and tissue ischemia with infarcts in the kidneys, lungs, and liver, similar to the pathology of SCD in humans. Similar to human SCD, RBCs from SCD mice have markedly enhanced adhesion to the vascular endothelium and several subendothelial matrix proteins. The increased sickle RBC adhesion likely plays a significant role in the vascular injury and obstruction observed in SCD. In addition, SCD mice also mimic the enhanced proinflammatory and procoagulant phenotype found in human SCD. Transplantation of sickle haematopoietic stem cells into mice deficient in fibrinogen (SCD-Fib-/- mice) results in a decrease in the number and size of organ infarcts suggesting that fibrin clot formation is critical for the development of HbS-induced focal tissue death. In agreement, pharmacologic and genetic manipulations that decrease thrombin generation in SCD mice result in decreased vascular stasis and measures of endothelial injury and inflammation. Thus, the increased activity of the inflammatory and haemostatic pathways likely contributes to the severe organ and vascular pathologies observed in SCD. Targeted modulation of these pathways should improve HbS-associated organ pathologies despite the persistence of the primary HbS genetic defect. In summary, Berkeley SCD mice provide an excellent model to study many aspects of the pathophysiology of and potential therapies for severe SCD in man.