Sickle cell disease (SCD) is a relatively common inherited hemolytic disorder in persons of African descent that is associated with end organ damage to many vital organs and reduced life expectancy. We briefly review the pathophysiology and treatment approaches to SCD. In the past decade, there has been a greater understanding of the complexity of vascular events, as well as the breadth of systems derangements that contribute to the pathobiology of SCD. Among these systems is the possible contribution played by 'hypercoagulability' in SCD. Recent research in humans and in animal models of SCD suggests that the time may be right for a renewed evaluation of emerging therapeutic agents that inhibit coagulation.

**Introduction**

Sickle Cell Anemia (homozygosity for the HbS gene) is the most common form of Sickle Cell Disease (SCD). Anemia associated with sickle shaped red cells on the blood smear was first described in a 20-year old dental student from Grenada in 1910 by Dr. James B. Herrick in Chicago. The abnormal sickle hemoglobin, HbS, causes affected red cells to adopt a characteristic crescentic ‘sickle’ shape upon deoxygenation and under the influence of other contributing factors such as hyperosmolarity, acidosis, or dehydration. In the United States, approximately 1 in 500 African-Americans is born with SCD, which approximates to about 70,000-75,000 individuals nationally. It is estimated that there are about 20,000-25,000 subjects with SCD in Europe(1), although the rapidly changing demographics of the population in many countries suggests that this number will increase significantly in the next several decades(2). In the U.S. black population, 7-8% are carriers of the sickle gene mutation, and are said to have ‘sickle trait’. This frequency equates to some 2.5 million subjects, and between 200 and 300 million worldwide. The phenotype of SCD varies by region around the world, depending on the particular haplotype (Senegal, Benin, Bantu, Cameroon, Bengal), as well as other characteristics including the mitigating effect of high levels of fetal hemoglobin and the occurrence of alpha-thalassemia gene deletions. The prevalence of sickle trait is about 10-13% in parts of Southern Turkey (3).

Despite the fact that SCD is the first disease in which a genetic disorder was linked to a mutation of a specific protein (β-globin)(4), there remains only one licensed pharmaceutical agent for its treatment. Based on its demonstrated efficacy in modulating the frequency and severity of acute pain crises (5), hydroxyurea was approved by the United States’ Food and Drug Administration (FDA) for this indication in 1998. However, at least in the United States, it has proven very difficult to ensure that all patients who could potentially benefit from this relatively inexpensive and safe therapy actually receive it. Despite the paucity of licensed pharmacologic agents, significant advances have been made in several clinical facets of the disease, including the demonstration that neonatal antibiotic therapy (6) and heptavalent pneumococcal conjugate vaccine (7) is crucial in the first years to prevent death from encapsulated organisms; the realization that transcranial doppler ultrasonography screening for cerebral vasculopathy and institution of a red cell exchange transfusion regimen can prevent overt cerebrovascular infarction in affected children(8); and the favorable outcomes with stem cell transplantation in selected patients (9). However, progress in the
Coagulation activation in SCD: a potential therapeutic target?

It is now widely accepted that SCD is associated with chronically elevated 'pre-thrombotic markers' including plasma thrombin-antithrombin complexes, prothrombin fragment 1.2, and D-dimers(13, 16). In addition, SCD patients typically have elevated levels of biomarkers that are suggestive of activation of vascular endothelium such as soluble vascular cell adhesion molecule-1 (VCAM-1), and we have shown that this is particularly the case in sickle cell patients with pulmonary hypertension compared to controls (17). We are currently conducting a double-blind phase II study to determine the effect of warfarin anticoagulation in subjects with elevated tricuspid jet velocity (clinicaltrials.gov identifier NCT01036802), who we and others have shown to have an overall poor prognosis for survival (18, 19). Autopsy studies demonstrate a high prevalence of in situ thrombosis involving the pulmonary vessels, similar to findings in nonsickle cell patients with pulmonary hypertension. The primary endpoint of this study is the effect of anticoagulation on pulmonary artery systolic pressure measured by Doppler echocardiography.

We have previously summarized the results of trials using anticoagulant or anti-platelet therapy in patients with SCD(13). In brief, many of these early studies, going back to the 1960s, were under-powered or poorly designed, and virtually all focused on pain crises (frequency and/or duration). The results of these studies were mixed, and generally unconvincing. More recently, a better quality prospective double-blinded study from Saudi Arabia randomized 253 patients with SCD in pain crisis to tinzaparin 175 IU/kg once daily or placebo. A significant reduction in the duration of crisis and the duration of hospitalization was shown in the group receiving low molecular weight heparin (20). The group performing this study suggested that LMWH should be routinely considered in the management of acute pain crises(21). While these study results are encouraging and of great interest, they require additional independent confirmation.

Several years ago, we demonstrated that whole blood tissue factor (WBTF) activity was elevated in patients with sickle cell disease(22). Similarly, an elevated number of tissue factor containing microparticles could be found in the blood of these patients (23). More recently, in a study of children with SCD, we have demonstrated that WBTF activity and D-dimer were highly correlated, and that WBTF or D-dimer correlated closely with biomarkers of hemolysis (24). In this study, WBTF also correlated closely with monocyte TF antigen expression by flow cytometry, suggesting that monocytes are, as expected, the principal contributors to TF activity in the WBTF activity assay. Although sickle plasma contains many inflammatory cytokines and other mediators such as CD40 ligand that could be responsible for up-regulating monocyte TF expression(25), another intriguing possibility is that TF expression is promoted by the adhesion of early 'stress' reticulocytes to monocytes via the alpha-4 integrin, which appears to occur in vivo(26, 27). This adhesive interaction could
conveniently explain the observed link between hemolysis and WBTF expression that has already been mentioned. Monocytes however may not be the only source of tissue factor in vivo; the presence of endothelial-associated TF has been shown in sickle mouse models (28) and in the form of circulating TF+ endothelial cells in humans (29).

The potential importance of these observations is borne out by experiments in sickle mouse models. Like their human counterparts, these animals demonstrate chronic hyperactivation of coagulation, inflammation, and of the endothelium. We recently demonstrated that antibody-mediated inhibition of TF in these animals not only led to the expected decreased generation of plasma thrombin-antithrombin complexes, but was also associated with lower plasma levels of markers of inflammation (interleukin-6 and serum amyloid A protein), reduced numbers of neutrophils in the lung, and lower plasma levels of markers of endothelial activation, such as sVCAM-1 (30). These pre-clinical models suggest that the unprecedented pipeline of new inhibitors of the coagulation pathway might provide exciting opportunities for improving outcomes in patients with SCD.

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References


