Red Cells Stick It to the Vessel Wall

By Alice Ma, MD

Many hemolytic anemias are also hypercoagulable states, and thrombosis contributes to the morbidity and mortality suffered by patients with such conditions. Additionally, coagulation abnormalities are part of the pathogenic mechanisms underlying some of these hemolytic processes. The scavenging of nitric oxide by plasma free hemoglobin is but one of the pathogenic mechanisms underlying the link between hemolysis and thrombosis.

This interaction was addressed by several speakers yesterday. In the Education Session on RBCs and Hemoglobinopathies, Dr. Maria Cappellini discussed three paradigms of thrombosis in hemolytic anemias. First, she introduced sickle cell disease and beta thalassemia as disorders in which thrombotic events, such as stroke, pulmonary hypertension, and venous thromboembolism, cause major morbidity and mortality. Next, she discussed paroxysmal nocturnal hemoglobinuria and speculated as to the mechanism of the thrombotic tendency of patients with this disorder. Lastly, she discussed the thrombotic microangiopathies as disorders characterized by microangiopathic hemolytic anemia and platelet microthrombi.

In the Education Session on Sickle Cell Anemia, Dr. Marilyn Telen spoke about the role of adhesion molecules and the vascular endothelium in the pathogenesis of sickle cell disease. Dr. Telen reviewed the experimental data showing that the endothelial lining is abnormal in sickle cell disease. She went on to show the evidence that sickle red cells (SS RBCs) adhere abnormally to the endothelium and extracellular matrix components, mediated (at least in animal models) primarily by red cell receptor LW (ICAM4) interaction with the integrin ligand $\alpha V\beta 3$ on the endothelial surface. Dr. Telen next discussed the role of inflammation in promoting vaso-occlusion in sickle cell disease, concluding that discoveries in the pathogenesis of vaso-occlusion will lead to more rational therapeutics in this disease. Targeting adhesion molecules, inflammatory mediators, and the sickling process itself will eventually provide for better therapies than just oxygen and analgesics, currently the mainstay of treatment of vaso-occlusive crises. Indeed, recent *in vitro* studies by Finnegan et al., *Am J Physiol Heart Circ Physiol* (2007), found that an $\alpha V\beta 3$ antagonist inhibits sickle red cell adhesion and vasooclusion.

Dr. Ken Ataga next tackled the issue of hypercoagulability in sickle cell disease. Certainly, patients with sickle cell disease are at increased risk for thrombotic events such as stroke, pulmonary hypertension, avascular necrosis, and venous thromboembolism. Additionally, patients with sickle cell disease also have higher levels of thrombin generation, depletion of natural anticoagulant proteins, increased tissue factor expression, and increased platelet activation, even in the non-crisis state. Despite the robust laboratory evidence for increased coagulation activity in sickle cell patients, Dr. Ataga reviewed the disappointing lack of good prospective clinical trials investigating whether anti-platelet agents and/or anticoagulants have an impact on the complications of sickle cell disease. It is clear that more data are needed before we fully understand the role of hypercoagulability in the pathogenesis of sickle cell disease.

To round out this year's sessions on hemoglobinopathies, don't miss the late-breaking abstract to be presented on Tuesday. Dr. Farmaki from the General Hospital of Corinth will present data on 50 patients with β-thalassemia major who were switched from chelation therapy using subcutaneous desferrioxamine (DFO) to an individualized intensive combination of both DFO and the oral chelator deferiprone (DFP). These patients had a 0 percent mortality rate and lower rates of endocrine and cardiac complications, when compared to historical controls, suggesting the synergy of this combination therapy in reversing iron overload and its sequelae.