

DK Kaul, Bronx Comprehensive Sickle Cell Center: Sickle Cell Adhesion

We propose that abnormal interaction of sickle (SS) cells with vascular endothelium is the initiating event leading to the development of vascular occlusion in sickle cell anemia. This is because increased SS cell adhesion is expected to result in delayed microvascular transit times, dense cell trapping, enhanced red cell sickling and vaso-occlusion. We posit that SS cell adhesion is multifactorial in nature, involving a host of modulating factors and receptor-ligand interactions. In the proposed studies, we will examine the "multifactorial nature" of SS cell adhesion, and explore its role in vascular occlusion in vivo. This proposal will focus on specific ligand-receptor interactions, emphasizing the role of endothelial activation/damage and red cell heterogeneity in SS cell adhesion. To this end, we will use state-of-the-art transgenic-knockout sickle mouse models and relevant ex vivo assay systems, and explore therapeutic approaches that would interfere with this pathologic interaction. Using intravital techniques and an integrated physiological approach, we will test the following: 1) Test the hypothesis that endothelial activation and damage is accompanied by expression of specific adhesion molecules that modulate SS cell adhesion to endothelium in vivo. To test this hypothesis we will investigate the role of adhesion molecules whose expression is potentially affected by endothelial activation and damage. We will evaluate the role of endothelial von Willebrand factor (vWf), P-selectin, laminin (a matrix protein) and endothelial  $\alpha V\beta 3$  integrin (a receptor to several adhesive proteins); 2) Test the hypothesis that sickle cell density classes are characterized by heterogenous distribution of adhesion receptors affecting their propensity to adhesion. To test this hypothesis, we will investigate sickle mouse red cell density populations (reticulocytes and dense cells) for certain adhesion receptors and evaluate their role in adhesion, with emphasis on the role of integrin-associated protein (IAP or CD47); 3) Test the hypothesis that NO will modulate red cell adhesion in vivo. We will test this hypothesis by: i) Investigation of the effect of NO promoting agents (e.g., L-arginine supplementation); ii) Evaluation of the effect of NO inhibition; iii) anti-oxidant therapy; iv) hydroxyurea therapy. Thus, we expect to identify new therapeutic approaches to alleviate adhesion-induced flow abnormalities and vaso-occlusion in sickle cell disease.