Protein disulfide isomerase (PDI) is a multifunctional oxidoreductase critical in thrombus formation. We studied the effects of deoxygenation on PDI activity in erythrocytes from humans with Sickle Cell Disease (SCD) and two sickle mouse models, BERK and βSAntilles. We show that deoxygenation of sickle erythrocytes increased surface-associated reductive capacity that was sensitive to antibodies against PDI (mAb PDI). We then studied sickle human erythrocytes and showed that PDI inhibition (quercentin-3-rutinoside [Q3R]) significantly reduced deoxy-stimulated dehydration and Gardos channel activity (P<0.03). We characterized erythrocyte density and calculated the D50. Both mAb PDI and Q3R significantly reduced D50 when compared to vehicle (P<0.0001) while PDI incubation increased cellular hydration status (P<0.01). Consistent with these data, Q3R or mAb PDI reduced hemolysis of human cells exposed to 20 mM 2-2'-azo-bis-(2-amidinopropane)dihydrochloride (AAPH); similar results were observed in BERK and βSAntilles mice. We then studied sickle mice expressing HbF; BERK(<1% HbF), BERKγM(25% HbF), and BERKγH(45% HbF). BERKγH had the lowest circulating and cell associated PDI activity among the three mouse types and mice with high HbF/F-cell ratio had low PDI activity. Thus, we posit that PDI activity is important for erythrocyte stability, survival and that its inhibition in SCD may represent a novel therapeutic target for improving its hematological and vascular complications.