Inhibition of endogenous APC activity exacerbates thrombo-inflammation in sickle mice at steady state

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Sickle Cell Disease (SCD) is caused by a single nucleotide mutation in the β-globin gene. This results in sickling of red blood cells, hemolytic anemia, vascular stasis, and hypercoagulability. Coagulation is controlled by a balance between procoagulant (eg, thrombin) and anti-coagulant (eg, activated protein C, APC) molecules. We have demonstrated a role for thrombin in inflammation and vascular stasis in SCD, yet the role of the endogenous anticoagulant APC has yet to be explored. Interestingly, SCD patients have lower levels of APC activity. We aimed to determine the role of endogenous APC activity in a mouse model of SCD.

Townes wild type (HbAA) and sickle (HbSS) mice (3-4 months) were treated with control IgG or SPC-54 (10 mg/kg, IP). Tissue and blood were collected 24 hours after antibody administration. APC inhibition did not impact anemia, but did increase circulating neutrophil and neutrophil:lymphocyte ratios in HbSS mice. We found that APC inhibition increased TAT, IL-6 and soluble p-Sel in HbAA mice, and significantly enhanced the already elevated levels of these markers in HbSS mice. Livers were stained with hematoxylin and eosin (H&E) and scored for congestion and hepatocyte necrosis. Lungs were also stained for neutrophils and quantified. Histologic evaluation of the livers of SPC-54-treated HbSS mice revealed enhanced vascular and sinusoidal congestion, but hepatic necrosis was not increased in HbSS mice. APC inhibition increased PMN counts in the lungs of HbSS and HbAA mice. These data suggests that endogenous APC plays an important role in mitigating thrombo-inflammation in SCD.