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POSTER ABSTRACTS

113.SICKLE CELL DISEASE, SICKLE CELL TRAIT AND OTHER HEMOGLOBINOPATHIES, EXCLUDING THALASSEMIAS: BASIC AND TRANSLATIONAL

20-HETE As an Emerging Target to Improve Renal Health in Sickle Cell Disease

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The kidney is one of the most severely affected organs in sickle cell disease (SCD), with glomerular hyperfiltration and microalbuminuria beginning in childhood, and progressing to chronic kidney disease (CKD) in majority of adults. Sickle individuals also suffer from acute kidney injury (AKI) often during characteristic vaso-occlusive crisis. Renal pathology in sickle cell nephropathy includes extensive microvascular congestions and thrombotic microangiopathy. The hypercoagulable and vasoconstrictive environment of SCD, in conjunction with medullary hypoperfusion and cortical hyperperfusion contributes to vaso-occlusive injury and deregulates intrarenal hemostasis leading to CKD development. Ischemic injury increases arachidonic acid hydroxylation producing 20-hydroxyeicosatetraenoic acid (20-HETE), which in turn triggers thrombosis and promotes vasoconstriction in the kidney. However, the role of 20-HETE in regulating renal hemostasis in SCD nephropathy has never been reported. We found that plasma 20-HETE is significantly elevated in SCD patients (n=9-11; $p<0.01$) compared to normal individuals. Similarly, transgenic SCD mice (SS), homozygous for human hemoglobin S, have increased plasma 20-HETE compared to control mice (AA), homozygous for human hemoglobin A (n=6; $p<0.01$). We have previously shown that elevated circulating heme mimicking hemolytic crisis triggers clinically relevant acute kidney injury (AKI) in SS mice (Blood (2020) 135(13): 1044-1048). We postulated that hemolytic stress may exacerbate 20-HETE production which in turn aggravates renal microvascular occlusion and vasoconstriction, leading to renal damage in SCD. Immunohistochemistry and biochemical experiments showed that the expression of CYP4A12a, a cytochrome 450-dependent enzyme responsible 20-HETE production in mice, is substantially elevated in the kidneys of SS mice compared to AA mice, associated with increased vascular congestion and renal thrombogenesis. Renal CYP4A12a and plasma 20-HETE were increased substantially following heme-induced AKI in SS mice, associated with a heightened expression of renal angiotensin II receptor 1 (ATIIR1), thus indicating induced vasoconstrictive activity. In vitro, we found that 20-HETE induced ATIIR1 expression in human renal glomerular endothelial cells (hRGEC), which was further exacerbated by low-concentration of heme challenge (5 mM for 24 hour). Nitro-oleic acid (NO_2-OA) is a nitrated fatty acid that binds ATIIR1 and inhibits angiotensin II induced vasoconstriction. Pretreatment with NO_2-OA reduced 20-HETE-dependent ATIIR1 expression in hRGEC, while NO_2-OA prophylaxis during hemin-induced AKI inhibited albuminuria, normalized plasma creatinine levels, and lowered the expression of ATIIR1 in SS mice kidneys. Overall, our data show that elevated 20-HETE levels during hemolytic stress may aggravate renal injury in SCD which can be prevented by NO_2-OA prophylaxis. Ongoing experiments will determine the direct effect of elevated 20-HETE in renal hemostasis and CKD development in SCD.

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