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POSTER ABSTRACTS

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

The Role of P-Selectin in Microvascular Hemodynamics and Cerebral Brain Volumes in Aging Sickle Cell Mice

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Cerebral vasculopathy has been linked to the development of cognitive impairment in sickle cell disease (SCD). We have previously demonstrated that 13-month-old sickle cell mice recapitulate features of cerebral vasculopathy such as tortuous vessels, microthrombi, and hypoperfusion seen in adults with SCD. Histologically, we also showed these mice have increased cerebral microvascular deposition of P-selectin and more frequent and larger microinfarcts compared to matched controls. We further showed that these mice developed evidence of cognitive deficit compared to matched controls. Based on these observations, we hypothesized P-selectin may play a critical role in development of cerebral micro vasculopathy and downstream pathologic sequalae such as microinfarcts by enhancing leukocyte-endothelial interactions. Furthermore, abundant evidence from non-sickle mice shows that microinfarcts can exacerbate small vessel changes including gray matter volume loss. Building on our prior work, in this study, we examined the effect of P-selectin deficiency on cerebral microvascular hemodynamics and leukocyte-endothelial interaction and well as changes in cortical and subcortical gray matter volume in aged sickle mice.

Male, P-selectin knockout (Psel KO) or intact (Psel WT) chimeric mice were generated by transplanting control (AA) or sickle (SS) bone marrow into P-selectin knockout (Psel $^{-/-}$) or C57BL/6 (B6) recipients. To assess the impact of vasculopathy and brain gray matter volume changes longitudinally, male mice were assessed at 12-, 14- or 16-month post-transplant. Hemodynamics (mean velocity, red blood cell (RBC) flux, white blood cell stalls in capillaries as well as venules) were obtained from line-scan images acquired using *in-vivo* two-photon microscopy, using custom and validated MATLAB scripts. Gray matter volumes in 26 cortical and subcortical brain regions with relevance to cognitive function, were derived from parcellation of T2-weighted magnetic resonance imaging after non-linear registration to Allen brain atlas T1 anatomical space. Parcellation was accomplished by registering the Paxinos atlas to the mouse T2 now in Allen space. Brain volume analyses was accomplished using Analyze 12 software. After the completion of in-vivo studies, brains were extracted for immunohistochemistry analysis. Statistical analysis was performed using two-way ANOVA.

The breakdown of the mice included in this study are; 14 B6 AA, 12 B6 SS, 12 Psel KO AA and 13 Psel KO SS. Given the high attrition rate in older mice, data from 12-, 14- and 16-month-old cohorts were combined. Mean age of B6 AA cohort was 13.1 months, 12.8 months for B6 SS, 13. 9 months for Psel KO AA and 13.6 months for Psel KO SS mice and were not statistically different. Psel KO sickle mice had a significantly lower mean capillary RBC velocity (1.733 mm/s vs 4.717 mm/s, $p < 0.01$) compared to Psel WT SS mice. In addition, Psel KO SS mice had relatively smaller (more normal) capillary diameter compared to Psel WT SS mice (6.248 um vs 8.613 um, $p < 0.001$). Interestingly, there was no statistically significant difference in RBC flux between Psel KO SS and Psel WT SS mice, however Psel KO SS mice show a lower red blood cell flux similar to that seen in Psel WT AA mice (**Figure 1**). Of the 26 brain regions that were assessed, Psel KO SS mice had larger measured gray matter volume in the frontal association cortex (3.01 ± 0.77 vs 3.66± 0.33 mm ^{3}, p= 0.0083), prelimbic cortex (1.72 ± 0.27 vs 1.95 ± 0.17 mm ^{3}, p=0.0079), hippocampus (17.67 ± 1.56 vs 16.21± 1.97 mm ^{3}, p=0.01)(**Figure 1**) including other regions such as lateral (2.12 ± 0.19 vs 1.88 ± 0.31 vs mm ^{3} p=0.0096) medial (1.84± 0.16 vs 1.64 ± 0.26 mm ^{3}, p=0.01), and ventral orbital cortex(1.95± 0.17 vs1.72 ± 0.27 mm ^{3}, p=0.01) and dorsolateral olfactory tract (1.46 6± 0.13 vs 1.31 ± 0.20 mm ^{3}, p=0.023 compared to the Psel WT SS mice (data not shown).

In conclusion, non-hematopoetic P-selectin deficiency improves cerebral vasculopathy as demonstrated by normalization of hemodynamics in sickle mice. We also show that Psel KO SS mice had larger brain gray matter volume in regions involved in cognitive function. Additional studies are needed to identify the underlying mechanism of improvement in brain gray matter volume as well as whether P-selectin could be potential target for reducing SCD associated neurological complications.

Disclosures No relevant conflicts of interest to declare.

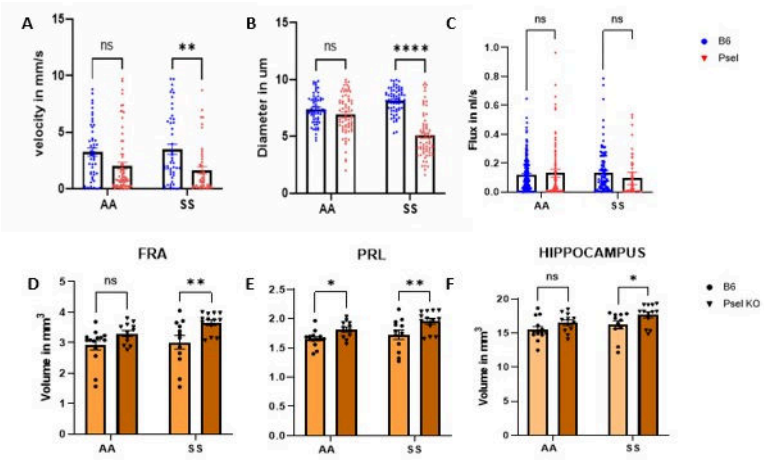

Figure 1. Cerebral hemodynamics and gray matter volumes are altered in P-selectin knockout sickle mice. A) Cortical microvascular velocity is lower in P-selectin knockout sickle mice B) P-selectin sickle mice had lower microvasculature diameter compared to P selectin intact mice. C) Red blood cell flux tended to lower in P-selectin knockout SS mice however there was no statistically significant difference. Gray matter volumes are increased in Pselectin knockout sickle mice in D) frontal association cortex (FRA), E) prelimbic area (PRL) and F) hippocampus.

Figure 1

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