Microglia depletion reduces CD8+ T-cell infiltration into the injured brain in aged mice after traumatic brain injury

Northwestern Medicine
Feinberg School of Medicine

Veronica Villanueva[1], Zhangying Jennie Chen[1,2], Kacie P Ford[1], Hyebin Han[1,2], and Steven J Schwulst[1]

[1]Department of Surgery, Division of Trauma and Critical Care, [2]Driskill Graduate Program in Life Sciences

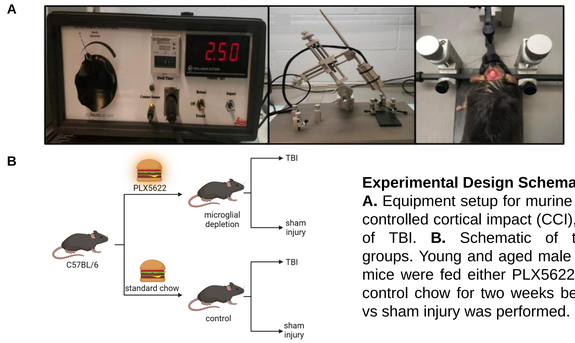
INTRODUCTION

Traumatic brain injury (TBI) afflicts over 3 million Americans every year. While TBI affects individuals of all ages, the elderly (aged 65 years and older) experience higher mortality and greater long-term neurocognitive morbidity compared to younger adults. Our lab has recently shown that age introduces an uninvited guest in the brains – the T cell. Infiltrating T cells can interact with microglia, the gatekeepers in the central nervous system and the main antigen-presenting cell in the brain, in age-associated neurodegenerative diseases. We previously published that aged mouse brains showed significant increases in T cells two months post-TBI. These T cells were largely CD8$^+$ T effector memory (EM) cells. Microglia are thought to play a role in recruitment of these inflammatory cells making the interplay between microglia and the peripheral immune system in TBI crucial for the development of new treatments and improved patient outcomes.

We hypothesize that depletion of microglia will attenuate accumulation of T-cells post-TBI

METHODS

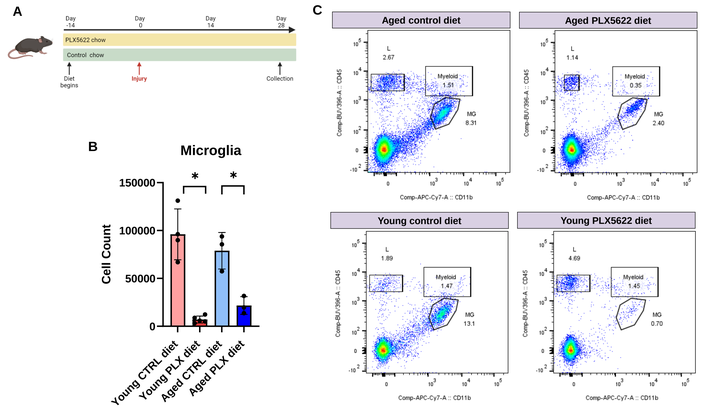
Use of PLX5622 to deplete microglia in the brain



Experimental Design Schematics
A. Equipment setup for murine model of controlled cortical impact (CCI), a model of TBI. **B.** Schematic of treatment groups. Young and aged male C57BL/6 mice were fed either PLX5622 chow or control chow for two weeks before CCI vs sham injury was performed.

RESULTS

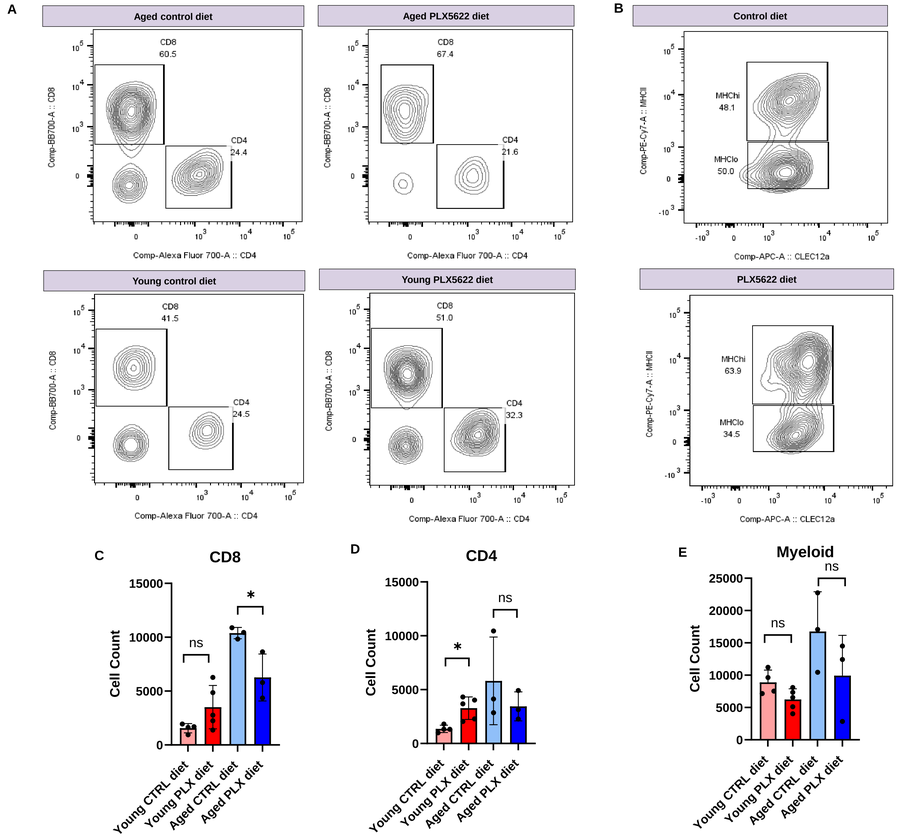
PLX5622 depletes microglia in aged and young mice



PLX5622 treatment led to a significant decrease in microglia. A. Schematic of treatment timeline. Male C57B/L mice were fed PLX5622 diet or control diet for two weeks before CCI, cells were then collected one month after injury. **B.** Quantification of microglia cell count for each group, **C.** Representation of flow cytometry results for each treatment group. N=3-5

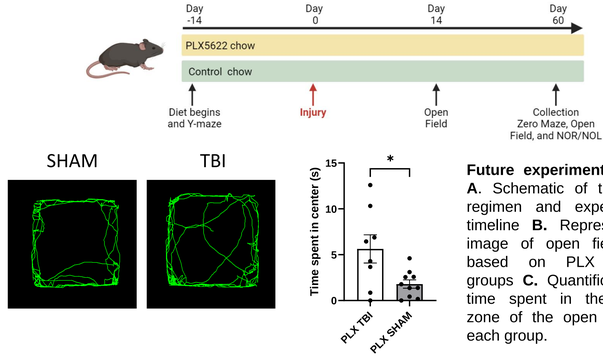
RESULTS

Microglial depletion reduces T-cell infiltration after TBI



Microglia depletion with PLX5622 led to reduced CD8+ T-cells in aged subjects post-TBI. A. Representation of CD3+ T-cell flow cytometry results for each treatment group 1-month post-TBI. **B.** Representation of MHCII^{hi} and MHCII^{lo} macrophage flow cytometry results comparing PLX5622 diet and control diet in aged subjects 1-month post-TBI. Quantification of **C.** CD8+ T-cells **D.** CD4+ T-cells and **E.** myeloid cell count for each group, N=3-5

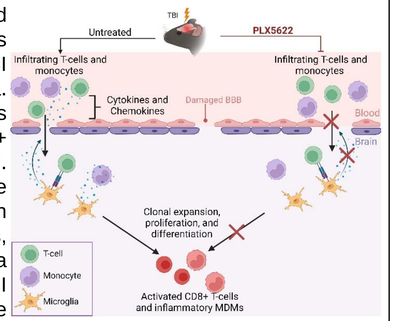
NEXT STEPS



Future experimental plan.
A. Schematic of treatment regimen and experimental timeline **B.** Representative image of open field data based on PLX treated groups **C.** Quantification of time spent in the center zone of the open field for each group.

CONCLUSIONS

We hypothesized that depletion of microglia would reduce the infiltration of T-cells after TBI in aged mice. Our previous data suggests an age-dependent response to TBI that is induced by microglia. Microglia depletion attenuates this response through reduction in CD8+ T-cells in the aged brain post-TBI. Previous studies displayed the negative impacts of CD8+ T-cells in the aged brain after TBI. Thus, microglia depletion may be a promising therapeutic in aged TBI subjects. Ongoing studies are focused on gene signature changes and neurocognitive impacts of microglia depletion in TBI.



ACKNOWLEDGEMENTS

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