Microglia depletion followed by repopulation attenuates cytotoxic T-cell infiltration into the aged brain after traumatic brain injury

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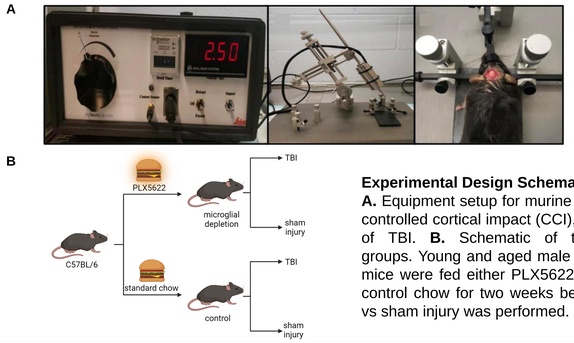
INTRODUCTION

Traumatic brain injury (TBI) afflicts over 69 million people every year. Patients over 65 years of age experience increased 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 hypothesized that microglia repopulation after TBI would attenuate accumulation of cytotoxic CD8+ T-cells in the injured brain in aged mice post-TBI and improve neurocognitive outcomes.

METHODS

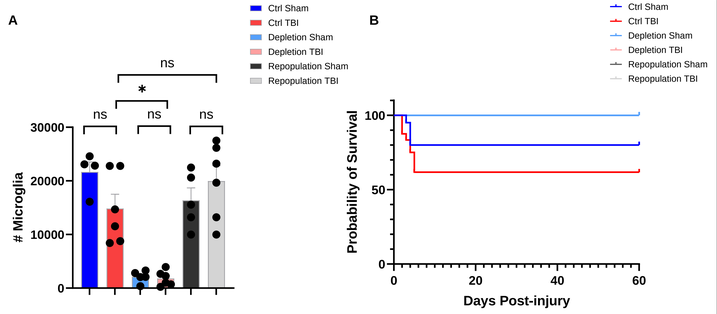
Use of PLX5622 to deplete microglia in the brain



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

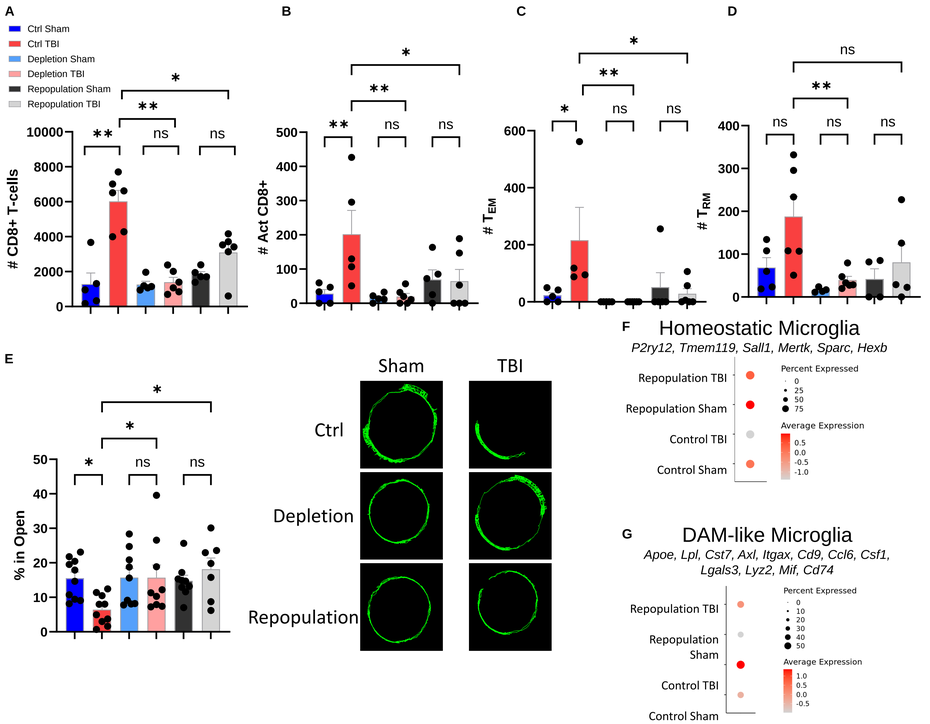
PLX5622 depletes microglia in aged mice and improves survival post-TBI



PLX5622 treatment led to a significant decrease in microglia and improved survival in aged mice. **(A)** Flow cytometry results displaying the number of microglia in the aged brain two-months post-TBI or -sham injury for each treatment group. **(B)** Survival curves for aged mice in each treatment group over 60-day experiments. The curves for Depletion Sham, Depletion TBI, Repopulation Sham, and Repopulation TBI are all 100 thus are overlapped by the Depletion Sham curve.

RESULTS

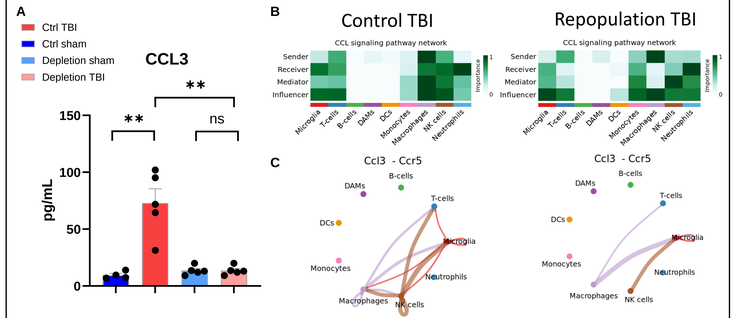
Microglial depletion reduces T-cell infiltration after TBI and improves neurocognitive outcomes



Microglia depletion and repopulation reduced CD8+ T-cells in aged subjects post-TBI and improved neurocognitive outcomes. Flow cytometry results displaying the number of **(A)** CD8+ T-cells, **(B)** activated cytotoxic T-cells, **(C)** effector memory T-cells, and **(D)** resident memory T-cells in the aged brain two-months post-TBI or -sham injury for each treatment group. **(E)** Zero maze results 55-days post-TBI or sham injury with representative images of movement patterns in each treatment and injury group. Dot plot displaying transcriptional profiles of microglia markers associated with **(F)** homeostasis and **(G)** disease-associated microglia (DAMs) for the control diet TBI and repopulation TBI groups

RESULTS

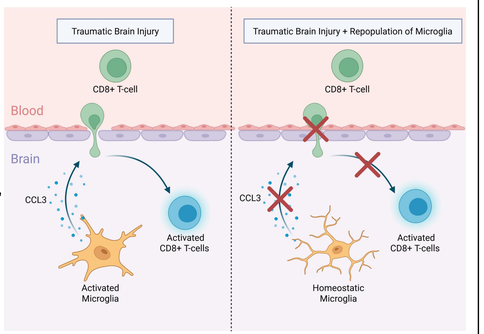
Microglia repopulation reduces CCL signaling post-TBI



Microglia depletion with PLX5622 led to reduced CCL signaling in aged subjects post-TBI. **(A)** Luminex results of CCL3 in the aged brain 2 months post-TBI or sham injury in the control diet and depletion groups. CellChat data displaying **(B)** cell-cell communication in the CCL signaling pathway network and **(C)** cell-cell communication within the ligand-receptor pair CCL3 to CCR5 in the aged brain 2 months post-TBI or sham injury.

CONCLUSIONS

We hypothesized that microglia repopulation post-TBI would attenuate accumulation of CD8+ T-cells in aged mice. Microglia depletion and repopulation attenuated cytotoxic CD8+ T-cell infiltration. Furthermore, microglia repopulation reduced DAM-like microglia persistence 2-months post-injury, reduced CCL signaling, improved neurocognitive outcomes and survival in aged mice. Ongoing studies will mechanistically address modes of inflammation and identify potential therapeutic targets to improve patient outcomes post-TBI.



ACKNOWLEDGEMENTS

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