FECAL MICROBIOTA TRANSPLANT WITH DONOR STOOL FROM APOE2 TARGETED REPLACEMENT MICE RESTORES GUT MICROBIAL COMMUNITY STRUCTURE IN A MURINE MODEL OF TRAUMATIC BRAIN INJURY

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Introduction

Apolipoprotein E (APOE) alleles impact pathogenesis and risk for multiple human diseases. In fact, the APOE 4 allele is the strongest genetic risk factor for sporadic Alzheimer's disease (AD) and portends a worse outcome after traumatic brain injury (TBI). Meanwhile the APOE 2 allele is the strongest genetic protective factor for AD. Our laboratory recently demonstrated that APOE2 targeted replacement mice have superior neurocognitive outcomes after TBI. It is also known that the gut microbial community structure has marked allelic disparity between the APOE genotypes offering a putative mechanism for the neurologic protection seen in the APOE2 allelic variant via the gut-brain axis.

Hypothesis

We hypothesized that fecal microbiota transplant (FMT) of donor stool from **APOE2 targeted replacement mice would restore the gut microbial community structure of wild type TBI mice to a preinjury state** while APOE4 FMT would lead to continued TBI-induced dysbiosis.

Methods

Figure 1. CCI

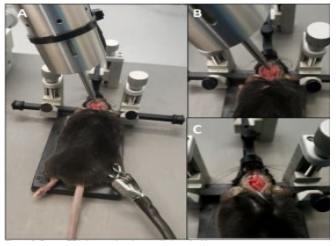
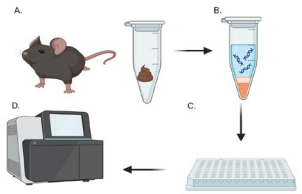
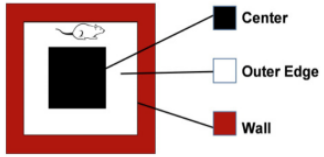


Figure 2. Sequencing



2. (A) 2 – 3 stool pellets are collected per mouse (B) DNA is extracted from the stool pellet (C) Samples are prepped and processed to achieve 16s RNA gene libraries D) Sequence the libraries on Illumina Miniseq sequencer.

Figure 3. Open Field



1. (A) The impacting tip is lowered onto the dura mater. (B) The impacting tip is set to a 2 mm depth and applied at 2.5 m/s (C) The impacting tip is lifted and the mouse is recovered from the stereotaxic frame

3. Mice were placed in the center of an enclosed box for the open field (OF) test for 5 minutes to test anxiety.

APOE2 Targeted Replacement Mice

Figure 4. Open Field

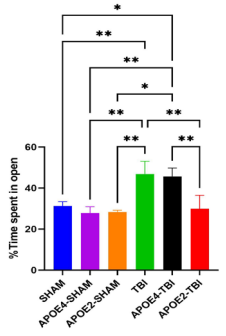
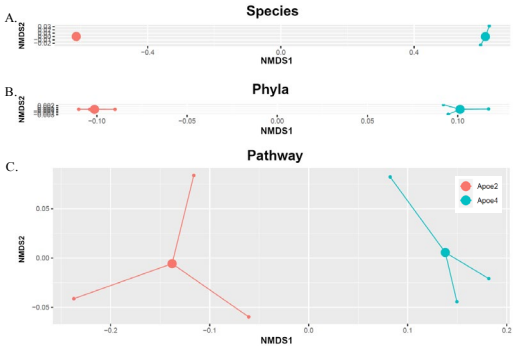


Figure 5. Community Composition

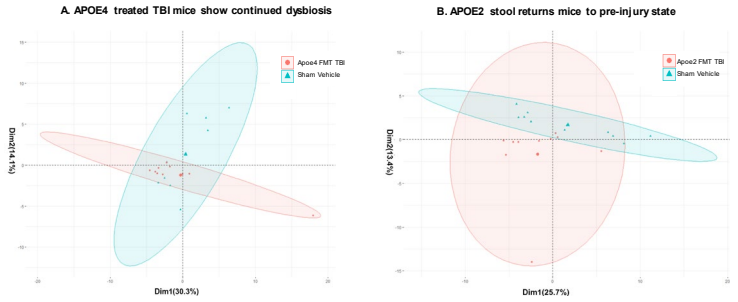


4. APOE2 targeted replacement mice exhibited pre-injury levels of anxiety while APOE4 targeted replacement mice and the control showed more time spent in the open area after injury.

5. (A) The distance between APOE2 and APOE4 groups exhibits the dissimilarities between species. (B) Similar to species, this shows the difference in composition of phyla between groups. (C) This exhibits the disparity between pathway compositions among the two groups.

APOE 2 FMT Alters Microbiome

Figure 6. Microbiome Diversity at Day 45



6. (A) PCoA plot depicting the differences in beta diversity between APOE4 FMT 45 days after TBI and its control (p=0.04). (B) PCoA plot depicting the differences in beta diversity between APOE2 FMT 45 days after TBI and its control. No significant differences can be seen (p=0.13).

Neurocognitive Behavior

Figure 7. Open Field Tracings

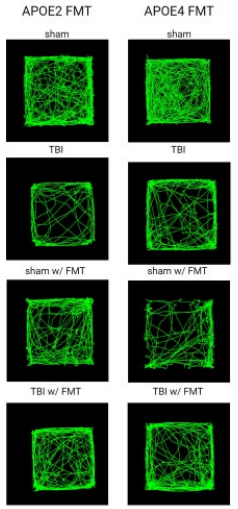
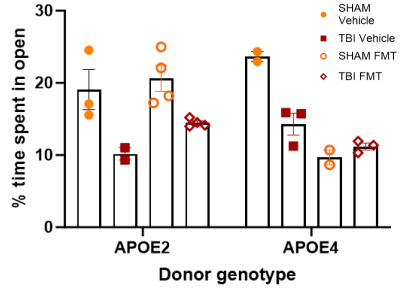


Figure 8. Open Field Data



7. Mice given APOE2 FMT after TBI had visually improved neurocognition based on the tracings while APOE4 FMT had negative effects on mice.

8. Quantitative data shows slight improvement in mice given APOE2 FMT after TBI compared to its control. Mice given APOE4 FMT after TBI showed a slight decrease as compared to its control.

Conclusions

- APOE2 FMT given to mice after TBI restored the gut back to a pre-injury state as well as showing slight improvements to neurocognitive behaviors.

- APOE4 FMT led to a continued dysbiosis of the gut after injury as well as hyper-anxious behaviors.

- This demonstrates a putative mechanism for the neuroprotection in APOE2 allelic variants in both human disease as well as in our laboratory model of TBI

Acknowledgments

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