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Gut microbiome perturbations influence brain amyloidosis only in the presence of microglia in APPPS1-21 mice

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Abstract

Background: In prior efforts, we demonstrated reduced amyloidosis and altered microgliosis in long-term antibiotics (abx)-treated APPPS1-21 male mice. Restoration of the gut microbiome into abx-treated male mice by fecal microbiota transfer (FMT) established a causality between the gut microbiome and amyloidosis. We have used FMT studies using our current short-term abx APPPS1-21 mice to evaluate the microbiome-microglia-amyloidosis axis.

Method: Short-term, postnatal abx (4mg/ml Kanamycin, 0.35mg/ml Gentamicin, 8500U/ml Colistin, 2.15mg/ml Metronidazole, 0.45mg/ml Vancomycin: post-natal day 14 to day 21) was performed. To establish causality, we performed FMT (200µl of 5mg/ml fecal slurry daily gavage) into abx-treated APPPS1-21 male mice. Pathogenicity of the gut microbiome in WT or Tg mice were confirmed using age-matched FMT from WT and Tg controls into abx-treated male mice. We performed total RNAseq transcriptome analysis to evaluate potential mechanism(s). The role of microglial cells were evaluated in PLX6522 (CSF-1 receptor inhibitor)-treated FMT-transplanted abx-treated APPPS1-21 male mice. Nine weeks old GF APPPS1-21 were used to characterize the amyloidosis and glial cells in both genders.

Result: An early life abx treatment resulted in gut microbiota changes in a sex-dependent manner. Only male mice showed reduced amyloidosis and altered microglial phenotypes. Age matched Tg FMT or WT FMT resulted in higher amyloidosis in abx-treated male mice. RNAseq analysis of total cortical RNA showed significantly different mRNA levels that occurred in a sex-specific manner and changes in abx-treated male mice were restored with FMT. GO term analysis showed gliogenesis and microglia development as significantly altered pathways in abx-treated male group only. To confirm the exact role of the microglia in this model, we employed PLX6522 in FMT-treated ABX-male mice. Microglia depletion did not result in an FMT-dependent increase in amyloidosis in abx-treated male mice. Finally, germ-free APPPS1-21 mice showed reduced amyloidosis that occurs in a sex-specific manner.

Conclusion: From GF APPPS1-21 and FMT-treated abx-male APPPS1-21 studies, we conclude that gut microbiome plays a critical role in modulating amyloidosis in APPPS1-21 mice. Furthermore, microglia mediates the effects of early life gut microbiota perturbations, which results in altered amyloidosis in APPPS1-21 male mice.