Circulating Peripheral Factors Induce Age-related Epigenetic Changes in Microglia which Induces a Primed Phenotype

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Microglia are the resident innate immune cells of the CNS

**Microglia**
- Derived from embryonic yolk sac
- Populate the brain during development
- Myeloid phenotype
- Age with the individual

Aged microglia are more pro-inflammatory at baseline

The brain becomes progressively inflammatory with age

n=5-9/group, one-way ANOVA, Dunnett post-hoc, * = p<0.05, ** = p<0.01, *** = p<0.005
Epigenetic antagonism of Ezh2 and Jmjd3

Epigenetic landscape of the brain changes with age

n=3, Student’s t-test, * = p<0.05
Inhibition of Ezh2 reduces pro-inflammatory cytokine production

n=6, mean+/−SEM, Student’s T-test, ** = p<0.01, *** = p<0.005
Aged plasma up-regulates pro-inflammatory genes in microglia

**Il1b**

**Il6**

**Tnfa**

n=12, mean +/- SEM, Student’s T-test, * = p<0.05, **** = p<0.0001
We hypothesized that the aged brain is epigenetically dysregulated by peripheral factors to induce a pro-inflammatory, primed phenotype.
Heterochronic parabiosis model

Heterochronic Parabiosis

Young | Aged

Accelerated aging | Rejuvenation

Pair house Parabiosis | Collect

Weeks

-1 0 1 2 3 4 5 6 7 8
Heterochronic parabiosis reverses epigenetic dysregulation of aging

n=9/group, 2-way ANOVA, Tukey post-hoc, * = p<0.05, **** = p<0.001
Young blood reduces age-associated increase in brain IFNγ and GM-CSF

n=9-10/group, 2-way ANOVA, Tukey post-hoc, * = p<0.05
Neuroinflammatory parabiosis model

Heterochronic

Aged isochronic

100ug LPS i.p.
Young blood rejuvenates age-associated primed phenotype

n=4-5, mean+/−SEM, Student’s T-test, * = p<0.05, ** = p<0.01
Conclusions
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