Altered Metabolism and DAM-signatures in Female Brains and Microglia with Aging
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Introduction

- Alzheimer’s Disease (AD) is a neurodegenerative disease characterized by neuroinflammation, Aβ plaque accumulation, and altered lipid and cholesterol processing.
- AD is more prevalent in women, and more severe in female AD patients, suggesting a potential protective role for E2 that is lost with menopause.
- Human microglia from aged females exhibit higher DAM and GLUT5 gene expression compared to males, which may be responsive to E2 supplementation.
- The work presented here was published in the Journal of Alzheimer’s Disease, 2021, and can be found here.

Hypothesis

We hypothesize that aging and estrogen levels regulate microglial metabolism, and the metabolic reprogramming associated with the increased AD risk in women.

Methods

Figure 1. A schematic of experiments carried out in BV-2 microglia using EGFR1 and EGFR2-specific agonists PPT and DPN, respectively. Figure 2. A. Lipoprotein Pathway Activity in BV-2 cells grown under 1% and 10% FBS. B. Lipase activity in male and female WT and 5XFAD mice. C. Total lipase activity in male and female WT and 5XFAD mice.

3. Female WT and 5XFAD Mice Exhibit Increased Lipoprotein Lipase Activity

Figure 3. A. Extracellular and intracellular LPL activity in whole brain tissue of 9-month-old wild type (WT) and 5XFAD male and female mice. B. Total lipase activity in male and female WT and 5XFAD mice.

4. Estrogen Decreases DAM Gene Expression and Cholesterol Efflux in BV-2 cells

Figure 4. A. Representative image of monocyte-derived microglia-like (MDM) cells. B. Normalized expression data from DMDM cells from an aged male and female donor, with female MDM cells treated with E2 for 48 hours. C. Representative brightfield image of MDM before FLIM analysis. D. FLIM analysis of MDM derived from 25 yo female or 56 yo female donors after treatment with vehicle (0.000001% Ethanol) or E2 for 48 hours.

5. Estrogen Increases Oxidative Metabolism and Glycolysis in Low

Figure 5. A. Glycolytic index of BV-2 microglia in 1% or 10% FBS containing media treated with equal volumes of media (control), ethanol (vehicle), or E2 dissolved in ethanol (E2). B. FLIR of BV-2 microglia in 1% or 10% containing media treated with equal volumes of media (control), ethanol (vehicle), or E2 dissolved in ethanol (E2). C. Heatmap of glycolytic intermediates from metabolomics data. D. Heatmap of TCA cycle intermediates from metabolomics data.

6. Estrogen Decreases Age-associated Gene Expression and Protein Signatures in Human Microglia

Figure 6. A. Representative image of monocyte-derived microglia-like (MDM) cells. B. Normalized expression data from MDM cells from an aged male and female donor, with female MDM cells treated with E2 for 48 hours. C. Representative brightfield image of MDM before FLIM analysis. D. FLIM analysis of MDM derived from 25 yo female or 56 yo female donors after treatment with vehicle (0.000001% Ethanol) or E2 for 48 hours.

Summary & Conclusion

- With aging, female’s brains and microglia exhibit exacerbated metabolic dysregulation.
- E2 inhibits expression of key genes involved in lipid and cholesterol processing as well as AD risk, leading to metabolic reprogramming.
- Our data suggest hormone replacement therapy in menopausal women may reverse microglial metabolic reprogramming, which contributes to the neuroprotective effects of AD.

Future Directions

- Investigate the mechanisms underlying estrogen-mediated inhibition of ERs (E2) on key microglial genes and the role of other hormones like testosterone and progesterone.
- Investigate the contributions of lipid processing in microglia and its impact on disease associated microglial phenotypes.
- Investigate sex differences in how fructose affects metabolism and dysregulation.
- Investigate the effects of novel drugs that target tissue-specific estrogen receptors and how this can influence microglial metabolism and activation state.

References

1. Zhang et al. (2016) PMID: 26687838
2. Vergehe et al. (2011) PMID: 21894349
4. Lynch (2020) PMID: 31704314
5. Wang et al. (2020) PMID: 32276671
6. Kassen et al. (2017) PMID: 28930663
8. Mapi et al. (2023) PMID: 37241833
9. O’Connor et al. (2023) PMID: 36902168
10. Guilford-Bestler et al. (2021) PMID: 34192939

Acknowledgments

This work has been published and can be found here.