Microbiome Influences Prenatal and Adult Microglia in a Sex-Specific Manner

Graphical Abstract

Highlights

- Microglia undergo sequential phases of differentiation during development
- The maternal microbiome influences microglial properties during prenatal stages
- The absence of the microbiome has a sex- and time-specific impact on microglia
- Microbiome depletions have acute and long-term effects on microglial properties

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In Brief

Microglia respond to environmental challenges, such as signals from the gut microbiome, in a sex- and time-dependent manner.

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SUMMARY

Microglia are embryonically seeded macrophages that contribute to brain development, homeostasis, and pathologies. It is thus essential to decipher how microglial properties are temporally regulated by intrinsic and extrinsic factors, such as sexual identity and the microbiome. Here, we found that microglia undergo differentiation phases, discernable by transcriptomic signatures and chromatin accessibility landscapes, which can diverge in adult males and females. Remarkably, the absence of microbiome in germ-free mice had a time and sexually dimorphic impact both prenatally and postnatally: microglia were more profoundly perturbed in male embryos and female adults. Antibiotic treatment of adult mice triggered sexually biased microglial responses revealing both acute and long-term effects of microbiota depletion. Finally, human fetal microglia exhibited significant overlap with the murine transcriptomic signature. Our study shows that microglia respond to environmental challenges in a sex- and time-dependent manner from prenatal stages, with major implications for our understanding of microglial contributions to health and disease.

INTRODUCTION

Microglia, the resident macrophages of the CNS, constitute the first line of defense against injury and infections. They originate from yolk-sac macrophages (YSM), enter the brain when the first neurons are generated (around embryonic day [E] 9.5 in mice) (Casano and Peri, 2015; Ginhoux and Prinz, 2015; Prinz et al., 2017), expand, and self-renew in adulthood (Tay et al., 2017a; Thion and Garel, 2017). Alongside their immune roles, recent studies have shown that both fetal and adult microglia also contribute to a variety of processes including brain development, homeostasis, and function. At the cellular or circuit level, microglia regulate synaptic transmission, synaptic pruning and formation, cell death and survival, as well as embryonic wiring (Hong et al., 2016; Ransohoff and El Khoury, 2015; Reemst et al., 2016; Schafer and Stevens, 2015; Tay et al., 2017b; Thion and Garel, 2017; Volk, 2017; Wolf et al., 2017). Consistent with their diverse roles, microglia have been linked to the initiation or progression of several developmental and neurodegenerative
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