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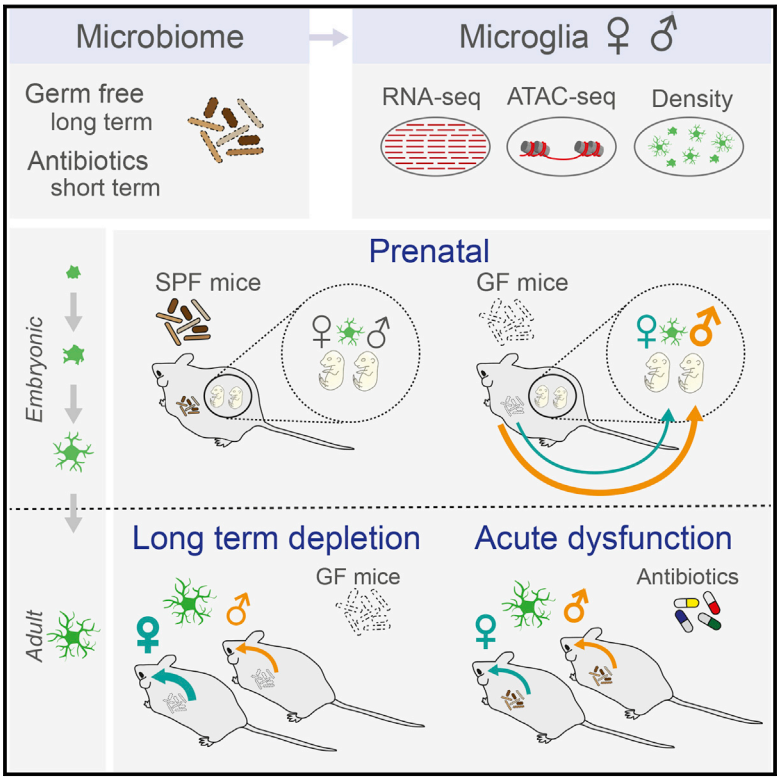
Microbiome Influences Prenatal and Adult Microglia in a Sex-Specific Manner

Graphical Abstract



Authors

Morgane Sonia Thion, Donovan Low, Aymeric Silvin, ..., Sven Pettersson, Florent Ginhoux, Sonia Garel

Correspondence

florent_ginhoux@immunol.a-star.edu.sg (F.G.), garel@biologie.ens.fr (S.G.)

In Brief

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

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

Morgane Sonia Thion,[1,16] Donovan Low,[2,16] Aymeric Silvin,[2,17] Jinmiao Chen,[2,17] Pauline Grisel,[1,17] Jonas Schulte-Schrepping,[3] Ronnie Blecher,[4] Thomas Ulas,[3] Paola Squarzoni,[1] Guillaume Hoeffel,[2,5] Fanny Coulpier,[1] Eleni Siopi,[6] Friederike Sophie David,[3] Claus Scholz,[3] Foo Shihui,[2] Josephine Lum,[2] Arlaine Anne Amoyo,[7] Anis Larbi,[2] Michael Poidinger,[2] Anne Buttgereit,[8] Pierre-Marie Lledo,[6] Melanie Greter,[8] Jerry Kok Yen Chan,[9,10] Ido Amit,[4] Marc Beyer,[3,11] Joachim Ludwig Schultze,[3,12] Andreas Schlitzer,[2,13] Sven Pettersson,[14,15] Florent Ginhoux,[2,18,19,*] and Sonia Garel[1,18,*]

[1]Institut de Biologie de l'Ecole normale supérieure (IBENS), Ecole Normale Supérieure, CNRS, INSERM, PSL Research University, 75005 Paris, France
[2]Singapore Immunology Network (SIgN), Agency for Science, Technology and Research (A*STAR), Singapore 138648, Singapore
[3]Genomics and Immunoregulation, Life and Medical Sciences (LIMES) Institute, University of Bonn, 53115 Bonn, Germany
[4]Department of Immunology, Weizmann Institute of Science, 76100 Rehovot, Israel
[5]Aix-Marseille Université, CNRS, INSERM, Centre d'Immunologie de Marseille-Luminy (CIML), 13288 Marseille, France
[6]Institut Pasteur, Unité Perception et Mémoire, CNRS, UMR 3571, F-75015 Paris, France
[7]National Cancer Centre, Singapore 169610, Singapore
[8]Institute of Experimental Immunology, University of Zurich, 8057 Zurich, Switzerland
[9]Department of Reproductive Medicine, KK Women's and Children's Hospital, Singapore 229899, Singapore
[10]KK Research Centre, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore 229899, Singapore
[11]Molecular Immunology in Neurodegeneration, German Center for Neurodegenerative Diseases (DZNE), 53127 Bonn, Germany
[12]Platform of Single Cell Genomics and Epigenomics at the German Center for Neurodegenerative Diseases and the University of Bonn, 53175 Bonn, Germany
[13]Myeloid Cell Biology, LIMES-Institute, University of Bonn, 53115 Bonn, Germany
[14]Lee Kong Chian School of Medicine and School of Biological Sciences, Nanyang Technological University, Singapore 639798, Singapore
[15]Department of Microbiology, Tumor and Cell Biology, Karolinska Institute, Stockholm 17165, Sweden
[16]These authors contributed equally
[17]These authors contributed equally
[18]These authors contributed equally
[19]Lead Contact
*Correspondence: florent_ginhoux@immunol.a-star.edu.sg (F.G.), garel@biologie.ens.fr (S.G.)
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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