

Microglia-derived TGF- β 1 Ligand Maintains Microglia Homeostasis via Autocrine Mechanism and Is Critical for Normal Cognitive Function in Adult Mouse Brain

October 31

Tuesday, 12:30 pm

Billings Building—Rosedale Room

SPEAKER:



Agnes Luo, Ph.D.

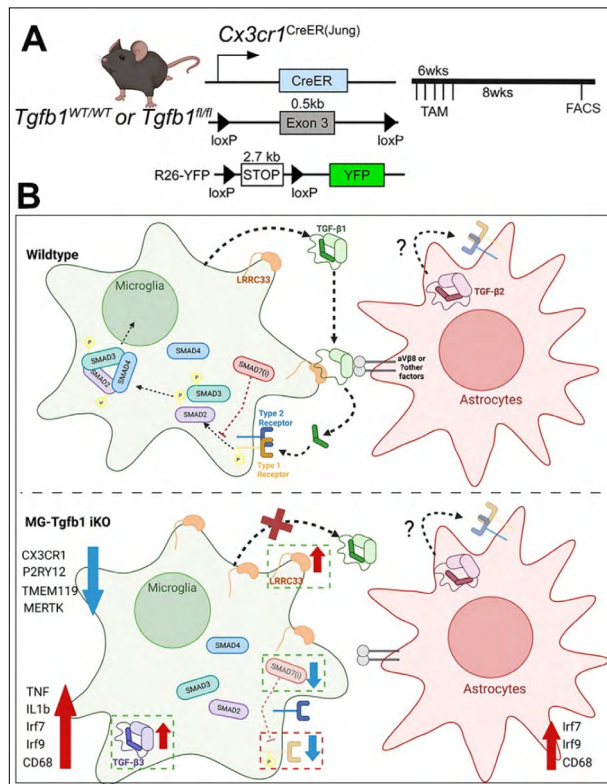
Professor and Vice Chair
Department of Molecular and Cellular Biosciences
College of Medicine
University of Cincinnati

Host: Rajiv R. Ratan, M.D., Ph.D.

For more information contact
Darlene White
daw9085@med.cornell.edu

Abstract

The long-term goal of our lab is to understand key components of the CNS that determine neuronal survival and function and to improve functional outcomes from CNS diseases. One of our research interests is to characterize how microglia affect the function of astrocytes and eventually determine the survival of neurons under both physiological and pathological conditions. TGF- β has recently been suggested as a key factor in the maintenance of microglia homeostasis under physiological conditions in the adult brain. While TGF- β signaling is essential for microglial function, the cellular source of TGF- β ligand and its spatial regulation remains unclear in the adult CNS. Our recent study supports that microglia, not astrocytes or neurons, are the primary producers of TGF- β 1 ligands needed for microglial homeostasis. Microglia (MG)-Tgfb1 inducible knockout (iKO) leads to the activation of microglia featuring a dyshomeostatic transcriptomic profile that resembles disease-associated microglia (DAMs), injury-associated microglia, and aged microglia, suggesting that microglial self-produced TGF- β 1 ligands are important in the adult CNS. Interestingly, astrocytes in MG-Tgfb1 iKO mice show a transcriptome profile that closely aligns with A1-like neurotoxic astrocytes. Additionally, using sparse mosaic single-cell microglia iKO of TGF- β 1 ligand, we established an autocrine mechanism for TGF- β signaling. MG-Tgfb1 iKO mice show cognitive deficits, supporting that precise spatial regulation of TGF- β 1 ligand derived from microglia is critical for the maintenance of brain homeostasis and normal cognitive function in the adult brain.



Publications:

- Luo F, Wang J, Zhang Z, You Z, Bedolla A, Okwubido-Williams F, Huang LF, Silver J, Luo Y. *Inhibition of CSPG receptor PTP α promotes migration of newly born neuroblasts, axonal sprouting, and recovery from stroke.* Cell Rep. 2022 Jul 26;40(4):111137. doi: 10.1016/j.celrep.2022.111137.
- Bedolla A, Mckinsey G, Ware K, Santander N, Arnold T, Luo Y. *Finding the right tool: a comprehensive evaluation of microglial inducible cre mouse models.* bioRxiv. 2023 Apr 17;. doi: 10.1101/2023.04.17.536878. PubMed PMID: 37131606; PubMed Central PMCID: PMC10153116. (Under Revision at Cell Reports)
- Bedolla A, Wegman E, Weed M, Paranjpe A, Alkhimovitch A, Ifergan I, McClain L, Luo Y. *Microglia-derived TGF- β 1 ligand maintains microglia homeostasis via autocrine mechanism and is critical for normal cognitive function in adult mouse brain.* bioRxiv. 2023 Jul 7;. doi: 10.1101/2023.07.05.547814. PubMed PMID: 37461569; PubMed Central PMCID: PMC10349967. (Manuscript reviewed by Immunity, under revision)