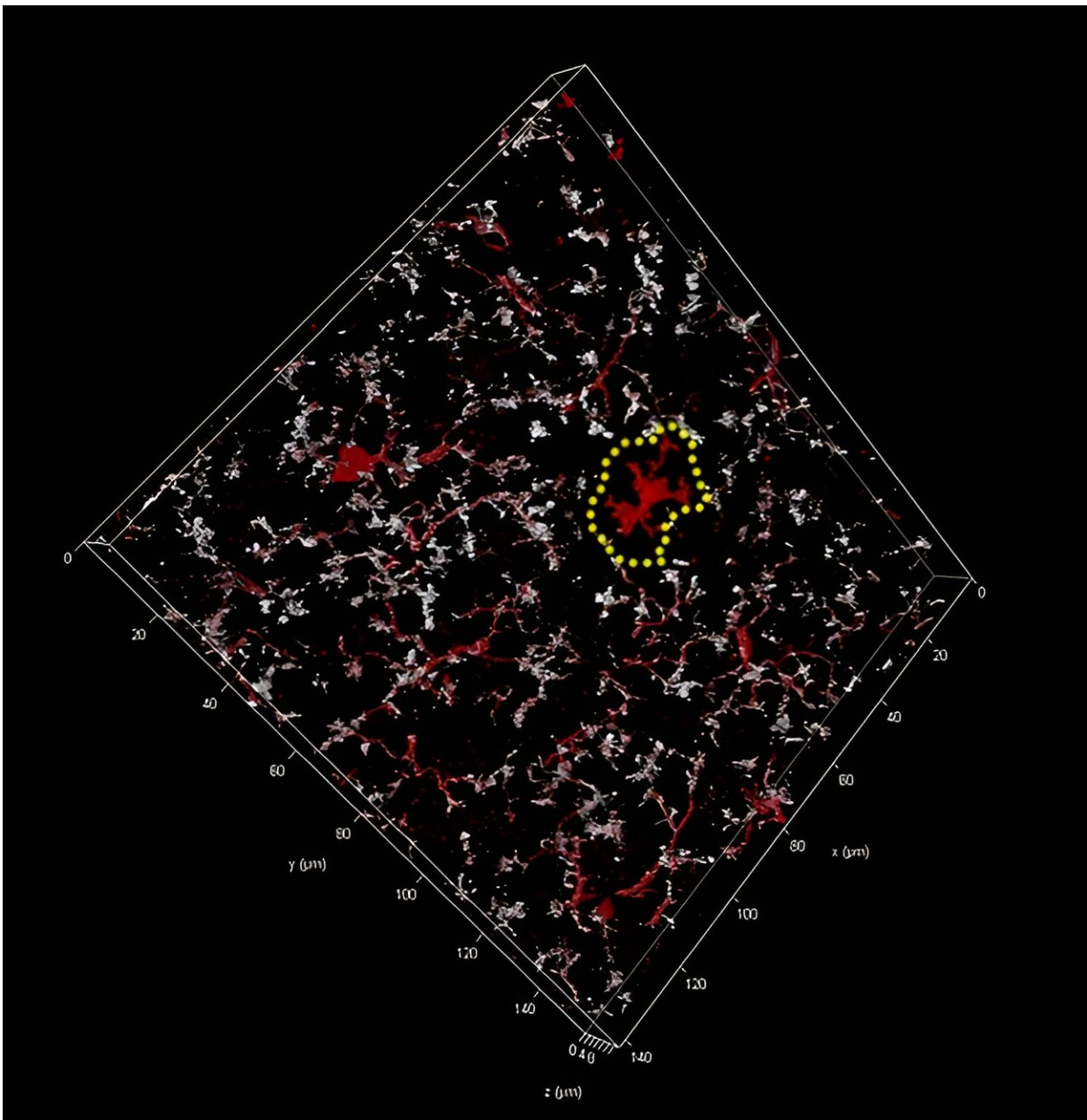


# Signaling pathway in brain helps maintain balance in microglia, prevent cognitive deficit

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A 3D rendered confocal image shows a single TGF- $\beta$ 1 knockout microglia being activated while it is surrounded by normal microglia that do not have the gene deletion. Credit: Agnes (Yu) Luo

A new study led by University of Cincinnati researchers sheds new light on the role of a signaling pathway in the brain to maintain health and prevent inflammation and cognitive deficits.

UC's Agnes (Yu) Luo, Ph.D., is corresponding author on the research, [published](#) in the journal *Nature Communications*, and focused on a [signaling pathway](#) called TGF- $\beta$  that plays a number of roles depending on where it is located in the body.

Luo explained that signaling pathways in the body control different cell functions and require two components: a type of molecule called a [ligand](#) and a receptor that the ligand binds to and activates to start the signaling.

Prior to this study, it was known that the TGF- $\beta$  signaling pathway was important in [brain](#) immune cells called microglia in maintaining their balance, but its role in maintaining cognitive function was largely unknown. Additionally, the precise source of the TGF- $\beta$  ligand in the brain was also unknown.

Luo said the researchers used state-of-the-art tools and found for the first time that microglia make the TGF- $\beta$  ligand in the brain to prevent neuroinflammation.

"Microglia cells are the innate immune cells of the brain, and what surprised us most is that they each make their own TGF- $\beta$  ligand," said Luo, professor and vice chair in the Department of Molecular and

Cellular Biosciences in UC's College of Medicine. "This TGF- $\beta$  ligand binds to the receptor on the microglia cell itself, and they use this signaling to stay in homeostasis. This self-produced ligand binds to receptors on the cell's surface to keep each cell in a constantly balanced--and not in an inflamed--state."

While it was previously known that TGF- $\beta$  signaling helps keep microglia in balance, Luo said it was not known that microglia make the ligands themselves in a "spatially and precisely controlled" manner carried out by each individual cell, a mechanism called autocrine signaling.

"You can think of these microglia cells as being, in a way, 'selfish,' as they only make the ligand to keep themselves in balance and not inflamed," said graduate student and study co-author Elliot Wegman. "This, thereby, provides a very precise mechanism to regulate local states of inflammation in the microenvironment of the brain."

Using animal models, the team additionally found that when the TGF- $\beta$  ligand is genetically deleted from microglia, it leads to global neuroinflammation in the brain.

"This suggests that the neuroinflammation in [microglia](#) is sufficient by itself without other causes to drive cognitive deficit," Luo said. "We show the direct cause and link between these events."

Moving forward, the team will investigate whether cognitive deficits can be slowed, stopped or potentially reversed by boosting the TGF- $\beta$  ligand and signaling pathway in the brain under conditions where TGF- $\beta$  signaling becomes compromised.

"We're investigating whether restoring the TGF- $\beta$  signaling pathway and revitalizing its signaling can then ameliorate disease-related or age-

associated cognitive deficits," she said. "The long-term goal of our research is to modify the brain environment to better support the survival of the neurons or promote repair of the brain after injury or damage."

**More information:** Alicia Bedolla et al, Adult microglial TGF $\beta$ 1 is required for microglia homeostasis via an autocrine mechanism to maintain cognitive function in mice, *Nature Communications* (2024).  
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