

Targeting microglia and inflammation in the Alzheimer's disease brain

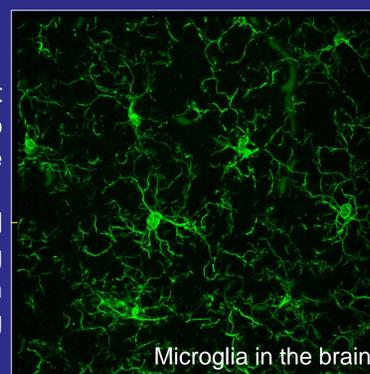
Green Lab

Department of Neurobiology and Behavior
Institute for Memory Impairments and Neurological Disorders
University of California, Irvine, CA



Microglia

- Microglia are the primary immune cells in the brain and serve to protect our brains from infections, as well as to clear away cellular debris caused by cell damage/death.
- Microglia are distributed throughout the brain and comprise approximately 10% of all cells in the CNS.
- Microglia can detect infectious agents and respond to them, mounting an inflammatory response through the production of pro-inflammatory cytokines (such as, TNF- α , IL-1 β , IL-6, and TGF- β).
- Once the infectious agents have been eradicated, microglia return to a quiescent state.

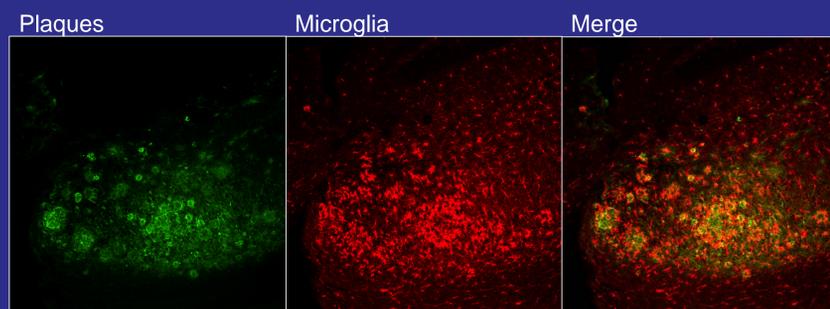


Microglia in the brain

- However, despite the protective role that microglia play in the normal brain, they go awry in the diseased brain and damage the local brain environment.
- They are negatively implicated in all neurodegenerative diseases, including Alzheimer's disease, as well as after brain injuries, such as those sustained following traumatic brain injury or stroke.

Microglia in the Alzheimer's disease brain

- Increased neuroinflammation is a key feature of the Alzheimer's disease (AD) brain, as well as in APP overexpressing transgenic mouse models.
- Recent genetic data has implicated a number of microglial genes in conveying increased risk of developing AD.
- Activated microglia surround extracellular plaques, attempting to clear the toxic deposits from the brain. Inevitably, this results in a chronic neuroinflammatory response and the increased production of pro-inflammatory cytokines and chemokines.



- Chronic neuroinflammation has the potential to lead to synaptic and neuronal loss, as well as exacerbate the progression of tau pathology.
- Therefore, the microglial response in the AD brain is likely harmful and contributes to the dementia associated with the disease.
- The Green lab is focused on manipulating microglia to prevent their harmful effects on the brain during disease and, in doing so, provide novel therapeutics for AD and other neurodegenerative diseases as well as after injury.

Microglia in the adult brain are fully dependent on CSF1R signaling for their survival

We have recently shown that microglia in the healthy adult mouse brain are fully dependent upon signaling through the colony-stimulating factor 1 receptor (CSF1R) for their survival. Administration of CSF1R inhibitors that cross the blood brain barrier lead to the rapid elimination of virtually all microglia from the brain within 7-21 days.

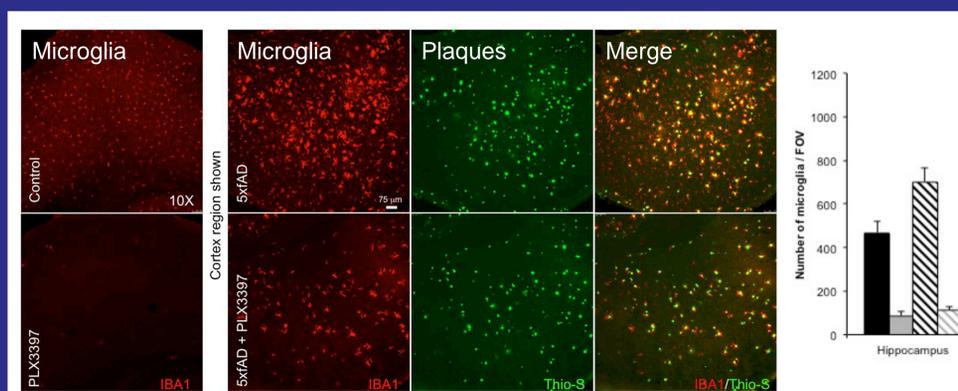


2-month old wild-type mice were treated with the CSF1R inhibitor PLX3397 for 21 days. A white dot was superimposed on each and every microglia (IBA1+ cell), showing the robust elimination of >95% of all microglia.

- Treatment with CSF1R inhibitors causes microglia to undergo cell death.
- Microglia remain eliminated for as long as treatment continues.
- Healthy mice depleted of microglia are phenotypically indistinguishable from untreated mice.
- This discovery means that we can now eliminate all microglia from the brain using a small molecular inhibitor.
- We can now eliminate microglia from the AD brain, as well as in related disorders and after injury, and determine their contribution to the disease as well as treatment potential.

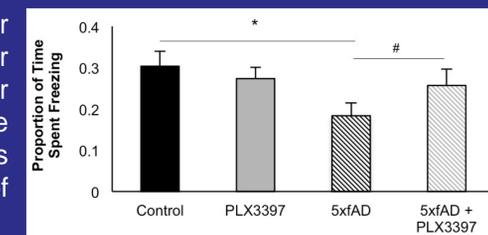
Elimination of microglia from AD mice

5xfAD transgenic mice represent an aggressive mouse model of AD. We treated 10-month old 5xfAD mice with the CSF1R inhibitor PLX3397 for 1 month, and discovered that we could indeed eliminate most microglia from the AD brain:

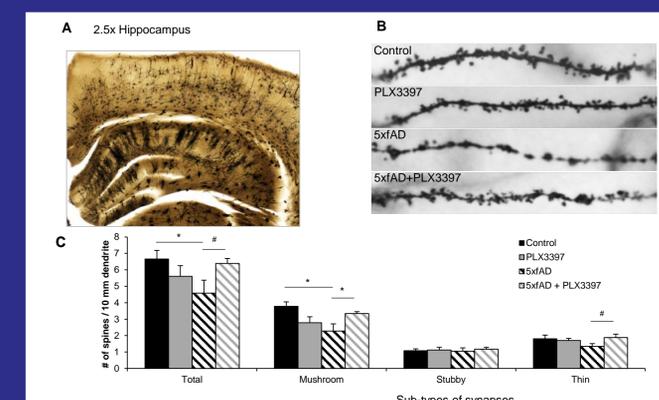


Elimination of microglia from AD mice rescues memory impairments

Mice were tested on contextual fear conditioning – a task that tests their memory. 5xfAD mice that no longer have microglia no longer have memory impairments. This suggests that microglia are key drivers of memory impairments in the disease.



Elimination of microglia from AD mice rescues synaptic deficits



Synapses are the connections between neurons. Synaptic loss is a key feature of AD brains, and the strongest correlate to dementia/memory loss. 5xfAD mice also show synaptic loss, which correlates with their memory loss. However, 5xfAD mice that no longer have microglia no longer have synaptic loss, implicating microglia in the loss of connectivity between neurons and related memory impairments.

Conclusions

- The Green lab has discovered that microglia in the adult mouse brain are fully dependent on signaling through the cell surface receptor known as CSF1R.
- We can administer small molecules that inhibit this receptor, leading to the elimination of virtually all microglia from the brain.
- As microglia are negatively implicated in AD, and most other brain disorders, this represents a breakthrough to 1) counteract the harmful effects of these cells through their removal, and 2) understand the role that they play in specific diseases.
- We have shown that we can eliminate all microglia from mouse models of AD and that this rescues the memory deficits in these mice. Thus, targeting of microglia is a promising potential treatment option for AD.

Acknowledgements:

These experiments were conducted by Elizabeth Spangenberg, Allison Najafi, Rafael Lee, and Monica Elmore, Ph.D.