Targeting microglia and inflammation in the Alzheimer’s disease brain

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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-1β, IL-6, and TGF-β).
- Once the infectious agents have been eradicated, microglia return to a quiescent state.

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.
- We have shown that we can eliminate all microglia from mouse models of AD.
- 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.

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.
- 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.

Elimination of microglia from AD mice rescues memory impairments
- Mice were tested on contextual fear conditioning – a task that tests their memory. 5xAD 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. 5xAD mice also show synaptic loss, which correlates with their memory loss. However, 5xAD 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.

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