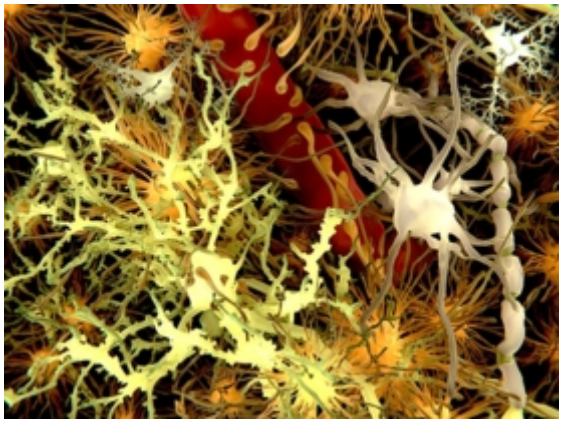
Rise of the Microglia

New research shows that the resident immune cells of the brain are involved in both development and disease

By Diana Kwon | October 23, 2015



©iStock.com

Microglia, the immune cells of the brain, have long been the underdogs of the glia world, passed over for other, flashier cousins, such as astrocytes. Although microglia are best known for being the brain's primary defenders, scientists now realize that they play a role in the developing brain and may also be implicated in developmental and neurodegenerative disorders. The change in attitude is clear, as evidenced by the buzz around this topic at this year's Society for Neuroscience (SfN) conference, which took place from October 17 to 21 in Chicago, where scientists discussed their role in both health and disease.

Activated in the diseased brain, microglia find injured neurons and strip away the synapses, the connections between them. These cells make up around 10 percent of all the cells in the brain and appear during early development. For decades scientists focused on them as immune cells and thought that they were quiet and passive in the absence of an outside invader. That all changed in 2005, when experimenters found that microglia were actually the fastest-moving structures in a healthy adult brain. Later discoveries revealed that their branches were reaching out to surrounding neurons and contacting synapses. These findings suggested that these cellular scavengers were involved in functions beyond disease.

The Brain's Sculptors

The discovery that microglia were active in the healthy brain jump-started the exploration into their underlying mechanisms: Why do these cells hang around synapses? And what are they doing?

For reasons scientists don't yet understand, the brain begins with more synapses than it needs. "As the brain is making its [connections], it's also eliminating them," says Cornelius Gross, a neuroscientist at the European Molecular Biology Laboratory. Microglia are critical to this process, called pruning: they gobble up synapses, thus helping to sculpt the brain by eliminating unwanted connections.* But how do microglia know which synapses to get rid of and which to leave alone?

New evidence suggests that a protective tag that keeps healthy cells from being eaten by the body's immune system may also shield against microglial activity in the brain. Emily Lehrman, a doctoral candidate in neuroscientist Beth Stevens's laboratory at Boston's Children's Hospital, presented these unpublished findings at this year's SfN. "The [protective tag]'s receptor is highly expressed in microglia during peak pruning," Lehrman says. Without an abundance of this receptor, the tag is unable to protect the cells, leading to excess engulfment by microglia and overpruning of neuronal connections.*

But pruning is not always a bad thing. Other molecules work to ensure that microglia remove weak connections, which can be detrimental to brain function. Cornelius Gross, a neuroscientist at the European Molecular Biology Laboratory, and his research group have been investigating the activity of fractalkine, a key molecule in neuron-microglia signaling whose receptors are found exclusively on microglia. "Microglia mature in a way that matches synaptogenesis, which sets up the hypothesis that neurons are calling out to microglia during this period," Gross says.

His lab found that removing the receptor for fractalkine created an overabundance of weak synaptic contacts caused by deficient synaptic pruning during development in the hippocampus, a brain area involved in learning and memory. These pruning problems led to decreased functional connectivity in the brain, impaired social interactions and increased repetitive behavior—all telltale signs of autism. Published last year in *Nature Neuroscience* (*Scientific American* is part of Springer Nature), this work was also presented at the conference.

see also:

- Health: Foods to Restore Your Intestinal Flora |
- Sustainability: Exxon Knew about Climate Change Almost 40 Years Ago |
- Tech: A Quick Guide to the Senate's Newly Passed Cybersecurity Bill |
- The Sciences: A Fossil Find Gets Entangled with South Africa's Apartheid Past

When Pruning Goes Awry

Studies have also found evidence for increased microglial activation in individuals with schizophrenia and autism; however, whether increased microglial activity is a cause or effect of these diseases is unclear. "We still need to understand whether pruning defects are contributing to these developmental disorders," Stevens says.

Some findings are emerging from studies on Rett syndrome, a rare form of autism that affects only girls. Dorothy Schafer, now at the University of Massachusetts Medical School, studied microglia's role in Rett syndrome while she was a postdoctoral researcher in Stevens's lab. Using mice with mutations in MECP2, the predominant cause of the disease, she found that while microglia were not engulfing synapses during early development, the phagocytic capacity (or the gobbling ability) of these cells increased during the late stages of the disease. These unpublished results suggest that microglia were responding secondarily to a sick environment and partially resolve a debate going on about what microglia do in Rett syndrome—in recent years some studies have shown that microglia can arrest the pathology of disease, whereas others have indicated that they cannot. "Microglia are doing something, but in our research, it seems to be a secondary effect," Shafer says. "What's going on is still a huge mystery."

Return of the Pruning Shears

As the resident immune cells, microglia act as sentinels, sensing and removing disturbances in the brain. When the brain is exposed to injury or disease, microglia surround the damaged areas and eat up the remains of dying cells. In Alzheimer's disease, for example, microglia are often found near the sites of beta-amyloid deposits, the toxic clumps of misfolded proteins that appear in the brain of affected people. On one hand, microglia may delay the progression of disease by clearing cellular debris. But it is also possible that they are contributing to disease.

Early synapse loss is a hallmark of many neurodegenerative disorders. Growing evidence points to the possibility that microglial pruning pathways seen in early development may be reactivated later in life, leading to disease. Unpublished data from Stevens's lab presented at the conference suggest that microglia are involved in the early stages of Alzheimer's and that blocking microglia's effects could reduce the synapse loss seen in Huntington's disease.

As a newly burgeoning field, there are still more questions than answers. Next year's conference is likely to bring us closer to understanding what these dynamic cells are doing in the brain. Once the underdogs, microglia may be the key to future therapeutics for a wide variety of psychiatric and neurodegenerative disorders.

*Clarification (10/27/15): Text updated to provide attribution.