Microglia controls neuron production as brain develops

February 27 2013

(Medical Xpress)—In a surprise breakthrough, researchers at the UC Davis MIND Institute and their colleagues have found that microglia remove healthy neural progenitor cells (NPCs) through phagocytosis to control neuron production during brain development. This newly discovered mechanism keeps neuron numbers in check, preventing brain overgrowth.

The discovery could open up new avenues for brain research and lead to therapies for a variety of neurological conditions.

The study was published online today in the *The Journal of Neuroscience*.

Microglia are the immune component cell of the central nervous system. Similar to macrophages, microglia provide the brain's primary defense against pathogens and foreign bodies, clear away dying cells and help repair neural damage. When inactive, they act as sentinels. When a problem is located, they activate and eliminate it. However, until recently, no one had realized the important roles they play in brain development.

"We have known for some time that neurons can undergo apoptosis, a form of cell death, and ultimately be removed by microglia," said Stephen Noctor, assistant professor in the Department of Psychiatry and Behavioral Sciences and the study's lead author. "But this is new. Microglia are actually eating healthy progenitor cells, thereby regulating

the number of neurons produced in the developing brain."

During development, NPCs produce neurons in the brain's proliferative zones. However, creating too many or too few neurons can have dire consequences.

"If you have too many cells, there's only so much trophic support (brain infrastructure for cell growth and survival) to keep neurons alive," Noctor said. "All these cells competing for resources could easily throw off connectional properties, altering the way surviving neurons interact. Likewise, having too few cortical cells would have profoundly negative consequences."

Studying tissue from primates and rats, the researchers noted that microglia colonize the proliferative zones of the prenatal brain. The researchers labeled the microglia and NPCs with antibodies and other markers to track microglial status—whether they were resting or active—and their interactions with progenitor cells. Microglia were concentrated in the proliferative zone where NPCs proliferate and produce new neurons.

The vast majority—95 percent—of microglia in the proliferative zone were activated. Even more importantly, they were engulfing and eating NPCs. However, the team had to determine the NPC's health status. If the NPCs were dead or dying, the microglial activity would not have been unusual, as removing these cells is one of their primary functions.

Dying cells conveniently provide "eat me" signals to microglia. For example, they express phosphatidylserine (PS) on their surface. The investigators found that PS-expressing cells could be found throughout the brain, but were not concentrated with microglia in the proliferative zones. Other experiments indicated that the NPCs being targeted by microglia were healthy cells.

"The progenitor cells being eaten didn't appear to be apoptotic or damaged in any way," said Dr. Noctor. "They appeared to be normal in every respect."

In addition, regional differences in the distribution of microglia point to another role for the cells. By selectively eliminating NPCs, and as a result neurons, they may contribute to the development of regional differences in brain architecture.

As time goes on, microglial cell distribution adjusts to the maturing brain. "Microglia are generated in the yolk sack and quickly become attracted to the proliferative zones in the brain, colonize that zones and have a feast," said Noctor. "However, after neurogenesis is over, they distribute throughout the brain to acquire their adult distribution. So if you look at an adult brain, there's an even distribution of microglial cells."

Having established that microglia eat healthy NPCs, the next step was to determine whether modulating their activity could alter NPC numbers. This could have profound clinical consequences. For example, a number of studies have shown that autistic children have larger brains. While there is limited evidence, at present, that microglia play a role in autism, this could be an important investigative path. In addition, this study could have implications for schizophrenia treatment.

"If a mother is exposed to a pathogen, such as influenza, in the first trimester, that increases the likelihood of schizophrenia," Noctor said. "Recent studies suggest that the schizophrenic brain has less grey matter. Together these data suggest the hypothesis that mothers might get an immune response in the first trimester, which our data shows increases the activation of microglia, and as a result microglia may take out too many progenitor cells in the developing brain."

To test this idea, the team treated rats with bacterial lipopolysaccharide (LPS), which generates an inflammatory response and activates microglia in prenatal brains. They also treated another group of pregnant rats with the antibiotic doxycycline (Dox), which suppresses microglial activation.

Increasing microglial activity in the LPS group significantly reduced the number of NPCs by 20 to 40 percent. Meanwhile, the Dox treatment, which inhibited the microglial activation, increased the number of NPCs by 20 percent. These changes in NPC numbers persisted well after birth.

Going a step further, the researchers used liposomal clodronate to remove microglia from the developing brain. The clodronate eliminated 90 percent of the microglia, which significantly increased the NPC population.

This direct relationship between microglial activity and neuron production could provide a clinical pathway to prevent schizophrenia and other disorders.

"We activated the microglial cells with different compounds," Noctor said. "There are also drugs on the market that deactivate microglia. We could potentially use these tools to control microglial activation in controlled studies to determine if this is a viable way to restore the brain's proper balance."

Provided by UC Davis