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How do adult brain circuits regulate new neuron production?

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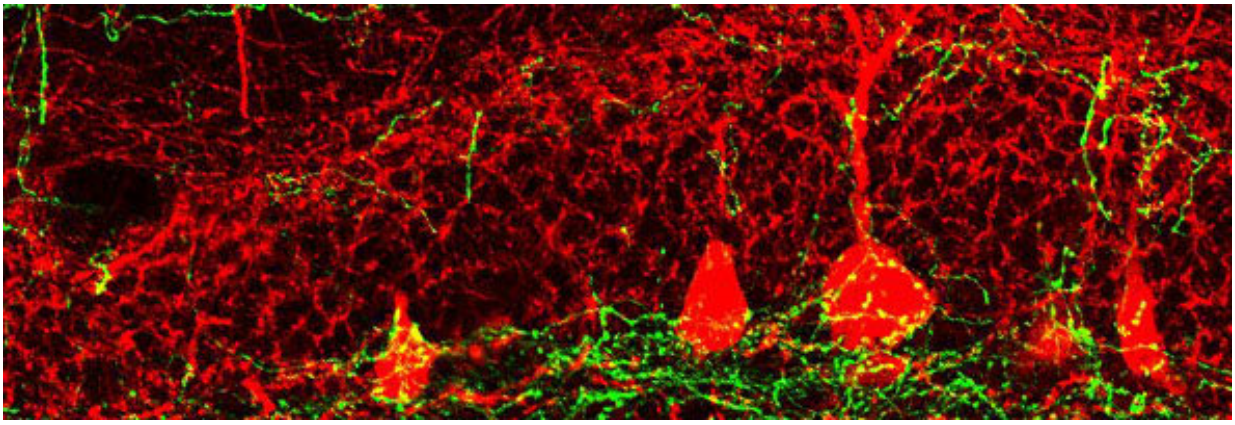

Confocal image showing a close association between medial septum-to-hippocampus GABA projections and local PV interneurons in the hippocampus. Credit: Song Lab, UNC School of Medicine

Before we are born, the developing brain creates an incredible number of neurons, which migrate to specific parts of the brain to ready us for life. Contrary to popular belief, genesis of new neurons does not stop at birth or even in childhood. In a few select areas of the brain, it can continue throughout adulthood, and is believed to be vitally important for certain forms of learning and memory, and in mood regulation. How neurogenesis is switched on and off is still not well understood, but UNC School of Medicine researchers led by Juan Song, PhD, assistant professor in the department of pharmacology, have just discovered a

major clue.

Reported as the cover story in *Cell Stem Cell*, the researchers identified a neurogenesis-controlling brain circuit that runs from near the front of the brain back to the hippocampus, a learning- and memory-related structure. The hippocampus is one of the major sites of neurogenesis in the adult human brain, and the circuit that Song's team has identified regulates this neuron-producing process.

"This circuit controls the activity of stem cells in the part of the hippocampus where neurogenesis occurs," said Song, a member of the UNC Neuroscience Center. "Our finding ultimately could have implications for understanding and treating many brain disorders arising from aberrant hippocampal neurogenesis, including epilepsy, schizophrenia, depression, and Alzheimer's disease."

Neural stem cells are like stem cells in other tissues and organs - they give birth, if needed, to new cells that replace dead or dying ones. Most of the neurons in the adult brain are wired tightly into complex circuits and are not replaced.

The chief exception is the dentate gyrus (DG) region of the hippocampus. Neurogenesis in the DG occurs throughout adult life and supports the hippocampus's crucial functions in storing and retrieving memories. DG neurogenesis has been linked to mood as well. In fact, scientists suspect that the mood-improving effects of antidepressant drugs and physical exercise arise at least in part from the boost they give to DG neurogenesis.

How the brain controls DG neurogenesis, dialing it up and down when needed, is a mystery that Song and her team have been trying to solve since Song started her lab at UNC in 2013. In a study published in the journal *Nature Neuroscience*, for example, they found that special local

hippocampal neurons called PV interneurons provide signals to DG newborn progeny that appear to be crucial for healthy neurogenesis.

In the new study, Song and colleagues discovered that this hippocampal PV interneuron-signaling is regulated by a GABA circuit coming from the medial septum, a cluster of neurons near the front of the brain.

"This medial septum GABA circuit works through the local PV interneurons in the hippocampus to instruct stem cells to become activated or to stay quiet," Song said. "This GABA circuit is unique, because local PV interneurons are excited by GABA, a brain neurotransmitter that normally inhibits neuronal activity."

When a neural stem cell becomes activated, it begins a process of cell division that ultimately yields new neurons that connect to existing brain circuits. In a healthy hippocampus over a normal life span, neurogenesis proceeds at only a low level. Resident stem cells remain mostly in a "quiescent" state, and the population of stem cells is maintained indefinitely.

Song and her team found that in mice, the medial septum-to-hippocampus circuit works to keep DG stem cells in this normal, low-activity state. It acts like a brake on DG stem cell activation, and thus helps maintain a healthy DG stem cell population.

By contrast, interfering with this circuit takes off the brake completely, allowing DG stem cells to become not just active but overactive. Specifically, Song's team found that in mice, this DG stem cell over-activation caused a burst of newly made neurons and a massive depletion of the resident DG stem cell population. Moreover, the new neurons produced in this excessive burst of neurogenesis seemed less healthy.

"Their appearance was abnormal," Song said. "Their dendrites - the root-

like stalks that receive inputs from other neurons - were too long and had too many crossings, suggesting impaired functions. It's likely that the production of these abnormal neurons in the hippocampus would lead to learning and memory deficits."

She and her team now want to determine whether the medial septum-to-hippocampus circuit can be targeted with therapies to protect DG stem cells and restore normal DG neurogenesis in cases where neurogenesis is abnormal. Alzheimer's, schizophrenia, depression, and certain forms of epilepsy all have been linked to deficits in DG neurogenesis. There have been hints too that Alzheimer's specifically involves losses of the medial septum neurons that connect to the hippocampus to control neurogenesis.

"In principle, restoring the normal signals from the circuit linking the medial septum to the hippocampus may offer therapeutic potential to treat disorders that involve abnormal DG neurogenesis," Song said.

She and her laboratory are currently studying the function of the medial septum-to-hippocampus circuit in the context of Alzheimer's mouse models.

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