MedicalXpress

Growth of new brain cells requires 'epigenetic' switch

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New cells are born every day in the brain's hippocampus, but what controls this birth has remained a mystery. Reporting in the January 1 issue of *Science*, neuroscientists at the Johns Hopkins University School of Medicine have discovered that the birth of new cells, which depends on brain activity, also depends on a protein that is involved in changing epigenetic marks in the cell's genetic material.

"How is it that when you see someone you met ten years ago, you still recognize them? How do these transient events become long lasting in the brain, and what potential role does the birth of new neurons play in making these memories?" says Hongjun Song, Ph.D., an associate professor of neurology and member of the Johns Hopkins Institute of Cell Engineering's NeuroICE. "We really want to understand how daily life experiences trigger the birth and growth of new neurons, and make long-lasting changes in the brain."

The researchers reasoned that making long-term memories might require long-term changes in brain cells. And one type of cellular change that has long-lasting effects is so-called epigenetic change, which can alter a cell's DNA without changing its sequence but does change how and which genes are turned on or off. So they decided to look at the 40 to 50 genes known to be involved in epigenetics, and see if any of them are turned on in mouse brain cells that have been stimulated with electroconvulsive therapy—shock treatment. "It's long been known that ECT induces neurogenesis in rodents and humans, so we used it as our test case to find what is triggered downstream to cause new cells to

grow," says Song.

One gene turned on in response to ECT was Gadd45b, a gene previously implicated in immune system function and misregulated in brain conditions like autism. To confirm Gadd45b is turned up in response to brain activity, the researchers also examined mice experiencing a different activity. Exposure to new surroundings, the team found, also turns on Gadd45b in brain cells.

To find out if Gadd45b is required for new brain-cell growth, the research team made mice lacking the Gadd45b gene and tested their ability to generate new brain cells after ECT. They injected the mice with a dye that marks new cells and three days after ECT examined the number of new cells containing that dye in brains from mice with and without the Gdd45b gene. They found that while normal brains showed a 140 percent increase in cell number after ECT, brains lacking Gadd45b only showed a 40 percent increase.

"The question then was, How does Gadd45b do this?" says Song. "It's been controversial that Gadd45b can promote epigenetic changes like global DNA demethylation, but we show that it can promote demethylation of certain genes."

The chemical methyl group, when attached to DNA near genes, can turn those genes off. This so-called epigenetic change is thought to silence genes a cell doesn't use.

By dissecting mature neurons from normal mouse brains and looking for the presence of methyl groups at certain genes known to promote cell growth, the researchers found that after ECT, these genes became demethylated.

However, doing the same thing with mice lacking Gadd45b resulted in

no demethylation, suggesting to the team that Gadd45b is indeed required for demethylation.

"We're really excited about this—it's the first time we've seen dynamic epigenetic DNA changes in response to brain activity," says Song.

"Now that we have the mice lacking Gadd45b, our next goal is to see if these mice have problems with learning and memory and how Gadd45b specifically promotes the demethylation to lead to these long-term changes in the brain."

Source: Johns Hopkins Medical Institutions