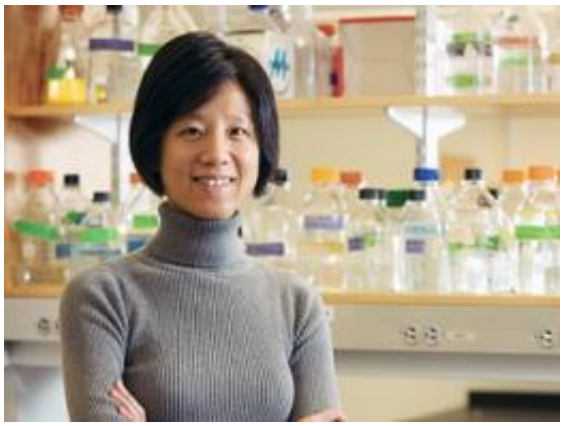
Neuroscientists identify a master controller of memory

22 December 2011, by Anne Trafton



Yingxi Lin, a member of the McGovern Institute for Brain Research and the the Frederick and Carole Middleton Career Development Assistant Professor of Brain and Cognitive Sciences. Photo courtesy Kent Dayton

When you experience a new event, your brain encodes a memory of it by altering the connections between neurons. This requires turning on many genes in those neurons. Now, MIT neuroscientists have identified what may be a master gene that controls this complex process.

The findings, described in the Dec. 23 issue of *Science*, not only reveal some of the molecular underpinnings of memory formation - they may also help neuroscientists pinpoint the exact locations of memories in the brain.

The research team, led by Yingxi Lin, a member of the McGovern Institute for Brain Research at MIT, focused on the Npas4 gene, which previous studies have shown is turned on immediately following new experiences. The gene is particularly active in the hippocampus, a brain structure known to be critical in forming long-term memories.

Lin and her colleagues found that Npas4 turns on a series of other genes that modify the brain's internal wiring by adjusting the strength of synapses, or connections between neurons. "This is a gene that can connect from experience to the eventual changing of the circuit," says Lin, the Frederick and Carole Middleton Career Development Assistant Professor of Brain and Cognitive Sciences.

To investigate the genetic mechanisms of memory formation, the researchers studied a type of learning known as contextual fear conditioning: Mice receive a mild electric shock when they enter a specific chamber. Within minutes, the mice learn to fear the chamber, and the next time they enter it, they freeze.

The researchers showed that Npas4 is turned on very early during this conditioning. "This sets Npas4 apart from many other activity-regulated genes," Lin says. "A lot of them are ubiquitously induced by all these different kinds of stimulations; they are not really learning-specific."

Furthermore, Npas4 activation occurs primarily in the CA3 region of the hippocampus, which is already known to be required for fast learning.

"We think of Npas4 as the initial trigger that comes on, and then in turn, in the right spot in the brain, it activates all these other downstream targets. Eventually they're going to modify synapses in a way that's likely changing synaptic inhibition or some other process that we're trying to figure out," says Kartik Ramamoorthi, a graduate student in Lin's lab and lead author of the paper.

Genetic regulation

So far, the researchers have identified only a few of the genes regulated by Npas4, but they suspect there could be hundreds more. Npas4 is a transcription factor, meaning it controls the copying of other genes into messenger RNA - the genetic material that carries protein-building instructions

from the nucleus to the rest of the cell. The MIT experiments showed that Npas4 binds to the activation sites of specific genes and directs an enzyme called RNA polymerase II to start copying them.

"Npas4 is providing this instructive signal," Ramamoorthi says. "It's telling the polymerase to land at certain genes, and without it, the polymerase doesn't know where to go. It's just floating around in the nucleus."

When the researchers knocked out the gene for Npas4, they found that mice could not remember their fearful conditioning. They also found that this effect could be produced by knocking out the gene just in the CA3 region of the hippocampus. Knocking it out in other parts of the hippocampus, however, had no effect. Though they focused on contextual fear conditioning, the researchers believe that Npas4 will also prove critical for other types of learning.

Gleb Shumyatsky, an assistant professor of genetics at Rutgers University, says that an important next step is to identify more of the genes controlled by Npas4, which should reveal more of its role in memory formation. "It's definitely one of the major players," says Shumyatsky, who was not involved in this research. "Future experiments will show how major a player it is."

The MIT team also plans to investigate whether the same neurons that turn on Npas4 when memories are formed also turn it on when memories are retrieved. This could help them pinpoint the exact neurons that are storing particular memories.

"We're hunting for the memory, and we think we can use Npas4 to mark where it is," Ramamoorthi says. "That's because it's turned on specifically and now we can label the cells and maybe fish out where in the brain the memory is sitting."

More information: Npas4 Regulates a Transcriptional Program in CA3 Required for Contextual Memory Formation, *Science*, 23 December 2011:
Vol. 334 no. 6063 pp. 1669-1675. DOI: 10.1126/science.1208049