Molecules of memory

Revelations about memory's mechanisms with implications for Alzheimer's and other illnesses

Those who have been following news about brain research over the last year should have no trouble remembering the name Yi Zhong. Three times since last October, Zhong, a professor at Cold Spring Harbor Laboratory, has published headline-grabbing research papers explaining at the level of individual molecules some of the mysteries about why we remember and forget things.

In this and related work, Zhong, along with colleagues at CSHL and in China, are not only adding to our fundamental understanding of the brain; they are progressing steadily along a path that could culminate in treatments for a range of serious illnesses involving memory impairment, from mental retardation to Alzheimer's disease.

Like others who have come before him, Zhong uses the fly as a comparatively simple model with which to study both the genetics and cell biology of neurons *in vivo* — in living, "behaving" animals. Because of a phenomenon called sequence conservation, many of the key genes in the fly brain involved in memory and learning have been preserved across eons of evolutionary history — so useful have they proven for survival — and have close cousins in the brains of mammals, including man. Improbable though it may seem, therefore, one can learn about the human brain by looking closely at the fly brain.

Zhong's approach is distinctive. Rather than beginning with the fly and working toward man, "we begin with the human being, and by this I mean working with the genes of people who are sick," he explains. Zhong looks for gene mutations known to cause nervous-system illness in humans, such as *NF1*, linked with neurofibromatosis. People with an *NF1* mutation — often inherited from a parent — can suffer learning defects and develop neurofibromas, tumors that split apart nerve fibers.

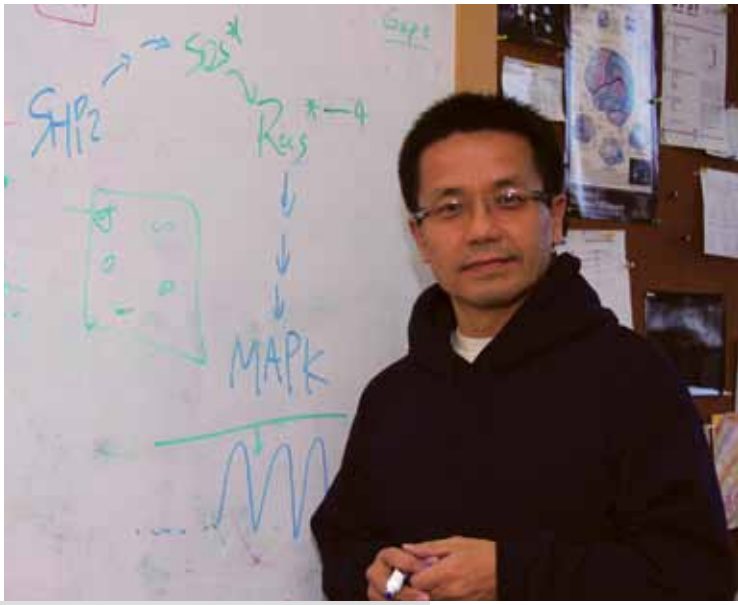
From a human gene known to cause trouble when mutated, Zhong moves to the fly. In neurofibroma, he was able to show how *NF1* mutations in fruit flies affect a pathway critical for learning. His team also discovered that *NF1* and another gene, called *corkscrew*, in the same biochemical pathway, also play a critical role in memory. That insight is pertinent in an illness called Noonan's syndrome. Noonan's causes characteristic facial malformations as well as deficiencies in long-term memory. It's fairly common, occurring with about the same frequency as Down syndrome.

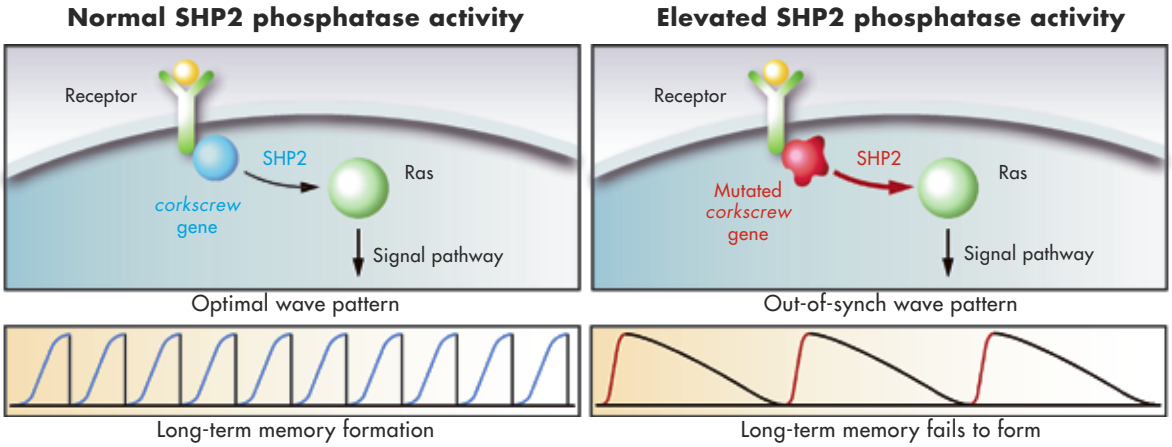
Noonan's, like neurofibromatosis, has been linked with gene mutations. In over 50% of Noonan's cases, a gene called *PTP11* is mutated. When switched on, it directs cells to manufacture a protein called SHP-2 phosphatase. This protein is in a class called protein tyrosine phosphatases, or PTPs, which perform the vital function of removing phosphate groups from molecules. The tweaking of molecules by adding and removing phosphates is an integral part of cell signaling. In Noonan's patients, *PTP11* mutations cause abnormally high activity of SHP-2 phosphatase.

corkscrew is the gene in fruit flies that corresponds with the human gene *PTP11*. Zhong and his team proceeded in their usual fashion: they engineered the human mutation associated with an illness (in this case, Noonan's) into the corresponding fly gene. Then they put the flies through a series of trials that they hoped would reveal new information about precisely how, within neurons, the mutation disrupted normal function, including memory function.

Surprising discovery

"We learned something that really surprised us," Zhong relates. It was the first of his lab's recent string of memory-related discoveries. They discovered the mechanism of something called the spacing effect, a phenomenon that "had long been known about, but that no one previously understood at the molecular level," Zhong says. Anyone





In flies, long-term memory forms only after 10 successive peaks and troughs of MAPK activity induced by training sessions; the pattern, and interval between waves (spacing effect) is affected by SHP-2 phosphatase levels.

who has studied for a test has probably experienced the spacing effect. Cramming information into your brain for long uninterrupted stretches is not likely to result in a high mark. We tend to remember what we learn for longer periods when we study at periodic intervals, spaced out between rest intervals.

But why and how? Zhong and his team discovered it is SHP-2 phosphatase that controls the spacing effect, by determining how long the resting intervals need to last so that long-term memories can form. Specifically, they found that under normal conditions (that is, when *corkscrew* is not mutated), as each learning period ends, SHP-2 phosphatase activity inside stimulated neurons triggers a wave of biochemical signals. "And the key," says Zhong, "is that these signals have to peak — rise above a certain threshold — before the next learning session can begin. Repeated formation and decay of the wave — 10 peaks and troughs, in the fly — is needed before a long-term memory can form."

When the *corkscrew* gene in flies is mutated and SHP-2 phosphatase activity is above normal, the "wave" pattern that Zhong describes falls out of synch. Long-term memories fail to form — the analogue of what happens, he postulates, in Noonan's patients who have the *PTP11* mutation. Perhaps most intriguing about this series of experiments is the fact that Zhong's team was able to reverse the memory deficiency in flies, in two ways. When the rest interval between "learning" sessions was increased from 15 to 40 minutes, long-term memories could form, despite the mutation; the same result was also obtained when SHP-2 activity was reduced to normal levels with the help of drugs. It's hypothesized that by increasing the rest period between learning sessions, people with learning disabilities like those that occur in Noonan's might be helped.

In February and March of this year, the team published additional important findings about memory. In one study, Zhong and colleagues at Tsinghua University in Beijing succeeded in specifying a single protein in neurons whose activity mediates three kinds of forgetting. This was big news. "Contrary to the prevailing view, we showed for the first time that the forgetting of short-term memories is an active process in the fly brain, not a passive one," Zhong summarizes. The team showed that by raising and lowering the activity of a protein called Rac (a member of the Rho family of small GTPases, important in cell signaling) they were able to speed and slow short-term memory erasure. By elevating Rac activity, they caused short-term memories to decay faster than normal — a process that worked in the opposite direction, too.

The team's next newsworthy paper, published in March, may be the most exciting of all. It also focused on the action of a single protein — this time, an enzyme called PI3 kinase. Long suspected of playing a protective role against mechanisms at work in the brains of Alzheimer's patients that impair memory, PI3 kinase proved in Zhong's new studies to have the opposite impact. When the team blocked it, they prevented the loss of memory in flies induced by the kind of plaques — toxic clumps of protein fragments — associated with memory loss in Alzheimer's.

"We still don't understand what the 'stuff' of memory is, in spite of the many advances in recent years. But we are getting to the bottom of the question," says Zhong. "The pleasing thought is that memory is just one example of how all information is encoded in the brain. This is work that is going to help with treatments for mental retardation, Alzheimer's and other illnesses associated with memory impairment. But it is also one of the best ways to find out very fundamental things about how the brain works."

Peter Tarr