Building the best brain: Researchers show how brain cell connections get cemented early in life

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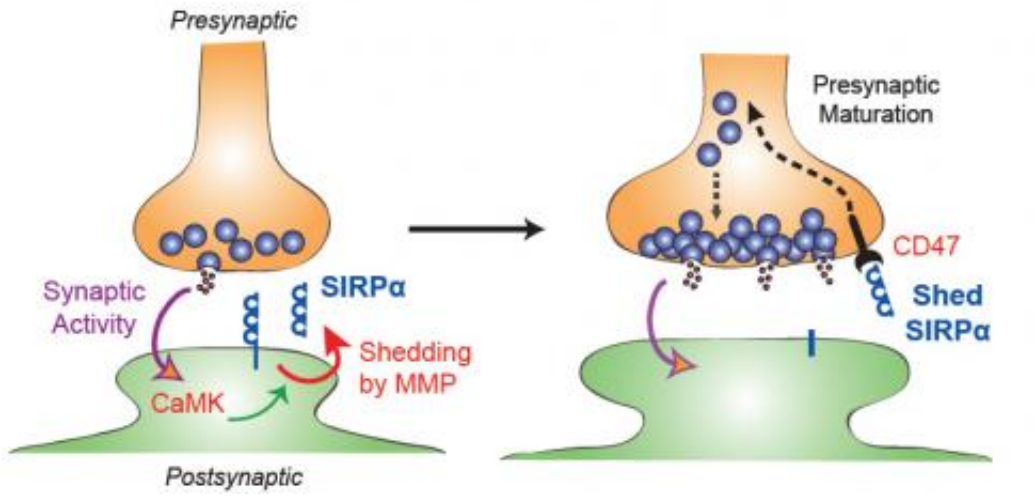

Two neighboring brain cells "talk" to one another by sending signals across a gap called a synapse. The more active the synapse during development, U-M researchers found, the more a protein called SIRP-alpha is cut loose from one cell, travels to the other, and helps stabilize the synapse for the future. Credit: Umemori Lab, University of Michigan

When we're born, our brains aren't very organized. Every brain cell talks to lots of other nearby cells, sending and receiving signals across connections called synapses.

But as we grow and learn, things get a bit more stable. The brain

pathways that will serve us our whole lives start to organize, and less-active, inefficient synapses shut down.

But why and how does this happen? And what happens when it doesn't go normally? New research from the University of Michigan Medical School may help explain.

In a new paper in *Nature Neuroscience*, a team of U-M neuroscientists reports important findings about how brain cells called neurons keep their most active connections with other cells, while letting other synapses lapse.

Specifically, they show that SIRP alpha, a protein found on the surface of various cells throughout the body, appears to play a key role in the process of cementing the most active synaptic connections between brain cells. The research, done in mouse brains, was funded by the National Institutes of Health and several foundations.

The findings boost understanding of basic brain development—and may aid research on conditions like autism, schizophrenia, epilepsy and intellectual disability, all of which have some basis in abnormal synapse function.

"For the brain to be really functional, we need to keep the most active and most efficient connections," says senior author Hisashi Umemori, M.D., Ph.D., a research assistant professor at U-M's Molecular and Behavioral Neuroscience Institute and assistant professor of biological chemistry in the Medical School. "So, during development it's crucial to establish efficient connections, and to eliminate inactive ones. We have identified a key molecular mechanism that the brain uses to stabilize and maturate the most active connections."

Umemori says the new findings on SIRP alpha grew directly out of

previous work on competition between neurons, which enables the most active ones to become part of pathways and circuits.

The team suspected that there must be some sort of signal between the two cells on either side of each synapse—something that causes the most active synapses to stabilize. So they set out to find out what it was.

SIRP-rise findings

The group had previously shown that SIRP-alpha was involved in some way in a neuron's ability to form a presynaptic nerve terminal—an extension of the cell that reaches out toward a neighboring cell, and can send the chemical signals that brain cells use to talk to one another.

SIRP-alpha is also already known to serve an important function in the rest of the body—essentially, helping normal cells tell the immune system not to attack them. It may also help cancer cells evade detection by the immune system's watchdogs.

In the new study, the team studied SIRP alpha function in the brain—and started to understand its role in synapse stabilization. They focused on the hippocampus, a region of the brain very important to learning and memory.

Through a range of experiments, they showed that when a brain cell receives signals from a neighboring cell across a synapse, it actually releases SIRP-alpha into the space between the cells. It does this through the action of molecules inside the cell—called CaMK and MMP—that act like molecular scissors, cutting a SIRP-alpha protein in half so that it can float freely away from the cell.

The part of the SIRP-alpha protein that floats into the synapse "gap" latches on to a receptor on the other side, called a CD47 receptor. This

binding, in turn, appears to tell the cell that the signal it sent earlier was indeed received—and that the synapse is a good one. So, the cell brings more chemical signaling molecules down that way, and releases them into the synapse.

As more and more nerve messages travel between the "sending" and "receiving" cells on either side of that synapse, more SIRP-alpha gets cleaved, released into the synapse, and bound to CD47.

The researchers believe this repeated process is what helps the cells determine which synapses to keep—and which to let wither.

Umemori says the team next wants to look at what happens when SIRP-alpha doesn't get cleaved as it should—and at what's happening in cells when a synapse gets eliminated.

"This step of shedding SIRP-alpha must be critical to developing a functional neural network," he says. "And if it's not done well, disease or disorders may result. Perhaps we can use this knowledge to treat diseases caused by defects in synapse formation."

He notes that the gene for the CD47 receptor is found in the same general area of our DNA as several genes that are suspected to be involved in schizophrenia.

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