Synaptic pruning: How neurons compete to lose their link

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In early development, neurons called mitral cells grow multiple branches to connect with multiple glomeruli. Like a bonsai, as development progresses branches get strengthen and pruned. But while researchers investigated closely the mechanism of branch strengthening, how pruning was induced remained under-studied. Kyushu University researchers found that when mitral cells receive the neurotransmitter glutamate, the subsequent signal triggers local suppression of RhoA, protecting that dendrite. At the same time, the depolarization activates the pruning machinery—controlled by RhoA—in dendrites that did not receive the glutamate input. The winner dendrite takes all. Credit: Kyushu University/Imai Lab

Researchers at Kyushu University have uncovered the mechanisms of a fundamental yet critically under-looked phase in brain development: synaptic pruning.

Using mouse mitral cells—a type of neuron in the olfactory system—the team found that when neurons receive a neurotransmitter signal, the receiving dendrite is protected through a series of chemical pathways. At the same time, the depolarization triggers other dendrites of the same cell to go through a different pathway that promotes pruning. Their study was published in the journal *Developmental Cell*.

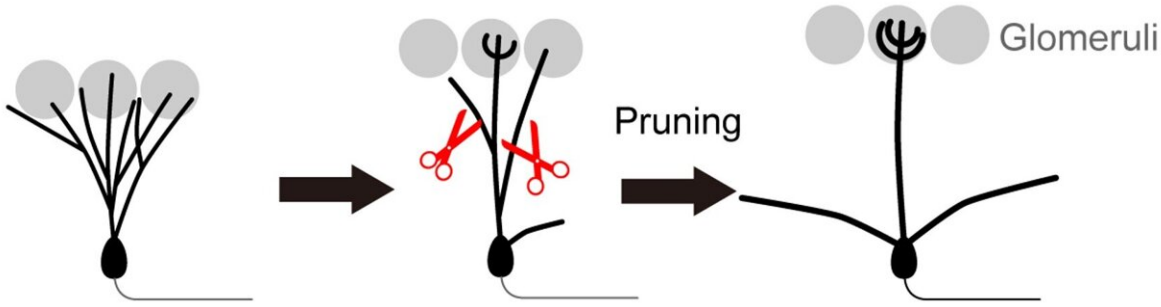
How neurons connect and remodel themselves is a fundamental question in neurobiology. The key concept behind proper networking is in neurons forming and strengthening connection with other neurons while pruning excessive and incorrect ones.

A common phrase in neural circuit remodeling is "fire together wire together" and "out of sync, lose your link." The former describing how neurons that pass signals between each other tend to strengthen connections, whereas the latter explains that without said signaling that connection diminishes," explains Professor Takeshi Imai from Kyushu University's Faculty of Medical Sciences, who led the study. "It's a refining process that is fundamental for proper brain maturation."

Over the decades, researchers—including Imai—have explored the fundamental process of how neurons form and strengthen their connections. However, there had been one major gap in the process that few people were examining: how the connections are eliminated.

"The elimination of neuronal connections, what we call pruning, was something everybody in the field knew about and observed. But if you look at the literature, there was a lack of study on the exact mechanism that drove the process," explains first author Satoshi Fujimoto.

Elimination of connections happen everywhere in the nervous system, for example in neuromuscular junctions, the neurons that send signals to your muscles to move. At first, the muscle fibers receive inputs from many motor neurons. As you grow, these connections are finetuned, where some are strengthened, and others are eliminated, until just one neuron connects to one muscle fiber. It is why you have awkward motor control and coordination at an early age.



From the moment mice are born, their mitral cells extend multiple dendrites into multiple glomeruli. They form branches and excitatory synapses in the glomerulus at around day three after birth. By day six, they form single dendrites through selective pruning. This makes it possible to receive information from only one type of olfactory receptor (odor sensor), which is the basis of odor discrimination. Credit: Kyushu University/Imai Lab

"We decided to investigate what exactly happens in neurons during remodeling, so, we looked into using mouse mitral cells, a type of cell housed in the olfactory bulb, the brain center involved in our sense of smell. In adults, mitral cells have a single connection to a signaling waystation called the glomerulus. But in early development mitral cells send branches into many glomeruli," states Fujimoto. "As time

progresses, these branches get pruned to leave a single strong connection. In the end, the mitral cells can sniff out only a specific type of smell."

First, the team found that spontaneous waves of the neurotransmitter glutamate in the olfactory bulb facilitate dendrite pruning. The team then focused on the mitral cell's inner signaling pathways. What they found was a unique protection/punishment machinery that would strengthen certain connections and kickoff the pruning of others.

"We found that in the mitral cells it was the signaling from glutamate that was essential for pruning. When glutamate binds to its receptor NMDAR in a dendrite, it suppresses the pruning machinery molecule called RhoA," continues Fujimoto. "This 'save-me' signal is important to protect it from pruning."

Upon the glutamate input, the mitral cell also depolarizes and fire a signal. The team also found that depolarization triggers the activation of RhoA in other dendrites of the same cell, and kicking off the pruning process. Simply put, the dendrite that receives the direct glutamate signal is protected, while the other dendrites get pruned.

"This 'punishment' signal for synapse elimination only acts on non-protected synapses, and it explains how only a strong connection becomes the winner and all the others mediating weak and noisy inputs become the losers," Imai explains.

The team's findings reveal new information of an over-looked but critical phase in neural development.

"Proper pruning of neuronal connections is just as important as the strengthening of the network. If it goes awry in either direction it can lead to different kinds of neurophysiological disorders. Too few connections have been linked to schizophrenia, whereas too many

connections have been found in people with autism spectrum disorder, for example," says Imai. "To understand these sorts of pathologies we need to look carefully at every step of development."

More information: Takeshi Imai, Activity-dependent local protection and lateral inhibition control synaptic competition in developing mitral cells in mice, *Developmental Cell* (2023). DOI: 10.1016/j.devcel.2023.05.004. www.cell.com/developmental-cel … 1534-5807(23)00237-X

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