Scientists reveal a molecule that may underpin neurological disorders

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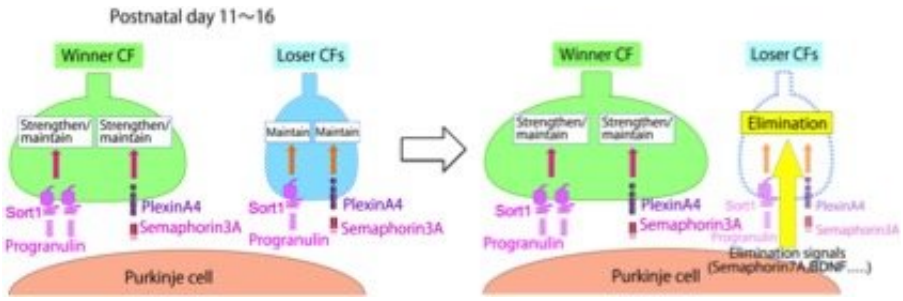

Progranulin derived from Purkinje cells (PCs) counteracts synapse elimination and reinforces the strongest (winner) climbing fiber (CF). Progranulin acts on developing CF synapses from Postnatal day 11 to 16 independently of Semaphorin3A, another retrograde signaling molecule that counteracts CF synapse elimination. Progranulin derived from PCs acts retrogradely onto its putative receptor Sort1 on CFs. Loser CFs are maintained by progranulin-Sort1 signal and Semaphorin3A-PlexinA4 signal, but they are eventually pruned by "elimination signals" such as Semaphorin7A and brain-derived neurotrophic factor (BDNF). Credit: 2018 Masanobu Kano.

Scientists from Japan have identified a molecule that aids a crucial "pruning" process in the brain that, if malfunctioning, could lead to disorders such as autism and dementia.

As the brain develops in utero and in early life, neurons and their connecting synapses branch out rapidly, like a tree. Over time, these connections become more refined and purposeful via a series of

molecular mechanisms that prune the connections. Just as a gardener trimming a tree, weaker branches are discarded to redirect nutrients to help nurture the stronger branches.

However, genetic and environmental mutations can misguide this process and eliminate far too many synapses or not nearly enough. Either extreme can result in a myriad of neuropsychiatric disorders from autism spectrum disorder to schizophrenia to dementia.

The research team was led by Masanobu Kano, professor in the Department of Neurophysiology at the Graduate School of Medicine at the University of Tokyo. The authors published their results today in the journal *Neuron*.

In a typically developing brain, a type of neuron called a Purkinje cell is furnished with climbing fibers. "Among multiple climbing fibers innervating each Purkinje cell in the neonatal cerebellum, a single climbing fiber is strengthened and maintained throughout an animal's life, whereas the other climbing fibers are weakened and eventually eliminated," Kano says. "Our goal was to identify a new molecule involved in strengthening and maintaining single climbing fiber inputs."

Kano and his team found that progranulin—a protein known to be involved in certain forms of dementia—also works to maintain developing climbing fiber inputs, counteracting the initial elimination. They studied a mouse model engineered without progranulin and found that climbing fibers were more quickly eliminated and climbing fiber input overall was significantly reduced.

"Our results provide a new insight into the roles of progranulin in the developing brain," says Kano. "We will continue to search molecules involved in synapse elimination in the developing cerebellum and, ultimately, we want to elucidate entire signaling cascades for synapse

elimination."

Although the researchers do not yet know how to effectively manipulate the molecule, it's possible that progranulin signaling may be a potential therapeutic target for neuropsychiatric disorders.

More information: Naofumi Uesaka, Manabu Abe, Kohtarou Konno, Maya Yamazaki, Kazuto Sakoori, Takaki Watanabe, Tzu-Huei Kao, Takayasu Mikuni, Masahiko Watanabe, Kenji Sakimura and Masanobu Kano, Retrograde Signaling from Progranulin to Sort1 Counteracts Synapse Elimination in the Developing Cerebellum, *Neuron* , DOI: 10.1016/j.neuron.2018.01.018

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