Neurexin controls cerebellar granule cells, offering insight into autism, schizophrenia mechanisms

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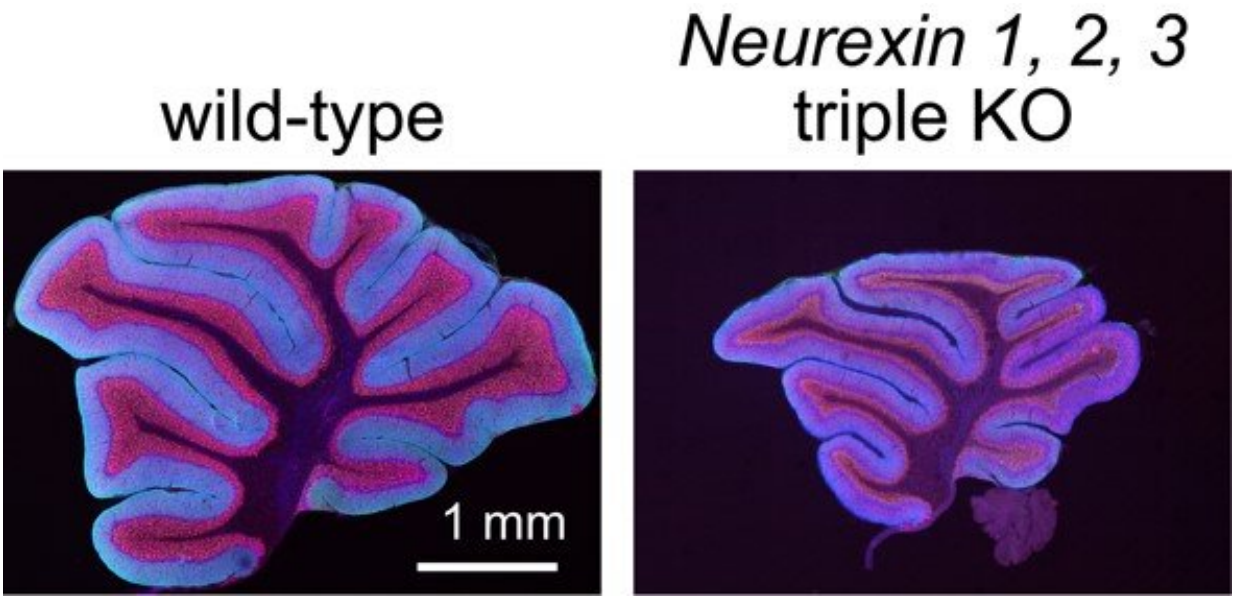

Fig. 1. Cerebellar granule cells cause cell death in mice lacking all neurexins 1, 2 and 3. The disappearance of cerebellar granule cells causes the cerebellum to atrophy. Credit: Takeshi Uemura, Shinshu University

Neurexin, associated with neurodevelopmental disorders, is an essential molecule for the survival of nerve cells called cerebellar granule cells in the cerebellum. A new study revealed that neurexin regulates the survival of cerebellar granule cells independently of synapses, which connect

nerve cells. Neurexin organizes the autocrine secretary machinery of neurotrophin essential for cerebellar granule cell survival and this study elucidated the mechanism of neural circuit formation for future research related to neurodevelopmental disorders such as autism and schizophrenia.

A research group led by Associate Professor Takeshi Uemura and Professor Katsuhiko Tabuchi of Shinshu University has elucidated a new molecular mechanism that controls the survival of cerebral nerve cells. Neurexin, a cell adhesion molecule at the presynaptic terminal associated with neurodevelopmental disorders, induces synaptogenesis by binding to the cell adhesion molecule at the synaptic post-synaptic terminal. It is a one-time transmembrane protein, and there are three genes (neurexins 1, 2, 3) in mammals. Neurexin localized at the presynaptic terminal interacts with cell adhesion molecules such as Cbln1-GluD2 and neuroligin localized at the postsynaptic terminal to induce synapse formation. Synapses transmit information between nerve cells. At excitatory synapses, nerve cell axons (presynaptic terminals) are formed at the site of input into spines on the dendrites of postsynaptic cells. A disorder of this formation is thought to be involved in the development of schizophrenia and autism.

The research group of Associate Professor Uemura and Professor Tabuchi analyzed the function of neurexin in cerebellar granule cells using genetically modified mice. There are four types of neurotrophic factors, which are secretory proteins, including the brain-derived neurotrophic factor. The brain-derived neurotrophic factor released extracellularly is involved in the survival and differentiation of nerve cells and the regulation of synaptic function by binding to its high-affinity receptor TrkB. This is also thought to be associated with neuropsychiatric disorders such as depression and schizophrenia.

The group found that this mechanism plays an essential role in the

survival of cerebellar granule cells, which are nerve cells existing in the cerebellar cortex. Parallel fibers, which are the axons of cerebellar granule cells, form excitatory synapses on the distal dendrites of cerebellar Purkinje cells. The results of this research are expected to be useful for elucidating the mechanism of neuronal circuit formation in the brain and for future research related to neurodevelopmental disorders such as autism. The results of this research were published in the online version of the journal *Cell Reports* on April 5, 2022.

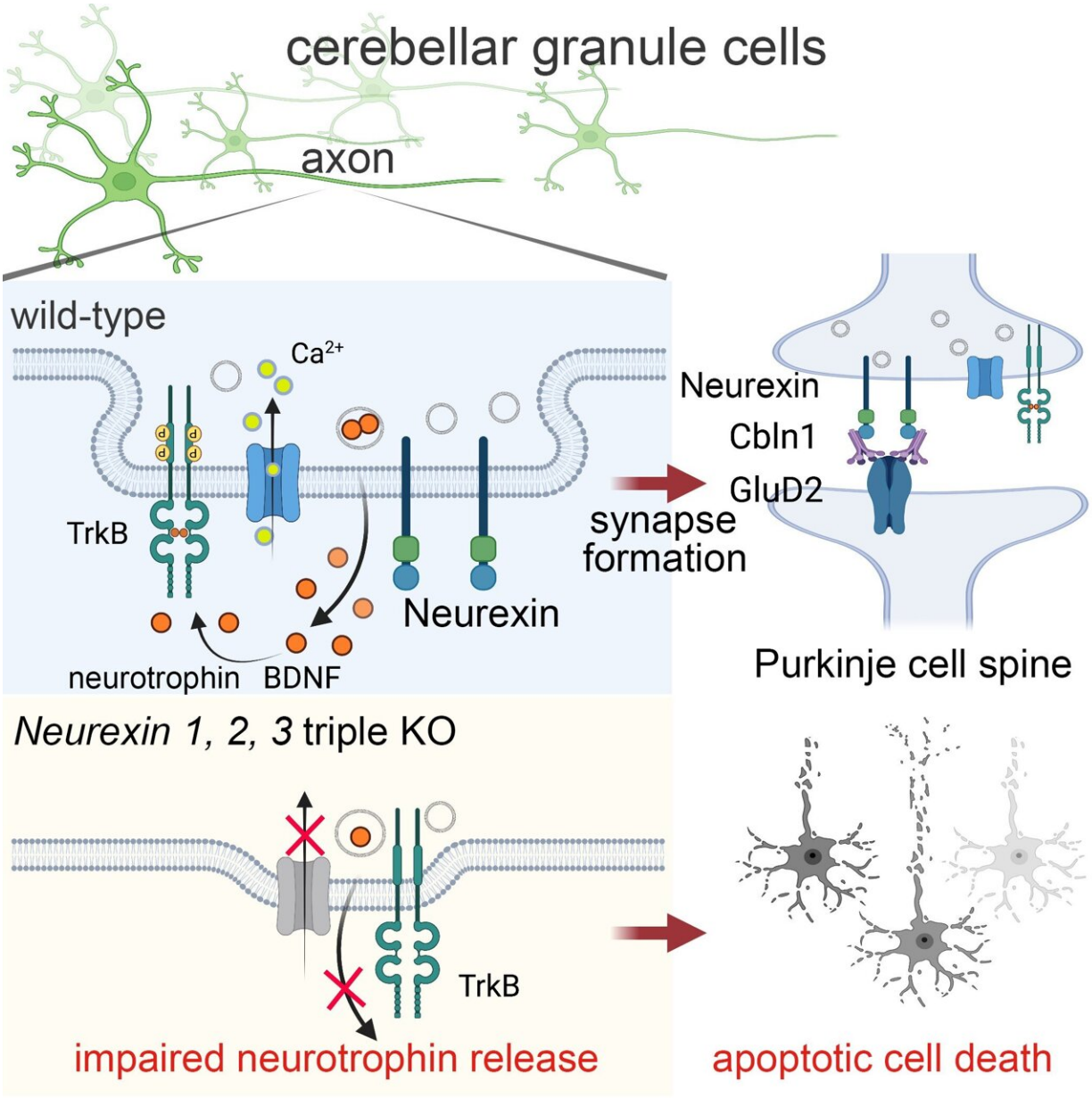

Fig. 2. In wild-type mice, cell survival is maintained by the autocrine action of neurotrophic factors released from the axons of cerebellar granule cells. In wild-type mice, neurexin binds to Cbln1-GluD2 and induces cerebellar synaptogenesis. Granule cells deficient in all neurexins 1, 2, and 3 have abnormal neurotrophic factor release mechanisms, resulting in induced programmed cell death. Credit: Takeshi Uemura, Shinshu University

The synaptic connections between nerve cells are one of the key steps in the formation and development of the brain. Synaptogenesis is known to be induced by the binding of cell adhesion molecules called synapse organizers present at the axon terminals and dendrites. Neurexins are the major synaptic organizers present in nerve axons. So far, from the research of Associate Professor Uemura's group, in the cerebellum, neurexins on the axons (parallel fibers) of cerebellar granule cells form a complex with Cbln1-GluD2 to induce and maintain parallel fiber–Purkinje cell synapse. Although it was shown that synaptic formation was induced, the details of the physiological role of neurexins in cerebellar granule cells were not well understood.

In mammals, neurexin has three genes (neurexin 1, 2, 3). In order to clarify the role of neurexin in cerebellar-granule cells, the group generated a genetically modified mouse that simultaneously deletes all three genes of neurexin specifically for cerebellar granule cells using the recombinant Cre-loxP system. The Cre-loxP system is where the Cre recombinase is a bacteriophage-derived enzyme that recognizes a 34-base pair DNA sequence and causes DNA recombination between two loxPs. When a region of an arbitrary gene is sandwiched between two loxP sequences and Cre recombinase is allowed to act, the DNA sequence between loxPs is excised, causing gene deletion.

By crossing a mouse that expresses Cre recombinase specifically in cerebellar granule cells with a mouse in which three genes of neurexin are sandwiched between loxP sequences, all neurexin 1, 2, and 3 genes were specifically deleted in cerebellar granule cells. In this genetically modified mouse, the cerebellum atrophy due to cell death of the cerebellar granule cells with development, and it was found that neurexin is an essential molecule for the survival of the cerebellar granule cells (Fig. 1). The neurexin requirement for cell survival was also reproduced in cultured cerebellar granule cells. In cultured cerebellar granule cells deficient in neurexin, action potential-induced calcium influx into axons was reduced and brain-derived neurotrophic factor secretion was reduced. It was also found that cell death was improved by adding the brain-derived neurotrophic factor. Although cultured cerebellar granule cells rarely form synapses, it is known that there is varicosity on the axon and that it has a presynaptic terminal-like structure containing many synaptic vesicles. It was found that neurexin deficiency does not correctly create this presynaptic terminal-like structure. This indicates that neurexin plays an important role in organizing the mechanism of neurotrophic factor release from axons, which is essential for the survival of cerebellar granule cells independently of synapses (Fig. 2).

With this study, the research group of Associate Professor Uemura and Professor Tabuchi clarified the basic principle of brain neural network formation through the elucidation of the function of cell adhesion molecules between synapses. By clarifying the role of neurexin in cerebellar granule cells, the understanding of the basic principle has been further advanced. Neurexin has been reported to be associated with neurodevelopmental disorders such as autism, and the results of this study will be useful for elucidating the mechanism of neural circuit formation and future research related to neurodevelopmental disorders such as autism, Tourette's and schizophrenia.

More information: Takeshi Uemura, Neurexins Play a Crucial Role in

Cerebellar Granule Cell Survival by Organizing Autocrine Machinery for Neurotrophins, *Cell Reports* (2022). DOI: 10.1016/j.celrep.2022.110624. www.cell.com/cell-reports/full … 2211-1247(22)00372-2