Molecular mechanism responsible for a neurodegenerative disease discovered

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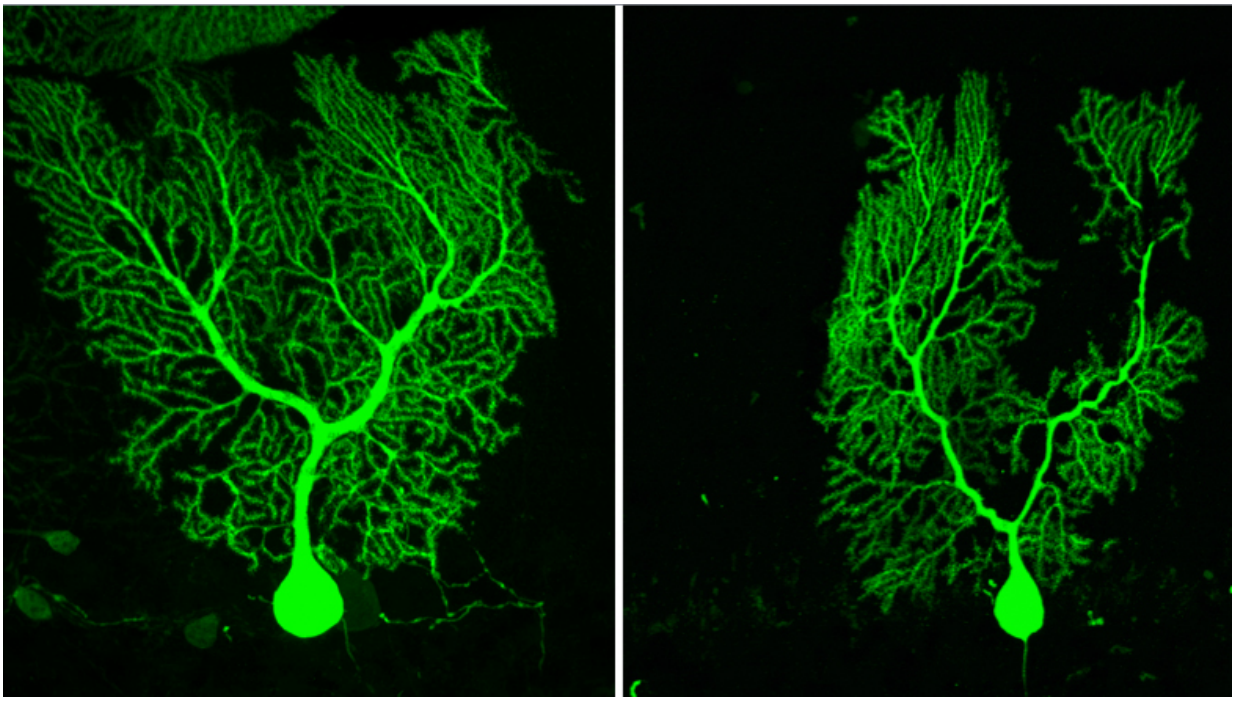

Left: A healthy Purkinje cell displaying an elaborate dendritic arbor covered in spines. Right: A Purkinje cell afflicted with Spinocerebellar ataxia type 1, showing classical hallmarks of degeneration such as shrunken and reduced dendrite arbors and spines. Credit: Institute of Cell Biology, University of Bern

Scientists from Bern have discovered a mechanism which is responsible for the degeneration of Purkinje cells in the cerebellum in a neurodegenerative disease called Spinocerebellar ataxia type 1. The

results of their study open up new avenues for the future treatment of cerebellum associated degenerative disorders.

Damage, degeneration or loss of neurons in the region of the brain that controls muscle coordination (cerebellum), results in ataxia. The symptoms include loss of voluntary coordination of muscle movements and the appearance of gait abnormality, loss of balance and speech problems. Cerebellar ataxias are progressive degenerative disorders which occur in adults either sporadically or can be inherited from parents. Unfortunately, the large majority of cerebellar ataxia cases are sporadic in nature and the causative mechanism for the development of ataxia remains largely unknown, which eventually hinders the development of therapy and negatively influences the quality of patient's life.

However, both the sporadic and inherited cases of cerebellar ataxia exhibit common pathophysiological characteristics such as the specific degeneration of the main cerebellar neurons; the Purkinje cells. Therefore, the team of Smita Saxena from the Institute of Cell Biology at the University of Bern set out to understand the potential mechanism involved in the development of ataxia and degeneration of Purkinje cells in Spinocerebellar ataxia type 1 (SCA1), a rare, incurable, inheritable neurodegenerative disease that can be modeled in mice.

Together with first author Céline Ruegsegger, a protein based screening of Purkinje cells was performed to identify changes that occur in these neurons at the time of ataxia appearance. The team discovered wide spread alterations in proteins which function at the synapse and identified a synaptic protein Homer-3 that is mainly present in Purkinje cell synapses to be reduced. Further, they found that Homer-3 decrease was related to the alteration in an important signaling pathway; mTORC1. This signaling pathway was responsible for regulating the expression of synaptic proteins such as Homer-3. Saxena and her team

have discovered a cellular mechanism in the cerebellum of SCA1 mice that specifically targets the degeneration of Purkinje cells and the findings present a promising future therapeutic target. The study was published in the scientific journal *Neuron*.

The team investigated why mTORC1 signaling was altered in the cerebellar Purkinje cells and not in other regions of the brain. By measuring activation state of Purkinje cells, they found that impaired mTORC1 signaling was due to defects in Purkinje cell associated neuronal circuitry mainly involving the climbing fibers. "In this context, the identification of circuit related alterations which play an important role in determining pathological alterations in Purkinje cells is important in understanding how the disease mechanism works and targets vulnerable components in defined neurons; in this case Purkinje cells", says Saxena.

Reinstating Homer-3 expression can ameliorate symptoms and delay pathology

After the identification of Homer-3 as being reduced early in the disease course, Céline Ruegsegger and Saxena tried to establish its causal role in the development of disease. By using a gene therapy approach they reintroduced Homer-3 expression in Purkinje cells of SCA1 mice. This slowed down the development of ataxia, ameliorated symptoms associated with loss of motor coordination and balance and restored Purkinje cell functionality.

"Interestingly, it has been known for some time that alterations in mTORC1 signaling in the cerebellum during development is associated with autistic behavior and intellectual disorder", said Saxena. "In our study, the novel finding is that similar signaling pathways can also be involved in adult cerebellar associated degenerative disorders such as

SCA1. This is an important step forward in understanding the process involved in developmental and degenerative disorders and identifies a potentially new therapeutic target for the future."

More information: Céline Ruegsegger et al. Impaired mTORC1-Dependent Expression of Homer-3 Influences SCA1 Pathophysiology, *Neuron* (2016). DOI: 10.1016/j.neuron.2015.11.033

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