Scientists find survival factor for keeping nerve cells healthy

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Scientists at the Babraham Institute have discovered a novel survival factor whose rapid transport along nerve cells is crucial for keeping them alive. The same factor seems likely to be needed to keep our nerves healthy as we age. These findings, published today in the online, open-access journal *PLoS Biology*, show that a molecule known as Nmnat2 provides a protective function; in its absence healthy, uninjured nerve cells start to degenerate and boosting levels of Nmnat2 can delay degeneration when the cells are injured. This suggests an exciting new therapeutic avenue for protecting nerves from disease and injury-induced degeneration.

This breakthrough by Drs Jon Gilley and Michael Coleman at Babraham, an institute of the Biotechnology and Biological Sciences Research Council (BBSRC), furthers our understanding of the basic biology of our nerves and provides new insight into the factors causing neurodegenerative diseases like Motor Neurone Disease and Multiple Sclerosis.

Neurodegenerative diseases are characterised by a loss of viable nerve cells, which in many cases has been shown to be preceded by degeneration of the axon. Axons are the long, slender projections from nerve cells, sometimes over a metre long, that carry messages to target cells such as other nerve or muscle cells, rather like a fibre-optic cable carrying outgoing messages. Although the disintegration and collapse of axons is seen in many neurodegenerative diseases, the factors driving this have remained elusive.

Unravelling the processes initiating axon degeneration is helping to understand mechanisms of disease progression. It also increases our potential to protect synapses and axons in disease using Nmnat2 as a therapeutic target.

"What is really exciting here is how a single, intrinsic protein affects nerve cell survival," explained Dr Coleman, a Group Leader at Babraham. "It offers a new approach to treating axonal disorders by specifically targeting this protein, or by targeting other steps in the same pathway that we hope to work on next."

Axonal transport is a remarkable process that traffics thousands of biochemical compounds needed for axon survival and function along every one of our hundred billion nerve cells, day and night, across distances that dwarf any other mammalian cell. We are not aware of it until it goes wrong but then the results can be devastating. Alzheimer's disease, glaucoma, motor neuron disease and multiple sclerosis are some of the neurodegenerative disorders that involve a block of axonal transport. Even the healthy ageing process shows a dramatic decline in axonal transport that may predispose us to these and other age-related disorders.

Coleman continued, "Think about the fate of a flower after its stem is cut. Without water it quickly wilts and dies. In water it lasts much longer but still dies earlier than on the plant, so water is the limiting factor for survival even if the flower needs other essential substances in the longer term.

There are some similarities when a nerve is injured. If a nerve is cut, axons beyond the injury site die within a couple of days because they lack essential proteins that are normally transported along the nerve.

"Like the flower's critical need for water, we found that one protein

seems to be a limiting factor for axon survival by a large margin", explained Coleman. "Other missing proteins have little effect on this timescale. Nerve cells do differ in that they die through an active process rather than withering away, but the process may still be triggered by one factor, or at most just a few."

Cultured nerve cells were used to find which of the many biochemical factors limit axon survival. This builds on earlier work in the Coleman lab, which revealed that a single, harmless genetic variation, the slow Wallerian degeneration (WldS) gene, can extend the survival of a cut axon tenfold. However, this cannot provide what axons normally need to survive because most animals and probably all people lack the WldS gene. Nevertheless, its identity provided vital clues.

The new research, supported by the MRC and BBSRC, has identified a key axon survival factor present in all of us, Nmnat2, without which axons quickly degenerate. Nmnat2 is metabolic enzyme situated in part of the cell known as the Golgi, and now the Babraham group also finds it in axons. This raises the possibility of manipulating its activity with drugs in order to protect or delay axons from degeneration.

"As Nmnat2 is present in all our nerves it could be modulated directly, whereas WldS would first have to be introduced to our nerves." Coleman said. "By understanding how Nmnat2 is trafficked along nerves, what regulates its stability, and what it does when it gets there, novel treatments could now be developed for thus far incurable neurodegenerative diseases."

More information: "Endogenous Nmnat2 is an Essential Survival Factor for Maintenance of Healthy Axons". DOI: 10.1371/journal.pbio.1000300