Neural protective protein has two faces

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(Medical Xpress) -- A protein produced by the central nervous system's support cells seems to play two opposing roles in protecting nerve cells from damage, an animal study by Johns Hopkins researchers suggests: Decreasing its activity seems to trigger support cells to gear up their protective powers, but increasing its activity appears to be key to actually use those powers to defend cells from harm.

Seth Blackshaw, Ph.D., an associate professor in the Solomon H. Snyder Department of Neuroscience at the Johns Hopkins University School of Medicine, explains that researchers have long suspected that central nervous system cells called glia play an important role in saving nerve cells from almost certain death after either an acute injury, such as a blow to the head, or chronic damage, such as that caused by Alzheimer's or Parkinson's disease. Glia — named after the Greek word for glue, since decades ago they were thought to play a very passive role in holding the central nervous system together — respond to an assault on nearby neurons in a dramatic way, puffing up to a larger size and turning off several genes involved in routine maintenance functions.

Previous research in cell cultures containing both neurons and glia showed that when the entire group was exposed to an assault, the reaction of the glia seemed to drive a response that protects cells from subsequent damage. However, Blackshaw says, it's been unclear exactly what glia are doing when they change in size and gene expression. Even whether this response is actually important for protection was uncertain, he adds, since it's been impossible to study this so-called glial reactivity without treating whole tissues that include neurons and other types of

cells that may exert their own protective effects.

Hoping to find a way to trigger glial reactivity without assaulting entire tissues, Blackshaw and his colleagues searched for proteins that could play an important role in this response. The team used Mueller glia as their model system. These glia are the most abundant type in the retina, and are highly likely to behave like other glia throughout the central nervous system, Blackshaw says.

The researchers' investigation eventually zeroed in on a protein called Lhx2. When they bred mutant mice that selectively lacked Lhx2 in the glia of the eye, these cells displayed the physical and genetic characteristics of being reactive all the time, even without any damaging stimulus. However, to the researchers' surprise, hitting the mutant animals' eyes with extraordinarily bright light caused considerably more damage to their retinas compared to the same stimulus in normal mice.

To understand why these reactive glia didn't produce the expected protective response, the researchers looked for other pro-survival proteins that glia produce under assault. In the mutant animals, these other proteins were conspicuously missing, Blackshaw says, suggesting that Lhx2 is necessary for glia to produce other protective proteins.

"Lhx2 seems to be a master regulator of glial reactivity, and we've shown here that it has two faces," Blackshaw says of these results, reported in the March 20 issue of the *Proceedings of the National Academy of Sciences*. While the protein's absence seems to be critical for triggering the physical and genetic changes glia use to bring their protective proteins to bear to help neurons survive, its presence is vital to produce these proteins in the first place. Levels of Lhx2 activity likely dip and then increase in glia exposed to an attack, he says, explaining both the initial glial reactivity researchers see under a microscope as well as the resulting neural protection.

Once researchers understand this mechanism better, Blackshaw adds, they may be able to craft drugs that stimulate glia to pump out more pro-survival proteins, making novel therapies for neurodegenerative diseases.

Other Hopkins researchers involved in this study include Jimmy de Melo, Katsuaki Miki, Amir Rattner, Phil Smallwood, Cristina Zibetti and Peter A. Campochiaro.

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