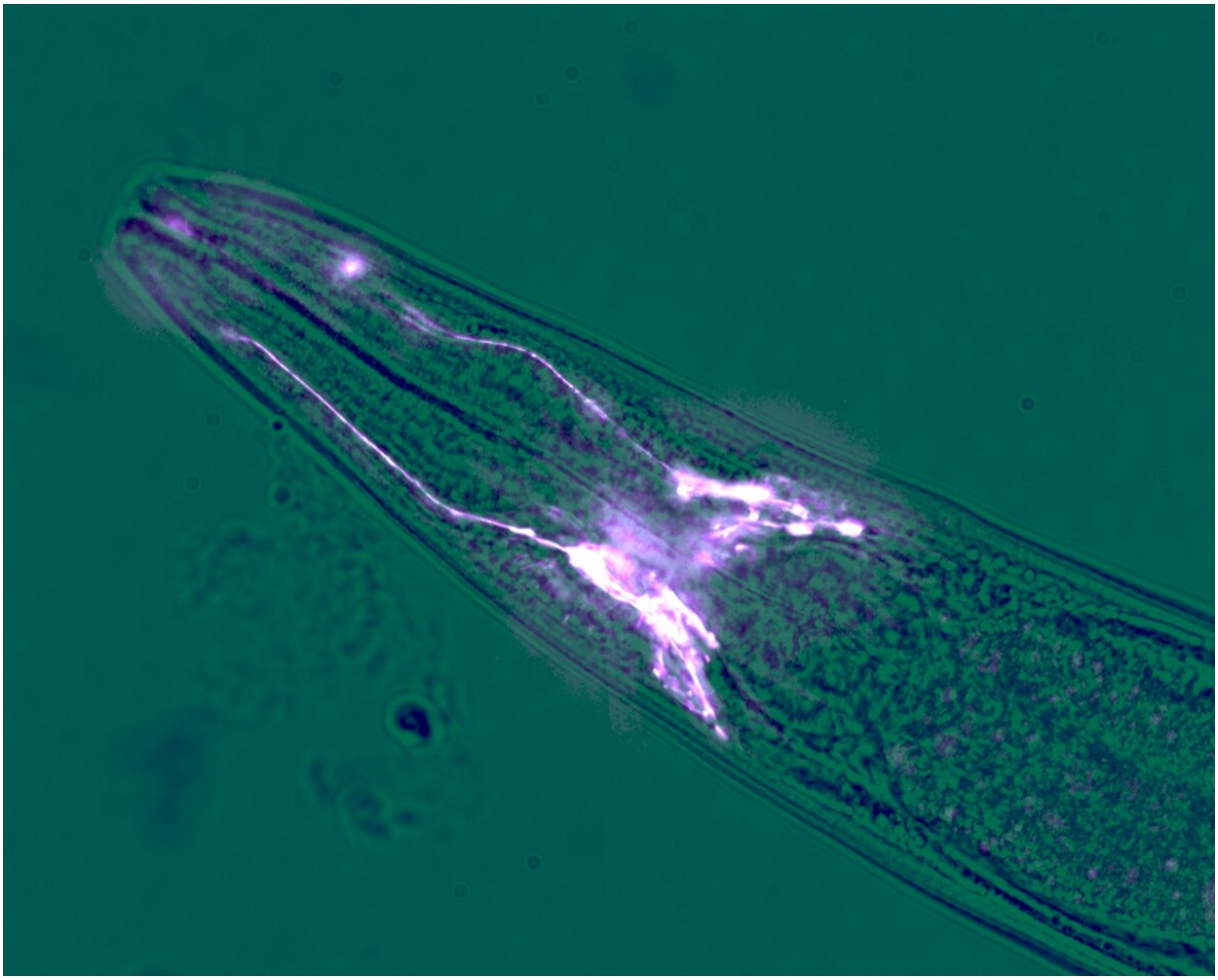
Brain cells protect muscles from wasting away

February 21 2020



The head of a roundworm, C. elegans. The glia that regulate the stress response in the worm's peripheral cells are highlighted. A mere four of these cells, known as CEPsh glial cells, protect the organism from age-related decline. Credit: Ashley Frakes, UC Berkeley

While many of us worry about proteins aggregating in our brains as we age and potentially causing Alzheimer's disease or other types of neurodegeneration, we may not realize that some of the same proteins are aggregating in our muscles, setting us up for muscle atrophy in old age.

University of California, Berkeley, scientists have now found brain cells that help clean up these tangles and prolong life—at least in worms (*Caenorhabditis elegans*) and possibly mice. This could lead to drugs that improve muscle health or extend a healthy human lifespan.

The research team's most recent discovery, published Jan. 24 in the journal *Science*, is that a mere four glial cells in the worm's brain control the stress response in cells throughout its body and increase the worm's lifespan by 75%. That was a surprise, since glial cells are often dismissed as mere support cells for the neurons that do the brain's real work, like learning and memory.

This finding follows a 2013 study in which the UC Berkeley group reported that neurons help regulate the stress response in peripheral cells, though in a different way than glial cells, and lengthen a worm's life by about 25%. In mice, boosting neuronal regulation increases lifespan by about 10%.

Together, these results paint a picture of the brain's two-pronged approach to keeping the body's cells healthy. When the brain senses a stressful environment—invading bacteria or viruses, for example—a subset of neurons sends electrical signals to peripheral cells to get them mobilized to respond to the stress, such as through breaking up tangles, boosting protein production and mobilizing stored fat. But because electrical signals produce only a short-lived response, the glial cells kick

in to send out a long-lasting hormone, so far unidentified, that maintains a long-term, anti-stress response.

"We have been discovering that if we turn on these responses in the brain, they communicate to the periphery to protect the whole organism from the age onset decline that naturally happens. It rewires their metabolism, it also protects against protein aggregation," said Andrew Dillin, UC Berkeley professor of molecular and cell biology and Howard Hughes Medical Institute (HHMI) investigator. As a result of the new study, "We think that glia are going to be more important than neurons."

While the roundworm *C. elegans* is a long way evolutionarily from humans, the fact that glial cells seem to have a similar effect in mice suggests that the same may be true of humans. If so, it may lead to drugs that combat muscle wasting and obesity and perhaps increase a healthy lifespan.

"If you look at humans with sarcopenia or at older mice and humans, they have protein aggregates in their muscle," Dillin said. "If we can find this hormone, perhaps it can keep muscle mass higher in older people. There is a huge opportunity here."

In a commentary in the same Jan. 24 issue of *Science*, two Stanford University scientists, Jason Wayne Miklas and Anne Brunet, echoed that potential. "Understanding how glial cells respond to stress and what neuropeptides they secrete may help identify specific therapeutic interventions to maintain or rebalance these pathways during aging and age-related diseases," they wrote.

How to extend lifespan

Dillin studies the seemingly simultaneous deterioration of cells throughout the body as it ages into death. He has shown in worms and

mice that hormones and neurotransmitters released by the brain keep this breakdown in check by activating a stress response in the body's cells and tuning up their metabolism. The response likely originated to fight infection, with the side effect of keeping tissues healthy and extending lifespan. Why our cells stop responding to these signals as we age is the big question.

Over the past decade, he and his colleagues have identified three techniques used by worms to keep their cells healthy and, consequently, longer-lived. Activating the body's heat shock response, for example, protects the cytoplasm of the cell. Stimulating the unfolded protein response protects the cells' energy producing structures, the mitochondria. The unfolded protein response is the cell's way of making sure proteins assume their proper 3-D structure, which is crucial for proper functioning inside the cell.

His latest discovery is that glia, as well as neurons, stimulate the unfolded protein response in the endoplasmic reticulum (ER). The ER is the cellular structure that hosts the ribosomes that make proteins—the ER is estimated to be responsible for the folding and maturation of as many as 13 million proteins per minute.

"A lot of the work we have done has uncovered that certain parts of the brain control the aging of the rest of the animal, in organisms from worms to mice and probably humans," Dillin said.

Two other interventions also increase lifespan in worms: diet restriction, which may call into play other anti-aging mechanisms, and reducing the production of a hormone called insulin-like growth factor (IGF-1).

Dillin's discoveries have already led to new treatments for diseases. He cofounded a company, Mitobridge Inc. (recently acquired by Astellas Pharma Inc.), based on the finding that certain proteins help tune up

mitochondria. A drug the company developed is now in phase II clinical trials for treating the damage that occurs when kidneys restart after sudden failure, such as during an operation.

He cofounded another company, Proteostatis Therapeutics, to develop a treatment for cystic fibrosis that is based on activating the unfolded protein response to repair ion channels in people with the disease.

The new discovery about how neurotransmitter and hormones impact the ER could have implications for diseases that involve muscle wasting, such as Huntington's disease and forms of myocytis.

Glial cells

In 2013, Dillin and his colleagues discovered that boosting expression of a protein called xbp-1s in sensory nerve cells in the worm brain boosts the misfolded protein response throughout the worm's body. Shortly afterward, postdoctoral fellow Ashley Frakes decided to see if the glial cells enshrouding these neurons were also involved. When she overexpressed the same protein, xbp-1s, in a subset of these glia (cephalic astrocyte-like sheath glia, or CEPsh), she discovered an even larger effect on peripheral cells, as measured by how they deal with a high-fat diet.

Frakes was able to pinpoint the four CEPsh glia responsible for triggering the ER response, because the *C. elegans* body is so well studied. There are only 959 cells in the entire worm, 302 of which are nerve cells, and 56 are glial cells.

The CEP neurons and CEPsh glia work differently, but additively, to improve metabolism and clean up protein aggregates as the worms slim down and live twice as long as worms without this protection from a high-fat diet.

"The fact that just a few cells control the entire organism's future is mind-boggling," Dillin said. "Glia work 10 times better than neurons in promoting this response and about twice as good in extending lifespan."

Frakes is currently trying to identify the signaling hormone produced by these glial cells, a first step toward finding a way to activate the response in cells that are declining in function and perhaps to create a drug to tune up human cells and stave off the effects of aging, obesity or other types of stress.

Frakes also found that the worms slimmed down because their fat stores, in the form of lipid droplets, were turned into ER. Another research group in Texas has shown that activating xbp-1s in the neurons of mice also has the effect of reducing fat stores and slimming the mice, protecting them from the effects of a high-fat diet and extending their lifespan.

"When they activate it in the neurons, they see the liver getting rid of fat, redistributing metabolic demands," Dillin said. "I think we would see the same thing in humans, as well."

More information: Ashley E. Frakes et al, Four glial cells regulate ER stress resistance and longevity via neuropeptide signaling in C. elegans, *Science* (2020). DOI: 10.1126/science.aaz6896

Provided by University of California - Berkeley