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# Study explains how a protein deficiency causes spinal muscular atrophy

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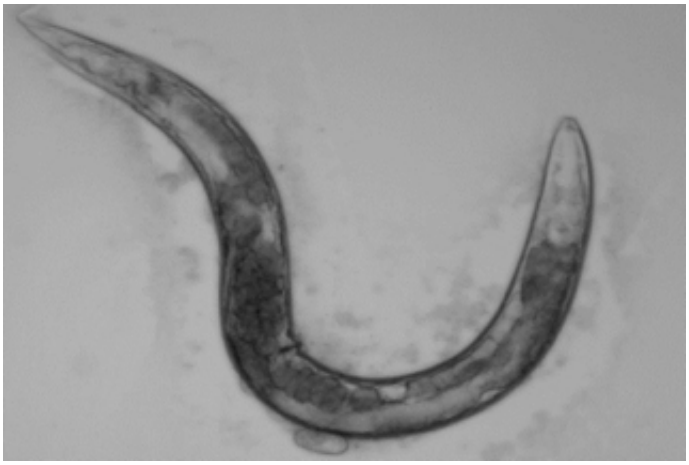

A study involving *C. elegans* worms (pictured) and human cells suggests that a deficiency of SMN protein leads to SMA by disrupting the important process of endocytosis. Credit: Anne Hart/Brown University

Scientists and doctors know that the devastating disease spinal muscular atrophy (SMA) arises from a problem with both copies of the SMN1 gene, leading to a lack of the survival motor neuron (SMN) protein. But they don't know why the lack of SMN protein causes spinal neurons to die, leading to muscle weakness in patients. A new study implicates a key cellular mechanism as defective in SMA for the first time, providing a new lead for developing future interventions.

The study also yielded a surprising twist: A mild version of the same

defect may also confer resistance to infection in carriers of the disease for whom only one copy of the gene has lost function.

SMA is the most common genetic cause of infant death in the U.S. and there is no effective treatment or cure, said corresponding author Anne Hart, professor of neuroscience at Brown University. The disease affects one in 10,000 children in Caucasian populations; both copies of the SMN1 gene are defective in patients. But about one in 40 people are carriers in that they have one defective and one functional copy of the SMN1 gene.

In the *Proceedings of the National Academy of Sciences*, Hart's team of researchers reported that that reduced levels of the SMN protein disrupt a cellular process called "endocytosis," which all cells normally use to recycle and redistribute proteins and membranes. Endocytosis is especially important in nerve cells, called neurons, because they must also rapidly release neurotransmitters to communicate with each other and with muscles, across connections called synapses, Hart said.

"Without this specialized neurotransmitter recycling and endocytosis, synaptic vesicles are not recycled fast enough to keep up with nerve and muscle cell activity," she said.

The process of endocytosis, however, is also exploited by infectious viruses and bacteria. So when this process is weakened in carriers who may have a more modest defect, it may make it harder for some pathogens to cause infections.

Most of the study's experiments were done in the roundworm *C. elegans*, which have an SMN gene and motor neurons—those that connect to muscle—that are very similar to humans, making them valuable models in which to study this disease. In worms with defective SMN gene copies, the researchers observed several signs of degraded endocytosis

and poor synapse structure, compared to worms with normal genes.

"Our results suggest that SMN loss perturbs both general and neuron-specific endocytosis," Hart said.

## Infection effect

The infection tests were done in human cells, including cells derived from SMA patients. There the researchers used the JC polyomavirus, which is pervasive in people, but typically only causes disease in people with weakened immune systems. They observed that the virus comparatively struggled to infect cells with reduced SMN levels.

While the study shows that reduced SMN disrupts endocytosis, it doesn't explain why. Hart said that's the next step in her work to defeat SMA.

For now, this study doesn't provide any proof that being an SMN carrier reduces a person's likelihood of becoming sickened by infections. That would require considerable further work by epidemiologists and infectious disease specialists.

"But no one has even considered this idea before," Hart said. "Here we have preliminary results suggesting this novel idea could be true. In the world of infectious disease genetics, we hope that SMN is now on the radar."

The result may also explain why, even though SMA is a devastating disease, carriers remain relatively common, Hart said. It could make sense from an evolutionary perspective.

"It seems possible that SMA is relatively common because carriers might be protected from infection," she said. "If carriers are more likely to survive and reproduce, then evolutionary pressure might favor carriers in

the long term, as is seen for sickle cell anemia and malaria infection."

**More information:** Decreased function of survival motor neuron protein impairs endocytic pathways, *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1600015113

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