

# Scientists explore a link between lethal childhood disease and age-related muscle decline

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Adopting some of the strategies behind successfully treating the childhood disease spinal muscular atrophy may enable development of

therapies to curb the muscle decline that accompanies aging, new research suggests.

At the heart of both disorders is the survival motor neuron protein, which is present throughout the body, and is important for keeping motor neuron cells alive and sending proper signals from the central nervous system to muscles. A [gene mutation](#) leading to reduced levels of this protein causes [spinal muscular atrophy](#) (SMA), and gene therapy is among three SMA therapeutics clinically available. The first children to receive the gene therapy are now 6 years old.

Based on what years of SMA research has shown about the importance of survival motor neuron protein to neuromuscular integrity, Ohio State University scientists are exploring links between the protein and sarcopenia, the age-related loss of skeletal muscle mass and strength.

Their new study in mice suggests a clear role for survival motor neuron (SMN) protein and muscle decline with aging: Levels of the protein in the spinal cords and [motor neurons](#) of advanced-age mice were 22% and 55% lower, respectively, than the levels in middle-aged mice, and those protein drops were accompanied by reduced muscle function.

"We found that SMN protein and aging are related—there is a decline in the protein with age and it correlates with a decline in neuromuscular function," said first author Maria Balch, a postdoctoral scholar in neuroscience in Ohio State's College of Medicine. "Based on what we know about SMA and therapeutics, we have background in targeting SMN protein—and it's possible that could be something down the line that could be applied to age-induced neuromuscular decline."

The research poster was presented today (Tuesday, Nov. 15, 2022) at Neuroscience 2022, the annual meeting of the Society for Neuroscience.

Two genes, SMN1 and SMN2, are involved in production of survival motor neuron protein. SMN1 does most of the work to produce the full-length protein and is vital to motor neuron survival and function. SMN2, which mostly makes a truncated form, contributes minimally to full-length protein production and could be thought of as an assistant—the presence of more copies of the SMN2 gene is associated with milder forms of SMA.

The Ohio State team found that mice engineered to express higher-than-normal levels of SMN protein had more overall neuromuscular resilience and recovered faster from nerve injury.

"That raised some questions," said senior Ohio State author Arthur Burghes, a professor of biological chemistry and pharmacology and [molecular genetics](#) who developed the mouse model that advanced SMA research. "Different people get different amounts of weakness with age. Why are some people completely resistant to it, and other people are more susceptible?"

"With aging and sarcopenia, there is an increased chance of injury due to falling. So it's an important problem."

Though the researchers speculate that a combination of genetics and behavior are at play, there is a chance, based on what they've found so far, that the problem could be addressed by coaxing the aging body to produce more SMN protein.

This new study compared a range of measures in mice separated by three age groups: 6-10 months, 21 months and 27 months, roughly equivalent in human years to 35-50, 55 and over 70.

In addition to observing the natural decrease in protein levels in the spinal cord and motor neurons with advancing age, researchers detected

other trends in the older mice: reductions in the number of motor units, or motor neurons plus the muscle cells they stimulate, as well as a decline in the function of muscles responding to nerve stimulation.

In terms of potential treatment approaches, the viral-mediated [gene therapy](#) currently in the clinic for infants with SMA isn't a likely solution due to the large amount of virus that would be required for an adult. The team is exploring other ways to increase SMN production.

"We know in the field of SMA that targeting an increase in SMN protein can be approached from different directions. If we can determine that this is a viable therapeutic target in aging, there's a lot of research we can lean on to help drive the direction of age-related therapeutics," Balch said.

The lead principal investigator was W. David Arnold, who is now at the University of Missouri. Co-authors include Prameela Bobbili, Hallie Harris, Rochelle Rodrigo, Deepti Chugh, Chitra Iyer and Anton Blatnik of Ohio State; and Florence Roussel and Annalisa Hartlaub of Nationwide Children's Hospital.

**More information:** Abstract: M. Balch et al, 477.15 / KK18—Age-associated reduction of survival motor neuron protein as a potential target for sarcopenia (2022)

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