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Failure in nerve-fiber navigation corrected in zebrafish model, suggests possibility of drug treatment

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Spinal muscular atrophy (SMA) is the leading genetic cause of death in children under 2, with no treatment other than supportive care. In the *Proceedings of the National Academy of Sciences*, researchers at Children's Hospital Boston show how loss or mutation of the SMA gene causes progressive muscle degeneration and weakness, and suggest a promising approach to treating the condition, sometimes referred to as a "Lou Gehrig's disease of babies."

Spinal muscular atrophy, or SMA, affects one in every 1 in 6,000-10,000 infants, but an estimated 1 in 35-40 people are carriers, according to the SMA Foundation. Infants with SMA are born with low muscle tone, and in many cases are too weak to breathe and swallow on their own; they usually die from respiratory failure.

The new findings reveal that loss of the SMA gene – and resulting depletion of a protein called SMN – makes nerve fibers from the spinal cord unable to navigate toward and form synapses (connections) with the muscles they're meant to control. But they also demonstrate that this problem could be reversed in a zebrafish model of the disease.

To figure out the function of the SMN protein, the researchers, led by Mustafa Sahin, MD, PhD, and Judith Steen, PhD, of Children's F.M. Kirby Neurobiology Center, began by asking what SMN interacts with. They used mass spectrometry, a technique from proteomics, to see what

proteins SMN binds to.

One protein, called HuD, was a strong hit. The team also showed that SMN and HuD are found together in the nerve fibers (axons) that branch from motor neurons, and that both bind to RNAs that seem to regulate the production of another protein, neuritin (also called cpg15).

Sahin then collaborated with Christine Beattie, PhD, (The Ohio State University) who had developed a zebrafish model of this disease. When the SMN protein was blocked in zebrafish embryos, the axons were clearly abnormal. "They branch in the wrong directions and don't really reach the right muscle," says Sahin. "We thought this could be due to neuritin loss and asked, 'can we put back neuritin and make the axons normal?'"

When they stimulated production of neuritin artificially – by injecting neuritin RNA into zebrafish embryos -- the axons branched normally from the spinal cord and made normal connections to muscle.

Sahin notes that neuritin is secreted outside the neuron, meaning it probably acts on a surface receptor. That makes neuritin or similarly-acting compounds good candidates for drug therapy. The next step is to find that neuritin receptor and drugs that would stimulate it, including modified forms or fragments of neuritin itself. In upcoming experiments, Sahin's team will shift to mice and try different ways of delivering neuritin or related compounds, and then see if muscle strength and survival improve.

Current research the SMA field focuses on making more of the depleted SMN protein itself. This is relatively easy to accomplish for cells in a culture dish, but it's hard to get artificially introduced SMN to function in motor neurons within the spinal cord, Sahin says. In mouse models, increasing SMN does appear to increase muscle strength, and the mice

live longer. But in human clinical trials, this approach has not yet produced positive results.

The discovery of neuritin suggests an alternative and possibly more direct way of trying to do the same thing; perhaps this would widen the window of opportunity for treatment. "SMA is such a devastating disease currently," says Sahin. "There is no cure. So far, we can only manage the symptoms and prevent complications.."

More information: *Proceedings of the National Academy of Sciences* Early Edition, week of June 6.

Provided by Children's Hospital Boston