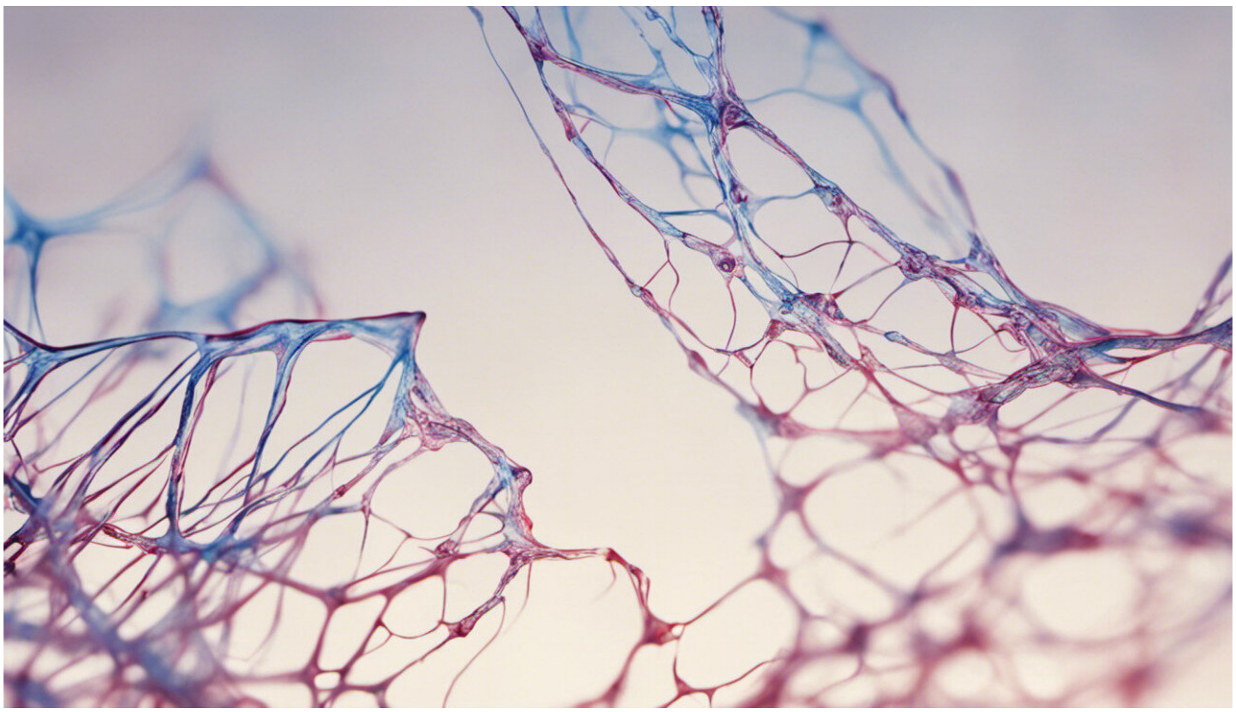
Researchers find elastic-like protein matrix that keeps nerves resilient

February 25 2014, by Amy Adams



Credit: AI-generated image (disclaimer)

Make a fist, and pity the nerve cells in your hand. Some are stretched taut across the outside of your fingers and others are squished within your palm. Despite that, they continue to do their jobs, sending signals to detect touch or pain and controlling your muscles to release the fist or clench it tighter.

The question is how.

If nerves were like floppy strings, the constant bending and stretching could damage their delicate membranes and prevent them from sending signals to and from the spinal cord.

Michael Krieg was pondering this issue of nerve resilience when he began studying some tiny roundworms whose nerves buckled and broke over time.

The worms had a mutation in a protein called spectrin, and spectrin had long been known to form an elastic lattice under the surface of red blood cells to help them bend and flex as they traverse the circulatory system.

Krieg wondered: If spectrin could help provide flexibility to blood cells, could it also help nerves withstand the push and pull of their daily lives?

The answer appears to be yes, according to work published Feb. 23 in *Nature Cell Biology*.

Weak nerves

Krieg is a postdoctoral fellow in the labs of Miriam Goodman, who studies the neurons that sense touch, and Alex Dunn, who is interested in the physical properties of cells. Bridging those labs, Krieg began studying the physical properties of nerves that sense touch, specifically the role of spectrin in keeping those nerves stable and able to transmit signals.

Goodman remembers the first time Krieg showed her the worms with the mutation and buckling nerves. "He called me over to look at the worms and I said, yeah, that's not normal." Goodman is an associate professor of molecular and cellular physiology in the Stanford School of

Medicine.

Alex Dunn, an assistant professor of chemical engineering, likened the nerves in these worms to old socks. "When we looked at bending we realized that this looked a lot like an old sock. It looked loose and floppy. We thought maybe what's going on is the spectrin is acting like elastic."

When other researchers had previously mixed that floppy-nerved mutant with another mutant worm that lacked the ability to move, the nerves remained intact well into the worm's old age. Without squishing and pulling in the immobile worm, the lack of spectrin was apparently not a problem. If the worms just held still, their nerves would have less need to be resilient. But they don't, and thus, apparently, the need for spectrin.

There are hints that the same might be true in people – some movement disorders appear to be caused by mutations in spectrin, and the spectrin protein is very similar in worms and people.

Sensing touch

Goodman's expertise is in nerves that sense touch. She had long wondered what it was in the nerve that detects pressure and transmits that signal to pores in the nerve membrane. Once opened, those pores, called ion channels, then send signals flying down the nerve to the spinal cord and up to the brain.

"How those channels get activated is something I'm intensely interested in understanding," Goodman said. "We began to wonder if spectrin also had a role in transmitting the mechanical energy carried by touch."

To find out, Krieg touched the worms in a lab dish to see what they did. Normally, the roundworms wiggle away when touched lightly on their sides. Worms with a spectrin mutation were about half as likely to notice the sensation.

All this seemed to add up to two things. First, spectrin might be a sort of elastic mesh under the nerve cell surface to allow the nerves to bend and flex and still send signals. Second, in the nerves that sense touch, the spectrin matrix might help to transmit touch to the ion channels.

Creating tension

Krieg went on to complete a tour de force of experiments ultimately showing that the spectrin matrix seems to hold the nerves in a state of tension that keeps them stable. Dunn goes back to socks. "If you imagine taking a sock and pulling it past its resting length it is straight. And when you release it part way it's still straight. But when the elastic is gone the sock doesn't hold its shape."

One of the experiments Krieg did to demonstrate this tension in the spectrin matrix came about as a happy coincidence.

Before Krieg had joined their labs, Dunn and Goodman had thought it would be helpful to develop a tool for studying force within cells. They'd gotten funding through Stanford Bio-X to created a springy fluorescent protein fragment that they can insert into other proteins within a cell. If that protein is being stretched, then their fragment glows cyan blue under fluorescent light. When the protein isn't stretched, the protein fragment glows yellow.

Krieg took advantage of this technique by inserting the springy fragment into spectrin in normal worms. When he looked at the touch-sensitive nerves, he found that the fragment glowed more cyan than yellow, showing that the spectrin was being stretching in those nerves, much like the elastic in Dunn's hypothetically stretched sock.

In fact, their spring is so sensitive they could estimate the force being placed on it by the spectrin network: about 2 piconewtons.

To put this in perspective, the force of an apple pushing down on a scale is about 1 newton. So, divide that apple into 1,000,000,000,000 pieces, and the force that just two of those pieces put on the scale is about the force generated by the spectrin in these nerves. That's not enough to hold a sock up, sure, but it's actually comparable to other types of forces and motors within a cell.

Krieg did this work in the nerves that sense touch, but said what he discovered might apply to all nerve types. "We think our results have a generalizing effect and apply to other neurons as well. It is not a unique property of touch receptors."

The scientists are now hoping to learn if spectrin creates the elastic that holds other types of nerves taut, what role spectrin plays in transmitting touch and also whether this discovery in the lowly worm applies broadly to other animals and to our own battered nerves.

More information: *Nature Cell Biology* (2014) DOI: 10.1038/ncb2915

Provided by Stanford University