Molecular springs produce a fly's sense of touch and hearing

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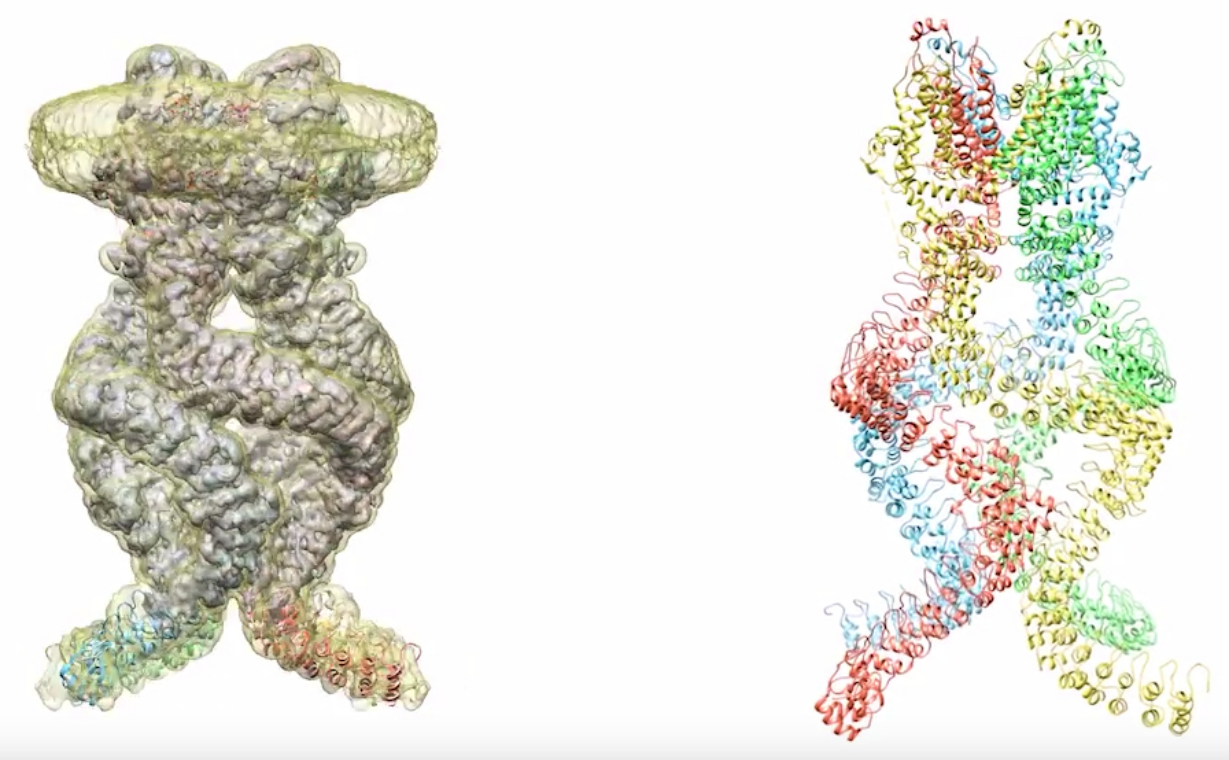

As senses go, there's nothing so immediate and concrete as our sense of touch. So it may come as a surprise that, on the molecular level, our sense of touch is still poorly understood.

Each of our senses relies on "receptor" molecules that turn signals like light, sound, and movement into electrical impulses for nerves to carry to the brain. Scientists have a fairly complete understanding of how receptors in the eye translate light into sight, and they've mapped many of the proteins in the nose and mouth that translate chemical signals into smell and taste.

But still mysterious are the "mechanoreceptors," which detect cells' motion to produce our senses of touch and hearing, and even pick up on our body's position and the flow of blood through our veins.

Now, UC San Francisco scientists have mapped in exquisite detail a protein complex called NOMPC (pronounced "nomp-see"), which acts as a mechanoreceptor in animals from fruit flies to fish and frogs. The structure, reported June 26, 2017 in *Nature*, reveals a machine that depends on a quartet of tiny springs that tether the complex to the cell's "skeleton" and react to its movement.

Though NOMPC is not found in mammals like us, the new structure gives scientists a better understanding of the subtle machinery that may allow our own sensory cells to detect touch.

In particular, the channels responsible for the human sense of hearing – which works by picking up subtle vibrations in the air – have thus far evaded detailed study. If, as some scientists hypothesize, a tethered receptor is responsible for our sense of hearing, it may well work much like NOMPC.

Springs Could Fine-Tune Channel's Sensitivity

The NOMPC receptor was mapped in such detail thanks to recent technological breakthroughs in a technique known as single particle electron cryo-microscopy. The laboratories of David Agard, PhD, and

Yifan Cheng, PhD, both Howard Hughes Medical Investigators and professors of biochemistry and biophysics at UCSF, have made major contributions to vast improvements in this technique's resolution and its ability to image proteins, like NOMPC, that sit in cell membranes.

Using this technique, the NOMPC receptor was revealed as a bundle of four identical proteins that sits in a cell's membrane, each with a spring-like tether reaching into the cell.

The NOMPC receptor's function has long been an interest for the lab of Yuh Nung Jan, PhD, the other senior author on the study, who is a Howard Hughes Medical Investigator and professor of physiology at UCSF. Previous experiments in the Jan lab have shown that the receptor does not respond to movements in the membrane alone, but that larger movements in the cytoskeleton – the network of structural fibers that allow the cell to hold its shape – cause bundle to open up, forming a hole in the cell's membrane. Charged ions rush through the hole into the cell, creating an electrical impulse that signals touch to the nervous system.

Previously mapped touch receptors float free in the cell membrane, responding only when their particular patch of the cell's surface changes shape. But the new structural data show how NOMPC's spring-like tethers might tie it to the cytoskeleton, potentially enabling the receptor to sense distant changes in the cell's shape.

"This is the first tethered receptor to be modeled in such detail," said Peng Jin, PhD, a postdoc in the Jan lab and one of the lead authors on the study. "We were surprised to see that nature has created its own tiny spring to tie the receptor to the cytoskeleton."

Do You Pull It? Push It? Twist It?

To fully understand how channels like NOMPC open and close,

scientists must observe the structure of the channels in both open and closed states. This is relatively easy for proteins that respond to light, like those in our retina, or to chemicals, like those in our nose and mouth, since they can be triggered remotely – by a beam of light or a chemical wash, respectively. But the proteins that coordinate the mechanical senses – like touch and hearing – must be directly pulled or twisted open by microscopic forces. This is challenging for scientists to do in a controlled way.

"It's difficult to apply a directional force to all these individual molecules," said David Bulkley, a postdoc in the Cheng lab and the other lead author on the study. "And we don't know which direction will activate the channel – do you pull it, do you push it, do you twist it?"

To work around this problem, the scientists are looking to find ways to force the channel open – perhaps by finding a molecule that binds to and locks open the protein, or by producing mutant versions of the protein which are stuck in the "open" position.

In the meantime, the team is also working to generate computational models of the protein. The high-resolution structure they've obtained will help them simulate in detail what happens when the tethers are put under tension.

More information: Peng Jin et al. Electron cryo-microscopy structure of the mechanotransduction channel NOMPC, *Nature* (2017). DOI: 10.1038/nature22981

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