

INNER WORKINGS

Unlocking the molecular mechanisms behind our sense of touch

Leah Shaffer, *Science Writer*

Molecular biologists don't typically conduct their research knee deep in muck, checking underground traps for an elusive mole. But Diana Bautista needed those moles to help her understand the mysterious underpinnings of humans' sense of touch. "The mechanisms that drive mechanical hypersensitivity and mechanical sensing have been really, a big black box in the field," says Bautista, an associate professor of cell and developmental biology at University of California, Berkeley.

Bautista's quarry, the star-nose mole, offers a rare opportunity to study a sense of touch few other creatures possess. The mole's centimeter-sized touch organ (the star of tentacles on its face) is bedecked with 100,000 nerve fibers, called mechanonociceptors. That is five times the number of fibers on a human hand (1). Mechanonociceptors are the first step in the journey of sending a touch signal to the brain. And the genes of this peculiar mole and its nerve fiber-packed nose could point to

molecular mechanisms underlying the enigmatic sense of touch.

Scientists are on the hunt for the ion channels or any signaling molecules involved in touch sensation. Thus far, these discoveries provide only a small window into the complex machinery of mechanosensation. Still, any step closer to mastering the circuitry that controls mechanical pain is a welcome development for patients and physicians overly reliant on potentially addictive opioids. And mechanosensation research goes far beyond touch and pain. Scientists are discovering that mechanosensory channels play a crucial role in the very function of internal organs.

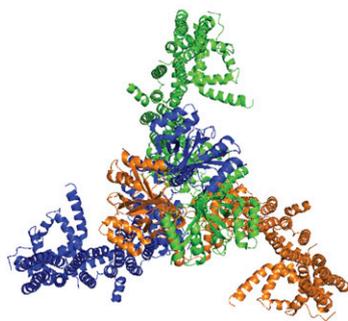
A Sense of Place

A basic understanding of the sense of touch has been elusive and for good reason. Unlike other senses, touch receptors are not limited to one location in the

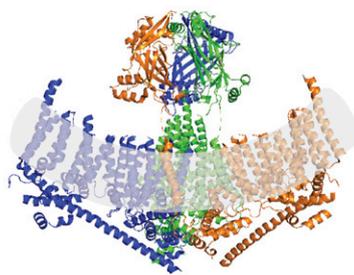


The genes of the star-nosed mole and its remarkable, nerve-fiber-packed nose could point to molecular mechanisms underlying the enigmatic sense of touch. Image courtesy of ScienceSource/Gary Meszaros.

Piezo1 ion channel (top view)



Piezo1 ion channel (side view)



Protein *piezo1* appears to have a key role in sensing mechanical forces. Image courtesy of Swetha Murthy (The Scripps Research Institute, La Jolla, CA).

body. There is a loose definition of “touch,” notes Ardem Patapoutian, a professor in the department of molecular and cellular neuroscience at The Scripps Research Institute. It can mean pain, gentle pressure, temperature sensation, and a sensation known as proprioception, a sense of your body’s location, also referred to as the sixth sense.

The act of sensing a mechanical force entails translating a physical stimulus into a bioelectrical signal. For decades, scientists knew that, much like other neurons, nerves associated with touch are equipped with ion channels that transduce that physical stimulus into the nerve cell.

But up until 2010, next to nothing was known about molecular underpinnings of those nerve fibers. That’s when researchers in Patapoutian’s lab discovered two genes that express ion channels crucial to nerve signaling (2). Although those genes were only the first two gears in a highly complex machine, the discovery was enough of a toehold to spur a vast expansion in the search for other core sensory ion channels.

Patapoutian’s lab used a mouse cell line to measure mechanically activated positively charged ion currents that are initiated during touch. Using a microarray, they determined which genes were turned on in that cell line and then knocked down those genes to see how it affected those currents. Two genes seemed to drastically reduce ion currents when knocked down, and increased currents when enhanced. The genes, dubbed *piezo1* and *piezo2*, (*piesi* is Greek for pressure), were later shown to encode mechanically activated ion channels but with different roles.

In 2014 (3), Patapoutian’s team confirmed in mouse behavioral studies that *piezo2* is central in detecting light touch. When they knocked out *piezo2* in mice, the response to gentle touch was greatly reduced compared with the control group, where most mice would withdraw their paw upon being swiped with a cotton swab. Six of the nine mice lacking *piezo2* would not respond at all to a swipe of the swab. However, there appeared to be no change compared with the control group in how the animals responded to pain from a tail clip, implying that *piezo2* is not the primary ion channel that transmits pain signals.

But *piezo2* does more. It plays a role in proprioception. Work led by Alexander Chesler’s team at

NIH confirmed this in a report published in 2016. Chesler found that two people with distinct neuromuscular disorders had a mutation that inactivated *piezo2* channels (4). These patients have some ability to feel light touch but are completely deficient in proprioception, making routine tasks like walking difficult. “When they close their eyes, they have no idea where their limbs are,” says Patapoutian.

“Clinically, this knowledge can be very useful as well,” Patapoutian adds. “If something is wrong with a person’s coordination, clinicians will first look to muscle or motor neuron problems, but now, they know to look at *piezo2* as well.” And by diagnosing a deficiency in proprioception, those individuals can receive training to make up for the lack of an internal compass by relying more on vision, according to Patapoutian.

Starring Role

Researchers were on the lookout for other players as well—enter the star-nose mole. Bautista has been studying the mole since she was a graduate student, but starting in 2012, her team analyzed the mole’s genome. The team found a particular abundance of genes expressed in the mole’s touch organ that didn’t show up in sensory neurons located in other parts of the mole’s body. That finding implies those genes specialize in mechanotransduction, the process by which applied pressure is converted to a bioelectrical signal. One of the molecules they identified through this process was signaling lipid sphingosine-1-phosphate (S1P) and its receptor (S1PR3). After seeing that same touch-signaling pathway expressed in human and mouse neurons, Bautista’s graduate student Rose Hill decided to take a closer look at the role of S1P.

In a study published in *eLife* in March, Hill and her colleagues (5) show that S1P and S1PR3 play a crucial role in determining the threshold beyond which we feel acute pain. This interplay between S1P and S1PR3 determines how much force is required to activate a type of nerve fiber that senses sharp pain—say a stubbed toe—according to Bautista. When this receptor is blocked in mice, they did not withdraw their paw when poked by a needle. The mice had an equally muted response to the pin-prick test when researchers inhibited production of S1P. However, researchers have yet to discover the identity of the ion channel that S1PR3 works with in delivering pain signals.

Human Touch

People probably have 10 different types of light-touch neurons that sense directions, texture, and velocities of touch, Patapoutian says. All these neurons work together to not just register a touch signal but relay information regarding where the touch came from or if the surface touched was hard or soft. In the case of gentle pressure on the skin, for example, *piezo2* is activated in both the nerve endings and a type of skin cell called a Merkel cell. Once *piezo2* is activated through a physical stimulus, this causes an ion influx into the nerve cell, which initiates the cell firing and sends a signal to the spinal cord and brain.

