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.

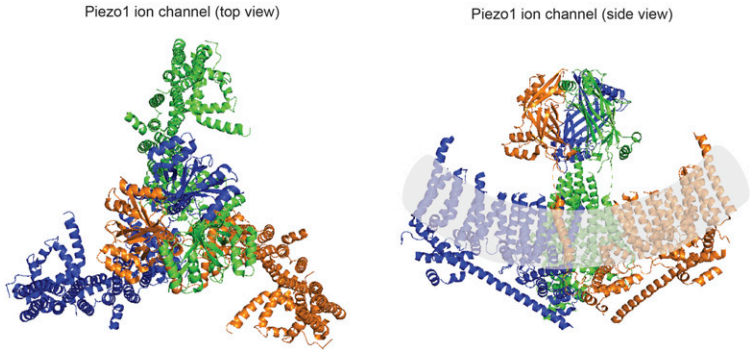
Bautista's quarry, the star-nose mole, offers a rare opportunity to study a sense of touch few other creatures possess. The mole's centimeter-sized touch organ (the star of tentacles on its face) is bedecked with 100,000 nerve fibers, called mechanonociceptors. That is five times the number of fibers 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.



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 withdrawal 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.

Yet to be hashed out are all the details of that interplay of nerve cells and merkel cells, which seem to function as an extension of this sensing circuit, says Ellen Lumpkin, associate professor of somatosensory biology at Columbia University, who has worked with Patapoutian in studying these skin cells (6). As researchers delve further into the mechanics of mechanosensation, they're discovering that many cells and signaling molecules appear to be multitaskers. Piezo2 likely takes on multiple roles in detecting different types of touch depending on yet-to-be discovered regulator molecules.

Lumpkin says it's been difficult to find key molecules likes piezo channels because all proteins react to physical and temperature stimulus. How do you tell if a protein is just reacting normally or it's actually part of the touch–sensory system? "You can push on a protein and it might respond to the push, but how do you decide if that's really its job in the body?" says Lumpkin. But Lumpkin, a co-author of the S1PR3 article, believes they found a receptor gene almost as important as one that encodes for an ion channel.

Mice don't respond to a painful poke when S1P or S1PR3 is inhibited. S1PR3, though, is not a transducer of pain signaling. "Instead it's a regulator of sensory signaling but a very, very important one," says Lumpkin. This nerve-cell receptor establishes the threshold at which, once a painful stimulus occurs, it will be transduced into the nerve cell. In essence, it's telling the cell's ion channel when to send a pain signal.

What's exciting about this, she adds, is that S1PR3 is a G-protein–coupled receptor, which is generally easy to target with drugs. Potential medicine that temporarily suppresses this receptor could be used to treat post-surgical pain or chemotherapy-induced neuropathy, which can be extremely painful, says Lumpkin. In principle, a drug that affects the S1PR3s would essentially block the signal before it even enters a nerve cell.

For now, Bautista continues to look to the star-nose mole for touch-specializing genes. Bautista's team can use their molecular database of mole genes as a starting point to finding more genes like *piezo2* that express ion channels, or receptors like S1PR3 that further fine tune how nerves react to touch.

Beyond Pain

Patapoutian says these discoveries have taken them beyond the realm of touch into the basic function of our organs. "Internal organs also experience very profound mechanical forces," he says. *Piezo1* seems to be involved with the internal workings of the cardiovascular system, explains Patapoutian. This actually isn't too surprising. Sensing mechanical force is important to the circulatory system; that's how blood vessels know to respond to changes in flow and constrict or dilate to keep blood pressure constant (7).

> **"Internal organs also experience very profound mechanical forces."**
>
> **—Ardem Patapoutian**

Last year, in a project with the lab of Harvard University cell biology professor Steve Liberles, Patapoutian found a role for *piezo2* in lung inflation (8). "Every breath you take, the lung, of course, expands," he says. And with that expansion, piezo2 is stimulated in a way that can, in turn, tell the lung when to retract, thus playing a role in regulation of breathing. Mice lacking the *piezo2* gene faced respiration problems such as overinflation of the lung.

But respiration is just the tip of the iceberg. There's mechanosensation involved in stomach stretch, bladder stretch, satiation, gastrointestinal function, and more. The role of touch in internal organs remains even more mysterious than the mechanisms of touch on our skin, says Patapoutian.

Bautista's lab, meanwhile, plans to use the star-nose mole genome to further elucidate mechanosensation. "That's been a goldmine," she says, "to go in and look at that."

1 Catania KC (2012) Evolution of brains and behavior for optimal foraging: A tale of two predators. *Proc Natl Acad Sci USA* 109:10701–10708.
2 Coste B, et al. (2010) Piezo1 and Piezo2 are essential components of distinct mechanically activated cation channels. *Science* 330:55–60.
3 Ranade SS, et al. (2014) Piezo2 is the major transducer of mechanical forces for touch sensation in mice. *Nature* 516:121–125.
4 Chesler AT, et al. (2016) The role of PIEZO2 in human mechanosensation. *N Engl J Med* 375:1355–1364.
5 Hill RZ, et al. (2018) The signaling lipid sphingosine 1-phosphate regulates mechanical pain. *Elife* 7:e33285.
6 Woo SH, et al. (2014) Piezo2 is required for Merkel-cell mechanotransduction. *Nature* 509:622–626.
7 Cahalan SM, et al. (2015) Piezo1 links mechanical forces to red blood cell volume. *Elife* 4:e07370.
8 Nonomura K, et al. (2017) Piezo2 senses airway stretch and mediates lung inflation-induced apnoea. *Nature* 541:176–181.