How Do You Feel? The Molecules That Sense Touch

Nobel Lecture, December 7, 2021, by
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INTRODUCTION

We often say that seeing is believing. But touching is also believing. Our sense of touch holds the capacity to connect us with the world and warn us of harm and hurt. The human body's ability to physically sense our surroundings helps us find our balance – both literally and figuratively – and affects our emotional health.

Figure 1. "Hair like mine," photo by Pete Souza (2009).

One of my favorite stories about the power of touch is the boy who, while visiting the White House, told President Obama that his friends said his hair was just like Obama's. The President lowered his head for the boy to feel his hair. The above photo is captivating, not only for this moment when the boy realizes the texture of the President's hair is indeed just like his own, but for the larger idea it conveys about the intimate, affective nature of touch.

But how exactly do you sense a gentle breeze or a cactus pricking your finger? How do you feel the embrace of a loved one? How do your fingers distinguish one texture of hair from another?

Our perception of reality is defined by all five of our senses, and scientists have made great inroads into understanding most of these senses. At a molecular level, we know what happens in our bodies when we smell, taste and see. How we sense touch is much more mysterious. To sense touch, pressure changes experienced by cells far in the periphery of our bodies – our skin, most often – must be translated into an electrical signal that neurons can understand.

When I put it in a single sentence like that, touch might not sound all that impressive. But I'm here to tell you that your sense of touch is amazing. If you run your fingers across a surface, you can sense indentations that are 500 times thinner than a human hair. Touch is closely related to proprioception, the ability of our brains to know, at all times, where our arms, legs and fingers are in space without looking at them. This is how you can close your eyes and still reach out in front of you to pick up a glass of water.

With touch, of course, comes pain as well. Acute pain, that warns us of danger in our environment, is essential for survival. Chronic pain, when the noxious stimulus is no longer there but pain persists, remains a major unmet medical need.

I was drawn to study the sense of touch because it was both so poorly understood and so important. This basic biological question was ripe to be answered.

THE SENSORY SYSTEM

The sensory neurons responsible for transmitting information on touch, proprioception and pain are mostly clustered in the peripheral nervous system's dorsal root ganglia (DRG). They are an incredibly diverse group of cells – some sense temperature and pain, while others respond to touch and proprioception. Some project to the skin, whereas others innervate internal organs or muscles. Despite their differences, all these cells gather information from the periphery and send it to the spinal cord and brain.

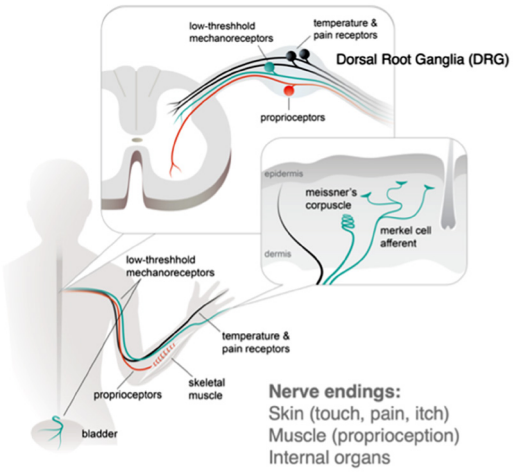

Figure 2. Mechanosensory neurons.

But how do these neurons detect physical forces such as temperature and pressure? We have known for quite a while that somatosensory neurons have specialized ion channels that are directly activated by pressure and temperature. But, until 12 years ago, the identity of the mechanically activated channels responsible for sensing touch and pain had remained elusive.

Searching for these sensors is very much like looking for a needle in a haystack; they are incredibly tiny. An average cell is about 10 micrometers in size – that's 500 times smaller than a grain of rice. And ion channels are about a hundred thousand times smaller than a cell. These channels are not something you can find by just looking through the eyepiece of a typical light microscope.

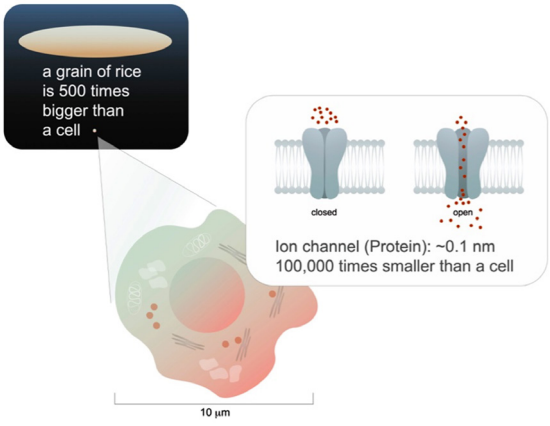

Figure 3. How big is an ion channel?

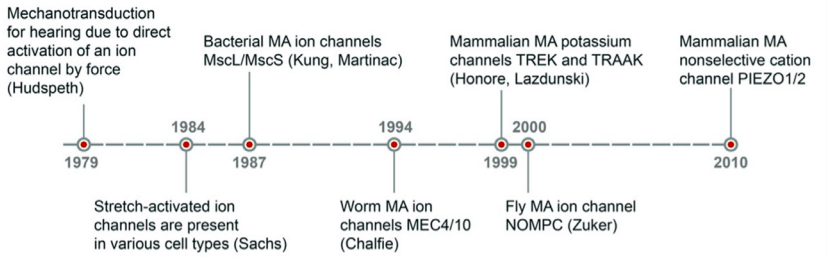

Figure 4. Timeline of discoveries – mechanically activated (MA) ion channels.

As a class, ion channels are electrical switches of neurons. They span the cell membrane and are either open or closed. When they are open, one single ion channel can let 10 million ions flow through every second. This flow is enough, with multiple channels, to actually change the voltage of the cell's membrane. This electric impulse then flows through the neuron and can propagate between neurons. Therefore, the easiest way to think about ion channels is to compare them to an electric switch that turns on a neuron.

Jim Hudspeth and his colleagues were the first to demonstrate the existence of mechanosensitive ion channels. His team was studying the sense of hearing and showed that traditional sensory signaling mechanisms would be too slow to explain the speed by which we can process sounds in the brain. Instead, Hudspeth hypothesized in 1979, a mechanically activated channel must be directly activated by the movement of hair cells in the ear. A few years later, in 1984, Fred Sachs and colleagues discovered stretch-activated ion channels in many cell types, showing that the ability for cells to sense mechanical forces was far more ubiquitous than simply allowing hearing.

Over the decades following these findings, other scientists went on to identify mechanically activated ion channels in bacteria, worms and flies. But time and again, these discoveries did little to help us understand human touch – the ion channels either had no homologs in mammals, or no apparent roles in sensing touch.

In 1999, Michel Lazdunski and Eric Honoré brought us a step closer when they discovered TREK and TRAAK, two mammalian mechanosensitive ion channels that conduct potassium. Activating these channels, however, inhibits rather than activates neuronal firing, so once more, we knew that they could not explain touch.

It was not until 2010 that my lab identified PIEZO1 and PIEZO2, the ion channels I will discuss today. Why did it take so long to identify these elusive mechanosensors? One reason is just how different they are from other sensors. The very first sensory transduction molecules identified,

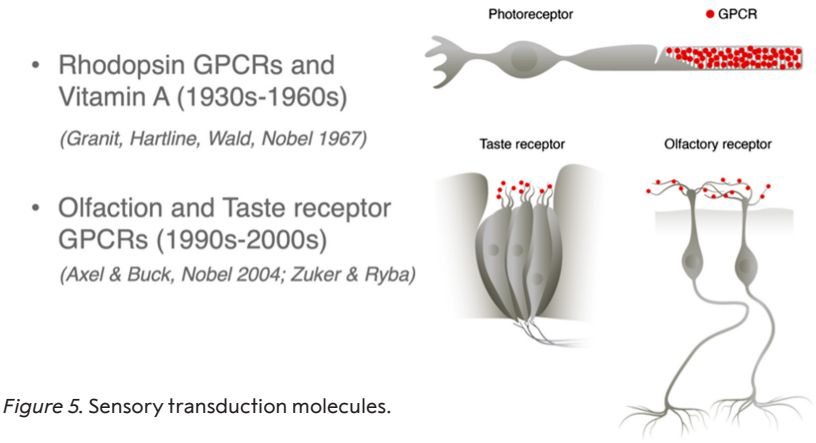

Figure 5. Sensory transduction molecules.

starting in the 1930s, were G-protein coupled receptors (GPCRs) that convert light into electrical signals for vision (Granit, Hartline, Wald, Nobel 1967). If you look at a photoreceptor in your eye, the part that senses light – the membrane of the rod's outer segment – is composed of more than 50 percent rhodopsin, a GPCR. Scientists could, and did, use biochemical approaches to purify and identify rhodopsin.

More recently, Axel & Buck (Nobel 2004), and Zuker & Ryba discovered the GPCRs responsible for our senses of smell and taste, respectively. These impressive findings were aided by the fact that these GPCRs are homologous to GPCRs such as rhodopsin.

We knew that the mechanosensors involved in touch were ion channels, not GPCRs. And ion channels, unfortunately, don't have robust homology among each other, so we really couldn't set out to narrow down a list of candidates using sequence homology. Instead, we had to turn to a functional genomic screen, a more involved undertaking.

THE DISCOVERY OF PIEZO1 AND PIEZO2

Our quest to discover the mechanosensors directly from the sensory neurons proved difficult and fruitless. We decided to take an alternative approach of looking for an easy-to-work-with cell line that expresses such a pressure sensor instead. The idea was that after we found the ion channel we were looking for in the cell line, we would then go back to in vivo studies to find its relevance. This was a reductionist approach, and we could have identified a mechanosensor that ended up not serving a role in touch. We took that risk!

Postdoctoral fellow Bertrand Coste, now a faculty member at Aix-Marseille University in France, spearheaded the efforts to identify these elusive mechanically activated channels.

While recording the electrical activity of a cell, Bertrand used a glass

Figure 6. Bertrand Coste (left) and Ardem Patapoutian.

probe and gently pushed the side of the cell. If the cell expressed a mechanically activated channel, we would observe currents when it was pushed. We screened a number of cell lines and discovered that Neuro2A cells have robust mechanically activated currents. Those became our cells of choice to start homing in on what these channels actually were.

Bertrand used bioinformatics tools to come up with about 300 genes that might possibly encode such an ion channel. All the candidate genes had domains that could traverse membranes more than once, and all were preferentially expressed in Neuro2A cells.

One by one, Bertrand worked through this list, testing whether each might encode a mechanically activated ion channel. He did this by knocking down each gene with an RNAi molecule, and then once again recording the effect of poking the cell on its electrical currents. If a gene was involved in sensing mechanical stimulation, then we assumed knocking it down with RNAi would prevent the Neuro2A cells from sensing that poke.

These experiments were painstakingly slow; to get quality data we could draw statistically significant conclusions from, Bertrand had to spend two or three days on each candidate gene. For a whole year, nothing showed up in those screens. Finally, we had this eureka moment when he tested the 72nd candidate and it wiped out this pressure-sensing ability of the Neuro2A cells.

This candidate was originally called “unknown family 38, member A” and we quickly renamed it PIEZO1, from the Greek word *piezi*, meaning pressure. Bertrand went on to clone the full-length PIEZO1, and when he

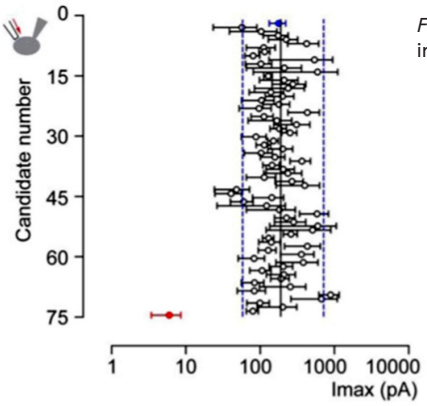

Figure 7. The difference in candidate 72.

expressed them in cells that don't normally sense pressure, such as HEK-293 cells – a line of embryonic kidney cells – the gene gave them the ability to respond to mechanical force (Coste et al, 2010, PMID 20813920).

We then searched the genome for related genes and showed that PIEZO1 has a sister that is also mechanically activated – we named it PIEZO2. The two proteins are about 40 percent identical in their amino acid sequence and we found PIEZO homologs in animals, plants and even pathogenic protozoa. Relatively speaking, they are also extremely large proteins. Mammalian PIEZO1 contains ~2,500 amino acids. All ion channels have domains that traverse the membrane – these domains form an actual channel within the plasma membrane that lets ions pass in and out of the cell. Most ion channels have 2 to 6 transmembrane domains. PIEZOs have 38, more transmembrane domains than any other protein in our genome.

To gain more insight into PIEZO1, Kei Saotome, in collaboration with Andrew Ward's lab at Scripps Research, used cryo-electron microscopy (cryoEM) to determine the structure of PIEZO1. Similar structures were also solved by the labs of Roderick MacKinnon and Bailong Xiao. CryoEM is really a transformative technology; it involves purifying the protein, putting it on a grid, freezing it, and taking images of it in this massive microscope.

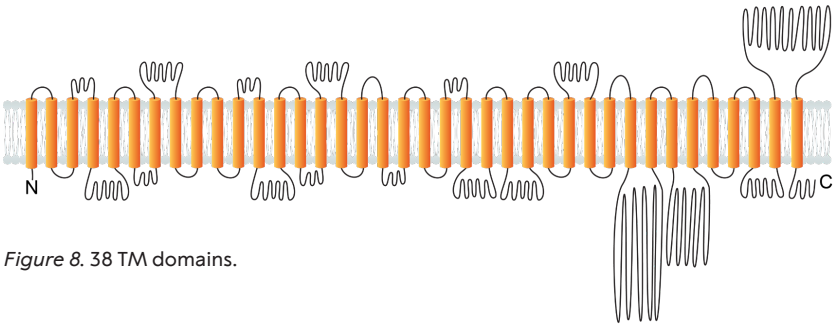

Figure 8. 38 TM domains.

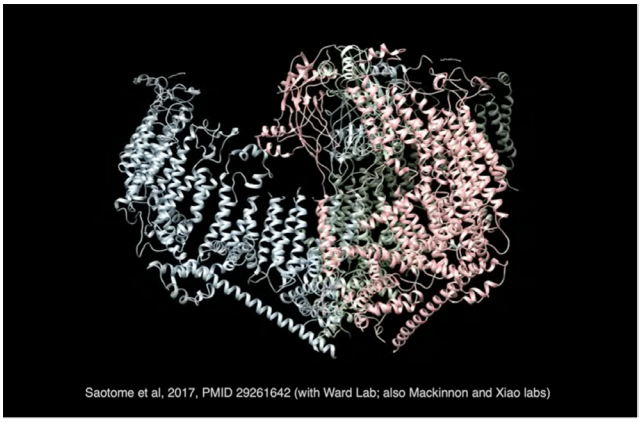

Figure 9. CryoEM structure of PIEZO1.

Through cryoEM, we obtained thousands of images of PIEZO proteins and used software to average together those images and build a molecular model of PIEZO's structure (Saotome et al, 2017, PMID 29261642). PIEZO1 is a homotrimer – three identical copies come together to form one complex. There is a central pore, and many other transmembrane domains that spread across the plasma membrane and presumably act as membrane tension sensors. If you look at a diagram of the structure, you immediately notice that the whole structure has an unusual upward bend. We think this is one of the ways PIEZO is primed to be activated by mechanical forces. The current working hypothesis on how PIEZO proteins work – first proposed by Rod MacKinnon – is that these channels sit in grooves within the plasma membrane. Any tension or stretch of the membrane causes the PIEZO proteins to flatten and activate.

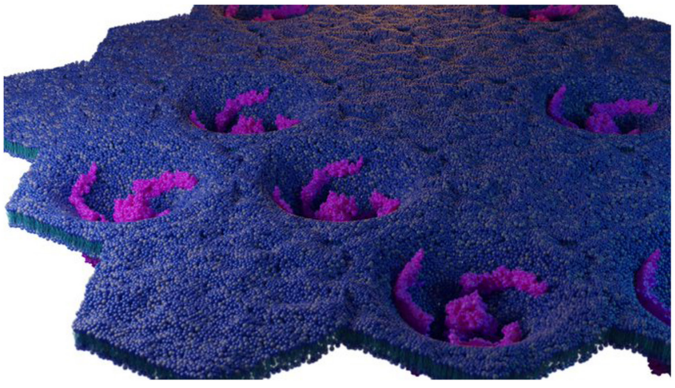

Figure 10. PIEZO in plasma membrane.

MOVING TO IN VIVO STUDIES

Once we had identified the PIEZO proteins, we were immediately intrigued by the relevance of these proteins to human health and disease. What is the role of PIEZO ion channels in the body? What happens when PIEZO is not present? What if there is too much of it?

To complement our in vitro work on PIEZO proteins, we have now spent considerable time elucidating the function of these proteins in vivo, working with both mouse models and human clinical data.

The first finding that further piqued my interest was when my lab showed that PIEZO2 is robustly expressed in a large subset of the sensory neurons of the DRGs. This suggested that we might have finally found the elusive sensor that is responsible for sensing touch and/or pain.

In one of our early in vivo experiments, we put pieces of tape on the backs of mice. Most mice really don't like this and try to remove it. But we made transgenic mice without any PIEZO2 and found that these mice weren't bothered at all. Without PIEZO2, they could no longer sense the tape. Sanjeev Ranade and Seung-Hyun Woo in my lab, as well as researchers in the Gary Lewin and Ellen Lumpkin labs, carried out that experiment in conjunction with many others to show that PIEZO2 is, indeed, the principal sensor for touch (Woo et al, 2014, PMID 24717433; Ranade et al, 2014, PMID 25471886).

We were then curious whether PIEZO2 was also required for proprioception. As I mentioned earlier, this is the sense of where your body is in space. I think this is perhaps the most important sense, and yet, most people don't know they have it. We already knew that proprioception requires similar DRG mechanosensory neurons as the sense of touch, but these proprioceptive neurons innervate muscles and tendons rather than the skin.

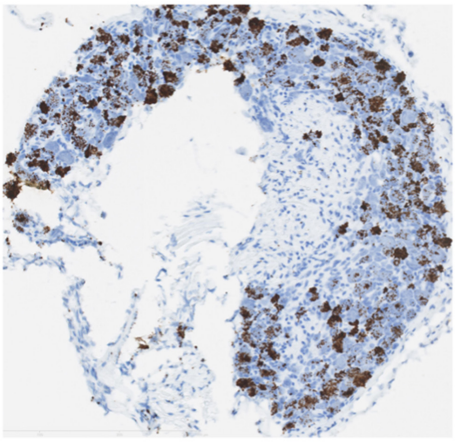

Figure 11. PIEZO2 in mouse dorsal root ganglia (DRGs).

Seung-Hyun Woo, in collaboration with Katie Wilkinson's and Thomas Jessell's labs, showed that in mice, PIEZO2 is required for proprioception. When we engineered mice to lack PIEZO2, the animals completely lacked coordination in their hind legs. Looking further, we found that stretching the muscles from PIEZO2-deficient animals did not induce the same neuronal activity in proprioceptive neurons as in wild type animals (Woo et al, 2015, PMID 26551544). This showed that the initial mechanotransduction step was compromised, as would be expected if PIEZO2 was the elusive channel responsible for proprioception.

Interestingly, the labs of Alexander Chesler and Carsten Bönnemann identified patients with loss of function mutations in PIEZO2, and these individuals have deficits in both their sense of touch and proprioception. If we ask someone without functioning PIEZO2 to walk in a straight line while blindfolded, they have a very difficult time performing this task (Chesler et al, 2016, PMID 27653382), something that most people can do easily.

What about pain?

Are PIEZO ion channels also responsible for conveying the sense of pain? Both in mice and humans, acute pain is quite normal without PIEZO2. We also investigated the role of PIEZO2 in tactile allodynia, which is pain caused by touch – this is a symptom of neuropathic pain but also occurs in conjunction with injuries, inflammation or sunburns. Swetha Murthy in my lab, as well as researchers in Alex Chesler's lab, demonstrated that PIEZO2 is a mediator of tactile allodynia both in mice and in men (Murthy et al, 2019, PMID 30305457). This opens up the possibility that blocking PIEZO2, in some instances, could be clinically relevant for people suffering from chronic pain.

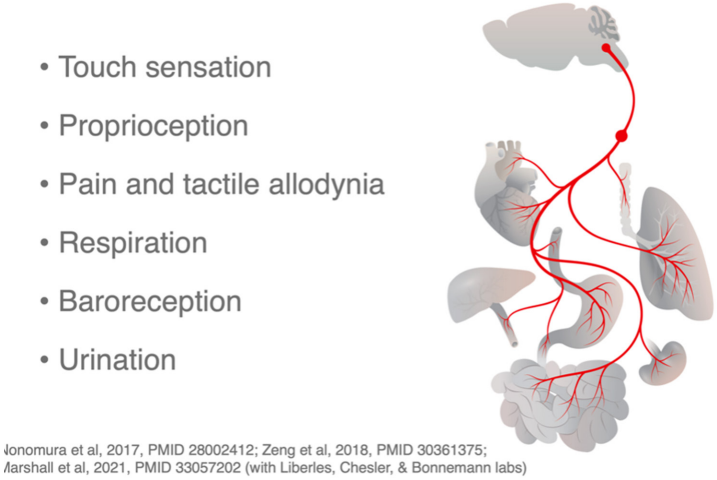

Figure 12. PIEZOs in somatosensation and interoception.

PIEZO2 IN INTEROCEPTION

PIEZO2 detects pressure in peripheral organs such as the skin and muscles in sensing stimuli relevant for touch, proprioception, and pain. But PIEZO ion channels are also found in sensory neurons that innervate internal organs. Indeed, distinct sets of nerve cells, originating from DRGs and other cranial ganglia including the nodose, innervate internal organs – including the lungs, heart, stomach and gut – and get mechanical and chemical information from them. However, the mechanism, and even the physiological role, of this mechanotransduction, was not well understood.

Over the last few years, Keiko Nonomura, Seung Woo, Wei-Zheng Zeng and Kara Marshall, in collaboration with the labs of Steve Liberles and Alex Chesler, began to investigate the role of PIEZOs in interoception – the perception of sensations inside the body (Nonomura et al, 2017, PMID 28002412; Zeng et al, 2018, PMID 30361375; Marshall et al, 2021, PMID 33057202).

Our findings in this area underscore just how critical the need to sense pressure is for our everyday functioning. PIEZO2 in sensory neurons that innervate the lungs can detect how much your lungs stretch with each breath. This information is used to control your breathing rate and make sure you're getting enough air. In nerves along the aortic arch – the main artery carrying blood away from the heart – PIEZOs sense pressure and their signaling helps mediate constant blood pressure.

You don't notice the sensation of your lungs stretching or the pressure on your blood vessels, of course, but some internal sensations you do notice. Your stretched out bladder alerts you that it needs to be emptied; we found that PIEZO2 is required for this important sense. In fact, people without functioning PIEZO2 learn to schedule their bathroom trips to avoid accidents since they don't get this warning sensation of a full bladder.

When you eat a large meal, you feel the pressure of a full stomach – something that seems very mechanical in nature. But we are not yet sure how much mechanical interoception plays a role in satiety; lots of research has instead focused on how the digestive system senses nutrients, for good reason. But we are just now actively carrying out research on how PIEZOs and the sensation of stretch might contribute to how much you eat, when you eat, and the development of diabetes and obesity.

BEYOND SENSORY NEUROBIOLOGY

Our journey in uncovering how mammals sense touch, pain and proprioception began with that eureka moment discovering PIEZO1, but in the end it was PIEZO2 that answered many of our questions related to the sense of touch.

Returning to PIEZO1, however, reveals how unexpected the twists and

turns of biological discovery can be. The fact that PIEZO2 mainly explains both our outward sense of touch and interoception does not mean that PIEZO1 is irrelevant. Rather, PIEZO1 is widely expressed in many tissues throughout the body, and our lab and many others have only just begun to explore the role of PIEZO1 in various biological processes and diseases.

We know that many non-neuronal cell types experience, sense and respond to mechanical forces. Blood vessels, for instance, experience shear force from blood flow, muscles get stretched, and many different cell types get mechanically indented. For example, red blood cells (RBCs) get squeezed through capillaries half their diameter as they circulate through our body. And the mechanism of mechanotransduction in most of these tissues remains unknown.

Indeed, my lab and others have shown that PIEZO1 is required for blood vessel formation during development as well as playing an important role in regulating bone density. Very recently, in collaboration with Medha Pathak's lab, we showed that PIEZO1 in the skin is involved in wound healing.

Finally, my lab and others have found various interesting and unexpected roles of PIEZO1 in red and white blood cells. We have strong genetic evidence that PIEZO1 plays an essential role in red blood cell volume regulation. In humans, mutations in PIEZO1 that cause increased channel activity are the primary cause of hereditary xerocytosis, a condition marked by dehydrated red blood cells (RBCs) (Albuisson et al, 2013, PMID 23695678). In mice, we see that too much PIEZO1 can lead to the same dehydration of RBCs, while removing PIEZO1 causes over-hydrated RBCs (Cahalan et al, 2015, PMID 26001274). The hypothesis, therefore, for normal function of PIEZO1 in red blood cells is that when they get squeezed through capillaries, RBCs actually shrink to more easily navigate these tiny vessels. In addition, Shang Ma in my lab showed that mice carry a gain-in-function PIEZO1, which provides protection against malaria infection in mice (Ma et al, 2018, PMID 29576450).

If excessive PIEZO1 signaling in RBCs is protective against murine malaria, our immediate next question was whether there are PIEZO1 gain-of-function mutations in regions that are endemic for malaria. We indeed found a subtle mutation in PIEZO1 – the deletion of one single amino acid – that is very prevalent in African populations. This allele, called E756del, is almost nonexistent in people of European ancestry. But one in three people of African descent carries at least one copy of this allele (Ma et al, 2018, PMID 29576450). That translates into about 400 million people carrying this allele, with about 40 million people being homozygous with two copies of the allele.

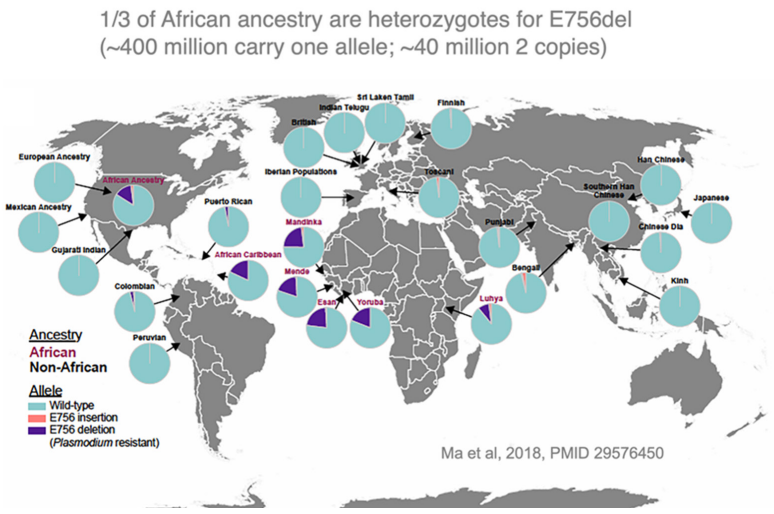

Figure 13. Frequency of E756del GOF PIEZO1 allele.

On its own, PIEZO1 E756del mutation does not cause disease. However, we are finding that there might be advantages and disadvantages to carrying this allele – similar to what is seen with sickle cell trait. We've established the potential of E756del to protect against malaria in mice. More work is needed to assess its relevance in humans.

As for potential downsides of this allele, we have recently shown that too much PIEZO1 signaling in the immune system cells, known as macrophages, causes increased phagocytosis and iron levels in the blood. This is not a good thing, as iron overload is associated with many pathologies, including organ failure.

Shang Ma received blood samples from more than 300 self-reported healthy African Americans. As expected, about one in three have the gain-

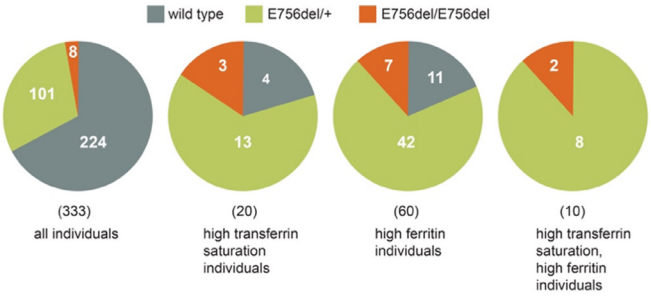

Figure 14. GOF PIEZO1 associated with higher serum iron.

of-function E756del allele, and a small number were homozygous for the allele. When we parse the data in a new way, however, looking only at people who have high levels of blood iron, we see a much higher percentage of E756del carriers, with more than three-quarters of all high-iron participants carrying at least one copy of E756del. In fact, if we use a more stringent cutoff for increased iron levels, all 10 people who fit this classification have at least one E756del allele (Ma et al, 2021, PMID 33571427).

Overall, we showed that E756del carriers are 12 times more likely to have high iron levels than noncarriers. Larger studies are, of course, required to confirm this risk factor and its clinical significance. In the future, we are eager to perform more genotype-phenotype association studies to find out whether other physiological processes, clinical variations, or diseases are impacted by mechanotransduction and the PIEZO proteins.

PLANTS AND BEYOND

I mentioned earlier that PIEZOs are conserved across evolution. So, flies and worms have PIEZO, many unicellular organisms have PIEZO, and plants have PIEZO ion channels. Plants also experience mechanical force. For example, when roots grow and encounter a harder surface in the soil, they must decide whether to go right through it or around it. Recently, Ali Reza Mousavi in my lab showed that PIEZO in plants is expressed in root tips. In Arabidopsis, he showed that without PIEZO, the ability of these roots to *penetrate* through a harder surface is compromised (Mousavi et

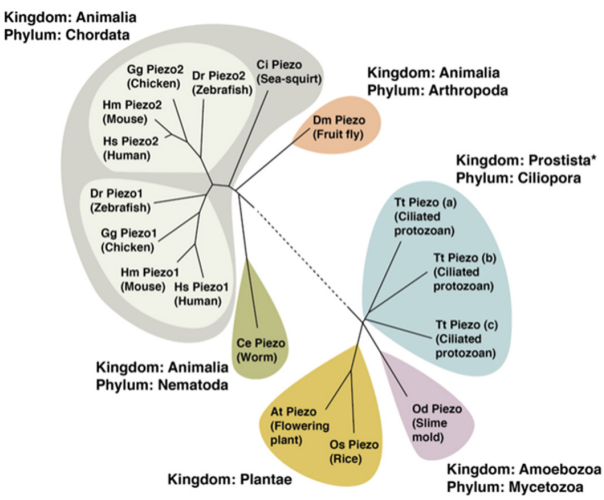

Figure 15. PIEZOs across phyla.

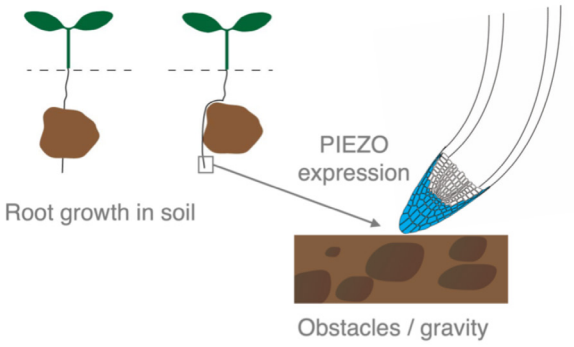

Figure 16. PIEZO in plants.

al, 2021, PMID 33975957). I find it absolutely fascinating that the same type of sensor that we use to sense touch is also used by plants to sense the stiffness of their surroundings. Evolution is indeed amazing.

In conclusion, we have shown that PIEZO2 is the principal mechanosensor for touch, proprioception and many interoceptive functions. We have also shown that PIEZO1 plays a predominant role in many non-neuronal cell types. Overall, studies in both human and mouse genetics are providing a foothold in unexpected roles of mechanotransduction in physiology and disease, including surprising roles such as regulating blood iron levels.

Finally, I believe there are more mechanosensors to be found. For example, for noxious pain, we know there's a separate channel that accounts for the pain we experience when, for example, a hammer hits our finger. However, the identity of this ion channel is unknown, making this field ripe for many more exciting discoveries.

ACKNOWLEDGEMENTS

I have many people to thank for their roles in my scientific journey. I fell in love with basic discovery research in Judy Lengyel's lab at UCLA, learned how to ask important questions in Barbara Wold's lab at Caltech, was inspired by Lou Reichardt at UCSF to take on high-risk endeavors, and discovered how to harness cutting-edge technologies from Pete Schultz at Scripps Research.

Learning from all these mentors, I have tried to build a laboratory environment at Scripps Research that emphasizes impact, collaboration and collegiality. I hope my lab members are always having as much fun as I am while pursuing such science. I'm exceedingly proud of how well they work with each other and with expert colleagues around the world. Indeed, one of the greatest joys of doing science is seeing the trainees blossom into independent thinkers, chasing important questions, in aca-

demia and industry. And of course, we could not have accomplished much without our collaborators from laboratories across the United States and beyond.

The importance of funding in biomedical research cannot be overstated. Howard Hughes Medical Institute affords freedom to pursue major innovations and has fueled my research program. The National Institutes of Health has been vital to the very existence of basic biomedical research in the U.S. During the COVID pandemic, I sincerely hope the United States, and indeed the world, has a renewed level of appreciation for the impact biology research has on human health.

I want to end with a personal note. Below, you can see a photo of my son Luca and me a few minutes after I received the call from Stockholm, and while the official announcement was being made. I am very grateful that my wife Nancy snapped this photo. I study the sense of touch, and this is indeed a very touching moment of pure joy.

My family is a profound source of happiness and the foundation of my ability to do science. And because this is 2021, with restricted in-person interactions due to the COVID pandemic, this photo took on added meaning as it spread the news of the Nobel Prize. And through social media, I received messages from around the world. Indeed, many congratulations came from people in Armenia and Lebanon where my ancestors and I were born.

I am grateful that the Nobel Prize has reconnected me with my roots and highlighted how internationalism, diversity and the exchange of ideas and people are so integral to progress. Thank you for the opportunity to share my science with you.

Figure 17. Luca and Ardem Patapoutian

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