People & Ideas

Marcos Sotomayor: Listening in on the cadherin family's secrets

Sotomayor studies how cadherin proteins mediate mechanotransduction and cell adhesion.

Growing up in Chile, Marcos Sotomayor was always interested in how things worked, and fascinated by his architect father's technical drawings of buildings and his artist mother's ability to create colorful sculptures. He also held an early interest in computers. Although he begged his parents for an Atari® game system like his friends had, they instead saved up for a PC, which Sotomayor used to teach himself programming during middle school.

The purchase paid off. For the past two and a half years, Sotomayor has run his own laboratory at The Ohio State University, using both computational and experimental tools to discover structure-function relationships in macromolecular complexes involved in mechanotransduction and selective cellular adhesion. One area of interest is focused on creating structural models of the two cadherin proteins that form "tip links," microscopic filaments in hair cells of the inner ear that play a crucial role in hearing. These proteins, protocadherin 15 and cadherin 23, meet in a handshake configuration; if the bond is broken, hearing is lost.

The work is an extension of his graduate and postdoctoral studies. After studying physics in college, Sotomayor came to the University of Illinois for a PhD. His advisor, Klaus Schulten, was a biophysicist impressed by Sotomayor's computational capabilities and put him to work, looking at the elastic properties of proteins and channels involved in mechanotransduction (1–3) and the role of calcium in maintaining the mechanical strength of cadherins (4). He furthered the work during postdoctoral studies with David Corey and Rachelle Gaudet at Harvard, where he did wet laboratory experiments for the first time and obtained the structure of the protocadherin 15–cadherin 23 bond (5), with implications for the larger cadherin family (6).

He recently spoke with *JCB* about his ongoing quest to study mechanotransduction in the inner ear and beyond.

MAKING THE SWITCH

How did you make the switch from physics to biology?

When I was in high school and then through college, biology was always about names and "black boxes" representing processes you had to memorize without understanding, and the pathways or names of this and that. With physics, if you knew a few equations you could derive anything. So biology was on the side for me. When I met Klaus, I told him, "Look, I've never done real biophysics. I know very little about biology. But I'm very interested and I'm very good at doing simulations." He said, "That's perfect, because we need someone who can understand simulations and can learn the biology on the way." That was a big adventure for me, really, because it was a drastic switch from what I'd been doing.

What are you working on now?

We want to get a structural view of all the proteins that are involved in the process of mechanotransduction in the inner ear, of the molecules that mediate our hearing and sense of balance. We have been obtaining crystal structures for different parts of the tip link made of protocadherin 15 and cadherin 23. Now we have structures for almost all of the "parts," or so-called EC repeats, in protocadherin 15. We want to model and simulate the entire tip link. This is important because some parts of the tip link are different—there is not just a chain of the same thing repeated over and over. The protein is very complex and it has some domains that lack calcium-binding sites, which might render the domains weaker and affect how force is transmitted to the ion channels that mediate sensory perception.

> "That was a big adventure for me, really, because it was a drastic switch from what I was doing."

PHOTO COURTESY OF MARCOS SOTOMAYOR

Marcos Sotomayor in Shilin, China

What other proteins are you looking at?

We are studying other members of the cadherin superfamily of proteins. We want to know if they use the same "handshake" found in tip links, or perhaps different modes of interaction. For instance, we have exciting results on protocadherin 19, which, when mutated, causes epilepsy. Why? Because it is involved in how neurons connect to each other. We also have intriguing structures of protocadherin 24, which forms similar links to the tip link but in the gut. Overall, we are learning about the many "faces" of cadherin handshakes.

SIMULATING ROCK CONCERTS

Tell me about your centrifuge force microscope.

In previous work, we used molecular dynamics simulations to predict the unbinding force of the tip link handshake. These simulations allowed us to "see" the unbinding process, something that cannot be done in any other way. Now we want to experimentally test the strength of the bond and the simulation predictions. To do so, a very talented undergraduate student, with the assistance of the inventors of the centrifuge microscope, built a version of it and wrote the code to control it. At the end of a rotating arm, we have proteins attached to a coverslip and bound to another set of proteins connected to beads.

Text and Interview by Karen Blum
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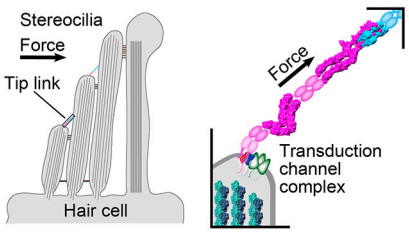

IMAGE COURTESY OF R. ARAVASECCHI AND M. SOTOMAYOR

Each inner-ear hair cell has a bundle of hair-like projections called stereocilia. When hair-cell bundles are deflected by sound vibrations, they pull on the tip links, which in turn open ion channels to trigger an electrical signal.

As the arm spins around, force will pull on the beads, which will pull on the protein complexes. We can use this to measure the forces required to unbind the proteins, with many single-molecule experiments being done in parallel in one spin. This unbinding is similar to what happens when you go to a rock concert and you put your ear next to the speaker. The sound is very loud so the forces are very large and may break your tip links, which is what we're trying to understand with this apparatus.

What are the clinical implications of your work?

Our work has a connection with disease because the proteins we are studying are involved in deafness and blindness (Usher syndrome), and also in epilepsy and cancer. We do not cure diseases, but I think a basic understanding of these proteins is essential, really, to understand how they work, and eventually to develop molecular therapies that can help alleviate these problems. In addition, most of the diseases associated with the proteins that we work on are inherited diseases. Hopefully through avenues like genetic counseling we could help prepare people whose children have a mutation in some of these proteins. Our work hints that giving this advice is actually possible, as the severity of deafness seems to be correlated with the biochemical effects of the corresponding mutations.

Do you have ultimate goals for your laboratory? What do you hope to find?

In the long term, I would like to understand how mechanotransduction happens at the molecular and cellular level: How do different systems transform mechanical force into electrical or biochemical signals? How do proteins deform under force? We would like to understand how that happens in the senses of touch, hearing, and balance, and also how it happens in all parts of the body that are constantly using specialized cells and proteins to deal with forces.

Another long-term question that we have is: How do cells arrange and connect to each other in very specific patterns to form tissues and organs as complex as the brain? How have these features evolved? In our laboratory, we combine both experiments and simulations to try to answer these questions, and I think that is key. We are not limited by methods; we go after a question, and we use whatever we can to find the answers.

"How do different systems transform mechanical force into electrical or biochemical signals?"

FOLLOWING THE TRAIL

What do you do for fun outside of work?

I am a bit of a workaholic. But I do enjoy playing ping pong and going to movies. I also enjoy traveling. I have been to many countries in Europe, which is always impressive and fun. I have also been to China, Thailand, and Cambodia; those are really amazing places that I was very ignorant about.

What do you like about traveling?

I like improvised trips. When I went to China for a conference in Beijing, I stayed for three extra weeks to travel around. A Chinese friend had told me about all the cities I should visit. So, during the meeting, I went to the travel agency in charge of helping us and said, "I want to go to all of these places but I want to go by train." They tried to tell me I had to go by plane but I didn't want to do that because it's the typical tourist thing to do. Finally, they said they would help me but there were two issues: I was telling them late, so they could not get all the tickets to me up front. In each city I would have to find the tickets for my next trip. And it was vacation time in China, so literally millions of people were traveling by train, and it was unclear if they could get me all the tickets I wanted.

I went to the train station in Beijing, which was huge and packed, and had to match the characters to find the right train. People were really kind because it was obvious I was lost and one of only a few foreigners there. Then in each city I would have to go to some random neighborhood to get the next set of train tickets. That was a lot of fun, actually, and I ended up visiting Xi'an, Chengdu, Kunming, Shilin, Jiuxiang, Guilin, and Yangshuo.

The ticket hunt was very much like what happens in science. As one chases certain goals, new discoveries lead you to the next step in the trip.

1. Sotomayor, M., D. Corey, and K. Schulten. 2005. *Structure*. 13:669–682.
2. Sotomayor, M., et al. 2007. *Biophys. J.* 92:886–902.
3. Sotomayor, M., and K. Schulten. 2007. *Science*. 316:1144–1148.
4. Sotomayor, M., and K. Schulten. 2008. *Biophys. J.* 94:4621–4633.
5. Sotomayor, M., et al. 2012. *Nature*. 492:128–132.
6. Sotomayor, M., R. Gaudet, and D. Corey. 2014. *Trends Cell Biol.* 24:524–536.

PHOTO COURTESY OF AISWARYA KRISHNAMOHAN

The Sotomayor laboratory