Scientists find mysterious family of proteins are cellular pressure sensors

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Scientists at Scripps Research have discovered that a mysterious family of cellular proteins called OSCAs and TMEM63s are a novel class of mechanosensitive ion channels.

Mechanosensitive ion channels convert biologically relevant physical forces into biochemical signals. For example, a plant's response to environmental cues like wind, water currents, or physical barriers depend on mechanosensation. In mammals, sense of touch, pain sensation and blood pressure regulation are performed by mechanosensitive ion channels. Despite their importance, very little is known about the molecules that perform these functions in plants and animals.

The scientists also deciphered the atomic structure of one member of the OSCA protein family, an advance that will allow them to study how these ion channels do their jobs, information that could be critical to identifying how dysfunctions in mechanosensing play a role in disease.

The original work to discover the role of OSCA proteins was led by Swetha Murthy, Ph.D., professional scientific collaborator in the lab of Ardem Patapoutian, Ph.D., professor at Scripps Research and investigator with the Howard Hughes Medical Institute. In her new *eLife* study, Murthy and her colleagues show that OSCA channels are not only pressure-sensitive ion channels, but they appear to have held onto their "mechanosensitive" properties as life evolved.

"We wanted to see if the mechanosensitivity properties were conserved across the 15 different members of the OSCA family, and across different species," says Murthy.

The new findings suggest the pressure-sensing abilities of these ion channels are indeed "conserved" among the types of OSCA channels. Furthermore, while OSCA channels are present in plants, their related proteins in animals, TMEM63s, are also mechanosensitive.

"This finding will facilitate the study of these channels in model organisms such as flies and mice and will help identify their role in human biological processes and other disease states linked to mechanosensation," says Murthy.

A follow-up study was led by Sebastian Jojoa Cruz, graduate student, and Kei Saotome, Ph.D., at Scripps Research, and published simultaneously in *eLife*. Working with Professor Andrew Ward, Ph.D., the researchers used an imaging technique called cryo-electron microscopy to study the structural details of a member of the OSCA family, called OSCA1.2.

This first look at OSCA's structure suggests that part of the protein may sit close enough to the cell membrane to sense membrane tension and translate that tension to the rest of the ion channel. The researchers are looking forward to investigating exactly how this pressure sensing process works.

"By revealing the first structural snapshot of an OSCA channel, we have provided a valuable starting point to unravel the details of a force sensation mechanism that is widespread throughout biology," says Saotome.

"Force is a difficult phenomenon to study at the molecular level, so

future studies will require innovative and multidisciplinary approaches," adds Ward. For example, molecular dynamics simulations of OSCA1.2, conducted by co-authors Alex Tsui and Mark Sansom, DPhil, at Oxford University, offer tantalizing clues about the role of lipids in channel function.

Saotome and Jojoa Cruz say it was "striking" to see how similar the OSCA structure was to the structure of an unrelated family of proteins called TMEM16, especially in the transmembrane domain. TMEM16s have diverse roles in membrane biology, including as ion channels and manipulators of the cell membrane. Therefore, the structural similarity could suggest this protein architecture is responsible for more biological functions than previously believed.

"The next step will be to determine the physiological role of these proteins in plants and animals," says Murthy.

More information: Swetha E Murthy et al, OSCA/TMEM63 are an evolutionarily conserved family of mechanically activated ion channels, *eLife* (2018). DOI: 10.7554/eLife.41844

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