Scientists identify protein that sends 'painful touch' signals

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In two landmark papers in the journal *Nature* this week, scientists at The Scripps Research Institute report that they have identified a class of proteins that detect "painful touch."

Scientists have known that sensory nerves in our skin detect pressure, pain, heat, cold, and other stimuli using specialized "ion channel" proteins in their outer membranes. They have only just begun, however, to identify and characterize the specific proteins involved in each of these sensory pathways. The new work provides evidence that a family of sensory nerve proteins known as piezo proteins are ion channel proteins essential to the sensation of painful touch.

The experiments in the new study were conducted in fruit flies, a model system for the sensory nervous system of mammals, where piezo proteins are also expressed, as well as in certain cell types in the ear, kidney, heart, and other tissues. Future studies will focus on the roles of piezo proteins in sensing sound, blood pressure, and related stimuli that press and/or stretch cell membranes.

"Researchers in this field have been trying for decades to identify pressure-transducing ion channel proteins that exist in mammals, and these piezo proteins are exceptionally strong candidates," said Ardem Patapoutian, a professor in the Department of Cell Biology and the Dorris Neuroscience Center at Scripps Research, and a senior investigator for both papers. "We now have solid clues that we can follow up to learn how the mechanotransduction pathway works and how

it is disrupted in diseases."

The two papers appear online in *Nature* on February 19, 2012.

Following the Path of Clues

Patapoutian's laboratory specializes in the study of sensory ion-channel proteins. When hit by a stimulus to which it is sensitive, one of these proteins typically will open its structure to allow charged calcium, sodium, or potassium molecules ("ions") to flow from the fluid outside the cell into the cell's interior. Ion channels that sense mechanical pressure are thought to open when the membrane in which they are embedded is distorted past a certain threshold. The resulting flow of charge can trigger other signals inside the cell, for example a nerve impulse within sensory neurons—and in a human, a sufficient number of these nerve impulses would be interpreted by the brain as a touch- or pressure-related feeling.

In a highly cited paper published in *Science* in late 2010, Patapoutian and his colleagues reported that two mouse proteins of previously unknown function exhibited properties of mechanotransducers. Cells to which these proteins were added drew in positively charged ions when subjected to mechanical pressure. Bertrand Coste, the first author of the paper, named the two closely related proteins piezo1 and piezo2—the prefix "piezo-" being derived from the ancient Greek word for pressure or squeezing.

"Since these proteins bore little resemblance to known ion channel proteins, the next step for us was to confirm that they are indeed ion channel proteins," Patapoutian said. The new studies take this step and more.

In the first of the new studies, lead authors Bertrand Coste, Bailong

Xiao, and their colleagues confirmed that piezo proteins are indeed ion channel proteins, and very large ones. "It assembles into a 'tetramer' complex of four piezo proteins, which appears to be the biggest plasma membrane ion channel yet discovered," said Coste, a research associate in the Patapoutian lab. The protein sequences within piezo also suggest that its ion channel structure weaves through the cell membrane more than 100 times.

Collaborating researchers in the laboratory of Mauricio Montal, a Distinguished Professor of Neurobiology at the University of California, San Diego, found that even in the absence of other proteins, piezo proteins could self-assemble into this tetramer complex, forming ion channels in artificial membranes known as lipid bilayers.

The second of the new studies involved experiments with the fruit fly Drosophila. Sung Eun Kim, first author of the study, genetically engineered a line of Drosophila that does not express the Drosophila piezo (dpiezo) gene. "We found that their larvae showed a severe loss of responsiveness to mechanical stimuli that would be expected to generate pain-related signals, though they responded normally to other kinds of stimuli such as heat and mild pressure," she said. Kim is a graduate student who divides her time between the Patapoutian lab and the lab of Scripps Research Assistant Professor Boaz Cook, who was co-principal investigator of this study.

Kim also used genetic "knockdown" techniques in Drosophila to show that interrupting dpiezo expression in certain sensory neurons could reproduce this loss of sensitivity. Finally, when she artificially reinstated dpiezo expression in larvae that had been born without the gene, they displayed normal sensitivity to strong pressure. "It's the first demonstration of a specific physiological function of a piezo family protein," said Cook.

The Patapoutian lab now is now conducting detailed follow-up studies of piezo and other possible mechanotransduction proteins. "In the next several years, we'll be trying to determine all the biological processes and diseases in which these pressure-sensing proteins play a role," he said.

More information: "Piezos Are Pore-Forming Subunits of Mechanically Activated Channels," *Nature* (2012).

Provided by The Scripps Research Institute