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Neurobiology

How your body knows to shout 'ouch'

by Lou Beaulieu-Laroche[1] | PhD Student

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[1]: McGovern Institute for Brain Research, Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, USA

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Why is holding hands enjoyable but stubbing fingers painful? Our body judges whether a physical force is "dangerous" depending on its intensity to decide if it is worth feeling painful to protect itself against additional damage. Here, we discover a long-awaited novel pain sensor in the skin.

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Ouch! — we often can't help shouting when stubbing a toe or getting a finger squashed in a door. These are everyday experiences that elicit pain. But how do we actually recognize those experiences as painful? Why is pain precious?

Pain sensing begins with specialized nerve cells, called nociceptors, that sense painful stimuli through our skin. These cells only sense mechanical forces that are too strong and therefore would cause unwanted tissue damage. In other words, they remain inactive when you shake hands, as it is "undangerous". Nociceptors contain sensors that convert mechanical forces into electrical signals to relay information to the brain. However, molecules working as pain sensors have not yet been identified. This missing information has limited our understanding of this painful experience and the development of therapies for pathological conditions, which cause unnecessary pain such as arthritis.

To identify the pain sensor, we selected a list of candidate molecules based on an ability to convert mechanical forces into electrical impulses and investigated them. We cultured "plain" cells — which have limited ability to sense mechanical forces — in the laboratory, and genetically engineered them to include one of these candidates. If cells gain the sensing ability after this manipulation, we can conclude that the artificially-introduced molecule should be responsible. To put this to a test, we poked different cells with a glass needle controlled through a videogame-like controller, and we quantified their force-sensing ability by measuring electrical impulses generated from the mechanical stimuli.

This allowed us to identify a new molecule — which we now name TACAN. Further analyses using pure TACAN molecule enabled us to ensure that it is indeed a mechanical stimuli sensor.

Next, we wanted to know whether TACAN contributes to mechanical force sensing in nociceptors, the natural cells where the TACAN sensor is found and expected to work. As expected, we found that TACAN is present in nociceptors. We then cultured nociceptors in the laboratory and genetically manipulated them to control the amount of TACAN within cells. Nociceptors generated drastically decreased electrical signals driven by mechanical stimuli when having a lower amount of TACAN. Thus, TACAN indeed participates in mechanical force sensing within nociceptors.

We now know that TACAN endows nociceptor cells with mechanical sensitivity, but is it necessary to sense painful mechanical stimuli in our daily lives? To address this question, we genetically removed TACAN from nociceptors in mice. A mouse is a model animal sharing many biological and genetic features with humans, meaning that what is observed in mice most likely occurs in humans as well. We observed that non-engineered normal mice withdrew paws when being mildly poked, but showed pain responses like licking paws after intense pokes. In contrast, mice without TACAN withdrew their paw reacting against both mild and robust pokes, indicating these engineered mice perceived all mechanical stimuli equally as non-painful. These results demonstrate that TACAN in nociceptor cells is essential for mice to sense intense stimuli as painful.

Overall, we identified TACAN, a molecule of previously unknown function, as a novel mechanical pain sensor. While we focused on the sensing mechanism in mice in this research, we expect that TACAN similarly functions in humans as well.

Our findings help extend our understanding of what happens when you stub a toe: When your toe hits a hard object quickly, the skin gets compressed and mechanically deformed. TACAN in nociceptors senses the intense mechanical stimuli and creates electrical impulses that are transported to the brain. Eventually, you can recognize it as pain and take actions to protect your body. While for most people this mechanical pain is a transient and necessary experience, some patients suffer from chronic pain conditions. The patients experience constant pain without external stimuli. Understanding further TACAN-based pain-sensing will open avenues to developing potential treatments by blocking pain at the source.