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The sensation of stretch

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Abstract

Piezo proteins have been shown to form large ion channels that serve a sensory function in fruitflies. The findings help to explain how Piezos convert mechanical force into biological signals. See Article p.176 & Letter p.209

An organism's ability to react to mechanical stimuli is crucial for its survival. One set of biological tools for sensing mechanical stress is the ion channels that open in response to tension in cell membranes, often called mechanosensitive channels (MSCs). Much progress has been made by studying MSCs in different systems[1], but one of the biggest breakthroughs came in 2010, when Ardem Patapoutian's group[2] identified a cation-selective MSC that responds directly to mechanical forces in the membrane of certain mouse cells. They found that two similar proteins — Piezo1 and Piezo2 — each can form MSCs in different cell types.

In two papers[3,4] published in this issue, Patapoutian's group presents another milestone in our understanding of mechanical transduction. The team reports that Piezo proteins form channels composed of four large identical subunits, and that the expression of these channels is directly related to nociceptive responses — neural processes associated with potentially harmful stimuli — in the larvae of the fruitfly *Drosophila melanogaster*. This is the first time that the detailed biophysical properties of a cation-selective MSC have been correlated with changes in behaviour.

In mice, Piezo1 contains about 2,500 amino acids and is arranged into more than 30 transmembrane domains — making it structurally different from other known ion channels. Patapoutian and colleagues previously reported[2] that the expression of Piezo1-encoding genes in various mechanically insensitive cells made those cells sensitive to mechanical stimuli. Furthermore, the conductance and inactivation properties of Piezo1 are similar to those of the first MSCs to be identified[5], which were found in non-sensory cells. Piezo1 is also the first MSC from a eukaryote (organisms such as plants and animals) that is known[6] to be inhibited by the peptide GsMTx4, a compound widely used as a channel blocker in the study of MSCs. Patapoutian's group now asks whether Piezo1 is itself an ion channel, or whether it modifies the activity of another channel (or another protein).

In the first of the two papers (page 176), Coste *et al.*[3] convincingly argue that Piezo1 proteins assemble to form a tetramer, on the basis of results from two complementary

methods. In the first approach, the authors attached a green fluorescent protein to Piezo1. They then used light to extinguish the fluorescence of the resulting construct, and observed the loss of fluorescence using single-molecule imaging techniques. The fluorescence diminished in four quantized steps, suggesting that Piezo1 assembles as a tetramer.

Coste and colleagues' second approach was to chemically crosslink the subunits of Piezo1. When the authors subjected the crosslinked sample to electrophoresis, they observed discrete bands on the electrophoretic sizing gel that could be explained by the formation of a tetramer. The team also used mass spectroscopy to show that no other proteins are associated with Piezo1, which suggests that Piezo1 does not exert its effects by modifying the activity of another protein. Whether the tetramer is indeed the functionally active channel formed by Piezo1 remains to be seen.

The authors found[3] that the tetrameric complex has a molecular mass of about 1.2 million daltons, that it has 120–160 transmembrane segments and that the monomer is different from those of other known channels. The large size of the tetramer is not obviously advantageous for mechanical activation, because structural changes associated with the activation of other MSCs are known to be small[7] (about an ångström). Furthermore, bacterial MSCs are highly sensitive to membrane tension[8], despite being considerably smaller than Piezo channels. The unusual architecture of the Piezo1 complex therefore indicates that we have more to learn about this protein family.

Coste *et al*. went on to demonstrate that purified Piezo1 could be reconstituted in planar lipid bilayers and liposomes (artificial vesicles made from lipid bilayers), and that these reconstituted proteins had conductance properties characteristic of a cation-selective ion channel. This means that auxiliary force-coupling structures, such as the cytoskeleton of cells, are not required to activate Piezo1 in membranes — although the authors' experiments did not prove that the reconstituted proteins were mechanosensitive.

In the second paper (page 209), Kim *et al*.[4] focus on a Piezo protein, DmPiezo, in *D. melanogaster*. Like Piezo1 and Piezo2 in mice, the authors found that DmPiezo responds to mechanical stimuli when expressed in human cells. When the researchers knocked out the Dm*piezo* gene from *Drosophila* larvae, the larvae's behavioural response to noxious mechanical stimuli was reduced compared with that of wild-type larvae, although their responses to other mechanical stimuli, such as gentle touch, were unaffected.

Similarly, by specifically depleting the levels of DmPiezo in the sensory neurons used for nociception in larvae, Kim *et al*. diminished the animals' response to noxious mechanical stimuli. This effect could be reversed by reintroducing DmPiezo into the larvae. However, knocking out Dm*piezo* did not completely abolish the nociceptive response, suggesting the presence of parallel signalling pathways for mechanosensitivity in the larvae. When the authors knocked out both Dm*piezo* and *pickpocket* (a gene that encodes another type of ion channel), they observed complete loss of nociception.

Mouse and *Drosophila* Piezo proteins share some characteristics — they exhibit similar mechanical sensitivity and time-dependent inactivation, for example. But there are also differences: mouse Piezo1 has a higher ion conductance than DmPiezo, and is more

sensitive to ruthenium red, a compound used to block the pores of the transient receptor potential (TRP) family of ion channels. The reactivity of ruthenium red with Piezo1 is a reminder that the compound cannot be used solely as a TRP channel inhibitor.

The study by Kim *et al*.[4] suggests that Piezo proteins are a new family of eukaryotic mechanosensitive channels. Perhaps the most pleasing aspect of their work, however, is the demonstration of a relationship between mechanical transduction and sensory processing: if force is applied to a cell containing DmPiezo, an influx of positive ions through the channel makes the cell interior more positive. The resulting change in potential across the membrane signals to the animal that a noxious stimulus is present. What could be simpler?

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