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CELL BIOLOGY

The sensation of stretch

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

PHILIP A. GOTTLIEB & FREDERICK SACHS

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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GENOMICS

Gorilla gorilla gorilla

The gorilla genome reveals that genetic similarities among humans and the apes are more complex than expected, and allows a fresh assessment of the evolutionary mechanisms that led to the primate species seen today. SEE ARTICLE P.169

RICHARD A. GIBBS & JEFFREY ROGERS

Humans and the apes are the living representatives of the superfamily Hominoidea, which also contains many extinct species. Deciphering the evolutionary relationships between these species is an essential step in our understanding of the biological richness of the planet, and of our own evolutionary history. The draft assembly of the whole-genome sequence of a female western lowland gorilla (*Gorilla gorilla gorilla*) named Kamilah (Fig. 1), presented by Scally *et al.*[1] on page 169 of this issue, provides insight into how a single hominid lineage separated into the extant human, chimpanzee and gorilla branches.

The authors' genome assembly, made possible by the advent of cheaper next-generation sequencing methods, is a much-anticipated addition to more than five-year-old Sanger sequence data on the gorilla genome. The latest assembly, like other contemporary mammalian genome data sets (except for human and mouse), has some gaps and shortcomings. Yet it is revelatory. The standard view of the primate evolutionary tree is that chimpanzees and humans share a more recent common ancestor with each other than either shares with gorillas. Accordingly, the most closely related sequence for any human gene should be found in the chimpanzee. However, Scally and colleagues' demonstrate that, although this is true for most genes, large fractions of the ape genomes contradict this simple pattern.

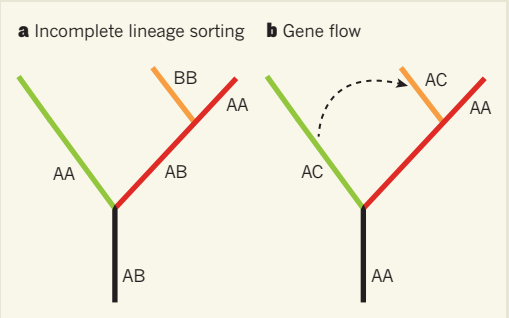
Molecular phylogenetics uses comparative analyses of DNA sequences to determine relatedness among species. Usually, a single individual of each species is sequenced, so genetic diversity within a species is overlooked. When the time between successive evolutionary branch points, or speciation events, is relatively long, the between-species genetic differences that accumulate after a single lineage divides into two descendent branches will stand out against the background of within-species variation. But if two or more evolutionary divergence events occur close together in time, the genetic variation present in the last common ancestor may be sorted randomly into the descendent lineages. In this model, different segments of a genome may have different phylogenetic relationships. This process, which leads to conflicting evolutionary trees for different genes, is called incomplete lineage sorting (ILS; Box 1).

Previous molecular-genetic studies[2,3] of humans, chimpanzees and gorillas show that the three lineages separated over a relatively short period of time, creating the opportunity for ILS. Scally and colleagues' whole-genome study verifies and substantially extends this analysis. They found that for 70% of the genomes of the three species, the chimpanzee sequences are more similar to the corresponding sequences in humans than to those in the gorilla, as expected. But for the remaining 30% of the genome, gorilla sequences share closer similarity with either human or chimpanzee sequences than these two share with each other. The authors also observed these ILS patterns reflected in relative levels of gene expression in the three species.

Other factors, such as gene flow between species after their initial divergence (Box 1), may also have contributed to these surprising relationships. There is evidence[4] for such gene flow between Neanderthals and the lineage that ultimately produced modern humans, and between morphologically differentiated non-human primate groups that

BOX 1

How incongruities in phylogenetic trees can arise



Scally and colleagues[1] found that in 30% of the western-lowland-gorilla genome, the DNA sequences are more similar to the corresponding sequences from the human or chimpanzee genomes than the sequences of these two species are to each other — although humans and chimpanzees are expected to have shared a more recent common ancestor with each other than either does with gorillas. Such inconsistencies between evolutionary relationships can result from various processes. **a**, One possible mechanism is incomplete lineage sorting. In this process, an ancestral species (black) divides into two descendent genetic lineages (green and red) and, soon after, one of those descendent lineages divides again (red and orange). The red and orange lineages are expected to be more genetically similar to one another than either is to the green lineage. However, if the ancestral species contained a gene with two alternative sequence variants (AB), either or both variants may be transmitted into the descendants. Over time, the descendent species will lose one of the two gene variants. Here, incomplete lineage sorting has resulted in the red species being more genetically similar to the green species (both AA) than to the orange species (BB) at this particular gene. **b**, Gene flow is another mechanism by which relationships between specific DNA sequences can fail to match the larger relationships between species. In this case, a newly evolved gene variant (C) is transferred from one genetic lineage to another by interbreeding that occurs after evolutionary separation has begun, but before complete genetic isolation is achieved. **R.A.G. & J.R.**