Neurosensory mechanotransduction

Martin Chalfie

Abstract | Neurons that sense touch, sound and acceleration respond rapidly to specific mechanical signals. The proteins that transduce these signals and underlie these senses, however, are mostly unknown. Research over the past decade has suggested that members of three families of channel proteins are candidate transduction molecules. Current studies are directed towards characterizing these candidates, determining how they are mechanically gated and discovering new molecules that are involved in mechanical sensing.

Spheroplast
A preparation of bacterial membrane that can be recorded electrophysiologically. Spheroplasts are produced by using a bacterial strain that conditionally does not allow cell division, thus allowing the formation of large membrane structures.

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Organisms sense a wide range of signals in their internal and external environments. These signals, whether radiant energy, chemical entities or physical forces, need to be converted or transduced into signals that can be used by the organism. The transduced signal can be electrical, such as the depolarization or hyperpolarization of the plasma membrane, can be chemical, as in the production of a second messenger, or can be transcriptional, as in the activation of gene expression by steroid hormones. One of the main challenges in the study of sensory systems is to discover the nature of the transduction process. The light-transducing molecule rhodopsin has been known for 130 years and olfactory receptors were discovered 17 years ago[1], but molecules that transduce physical forces have been more difficult to identify.

All cells interact physically with their surroundings, and can do so on various timescales. Animals and plants, for example, respond to touch, and all cells respond to changes in osmolarity. The growth and organization of tissues is regulated by physical contact between cells. Indeed, cancer can be thought of as a disease in which the physical regulation of cell growth has been removed.

Rather than discussing all of the physical signals that cells can react to (reviewed in REF. 2), I summarize the progress that has been made towards discovering the transducing molecules, particularly channel proteins, in mechanosensory cells. These are specialized cells in the nervous system of animals that have evolved to respond to physical forces (FIG. 1). In mammals, mechanosensory cells include those that respond to touch, sound, acceleration, muscle and tendon stretch and to changes in blood pressure. These mammalian cells have diverse structures but they share one feature: the nature of their transduction molecules is unknown (BOX 1).

The quest for neurosensory molecules

One of the most influential observations in the field of mechanosensation is that neurosensory transduction is extremely rapid. This observation was first made by Corey and Hudspeth[3] using hair cells from the bullfrog sacculus. They found that movement of the hair bundle produced an electrical response within 40 μs. Because this rate was faster than that seen for light-stimulated channel closing in the vertebrate retina (of the order of tens of milliseconds), which involves a chemical intermediate, they suggested that transduction might be too rapid to involve a chemical intermediate (unless its action was needed in its immediate vicinity) and that the electrical response must result from the direct gating of a transduction channel. Similar submillisecond responses that were recorded from *Drosophila melanogaster* bristle mechanoreceptors[4], *Caenorhabditis elegans* touch receptor neurons[5] and *D. melanogaster* chordotonal hearing receptors[6] led to the same conclusion. These observations have focused the search for transduction molecules to the identification of putative transduction channels that, perhaps by association with other proteins, are directly gated by mechanical force.

Several different strategies have been used to identify channels and other components that transduce mechanical force. Investigators have directly assayed for mechanically gated channels. For bacteria, the observation that membrane stretch of spheroplasts could open a channel[7] provided an assay that led to the discovery of the bacterial mechanosensitive channel of large conductance (MscL)[8]. Other channels, particularly certain classes of K^+ channels (see below) that were not previously suspected of being gated by mechanical forces, were shown to be regulated by membrane stretch when expressed in heterologous cells. Unfortunately, applying force to membranes seems to activate a small number of channels; several candidate transduction channels are

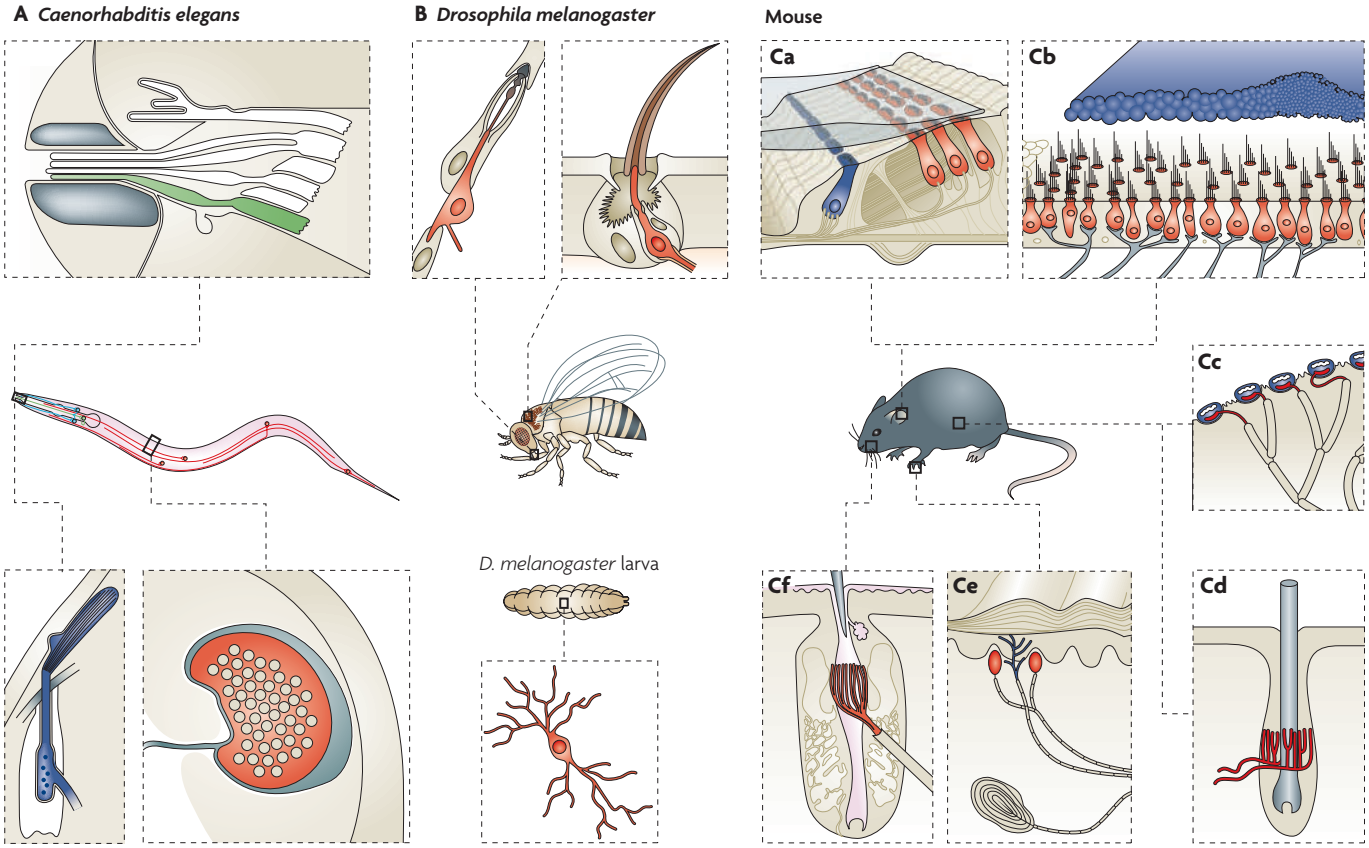

Figure 1 | **A gallery of mechanosensitive cells. A** | The touch receptor neurons (red), the ciliated ASH neurons (green) and the CEP neurons (blue) of *Caenorhabditis elegans*. Enlargements show (clockwise from the top): the ciliated ending of an ASH cell in the amphid at the nose of the animal, a cross-section of an ALM receptor for gentle touch showing its prominent bundle of microtubules and extracellular matrix (dark grey), and the ciliated ending of a CEP neuron and its association with the cuticle (grey). **B** | The chordotonal organ (top left panel), the external bristle (top right panel) and a multidendritic cell (bottom panel) of *Drosophila melanogaster*. The sensory neuron is shown in red. **C** | The inner (red) and outer (blue) hair cells of the auditory system, in the organ of Corti (**Ca**) and in the sacculus (**Cb**); the hair cells of the vestibular apparatus (**Cc**) and various cells and sensory organs in the skin (Merkel cells (blue) and Merkel disks (red); the palisade endings (**Cd**); the Meissner-like corpuscles, the Pacinian-like corpuscles and intraepidermal endings (**Ce**); and lanceolatae endings in mammals (**Cf**). Figure is modified, with permission, from REF. 100 © (2002) Annual Reviews.

not activated by membrane stretch when expressed in heterologous cells.

Researchers have also used genetic screens to identify mutants that are defective in mechanosensation. By cloning the affected genes, one can identify proteins that are essential for the process. Genetic screening was first used to identify touch-insensitive mutants in *C. elegans*[9–11], but has subsequently been used to find mutants that are defective in nose touch in *C. elegans*[12], bristle mechanosensation and hearing in *D. melanogaster*[13,14], hearing and lateral line mechanosensation in zebrafish[15,16] and hearing in mice[17,18]. In addition, numerous inherited human conditions that give rise to deafness have also been studied (see REF. 19 and the Review by Jaalouk and Lammerding[101] in this issue). Although the genetic approach has proven useful, it has various limitations (BOX 2). Investigators have also studied homologues of proteins that were identified by the other methods, but this approach has had variable success (see below).

Putative mechanosensory channels

These various efforts have identified three classes of channel proteins. These proteins are currently being considered to be candidate mechanosensory transduction molecules in animals: DEG/ENaC (degenerin (also known as ACCN1)/epithelial Na^+ channel (ENaC; also known as SCNN1)) subunits, transient receptor potential (TRP) proteins and two-pore-domain K^+ channel (K_{2P}; also known as KCNK) subunits.

DEG/ENaC channels in mechanosensation. The DEG/ENaC proteins are membrane proteins that have two transmembrane domains that are coupled by a large extracellular domain. The crystallographic structure of the channel that is formed by one member of the family (the chicken acid-sensing ion channel 1 (ASIC1)) has recently been determined[20]. Evidence that these proteins form channels (FIG. 2) that are involved in mechanosensation comes from work on the receptors for gentle touch in *C. elegans*. Two genes that encode DEG/ENaC

Box 1 | **The difficulties of identifying mehanosensory transduction molecules**

Several difficulties have impeded the search for the transducing molecules that are involved in neurosensory mechanotransduction. First, the sensory cells or their receptor endings are sparse (the dispersed touch receptors in skin or the 15,000 or so hair cells in the cochlea). The rarity of the cells makes the collection of suitable numbers for biochemical studies (as was done for rod cells in the retina) difficult. Second, estimates of the number of transducing molecules suggest that they are low. For example, each vertebrate hair cell is thought to have approximately 50–100 copies of each transduction channel complex[88,94,95]. Third, and perhaps most importantly, assaying the function of candidate transduction molecules in heterologous systems can be difficult. The assay is not a problem when the molecules (most of which are currently thought to be membrane channels) can be gated by changes in physical force in the lipid bilayer, such as by changing osmotic pressure or by manipulating the membrane physically. Such manipulation has been used to identify and characterize channels that are needed to respond to changes in osmolarity in bacteria[8,82]. Unfortunately, such membrane manipulation does not activate many eukaryotic channels that are candidate mechanosensory receptors. Either these molecules are false candidates, they transduce forces that are not applied to the membrane or they require other proteins to function.

proteins — mechanosensory abnormality 4 (*mec-4*) (REF. 21) and *mec-10* (REF. 22) — are expressed in the touch receptor neurons and can be mutated to produce touch-insensitive animals[10]. Loss of *mec-4* activity abolishes the mechanosensory current that is recorded from *C. elegans* touch receptor neurons both when the animal is touched and when the touch is removed[5]. This result shows that MEC-4 is essential for this dual-directional touch sensitivity, but it does not indicate that MEC-4 is the transduction molecule (BOX 1). Analysis of unusual alleles of *mec-4* and *mec-10*, however, supported the hypothesis that MEC-4 and MEC-10 are part of the transduction apparatus[5]. These alleles — which have altered equivalent amino acids near the pore-forming part of the molecule — cause touch insensitivity by changing the ion selectivity of the mechanosensory current (making it less sodium selective), instead of abolishing the current entirely. This selective change of the transduction response and the rapidity of the response (see above) strongly suggest that these proteins transduce touch.

The MEC-4 and MEC-10 proteins are not the only components of the transduction apparatus. Two other membrane proteins colocalize and interact with MEC-4 and MEC-10 and are crucial for touch sensitivity. These proteins are the prohibitin-domain protein MEC-2 (REFS 23,24) and the paraoxonase-like protein MEC-6 (REF. 25). Both proteins greatly increase channel activity (by 30–45-fold), when co-expressed with an activated version of MEC-4 in *Xenopus laevis* oocytes, without affecting the amount of protein that is localized to the surface of the oocyte. Recent observations of single channel patches from *X. laevis* oocytes[26] showed that the addition of these proteins did not change the properties of the activated channels. The increase of activity, therefore, probably derives from an increase in the number of functional (that is, open) channels that are present in the patch.

These results and studies of MEC-2, MEC-6 or similar proteins support the hypothesis that MEC-2 and MEC-6 are needed for channel function because they affect the lipid environment of the channels. MEC-2 and podocin, a similar protein from the mammalian kidney, bind to cholesterol[27]. Cholesterol is needed for *C. elegans* touch sensitivity, and a mutation that lowers MEC-2 binding to cholesterol makes animals more insensitive to touch when cholesterol levels are reduced[27]. The MEC-6-like proteins in humans, paraoxonase 1 and paraoxonase 3, are thought to regulate cholesterol oxidation in high-density lipoprotein (HDL) particles[28]. These observations suggest that the regulation of the lipid environment, particularly the use of cholesterol, is important for the function of the *C. elegans* transduction complex.

Although DEG/ENaC channels transduce mechanical signals in *C. elegans*, their role in mechanical signalling in other organisms is unclear. Two homologues in *D. melanogaster*, Pickpocket and Ripped Pocket, which were identified mainly because of their similarity to the *C. elegans* proteins[29,30], might be potential mechanoreceptors, but this has not been supported by subsequent research[31,32]. In mammals, the situation is equally as uncertain. Several mechanosensory cells in the skin express different DEG/ENaC proteins (αENaC, βENaC, γENaC, ASIC2 and ASIC3)[33–37]. The loss in mice of either ASIC2, ASIC3 or both proteins, however, did not induce touch defects[38], or alternatively produced modest defects[35,36]. Loss of ASIC proteins also produced modest effects on gastrointestinal mechanosensitivity[39]. The problem in these experiments is that if the channels are heteromeric, loss of any one protein might alter but not abolish the response. Acid-sensing by ASIC1A, ASIC2A and ASIC3 (REF. 40) and Na^+ flux through the ENaC channels[41] depend on the subunit composition.

Recent experiments in mice have suggested that mutations in two different *mec-2*-like genes reduce touch reception[42,43]. These results cannot be taken as an indication that their protein products are part of a DEG/ENaC complex, as is found in *C. elegans*, because the mammalian MEC-2-like protein podocin can bind and regulate the activity of TRPC6 channels[27].

TRP channels in mechanosensation. The TRP family of channel proteins were named for the *D. melanogaster* gene, the product of which was the first known member of the family[44]. The TRP channels seem to mediate many forms of sensory perception, including mechanosensation[45,46]. The finding that many TRP channels are needed for or influence mechanosensory processes (see below) hints that these channels might act as transducers, but direct evidence has been lacking.

Prohibitin domain
(PHB domain). A 150 amino-acid sequence that is found in several proteins in prokayotes and eukaryotes. Human PHB proteins include prohibitin, stomatin and podocin. The PHB domain in *C. elegans* MEC-2 and mouse podocin allows the binding of cholesterol.

Paraoxonase
A family of proteins in humans, two of which are associated with high-density lipoprotein particles and another is localized to the plasma membrane in a wide range of cells. A similar protein, MEC-6, is needed for touch sensitivity in *C. elegans*.

Chordotonal organ
The mechanosensory structure that is used in insects for mechanosensation and hearing.

Proprioception
The sense of body position and movement.

The first indication that these proteins might have a role in mechanosensory transduction came from studies of the TRP gene *osm-9* in *C. elegans*[47]. These studies showed that *osm-9* was needed not only for nose touch but also for olfaction. Because *osm-9* is needed for several sensory modalities, its role in mechanosensation — whether as a transduction molecule or as a modulator molecule — is unclear.

More direct involvement of a TRP channel in mechanosensation came from the study of the *no mechanoreceptor potential C* (*nompC*) gene in *D. melanogaster*[4,13]. A putative null mutation of this gene leads to the loss of the receptor potential peak that follows stimulation of the bristle mechanosensors. However, a small (10% of the potential peak) current occurs when the mutant bristles are stimulated, so the role of NOMPC as the transducer molecule is unclear. NOMPC is also needed for the chordotonal organs in Johnston's organ, the *D. melanogaster* ear, but its loss does not eliminate sound-induced receptor potentials[48]. Because NOMPC is needed for the mechanically induced amplification that is exhibited by the Johnston's organ — a process that is thought to involve transduction — Göpfert *et al.*[49] have argued that NOMPC is needed, at least in part, for transduction in fly hearing. The authors further postulated that a second, unknown transduction channel is also involved.

NompC-like genes are found in *C. elegans*[4] and zebrafish[50]. In *C. elegans*, some cells that express the *nompC*-like gene (such as the CEP neurons in FIG. 1) respond to the mechanical presence of bacteria or small beads (that is, they seem to respond to texture[51]); other *nompC*-like gene-expressing neurons seem to be needed for proprioception[52]. Mutation of the *C. elegans* gene abolishes proprioception[52]; the animals have not been tested directly for the texture response. In zebrafish, reduction of the *nompC* (also known as *trpn1*) gene using morpholino oligonucleotides causes deafness, a circling behaviour that is indicative of the loss of the vestibular sense, and a loss of microphonic potentials that result from mechanical stimulation of the lateral line hair cells. Together, these data suggest an evolutionarily conserved (but undefined) role for the NOMPC channels in mechanosensation. Curiously, similar proteins have not been found in mammals[50,53].

Several other TRP channels have been implicated in various forms of mechanosensation. The *D. melanogaster* TRPV genes *nanchung* and *inactive* are needed for hearing and for the electrical response of chordotonal neurons in the Johnston's organ[54,55]. Both protein products are needed for their localization to the cilia of chordotonal neurons, and both are activated by hypo-osmotic shock when heterologously expressed in Chinese hamster ovary cells. Göpfert *et al.*[49] have argued that these channels are not hearing tranduction channels, although they might still be mechanically gated[56]. In *C. elegans*, the TRPV proteins OSM-9 and OCR-2 are required for osmosensation, mechanosensation and chemosensation, and, as with the *D. melanogaster* proteins, they are mutually required for their localization to cilia[47,57]. Osmolarity regulation has also been suggested for mammalian TRPV genes[58]. The TRPA *painless* gene in *D. melanogaster* is needed for the response to both harsh touch and a heated probe[59]. Further support for a role of TRP channels in mechanical responses comes from work in yeast that shows that the TRP-like protein TRPY1 (also known as YVC1) is needed for the vacuolar response to increased osmolarity, and also shows that patches from the vacuoles that contain TRPY1 channels can be gated by applied pressure[60].

Other TRP channels were initially thought to be involved in mechanosensation, but subsequent research has questioned this. Corey *et al.*[61] suggested that the mammalian TRPA1 might be the long-sought hair cell transduction channel, but this group and others subsequently found that transgenic mice that lack this channel are not deaf[62,63]. The role of TRPA1 in mediating noxious touch is unclear. One group found a reduction in this response in transgenic mice[63], but another group did not[62]. Reduction of TRPA1 using morpholino oligonucleotides in zebrafish also reduced hair cell activity[61], but a recent study that examined knockout mutants found no reduction in hair cell function[64].

The suggestion that TRPC1 (REF. 65) forms a stretch-activated channel has also been recently challenged[66]. It was found that the heterologous expression systems that were used in the original study had variable, intrinsic stretch-activated currents, so that the activity in TRPC1-transfected cells could not be distinguished from control cells. This study also questioned whether TRPC6 forms a stretch-activated channel, as previously suggested[67]. However, their case is not as strong, because they tested heterologous expression in a different cell line. The TRPC6 channel has also been proposed as a mechanically gated channel in the kidney[27].

Box 2 | Limitations of genetics to identify mechanosensory molecules

Genetic screens for mutants that have lost mechanosensory function can identify candidate genes that are essential for mechanosensation, but such screens can simultaneously be both too broad and too restrictive. Screens can be overly broad because mutations might affect transduction indirectly, therefore interfering with processes that are upstream (such as the production or differentiation of the sensory cell) or downstream (such as the amplification of the transduced signal) of transduction. A selective downstream effect was found for the *glr-1* gene, which encodes a glutamate receptor, in *Caenorhabditis elegans*[12]. The *C. elegans* ASH neurons sense touch to the nose and several other sensory signals, but *glr-1* is only needed for nose touch. Insensitivity, however, is due to loss of *glr-1* in postsynaptic but not ASH neurons. Conversely, a gene that has a developmental role might also have a direct effect. For example, extracellular matrix proteins organize the mechanosensory transduction complex in *C. elegans* touch receptor neurons, but might also be needed for transduction[72].

Genetic schemes are often too restrictive because they can miss pleiotropically or redundantly acting genes, which leads to either general effects or no obvious mutant phenotype, respectively. The difficulty of identifying transducers of mechanical stimuli in vertebrates might be due to these problems. In addition, attempts to obtain mutants with defects in mechanosensation usually look for the loss of sensation. Screens for mutants with enhanced sensitivity are more difficult. Screens for suppressor mutations could potentially identify mutations that increase touch sensitivity, but these have been done rarely (for example, REF. 91).

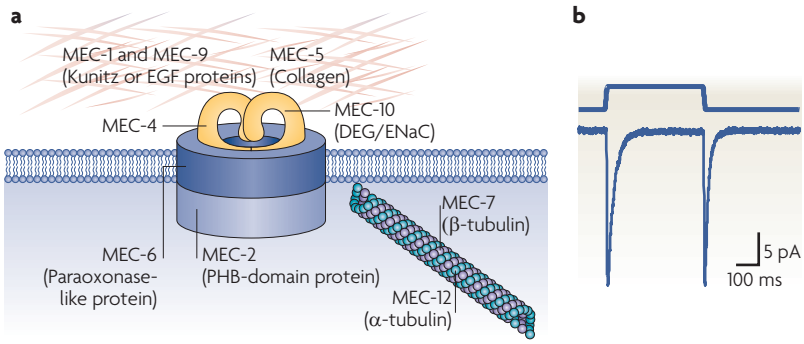

Figure 2 | **Gentle touch in *Caenorhabditis elegans*. a** | Proteins that are needed in the touch receptor neurons. The extracellular proteins mechanosensory abnormality 1 (MEC-1) and MEC-9 (which have multiple epidermal growth factor (EGF) and Kunitz domains) and MEC-5 (collagen in mammals) might associate with the DEG/ENaC (degenerin (also known as ACCN1)/epithelial Na^+ channel (ENaC; also known as SCNN1)) complex, which consists of MEC-2, MEC-4, MEC-6 and MEC-10. The specialized microtubules with MEC-7 and MEC-12 tubulins are needed for touch sensitivity, but probably do not associate with the channel complex. **b** | Electrophysiological response of a PLM touch receptor neuron. Force (top trace) elicits an inward current (bottom trace) that rapidly adapts when the animal is touched and when the touch is removed. PHB, prohibitin domain. Image in part **a** is modified, with permission, from REF. 92 © (2007) Springer. Image in part **b** is modified, with permission, from *Nature Neuroscience* REF. 5 © (2005) Macmillan Publishers Ltd. All rights reserved.

K^+ channels in mechanosensation. Several types of K^+ channels can be gated by mechanical force, but their involvement in perception has not been shown. Gu *et al.*[68] found that the *D. melanogaster* Shaker protein (with its amino-terminal regulation domain removed) could be activated and inactivated by membrane stretch when expressed in *X. laevis* oocytes. Patel, Honoré and co-workers found that three types of K_{2P} channels, the TREK1 (also known as KCNK2), TREK2 (also known as KCNK10) and TRAAK channels, are mechanically gated (reviewed in REF. 69). In the past, these channels were thought to contribute to the negative resting membrane potential of cells. However, the discovery that these channels can be stretch activated invites speculation that they function in mechanosensory perception. A *Trek1*-knockout mouse has an intriguing touch sensitivity phenotype: these animals are more, not less, sensitive to gentle touch[70]. Alloui *et al.*[70] suggest that TREK1 could counter an unidentified transduction channel that depolarizes skin sensory cells. If such dual channel responses to touch are common, then the K_{2P} channels might have an important and previously unrecognized role in mechanosensory signalling. Whether these channels are part of a larger signalling complex with the depolarizing channels or are needed independently for recovery from depolarization caused by the mechanical stimuli remains to be seen.

Cell structures and mechanosensation

The involvement of several different channel families in mechanosensory transduction is, perhaps, not surprising given the large range of cell shapes and structures that seem to transduce mechanical signals (FIG. 1). In particular, the cells differ with regard to distinct cytoskeletal elements and extracellular components. Because of the uniqueness of many of these structures, investigators have puzzled over their roles in mechanosensation.

Many cells have distinctive cytoskeletal arrays. Some animal cells have ciliated endings (for example, the bristle and chordotonal neurons of insects and the ASH nose touch neurons of *C. elegans*). Other cells, such as the hair cells in the vertebrate vestibular and auditory systems, have prominent actin-containing stereocilia in addition to the ciliated kinocilium. Further cells, such as the neurons that detect gentle touch in *C. elegans* and other nematodes, have prominent bundles of large-diameter microtubules. Finally, the cells that respond to body touch in insects and in the skin of vertebrates have processes that branch extensively but do not have specialized cytoskeletal structures.

The role of the cytoskeleton has been investigated by disrupting it through genetic or chemical manipulation. For example, mutation of the α-tubulin gene *mec-12* or the β-tubulin gene *mec-7* results in the elimination of the large-diameter microtubules of *C. elegans* touch receptor neurons[10]. Because the resulting cells have the smaller-diameter microtubules that are found in other *C. elegans* neurons, they grow and appear to be grossly normal, but animals are touch insensitive. Electrophysiological examination of the cells, however, has shown that a small mechanosensory current remains in touch neurons that lack *mec-7* activity[5]. This result suggests that the specialized microtubules are important but not essential for mechanosensory transduction. Mutations that eliminate cilia or affect cilia-mediated transport also eliminate mechanosensory function in *C. elegans*[71] and *D. melanogaster* bristles (reviewed in REF. 56).

The problem with these experiments is that because the cytoskeleton is involved in so many cellular functions,

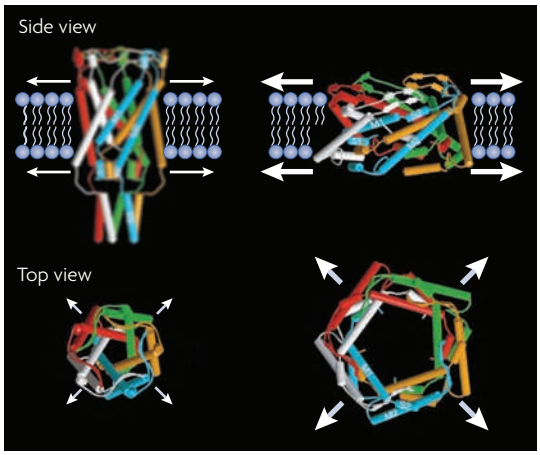

Figure 3 | **Mechanosensory transduction in bacteria.** Bacterial channels, such as the mechanosensitive channel of large conductance (MscL), are gated through forces in the lipid bilayer. As the bacterium swells, changing forces in the membrane rearrange the channel from a closed to an open configuration. Figure is reproduced, with permission, from *Nature* REF. 81 © (2005) Macmillan Publishers Ltd. All rights reserved.

Stereocilium
An actin-containing projection in a vertebrate hair cell.

Kinocilium
The single projection in each vertebrate hair cell that contains a microtubule axoneme.

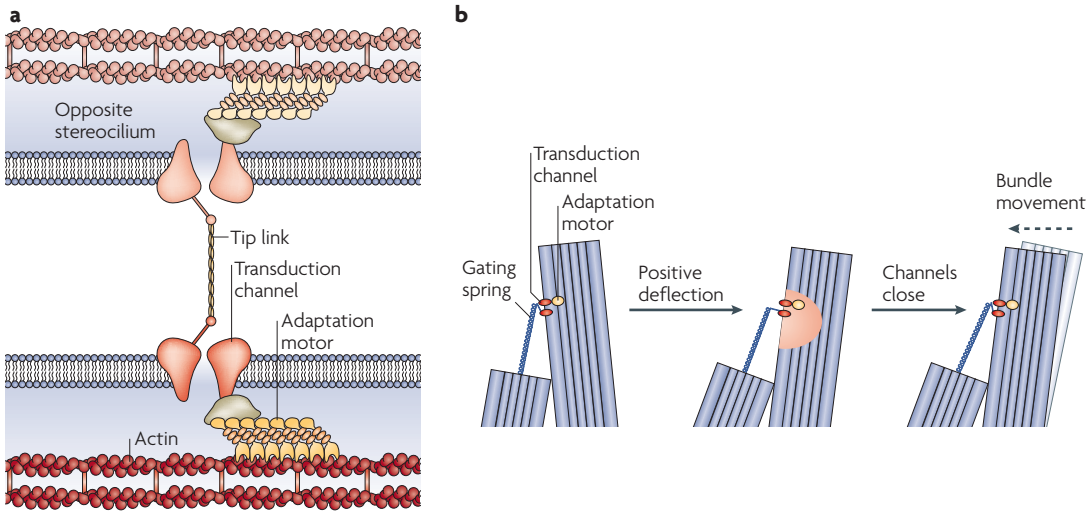

Figure 4 | **Dual-tether model. a** | Channels in adjacent stereocilia of auditory and vestibular hair cells are thought to be tethered to extracellular tip links and to the intracellular actin cytoskeleton through the adaptation motor. The directional response of the cells is consistent with a dual-tethered model. **b** | Transduction and fast adaptation in stereocilia. Positive deflection (left to middle panel) opens the channel, allowing Ca^{2+} entry (pink). Channel closure (right panel) leads to bundle movement in the opposite direction. Images in parts **a** and **b** are modified, with permission, from *Nature* REF. 86 © (2001) Macmillan Publishers Ltd. All rights reserved.

a direct role in sensory transduction is hard to distinguish from other functions. As with the channels, loss of cytoskeleton could have direct and indirect roles in mechanosensation, even for specialized structures. For example, loss of expression of the *mec-7* and *mec-12* tubulin genes in *C. elegans* affects the distribution but not the production of mechanosensory puncta[72,73]. These defects could cause the touch insensitivity that is found in *mec-7* and *mec-12* mutants. However, late disruption of the microtubules does not cause these defects, but does result in touch insensitivity in adults (A. Bounoutas and M.C., unpublished observations). This suggests that touch sensitivity requires the specialized microtubules, but given the residual mechanosensory current that is seen in *mec-7* mutants[5], their role is unclear.

Mechanosensory cells often have specialized extracellular components that are required for their function. Tip links, the thin extracellular strands that connect the tips of stereocilia to the upper shaft of adjacent stereocilia in auditory hair cells[74], are prominent examples. Two proteins have been found to be important components of the tip links — cadherin 23 and protocadherin 15 (REFS 75–78). Loss of these proteins in mice and humans leads to disorganized stereocilia and hearing loss. Attachment to extracellular structures is also important for insect bristle mechanoreceptors[79] and for *C. elegans* touch receptor neurons[72,80].

A major question that remains unanswered for most sensory systems is the role that these specialized structures have in transduction. Are they needed for the organization of the transduction apparatus or are they integrally required for the transduction? Distinctly different models for transduction have evolved based on whether extracellular and intracellular interactions are needed for mechanosensory perception.

Potential gating mechanisms

Considerable debate exists regarding the nature of the gating process in mechanical systems, and several types of models have been proposed for how force opens mechanosensory transduction channels (FIGS 3–5). The main question is whether force is conveyed through the lipid bilayer or by associated structures. Three models have been proposed for the gating of mechanosensory channels. First, changes in forces in the lipid bilayer affect channel conformation (and no other proteins are needed); second, stretching between tethered intracellular and extracellular structures opens the channels (membrane forces do not have a role); and third, movement of a single tether to the channel alters the interaction of the channel with the membrane and the forces within it, thereby opening the channel. The second and third models predict that extracellular and/or cytoplasmic tethers transmit the stimulus force to the channels.

The membrane force model. The simplest model, which involves only membrane forces, derives from studies of the MscL and MscS mechanosensitive channels of bacteria (reviewed in REF. 81). These channels were the first mechanosensitive channels to be identified. Each channel is formed from multimers of single membrane proteins, and when both are eliminated in *Escherichia coli*, the bacteria fail to adapt to osmotic stress[82]. Only the forces in the membrane and no other proteins are required to gate these channels (FIG. 3). The exact nature of the gating is still under study. Two recent papers[83,84] suggest that stretching the membrane causes the MscS channel to open because its membrane helices tilt. Because membrane stretch opens Shaker and the K_{2P} channels, these channels might be regulated in an analogous fashion, as might the recently discovered MscS-like channels in plants (BOX 3).

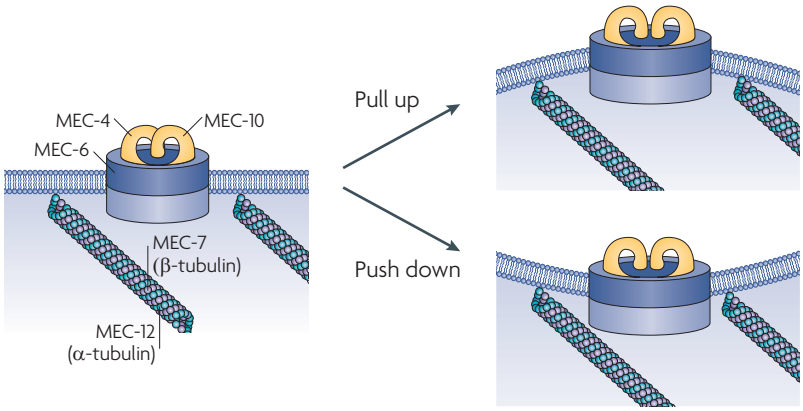

Figure 5 | **Single-tether model.** Based on the concepts of Kung[81], we have suggested a single-tether model for the mechanosensory abnormality 4 (MEC-4) channel, which is needed for gentle touch in *Caenorhabditis elegans*[92]. Movement of the channel through its connection to extracellular matrix proteins will change the interaction with the membrane, thereby leading to the opening of the channel. Such a model explains how the channel can be opened by both the application and the removal of touch. Figure is reproduced, with permission, from REF. 92 © (2007) Springer.

Dual-tether model. As discussed above, most mechanosensing cells in animals have specialized structures that seem to be important for sensory function. These structures might have a direct role in transduction. This would predict gating through the tethering of these structures to the transduction channel, which usually involves both intracellular and extracellular tethers[85,86]. The first such dual-tether model was proposed for vertebrate hair cell transduction. In this model, the hypothetical transduction channel is tethered to the extracellular tip links that connect the stereocilia and to the actin filaments of the internal cytoskeleton (for example, see REF. 86) (FIG. 4). Bending the stereocilia stretches the channel between these two tethering points and effectively opens the channel like a trap door. Forces in the membrane are not needed to open the channel. One consequence of this model is that transduction is unidirectional: only movement of the stereocilia in the direction that stretches the tethered connections will open the channels.

This model derives from electrophysiological experiments that suggest that the channel is a gated spring, the opening of which can be modulated[87]. This suggestion comes from electron microscopy observations of filamentous strands (tip links) that join the stereocilia of the hair cells[74] and from calcium imaging experiments, which suggest that transduction leads to calcium entry at the tips of the stereocilia[88]. This dual tether model is attractive because it accounts for the anatomy of the hair cells, the directionality of the response to bundle displacement[89] and the finding that loss of tip links by chelation of calcium[90] or by mutation of genes for tip-link proteins (see above) abolishes transduction. Because the hair cell transduction channel has not been identified, however, this model remains an intriguing speculation.

Recent evidence suggests that chordotonal organs transduce sound through a gating-spring mechanism[6], so these cells might use a dual-tether mechanism. A dual-tether model was proposed to explain the transduction that involves *C. elegans* touch receptor neurons[91], but recent results suggest that this model is unfavourable (see above).

Single-tether model. In an incisive review, Kung[81] suggested that both membrane forces and tethering contribute to channel gating. In this model, movement relative to the membrane is important for the gating. Manipulation of a single tether repositions the channel vis-à-vis the membrane, thereby resulting in a change of forces that gate the channel in a similar way to that of the bacterial channels.

The difference between the membrane force model and this single-tether model is that in the first, changes in forces in the membrane (produced by the swelling of the cell) influence channel opening, whereas in the second, the repositioning of the channel puts it under different forces in the membrane. One of the consequences of this model is that moving the channel into or out of the plane of the membrane would open the channel. As such, this model would allow for the dual directional signalling that is seen, for example, in the *C. elegans* touch receptor neurons. We have proposed such a model for these cells with the association of the extracellular matrix proteins as the single tether[92] (FIG. 5). Testing this type of model by reconstitution would be difficult, however, because it posits connections of the channel with tethering proteins, and the tether would need to be reconstructed. This difficulty might explain why some putative channels cannot be mechanically gated *in vitro*.

Box 3 | **MscS-like channels in plants**

Given the deep understanding that has been gained for the bacterial channels, the finding that eukaryotes lack mechanosensitive channel of large conductance (MscL)-like channels is disappointing. Animals also seem to lack MscS-like channels, but these channels have homologues in plants[82,96]. Research in *Arabidopsis thaliana*[97,98] and *Chlamydomonas reinhardtii*[99] has shown that these channels can be gated mechanically. Unfortunately, mutation of the genes for these proteins does not result in detectable mechanosensitive phenotypes. For example, mutation of the five MscS-like genes that are expressed in *A. thaliana* roots eliminated mechanosensitive currents in protoplasts, but resulted in plants that were indistinguishable from wild type[98]. Two other *A. thaliana* genes could rescue the bacterial genes, so had retained mechanosensitive properties[97], a result that suggests they are gated in a similar way to the bacterial homologues. A mechanosensory role for these genes, however, has not been identified.

Conclusions and future directions

Depending on one's point of view, the problem of mechanosensation in animals is either exciting or vexing. Most candidate channels are either channels that are needed for mechanical signalling that have not been shown to be mechanically gated, or are mechanically gated channels with no connection to mechanosensation. The strongest candidate in animals is the MEC-4 channel complex in *C. elegans*, but the TREK1 channel in mammals (albeit in the novel role of modulating the mechanosensory response) and the TRP channels remain appealing candidates. Future work in the field will undoubtedly be directed towards proving that

Connexin
A gap junction and hemijunction protein that is found in vertebrates.

Pannexin
A gap junction and hemijunction protein that is found in vertebrates and invertebrates. The invertebrate proteins were originally called innexins.

known candidates transduce mechanical signals. In part, this analysis will involve the expression *in vivo* of modified proteins that can potentially alter the transduction response.

Genetics has been an important tool in the discovery of candidate mechanoreceptors, and this identification has led to subsequent investigations of homologous proteins. Although considerable efforts have been undertaken to determine whether similar channels function as mechanotransducers, few of these candidates have been shown to be transduction molecules. The DEG/ENaC proteins provide a good example. Although MEC-4 has a proven mechanosensory activity, the functions of other DEG/ENaC proteins in mechanical sensing have been more difficult to demonstrate. One possible problem in studying the putative mechanosensory function of other members of a protein family is that genetic redundancy might be obscuring mechanosensory activity. In bacteria, for example, both MscL and MscS channels must be absent for an osmotic phenotype to be seen. The incomplete loss of the mechanosensory potentials in bristle receptors and a minor defect in hearing in *nompC* mutants in *D. melanogaster* also suggest redundancy. Furthermore, although touch-insensitive mutants have been found in *C. elegans*, *D. melanogaster* and zebrafish, to my knowledge an inherited condition in humans or mice that is characterized by a loss of touch insensitivity without the loss of sensory endings has not been identified. Mechanosignalling molecules in mammals might have been missed because multiple overlapping transduction complexes might sense touch and other mechanical senses. Further research on mouse strains in which multiple genes have been knocked out is needed in the future.

Given the present state of our knowledge of candidate mechanosensory channels and the diversity of cells that respond to mechanical stimuli, we are likely to find further transducing channels in the future. Some might come from the analysis of new channel families — perhaps, for example, the connexin or pannexin hemichannels. Other candidates will probably appear in new high-throughput genetic screens[64] or from the increased use of whole genome approaches from systems biology, such as genome-wide microarray analysis and RNA interference screens, applied to mechanosensory cells. For example, microarray analysis of overrepresented genes in the touch receptor neurons of *C. elegans*[93] identified a K_{2P} channel gene that is highly expressed in the cells (the function of which has not been tested).

Although considerable progress has been made over the past 10 years (from having no candidate transducers to having many), all of the major questions remain. We still need to identify the proteins that transduce mechanical signals in sensory neurons (particularly vertebrate hair cells), to determine whether they must be channels, to learn how transduction occurs and to understand how other cellular components, including the lipid environment, affect transduction. I am optimistic, however, that the next 10 years will bring us the answers to many of these questions.

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DATABASES
Entrez Gene: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene
mec-4 | *mec-10* | *nanchung* | *nompC* | *painless* | *trpn1*
UniProtKB: http://www.uniprot.org
ACCN1 | ASIC1 | ASIC2 | ASIC3 | MEC-2 | MEC-6 | OCR-2 | OSM-9 | paraoxonase 1 | paraoxonase 3 | SCNN1 | TRPA1 | TRPC1 | TRPC6 | YVC1

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