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TRP channels in mechanosensation

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Channels of the TRP superfamily have sensory roles in a wide variety of receptor cells, especially in mechanosensation. In some cases, the channels appear to be directly activated by mechanical force; in others, they appear to be downstream of a messenger pathway initiated by force on a non-channel sensor. A remaining challenge for most of these mechanosensory TRPs is to clarify the specific mechanism of activation.

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Introduction

Voltage-gated ion channels are wonderfully simple. Oh, some would argue that it has taken 60 years of hard work, recognized by three Nobel prizes, to unlock their secrets. But they are compact little machines, with one part of the protein instantly feeling the transmembrane potential and another part cocking slightly outward to open the pore. From Hodgkin and Huxley's embrace of a voltage clamp that conveys stimuli in microseconds, to electric eels that make gallons of channel protein, to convenient mutant flies, and to bacteria with representative homologs for crystallization, we have had, in Hans Bethe's wonderful phrase, an unfair advantage over voltage-gated channels.

By contrast, mechanically activated channels — those that are opened directly by mechanical force — have for the most part had an unfair advantage over us. With the notable and elegant exception of the bacterial MscL channel, the structure and gating of which are largely understood but that has no eukaryotic counterpart [1], we are largely ignorant both of the identity of mechanically activated channels and of how a force stimulus acts to open them. Although a number of candidate channels have now been identified, several fundamental issues (Figure 1) are only beginning to be addressed in each system. First, does a candidate channel carry the mechanically activated transduction current, or is it just required to create a favorable environment for transduction? Second, if the channel carries the current, is it directly activated by mechanical stimuli, or instead by a second messenger from another mechanically sensitive element? Third, is force delivered to the mechanically sensitive protein by structural proteins or — as for MscL — by membrane lipid tension? Fourth, does mechanical activation of a channel indicate a physiological role in mechanosensation, or does it reflect inappropriate activation in an experimental situation by forces that are never duplicated in nature?

Recently, channels of the transient receptor potential TRP superfamily have been recognized as participating in a variety of sensory systems, including mechanosensation [2]. Here, we review candidate mechanosensors among the TRP channels with regard to the issues raised above.

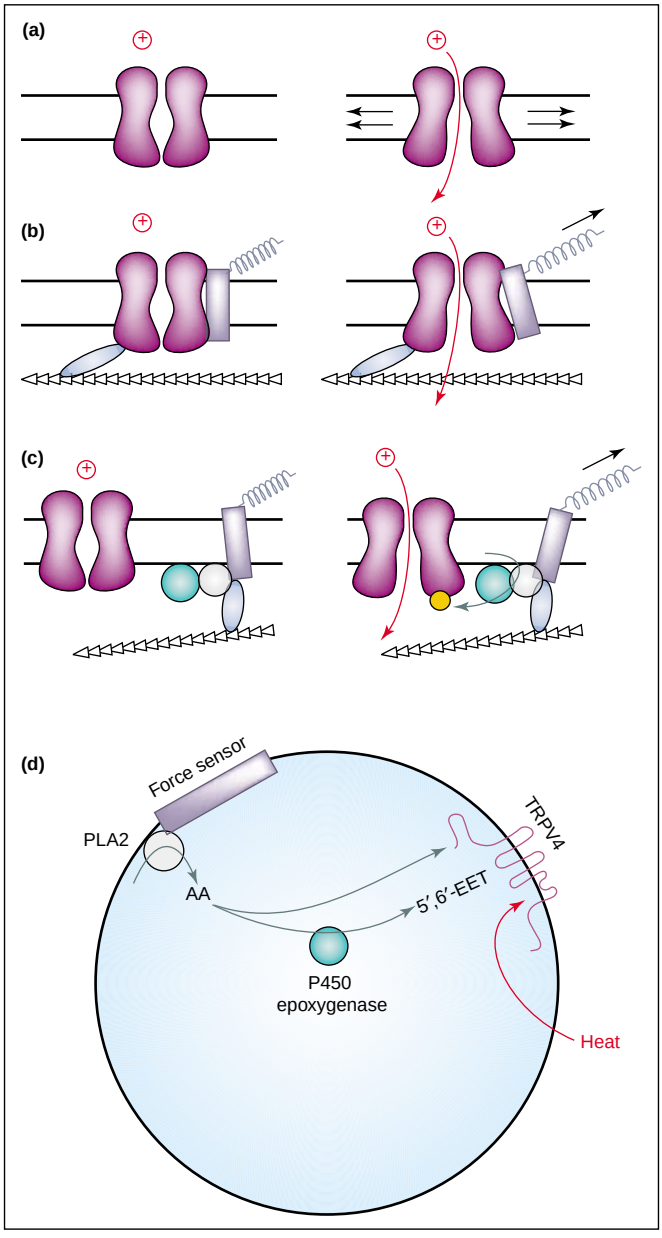
The first TRP channel was identified as the gene product defective in a blind *Drosophila* mutant [2]. Homologs have now been found in many animals, both vertebrate and invertebrate. Animal genomes carry between about 10 and 50 homologs, which have been divided into seven subfamilies: TRPC, TRPM, TRPV, TRPN, TRPA, TRPP and TRPML [2]. Not all subfamilies occur in all animals, and some subfamilies (TRPV, TRPP) contain distinct subgroups as well. TRPs have a molecular architecture similar to that of voltage-gated ion channels, with each subunit containing six transmembrane domains (usually) and subunits arranged to form a tetrameric channel. TRPs are generally nonselective cation channels. Although TRP channels have many roles in neuronal and non-neuronal cells, they are conspicuously involved in sensory function, being essential (in one species or another) for vision, hearing, taste, olfaction, pheromone sensation, mechanosensation and thermosensation [2]. Some are activated directly by sensory stimuli, but others are activated by a variety of second-messengers.

TRPY

TRP channels are found primarily in metazoans, but one TRP channel (Yvc1p, now called TRPY1) is present in yeast. It is thought to be mechanically activated, because a 300–400 pS channel in the wild type yeast vacuole, which is activated by pipette pressure or by osmotic swelling, is absent in a strain of yeast (*yvc1*Δ) that lacks TRPY1 [3•].

It is not clear whether TRPY1 is directly activated by membrane tension, because the channel has not been

Figure 1



Various mechanisms for activation of ion channels (violet) by mechanical stimuli. **(a)** Direct activation by force conveyed through lipid tension. **(b)** Direct activation by force conveyed through structural proteins. Linking proteins might be intracellular, or extracellular, or both, and force might be parallel or normal to the membrane. **(c)** Indirect activation by force conveyed to a mechanically sensitive protein that does not form the channel. A second messenger carries the signal to a ligand-activated channel. **(d)** Various activation pathways for TRPV4. Current evidence suggests that a force sensor responding to membrane tension activates phospholipase A2 (PLA2), producing arachidonic acid (AA). AA can directly activate TRPV4 or be metabolized to 5′,6′-EET by P450 epoxygenase to activate the channel. TRPV4 is also activated by temperature, probably directly.

reconstituted and activated in liposomes. However, expression in *yvc1*Δ yeast of two rather distant fungal homologs from *Kluyveromyces lactiswere* and *Candida albicans* restored the mechanosensitivity [4]. It could be that these homologs bind to endogenous linking proteins in yeast, but their evolutionary distance makes this less likely. It is more likely that this is a direct response to membrane tension.

Vertebrate TRPV

Channels of the vanilloid receptor (TRPV) group in vertebrates are well known for sensing heat, but some

might also be activated by mechanical stimuli. TRPV4 expressed in heterologous systems is activated by osmotic stimuli that cause cell swelling [5,6]. Moreover, mice lacking TRPV4 have reduced regulation of serum osmolarity [7], and reduced sensitivity to noxious mechanical stimuli [8].

Is TRPV4 directly activated by mechanical force? Many other stimuli activate TRPV4, such as warm temperature, acidic pH, and chemical compounds (4α-phorbol didecanoate, citrate, arachidonic acid [AA], and 5′,6′-epoxyeicosatrienoic acid [5′,6′-EET]), suggesting indirect activation through a second messenger (Figure 1d). Vriens *et al.* [9••] demonstrated that activation of TRPV4 by swelling is dependent on phospholipase A2 (PLA2), which generates AA, and on cytochrome P450 epoxygenase, which metabolizes AA to 5′,6′-EET. They also showed that AA and 5′,6′-EET could directly activate TRPV4 in a membrane patch. Osmotic activation of TRPV4 apparently occurs through the activation of TRPV4 by lipid metabolites, so there must be an upstream element that is the real mechanosensor.

Some evidence has implicated other vertebrate TRPV channels in mechanosensation. TRPV1 is expressed in bladder epithelia, and mice lacking TRPV1 have a reduced response to bladder filling [10]. TRPV2 is expressed in aortic myocytes, and can be activated by membrane stretch and hypotonic stimulation [11]. Whether these TRPV channels can directly sense and respond to mechanical stimuli or are activated through secondary messenger systems is unknown.

Invertebrate TRPV

OSM-9 and OCRs in worms

A search for nematode mutants with defective responses to odorants, high osmotic strength and touch to the nose revealed *osm-9*, a gene that encodes a TRP channel [12]. Four homologous genes, *ocr-1* to *ocr-4*, encoding the OCR channels, were later identified in the *C. elegans* genome [13]. These five TRP channels are most closely related to the vertebrate TRPVs, but form a separate, invertebrate branch of that family. Remarkably, addition of mammalian TRPV4 rescues a worm mutant that lacks OSM-9, indicating some functional similarity [14].

Each of the OCR channels is expressed in different sets of sensory neurons and — perhaps by forming a multimeric channel with OSM-9 — appears to mediate different sensitivities. So, for example, OSM-9 and OCR-2 are expressed in the mechanosensitive ASH neurons and are needed for sensitivity to nose touch and osmotic stimuli [13]. Perhaps OCR-2 is a mechanosensitive TRP. However, OCR-2 is also needed for sensitivity to noxious odors, suggesting indirect activation [13]. Moreover, certain mutants in biosynthetic enzymes for polyunsaturated fatty acids abolish the mechanosensitivity mediated by OCR-2, indicating that arachidonic acid and eicosapentaenoic acid are needed for mechanosensation, perhaps as activators of the channel [15•]. Testing mechanical activation of heterologously expressed OCR-2 channels will help to determine whether they are directly mechanosensitive.

Nanchung and inactive in flies

Channels of the invertebrate TRPV group are also needed for auditory transduction in *Drosophila*. Hearing in flies is mediated by Johnston's organ, a group of several hundred ciliated neurons that send processes to the joint between the second and third antennal segments (Figure 2) [16]. These neurons express both the fly ortholog of OSM-9, called *inactive*, and the fly ortholog of OCR-4, called *nanchung* [17,18••]. Antibodies to both Nanchung (NAN) and inactive (IAV) proteins specifically label the neuronal processes, and mutants lacking either protein show inappropriate distribution of the other, suggesting that — similar to OSM-9 and OCR-4 — these channel proteins function together. Both proteins are also expressed in embryonic chordotonal organs.

Mutants of NAN or IAV have an uncoordinated phenotype and lack auditory nerve responses [17,18••]. If NAN and/or IAV form the auditory transduction channel itself, their fast response to auditory stimuli (~500 Hz) suggests they are directly activated by force. Thus, these two TRPVs are among the best candidates for mechanically activated TRP channels.

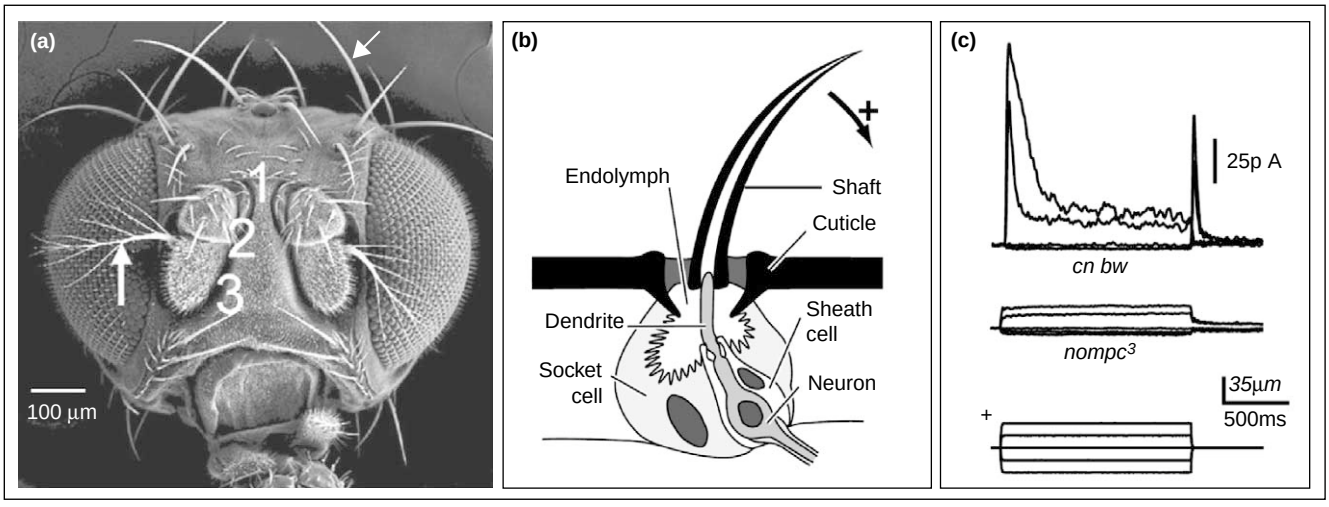
TRPN

One of the first TRP channels identified to have a clear role in mechanosensation was the *Drosophila* NompC (now TRPN). Zuker and colleagues [19] screened fly larvae for uncoordination and defects in withdrawal from a touch stimulus and identified 20 complementation groups with such defects. One of the genes identified with positional cloning encodes a TRP with an extended N terminus of 29 ankyrin domains.

In situ hybridization revealed expression of TRPN in a variety of ciliated mechanoreceptor organs of adult flies, including the bristles (Figure 2). Electrophysiological recording from individual bristle shafts showed a transient receptor current with a very short latency of 200 μs — too short to involve a second messenger — and this was abolished in mutants with stop mutations preceding the transmembrane domains (Figure 2; [19]). Thus, the transduction channels in bristles are likely to be directly activated by mechanical stimulus, and the fly TRPN is at least necessary for transduction. It will be important to show that TRPN is in the receptor neurons and located in their sensory dendrites, and to show that it forms the pore.

A single TRPN is also present in the genome of *C. elegans*, in which it is expressed in ciliated mechanoreceptor

Figure 2



Structure of the hearing and touch organs of *Drosophila*. **(a)** Antennae and sensory bristles on the head. The antenna comprises three segments (numbered) and the arista (arrow). Sound moving the arista causes flexion at the 2–3 joint. Mechanosensitive bristles (arrowhead) occur all over the body surface. (Reproduced with permission from Nature Publishing Group (http://www.nature.com/) and Kim *et al*. 2003 [17].) **(b)** Schematic of a sensory bristle. Receptor current can be recorded through the endolymph in a cut bristle shaft. **(c)** Receptor current evoked by mechanical deflection (bottom) of a bristle in a wild type (top) or nompC mutant (middle) fly. (Parts b and c reproduced with permission from Walker *et al*. [19] copyright 2000 AAAS.)

neurons. A short segment of the N terminus, fused to green fluorescent protein (GFP), is sufficient to target the fusion protein to the sensory dendrites in the worm's nose [19]. The localization suggests a role in mechanosensation, but there are as yet no functional studies to confirm this.

Recently, Nicolson and colleagues [20••] found a TRPN in the zebrafish genome. In situ hybridization showed that TRPN is expressed by hair cells of the inner ear. When zebrafish eggs were injected with morpholino oligonucleotides to block correct splicing of the TRPN mRNA, the larvae were often deaf and displayed a balance disorder. Two experiments have suggested that TRPN is needed for mechanotransduction in hair cells. First, hair cells of the lateral line organs of fish, which are situated on the body wall to sense water currents (Figure 3a), did not produce an extracellular receptor potential in the morpholino-injected fish in response to a vibrational stimulus [20••]. Second, the fluorescent dye FM1-43 passes through hair-cell transduction channels [21], and so dipping a fish in micromolar dye labels functional hair cells in seconds (Figure 3b). Morpholino injection to block expression of the fish TRPN abolished dye labeling [20••].

Zebrafish TRPN is, thus, necessary for mechanotransduction in both inner ear and lateral line hair cells. Whether it carries the transduction current remains to be seen.

Surprisingly, the genomes of higher vertebrates do not have a TRPN. Several fish and at least three amphibian species have a TRPN, but it has not been found in reptiles, birds or mammals. It is not a pseudogene in these organisms, but is simply gone, suggesting a chromosomal deletion.

TRPML

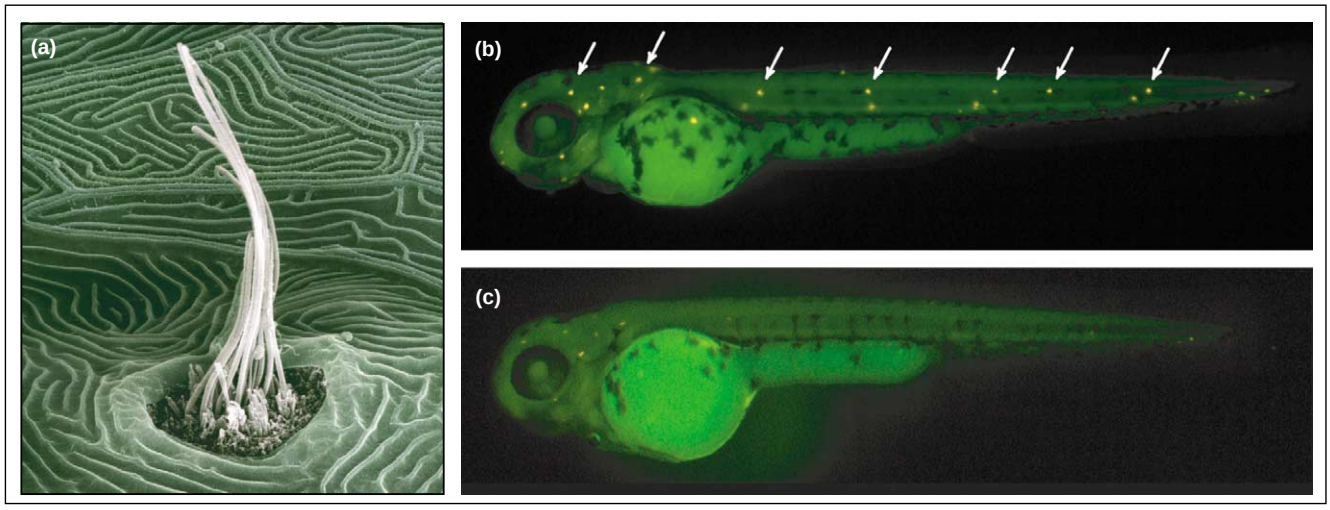
The varitint-waddler mouse is deaf and shows progressive disorganization of hair-cell stereocilia. Positional cloning revealed point mutations in TRPML3, also called mucolipin 3 [22], raising the possibility that this protein forms the hair-cell transduction channel in mammals. However, antibodies to TRPML3 showed the greatest concentration in cytoplasmic compartments, and other TRPMLs are associated with vesicle trafficking, so it seems more likely that TRPML3 is needed for the normal development of the stereocilia [22].

TRPA

The hair cell transduction channel is located at the tips of stereocilia and is pulled open by filamentous tip links that connect adjacent stereocilia. It is a non-selective cation channel with a pore that is nearly 12 nm in diameter, which has high Ca^{2+} permeability and can pass some large organic dyes such as FM1-43 [21,23]. These permeation properties are similar to those of most TRP channels, so a TRP has been suspected as the transduction channel for some time.

Lacking an obvious candidate in the mouse genome, Corey *et al*. [24•] screened all 33 mouse TRP channels using *in situ* hybridization in the inner ear. Probes for the

Figure 3



The lateral line organ of zebrafish. **(a)** An individual neuromast containing ~10 hair cells (white), surrounded by scales (green). (Reproduced with permission from Nicolson *et al*. [41]) **(b)** Zebrafish embryo, with neuromasts (arrows) fluorescently labeled by brief exposure to the dye FM1-43. **(c)** Zebrafish injected at the one-cell stage with a morpholino targeting TRPA1a. Dye labeling is greatly reduced. (Parts b and c reproduced with permission from Nature Publishing Group (http://www.nature.com/) and Corey *et al*. [24•].)

TRPA1 channel (previously ANKTM1) labeled the hair-cell regions of the inner ear but the label was weak, as perhaps expected for a channel of low abundance. Hair cells of the mouse utricle become mechanically responsive at embryonic day 17 (E17), and quantitative reverse transcriptase–polymerase chain reaction (RT–PCR) showed that TRPA1 mRNA appeared at E17, whereas other TRPs tested did not [24•].

An antibody to the mouse TRPA1 C-terminus labeled hair-cell stereocilia in mouse utricle and cochlea, and the label was clearly concentrated towards the tips of stereocilia in bullfrog hair cells [24•]. In all these hair cells, the label was also observed in the kinocilia, which are not thought to participate in mechanotransduction. Similar to the labeling for the tip-link protein cadherin 23 [25], the TRPA1 label disappeared from stereocilia tips when tip links were chemically cut, suggesting that the hair cell rapidly recycles damaged transduction components.

Zebrafish have two TRPA1 orthologs: TRPA1a and TRPA1b. Morpholinos targeting TRPA1a but not TRPA1b greatly reduced FM1-43 labeling of both inner ear and lateral line hair cells (Figure 3b,c). The inner ear microphonic potential produced by vibration was also reduced by morpholinos [24•]. Thus, morpholino injections for TRPN and TRPA1a have nearly identical consequences in zebrafish hair cells, raising the question of whether these two might form a heteromultimeric channel, or whether one is simply necessary for the mechanosensation by the other.

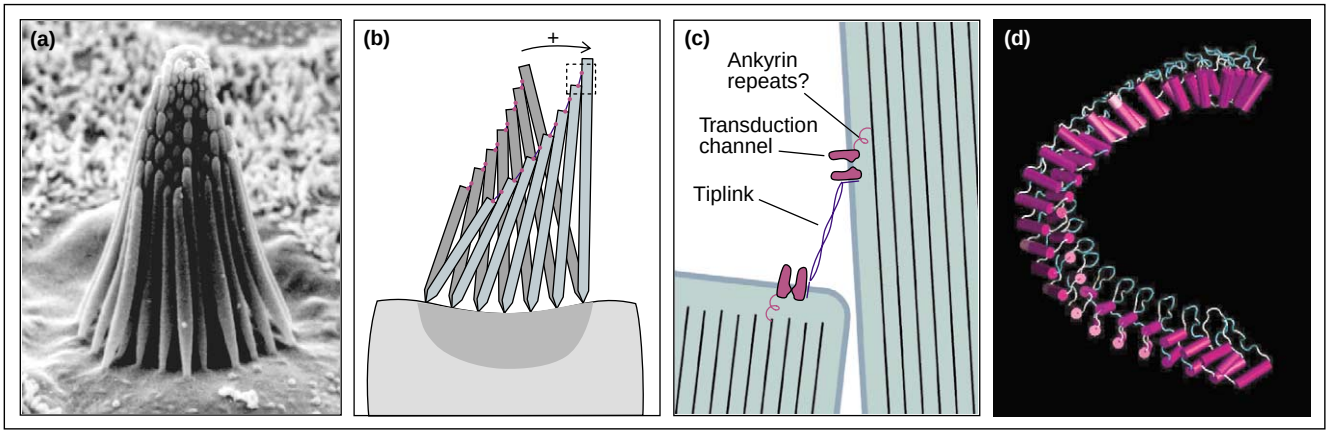
Inhibition of protein expression in mouse hair cells, in this case by infection of embryonic utricle hair cells with adenoviruses encoding siRNAs targeting TRPA1, greatly reduced FM1-43 accumulation by infected hair cells. The transduction current was reduced by 80–90% in infected hair cells, but the residual current was normal in all respects, suggesting a simple elimination of functional channels rather than nonspecific toxicity [24•].

TRPA1 is both necessary for transduction and in the right place to be the transduction channel. Because hair cell transduction channels open within 10–20 μs they are thought to be directly gated, probably by structural proteins rather than lipid. Still to be tested is whether TRPA1 senses mechanical stimuli and whether it is a pore-forming subunit of the transduction channel.

A unique feature of TRPN1 and TRPA1, the two TRPs implicated in hair-cell function, is that they have N-terminal domains with a large number (17 or 29) of ankyrin repeats — more, perhaps, than could be needed for binding to other proteins. The crystal structure and molecular modeling [26,27] indicate that this domain is elastic, suggesting that extension of this part of the channel conveys tension to the pore-forming region (Figure 4d) [27].

Drosophila have four TRPA homologs most of which are activated by heat, but one, 'painless', is expressed in the sensory endings of multidendritic nociceptors, and is needed for sensation of both noxious heat and noxious

Figure 4



Mechanotransduction by vertebrate hair cells. **(a)** A single hair bundle from a frog vestibular hair cell. Stereocilia heights increase uniformly towards the kinocilium. **(b)** Positive deflection of the hair bundle increases the distance between adjacent stereocilia tips. **(c)** Transduction apparatus in the stereocilia tips. The tip link, probably composed of cadherin 23, extends between adjacent membranes and is associated with one or two transduction channels at each end. The transduction channel, probably incorporating TRPA1, is elastically linked to the actin cytoskeleton. (Reproduced with permission from Sotomayor *et al*. 2005 [27].) **(d)** The crystal structure of a polyankyrin domain similar to that in TRPA1, in this case with 24 ankyrin repeats. Molecular dynamics modeling suggests that it is an elastic element.

mechanical stimuli [28]. How mechanical stimuli activate the painless channel is unclear.

TRPP

Polycystic kidney disease (PKD) is an autosomal-dominantly inherited disease causing progressive development of cysts in the kidney and liver. Nearly all cases result from mutations in either the *PKD1* or the *PKD2* genes, both of which encode proteins of the TRPP family [29]. The PKD1s are very large proteins with 10–12 transmembrane domains and long N-terminal extensions, whereas the PKD2 group are smaller and have 6 transmembrane domains. It is clear that PKD2s conduct ions, but PKD1s might be accessory subunits.

PKD1 and PDK2, when expressed together in cultured cells, form functional ion channels [30]. They are co-localized in the short primary cilia of kidney epithelial cells, which enable Ca^{2+} influx when stimulated with fluid flow [31•]. Cells from mutant mice lacking PKD1 do not show flow-activated Ca^{2+} influx, nor do cells treated with antibodies that bind extracellular epitopes of either PKD1 or PKD2 [31•].

PKD2 is also located in the embryonic nodal cilia that sense fluid flow from nearby motile cilia and are involved in determining the left–right body axis [32]. Lack of PKD2 can cause *situs inversus* [33].

Although PKD1 and PKD2 are clearly needed for flow-induced Ca^{2+} influx, the temporal resolution of Ca^{2+} imaging is too slow to determine whether the PKD1–PDK2 channel complex detects flow directly, or indirectly through other mechanosensitive signaling molecules.

Similarly, the nematode PKD homologs lov-1 and pkd2 are located in the male-specific sensory cilia and are needed for mating, in a role that is likely to be mechanosensory [34–36]. The mechanism of gating is not known.

TRPC1

Stretch applied to frog oocyte membranes by suction on a patch pipette activates a nonselective cation channel of ~40 pS conductance. Isolation of a membrane fraction that contained stretch-activated channel activity revealed a protein of ~80 kDa molecular mass, which was recognized by an antibody to TRPC1 [37•]. Expression of TRPC1 in oocytes increased the number of stretch-activated channels, and treatment of native oocytes with antisense RNA reduced the endogenous level of TRPC1 immunoreactivity and stretch-channel activity. Expression of TRPC1 in CHO-K1 cells also produced stretch-activated channels with similar conductance [38]. These examples are evidence that the endogenous stretch-activated channel in oocytes is a TRPC1, and reconstitution experiments suggest that the channel is directly activated by lipid tension.

Does the mechanical sensitivity of TRPC1 have a physiological function? In oocyte membranes, TRPC1 is not very sensitive: from the surface tension required for opening, we can estimate an area increase upon opening of ~3 nm^2, equivalent to a diameter increase of ~0.2 nm. By contrast, the MscL channel, which has clearly evolved to sense membrane tension, increases its diameter by

about 2.5 nm upon opening (from 4.7 to 7.2 nm) [38]. The hair-cell transduction channel, specialized to detect small movements, moves by about 2.5 nm upon opening [39,40]. However, it might be that the large forces that can be applied by patch pipette suction are able to open channels that are not normally mechanosensors *in vivo*.

Conclusions

Some mechanosensitive TRP channels, especially TRPY and TRPC1, are likely to be activated by membrane lipid tension. Others, including TRPN, TRPA1, the invertebrate TRPVs Nanchung and Inactive, and perhaps PKD2, are probably directly activated by mechanical force delivered through structural proteins. Still others, including osmotically activated channels such as the mammalian TRPV4, are more likely to be activated indirectly by a second messenger. Future work must focus on determining the specific mechanisms of activation.

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