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Review

Mechano-Gated Ion Channels in Sensory Systems

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Living organisms sense their physical environment through cellular mechanotransduction, which converts mechanical forces into electrical and biochemical signals. In turn, signal transduction serves a wide variety of functions, from basic cellular processes as diverse as proliferation, differentiation, migration, and apoptosis up to some of the most sophisticated senses, including touch and hearing. Accordingly, defects in mechanosensing potentially lead to diverse diseases and disorders such as hearing loss, cardiomyopathies, muscular dystrophies, chronic pain, and cancer. Here, we review the status of mechanically activated ion channel discovery and discuss current challenges to define their properties and physiological functions.

Introduction

In contrast to the detection of photons for vision or chemical cues for olfaction and taste, relatively little is known about the molecular machinery of mechanotransduction. In addition to highly specialized sensory cells involved in the senses of hearing, touch, and proprioception, every cell seems capable of mechanical stress sensation via changes in conformation of proteins or macromolecular protein complexes. Through these "mechanosignalosomes," cells integrate a variety of mechanical stimuli such as shear stress, tension, torsion, and compression and translate them into short-term effects (i.e., changes in ion concentrations and voltage) and long-term effects via changes in gene expression. A wide array of membrane-associated molecules is involved in mechanotransduction, including ion channels, specialized cytoskeletal proteins, cell junction molecules, and G-protein-coupled receptors and kinases, among many others (Matthews et al., 2010; Anishkin and Kung, 2013).

It has long been known that sensing touch and sound waves require unique ion channels that detect pressure (Corey and Hudspeth, 1979). Only recently, however, studies directed toward characterizing ion channels as transduction molecules have identified promising molecular candidates. Although several important points pertaining to the properties and functions of these channels remain to be clarified, these discoveries represent a major breakthrough in the field of mechanosensation. Here, we highlight emerging themes from papers in the recent literature, from the identification of new force-sensing ion channels in different species to structural/mechanistic aspects that make these channels tailored to transduce mechanical inputs.

Mechano-Gated versus Mechanosensitive Ion Channels

Mechanosensation has been the most elusive sensory modality with regard to the identification of proteins that mediate mechanical transduction. Prime candidates for force transducers are channels whose open probability changes reversibly with membrane tension, i.e., mechanosensitive (MS) channels. MS channels represent a diverse population of ion channel classes with different biophysical properties. This is due to the loose definition of MS channels, as many ion channels are found to be sensitive to mechanical stimuli. MS channels can be divided into two categories: those that respond to membrane tension because evolutionary design provides them with specialized mechanosensor motifs/mechanical gates or an overall structure that renders them susceptible to membrane tension (Sukharev and Sachs, 2012) and those that are susceptible to stretch because a gating domain is inherently sensitive to membrane tension (Bagriantsev et al., 2011; Hao et al., 2013; Morris, 2011). The former defines a class of bona fide mechano-gated ion channels, whereas the latter regroups a variety of mechanosusceptible ion channels. Both have specific physiological functions.

Yet it has been remarkably difficult to identify mechanotransducer channels and to show that candidates are force gated (Christensen and Corey, 2007). Except for the prokaryote osmotic safety valves—the MsC channels, which are well characterized but do not have homologs in animals (Kung, 2005)—evidence that a particular MS channel behaves as mechanotransducer remains rare in eukaryotic cells. Technical difficulties, along with functional redundancy and heteromeric nature of channel complexes, could account for difficulties in identifying a single channel type that is responsible for mechanotransducer currents. To date, only three classes of ion channels satisfy all of the criteria for bona fide mechano-gated channels in eucaryotes—namely DEG/ENaC, TRPN, and Piezo (Figure 1).

New Insights from Touch-Related Systems

Caenorhabditis elegans

A variety of elegant studies have successfully demonstrated that the TRPN1 channel—also called TRP-4 in *Caenorhabditis elegans* (*C. elegans*) and NompC in *Drosophila*—is a bona fide

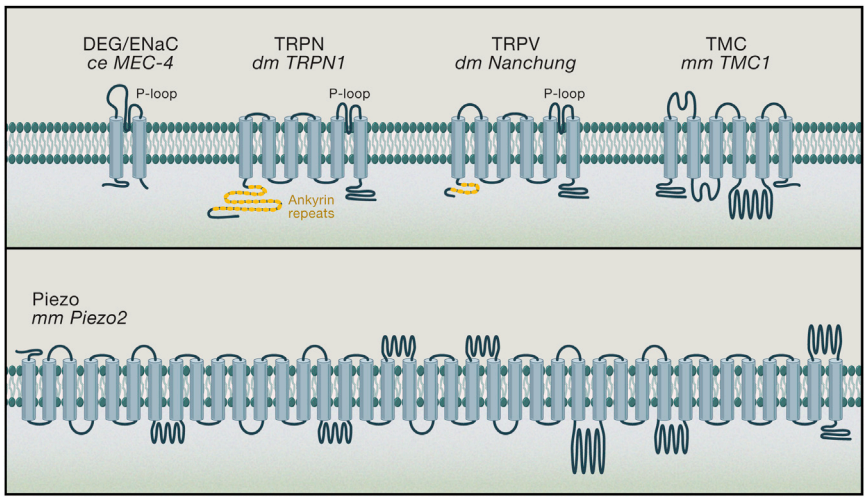

Figure 1. Topology of Mechano-Gated Channel Subunits

Schematic of predicted transmembrane topologies of ceMEC-4, dmTRPN1, dmNanchung (adapted from Christensen and Corey, 2007), mmTMC1 (adapted from Labay et al., 2010), and mmPiezo2. Piezo2 is predicted to harbor 39 TM domains with phobius prediction program. Protein structures depict the predicted pore region (P loop) and the ankyrin repeats.

mechano-gated channel involved in mechanotransduction in invertebrate species. *C. elegans* TRPN1 is involved in the basal slowing response, a phenomenon by which worms reduce their locomotion speed upon mechanical contact with a food source (Kang et al., 2010). TRPN1 is expressed in the cephalic neuron (CEP), a mechanosensory ciliated dopaminergic neuron that is present at the nose tip of the worm (Figure 2A). TRPN1 is localized to the cilium of CEP, where mechanotransduction most probably occurs. *trpn1* mutant worms are defective in mechanosensation, such as the basal slowing response, and lack rapidly adapting mechanoreceptor current in CEP (Kang et al., 2010). Remarkably, specific expression of TRPN1 in CEP neurons of *trpn1* mutants rescues mechanoreceptor current as well as basal slowing response. In addition, mutations in the predicted pore region of TRPN1 abolish the function or alter the ion selectivity of mechanotransduction channels, establishing that TRPN1 serves as a pore-lining subunit of a mechanotransduction channel in *C. elegans* CEPs.

The situation is sensibly different in the *C. elegans* ASH neuron (Figure 2A), a polymodal nociceptor that triggers defensive avoidance behavior in response to multiple aversive stimuli, including chemical, osmotic, and mechanical cues (harsh nose touch). ASH neurons express *deg-1* and *unc-8*, two *deg/ENaC* genes, and *osm-9* and *ocr-2*, two *trpv* channel genes. Patch-clamp experiments have shown that mechanoreceptor current in ASH neurons is sensitive to amiloride and is carried primarily by sodium ions, two trademarks of DEG/ENaC channels. Importantly, deletion of *deg-1* abolishes 80% of the total mechanoreceptor current, whereas deletion of either *unc-8* or *trpv* genes has no effects (Geffeney et al., 2011). With good faithfulness to the criteria for mechanotransducer channels, mutations in the pore region of DEG-1 alter ionic selectivity of ASH mechanoreceptor current (Geffeney et al., 2011). These results favor the view that DEG-1 is the pore-forming subunit of the main mechanotransduction channel in ASH neurons. However, this study also revealed a residual mechanoreceptor current carried nonselectively by cations that persists in *unc-8; deg-1* and *osm-9ocr-2; deg-1* mutants. This suggests that another yet unidentified mechano-gated channel exists in ASH neurons and questions the redundancy and functional interaction between the two.

Other polymodal nociceptive neurons in *C. elegans* are the multidendritic PVD neurons that detect extreme temperatures as well as noxious mechanical stimuli (Figure 2A). Cell ablation experiments have implicated PVD neurons in avoidance of harsh body touch. PVD neurons express a variety of *deg/ENaC*- and *trp*-related genes. Mechanical-stimulation-evoked calcium responses in multidendritic PVD neurons are abrogated in *mec-10* mutants and in worms in which *degt-1*, another *deg/ENaC* gene, has been knocked down (Chatzigeorgiou et al., 2010). These worms also exhibit significant defects in harsh touch escape behavior. Likewise, deletion of *mec-10* or *degt-1* selectively abolishes harsh touch calcium responses in ALM neurons, another class of polymodal sensory neurons that respond to both harsh and gentle touch (Figure 2A). Thus, MEC-10 and DEGT-1 are essential for harsh touch mechanosensation in PVD as well as ALM neurons. Consistent with MEC-10 and DEGT-1 being part of a mechanotransduction complex, the two proteins colocalize throughout PVD dendritic branches. Further electrophysiological characterization of MEC-10/DEGT-1-dependent currents, combined with genetic manipulation, will help to determine their respective contribution as pore-forming subunits of the harsh touch mechanosensory channel complex.

The genetic requirement of MEC-10 for harsh touch responses contrasts with its formerly described role in gentle touch sensing. Earlier works have established that gentle touch in ALM neurons depends, although to a variable extent, on both MEC-4 and MEC-10 (O'Hagan et al., 2005; Arnadóttir et al., 2011). Therefore, the contribution of MEC-10 to both gentle and harsh touch raises the question as to whether touch modality is a function of the cell type or of the molecular composition of the mechanotransducer complex. The above findings are consistent with the possibility that MEC-4/MEC-10 channels mediate low-threshold mechanical responses in ALM neurons, whereas MEC-10/DEGT-1 channels instead mediate high-threshold mechanical responses in the same cells. Although these studies are a step toward identifying the components of mechanotransducer channel complex in worm PVD and ALM neurons, the exact function of each channel subunit remains to be defined, together with the mechanisms that orchestrate and regulate their specific assembly.

Drosophila melanogaster

Two types of sensory neurons called class III and class IV dendritic arborization neurons cover the body wall *of Drosophila*

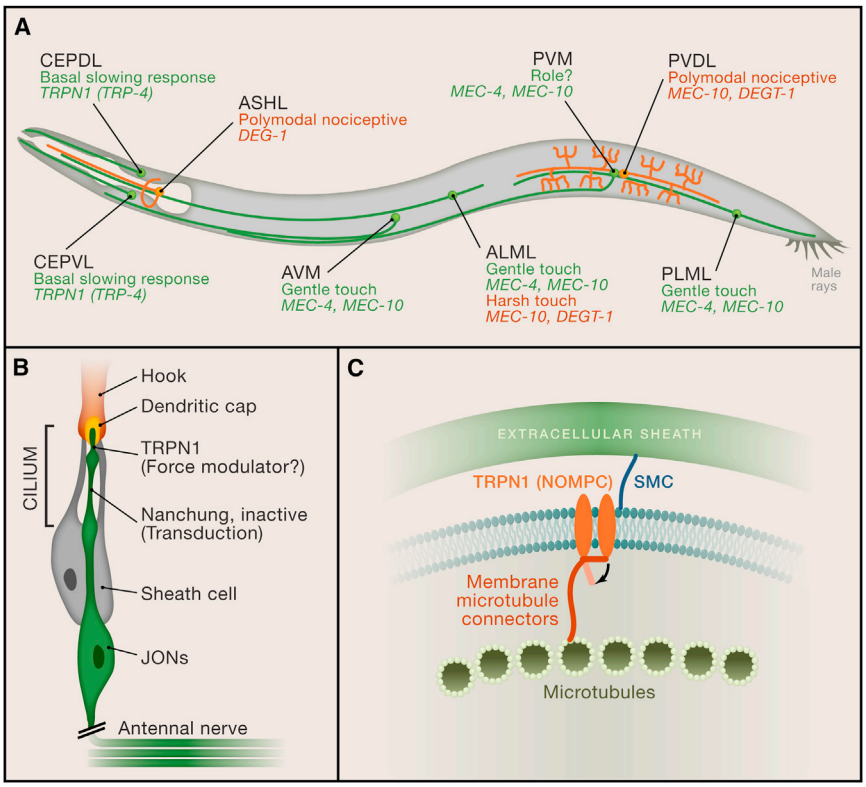

Figure 2. Mechanoreceptors in Invertebrates

(A) The cartoon depicts mechanosensory neurons in a male nematode, together with sensory modalities and candidate mechanotransduction channels. Only the left-side neurons of paired symmetrical neurons (CEPDs, CEPVs, ASHs, ALMs, PVDs, and PLMs) are represented for clarity sake.

(B) Localization of TRPN1 and Nanchung/Inactive in *Drosophila* hearing apparatus. Sound wave vibrations transmitted up to the hook cause mechanical stimulation of the cilium of Johnston's organ neurons (JONs).

(C) Dual-tether model of the mechanotransduction channel in *Drosophila* campaniform mechanoreceptors (Liang et al., 2013). TRPN1 ankyrin repeats form membrane-microtubule connectors (MMC), tethering the channel to the cytoskeleton. Sheat-membrane connectors (SMC) link elements in the membrane to extracellular structures. Mechanical disturbance stretches the channel between these two tethering points and opens the channel like a trap door (arrow). Note that the properties of TRPN1 are also compatible with a single-tether model (see Kung, 2005).

larvae. Cellular and behavioral investigations have shown that class III dendritic arborization neurons contribute to gentle touch sensation, whereas class IV dendritic arborization neurons are necessary for sensing noxious mechanical stimuli in addition to noxious heat (Yan et al., 2013). High levels of TRPN1 are found in the soma and dendrites of class III neurons. *trpn1* null mutant larvae show severe defects in the behavioral responses to gentle touch. Class III neurons from *trpn1* null mutant larvae fail to respond to touch stimuli, a function that can be restored by expression of TRPN1 in deficient neurons (Yan et al., 2013). In addition, ectopic expression of TRPN1 confers light touch sensitivity to the otherwise gentle-touch-insensitive class IV neurons, whereas heterologous expression of TRPN1 in *Drosophila* S2 cells yielded mechanosensitive nonselective cation channels. Moreover, point mutations introduced in the putative pore region alter channel unitary conductance and ion selectivity, supporting the notion that TRPN1 is a pore-forming subunit of the mechanotransduction channel involved in *Drosophila* larvae gentle touch (Yan et al., 2013).

Class IV dendritic arborization neurons use a different set of mechanosensitive channels for sensing noxious mechanical cues. These neurons express the *pickpocket* gene, which encodes a DEG/ENaC subunit (Zhong et al., 2010), and Dm*piezo*, which encodes a member of a new family of mechanically activated nonselective cation channels (Coste et al., 2010, 2012). Earlier work has suggested that *pickpocket* is required for mechanical nociception because larvae mutants for *pickpocket* show reduced nociception behaviors in response to harsh mechanical stimuli. However, evidence that *pickpocket* contributes to mechanically activated currents in class IV polymodal nociceptive neurons is lacking. On the other hand, genetic ablation of Dm*piezo* in class IV neurons impairs mechanical nociception, but not gentle touch or noxious temperature detection (Kim et al., 2012). Importantly, patch-clamp recordings of *pickpocket*-positive neurons reveal mechanically activated cation currents that depend on Dm*piezo* (Kim et al., 2012). These data suggest that Dm*piezo* functions in *pickpocket*-positive neurons to mediate mechanical nociception. In addition, combining both Dm*piezo* and *pickpocket* knockdowns results in an additive loss of the avoidance response to noxious stimuli (Kim et al., 2012), suggesting that Piezo and DEG/ENaC channel activities are not interdependent and mobilize two parallel signaling pathways to regulate mechanosensory nociception.

Mouse Touch

Although mechanically activated cation currents present in rodent sensory neurons are relatively well described in biophysical terms (Hu and Lewin, 2006; Hao and Delmas, 2010; Rugiero et al., 2010), the molecular identity of mechanotransducer channels that contribute to the senses of touch and pain remain largely unknown (Delmas et al., 2011). The recently discovered piezo proteins are putative candidates (Figure 1). Piezo1 (known as FAM38A) and Piezo2 (known as FAM38B) are expressed in mammalian skin and sensory neurons, respectively (Coste et al., 2010). Piezo2 is found at significant levels in subsets of myelinated and unmyelinated sensory neurons and therefore could play a role in mechanotransduction of both innocuous and noxious mechanical stimuli. Because Piezo2 constitutive knockout mice died at birth (Dubin et al., 2012), a definite demonstration of the role of Piezo2 in touch and nociception awaits data from conditional knockout mice. Meanwhile, siRNA knockdown of Piezo2 abolishes rapidly adapting mechanically

activated currents in mouse sensory neurons (Coste et al., 2010). Piezo2 is enhanced in overexpression systems as well as in a subclass of nociceptive neurons by potent inflammatory algogens through activation of PKA/PKC, suggesting a contribution of Piezo2 activity to inflammatory mechanical hyperalgesia (Dubin et al., 2012). The Epac-selective cAMP analog 8-pCPT also sensitizes heterologously expressed Piezo2 as well as mechanically evoked rapidly adapting currents in putative low-threshold mechanoreceptors (Eijkelkamp et al., 2013). Intrathecal antisense oligonucleotide treatment further demonstrates that sensitization of Piezo2 contributes to Epac1-dependent allodynia as well as mechanical allodynia in different models of chronic neuropathic pain (Eijkelkamp et al., 2013). Future research will determine the underlying molecular mechanisms by which Piezo2 sensitization contributes to mechanical allodynia and hyperalgesia.

Pointing out a potential mechanosensory role in nonneuronal cells, recent studies have linked Piezo1 mutations with dehydrated hereditary stomatocytosis (DHS), a congenital human hemolytic anemia associated with red blood cell cation leak causing dehydration (Albuisson et al., 2013; Andolfo et al., 2013; Zarychanski et al., 2012). Mutant channels in dehydrated DHS have delayed channel inactivation (Albuisson et al., 2013; Bae et al., 2013), which might increase Piezo1 signaling during repeated cycles of membrane deformation during passage through the vasculature. Gain-of-function mutations of Piezo2 also affecting inactivation kinetics have been linked with a subtype of distal arthrogryposis (Coste et al., 2013), an autosomal dominant disease characterized by multiple disorders, including distal contractures and restrictive lung disease. It remains to be determined whether these subtle alterations in Piezo channel function are the main basis for these diseases or whether alteration of other functions (e.g., structural) of Piezo proteins also contributes to the phenotypic observations. For example, Piezo1 has been shown to modulate integrin function and regulates cell migration in lung epithelial cells (McHugh et al., 2010, 2012).

New Insights from Hearing

Hearing in Flies

Ever since being identified in a screen to fruit flies that show abnormal responses to deflection of tactile bristles, TRPN1 has been hypothesized to be a component of the elusive mechanotransduction apparatus for hearing. The *Drosophila* auditory organ is termed the Johnston's organ. This chordotonal organ houses specialized subsets of mechanosensory neurons that detect sound transduced through vibration of the antennal capsule (hearing), as well as position with respect to gravity (graviception). In the presence of sound stimuli, mechanical movements of the antennal segments cause the dendrites of Johnston's organ neurons (JONs) to be stimulated, initiating an electrochemical response in the peripheral nervous system (Figure 2B). TRPN1 locates in the distal cilium of Johnston's organ neurons (JONs), an appropriate location to play a direct role in transduction. Accordingly, TRPN1 has been shown to be required for active amplification (sound-evoked antennal motion) and normal mechanical compliance of the *Drosophila* antenna (Göpfert et al., 2006; Effertz et al., 2012), two processes that are thought to reflect opening of mechanotransduction channels.

At this point, the information supports the candidacy of TRPN1 as a core component of the mechanosensitive apparatus. As discussed above, it has all of the attributes of a mechano-gated channel and is well positioned to act as a transducer of mechanical forces. However, a number of observations deviate from this model. First, loss of TRPN1 in JONs only half-reduces sound-evoked electrical activity in the antennal nerve (Göpfert et al., 2006), lending speculation that another channel might play a redundant function. Remnant sound-evoked antennal nerve potentials in *trpn1* nulls have been attributed to TRPN1-independent gravity sensory neurons that coexist with auditory sensory neurons in the Johnston's organ (Effertz et al., 2011). Second, TRPN1 coexists with Nanchung and Inactive, two TRPV family members that likely form heteromeric channels in the fly's JONs. *Nanchung* and *Inactive* mutant flies lack sound-evoked field potentials in the antennal nerve and, accordingly, are deaf. However, Nanchung and Inactive are not viewed as forming the fly's transducer channel for hearing because they localize to the proximal cilium of JONs and are absent from the ciliary tips that are in contact with the dendritic caps. The prevailing view, therefore, is that TRPVs act downstream of the primary mechanotransducer, thereby amplifying subthreshold transducer depolarizations down to JON cell bodies (Göpfert et al., 2006; Kamikouchi et al., 2009).

The idea that the TRPN1 channel is the *Drosophila* transducer for hearing has been recently challenged by Lehnert and coworkers (2013). To circumvent technical difficulties inherent to recordings from individual JONs, the authors developed a noninvasive method for monitoring sound-evoked transducer signals. They recorded from giant fiber neurons that have the particularity to be coupled to JON axons through gap junctions. Using this recording method, in conjunction with genetic manipulations, they dissected the relative roles of TRPN1 and Nanchung/Inactive channels in subthreshold responses to sound. Against the odds, they found that mechanical transduction currents are abolished by deleting either Nanchung or Inactive but persist in the absence of TRPN1. Although it remains to be determined whether Nanchung and Inactive function as force-gated channels, these results argue that TRPVs, but not TRPN1, are components of the transduction complex. What then may be the function of TRPN1? Lehnert et al. (2013) found that generator currents in JONs are more sensitive to movement when TRPN1 is present, suggesting that TRPN1 amplifies mechanical stimulus and exerts resting forces on the transduction complex. A model emerging from this work is that TRPN1 might function upstream to Nanchung and Inactive channels, regulating mechanical sensitivity of the mechanotransducer complex. The mechanism by which TRPN1 provides this essential sensory function "at distance" is not yet clear but might involve TRPN1 connection to microtubules that run longitudinally through the dendrite. What makes this model intriguing, therefore, is the implication of two putative mechanosensitive channels at different locations in the dendrite of JONs, indicating that TRPN1 is likely to do a lot more than just behave as an ion channel.

Hearing in Mammals

The mechanotransduction channels in hair cells have been localized to the distal tips of the stereocilia (Beurg et al., 2009). Here, fine extracellular strands, termed tip links, connect each stereocilium with its taller neighbor. It has been proposed that the tip links pull on and gate the channels in response to mechanical stimulation of stereocilia. Although analyses of mutations associated with deafness in humans and mice have enabled identification of some of the molecular constituents of the transduction apparatus, including the tip link components cadherin 23 and protocadherin 15 (Kazmierczak and Müller, 2012), the identity of the hair cell's transduction channel remains controversial. Electrophysiological recordings have shown that the transduction channel is a nonselective cation channel of large conductance with preference for calcium ions (Peng et al., 2011). Recent work has indicated that two isoforms of the transmembrane channel-like family, TMC1 and TMC2, are required for hair cell mechanotransduction (Kawashima et al., 2011) (Figure 2). These subunits encode six-span integral membrane proteins but lack sequence similarity with known ion channels (Labay et al., 2010). The *Tmc1* gene is linked to deafness in humans, and semidominant or recessive alleles of *Tmc1* cause hearing loss in mice. Mice with a targeted deletion of *Tmc1* and *Tmc2* showed deafness and lacked mechanotransduction currents in hair cells. These results suggest that TMC1 and TMC2 may be components of the mechanotransduction complex. In line with this, Kim and Fettiplace (2013) have recently demonstrated that TMC1 and TMC2 regulate the tonotopic gradient in the calcium selectivity of hair cell mechanotransduction channels, suggesting that TMC proteins contribute to the pore region or act as chaperones that specify channel composition. The strongest evidence that TMCs are pore-forming subunits of the mechanotransduction channel(s) is derived from the $tmc1^{Bth}$ mutant mouse, which has reduced single-channel current levels and calcium permeability (Pan et al., 2013). The $tmc1^{Bth}$ mouse carries a point mutation that causes a methionine-to-lysine substitution at residue 412, which is part of the short extracellular loop between the third and fourth transmembrane domains. Whether this residue is part of the pore vestibule that contributes to permeation properties remains to be determined. Definitive evidence that TMC1 and TMC2 constitute mechanosensitive channels requires in vitro data that can attribute ion channel properties to TMC proteins reminiscent to those of the native hair cell mechanotransduction channel. Of relevance, the *C. elegans* TMC1 is expressed in ASH polymodal nociceptors and encodes a sodium sensor that functions in salt taste chemosensation (Chatzigeorgiou et al., 2013). *Tmc1* mutant worms show no apparent defects in nose touch avoidance, suggesting that TMC1 does not contribute to mechanosensation in ASH neurons. Another recently characterized protein that regulates transduction channels in mouse hair cells is the tetraspan membrane protein of hair cell stereocilia (TMHS). Mechanotransduction is impaired in TMHS-deficient hair cells (Xiong et al., 2012). TMHS binds to the tip link component protocadherin 15 and regulates transducer channel conductance and adaptation. These results indicate that TMHS may be an accessory subunit of the hair's cell mechanotransduction apparatus that couples transduction channels to tip links.

Gating Mechanisms of Mechanotransducer Channels

The mechanisms of force-dependent activation of transducer channels have not yet been established. Initially, the expectation was that mechano-gating motifs common to mechanotransducer channels would be uncovered. However, the structures of mechano-gated ion channels (DEG/ENaC, TRPN, and Piezo) and current contenders (Nanchung/Inactive and TMC) show no such domains (Figure 1).

Two primary models have been proposed for mechano-gating: the lipid bilayer stretch model evidenced by microbial MS channels and the more sophisticated tether model of eukaryotes by which tethers pull open the transduction channel. The latter model is exemplified by the MEC complex in which MEC-4 and MEC-10 line the channel pore while MEC-2 and MEC-6 serve as links to the cytoskeleton and extracellular matrix, respectively. Another domain that attracted much attention recently is the ankyrin repeat domain that is present in many TRP channels but is particularly prominent in TRPN1. TRPN1 harbors 29 ankyrin repeats in its N-terminal tail, which may mediate the protein-protein interaction of a tethered mechanism. Consistently, ankyrin repeats are required for TRPN1 association to microtubules and proper targeting of TRPN1 to the distal part of chordotonal ciliary tips in *Drosophila* (Cheng et al., 2010). Thus, TRPN1 may be anchored to both the cytoskeleton and the extracellular matrix of the dendritic caps at the ciliary tip. This tethering arrangement may also hold for *C. elegans* CEP neurons (Kang et al., 2010) and could potentially promote gating movements of TRPN1 channels upon mechanical stimulation.

Elegant work by Liang et al. (2013) demonstrates that the ankyrin repeat domain of TRPN1 in fly campaniform receptors probably functions as a gating spring. Using electron microscopy, the authors showed that TRPN1 ankyrin repeats contribute structurally to fine filaments, termed "membrane integrated connectors" (MMCs), which attach the membrane intracellularly to microtubules (Figure 2C). These MMCs are nearly absent in TRPN1 mutant flies. Further ultrastructural and modeling studies suggest that MMCs provide most of the compliance in the distal tip, suggesting that these filamentous structures, and thus TRPN1 ankyrin repeats, might function as gating springs (Figure 2C).

Mammals lack TRPN1 and accordingly must use other channel proteins for mechanotransduction. Great emphasis has been placed in the ankyrin-rich TRPA1, but it has not yet lived up to the expectations. Piezo proteins are an evolutionarily conserved ion channel family that lack sequence similarity to all known ion channels (Coste et al., 2010). They are large proteins with 30–40 putative transmembrane domains that multimerize likely as homotetramers (Coste et al., 2012). Biochemical purification and reconstitution of mouse Piezo1 into artificial lipid bilayers produce ion channels displaying constitutive activity. Unlike bacterial MsC channels, their ability to be gated by mechanical forces is not conserved in these minimal systems, raising the question of the conditions that allow mechano-gating of Piezos. Intriguingly, no associated proteins have been detected by mass spectrometry in purified mouse Piezo1 complexes, suggesting that Piezo proteins are not anchored to the extracellular matrix or cytoskeleton through protein-protein interaction. As seen with bacterial MsC (Arnadóttir and Chalfie,

2010), Piezos may be gated by changes in the channel-lipid membrane interaction without the need for other proteins. In addition, specific lipids in the membrane may be required to confer mechanotransduction properties to Piezo channels. The unique structure of Piezo channels, which are predicted to encompass 120–160 transmembrane domains per functional tetramer, could potentially promote such interaction with lipids. Future studies are needed to reveal the relationships between the domains that transmit force from the lipid bilayer to the channel gate.

Conclusions

A variety of mechano-gated ion channels have been identified in the past few years. The rich diversity of their structural designs suggests that adaptive evolution of mechanosensors has occurred independently multiple times. Current studies are directed toward characterizing these candidates and determining how they are mechanically gated. Despite considerable progress, major questions remain. What is the identity of the transduction channel(s) in vertebrate sensory neurons and hair cells? Is force conveyed through the lipid bilayer or by extracellular and intracellular tethers? Do mechanosensitive channels locate within functionally specialized subcellular compartments, e.g., mechano-signalosomes? What domains define the pore structure and the mechanosensor of Piezo and TMC proteins? What is the functional consequence of changes in subunit composition of transducer channels? Given that a single sensory cell may express multiple mechanosensitive channels, how do cells integrate the specific information regarding the relevant stimulus? As always, insights into mechanotransduction mechanisms will come from studies of biological problems spanning different functions and species.

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