JGP Journal of General Physiology

VIEWPOINT

Mechanotransduction by Membrane Proteins

Mechanosensitive membrane proteins: Usual and unusual suspects in mediating mechanotransduction

Miriam B. Goodman[1*], Elizabeth S. Haswell[2*], and Valeria Vásquez[3*]

This Viewpoint, which accompanies a Special Issue focusing on membrane mechanosensors, discusses unifying and unique features of both established and emerging mechanosensitive (MS) membrane proteins, their distribution across protein families and phyla, and current and future challenges in the study of these important proteins and their partners. MS membrane proteins are essential for tissue development, cellular motion, osmotic homeostasis, and sensing external and self-generated mechanical cues like those responsible for touch and proprioception. Though researchers' attention and this Viewpoint focus on a few famous ion channels that are considered the usual suspects as MS mechanosensors, we also discuss some of the more unusual suspects, such as G-protein coupled receptors. As the field continues to grow, so too will the list of proteins suspected to function as mechanosensors and the diversity of known MS membrane proteins.

Introduction

Some of the best and most important things in life have components that are mechanical—eating and excreting, moving and mating, touching and feeling, hearing and learning, developing and growing. These processes, as well as resistance to mechanical damage and the maintenance of turgor, tension, and other physical states, depend on membrane-based mechanosensors. Cells continuously face mechanical cues such as osmotic stress and stretch, and depend on the fast response (milliseconds) of mechanoelectrical transducers to control cellular cascades that occur on larger timescales (seconds to days). Mechanosensitive (MS) ion channels (the main focus of this Viewpoint) are the usual suspects for mediators of rapid responses to mechanical cues. G-protein coupled receptors (GPCRs) are examples of more unusual suspects, and evidence is emerging that they can mediate responses on slower time scales than MS ion channels.

Simple models for activation of MS ion channels and GPCRs posit that mechanical force catalyzes the transition between inactive and active conformations. Deciphering how this takes place is a vibrant area of research that is highlighted in this Special Issue. In the case of MS ion channels, the two most prominent mechanisms are the force-from-lipid (FFL; Kung, 2005; Teng et al., 2015) and the force-from-filament (FFF; Katta et al., 2015) principles of force delivery. In the FFL principle, active and inactive conformations differ in one or more characteristics, including cross-sectional area, thickness within the bilayer, and induced bilayer curvature. Switching between conformations depends on forces in the membrane bilayer, such as tension and lateral pressure, and its mechanical properties, such as stiffness. In the FFF principle, mechanical force is conveyed to the channel via displacement of one or more protein filaments that link the channel to extracellular and/or intracellular structures. Far from being mutually exclusive, the FFL and FFF principles may act in concert to elevate sensitivity to mechanical stress and enable each MS ion channel to operate consistently with its physiological role and cellular environment.

In this Viewpoint, we discuss features of established and suspected MS membrane proteins, their distribution across protein families and phyla, and current and future challenges in the study of these important proteins and their partners. As many of the studies in this virtual Special Issue pertain to the function of PIEZO1 and PIEZO2, we highlight these proteins in a separate section. We also note that rather than building a comprehensive catalog of MS membrane proteins, we draw examples from the literature in the hope of inspiring accelerated

[1]Department of Molecular and Cellular Physiology, Stanford University, Stanford, CA, USA; [2]Department of Biology, Center for Engineering Mechanobiology, Washington University in St. Louis, St. Louis, MO, USA; [3]Department of Physiology, College of Medicine, University of Tennessee Health Science Center, Memphis, TN, USA.

Correspondence to Miriam B. Goodman: mbgoodman@stanford.edu

*The authors are listed alphabetically by surname. This work is part of a special issue on mechanotransduction by membrane proteins.

discovery of the biophysics and physiology of membrane mechanosensors. To date, there has been no single path leading to the discovery of MS membrane proteins. Some MS channels, like the MS channels of small and large conductances (MscS and MscL, respectively), have been uncovered through purification and biochemical reconstitution. Unbiased genetic studies identified MEC-4 and MEC-10, paralogous channels belonging to the DEG/ENaC/ASIC superfamily; NOMPC, a TRP channel that is absent from mammalian genomes; TMC1, a.k.a. transmembrane channel-like 1; and OSCA1, a hyperosmolarity-activated calcium channel. Candidate gene screens uncovered PIEZOs and additional OSCA-like channels, while explorations based upon homology yielded the MscS-like (MSL) channels. The idea that GPCRs are mechanosensitive is emerging from structure–function studies of adhesion GPCRs, and has been reinforced by genetic analyses linking their expression to mechanical sensing.

Rules of evidence

What evidence is needed to advance a given membrane protein from a suspected mechanosensor to a confirmed mechanosensor? At least two of the criteria previously established for mechanosensors involved in sensory mechanotransduction (Ernstrom and Chalfie, 2002; Arnadóttir and Chalfie, 2010; Katta et al., 2015) are broadly applicable to all mechanosensors: function and mimicry.

Function

The protein must be required for responses to mechanical stimuli. These responses should occur on a timescale consistent with the type of putative mechanosensor: ion channels respond in milliseconds or less; other mechanosignaling pathways are slower. Genetic loss-of-function experiments could produce ambiguous results due to redundancy or indirect effects. Combining reverse genetics with the analysis of mutations that change the biophysical properties (e.g., ion selectivity, gating) of the response to mechanical stimulation can help to resolve the ambiguity. This approach was used successfully for channels involved in mechano-electrical transduction channels in *Caenorhabditis elegans* mechanoreceptor neurons (O'Hagan et al., 2005; Kang et al., 2010) and mouse auditory hair cells (Pan et al., 2018; Pan et al., 2013; Beurg et al., 2015a; Beurg et al., 2021).

Mimicry

As long as a suspected mechanosensor protein functions autonomously, it should retain its MS activity when expressed in another cell or when reconstituted in a lipid bilayer. However, this criterion may not be met if the suspected mechanosensor requires protein or lipid partners that are absent from the heterologous system, if it fails to traffic properly in transfected cells, or if tools available for mechanical stimulation are insufficient to activate it in a heterologous system. Although the mimicry concept is straightforward, experiments testing for it have been problematic. For instance, endogenous MS channels in heterologous cells can function as false mimics (Gottlieb et al., 2008). Complications from endogenous MS channels can be reduced by CRISPR/Cas9 gene editing techniques (Cahalan et al., 2015; Dubin et al., 2017; Moroni et al., 2018). Furthermore, purification and reconstitution of a putative mechanosensor could uncover responses to mechanical stimuli that are suppressed in native tissues, leading to a false positive. These conceptual complications imply that missteps in the field are likely. For instance, several TRP channels initially suspected to be mechanosensitive did not meet one or both of these criteria (Geffeney et al., 2011; Nikolaev et al., 2019; Corey et al., 2004). In summary, gathering and solidifying the multiple lines of evidence needed to establish that a suspected target protein is a true biological mechanosensor is a significant undertaking and is rarely, if ever, accomplished in a single paper.

The usual suspects—MS ion channels

Force-gated or MS channels are found in protein superfamilies that vary in their phylogenetic distribution (Fig. 1). This is not the only axis of variation, however. Several MS channel monomers have only two transmembrane helices, while others are predicted to contain many more than four. For instance, the bacterial MscK ion channel has 11 transmembrane helices (Mount et al., 2022) and animal PIEZO channel monomers have 38 transmembrane helices (Yang et al., 2022; Wang et al., 2019a). Some MS channels assemble as dimers or trimers, others as tetramers, and still others as pentamers or heptamers. Some, like DEG/ENaC/ASICs and TMCs, operate together with many protein partners. Others in bacteria (MscS, MscL), plants (MSLs, PIEZOs, OSCAs), and animals (PIEZOs, two-pore domain K^+ channels) can operate autonomously.

Curiously, there is no known amino acid sequence or structural motif that distinguishes MS channels from their cousins who do not appear to be affected by mechanical force. At present, it is not known if ancestral isoforms in these multifunctional superfamilies were all mechanosensitive, and this feature was lost in some proteins, or if mechanosensitivity is a derived innovation. Phylogenetic studies of some MS channels favor the latter viewpoint (Pivetti et al., 2003; Nishii et al., 2021).

MS channel function in context

MS receptors that sense perturbations of osmotic pressure

Several MS channels help cells sense changes in osmotic pressure and initiate the appropriate physiological responses. For instance, MscS and MscL operate as part of a concerted response to protect bacteria from osmotic challenges of different magnitudes (Levina et al., 1999; Martinac et al., 1987; Sukharev, 2002; Sukharev et al., 1994). They were discovered and cloned via painstaking purification and reconstitution from bacteria and allele replacement, respectively (Sukharev et al., 1994; Levina et al., 1999). The eukaryotic MSL channels have diverse functions in plant and fungal cells (Basu and Haswell, 2017). For instance, the *Arabidopsis* MSL8 protein plays pivotal roles in pollen rehydration and germination (Hamilton et al., 2015), and MSL10 is key for cellular responses to swelling (Basu and Haswell, 2020). MSL10 and its homologs are implicated in other specialized functions, including long-distance damage signaling (Moe-Lange et al., 2021) and prey detection by carnivorous plants (Procko et al., 2021).

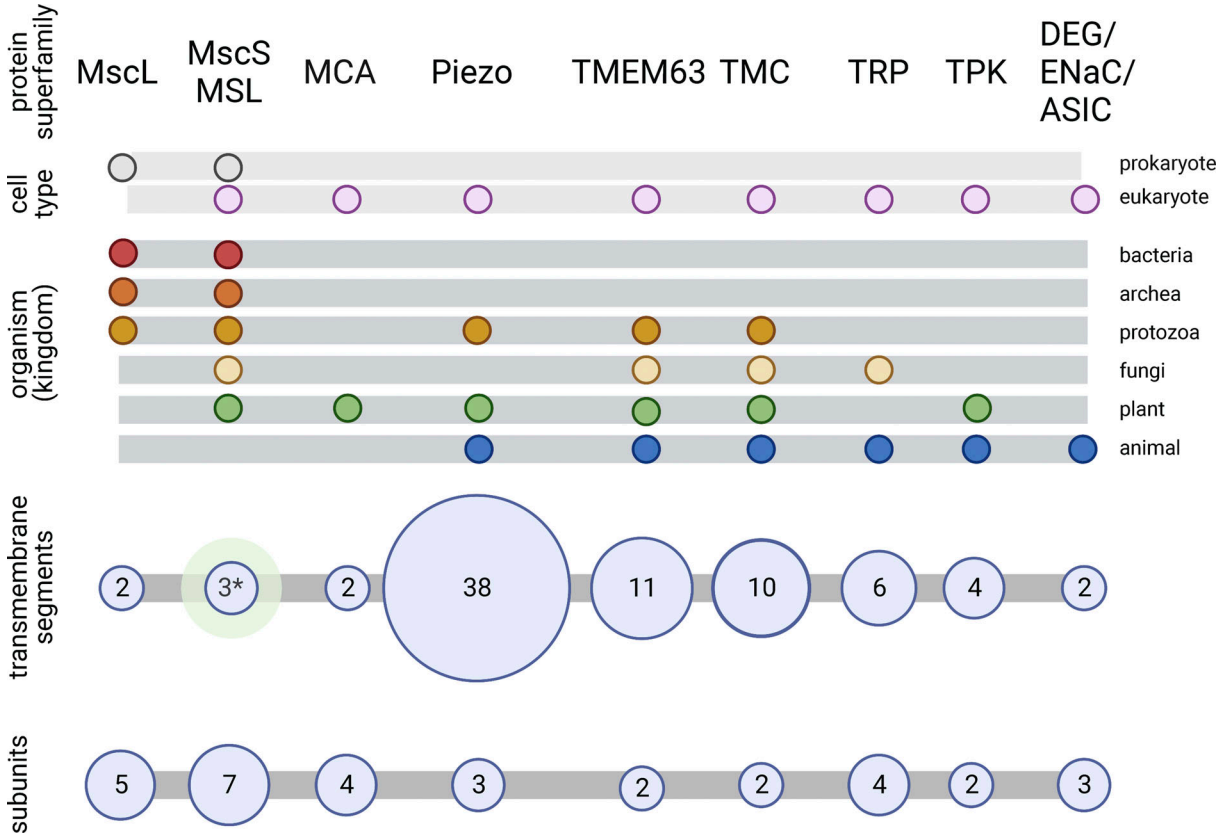

Figure 1. **Protein families that include MS ion channels across phyla.** Ion channel superfamilies known to contain at least one ion channel that: (1) is linked to sensory mechanoelectrical transduction in vivo, (2) is activated by mechanical force in heterologous cells, and/or (3) produces mechanochemical ion flux following purification and reconstitution. The TRP, TPK, and DEG/ENaC/ASIC channel superfamilies contain many ion channels that are considered indifferent to mechanical stimuli. Established MS channels in these superfamilies include NOMPC/TRP-4 and TRPY1; MEC-4, MEC-10, and DEG-1; TREK and TRAAK. In the transmembrane segment row, the circle area is proportional to the number of TM segments. MscS channels have three transmembrane segments, while MSL channels have a variable number shown as a green halo. In the subunit row, the area of each circle is proportional to the subunit number. MscL, mechanosensitive channel of large conductance; MscS, mechanosensitive channel of small conductance; MCA, Mid1-complementing activity; PIEZO includes FAM38; TMEM63 includes OSCA1 (reduced hyperosmolality induced $[Ca^{2+}]_i$ increase); TMC, transmembrane channel-like proteins; DEG/ENaC/ASIC, Degenerin, ENaC (epithelial Na^+ channel), ASIC (acid-sensing ion channel); TPK, two-pore domain K^+ channels; TRP, transient receptor potential channels. Created with BioRender.com.

The awesome power of plant genetics led to the discovery of another major family of eukaryotic MS ion channels, the OSCA family of cation channels. OSCA1 (reduced hyperosmolality induced $[Ca^{2+}]_i$ increase 1) was discovered in a screen for *Arabidopsis thaliana* mutants with altered calcium signaling in response to hyperosmotic shock and is required for guard cell closing during drought stress (Yuan et al., 2014; Hou et al., 2014). Multiple cryo-EM structures of plant OSCA channels in the closed state reveal a dimeric channel with two pores and lipid-filled crevices (Zhang et al., 2018; Maity et al., 2019; Liu et al., 2018; Jojoa-Cruz et al., 2022), but the biophysical mechanism of gating remains poorly understood. Other key questions for the future include how OSCA signaling is linked to guard cell function and whether OSCA homologs involved in immune signaling (Thor et al., 2020) and implicated in Venus flytrap closure (Procko et al., 2021; Iosip et al., 2020; Scherzer et al., 2022) are also mechanosensitive.

TMEM63 proteins belong to the same superfamily as OSCA and are also proposed to mediate response to hyperosmotic shock (Zhao et al., 2016). When expressed in mammalian cells, plant and animal OSCA/TMEM63 channels activate in response to both hyper- and hypo-osmotic stimulation (Du et al., 2020). Exactly how these channels are activated within their native cellular context(s) remains to be resolved, however. For instance, TMEM63 may function in insect hygrosensation because it is activated in antennal sensory neurons that bend in response to changes in humidity (Li et al., 2022). In mammals, the TMEM63B protein is expressed in outer hair cells in the inner ear of mammals and is needed for hearing (Du et al., 2020). The deafness phenotype results from degeneration of the outer hair cells, however, leaving open the question of how TMEM63B is needed for outer cell survival. Disparate findings regarding how OSCA and TMEM63 proteins respond to osmotic stimulation may in part reflect the specialized ways in which plant and animal cells respond to osmotic challenges.

PIEZO proteins serve many physiological functions in animals and plants

Among other functions, animal PIEZO1 channels are important regulators of red blood cell volume (Ma et al., 2018; Zarychanski

et al., 2012; Glogowska et al., 2017), wound healing (Holt et al., 2021b), and neuromuscular function (Millet et al., 2022; Bai et al., 2020). The paralogous PIEZO2 channels underpin many aspects of somatosensation and proprioception in mammals (Chesler et al., 2016; Ranade et al., 2014; Woo et al., 2015; Ikeda et al., 2014), fish (Faucherre et al., 2013), and birds (Schneider et al., 2017). In nematodes and insects, PIEZO proteins are vital for feeding (Min et al., 2021; Millet et al., 2022; Wang et al., 2020; Hughes et al., 2022) and mechanical nociception (Kim et al., 2012). PIEZO channels are also widely distributed throughout the plant lineage where they localize to the membrane of the vacuole (Radin et al., 2021) rather than to the plasma membrane. Plant PIEZOs are required for normal calcium transients and vacuole morphology in tip-growing cells in moss protonemata and *Arabidopsis* pollen tubes (Radin et al., 2021); for normal root growth on hard media, calcium transients in response to touch (Radin et al., 2021; Mousavi et al., 2021); and for defense against systemic viral infection (Zhang et al., 2019).

Many MS channels sense touch, sound, motion, and other mechanical stimuli

Among the first ion channels shown to function as mechano-electrical transduction channels in sensory neurons were the *C. elegans* members of the DEG/ENaC/ASIC superfamily, MEC-4 and MEC-10 (O'Hagan et al., 2005), and the *Drosophila* TRP superfamily protein NOMPC (Walker et al., 2000; Yan et al., 2013) and its *C. elegans* ortholog TRP-4 (Li et al., 2006; Kang et al., 2010). MEC-4, MEC-10, and NOMPC were identified through unbiased genetic screens for touch-defective mutant animals (Driscoll and Chalfie, 1991; Huang and Chalfie, 1994; Chalfie and Au, 1989; Kernan et al., 1994). TRP channels are absent from land plants and bacteria, but present in the genomes of most, if not all, animals and single-celled eukaryotes including green algae, paramecia, and some yeast species (Himmel and Cox, 2020; Liebeskind et al., 2015). The DEG/ENaC/ASICs are more exclusive: they are present only in metazoan animals (Liebeskind et al., 2015).

The *C. elegans* MEC-4 and MEC-10 proteins are co-expressed in touch receptor neurons and contribute to low-threshold touch sensitivity (a.k.a. gentle touch; Driscoll and Chalfie, 1991; Huang and Chalfie, 1994; O'Hagan et al., 2005; Arnadóttir et al., 2011; Chatzigeorgiou et al., 2010a; Suzuki et al., 2003) and substrate vibration (Kubanek et al., 2018; Zhou et al., 2022). Other DEG/ENaC/ASIC proteins contribute to nociception in *C. elegans* and *Drosophila* larvae (Geffeney et al., 2011; Chatzigeorgiou et al., 2010b; Zhong et al., 2010; Mauthner et al., 2014) and to proprioception (Tao et al., 2019; Jang et al., 2019; Adams et al., 1998).

The NOMPC channel plays a central role in insect hearing (Kamikouchi et al., 2009; Effertz et al., 2011; Lehnert et al., 2013; Walker et al., 2000) and proprioception in insects and nematodes (Das et al., 2021; Li et al., 2006;Wang et al., 2019b; Cheng et al., 2010). This channel also functions in the lateral line hair cells of zebrafish (Sidi et al., 2003), indicating that NOMPC's contribution as a mechanosensor is not limited to invertebrates. Mammals lack a NOMPC or TRPN channel ortholog (Peng et al., 2015; Goodman and Schwarz, 2003), suggesting that mechanosensitivity in these channels was either lost in vertebrate lineages or selectively acquired in invertebrates. Mechanical gating of the NOMPC channel depends on links to the microtubule cytoskeleton (Zhang et al., 2015; Wang et al., 2021; Liang et al., 2013), and structural studies reveal a spring-like structure composed of 29 ankyrin repeats in its N-terminal domain (Jin et al., 2017). Molecular dynamics simulations support a model in which channels activate in response to compression of the ankyrin repeat domain (Wang et al., 2021), a process that seems likely to be mediated by NOMPC-microtubule linkages in native cells.

The transmembrane channel-like (TMC) proteins came to light through genetic studies of deafness in humans (Kurima et al., 2002) and mice (Vreugde et al., 2002). Based on sequence similarity and a cryo-EM structure (Jeong et al., 2022), TMC proteins assemble as dimers and resemble the TMEM16 family of lipid scramblases (Ballesteros et al., 2018; Pan et al., 2018). There is ample evidence supporting the idea that TMC1 is a pore-forming subunit of the MS channel responsible for mechanotransduction during hearing (Pan et al., 2018; Beurg et al., 2015a; Beurg et al., 2021). Consistent with a conserved role in animal sensory mechanotransduction, fruit flies rely on TMC to discern food texture (Zhang et al., 2016). Although TMC isoforms do seem to traffic to the plasma membrane in heterologous cells (Kawashima et al., 2011; Labay et al., 2010; Beurg et al., 2015b; Wang et al., 2016; Zhao et al., 2014), two vertebrate isoforms form functional and MS channels when purified and reconstituted in liposomes (Jia et al., 2020). Additional studies are needed to decipher what regulates the assembly of endogenous TMC-containing complexes and what factors are needed to reconstruct these complexes in heterologous cells.

Evidence for FFL-based mechanosensitivity

Purified and reconstituted MscS, MscL, MSL1, MSL8, MSL10, TRAAK, TREK-1, TREK-2, and PIEZO1 channels are activated by increases in membrane tension and, therefore, are thought to gate using an FFL mechanism (Lee et al., 2016; Hamilton et al., 2015; Maksaev and Haswell, 2012; Sukharev, 2002; Sukharev et al., 1994; Brohawn et al., 2014; Aryal et al., 2017). Consistent with the idea that the FFL principle also holds in cells, PIEZO1 channels are mobile and do not colocalize with the actin cytoskeleton in mammalian red blood cells (Vaisey et al., 2022). Consistent with theoretical predictions of the energetics of force-gating (Sukharev and Corey, 2004), angstrom-scale structures of MS channels suggest that forces from lipids increase the cross-sectional area that a channel occupies in the plasma membrane (Fig. 2).

Closed and open state cryo-EM structures of *At*MSL1, a MscS homolog that localizes to plant mitochondria, suggest an analogous gating mechanism with a literal wrinkle. The transmembrane domains of MSL1 are cup-shaped in the closed state but linear in the open state structure, suggesting that the closed-state channel deforms the membrane into tiny dimples, which are then flattened out once membrane tension is added, driving the transition to the open-state channel (Deng et al., 2020). A cryo-EM structure of the Venus flytrap homolog of MSL10 has a similar membrane-bending transmembrane domain (Procko

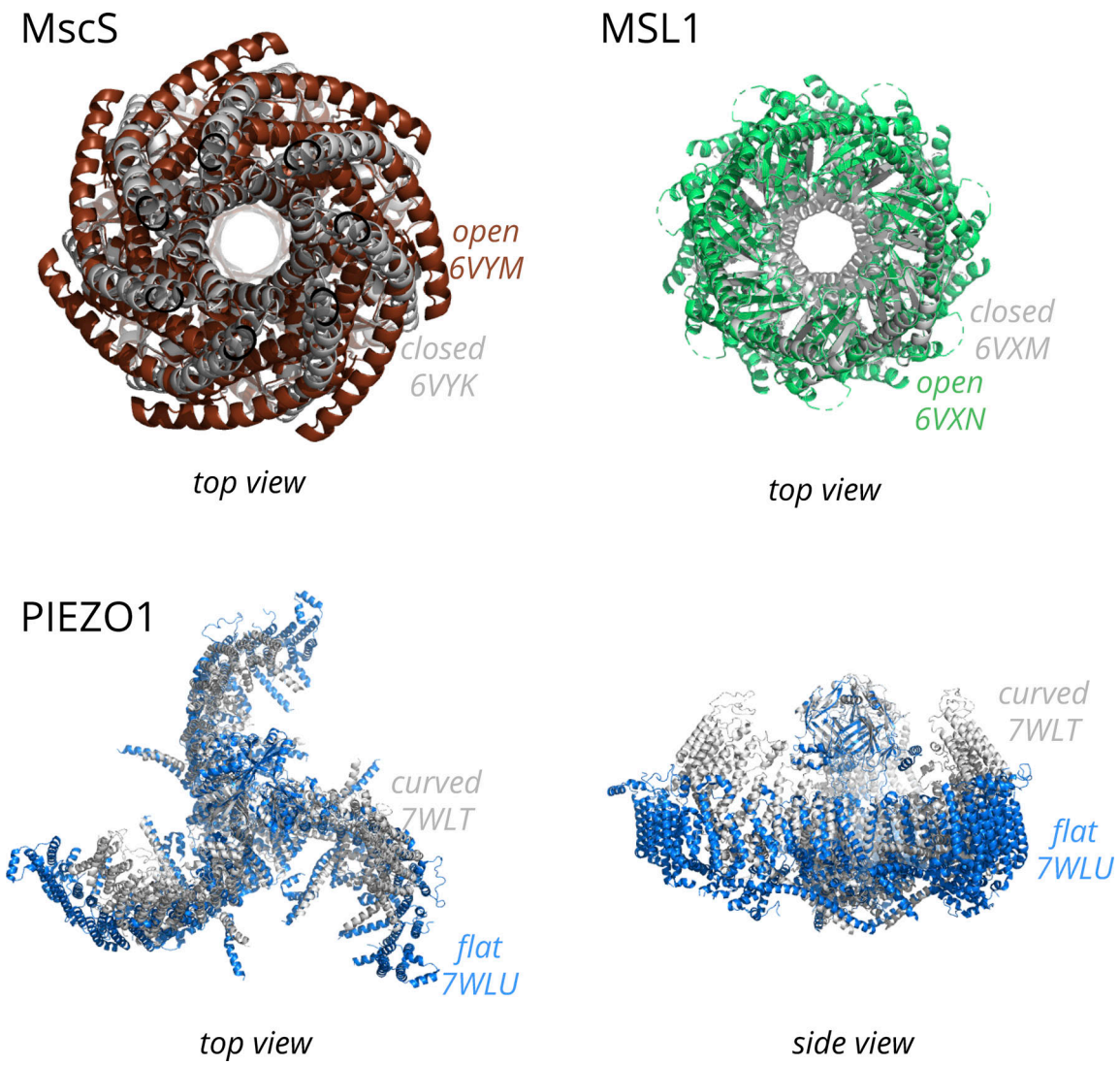

Figure 2. **Open (conducting-like) conformations of FFL channels are wider or flatter than closed (non-conducting-like) conformations.** In all panels, a non-conducting (either closed or inactive) state is shown in gray and the conducting (open or active) state is rendered in color. Each pair of structures was aligned and rendered in Pymol from the indicated PDB accession nos. and displayed at its own scale. Sources: MscS (Zhang et al., 2021); MSL1 (Deng et al., 2020); PIEZO1 (Yang et al., 2022).

et al., 2021; Jojoa-Cruz et al., 2022). A related gating mechanism is proposed for PIEZO channels, which are structurally and evolutionarily unrelated to MscS and MSL channels. Specifically, giant PIEZO monomers assemble into trimers that appear to bend the membrane bilayer (Guo and MacKinnon, 2017; Wang et al., 2019a; Yang et al., 2022), an effect proposed to prime the channel for activation in response to membrane stretch (Lin et al., 2019). Collectively, these findings suggest a conserved interplay of channel architecture, channel–membrane interactions, and mechanosensitivity among MS channels operating in the FFL gating mode.

Evidence for FFF-based mechanosensitivity

The FFF principle is thought to govern activation of the NOMPC and TMC1/2 channels. NOMPC is connected to the intracellular microtubule cytoskeleton (Liang et al., 2013; Zhang et al., 2015). By contrast, TMC1/2 channels are thought to be connected to tip links, specialized extracellular filaments that attach stereocilia to one another in vertebrate hair cells (reviewed in Zheng and Holt, 2021; Holt et al., 2021a). Although the filament linking NOMPC to microtubules is integral to the channel protein itself (Zhang et al., 2015; Jin et al., 2017; Liang et al., 2011), the connection between TMC1/2 channels and tip links is proposed to be mediated by other proteins such as LHFPL5 and TMIE (Zheng and Holt, 2021). The proteins comprising this mechanotransduction apparatus have been uncovered through genetics in humans, mice, and fish (Holt et al., 2021a). Although nematodes do not have ears, they do harbor a TMC complex that includes orthologs of the proteins found in vertebrates (Jeong et al., 2022; Tang et al., 2020).

Ion channels required for hearing are not the only membrane mechanosensors likely to depend on protein filaments for their in situ activation. Other candidates that may depend on extracellular filaments include the MEC-4–dependent channels

responsible for touch in *C. elegans* (Das et al., 2022 *Preprint*; Emtage et al., 2004; Sanzeni et al., 2019; Katta et al., 2019) and adhesion GPCRs proposed to activate in response to mechanical forces applied to their extracellular domains (Lin et al, 2022a; Wilde et al, 2022).

It has also become apparent that channels activated by FFL mechanisms could be modulated by FFF and vice versa. For instance, PIEZO2 requires cytoskeletal elements such as filamentous actin and tubulin for normal function (Eijkelkamp et al., 2013; Romero et al., 2020; Verkest et al., 2022). Furthermore, both PIEZO1 and PIEZO2 are reported to be biochemically and functionally tethered to the actin cytoskeleton via the cadherin-β-catenin mechanotransduction complex in MDCK epithelial cells (Wang et al., 2022). Together, these data imply that complex interactions between the membrane and filaments work in concert to tune PIEZO channel function and identify these proteins as channels sensitive to forces delivered by both lipids (FFL) and filaments (FFF).

MS channel function is shaped by bilayer composition

Several lines of evidence indicate that the composition of the membrane bilayer helps to fine-tune the sensitivity of MS channels. For instance, genetic perturbation of lipid biosynthesis in *C. elegans* implicates lipids containing the polyunsaturated fatty acid arachidonic acid as regulators of neuronal membrane stiffness and MEC-4–dependent touch sensation (Vásquez et al., 2014). More direct evidence for the role of lipid composition in mechanosensitivity comes from reconstitution of MscL and MscS channels in bilayers (Ridone et al., 2018). When MscL is reconstituted in bilayers composed of lipids with short-chain fatty acids, it is more sensitive to membrane tension than when reconstituted with longer-chain fatty acids (Perozo et al., 2002). Structurally, MscS channels reconstituted in lipid nanodiscs appear to have lipids tightly bound to the channel (Zhang et al., 2021; Rasmussen et al., 2019; Reddy et al., 2019). A non-conducting state is favored in thicker bilayers, and thinning the bilayer by removing lipids from the nanodisc destabilizes this conformation (Zhang et al., 2021).

The two-pore domain K^+ channels, TRAAK and TREK-1, are activated by perfusion of free fatty acids (Fink et al., 1998; Maingret et al., 2000; Kim et al., 2001) and seem to bind lipids (Schrecke et al., 2021; Cabanos et al., 2017), suggesting that their mechanosensitivity also depends on protein–lipid interactions. Since PIEZO1 channels induce membrane bending (Guo and MacKinnon, 2017; Yang et al., 2022; Lin et al., 2019), they are sensitive to the mechanical and biochemical properties of membrane phospholipids and the presence of cholesterol (Ridone et al., 2020; Shi et al., 2020; Romero et al., 2019). This feature is shared by PIEZO2, as found in coarse-grained molecular dynamics simulation (Lin et al, 2022b; this Special Issue). Indeed, enriching cell membranes in margaric (heptadecanoic) acid, an odd-chain saturated fatty acid, increases bending stiffness and inhibits PIEZO1 and PIEZO2 channel activity (Romero et al., 2019; Romero et al., 2020). These examples illustrate that mechanosensitivity depends on the intimate interplay of lipid bilayers and MS channels. New experimental tools for determining the biochemical composition and mechanical properties of native lipid bilayers and for perturbing these factors would accelerate efforts to fully understand MS channel function in context.

The unusual suspects—GPCRs as membrane mechanosensors

GPCRs play a conserved role in light and chemical sensing, signaling via trimeric G proteins and/or β-arrestin to modulate ion channels or soluble second messengers like Ca^{2+} ions, cAMP, or cGMP. However, evidence is emerging that some GPCRs may respond to mechanical forces in addition to light or chemical ligands. For instance, genetic dissection implicates light-activated opsins (Rh5, Rh6, and NINAE) and an adhesion GPCR latrophilin (dCIRL) in hearing and proprioception in adult and larval fruitflies, respectively (Senthilan et al., 2012; Zanini et al., 2018). Deficits seen in Rh6, NINAE, and dCIRL mutant larvae include disrupted locomotion and reduced mechanically activated neural responses in proprioceptors (Zanini et al., 2018; Scholz et al., 2015, 2017). Although all of these GPCRs satisfy the first rule of evidence for functioning as a membrane mechanosensor, additional studies are needed to directly investigate their contribution to cellular and behavioral responses.

Like other latrophilins, dCIRL has a very large extracellular region that includes an autoproteolytic GAIN domain. Increasing the size of the large extracellular domain of dCIRL disrupts mechanically evoked neural responses, but disabling autoproteolysis by the GAIN domain leaves these responses intact (Scholz et al., 2017). The *C. elegans* latrophilin ortholog, LAT-1, is also expressed in mechanoreceptor neurons and seems to be required for the function of the male-specific mechanosensory organs essential for mating (Matúš et al., 2022). Transgenic expression of the extracellular N-terminal fragment of LAT-1 rescues these phenotypes in *lat-1* mutants, again implicating the extracellular regions of latrophilin in sensory mechanotransduction.

Several other GPCRs are implicated in mechanosensing in the vascular, immune, and nervous systems (see Dunn et al., 2019, and Table 1). Much of the evidence that GPCRs are MS consists of findings that cytoplasmic signals induced by shear stress, vibration, or centrifugation depend on GPCR receptor expression. Intramolecular FRET has also been applied to monitor conformational changes in GPCRs evoked by osmotic stimulation and shear stress (Erdogmus et al., 2019). This approach showed that the histamine receptor HR1 responds to hypo-osmotic saline, independent of agonist binding, and these responses depend on the C-terminal helix 8 (Erdogmus et al., 2019). GPR126 is activated by its binding partners in the extracellular matrix (ECM), collagen IV, and laminin211 (Petersen et al., 2015; Paavola et al., 2014), an effect that is potentiated by mechanical force applied using an atomic force microscope (AFM; Mitgau et al., 2022).

GPR68 (a.k.a. OGR1) is emerging as a candidate membrane mechanosensor based on a cell-based screen (Xu et al., 2018) and for its responses to cell stretching (Wei et al., 2018). GPR68 is conserved and proposed to play an important role in the vascular system based on its expression in endothelial cells and its role in shear-stress sensing in cell lines and primary endothelial cells (Xu et al., 2018). Building on these findings and engineering of other GPCRs, Ozkan et al. (2021) transformed GPR68 into a

Table 1. **GPCRs proposed to be mechanosensitive.**

GPCR	Other names	Tested mechanical stimuli
AT1R	Angiotensin II receptor 1	Shear stress; cell stretch; hypoosmotic saline
B2R	Bradykinin receptor 2	Shear stress; hypoosmotic saline
H1R	Histamine receptor 1	Cell indentation; hypoosmotic saline
GPR68	OGR1 [ovarian cancer G-protein coupled receptor 1]	Shear stress; cell stretch
Rh5, Rh6, NINA-E	Insect rhodopsins	Required for mechanosensory function
ADGRG5	GPR114	Centrifugation of cell suspension
ADGRG6	GPR126	Centrifugation of cell suspension; vibration of adherent cells; AFM pushing/pulling
ADGRG1	GPR56	AFM pushing/pulling
ADGRD1	GPR133	Centrifugation of cell suspension
ADGRL1	Latrophilin-1, CIRL-1, CL1, dCIRL	Inferred based on role in cell–cell adhesion; required for mechanosensory function in fruit flies and nematodes
ADGRL2	Latrophilin-2, CIRL-2, CL2	
ADGRL3	Ltrophilin-3, CIRL-3, CL3	

Interested readers may consult these reviews for additional discussion: Liebscher et al, 2021; Lin et al, 2022a; Wilde et al, 2022.

fluorescent reporter of shear stress by inserting a circularly permuted GFP into an intracellular loop in the protein. The resulting probe, iGlow, is sensitive both to chemical ligands and shear stress (Ozkan et al., 2021). Although they have attracted less attention than channels, the investigation of MS GPCRs could provide new insight into the role of mechanics in cell–cell and cell–matrix interactions and the molecular basis of shear stress sensing. Future studies may uncover both novel biology and biophysics of membrane mechanosensors.

Coda

The features that enable mechanosensitivity in cells that differ vastly in size, turgor, and other mechanical aspects remain mysterious and will continue to draw attention from researchers seeking to decipher the interplay of mechanics and biological function. For known and emerging MS membrane proteins, however, some conclusions can be drawn. First, these proteins exist in at least two conformations. Second, the application of mechanical force favors the activated conformation that enables transmembrane ion flux (ion channels) or induces intracellular biochemical signaling pathways (GPCRs). For proteins operating in the FFL mode, the active conformation typically occupies a larger area in the lipid bilayer than the closed conformation. The active conformation may also involve reduced curvature or thinning within the plane of the membrane (Fig. 2). How the active conformation of proteins operating under a FFF principle differs from the closed and/or inactive state is murkier, and clarification will almost certainly depend on future structural studies. Third, no MS protein functions in isolation; all depend on the physicochemical properties of the membrane in which it is embedded, and some also depend on filaments linking the membrane to the ECM, cell wall, or cytoskeleton. In summary, force sensing in biology underpins many fundamental and evolutionarily adaptive functions, including growth and homeostasis, external and internal sensation, moving, eating, and mating. The catalog of MS transmembrane proteins enabling these functions is diverse and continues to expand. Biophysical studies of this MS protein catalog have uncovered some unifying themes for activation, and future studies will help to clarify these mechanisms and reveal new ones.

Acknowledgments

Jeanne M. Nerbonne served as editor.

We thank the members of our laboratories, A. Ricci, and J. Art, for their feedback on early drafts of the manuscript.

The authors are supported by grants from the National Institutes of Health (R35NS105092 to M.B. Goodman; R01GM133845 to V. Vásquez), the National Science Foundation (MCB 1929355), and by a Howard Hughes Medical Institute-Simons Faculty Scholar Grant (55108530 to E.S. Haswell).

The authors declare no competing financial interests.

References

Adams, C.M., M.G. Anderson, D.G. Motto, M.P. Price, W.A. Johnson, and M.J. Welsh. 1998. Ripped pocket and pickpocket, novel *Drosophila* DEG/ENaC subunits expressed in early development and in mechanosensory neurons. *J. Cell Biol.* 140:143–152. https://doi.org/10.1083/jcb.140.1.143

Arnadóttir, J., and M. Chalfie. 2010. Eukaryotic mechanosensitive channels. *Annu. Rev. Biophys.* 39:111–137. https://doi.org/10.1146/annurev.biophys.37.032807.125836

Arnadóttir, J., R. O'Hagan, Y. Chen, M.B. Goodman, and M. Chalfie. 2011. The DEG/ENaC protein MEC-10 regulates the transduction channel complex in *Caenorhabditis elegans* touch receptor neurons. *J. Neurosci.* 31:12695–12704. https://doi.org/10.1523/JNEUROSCI.4580-10.2011

Aryal, P., V. Jarerattanachat, M.V. Clausen, M. Schewe, C. McClenaghan, L. Argent, L.J. Conrad, Y.Y. Dong, A.C.W. Pike, E.P. Carpenter, et al. 2017. Bilayer-mediated structural transitions control mechanosensitivity of the TREK-2 K2P Channel. *Structure*. 25:708–718.e2. https://doi.org/10.1016/j.str.2017.03.006

Bai, X., J. Bouffard, A. Lord, K. Brugman, P.W. Sternberg, E.J. Cram, and A. Golden. 2020. Caenorhabditis elegans PIEZO channel coordinates multiple reproductive tissues to govern ovulation. *Elife*. 9:e53603. https://doi.org/10.7554/eLife.53603

Ballesteros, A., C. Fenollar-Ferrer, and K.J. Swartz. 2018. Structural relationship between the putative hair cell mechanotransduction channel TMC1 and TMEM16 proteins. *Elife*. 7:e38433. https://doi.org/10.7554/eLife.38433

Basu, D., and E.S. Haswell. 2017. Plant mechanosensitive ion channels: An ocean of possibilities. *Curr. Opin. Plant Biol.* 40:43–48. https://doi.org/10.1016/j.pbi.2017.07.002

Basu, D., and E.S. Haswell. 2020. The mechanosensitive ion channel MSL10 potentiates responses to cell swelling in *Arabidopsis* seedlings. *Curr. Biol.* 30:2716–2728.e6. https://doi.org/10.1016/j.cub.2020.05.015

Beurg, M., A.C. Goldring, and R. Fettiplace. 2015a. The effects of Tmc1 Beethoven mutation on mechanotransducer channel function in cochlear hair cells. *J. Gen. Physiol.* 146:233–243. https://doi.org/10.1085/jgp.201511458

Beurg, M., W. Xiong, B. Zhao, U. Müller, and R. Fettiplace. 2015b. Subunit determination of the conductance of hair-cell mechanotransducer channels. *Proc. Natl. Acad. Sci. USA*. 112:1589–1594. https://doi.org/10.1073/pnas.1420906112

Beurg, M., L.A. Schimmenti, A. Koleilat, S.S. Amr, A. Oza, A.J. Barlow, A. Ballesteros, and R. Fettiplace. 2021. New Tmc1 deafness mutations

impact mechanotransduction in auditory hair cells. *J. Neurosci.* 41: 4378–4391. https://doi.org/10.1523/JNEUROSCI.2537-20.2021
Brohawn, S.G., Z. Su, and R. MacKinnon. 2014. Mechanosensitivity is mediated directly by the lipid membrane in TRAAK and TREK1 K^+ channels. *Proc. Natl. Acad. Sci. USA.* 111:3614–3619. https://doi.org/10.1073/pnas.1320768111
Cabanos, C., M. Wang, X. Han, and S.B. Hansen. 2017. A soluble fluorescent binding assay reveals PIP2 antagonism of TREK-1 channels. *Cell Rep.* 20: 1287–1294. https://doi.org/10.1016/j.celrep.2017.07.034
Cahalan, S.M., V. Lukacs, S.S. Ranade, S. Chien, M. Bandell, and A. Patapoutian. 2015. Piezo1 links mechanical forces to red blood cell volume. *Elife.* 4:e07370. https://doi.org/10.7554/eLife.07370
Chalfie, M., and M. Au. 1989. Genetic control of differentiation of the *Caenorhabditis elegans* touch receptor neurons. *Science.* 243:1027–1033. https://doi.org/10.1126/science.2646709
Chatzigeorgiou, M., L. Grundy, K.S. Kindt, W.-H. Lee, M. Driscoll, and W.R. Schafer. 2010a. Spatial asymmetry in the mechanosensory phenotypes of the *C. elegans* DEG/ENaC gene mec-10. *J. Neurophysiol.* 104:3334–3344. https://doi.org/10.1152/jn.00330.2010
Chatzigeorgiou, M., S. Yoo, J.D. Watson, W.-H. Lee, W.C. Spencer, K.S. Kindt, S.W. Hwang, D.M. Miller III, M. Treinin, M. Driscoll, and W.R. Schafer. 2010b. Specific roles for DEG/ENaC and TRP channels in touch and thermosensation in *C. elegans* nociceptors. *Nat. Neurosci.* 13:861–868. https://doi.org/10.1038/nn.2581
Cheng, L.E., W. Song, L.L. Looger, L.Y. Jan, and Y.N. Jan. 2010. The role of the TRP channel NompC in *Drosophila* larval and adult locomotion. *Neuron.* 67:373–380. https://doi.org/10.1016/j.neuron.2010.07.004
Chesler, A.T., M. Szczot, D. Bharucha-Goebel, M. Čeko, S. Donkervoort, C. Laubacher, L.H. Hayes, K. Alter, C. Zampieri, C. Stanley, et al. 2016. The role of PIEZO2 in human mechanosensation. *N. Engl. J. Med.* 375: 1355–1364. https://doi.org/10.1056/NEJMoa1602812
Corey, D.P., J. García-Añoveros, J.R. Holt, K.Y. Kwan, S.-Y. Lin, M.A. Vollrath, A. Amalfitano, E.L.-M. Cheung, B.H. Derfler, A. Duggan, et al. 2004. TRPA1 is a candidate for the mechanosensitive transduction channel of vertebrate hair cells. *Nature.* 432:723–730. https://doi.org/10.1038/nature03066
Das, A., J.A. Franco, L. Wang, D. Chapman, L.M. Wang, C. Jaisinghani, B.L. Pruitt, and M.B. Goodman. 2022. Conserved basal lamina proteins, laminin and nidogen, are repurposed to organize mechanosensory complexes responsible for touch sensation. *bioRxiv.* (Preprint posted February 11, 2022). https://doi.org/10.1101/2022.02.11.479800
Das, R., L.-C. Lin, F. Català-Castro, N. Malaiwong, N. Sanfeliu-Cerdán, M. Porta-de-la-Riva, A. Pidde, and M. Krieg. 2021. An asymmetric mechanical code ciphers curvature-dependent proprioceptor activity. *Sci. Adv.* 7:eabg4617. https://doi.org/10.1126/sciadv.abg4617
Deng, Z., G. Maksaev, A.M. Schlegel, J. Zhang, M. Rau, J.A.J. Fitzpatrick, E.S. Haswell, and P. Yuan. 2020. Structural mechanism for gating of a eukaryotic mechanosensitive channel of small conductance. *Nat. Commun.* 11:3690. https://doi.org/10.1038/s41467-020-17538-1
Driscoll, M., and M. Chalfie. 1991. The *mec*-4 gene is a member of a family of *Caenorhabditis elegans* genes that can mutate to induce neuronal degeneration. *Nature.* 349:588–593. https://doi.org/10.1038/349588a0
Du, H., C. Ye, D. Wu, Y.-Y. Zang, L. Zhang, C. Chen, X.-Y. He, J.-J. Yang, P. Hu, Z. Xu, et al. 2020. The cation channel TMEM63B is an osmosensor required for hearing. *Cell Rep.* 31:107596. https://doi.org/10.1016/j.celrep.2020.107596
Dubin, A.E., S. Murthy, A.H. Lewis, L. Brosse, S.M. Cahalan, J. Grandl, B. Coste, and A. Patapoutian. 2017. Endogenous Piezo1 can confound mechanically activated channel identification and characterization. *Neuron.* 94:266–270.e3. https://doi.org/10.1016/j.neuron.2017.03.039
Dunn, H.A., C. Orlandi, and K.A. Martemyanov. 2019. Beyond the ligand: Extracellular and transcellular G Protein-coupled receptor complexes in physiology and pharmacology. *Pharmacol. Rev.* 71:503–519. https://doi.org/10.1124/pr.119.018044
Effertz, T., R. Wiek, and M.C. Göpfert. 2011. NompC TRP channel is essential for *Drosophila* sound receptor function. *Curr. Biol.* 21:592–597. https://doi.org/10.1016/j.cub.2011.02.048
Eijkelkamp, N., J.E. Linley, J.M. Torres, L. Bee, A.H. Dickenson, M. Gringhuis, M.S. Minett, G.S. Hong, E. Lee, U. Oh, et al. 2013. A role for Piezo2 in EPAC1-dependent mechanical allodynia. *Nat. Commun.* 4:1682. https://doi.org/10.1038/ncomms2673
Emtage, L., G. Gu, E. Hartwieg, and M. Chalfie. 2004. Extracellular proteins organize the mechanosensory channel complex in *C. elegans* touch receptor neurons. *Neuron.* 44:795–807. https://doi.org/10.1016/j.neuron.2004.11.010
Erdogmus, S., U. Storch, L. Danner, J. Becker, M. Winter, N. Ziegler, A. Wirth, S. Offermanns, C. Hoffmann, T. Gudermann, et al. 2019. Helix 8 is the essential structural motif of mechanosensitive GPCRs. *Nat. Commun.* 10: 5784. https://doi.org/10.1038/s41467-019-13722-0
Ernstrom, G.G., and M. Chalfie. 2002. Genetics of sensory mechanotransduction. *Annu. Rev. Genet.* 36:411–453. https://doi.org/10.1146/annurev.genet.36.061802.101708
Faucherre, A., J. Nargeot, M.E. Mangoni, and C. Jopling. 2013. *piezo2b* regulates vertebrate light touch response. *J. Neurosci.* 33:17089–17094. https://doi.org/10.1523/JNEUROSCI.0522-13.2013
Fink, M., F. Lesage, F. Duprat, C. Heurteaux, R. Reyes, M. Fosset, and M. Lazdunski. 1998. A neuronal two P domain K^+ channel stimulated by arachidonic acid and polyunsaturated fatty acids. *EMBO J.* 17:3297–3308. https://doi.org/10.1093/emboj/17.12.3297
Geffeney, S.L., J.G. Cueva, D.A. Glauser, J.C. Doll, T.H.-C. Lee, M. Montoya, S. Karania, A.M. Garakani, B.L. Pruitt, and M.B. Goodman. 2011. DEG/ENaC but not TRP channels are the major mechanoelectrical transduction channels in a *C. elegans* nociceptor. *Neuron.* 71:845–857. https://doi.org/10.1016/j.neuron.2011.06.038
Glogowska, E., E.R. Schneider, Y. Maksimova, V.P. Schulz, K. Lezon-Geyda, J. Wu, K. Radhakrishnan, S.B. Keel, D. Mahoney, A.M. Freidmann, et al. 2017. Novel mechanisms of PIEZO1 dysfunction in hereditary xerocytosis. *Blood.* 130:1845–1856. https://doi.org/10.1182/blood-2017-05-786004
Goodman, M.B., and E.M. Schwarz. 2003. Transducing touch in *Caenorhabditis elegans*. *Annu. Rev. Physiol.* 65:429–452. https://doi.org/10.1146/annurev.physiol.65.092101.142659
Gottlieb, P., J. Folgering, R. Maroto, A. Raso, T.G. Wood, A. Kurosky, C. Bowman, D. Bichet, A. Patel, F. Sachs, et al. 2008. Revisiting TRPC1 and TRPC6 mechanosensitivity. *Pflugers Arch.* 455:1097–1103. https://doi.org/10.1007/s00424-007-0359-3
Guo, Y.R., and R. MacKinnon. 2017. Structure-based membrane dome mechanism for Piezo mechanosensitivity. *Elife.* 6:e33660. https://doi.org/10.7554/eLife.33660
Hamilton, E.S., G.S. Jensen, G. Maksaev, A. Katims, A.M. Sherp, and E.S. Haswell. 2015. Mechanosensitive channel MSL8 regulates osmotic forces during pollen hydration and germination. *Science.* 350:438–441. https://doi.org/10.1126/science.aac6014
Himmel, N.J., and D.N. Cox. 2020. Transient receptor potential channels: Current perspectives on evolution, structure, function and nomenclature. *Proc. Biol. Sci.* 287:20201309. https://doi.org/10.1098/rspb.2020.1309
Holt, J.R., M. Tobin, J. Elferich, E. Gouaux, A. Ballesteros, Z. Yan, Z.M. Ahmed, and T. Nicolson. 2021a. Putting the pieces together: The hair cell transduction complex. *J. Assoc. Res. Otolaryngol.* 22:601–608. https://doi.org/10.1007/s10162-021-00808-0
Holt, J.R., W.-Z. Zeng, E.L. Evans, S.-H. Woo, S. Ma, H. Abuwarda, M. Loud, A. Patapoutian, and M.M. Pathak. 2021b. Spatiotemporal dynamics of PIEZO1 localization controls keratinocyte migration during wound healing. *Elife.* 10:e65415. https://doi.org/10.7554/eLife.65415
Hou, C., W. Tian, T. Kleist, K. He, V. Garcia, F. Bai, Y. Hao, S. Luan, and L. Li. 2014. DUF221 proteins are a family of osmosensitive calcium-permeable cation channels conserved across eukaryotes. *Cell Res.* 24:632–635. https://doi.org/10.1038/cr.2014.14
Huang, M., and M. Chalfie. 1994. Gene interactions affecting mechanosensory transduction in *Caenorhabditis elegans*. *Nature.* 367:467–470. https://doi.org/10.1038/367467a0
Hughes, K., A. Shah, X. Bai, J. Adams, R. Bauer, J. Jackson, E. Harris, A. Ficca, P. Freebairn, S. Mohammed, et al. 2022. Distinct mechanoreceptor pezo-1 isoforms modulate food intake in the nematode *Caenorhabditis elegans*. *G3.* 12:jkab429. https://doi.org/10.1093/g3journal/jkab429
Ikeda, R., M. Cha, J. Ling, Z. Jia, D. Coyle, and J.G. Gu. 2014. Merkel cells transduce and encode tactile stimuli to drive Aβ-afferent impulses. *Cell.* 157:664–675. https://doi.org/10.1016/j.cell.2014.02.026
Iosip, A.L., J. Böhm, S. Scherzer, K.A.S. Al-Rasheid, I. Dreyer, J. Schultz, D. Becker, I. Kreuzer, and R. Hedrich. 2020. The Venus flytrap trigger hair-specific potassium channel KDM1 can reestablish the K^+ gradient required for hapto-electric signaling. *PLoS Biol.* 18:e3000964. https://doi.org/10.1371/journal.pbio.3000964
Jang, W., S. Lee, S.-I. Choi, H.-S. Chae, J. Han, H. Jo, S.W. Hwang, C.-S. Park, and C. Kim. 2019. Impairment of proprioceptive movement and mechanical nociception in *Drosophila melanogaster* larvae lacking Ppk30, a *Drosophila* member of the degenerin/epithelial sodium channel family. *Genes Brain Behav.* 18:e12545. https://doi.org/10.1111/gbb.12545

Jeong, H., S. Clark, A. Goehring, S. Dehghani-Ghahnaviyeh, A. Rasouli, E. Tajkhorshid, and E. Gouaux. 2022. Structures of the TMC-1 complex illuminate mechanosensory transduction. *Nature*. 610:796–803. https://doi.org/10.1038/s41586-022-05314-8

Jia, Y., Y. Zhao, T. Kusakizako, Y. Wang, C. Pan, Y. Zhang, O. Nureki, M. Hattori, and Z. Yan. 2020. TMC1 and TMC2 proteins are pore-forming subunits of mechanosensitive ion channels. *Neuron*. 105:310–321.e3. https://doi.org/10.1016/j.neuron.2019.10.017

Jin, P., D. Bulkley, Y. Guo, W. Zhang, Z. Guo, W. Huynh, S. Wu, S. Meltzer, T. Cheng, L.Y. Jan, et al. 2017. Electron cryo-microscopy structure of the mechanotransduction channel NOMPC. *Nature*. 547:118–122. https://doi.org/10.1038/nature22981

Jojoa-Cruz, S., K. Saotome, C.C.A. Tsui, W.-H. Lee, M.S.P. Sansom, S.E. Murthy, A. Patapoutian, and A.B. Ward. 2022. Structural insights into the Venus flytrap mechanosensitive ion channel Flycatcher1. *Nat. Commun.* 13:850. https://doi.org/10.1038/s41467-022-28511-5

Kamikouchi, A., H.K. Inagaki, T. Effertz, O. Hendrich, A. Fiala, M.C. Göpfert, and K. Ito. 2009. The neural basis of *Drosophila* gravity-sensing and hearing. *Nature*. 458:165–171. https://doi.org/10.1038/nature07810

Kang, L., J. Gao, W.R. Schafer, Z. Xie, and X.Z.S. Xu. 2010. *C. elegans* TRP family protein TRP-4 is a pore-forming subunit of a native mechanotransduction channel. *Neuron*. 67:381–391. https://doi.org/10.1016/j.neuron.2010.06.032

Katta, S., M. Krieg, and M.B. Goodman. 2015. Feeling force: Physical and physiological principles enabling sensory mechanotransduction. *Annu. Rev. Cell Dev. Biol.* 31:347–371. https://doi.org/10.1146/annurev-cellbio-100913-013426

Katta, S., A. Sanzeni, A. Das, M. Vergassola, and M.B. Goodman. 2019. Progressive recruitment of distal MEC-4 channels determines touch response strength in *C. elegans*. *J. Gen. Physiol.* 151:1213–1230. https://doi.org/10.1085/jgp.201912374

Kawashima, Y., G.S.G. Géléoc, K. Kurima, V. Labay, A. Lelli, Y. Asai, T. Makishima, D.K. Wu, C.C. Della Santina, J.R. Holt, and A.J. Griffith. 2011. Mechanotransduction in mouse inner ear hair cells requires transmembrane channel-like genes. *J. Clin. Invest.* 121:4796–4809. https://doi.org/10.1172/JCI60405

Kernan, M., D. Cowan, and C. Zuker. 1994. Genetic dissection of mechanosensory transduction: Mechanoreception-defective mutations of *Drosophila*. *Neuron*. 12:1195–1206. https://doi.org/10.1016/0896-6273(94)90437-5

Kim, S.E., B. Coste, A. Chadha, B. Cook, and A. Patapoutian. 2012. The role of *Drosophila* Piezo in mechanical nociception. *Nature*. 483:209–212. https://doi.org/10.1038/nature10801

Kim, Y., H. Bang, C. Gnatenco, and D. Kim. 2001. Synergistic interaction and the role of C-terminus in the activation of TRAAK K^+ channels by pressure, free fatty acids and alkali. *Pflugers Arch.* 442:64–72. https://doi.org/10.1007/s004240000496

Kubanek, J., P. Shukla, A. Das, S.A. Baccus, and M.B. Goodman. 2018. Ultrasound elicits behavioral responses through mechanical effects on neurons and ion channels in a simple nervous system. *J. Neurosci.* 38:3081–3091. https://doi.org/10.1523/JNEUROSCI.1458-17.2018

Kung, C. 2005. A possible unifying principle for mechanosensation. *Nature*. 436:647–654. https://doi.org/10.1038/nature03896

Kurima, K., L.M. Peters, Y. Yang, S. Riazuddin, Z.M. Ahmed, S. Naz, D. Arnaud, S. Drury, J. Mo, T. Makishima, et al. 2002. Dominant and recessive deafness caused by mutations of a novel gene, TMC1, required for cochlear hair-cell function. *Nat. Genet.* 30:277–284. https://doi.org/10.1038/ng842

Labay, V., R.M. Weichert, T. Makishima, and A.J. Griffith. 2010. Topology of transmembrane channel-like gene 1 protein. *Biochemistry*. 49:8592–8598. https://doi.org/10.1021/bi1004377

Lee, C.P., G. Maksaev, G.S. Jensen, M.W. Murcha, M.E. Wilson, M. Fricker, R. Hell, E.S. Haswell, A.H. Millar, and L.J. Sweetlove. 2016. MSL1 is a mechanosensitive ion channel that dissipates mitochondrial membrane potential and maintains redox homeostasis in mitochondria during abiotic stress. *Plant J.* 88:809–825. https://doi.org/10.1111/tpj.13301

Lehnert, B.P., A.E. Baker, Q. Gaudry, A.-S. Chiang, and R.I. Wilson. 2013. Distinct roles of TRP channels in auditory transduction and amplification in *Drosophila*. *Neuron*. 77:115–128. https://doi.org/10.1016/j.neuron.2012.11.030

Levina, N., S. Tötemeyer, N.R. Stokes, P. Louis, M.A. Jones, and I.R. Booth. 1999. Protection of *Escherichia coli* cells against extreme turgor by activation of MscS and MscL mechanosensitive channels: Identification of genes required for MscS activity. *EMBO J.* 18:1730–1737. https://doi.org/10.1093/emboj/18.7.1730

Li, S., B. Li, L. Gao, J. Wang, and Z. Yan. 2022. Humidity response in *Drosophila* olfactory sensory neurons requires the mechanosensitive channel TMEM63. *Nat. Commun.* 13:3814. https://doi.org/10.1038/s41467-022-31253-z

Li, W., Z. Feng, P.W. Sternberg, and X.Z.S. Xu. 2006. A *C. elegans* stretch receptor neuron revealed by a mechanosensitive TRP channel homologue. *Nature*. 440:684–687. https://doi.org/10.1038/nature04538

Liang, X., J. Madrid, R. Gärtner, J.-M. Verbavatz, C. Schiklenk, M. Wilsch-Bräuninger, A. Bogdanova, F. Stenger, A. Voigt, and J. Howard. 2013. A NOMPC-dependent membrane-microtubule connector is a candidate for the gating spring in fly mechanoreceptors. *Curr. Biol.* 23:755–763. https://doi.org/10.1016/j.cub.2013.03.065

Liang, X., J. Madrid, H.S. Saleh, and J. Howard. 2011. NOMPC, a member of the TRP channel family, localizes to the tubular body and distal cilium of *Drosophila* campaniform and chordotonal receptor cells. *Cytoskeleton* 68:1–7. https://doi.org/10.1002/cm.20493

Liebeskind, B.J., D.M. Hillis, and H.H. Zakon. 2015. Convergence of ion channel genome content in early animal evolution. *Proc. Natl. Acad. Sci. USA*. 112:E846–E851. https://doi.org/10.1073/pnas.1501195112

Liebscher, I., O. Cevheroğlu, C.-C. Hsiao, A.F. Maia, H. Schihada, N. Scholz, M. Soave, K. Spiess, K. Trajković, M. Kosloff, and S. Prömel. 2021. A guide to adhesion GPCR research. *FEBS J.* https://doi.org/10.1111/febs.16258

Lin, H.-H., K.-F. Ng, T.-C. Chen, and W.-Y. Tseng. 2022a. Ligands and beyond: Mechanosensitive adhesion GPCRs. *Pharmaceuticals*. 15:219. https://doi.org/10.3390/ph15020219

Lin, Y.-C., Y.R. Guo, A. Miyagi, J. Levring, R. MacKinnon, and S. Scheuring. 2019. Force-induced conformational changes in PIEZO1. *Nature*. 573:230–234. https://doi.org/10.1038/s41586-019-1499-2

Lin, Y., A. Bunyan, and B. Corry. 2022b. Characterizing the lipid fingerprint of the mechanosensitive channel Piezo2. *J. Gen. Physiol*. 154:202113064. In this issue. https://doi.org/10.1085/jgp.202113064

Liu, X., J. Wang, and L. Sun. 2018. Structure of the hyperosmolality-gated calcium-permeable channel OSCA1.2. *Nat. Commun.* 9:5060. https://doi.org/10.1038/s41467-018-07564-5

Ma, S., S. Cahalan, G. LaMonte, N.D. Grubaugh, W. Zeng, S.E. Murthy, E. Paytas, R. Gamini, V. Lukacs, T. Whitwam, et al. 2018. Common PIEZO1 allele in African populations causes RBC dehydration and attenuates plasmodium infection. *Cell*. 173:443–455.e12. https://doi.org/10.1016/j.cell.2018.02.047

Maingret, F., A.J. Patel, F. Lesage, M. Lazdunski, and E. Honoré. 2000. Lysophospholipids open the two-pore domain mechano-gated K^+ channels TREK-1 and TRAAK. *J. Biol. Chem.* 275:10128–10133. https://doi.org/10.1074/jbc.275.14.10128

Maity, K., J.M. Heumann, A.P. McGrath, N.J. Kopcho, P.-K. Hsu, C.-W. Lee, J.H. Mapes, D. Garza, S. Krishnan, G.P. Morgan, et al. 2019. Cryo-EM structure of OSCA1.2 from Oryza sativa elucidates the mechanical basis of potential membrane hyperosmolality gating. *Proc. Natl. Acad. Sci. USA*. 116:14309–14318. https://doi.org/10.1073/pnas.1900774116

Maksaev, G., and E.S. Haswell. 2012. MscS-like10 is a stretch-activated ion channel from *Arabidopsis thaliana* with a preference for anions. *Proc. Natl. Acad. Sci. USA*. 109:19015–19020. https://doi.org/10.1073/pnas.1213931109

Martinac, B., M. Buechner, A.H. Delcour, J. Adler, and C. Kung. 1987. Pressure-sensitive ion channel in *Escherichia coli*. *Proc. Natl. Acad. Sci. USA*. 84:2297–2301. https://doi.org/10.1073/pnas.84.8.2297

Matúš, D., W.B. Post, S. Horn, T. Schöneberg, and S. Prömel. 2022. Latrophilin-1 drives neuron morphogenesis and shapes chemo- and mechanosensation-dependent behavior in *C. elegans* via a trans function. *Biochem. Biophys. Res. Commun.* 589:152–158. https://doi.org/10.1016/j.bbrc.2021.12.006

Mauthner, S.E., R.Y. Hwang, A.H. Lewis, Q. Xiao, A. Tsubouchi, Y. Wang, K. Honjo, J.H.P. Skene, J. Grandl, and W.D. Tracey Jr. 2014. Balboa binds to pickpocket in vivo and is required for mechanical nociception in *Drosophila* larvae. *Curr. Biol.* 24:2920–2925. https://doi.org/10.1016/j.cub.2014.10.038

Millet, J.R.M., L.O. Romero, J. Lee, B. Bell, and V. Vásquez. 2022. *C. elegans* PEZO-1 is a mechanosensitive ion channel involved in food sensation. *J. Gen. Physiol.* 154:e202112960. https://doi.org/10.1085/jgp.202112960

Min, S., Y. Oh, P. Verma, S.C. Whitehead, N. Yapici, D. Van Vactor, G.S. Suh, and S. Liberles. 2021. Control of feeding by Piezo-mediated gut mechanosensation in *Drosophila*. *Elife*. 10:e63049. https://doi.org/10.7554/eLife.63049

Mitgau, J., J. Franke, C. Schinner, G. Stephan, S. Berndt, D.G. Placantonakis, H. Kalwa, V. Spindler, C. Wilde, and I. Liebscher. 2022. The N terminus of adhesion G protein-coupled receptor GPR126/ADGRG6 as allosteric

force integrator. *Front. Cell Dev. Biol.* 10:873278. https://doi.org/10.3389/fcell.2022.873278

Moe-Lange, J., N.M. Gappel, M. Machado, M.M. Wudick, C.S.A. Sies, S.N. Schott-Verdugo, M. Bonus, S. Mishra, T. Hartwig, M. Bezrutczyk, et al. 2021. Interdependence of a mechanosensitive anion channel and glutamate receptors in distal wound signaling. *Sci. Adv.* 7:eabg4298. https://doi.org/10.1126/sciadv.abg4298

Moroni, M., M.R. Servin-Vences, R. Fleischer, O. Sánchez-Carranza, and G.R. Lewin. 2018. Voltage gating of mechanosensitive PIEZO channels. *Nat. Commun.* 9:1096. https://doi.org/10.1038/s41467-018-03502-7

Mount, J., G. Maksaev, B.T. Summers, J.A.J. Fitzpatrick, and P. Yuan. 2022. Structural basis for mechanotransduction in a potassium-dependent mechanosensitive ion channel. *Nat. Commun.* 13:6904. https://doi.org/10.1038/s41467-022-34737-0

Mousavi, S.A.R., A.E. Dubin, W.-Z. Zeng, A.M. Coombs, K. Do, D.A. Ghadiri, W.T. Keenan, C. Ge, Y. Zhao, and A. Patapoutian. 2021. PIEZO ion channel is required for root mechanotransduction in *Arabidopsis thaliana*. *Proc. Natl. Acad. Sci. USA.* 118:e2102188118. https://doi.org/10.1073/pnas.2102188118

Nikolaev, Y.A., C.D. Cox, P. Ridone, P.R. Rohde, J.F. Cordero-Morales, V. Vásquez, D.R. Laver, and B. Martinac. 2019. Mammalian TRP ion channels are insensitive to membrane stretch. *J. Cell Sci.* 132:jcs238360. https://doi.org/10.1242/jcs.238360

Nishii, K., M. Möller, and H. Iida. 2021. Mix and match: Patchwork domain evolution of the land plant-specific Ca^{2+}-permeable mechanosensitive channel MCA. *PLoS One.* 16:e0249735. https://doi.org/10.1371/journal.pone.0249735

O'Hagan, R., M. Chalfie, and M.B. Goodman. 2005. The MEC-4 DEG/ENaC channel of *Caenorhabditis elegans* touch receptor neurons transduces mechanical signals. *Nat. Neurosci.* 8:43–50. https://doi.org/10.1038/nn1362

Ozkan, A.D., T. Gettas, A. Sogata, W. Phaychanpheng, M. Zhou, and J.J. Lacroix. 2021. Mechanical and chemical activation of GPR68 probed with a genetically encoded fluorescent reporter. *J. Cell Sci.* 134:jcs255455. https://doi.org/10.1242/jcs.255455

Paavola, K.J., H. Sidik, J.B. Zuchero, M. Eckart, and W.S. Talbot. 2014. Type IV collagen is an activating ligand for the adhesion G protein-coupled receptor GPR126. *Sci. Signal.* 7:ra76. https://doi.org/10.1126/scisignal.2005347

Pan, B., N. Akyuz, X.-P. Liu, Y. Asai, C. Nist-Lund, K. Kurima, B.H. Derfler, B. György, W. Limapichat, S. Walujkar, et al. 2018. TMC1 Forms the pore of mechanosensory transduction channels in vertebrate inner ear hair cells. *Neuron.* 99:736–753.e6. https://doi.org/10.1016/j.neuron.2018.07.033

Pan, B., G.S. Géléoc, Y. Asai, G.C. Horwitz, K. Kurima, K. Ishikawa, Y. Kawashima, A.J. Griffith, and J.R. Holt. 2013. TMC1 and TMC2 are components of the mechanotransduction channel in hair cells of the mammalian inner ear. *Neuron.* 79:504–515. https://doi.org/10.1016/j.neuron.2013.06.019

Peng, G., X. Shi, and T. Kadowaki. 2015. Evolution of TRP channels inferred by their classification in diverse animal species. *Mol. Phylogenet. Evol.* 84:145–157. https://doi.org/10.1016/j.ympev.2014.06.016

Perozo, E., A. Kloda, D.M. Cortes, and B. Martinac. 2002. Physical principles underlying the transduction of bilayer deformation forces during mechanosensitive channel gating. *Nat. Struct. Biol.* 9:696–703. https://doi.org/10.1038/nsb827

Petersen, S.C., R. Luo, I. Liebscher, S. Giera, S.-J. Jeong, A. Mogha, M. Ghidinelli, M.L. Feltri, T. Schöneberg, X. Piao,et al. 2015. The adhesion GPCR GPR126 has distinct, domain-dependent functions in Schwann cell development mediated by interaction with laminin-211. *Neuron.* 85:755–769. https://doi.org/10.1016/j.neuron.2014.12.05

Pivetti, C.D., M.-R. Yen, S. Miller, W. Busch, Y.-H. Tseng, I.R. Booth, and M.H. Saier Jr. 2003. Two families of mechanosensitive channel proteins. *Microbiol. Mol. Biol. Rev.* 67:66–85. https://doi.org/10.1128/MMBR.67.1.66-85.2003

Procko, C., S. Murthy, W.T. Keenan, S.A.R. Mousavi, T. Dabi, A. Coombs, E. Procko, L. Baird, A. Patapoutian, and J. Chory. 2021. Stretch-activated ion channels identified in the touch-sensitive structures of carnivorous Droseraceae plants. *Elife.* 10:e64250. https://doi.org/10.7554/eLife.64250

Radin, I., R.A. Richardson, J.H. Coomey, E.R. Weiner, C.S. Bascom, T. Li, M. Bezanilla, and E.S. Haswell. 2021. Plant PIEZO homologs modulate vacuole morphology during tip growth. *Science.* 373:586–590. https://doi.org/10.1126/science.abe6310

Ranade, S.S., S.-H. Woo, A.E. Dubin, R.A. Moshourab, C. Wetzel, M. Petrus, J. Mathur, V. Bégay, B. Coste, J. Mainquist, et al. 2014. Piezo2 is the major transducer of mechanical forces for touch sensation in mice. *Nature.* 516:121–125. https://doi.org/10.1038/nature13980

Rasmussen, T., V.J. Flegler, A. Rasmussen, and B. Böttcher. 2019. Structure of the mechanosensitive channel MscS embedded in the membrane bilayer. *J. Mol. Biol.* 431:3081–3090. https://doi.org/10.1016/j.jmb.2019.07.006

Reddy, B., N. Bavi, A. Lu, Y. Park, and E. Perozo. 2019. Molecular basis of force-from-lipids gating in the mechanosensitive channel MscS. *Elife.* 8:e50486. https://doi.org/10.7554/eLife.50486

Ridone, P., S.L. Grage, A. Patkunarajah, A.R. Battle, A.S. Ulrich, and B. Martinac. 2018. "Force-from-lipids" gating of mechanosensitive channels modulated by PUFAs. *J. Mech. Behav. Biomed. Mater.* 79:158–167. https://doi.org/10.1016/j.jmbbm.2017.12.026

Ridone, P., E. Pandzic, M. Vassalli, C.D. Cox, A. Macmillan, P.A. Gottlieb, and B. Martinac. 2020. Disruption of membrane cholesterol organization impairs the activity of PIEZO1 channel clusters. *J. Gen. Physiol.* 152:e201912515. https://doi.org/10.1085/jgp.201912515

Romero, L.O., R. Caires, A.R. Nickolls, A.T. Chesler, J.F. Cordero-Morales, and V. Vásquez. 2020. A dietary fatty acid counteracts neuronal mechanical sensitization. *Nat. Commun.* 11:2997. https://doi.org/10.1038/s41467-020-16816-2

Romero, L.O., A.E. Massey, A.D. Mata-Daboin, F.J. Sierra-Valdez, S.C. Chauhan, J.F. Cordero-Morales, and V. Vásquez. 2019. Dietary fatty acids fine-tune Piezo1 mechanical response. *Nat. Commun.* 10:1200. https://doi.org/10.1038/s41467-019-09055-7

Sanzeni, A., S. Katta, B. Petzold, B.L. Pruitt, M.B. Goodman, and M. Vergassola. 2019. Somatosensory neurons integrate the geometry of skin deformation and mechanotransduction channels to shape touch sensing. *Elife.* 8:e43226. https://doi.org/10.7554/eLife.43226

Scherzer, S., S. Huang, A. Iosip, I. Kreuzer, K. Yokawa, K.A.S. Al-Rasheid, M. Heckmann, and R. Hedrich. 2022. Ether anesthetics prevents touch-induced trigger hair calcium-electrical signals excite the Venus flytrap. *Sci. Rep.* 12:2851. https://doi.org/10.1038/s41598-022-06915-z

Schneider, E.R., E.O. Anderson, M. Mastrotto, J.D. Matson, V.P. Schulz, P.G. Gallagher, R.H. LaMotte, E.O. Gracheva, and S.N. Bagriantsev. 2017. Molecular basis of tactile specialization in the duck bill. *Proc. Natl. Acad. Sci. USA.* 114:13036–13041. https://doi.org/10.1073/pnas.1708793114

Scholz, N., J. Gehring, C. Guan, D. Ljaschenko, R. Fischer, V. Lakshmanan, R.J. Kittel, and T. Langenhan. 2015. The adhesion GPCR latrophilin/CIRL shapes mechanosensation. *Cell Rep.* 11:866–874. https://doi.org/10.1016/j.celrep.2015.04.008

Scholz, N., C. Guan, M. Nieberler, A. Grotemeyer, I. Maiellaro, S. Gao, S. Beck, M. Pawlak, M. Sauer, E. Asan, et al. 2017. Mechano-dependent signaling by Latrophilin/CIRL quenches cAMP in proprioceptive neurons. *Elife.* 6:e28360. https://doi.org/10.7554/eLife.28360

Schrecke, S., Y. Zhu, J.W. McCabe, M. Bartz, C. Packianathan, M. Zhao, M. Zhou, D. Russell, and A. Laganowsky. 2021. Selective regulation of human TRAAK channels by biologically active phospholipids. *Nat. Chem. Biol.* 17:89–95. https://doi.org/10.1038/s41589-020-00659-5

Senthilan, P.R., D. Piepenbrock, G. Ovezmyradov, B. Nadrowski, S. Bechstedt, S. Pauls, M. Winkler, W. Möbius, J. Howard, and M.C. Göpfert. 2012. *Drosophila* auditory organ genes and genetic hearing defects. *Cell.* 150:1042–1054. https://doi.org/10.1016/j.cell.2012.06.043

Shi, J., A.J. Hyman, D. De Vecchis, J. Chong, L. Lichtenstein, T.S. Futers, M. Rouahi, A.N. Salvayre, N. Auge, A.C. Kalli,et al. 2020. Sphingomyelinase disables inactivation in endogenous PIEZO1 channels. *Cell Rep.* 33:108225. https://doi.org/10.1016/j.celrep.2020.108225

Sidi, S., R.W. Friedrich, and T. Nicolson. 2003. NompC TRP channel required for vertebrate sensory hair cell mechanotransduction. *Science.* 301:96–99. https://doi.org/10.1126/science.1084370

Sukharev, S. 2002. Purification of the small mechanosensitive channel of *Escherichia coli* (MscS): The subunit structure, conduction, and gating characteristics in liposomes. *Biophys. J.* 83:290–298. https://doi.org/10.1016/S0006-3495(02)75169-2

Sukharev, S., and D.P. Corey. 2004. Mechanosensitive channels: Multiplicity of families and gating paradigms. *Sci. STKE.* 2004:re4. https://doi.org/10.1126/stke.2192004re4

Sukharev, S.I., P. Blount, B. Martinac, F.R. Blattner, and C. Kung. 1994. A large-conductance mechanosensitive channel in *E. coli* encoded by mscL alone. *Nature.* 368:265–268. https://doi.org/10.1038/368265a0

Suzuki, H., R. Kerr, L. Bianchi, C. Frøkjaer-Jensen, D. Slone, J. Xue, B. Gerstbrein, M. Driscoll, and W.R. Schafer. 2003. In vivo imaging of *C. elegans* mechanosensory neurons demonstrates a specific role for the MEC-4 channel in the process of gentle touch sensation. *Neuron.* 39:1005–1017. https://doi.org/10.1016/j.neuron.2003.08.015

Tang, Y.-Q., S.A. Lee, M. Rahman, S.A. Vanapalli, H. Lu, and W.R. Schafer. 2020. Ankyrin Is an intracellular tether for TMC mechanotransduction channels. *Neuron*. 107:759–761. https://doi.org/10.1016/j.neuron.2020.07.031

Tao, L., D. Porto, Z. Li, S. Fechner, S.A. Lee, M.B. Goodman, X.Z. Shawn Xu, H. Lu, and K. Shen. 2019. Parallel processing of two mechanosensory modalities by a single neuron in *C. elegans*. *Dev. Cell*. 51:617–631.e3. https://doi.org/10.1016/j.devcel.2019.10.008

Teng, J., S. Loukin, A. Anishkin, and C. Kung. 2015. The force-from-lipid (FFL) principle of mechanosensitivity, at large and in elements. *Pflugers Arch.* 467:27–37. https://doi.org/10.1007/s00424-014-1530-2

Thor, K., S. Jiang, E. Michard, J. George, S. Scherzer, S. Huang, J. Dindas, P. Derbyshire, N. Leitão, T.A. DeFalco, et al. 2020. The calcium-permeable channel OSCA1.3 regulates plant stomatal immunity. *Nature*. 585: 569–573. https://doi.org/10.1038/s41586-020-2702-1

Vaisey, G., P. Banerjee, A.J. North, C.A. Haselwandter, and R. MacKinnon. 2022. Piezo1 as a force-through-membrane sensor in red blood cells. *Elife*. 11:e82621. https://doi.org/10.7554/eLife.82621

Vásquez, V., M. Krieg, D. Lockhead, and M.B. Goodman. 2014. Phospholipids that contain polyunsaturated fatty acids enhance neuronal cell mechanics and touch sensation. *Cell Rep.* 6:70–80. https://doi.org/10.1016/j.celrep.2013.12.012

Verkest, C., I. Schaefer, T.A. Nees, N. Wang, J.M. Jegelka, F.J. Taberner, and S.G. Lechner. 2022. Intrinsically disordered intracellular domains control key features of the mechanically-gated ion channel PIEZO2. *Nat. Commun.* 13:1365. https://doi.org/10.1038/s41467-022-28974-6

Vreugde, S., A. Erven, C.J. Kros, W. Marcotti, H. Fuchs, K. Kurima, E.R. Wilcox, T.B. Friedman, A.J. Griffith, R. Balling, et al. 2002. Beethoven, a mouse model for dominant, progressive hearing loss DFNA36. *Nat. Genet.* 30:257–258. https://doi.org/10.1038/ng848

Walker, R.G., A.T. Willingham, and C.S. Zuker. 2000. A *Drosophila* mechanosensory transduction channel. *Science*. 287:2229–2234. https://doi.org/10.1126/science.287.5461.2229

Wang, J., J. Jiang, X. Yang, G. Zhou, L. Wang, and B. Xiao. 2022. Tethering Piezo channels to the actin cytoskeleton for mechanogating via the cadherin-β-catenin mechanotransduction complex. *Cell Rep.* 38:110342. https://doi.org/10.1016/j.celrep.2022.110342

Wang, L., H. Zhou, M. Zhang, W. Liu, T. Deng, Q. Zhao, Y. Li, J. Lei, X. Li, and B. Xiao. 2019a. Structure and mechanogating of the mammalian tactile channel PIEZO2. *Nature*. 573:225–229. https://doi.org/10.1038/s41586-019-1505-8

Wang, L.-X., C.-D. Niu, Y. Zhang, Y.-L. Jia, Y.-J. Zhang, Y. Zhang, Y.-Q. Zhang, C.-F. Gao, and S.-F. Wu. 2019b. The NompC channel regulates *Nilaparvata lugens* proprioception and gentle-touch response. *Insect Biochem. Mol. Biol.* 106:55–63. https://doi.org/10.1016/j.ibmb.2018.11.005

Wang, P., Y. Jia, T. Liu, Y.-N. Jan, and W. Zhang. 2020. Visceral mechanosensing neurons control *Drosophila* feeding by using Piezo as a sensor. *Neuron*. 108:640–650.e4. https://doi.org/10.1016/j.neuron.2020.08.017

Wang, X., G. Li, J. Liu, J. Liu, and X.Z.S. Xu. 2016. TMC-1 mediates alkaline sensation in *C. elegans* through nociceptive neurons. *Neuron*. 91:146–154. https://doi.org/10.1016/j.neuron.2016.05.023

Wang, Y., Y. Guo, G. Li, C. Liu, L. Wang, A. Zhang, Z. Yan, and C. Song. 2021. The push-to-open mechanism of the tethered mechanosensitive ion channel NompC. *Elife*. 10:e58388. https://doi.org/10.7554/eLife.58388

Wei, W.-C., F. Bianchi, Y.-K. Wang, M.-J. Tang, H. Ye, and M.D. Glitsch. 2018. Coincidence detection of membrane stretch and extracellular pH by the proton-sensing receptor OGR1 (GPR68). *Curr. Biol.* 28:3815–3823.e4. https://doi.org/10.1016/j.cub.2018.10.046

Wilde, C., J. Mitgau, T. Suchý, T. Schöneberg, and I. Liebscher. 2022. Translating the force-mechano-sensing GPCRs. *Am. J. Physiol. Cell Physiol.* 322:C1047–C1060. https://doi.org/10.1152/ajpcell.00465.2021

Woo, S.-H., V. Lukacs, J.C. de Nooij, D. Zaytseva, C.R. Criddle, A. Francisco, T.M. Jessell, K.A. Wilkinson, and A. Patapoutian. 2015. Piezo2 is the principal mechanotransduction channel for proprioception. *Nat. Neurosci.* 18:1756–1762. https://doi.org/10.1038/nn.4162

Xu, J., J. Mathur, E. Vessières, S. Hammack, K. Nonomura, J. Favre, L. Grimaud, M. Petrus, A. Francisco, J. Li, et al. 2018. GPR68 senses flow and is essential for vascular physiology. *Cell*. 173:762–775.e16. https://doi.org/10.1016/j.cell.2018.03.076

Yan, Z., W. Zhang, Y. He, D. Gorczyca, Y. Xiang, L.E. Cheng, S. Meltzer, L.Y. Jan, and Y.N. Jan. 2013. Drosophila NOMPC is a mechanotransduction channel subunit for gentle-touch sensation. *Nature*. 493:221–225. https://doi.org/10.1038/nature11685

Yang, X., C. Lin, X. Chen, S. Li, X. Li, and B. Xiao. 2022. Structure deformation and curvature sensing of PIEZO1 in lipid membranes. *Nature*. 604: 377–383. https://doi.org/10.1038/s41586-022-04574-8

Yuan, F., H. Yang, Y. Xue, D. Kong, R. Ye, C. Li, J. Zhang, L. Theprungsirikul, T. Shrift, B. Krichilsky, et al. 2014. OSCA1 mediates osmotic-stress-evoked Ca^{2+} increases vital for osmosensing in *Arabidopsis*. *Nature*. 514: 367–371. https://doi.org/10.1038/nature13593

Zanini, D., D. Giraldo, B. Warren, R. Katana, M. Andrés, S. Reddy, S. Pauls, N. Schwedhelm-Domeyer, B.R.H. Geurten, and M.C. Göpfert. 2018. Proprioceptive opsin functions in *Drosophila* larval locomotion. *Neuron*. 98: 67–74.e4. https://doi.org/10.1016/j.neuron.2018.02.028

Zarychanski, R., V.P. Schulz, B.L. Houston, Y. Maksimova, D.S. Houston, B. Smith, J. Rinehart, and P.G. Gallagher. 2012. Mutations in the mechanotransduction protein PIEZO1 are associated with hereditary xerocytosis. *Blood*. 120:1908–1915. https://doi.org/10.1182/blood-2012-04-422253

Zhang, M., D. Wang, Y. Kang, J.-X. Wu, F. Yao, C. Pan, Z. Yan, C. Song, and L. Chen. 2018. Structure of the mechanosensitive OSCA channels. *Nat. Struct. Mol. Biol.* 25:850–858. https://doi.org/10.1038/s41594-018-0117-6

Zhang, W., L.E. Cheng, M. Kittelmann, J. Li, M. Petkovic, T. Cheng, P. Jin, Z. Guo, M.C. Göpfert, L.Y. Jan,et al. 2015. Ankyrin repeats convey force to gate the NOMPC mechanotransduction channel. *Cell*. 162:1391–1403. https://doi.org/10.1016/j.cell.2015.08.024

Zhang, Y., C. Daday, R.-X. Gu, C.D. Cox, B. Martinac, B.L. de Groot, and T. Walz. 2021. Visualization of the mechanosensitive ion channel MscS under membrane tension. *Nature*. 590:509–514. https://doi.org/10.1038/s41586-021-03196-w

Zhang, Y.V., T.J. Aikin, Z. Li, and C. Montell. 2016. The basis of food texture sensation in *Drosophila*. *Neuron*. 91:863–877. https://doi.org/10.1016/j.neuron.2016.07.013

Zhang, Z., X. Tong, S.-Y. Liu, L.-X. Chai, F.-F. Zhu, X.-P. Zhang, J.-Z. Zou, and X.-B. Wang. 2019. Genetic analysis of a Piezo-like protein suppressing systemic movement of plant viruses in *Arabidopsis thaliana*. *Sci. Rep.* 9: 3187. https://doi.org/10.1038/s41598-019-39436-3

Zhao, B., Z. Wu, N. Grillet, L. Yan, W. Xiong, S. Harkins-Perry, and U. Müller. 2014. TMIE is an essential component of the mechanotransduction machinery of cochlear hair cells. *Neuron*. 84:954–967. https://doi.org/10.1016/j.neuron.2014.10.041

Zhao, X., X. Yan, Y. Liu, P. Zhang, and X. Ni. 2016. Co-expression of mouse TMEM63A, TMEM63B and TMEM63C confers hyperosmolarity activated ion currents in HEK293 cells. *Cell Biochem. Funct.* 34:238–241. https://doi.org/10.1002/cbf.3185

Zheng, W., and J.R. Holt. 2021. The mechanosensory transduction machinery in inner ear hair cells. *Annu. Rev. Biophys.* 50:31–51. https://doi.org/10.1146/annurev-biophys-062420-081842

Zhong, L., R.Y. Hwang, and W.D. Tracey. 2010. Pickpocket is a DEG/ENaC protein required for mechanical nociception in *Drosophila* larvae. *Curr. Biol.* 20:429–434. https://doi.org/10.1016/j.cub.2009.12.057

Zhou, W., X. Wang, K. Wang, U. Farooq, L. Kang, L. Niu, and L. Meng. 2022. Ultrasound activation of mechanosensory ion channels in *Caenorhabditis elegans*. *IEEE Trans. Ultrason. Ferroelectr. Freq. Control*. 69: 473–479. https://doi.org/10.1109/TUFFC.2021.3120750