Feeling Force: Physical and Physiological Principles Enabling Sensory Mechanotransduction

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Annu. Rev. Cell Dev. Biol. 2015. 31:347–71

The *Annual Review of Cell and Developmental Biology* is online at cellbio.annualreviews.org

This article's doi:
10.1146/annurev-cellbio-100913-013426

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Keywords

hearing, touch, proprioception, mechanobiology, mechanosensory, mechanosensitive ion channels

Abstract

Organisms as diverse as microbes, roundworms, insects, and mammals detect and respond to applied force. In animals, this ability depends on ionotropic force receptors, known as mechanoelectrical transduction (MeT) channels, that are expressed by specialized mechanoreceptor cells embedded in diverse tissues and distributed throughout the body. These cells mediate hearing, touch, and proprioception and play a crucial role in regulating organ function. Here, we attempt to integrate knowledge about the architecture of mechanoreceptor cells and their sensory organs with principles of cell mechanics, and we consider how engulfing tissues contribute to mechanical filtering. We address progress in the quest to identify the proteins that form MeT channels and to understand how these channels are gated. For clarity and convenience, we focus on sensory mechanobiology in nematodes, fruit flies, and mice. These themes are emphasized: asymmetric responses to applied forces, which may reflect anisotropy of the structure and mechanics of sensory mechanoreceptor cells, and proteins that function as MeT channels, which appear to have emerged many times through evolution.

Contents

INTRODUCTION

Animals have evolved sensory cells to detect most, if not all, of the Earth's physical stimuli, including heat, mechanical force, chemical ligands, and light. Heat and force are ubiquitous, universal, and govern all matter and manner of chemical reactions. Still, animal sensation exploits minute variations in both external and internal forces so that animals can navigate, communicate, and thrive in the world. For an animal to feel force, force must be transmitted through biological structures and materials that are linked to mechanoreceptor cells and molecular sensors within. Sound perception, or hearing, depends on the conversion of sound waves into mechanical displacements in the inner ear and the ability of hair cells to detect fluid motion and convert this energy into electrical signals. Body position sensing, or proprioception, depends on how muscle tension and joint position affect the mechanical stress and strain of embedded somatosensory neurons and the ability of these neurons to generate electrical signals that encode such mechanical inputs. Similarly, tactile sensation, or touch, depends on how mechanical loads applied to the skin produce changes in mechanical stress and strain of somatosensory neurons embedded in the skin.

Strain: deformation of a material due to stress

Stress: force applied to the surface of a material

MeT: mechanoelectrical transduction

This review concerns the process of feeling force. It incorporates emerging knowledge of mechanical signal transmission, the organs and mechanoreceptor cells that perform these functions, and the proteins that form the ion channels that convert mechanical signals into electrical signals. For clarity and convenience, we focus on a subset of sensory modalities—hearing and touch—in selected animals. Specifically, we cover hearing in mammals and tactile sensation in *Caenorhabditis elegans* (nematodes), *Drosophila melanogaster* (fruit flies), and laboratory mice. Additionally, we review current knowledge about the phylogeny of proteins thought to form mechanoelectrical transduction (MeT) channels in eukaryotes.

SPECIALIZED MECHANORECEPTOR CELLS

Most, if not all, metazoan mechanoreceptor cells are embedded in complex tissues that play critical but poorly understood roles in mechanical signal transmission. Beyond this shared association with surrounding tissues, however, few clear morphological motifs that uniformly distinguish mechanoreceptor cells have been found. Instead, they are characterized by a stunning diversity of form and function both within and between animals. For instance, every vertebrate animal has dorsal root ganglion (DRG) sensory neurons that innervate the skin as free nerve endings, in association with specialized corpuscular endings and hair follicles (Lechner & Lewin 2013, Lumpkin et al. 2010, Zimmerman et al. 2014), as well as many others that innervate muscles, joints, the aortic arch, and most, if not all, internal organs (Proske & Gandevia 2012, Robinson & Gebhart 2008). As such, DRG neurons mediate not only conscious tactile and pain perception but also proprioception (Proske & Gandevia 2012). Insects harbor diverse cuticle structures sensitive to self-motion, external touch, and sound that are innervated by sensory neurons (Field & Matheson 1998, Kernan 2007). Even tiny *C. elegans* nematodes have at least eight classes of putative mechanoreceptor neurons that differ in the tissues they innervate and behaviors they regulate (Goodman 2006, Schafer 2014).

We do not attempt a comprehensive catalog of this awesome diversity here. Instead, we focus on examples that illustrate two concepts. The first is the observation that the architecture of many, but not all, mechanoreceptor organs is anisotropic and such structures can confer direction selectivity. The second is that encapsulating tissues play crucial roles in mechanical signal transmission. Such tissues may be passive or active mechanical filters, as discussed in the landmark studies of Loewenstein & Mendelson (1965, Mendelson & Loewenstein 1964).

Anisotropy: the property of being directionally dependent; here, anisotropy refers to a difference in mechanical properties based on perturbation direction

Asymmetric Architecture of Mechanoreceptor Organs and Cells

Bristles, scales, and hairs cover the bodies of insects, fish, and furred mammals, respectively. These protuberances emanate from the body surface as tapered, curved structures aligned with the anterior-posterior body axis in insects and the rostral-caudal axis in mammals, and many function as mechanoreceptor organs. Such structures offer more resistance when bent away from the body surface toward the head. This is a mechanical feature that may confer direction selectivity on the mechanoreceptor neurons embedded within bristles and surrounding hair follicles. Bristles in insects are chitinous structures whose architecture and orientation along the body axes are under control of planar cell polarity pathways and the intracellular cytoskeleton (Bitan et al. 2010, Fabre et al. 2008, Tilney & DeRosier 2005).

Deflecting large (macrochaete) bristles toward the body surface activates transepithelial mechanoreceptor potentials and currents in *Drosophila*, whereas deflection in the opposite direction decreases these signals (**Figure 1*a***) (Kernan et al. 1994, Walker et al. 2000). Notably, deflection in the orthogonal direction has little, if any, effect on the transepithelial current (Walker et al. 2000). Similar results have been described in spiders (Foelix 1985), suggesting that the architectural anisotropy seen in bristle-associated mechanoreceptor cells is a general mechanism for direction-selective activation of the embedded mechanoreceptor neurons.

The link between architectural anisotropy and direction-selective mechanoresponses is more complex for the sensory neurons associated with hairy skin in mammals. For instance, most of the mechanoreceptor neurons that innervate facial whiskers, or vibrissae, respond most vigorously to deflection along the rostral-caudal axis (Dykes 1975, Gottschaldt & Vahle-Hinz 1981, Kwegyir-Afful et al. 2008, Lichtenstein et al. 1990, Williams & Kramer 2010). Due to their tapered shape and flexible material properties, whiskers themselves are mechanically tuned. This resonance plays

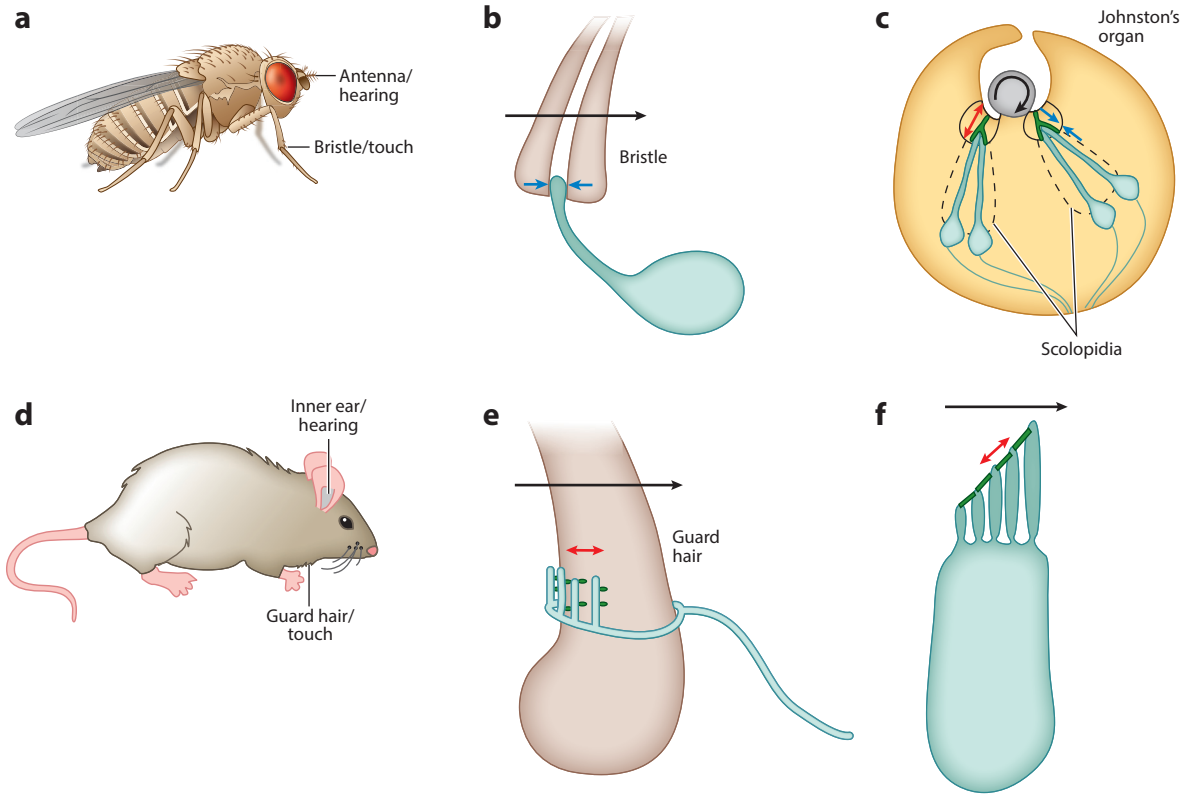

Figure 1

Asymmetric architecture of sensory mechanoreceptor cells for touch and hearing. (*a*) *Drosophila melanogaster* showing the position of selected macrochaete bristles and the antennal hearing organ that harbors Johnston's organ. (*b*) *Drosophila* bristle mechanoreceptors are activated by deflection of the bristle toward the body surface (*black arrow*), which compresses the sensory dendrite (*blue arrows*) (Thurm 1965). (*c*) Scolopidia in Johnston's organ harbor ciliated mechanoreceptor neurons surrounded by a scolopale cell (*dotted line*) and attached to the cuticle by a dendritic cap (*green*). Rotation of the antenna (*gray*) is thought to apply tension to the scolopidia on one side (*red arrows*) and to compress those on the other side (*blue arrows*). (*d*) Mouse showing the position of some guard hairs and the ear. (*e*) Aδ-LTMR lanceolate endings on the caudal side of mouse guard hair follicles respond to deflection of the hair away from the body surface (*black arrow*). Hair deflection is proposed to apply tension (*red arrows*) to the sensory endings via linkers (*dark green*) observed in electron micrographs (Li et al. 2011). (*f*) Vertebrate hair cells respond when stereocilia are deflected toward the tallest stereocilium (*black arrow*), pulling on the tip links in between (*red arrows*). Abbreviation: LTMR, low-threshold mechanoreceptor.

an important role in the tactile acuity of whisker-associated mechanoreceptor neurons (see Hires et al. 2013, Williams & Kramer 2010), emphasizing the role played by tactile organ architecture in their function.

The data concerning body hairs are less clear. Some studies report direction-selective activation of low-threshold mechanoreceptors (LTMRs) (Maruhashi et al. 1952, Tuckett 1978), and others report no evidence of direction selectivity (Brown & Iggo 1967). This discrepancy could reflect the fact that the relationship between a given LTMR nerve fiber and its peripheral sensory endings was not known. Fortunately, recent work is beginning to decipher this relationship by combining the ability to tag selected subsets of sensory neurons with fluorescent proteins and the ability to obtain intracellular recordings in vivo (Li et al. 2011, Rutlin et al. 2014). In this way, we now

appreciate which LTMRs innervate different types of hairs in mice and that one class, Aδ-LTMRs, responds preferentially to hair deflection away from the body surface in the rostral direction (Rutlin et al. 2014). Similar to how Merkel cells in touch domes are concentrated on the caudal side of guard hairs, these Aδ-LTMR fibers innervate awl, auchene, and zigzag hairs in a polarized manner, extending sensory endings around the caudal aspect of the hair follicle (**Figure 1*b***) (Chang & Nathans 2013, Rutlin et al. 2014). Mutants that abrogate the polarized distribution of sensory endings and leave hair shafts intact likewise abrogate the direction selectivity of the mechanoresponse (Rutlin et al. 2014). Thus, direction selectivity of murine Aδ-LTMRs depends on the asymmetric distribution of sensory endings. Consistent with this idea, Aβ-LTMR fibers that form nonpolarized endings around hair follicles appear to lack direction selectivity (see Rutlin et al. 2014 and references therein).

The ears of insects and vertebrates are refined structures crucial for the rapid encoding of sound into neural signals. In the vertebrate inner ear, this function is performed by mechanoreceptor hair cells that sport organized hair bundles of interconnected, modified microvilli known as stereocilia. All mature hair bundles are asymmetric, and the stereocilia resemble a staircase composed of successive rows that increase in height across the bundle. As in insect bristles (Tilney & DeRosier 2005), the shaft of each stereocilium is supported by cross-linked actin filaments. Along the major axis of the bundle, the tip of each stereocilium is linked to the shaft of its taller neighbor by helical filaments composed of atypical cadherins called tip links. Several recent reviews discuss hair bundle structure, tip links, the proteins responsible for building and maintaining the structure of hair bundles, and the role of these proteins in hearing and deafness (see Effertz et al. 2015, Fettiplace & Kim 2014, Hudspeth 2014).

In mature hair cells, deflecting the bundle toward the tallest rank activates MeT channels, whereas movement in the opposite direction closes them (**Figure 1*c***). Displacement in the orthogonal direction has little or no effect (Hudspeth & Corey 1977). Such direction selectivity depends on the relationship between the stimulus direction and the bundle's plane of symmetry. In particular, MeT channel activation is proportional to the cosine of the angle between the stimulus direction and the axis of symmetry. Fettiplace & Kim (2014) discuss the consequences of this architectural anisotropy and direction selectivity in terms of cochlea organization and its sensitivity to low-intensity sound. In brief, the uniform orientation of hair bundles, with respect to the sound-induced motions that cause deflection in vivo, reflects this direction selectivity and likely helps increase sensitivity. This organization depends on the proper elaboration of planar cell polarity signaling pathways that organize the hearing organ during development (Ezan & Montcouquiol 2013, Sienknecht et al. 2014).

The direction-selective activation of body hairs and auditory hair cells underscores how architecture guides function and may reflect shared planar cell polarity signaling pathways that organize sensory organs' development (Chang & Nathans 2013, Ezan & Montcouquiol 2013, Fabre et al. 2008, Sienknecht et al. 2014).

The Role of Encapsulating Tissues in Mechanosensation

Sensory mechanoreceptor cells invade organs and are embedded within complex structures that filter or amplify mechanical cues. The tissues that encapsulate somatosensory neurons contribute to touch sensation, whereas those associated with hearing organs amplify responses to mechanical cues and contribute to frequency selectivity.

In insect campaniform receptors, which detect minute deformations or strain in the cuticle during insect flight (Dickinson 2006), mechanical amplification arises from a cuticular structure that concentrates stress at the tip (Mani & Menon 2010). This stress is thought to be transmitted via

Scolopidium/ scolopidia: a mechanosensory unit consisting of a shaft-forming scolopale cell and a cap cell enclosing a ciliated sensory neuron

intracellular microtubules (MTs) to MeT channels (Liang et al. 2013, 2014). Extracellular structures that transmit mechanical signals are also important in Pacinian corpuscles (PCs), specialized epithelial sensory endings that are tuned to high-frequency stimuli and only detect transient stimuli (Loewenstein & Mendelson 1965, Loewenstein & Skalak 1966, Mendelson & Loewenstein 1964, Sato 1961). In a PC, the endings of rapidly adapting, low-threshold Aβ fibers are surrounded by a multilayered lamellar structure that is thought to act as a high-pass filter (Loewenstein & Mendelson 1965, Loewenstein & Skalak 1966).

Similar to neurons innervating PCs, *C. elegans* touch receptor neurons (TRNs) exhibit rapidly adapting mechanoreceptor currents at the onset and offset of step stimuli (O'Hagan et al. 2005). Like mammalian mechanoreceptor neurons, *C. elegans* TRNs are embedded within epidermal cells and have a specialized extracellular matrix (ECM) (Chalfie & Sulston 1981). Mutants lacking ECM proteins encoded by the *mec-1*, *mec-5*, and *mec-9* genes are touch-insensitive, and the native MeT channel is retained within the cell body but absent from the sensory dendrite (Du et al. 1996, Emtage et al. 2004). The protein encoded by *mec-5* is an atypical collagen that localizes to the ECM and is associated with TRNs in vivo (Cueva et al. 2007). Collagens are also important for long-distance mechanical signal transmission in other systems (Guo et al. 2012), highlighting the importance of understanding the mechanical properties of encapsulating tissues.

Another example is the vertebrate inner ear, which contains sensory hair cells firmly anchored to nonsensory cells and arrayed along the surface of the fibrous basilar membrane, with the acellular tectorial membrane above. It has been known for decades that variation in the mechanical properties of the basilar membrane enables frequency decomposition in the mammalian inner ear (Fettiplace & Kim 2014, Hudspeth 2014). However, we are still learning how other structures in the organ of Corti contribute to mechanical signal transmission, filtering, and amplification. For instance, the overlying tectorial membrane has a longitudinal gradient of stiffness; this is consistent with a role in frequency decomposition that may complement the basilar membrane's contribution (for reviews, see Meaud & Grosh 2010, Richardson et al. 2008). However, the two membranes are not independent of one another: At any given point along the cochlea, they are directly connected to one another by outer hair cells (OHCs). Indeed, models that consider the movement of both membranes better account for measured properties of basilar membrane movement (Meaud & Grosh 2010).

In addition to passive mechanical filtering, the interaction of sensory cells with their encapsulating tissues in mechanosensory organs allows active mechanical amplification. Voltage-dependent length changes in OHCs of mammals may dynamically affect basilar and tectorial membrane movements, which in turn modulate deflection of hair bundles on inner hair cells (IHCs) (Hudspeth 2014). Such changes in cell length depend on expression of the prestin protein, which is required for normal hearing. Even IHCs, which already have intrinsic preferences for certain frequencies (reviewed in Fettiplace & Fuchs 1999), display active bundle movements, with bundle properties changing as a result of the opening of mechanotransduction channels and subsequent adaptation of their tip links (for reviews, see Fettiplace 2006, Maoiléidigh et al. 2012).

Johnston's organ (JO) is a chordotonal sensory organ that subserves hearing in fruit flies, mosquitos, and honeybees. Like the vertebrate organ of Corti, the JO depends on nonlinear mechanical amplification to enhance sensitivity to sound (Geurten et al. 2013, Kamikouchi et al. 2010, Nadrowski et al. 2008). Such nonlinearities were first observed using laser Doppler vibrometry (LDV) to measure spontaneous and sound-induced movement of the third antennal segment, or arista. The arista acts as a sound receiver (Göpfert & Robert 2002), transforming sound into rotation to produce a strain sensed by the array of scolopidia that compose the JO (**Figure 1*d***). LDV continues to be a promising approach for characterizing the biomechanics of mechanoreceptor organs, as shown by measurements of picometer-scale movements of the tissue surrounding

scolopidia in the cicada tympanal organ (Windmill et al. 2009). Active mechanical amplification in the JO of mosquitoes depends on both the transduction apparatus (Nadrowski et al. 2008) and dynein-tubulin motors (Warren et al. 2010).

In some cases, encapsulating tissues may do double duty as both passive and active filters. For instance, touch domes are clusters of modified keratinocytes known as Merkel cells that are intercalated within epidermal keratinocytes and associated with one slowly adapting Aβ fiber (Iggo & Muir 1969). This Merkel cell–neurite complex is responsible for communicating sustained touch or low-frequency vibration. Recent work provides an idea of how the Merkel cell and the sensory neuron ending interact. Unexpectedly, both cells are mechanosensitive, and the combination of their responses is what gives the receptor its characteristic slowly adapting response to stimuli (Ikeda et al. 2014, Maksimovic et al. 2014, Woo et al. 2014). Fine, actin-packed protrusions that extend into the surrounding keratinocytes (Iggo & Muir 1969) may be sites of MeT transduction in the Merkel cells. This possibility opens the door to the idea of mechanical filtering through the interaction of Merkel cells and surrounding nonexcitable skin cells. Indeed, a recent model combines estimated skin mechanics, neuronal dynamics, and a network model to understand how signals from different Merkel cells along different branches are integrated, as well as how the asymmetric grouping of Merkel cells could contribute to a higher mechanical sensitivity than an even distribution (Lesniak et al. 2014). Detailed knowledge of skin mechanics could improve the predictive capabilities of this model (Wang et al. 2013). Taken together, the available data indicate that mechanosensation across the animal kingdom relies on active and passive mechanical amplification.

Young's modulus (*E*): constant describing the relationship between stress and strain in purely elastic material

PHYSICAL BIOLOGY OF MECHANOSENSATION

How a given mechanoreceptor cell responds to force depends on its architecture, association with surrounding tissue, and mechanical properties. Recent work suggests that cells sense strain rather than stress (De et al. 2008, Faust et al. 2011). That is, force cannot be sensed directly—its impact is read out as changes in length, shape, strain, position, or the lifetime of biomolecular interactions (Hoffman et al. 2011, Iskratsch et al. 2014, Radmacher et al. 1996, Thomas et al. 2008).

All living cells are composed of active, anisotropic, and nonlinear materials—in other words, their mechanical properties are complex. Nevertheless, knowledge about such properties can enable predictions about their behavior under force based on quantitative models borrowed from engineering and materials science (Radmacher et al. 1996). This approach has been applied to cell physiology and animal development (Biswas et al. 2015, Krieg et al. 2008).

How does thinking about cell mechanics affect understanding of mechanosensation? Consider a mutant in which applied force fails to activate MeT channels in a given mechanoreceptor cell. This outcome could reflect a change in mechanics such that the cell is too soft to transmit force to the MeT channel. Consistent with this idea, mutations that affect MTs in *Drosophila* (Liang et al. 2014) and *C. elegans* (Bounoutas et al. 2009, O'Hagan et al. 2005) decrease sensitivity to external mechanical stimuli, an effect proposed to reflect a decrease in the stiffness of the mechanoreceptor neuron (Liang et al. 2014). On the other hand, what if the cell or tissue is too stiff to deform sufficiently? Decreased signaling by baroreceptors during atherosclerosis and calcification of arterial walls may be examples of this second scenario (Chesterton & McIntyre 2005, Thrasher 2004). These two examples of opposite mechanisms underscore the importance of cell and tissue mechanics knowledge for understanding disruption of sensory mechanotransduction.

What Material Properties Are Important to Cells?

In a simple, solid material like rubber, the force-deformation, or stress-strain, relationship is linear and has a constant and time-invariant elastic or Young's modulus (*E*) (**Figure 2*a***). Whereas stiffness

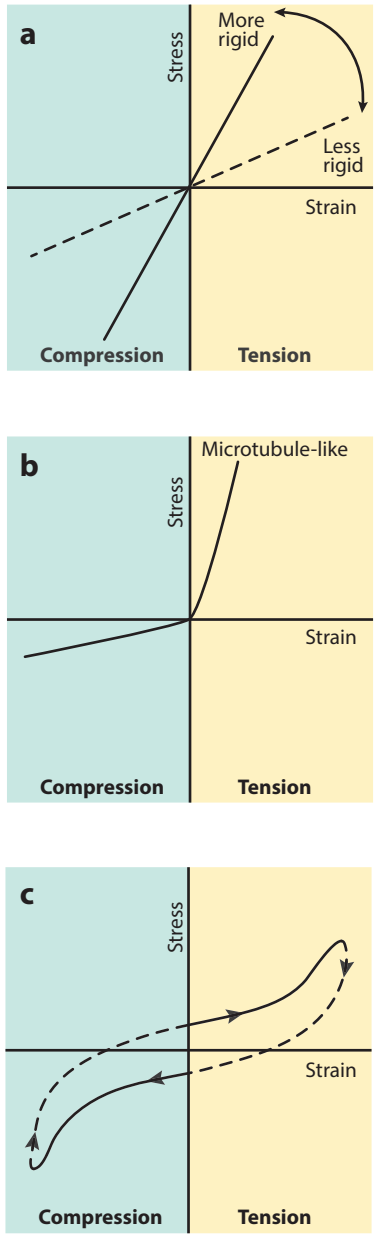

Figure 2

Relationship between stress and strain. (*a*) The slope of the stress-strain curve for a material represents its Young's modulus, *E*, and is constant for isotropic materials. (*b*) Anisotropic materials differ in their response to compression and tension and cannot be described by a single Young's modulus, evident as nonlinearities in the stress-strain curve. For instance, microtubules have highly anisotropic mechanical properties (Tuszynski et al. 2005). (*c*) Viscoelastic materials have more complex stress-strain relationships: Depending on their composition, they show a strong hysteresis between the loading (*solid*) and unloading (*dashed*) cycles.

is a structural property, Young's modulus is a material property and is independent of object size and shape. For instance, springs made of rubber and steel could have the same spring constant or stiffness, but because of the difference in the materials, E cannot be the same. Isotropic linear solids have the same E when they are compressed as when they are extended. The complexity of cells, by contrast, means that the deformation evoked by applied force depends on whether the force induces compression or extension (**Figure 2*b***). In neurons, compression, but not extension, can lead to aberrant buckling in certain mutant conditions (Krieg et al. 2014). Such nonlinear mechanical properties have been linked to the organization and composition of the cytoskeleton (reviewed in Boal 2013, Fletcher & Mullins 2010).

In addition to displaying solid-like properties on short timescales, cells and tissues can also have fluid-like properties on long timescales—they are said to be viscoelastic. Because biological materials are held together by weak noncovalent interactions, many of which are force sensitive (Hoffman et al. 2011), force application can lead to rapid dissociation of those interactions, dissipating associated energy. As a result, the material does not relax to its initial configuration but retains a memory if no active remodeling processes restore its initial shape. This discrepancy between loading and unloading is reflected in a hysteresis in the stress-strain curve (**Figure 2*c***).

Buckling: a structural instability resulting from compressive forces; involves bending or twisting outside the axis of compression

Persistence length: a mechanical property quantifying the stiffness of a polymer; essentially the longest length at which a polymer acts like a rod

Mechanical Anisotropy of Load-Bearing Molecules

As discussed above, many mechanoreceptor cells have asymmetric structures and respond to applied forces in an asymmetric manner. At the molecular level, such asymmetric responses may also depend on anisotropies and nonlinearities, or differential responses to tension and compression, in the structural molecules that carry mechanical loads. In other words, the architectural asymmetry in mechanoreceptor cells or sensory organs determines the type of stress, either tensile or compressive, that occurs, and anisotropy in load-bearing molecules allows the cell to preferentially transmit the preferred variety. To illustrate this idea, we consider the links that extend from the tip of a stereocilium to the shaft of its taller neighbor (**Figure 1*f***). These tip links are thought to transfer force to MeT channels when the hair bundle is deflected toward the tallest stereocilium. The tip links appear to transfer tensile forces but not compressive ones, because the structures are extended when stereocilia are deflected in the positive direction toward the taller stereocilia and buckled in relaxed or compressed configurations (Kachar et al. 2000).

The ability to withstand tension but not compression is shared by certain intracellular or cytoskeletal filaments such as those formed by spectrin proteins. Spectrins assemble into α_2/β_2-tetramers that can be up to 200 nm long when fully extended. They assemble into hexagonal networks in red blood cells (Liu et al. 1987) and cylindrical networks in axons (Xu et al. 2013). Spectrin tetramers have a persistence length of only 20 nm in solution (Boal 2013) and are proposed to form superhelices that vary in length, width, and pitch, with an estimated resting length of 55–65 nm in hexagonal networks (Brown et al. 2015). Despite this conformational flexibility, spectrin tetramers appear to be present at their fully extended length in axons (Xu et al. 2013), suggesting that they are actively extended or held under pre-stress (tension). Consistent with this idea, recent measurements show that spectrin is subjected to tension in living neurons and other cell types (Krieg et al. 2014, Meng & Sachs 2012). Considered together with the finding that disrupting spectrin networks impairs touch sensation in *C. elegans* (Krieg et al. 2014), these observations that suggest a role for mechanically anisotropic filaments in force transmission and touch sensation.

Intermediate filaments are ubiquitous structures inside cells that are formed by proteins belonging to several families. They can withstand intense tensile stress and help stabilize cells against external mechanical loads. For instance, lamins provide shape and mechanical rigidity to the nucleus and are a major determinant of cell deformability (Swift et al. 2013). Keratins are major

cytoskeletal filaments in the skin and contribute to the tensile strength of epithelia. This tensile strength is thought to originate in their high extensibility and the unusual ability of individual subunits to slide easily past one another (Guzmán et al. 2006, Qin et al. 2009). Indeed, keratin and other intermediate filaments can stretch to several times their original length before breaking (Herrmann et al. 2007, Kreplak & Fudge 2007).

Dashpot: a damping element that resists motion through viscous friction

Rheological: pertaining to the study of the flow of matter

In contrast to spectrin and intermediate filaments, MTs resist compression before buckling and can endure larger loads when embedded in viscous cytoplasm (Brangwynne et al. 2006). Individual MTs break when bent (Odde et al. 1999), as bending requires compression on the concave side and extension on the convex side, distorting the MT lattice. However, MTs can be bent to very high curvatures in vitro (Liu et al. 2011). A solution to this paradox may come from the architecture of MTs: The protofilaments that form MTs can slide past one another and twist, thereby mitigating bending stress (Pampaloni & Florin 2008). Therefore, mutations that weaken or strengthen interprotofilament bonds may render MTs less flexible and more prone to fracture. The physical interaction of these and other cellular elements confers resistance to compression, extension, and stiffness, which are mechanical properties that can be described by models common in standard mechanics.

Models for Mechanobiology: Viscoelasticity, Poroelasticity, and Tensegrity

The simplest and most widely employed mechanical models describe the cell as a homogenous, linear viscoelastic material with both solid and fluid properties. A viscoelastic material has the ability to store mechanical energy upon stimulation but relaxes over time (**Figure 3*a*,*b***). In these models, the elastic, or solid, elements are represented as springs whose relaxation is damped by the viscous, or fluid, material represented as a dashpot or shock absorber. For simplicity and mathematical tractability, a single timescale is commonly assumed and used as a classification tool in cell physiology. It is also beneficial for developing models that provide quantitative predictions and enable comparisons of potential differences within and between sensory cells.

The most widely employed variations of the viscoelastic models are the Maxwell model and the Kelvin-Voigt model (Moeendarbary & Harris 2014). These models differ in how the spring and dashpot are loaded. In the Maxwell model, they are loaded in series, such that any force on the spring will unavoidably relax owing to the dashpot. Thus, the material is more fluid-like and cannot store energy to maintain a prestressed spring. In the Kelvin-Voigt model, the dashpot and spring act in parallel and therefore can store energy and preserve a prestress in the spring. Kelvin-Voigt models have been widely used in mechanobiology to understand the mechanics of actin stress fibers (Kumar et al. 2006, Tanner et al. 2010), as well as how prestressed TRNs contribute to the activation of MeT channels in *C. elegans* (Krieg et al. 2014). Unfortunately, viscous and elastic contributions to cell mechanics are difficult to decouple experimentally. Furthermore, as a result of the mismatch between the basic assumptions of these models (single phase, isotropicity) and the actual properties of cells, the dynamics of cellular deformations in response to stress are hard to predict, which has prompted the development of more experimentally accessible theories.

Poroelastic theory assumes a biphasic material in which the cell is modeled as an elastic meshwork consisting of scaffolding proteins, the cytoskeleton, and organelles, with an interstitial fluid, such as a viscous cytosol, penetrating the meshwork (**Figure 3*c*,*d***). Here, viscoelastic relaxation and time-dependent reorganization during stress are reflected in the timescale for redistribution of the cytosol as it diffuses through the network of elastic strings and cables (Mitchison et al. 2008). Thus, a single experimental parameter, the poroelastic diffusion constant D, describes the rheological properties of the cell, in which $D = Ez^2/n$ (Moeendarbary & Harris 2014). A larger relaxation (and larger D) can result from larger pore size (z) or elasticity (E) of the drained elastic matrix, or lower

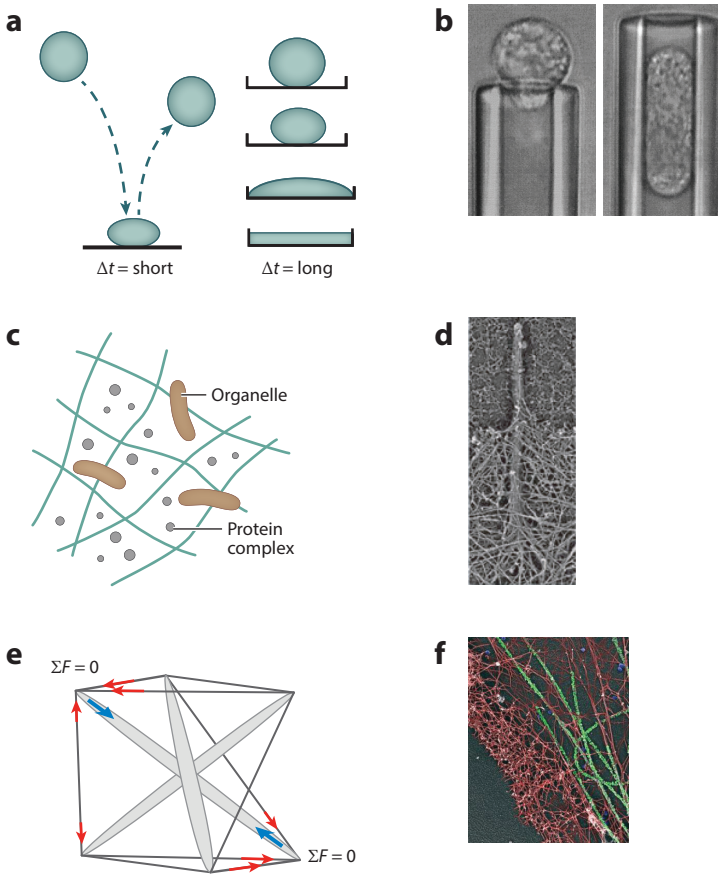

Figure 3

Common mechanical models for understanding the mechanics of cells and tissues. (*a*) Viscoelastic models: Cellular materials react differently on different timescales (Δt). Elastic properties dominate during fast loading (*left*), whereas material begins to flow and show its viscous properties on long timescales (*right*). (*b*) A single cell aspirated into a micropipette forms a hemispherical protrusion on short timescales (*left*) but begins to flow completely into the pipette on long timescales (*right*). Panel *b* adapted from Hochmuth (2000). (*c*) Poroelastic model: a porous matrix is drained with a viscous cytosol containing solutes, proteins, and organelles. Panel *c* adapted from Zhou et al. (2013). (*d*) Scanning electron micrograph of the dense meshwork of cytoskeletal filaments just below the plasma membrane, representing a putative poroelastic matrix. Panel *d* adapted from Svitkina et al. (2003). (*e*) Tensegrity model: Structures are stabilized by internal compressive and tensile forces that balance each other such that the net force at any node is zero. Hypothetical tensile (*red*) and compressive (*blue*) forces on cables and rods, respectively, are depicted as arrows. (*f*) Pseudocolored electron micrograph showing the intimate interaction between microtubules (*green*) and actin filaments (*red*) in a neuronal growth cone. Adapted from Burnette et al. (2008).

viscosity (η) of the interstitial fluid. In poroelastic materials, pore size dominates over the elasticity of the drained matrix and thus determines the rheological behavior (Moeendarbary et al. 2013).

Viscoelastic models do not account for the relative movement of fluid and solid phases. As such, a poroelastic model could be useful for describing cell behavior in conditions that favor fluid movement through the meshwork, such as those involving fast loading with slow repetitions (Mitchison et al. 2008). Fast loading rates in slow cycles occur in touch receptors and proprioceptors in the

skin, joints, and muscles; the blood vessels during each heartbeat; and the lungs with each breath. Indeed, propagation of mechanical stress has previously been explained using poroelastic theory (Moeendarbary & Harris 2014). Moreover, such loading conditions likely play roles during *C. elegans* locomotion, during which different body parts continuously experience rapid deformations and strains up to 40% (Krieg et al. 2014). Because a key specialization of *C. elegans* TRNs and other mechanoreceptor cells involves distinctive microtubule-based structures, force transmission in these systems could be explained by another mechanism.

The tensegrity, or tensional integrity, model was developed to explain how the cytoskeleton changes shape during cell motility, remains dynamic without falling apart, and responds rapidly to both external and internal mechanical perturbations (**Figure 3*e*,*f***). Inspired by a school of architecture, it is a concept developed specifically for cells, setting it apart from previously discussed models of viscoelasticity and poroelasticity. Tensegrity describes cells and their mechanical properties as arising from a combination of prestressed viscoelastic elements and compressed struts bathed in a viscous cytosol, which exert force on each other to stabilize the whole structure (Ingber et al. 2014). As cells exist in an environment in which local forces dominate, the tensegrity model helps us understand changes in cell shape based on internally generated forces, without the need for an externally applied compressive load. For instance, if tension becomes polarized in an axial direction, a geodesic structure, such as a three-dimensional hexagonal array, will reorganize spontaneously into bundles or tubes (Ingber 1993). Consistent with this idea, and as mentioned above, the spectrin network associates into a biconcave hexagonal array within red blood cells (Liu et al. 1987) but assembles into long cylinders within the axons of neurons (Xu et al. 2013).

The tensegrity heuristic has been used extensively to explain long-range transmission of mechanical forces across many scales within cells (Ingber et al. 2014, Wang et al. 2009). Within this framework, mechanical signal transmission involves elastic wave propagation along prestressed filaments (Ingber et al. 2014). This ultrafast, long-range transport of a local mechanical signal to distant sites through a viscous cytoplasm stands in stark contrast to the limitations of homogenous viscoelastic materials, in which force is propagated equally in all three dimensions and consequently decays rapidly. Under the viscoelastic model, local forces can only have local consequences.

Evidence that force transfer to MeT channels may occur along prestressed filaments comes from an elegant study by Hayakawa et al. (2008). Here, applying direct force to stress fibers using phalloidin-decorated beads activated calcium channels at the opposite site of the cell. It is not clear whether force is transferred directly to the channel or transmitted to nearby structures and then through the membrane, as both are possible pathways for ion channel gating.

IONOTROPIC RECEPTORS FOR MECHANICAL CUES

Mechanical cues in the form of sound, touch, or self-movement activate ion channels in milliseconds or less. Hence, it is widely assumed that mechanical signals are detected by ionotropic receptors known as MeT channels. Through a confluence of genetic, biophysical, and biochemical investigations, members of four classes of membrane proteins have been linked to sensory mechanotransduction in animals and are proposed to function as pore-forming subunits of MeT channels: transient receptor potential (TRP), degenerin/epithelial Na^+ channel (DEG/ENaC), Piezo, and transmembrane channel–like (TMC) proteins. Except for TMC proteins, at least one member of each family forms ion channels in heterologous cells with the same ion selectivity as the native MeT currents. The *C. elegans* TMC-1 protein forms channels in heterologous cells (Chatzigeorgiou et al. 2013); it is unclear whether this property extends to other members of the TMC family. Genes encoding TRP and DEG/ENaC channel proteins were first linked to

DEFINING SENSORY MECHANOELECTRICAL (MeT) CHANNELS

1. **Position:** The channel should localize to the relevant sensory cell and to the correct position with the cell.
2. **Function:** The channel must be necessary to trigger the electrical response of the sensory cell rather than for subsequent amplification, filtering, or signaling. If possible, it is best to eliminate or modify channel function by genetic mutation.
3. **Mimicry:** When the putative mechanoelectrical transduction (MeT) channel is expressed in ectopic cells in vivo, expressed in heterologous cells in culture, or reconstituted in lipid bilayers, the current it carries should recapitulate the properties of the native current. Such properties include, but are not limited to, activation by agonists, inhibition by antagonists, and ion selectivity.
4. **Mechanosensitivity:** Mechanical force should activate the channel under the same conditions used to determine mimicry.

mechanosensation in fruit flies and nematodes through genetic screens for mutants with impaired touch sensation (Chalfie & Au 1989, Chalfie & Sulston 1981, Kernan et al. 1994). The genes encoding mammalian TMC-1 and TMC-2 have been linked to hearing deficits in humans and in mice (Kawashima et al. 2011).

The quest to identify pore-forming subunits of sensory MeT channels has been guided by four criteria, first enumerated by Ernstrom & Chalfie (2002) and summarized in the sidebar, Defining Sensory Mechanoelectrical (MeT) Channels. This knowledge is crucial for investigations of how mechanical signals might activate any given channel in vivo and ex vivo as well as for a broader understanding of the evolution of cellular mechanotransduction.

As with any set of general organizing principles, there are caveats to consider and the potential for both false positives and false negatives (type I and type II errors, respectively). For instance, an inability to detect a given protein in the relevant cell or in the correct position within the cell may reflect a lack of tools with sufficient specificity and sensitivity rather than an absence of the protein from the predicted location (type II error). This may be particularly problematic in vertebrate auditory hair cells and *C. elegans* TRNs, which are thought to have fewer than 200 functional MeT channels per cell (Beurg et al. 2009, O'Hagan et al. 2005). Incomplete or missing knowledge of the correct subcellular position of a channel also hampers evaluation of this criterion. The case of auditory hair cells is instructive: Early work showed that channels carrying mechanotransduction currents localized to the tips of stereocilia (Hudspeth 1982), but left open the question of whether channels were present on the top or sides of individual stereocilia or in both locations. Currently, it is believed that hair cell MeT channels reside in the tips of shorter stereocilia and are absent from the tallest rows (Beurg et al. 2009).

Testing the second criterion is likewise fraught with complexity. Classic methods in cell physiology, such as extracellular or intracellular recordings of membrane potential, and newer methods, such as calcium imaging, cannot distinguish between proteins essential to form MeT channels and those essential for downstream signaling. Such ambiguity can lead to type I errors. The case of mechanotransduction by the *C. elegans* nociceptor ASH illustrates this concept: Genes encoding the OSM-9 and OCR-2 TRP channels are needed for behavioral responses to nose touch and for nose touch–induced calcium transients (Colbert et al. 1997, Hilliard et al. 2004, Tobin et al. 2002) but are entirely dispensable for native MeT currents (Geffeney et al. 2011). Instead, the major MeT current is carried by a DEG/ENaC protein (Geffeney et al. 2011), and OSM-9 and OCR-2

contribute to depolarization-activated currents (S.L. Geffeney & M.B. Goodman, unpublished data). Currently, whole-cell voltage-clamp recording from identified mechanoreceptor neurons is the best method for separating MeT currents from other currents. It has been used to link DEG/ENaCs (Arnadóttir et al. 2011, Geffeney et al. 2011, O'Hagan et al. 2005), TRPs (Kang et al. 2010, Kim et al. 2012), Piezo proteins (Ikeda et al. 2014, Kim et al. 2012, Maksimovic et al. 2014, Woo et al. 2014), and TMC proteins (Kawashima et al. 2011, Kim et al. 2013, Pan et al. 2013) to native MeT currents in mechanoreceptor cells in nematodes, fruit flies, and mice.

Another approach to separate MeT currents from downstream signaling exploits cell-specific expression of the blue light–activated ion channel, Channelrhodopsin 2, by asking whether loss of the putative MeT channel can be bypassed by blue light stimulation (Husson et al. 2012, Hwang et al. 2007, Krieg et al. 2014, Mauthner et al. 2014, Vásquez et al. 2014). In this scenario, genetic disruption of a MeT channel protein will impair responses to mechanical cues but not to blue light. Conversely, genetic disruption of channels essential for downstream signaling will impair responses to both mechanical cues and blue light, as found for certain TRP channels expressed in *C. elegans* nociceptors (Husson et al. 2012).

Tests of the second criterion can also lead to type II errors if the putative MeT channel is a nonessential subunit of a bona fide MeT channel complex and genetic deletion has little or no effect. For example, loss of the MEC-10 protein has little effect on either MeT currents or TRN-mediated behavioral responses (Arnadóttir et al. 2011). However, analysis of missense or point mutations reveals that MEC-10 alters the properties of the native MeT current (ion selectivity) and functions as a pore-forming subunit of the native MeT channel complex (Arnadóttir et al. 2011, O'Hagan et al. 2005).

It is straightforward to determine whether a given candidate protein can form channels whose properties, such as ion selectivity and ligand sensitivity, match the in vivo current as is required by the third criterion. The set of such properties is not likely to be unique to MeT currents generally or even to a specific native MeT current, however. The final criterion has been met only for a subset of the proteins currently identified as pore-forming subunits of native MeT channels in animal sensory cells. The most prominent is the *Drosophila* NOMPC protein, or dTRPN1, which confers mechanosensitivity on nonsensory neurons (Gong et al. 2013) and functions as a mechanosensitive channel in heterologous cells (Yan et al. 2013). For MeT channel complexes that may depend on elaborate and specialized cellular structures that focus force on the channel, meeting this criterion may exceed current experimental capabilities.

Taxonomy of Putative Pore-Forming Mechanoelectrical Transduction Channel Subunits

The types of proteins linked to the formation of excitatory MeT channels differ in their distribution across kingdoms and phyla (**Figure 4**). Whereas the oft-studied and well-understood stretch-activated channels MscS and MscL have homologs in bacteria, archaea, and eukaryotes, including fungi, protozoans, algae, and plants, they have yet to be detected in animals. By contrast, orthologs of TRPs, Piezo, DEG/ENaCs, and TMC proteins are largely absent from bacteria or archaea but are distributed broadly among eukaryotes. Of these four protein classes, only TRPs have clear orthologs in fungi, and only the Piezo proteins appear to have orthologs in plants. Genes encoding predicted DEG/ENaC proteins are widely dispersed among metazoans but believed to be absent from plants, algae, fungi, and protozoans. Whereas the exact physiological function of most of these orthologs is unknown, it is unlikely that all contribute to MeT channel complexes; only a subset of the better-studied animal TRPs, DEG/ENaCs, Piezos, and TMCs contribute to the formation of MeT channels in sensory mechanoreceptor cells.

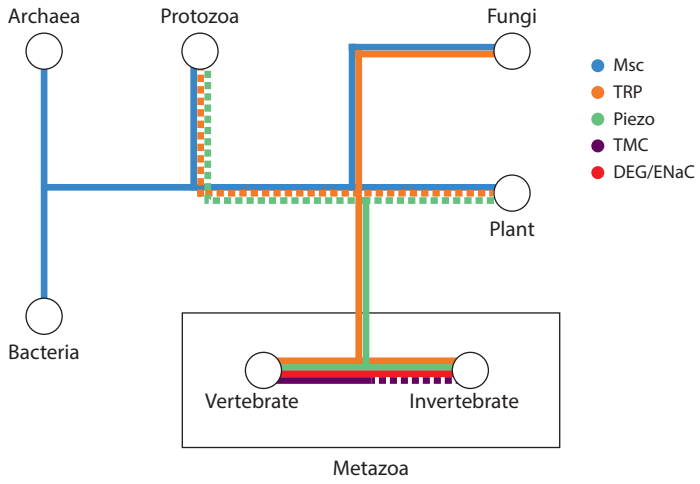

Figure 4

Taxonomy of established and putative excitatory mechanoelectrical transduction channels: Msc, mechanosensitive channel proteins including MscS, MscM, and MscL; TRP, transient receptor potential proteins; Piezo, Piezo proteins, also known as FAM38A and FAM38B; TMC, transmembrane-channel like proteins; DEG/ENaC, degenerins, epithelial sodium channels, and acid-gated ion channels. Each channel family has a distinct distribution across kingdoms and phyla. Dashed lines indicate where channels are present or predicted from genome sequence, but have yet to be linked to mechanosensation in experimental studies. Information synthesized from investigation of the PFAM database and the following reports: Bagriantsev et al. (2014); Goodman & Schwarz (2003); Kloda & Martinac (2002); Kurusu et al. (2013); Martinac & Kloda (2003); Pivetti et al. (2003); Prole & Taylor (2012, 2013); Wolstenholme et al. (2010); Zelle et al. (2013).

Transient Receptor Potential Ion Channels

The *Drosophila melanogaster* NOMPC, or dTRPN1, protein appears to meet the four criteria listed in the sidebar, Defining Sensory Mechanoelectrical (MeT) Channels, though some uncertainties remain about its in vivo gating mechanism. Like other TRP channel proteins, it is predicted to have six transmembrane domains and intracellular amino and carboxy termini. Its amino terminus has 23 ankyrin repeat domains that are proposed to function as a flexible linker to the cytoskeleton (Liang et al. 2013). To date, NOMPC has been linked to a wide variety of mechanosensory functions in *Drosophila*. It is needed for body touch sensation (cutaneous sensation) (Cheng et al. 2010, Tsubouchi et al. 2012, Walker et al. 2000, Yan et al. 2013) and contributes to hearing (Effertz et al. 2011, Kamikouchi et al. 2009, Zhang et al. 2013).

dTRPN1 is expressed in mechanoreceptor neurons innervating macrochaete bristles, campaniform receptors, chordotonal organs that mediate hearing and proprioception, and the nonciliated multidendritic (md) neurons that tile the body surface in larvae (Effertz et al. 2011, Liang et al. 2010, Walker et al. 2000, Yan et al. 2013). dTRPN1 is needed for mechanosensation, as evidenced by the partial loss of deflection-activated currents in bristle sensilla (Liang et al. 2013, Walker et al. 2000), the complete loss of indentation-induced action potentials in campaniform sensilla (Gong et al. 2013, Liang et al. 2013, Yan et al. 2013), and the loss of calcium transients and voltage signals in md neurons (Gong et al. 2013, Yan et al. 2013). The dTRPN1 protein can be reconstituted in heterologous cells and activated by mechanical stimulation (Yan et al. 2013).

Degenerin/Epithelial Sodium Channels

The DEG/ENaC proteins define a family of proteins that assemble as trimers to form sodium-selective, nonvoltage-gated ion channels in metazoans. Few, if any, DEG/ENaC homologs have been detected in plants, fungi, bacteria, or archaea (Goodman & Schwarz 2003). The DEG/ENaC family also includes acid-sensitive ion channels (ASICs), and its members are expressed in diverse mechanoreceptor neurons in *C. elegans* (Arnadóttir & Chalfie 2010, Goodman & Schwarz 2003), *Drosophila* (Zelle et al. 2013), and mammals (Geffeney & Goodman 2012, Lin et al. 2015). Three *ASIC* genes are expressed in DRG neurons, but genetic disruption of ASIC protein expression has mild effects, a finding that has led many to suggest that they are not critical for MeT channel function in mammals (reviewed in Lin et al. 2015). Uncertainties arising from genetic targeting strategies (Lin et al. 2015) and mapping between functionally and anatomically defined mechanoreceptor neuron subtypes suggest that the door to this hypothesis may not be tightly closed. Indeed, mammalian ASICs are targets of several naturally occurring peptide toxins that affect sensation (Bohlen et al. 2012, Diochot et al. 2013, Escoubas et al. 2000), which suggests that disrupting their function in the peripheral nervous system confers a selective advantage on toxin-producing animals and favors the idea that these channels have an important role to play in mammals as well as in invertebrates.

In worms and flies, defects in the genes encoding DEG/ENaC proteins alter sensitivity to mechanical loads applied to the body surface. MEC-4 is a DEG/ENaC protein that localizes to discrete puncta in *C. elegans* TRNs (Cueva et al. 2007, Emtage et al. 2004). Null mutations in the *mec-4* gene render worms touch-insensitive (Chalfie & Au 1989) and eliminate MeT currents in vivo (O'Hagan et al. 2005). Like currents carried by MEC-4 expressed in heterologous cells (Chelur et al. 2002, Goodman et al. 2002), native MeT currents depend on extracellular Na^+ ions and are blocked by the diuretic amiloride (O'Hagan et al. 2005). Collectively, these data indicate that MEC-4 meets three of the four criteria in the sidebar, Defining Sensory Mechanoelectrical (MeT) Channels. However, efforts to activate MEC-4–dependent channels by mechanically stimulating membrane patches that have been sampled from heterologous cells, such as *Xenopus* oocytes, have yet to be successful (A.L. Brown & M.B. Goodman, unpublished data).

Some 30 genes are predicted to encode DEG/ENaC proteins in *Drosophila* (Zelle et al. 2013), including at least two, PPK1 and PPK26 (aka Balboa), that are coexpressed in md sensory neurons (class IV). Class IV neurons innervate each body segment in larval animals and mediate avoidance of noxious mechanical and thermal stimuli (Tracey et al. 2003). Disrupting PPK1 and PPK26 function affects larval locomotion as well as behavioral responses to mechanical loads applied to the skin surface (Gorczyca et al. 2014, Guo et al. 2014, Mauthner et al. 2014), indicating that these DEG/ENaC proteins function in both proprioception and nociception. Neither PPK1 nor PPK26 is expressed properly in the absence of its partner (Gorczyca et al. 2014, Guo et al. 2014, Mauthner et al. 2014), implying that they form a heteromeric channel. Neither contributes to thermal sensitivity, which appears to depend on the TRP channels Painless and TRPA1. Class IV md neurons also express Piezo, which is needed for mechanical nociception (Kim et al. 2012) but is dispensable for locomotion (Guo et al. 2014). It remains to be determined whether PPK1 and PPK26 are needed for electrical responses to mechanical stimulation and how their activation and subcellular localization differ from that of Piezo.

Piezo Proteins

The Piezo proteins are behemoths (500 kDa) expressed in diverse tissues (Coste et al. 2010, 2012). Expressing Piezo1 and Piezo2 in heterologous cells generates mechanosensitive, nonselective cation currents thought to resemble those in native tissues. The Piezo2 protein is expressed in a subset of the DRG neurons that innervate skin, muscle, and internal organs in mammals

(Coste et al. 2013, Ranade et al. 2014). Although disrupting the genomic locus leads to embryonic lethality in mice, focused disruption has revealed that Piezo2 endows Merkel cells in the skin with the ability to detect indentation in touch domes (Maksimovic et al. 2014, Woo et al. 2014) and deflection of whiskers (Ikeda et al. 2014). Additionally, loss of Piezo2 function in DRGs eliminates sensitivity to innocuous stimuli, assessed through behavioral assays and electrical recordings of stimulus-induced changes in firing rate (Ranade et al. 2014). Future work is needed to clarify the subcellular localization of Piezo2 in peripheral nerve endings and accessory cells, such as Merkel cells, and to learn more about how such channels are activated in vivo.

The current findings also raise intriguing questions about how MeT channels respond to transient mechanical cues. In particular, it has long been known that MeT currents differ among DRG neurons studied in vitro: Some rapidly adapt, whereas others adapt more slowly (Delmas et al. 2011, Lechner & Lewin 2013, Zimmerman et al. 2014). Moreover, native currents rarely adapt completely, and current remains at steady state. Currents carried by Piezo2 expressed in HEK293T cells adapt at rates closer to those of rapidly adapting native currents than to those of slowly adapting currents (Coste et al. 2010, Dubin et al. 2012, Eijkelkamp et al. 2013). The difference between the in vivo variation in adaptation rate and the stability of adaptation rates in ex vivo recordings of Piezo2 currents implies that factors present in sensory neurons but absent from heterologous cells refine the in vivo responses of MeT channels.

Lessons Being Learned

Ionotropic receptors for mechanical stimuli, or MeT channels, appear to have emerged independently many times. To illustrate this idea, we compare the distribution of MscS-like proteins and DEG/ENaC proteins. Whereas sequences predicted to encode MscS-like proteins are found in bacteria, archaea, and plants, they have yet to be detected in any metazoan. Conversely, sequences predicted to encode DEG/ENaC proteins are found in most, if not all, metazoans and have yet to be detected in any bacterial, archaeal, or plant genomes. Thus, from an evolutionary perspective, the mechanosensitivity of MscS-like proteins is independent of that found in certain DEG/ENaC proteins.

Additionally, no single class of ion channel proteins holds a monopoly on mechanosensitivity, and no specific primary sequence motif or structural domain has been discovered that identifies animal MeT channels. This differs from other classes of ion channels, for which the number of transmembrane domains and the sequence of selectivity filters are sufficient to make predictions about gating modes and ion selectivity. For instance, it is possible to use the primary amino acid sequence to distinguish between voltage-gated calcium channels and voltage-gated sodium channels with a high degree of confidence. Should future work reveal such a sequence or structural motif for animal MeT channels, it would certainly accelerate understanding of the function of diverse mechanoreceptor cells across taxa and of the molecular basis for force-dependent gating.

MECHANOELECTRICAL TRANSDUCTION CHANNEL GATING MECHANISMS: DO THEY INVOLVE LIPIDS, PROTEINS, OR BOTH?

When force is transferred to MeT channels, closed, nonconducting channels are converted into open, conducting ion pores. Recognizing that all ion channels are embedded in a lipid bilayer and motivated by a search for a unifying biophysical principle, Kung, Anishkin, and colleagues (Anishkin & Kung 2013, Anishkin et al. 2014, Kung 2005) have put forward the force-from-lipid principle. In this scenario, force is transmitted to MeT channels via the lipid bilayer in the form of a change in tension or through the action of stiffened lipid platforms that rearrange in response to forces delivered to transmembrane complexes. The role of the lipid platforms is to

suppress mechanical noise and redistribute forces to the mechanosensitive channel embedded therein. Protein reinforcement could then confine force within the platforms, thus eliminating the need to deform the entire plasma membrane (Anishkin et al. 2014).

Some channels are activated by increased membrane tension when reconstituted in pure lipid bilayers. These channels include MscS, MscL (Haswell et al. 2011, Kung et al. 2010), and two-pore potassium channels, such as TREK and TRAAK (Brohawn et al. 2014). A prevailing model of how such activation takes place is that membrane tension catalyzes channel gating because the open state of the channel has a larger cross-sectional area than the closed state (Sukharev & Corey 2004). At the molecular level, tension thins the membrane and induces a hydrophobic mismatch between the channel in its closed state, which is relieved when the channel assumes its open state (Phillips et al. 2009). Although many ion channels do indeed show sensitivity to membrane tension in non-native lipid environments, this may not always be the gating mechanism employed in vivo.

Alternative hypotheses involve physical interaction of the MeT channel with elastic filaments connected to the cytoskeleton, the extracellular matrix, or both (Kung 2005). Such a mechanism, which could be considered a force-from-filament principle, has long been thought to account for activation of MeT channels in vertebrate hair cells, and tension regulation in these filaments provides a possible mechanism for adaptation (reviewed in Gillespie & Müller 2009). Not only the hair cell MeT channel but also the NOMPC TRP channel and DEG/ENaCs have been proposed to depend on filaments connecting channels directly to the cytoskeleton or extracellular matrix. Despite tremendous progress in discovering the ion channels that form MeT channels in sensory mechanoreceptor cells, our understanding of how such MeT channels are activated in their native environments remains incomplete. Critical questions include how to decipher the contribution of cell and tissue mechanics to mechanical signal transmission in vivo and the relative contributions of the force-from-lipid and force-from-filament principles. Reconstituting purified channels in lipid bilayers is an elegant method for determining whether the force-from-lipid principle is sufficient to activate a given candidate MeT channel, but it cannot exclude a role for the force-from-filament principle within native tissues. At the same time, the mechanical filtering and amplification carried out by engulfing tissues complicate direct application of mechanical loads in vivo. New tools to visualize the effects of forces applied to mechanoreceptor cells during sensory stimulation in situ would accelerate efforts to understand how animals feel force.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

We thank members of the Goodman and Pruitt laboratories for input and apologize to colleagues whose fine research we were unable to address or unintentionally misrepresented because of constraints on time and space. This work was supported by research grants (R01NS047715, R01NS092099, R01EB006745 to M.B.G.) and fellowships (F31NS093825 to S.K., K99NS089942 to M.K.) from NIH.

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